XJENZA ONLINE

VOLUME 10 Special Issue, 2022

www.xjenza.org

RIDT
The University of Malta Research, Innovation & Development Trust

MCS
MALTA CHAMBER OF SCIENTISTS

Science Journal of the Malta Chamber of Scientists

Guest Editor: Giuseppe Di Giovanni

Mediterranean Neuroscience Society

Why a MNS?

Research on brain function in health and disease is among the priorities for today's societies, and several indicators put the Mediterranean research area among strategic issues for building new profitable relationships. Many South-North collaborations and networks have emerged in recent years through bilateral and multi-lateral actions, supported by the EU or by international and national actions, whether for setting up teaching curricula, or by building human potential. The MNS is created to support and help strengthening all initiatives that bring together Mediterranean neuroscientists.

The previously successfully held Mediterranean Conferences of Neuroscience were organized in Montpellier in 1997, Marrakech in 2006, Alexandria in 2009, Istanbul in 2012, Pula – Sardinia in 2015, St. Julian – Malta in 2017, and Marrakech again in 2019. These conferences gather up to 400 scientists from all Mediterranean and other countries, and offer a rich program with world-class lectures, symposia, poster sessions and social events. These meetings have proved to be highly beneficial, not only for the scientific exchanges, but also in terms of training opportunities for students and young researchers.

Objectives of the MNS

The MNS works towards three main objectives:

- Strengthen exchanges between Mediterranean neuroscientists
- Promote education in Neuroscience and increase public awareness
- Sustain the Mediterranean Neuroscience Conference

To reach these objectives, the MNS's policy is to work in close cooperation with existing national and international Neuroscience and Scientific Societies.

Contact information

Mediterranean Neuroscience Society – MNS
https://www.medneuroscisociety.org/
E-mail: info@medneuroscisociety.org

Xjenza Online: Science Journal of the Malta Chamber of Scientists
www.xjenza.org

Editorial Board

Xjenza Online: Science Journal of the Malta Chamber of Scientists
www.xjenza.org

Chronological List of Past and Present Editors of Xjenza
The Journal of the Malta Chamber of Scientists

2018 –
Editor: Cristiana Sebu
Senior Editors: *Sebastiano D'Amico, David Magri*
Associate Editors: *Sandro Lanfranco, Ian Thornton, Gianluca Valentino, Ian Cassar, Alexandra Bonnici, Joseph Galea, Pierre Vella, Lourdes Farrugia, Godfrey Baldacchino, Liberato Camilleri*
Xjenza Online Vol. 10 Special Iss. MNS Proceedings (2022)
Xjenza Online Vol. 9 Special Iss. (2021)
Xjenza Online Vol. 9 Iss. 2 (2021)
Xjenza Online Vol. 9 Iss. 1 (2021)
Xjenza Online Vol. 8 Iss. 2 (2020)
Xjenza Online Vol. 8 Iss. 1 (2020)
Xjenza Online Vol. 7 Iss. 2 (2019)
Xjenza Online Vol. 7 Iss. 1 (2019)
Xjenza Online Vol. 6 Iss. 2 (2018)
Xjenza Online Vol. 6 Iss. 1 (2018)

2013 – 2017
Editor: Giuseppe Di Giovanni
Associate Editors: *David Magri, Ian Thornton, Ian Cassar, Philip Farrugia, Sebastiano D'Amico, Nicholas Sammut, David Mifsud, Godfrey Baldacchino, Liberato Camilleri, Carmel Cefai*
Xjenza Online Vol. 5 Iss. 2 (2017)
Xjenza Online Vol. 5 SI MNS Proceedings (2017)
Xjenza Online Vol. 5 Iss. 1 (2017)
Xjenza Online Vol. 5 Virtual Issue COST (2017)
Xjenza Online Vol. 4 Iss. 2 (2016)
Xjenza Online Vol. 4 Iss. 1 (2016)
Xjenza Online Vol. 3 Iss. 2 (2015)
Associate Editors: *David Magri, Ian Thornton, Ian Cassar, Philip Farrugia, Sebastiano D'Amico, Nicholas Sammut, Joseph Galea, David Mifsud, Sandro Lanfranco, Mario Valentino, Godfrey Baldacchino, Liberato Camilleri*
Xjenza Online Vol. 3 Iss. 1 (2015)
Xjenza Online Vol. 2 Iss. 2 (2014)
Xjenza Online Vol. 2 Iss. 1 (2014)
Xjenza Online Vol. 1 Iss. 2 (2013)
Xjenza Online Vol. 1 Iss. 1 (2013)

2003 – 2007
Editors: Joseph N. Grima and Richard Muscat
Xjenza Vol. 12 (2007)
Xjenza Vol. 11 (2006)
Xjenza Vol. 10 (2005)
Xjenza Vol. 9 (2004)
Xjenza Vol. 8 (2003)

1996 – 2002
Editor: Angela Xuereb
Associate Editor: *Richard Muscat*
Xjenza Vol. 7 (2002)
Xjenza Vol. 6 (2001)
Associate Editors: *Martin Ebejer and Richard Muscat*
Xjenza Vol. 5 (2000)
Xjenza Vol. 4 Iss. 2 (1999)
Xjenza Vol. 4 Iss. 1 (1999)
Associate Editors: *Martin Ebejer, Richard Muscat, and Christian A. Scerri*
Xjenza Vol. 3 Iss. 2 (1998)
Xjenza Vol. 3 Iss. 1 (1998)
Associate Editors: *Martin Ebejer, Richard Muscat, Christian A. Scerri and Emmanuel Sinagra*
Xjenza Vol. 2 Iss. 2 (1997)
Xjenza Vol. 2 Iss. 1 (1997)
Xjenza Vol. 1 Iss. 2 (1996)
Xjenza Vol. 1 Iss. 1 (1996)

Scope of Journal

Xjenza Online is the Science Journal of the Malta Chamber of Scientists and is published in an electronic format. Xjenza Online is a peer-reviewed, open access international journal. The scope of the journal encompasses research articles, original research reports, reviews, short communications and scientific commentaries in the fields of: mathematics, statistics, geology, engineering, computer science, social sciences, natural and earth sciences, technological sciences, linguistics, industrial, nanotechnology, biology, chemistry, physics, zoology, medical studies, electronics and all other applied and theoretical aspect of science.

The first printed issue of the journal was published in 1996 and the last (Vol. 12) in 2007. The publication of Xjenza was then ceased until 2013 when a new editorial board was formed with internationally recognised scientists, and Xjenza was relaunched as an online journal, with two issues being produced every year. One of the aims of Xjenza, besides highlighting the exciting research being performed nationally and internationally by Maltese scholars, is to provide a launching platform into scientific publishing for a wide scope of potential authors, including students and young researchers, into scientific publishing in a peer-reviewed environment.

Instructions for Authors

Xjenza is the Science Journal of the Malta Chamber of Scientists and is published by the Chamber in electronic format on the website: http://www.mcs.org.mt/index.php/xjenza. Xjenza will consider manuscripts for publication on a wide variety of scientific topics in the following categories

1. Research Articles
2. Communications
3. Review Articles
4. Notes
5. Research Reports
6. Commentaries
7. News and Views
8. Invited Articles and Special Issues
9. Errata

Research Articles form the main category of scientific papers submitted to Xjenza. The same standards of scientific content and quality that applies to Communications also apply to Research Articles.

Communications are short peer-reviewed research articles (limited to three journal pages) that describe new important results meriting urgent publication. These are often followed by a full Research Article.

Review Articles describe work of interest to the wide community of readers of Xjenza. They should provide an in-depth understanding of significant topics in the sciences and a critical discussion of the existing state of knowledge on a topic based on primary literature sources. Review Articles should not normally exceed 6000 words.Authors are strongly advised to contact the Editorial Board before writing a Review.

Notes are fully referenced, peer-reviewed short articles limited to three journal pages that describe new theories, concepts and developments made by the authors in any branch of science and technology. Notes need not contain results from experimental or simulation work.

Research Reports are extended reports describing research of interest to a wide scientific audience characteristic of Xjenza. Please contact the editor to discuss the suitability of topics for Research Reports.

Commentaries Upon Editor's invitation, commentaries discuss a paper published in a specific issue and should set the problems addressed by the paper in the wider context of the field. Proposals for Commentaries may be submitted; however, in this case authors should only send an outline of the proposed paper for initial consideration. The contents of the commentaries should follow the following set of rules: 3000 words maximum, title 20 words maximum, references 10 maximum (including the article discussed) and figures/tables 2 maximum.

News and Views The News section provides a space for articles up to three journal pages in length describing leading developments in any field of science and technology or for reporting items such as conference reports. The Editor reserves the right to modify or reject articles for consideration as News.

Invited Articles and Special Issues Xjenza regularly publishes Invited Articles and Special Issues that consist of articles written at the invitation of the Editor or another member of the editorial board.

Errata Xjenza also publishes errata, in which authors correct significant errors of substance in their published manuscripts. The title should read: Erratum: "Original title" by ***, Xjenza, vol. *** (year). Errata should be short and consistent for clarity.

Submission of Manuscripts

Manuscripts should be sent according to the guidelines given hereafter to xjenza@mcs.org.mt.

Referees All manuscripts submitted to Xjenza are peer reviewed. Authors are requested to submit with their manuscript the names and addresses of three referees, preferably from overseas. Every effort will be made to use the recommended reviewers; however the editor reserves the right to also consult other competent reviewers.

Conflict of Interest Authors are expected to disclose any commercial or other types of associations that may pose a conflict of interest in connection to with the submitted manuscript. All funding sources supporting the work, and institutional or corporate affiliations of the authors, should be acknowledged on the title page or at the end of the article.

Policy and Ethics The work presented in the submitted manuscript must have been carried out in compliance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (http://www.wma.net/en/30publications/10policies/b3/index.html); EU Directive 2010/63/EU for animal experiments (http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm); Uniform Requirements for manuscripts submitted to Biomedical journals (http://www.icmje.org). This must be stated at an appropriate point in the article.

Submission, Declaration and Verification Author(s) must only submit work that has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that is not under consideration for publication elsewhere, that has been approved for publication by all authors, and tacitly or explicitly, by the responsible authorities where the work was carried out, and that, if accepted, will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

Permissions It is the responsibility of the corresponding author of a manuscript to ensure that there is no infringement of copyright when submitting material to Xjenza. In particular, when material is copied from other sources, a written statement is required from both the author and/or publisher giving permission for reproduction.

Manuscripts in press, unpublished data and personal communications are discouraged; however, corresponding authors are expected to obtain permission in writing from at least one author of such materials.

Preparation of Manuscripts

Xjenza accepts submissions in MS Word, Libre Office Writer and LaTeX, the latter being the preferred option. Anyone submitting in LaTeX should use the journal template, the latest version of which can be found at http://github.com/hicklin/Xjenza-Journal-Template. All the necessary files to run the LaTeX document should be supplied together with the rendered PDF.

If a word processor is used the styling should be kept to a minimum. Bold face and italic fonts, as well as subscript and superscript text may be used as required by the context. Text should be in single-column format and the word processor options should not be used in order to justify text or hyphenate words. Alongside the native format of the word processer, a PDF file, generated by the word processor, must be provided. Furthermore, artwork should be in accordance with the artwork guidelines given below and must be submitted separately from the word processor file. Similarly, the bibliographic data of the cited material should be submitted separately as an Endnote (*.xml), Research Information Systems (*.ris), Zotero Library (zotero.splite) or a BibTeX (*.bib) file.

Article Structure

A manuscript for publication in Xjenza will typicall have the following components: Title page, Abstract, Keywords, Abbreviations, Introduction, Materials and Methods, Results, Discussion, Conclusions, Appendices and References.

The manuscript will be divided into clearly defined and numbered sections. Each numbered subsection should have a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text, i.e. refer to the subsection by the section number.

Title page

- The title should be concise yet informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- Author names and affiliations. Indicate the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript number immediately after each author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address.
- Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, including post-publication. Ensure that telephone and fax numbers (with country and area code) are provided in addition to the e-mail address and complete postal address. Contact details must be kept up to date by the corresponding author.
- Present/permanent address. If an author has changed the address since the work described, this can be indicated as a footnote to the author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract A concise and factual abstract is required of up to about 250 words. The abstract should state briefly the background and purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, references and non-standard abbreviations should be avoided. If essential, these must be defined at first mention in the abstract itself.

Abbreviations Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention as well as in the footnote and should be used consistently throughout the text.

Introduction State the objectives of the work and provide an adequate background, avoid a detailed literature survey or a summary of the results.

Materials and Methods Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

Results Results should be clear and concise. Numbered/tabulated information and/or figures should also be included.

Discussion This should explore the significance of the results of the work, yet not repeat them. Avoid extensive citations and discussion of published literature. A combined section of Results and Discussion is often appropriate.

Conclusions The main conclusions based on results of the study may be presented in a short Conclusions section. This may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Acknowledgements Collate acknowledgements in a separate section at the end of the article before the references. Do not include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided assistance during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Units Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI. Anyone using LaTeX should use the package siunitx in all cases.

Footnotes Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes by a superscript number in the text and list the footnotes separately at the end of the article. Do not include footnotes in the Reference list.

Table Footnotes Indicate each footnote in a table with a superscript lower case letter.

Artwork Electronic artwork general instructions:

- Make sure you use uniform lettering and sizing of your original artwork.
- Save text in illustrations as 'graphics' or enclose the font.
- Only use the following fonts in your illustrations: Arial, Courier, Times, Symbol or Computer Modern Roman, the latter is preferred.
- Number the illustrations according to their sequence in the text.
- Name your artwork files as 'fig$x$' or 'tab$x$' where x corresponds to the sequence number in your document.

- Provide captions to illustrations separately.
- Produce images near to the desired size of the printed version or grater.
- Make sure that the artwork has no margins and borders.
- Submit each figure as a separate file.

Formats Regardless of the application used, when your electronic artwork is finalised its file format should be one of the following (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

- PDF or SVG: Vector drawings. Embed the font or save the text as 'graphics'.
- JPEG or PNG: Color or grayscale photographs (halftones): always use a minimum of 300 dpi.
- JPEG or PNG: Bitmapped line drawings: use a minimum of 1000 dpi.
- JPEG or PNG: Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.

Where possible use a vector format for your artwork (PDF or SVG). If this is not possible, supply files that have and adequate resolution.

Colour Artwork Make sure that color artwork files are in an acceptable format (JPEG, PNG, PDF or SVG) and have the correct resolution.

Figure Captions Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum, but explain all symbols and abbreviations used.

Tables Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be moderate with the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Large tables should be submitted in CSV format.

Citations and References Reference and citation styles for manuscripts submitted to Xjenza should be in accordance to the APA v6 style.

Citation in text References to cited literature in the text should be given in the form of an author's surname and the year of publication of the paper with the addition of a letter for references to several publications of the author in the same year. For further information regarding multiple authors consult the APA v6 guidelines. Citations may be made directly

Kramer et al. (2010) have recently shown . . .

or parenthetically

as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999).

Groups of references should be listed first alphabetically, then chronologically. When writing in LaTeX use `\textcite{}` and `\parencite{}` for the respective cases mentioned.

The reference section Every reference cited in the text should also be present in the reference list (and vice versa). The reference list should also be supplied as an Endnote (*.xml), Research Information Systems (*.ris), Zotero Library (zotero.splite) or a BiBTeX (*.bib) file. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication. Consult the APA v6 guidelines for multiple authors. Below are some examples of referencing different bibliographic material.

Reference to a Journal Publication

Agree, E. M. and Freedman, V. A. (2011). A Quality-of-Life Scale for Assistive Technology: Results of a Pilot Study of Aging and Technology. *Phys. Ther.*, 91(12):1780–1788.

McCreadie, C. and Tinker, A. (2005). The acceptability of assistive technology to older people. *Ageing Soc.*, 25(1):91–110.

Reference to a Book

Brownsell, B. (2003). *Assistive Technology and Telecare: Forging Solutions for Independent Living*. Policy Press, Bristol.

Fisk, M. J. (2003). *Social Alarms to Telecare: Older People's Services in Transition*. Policy Press, Bristol, 1st edition.

Reference to a Chapter in an Edited Book

Brownsell, S. and Bradley, D. (2003). New Generations of Telecare Equipment. In *Assist. Technol. Telecare Forg. Solut. Indep. Living*, pages 39–50.

Web references The full URL should be given together with the date the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately or can be included in the reference list.

References in a Special Issue Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Journal Abbreviations Journal names should be abbreviated according to:

-Index Medicus journal abbreviations: http://www.nlm.nih.gov/tsd/serials/lji.html;

-List of title word abbreviations: http://www.issn.org/2-22661-LTWA-online.php;

-CAS (Chemical Abstracts Service): http://www.cas.org/sent.html.

Video data Xjenza accepts video material and animation sequences to support and enhance the presentation of the scientific research. Authors who have video or animation files that they wish to submit with their article should send them as a separate file. Reference to the video material should be clearly made in text. This will the modified into a linked to the paper's supplementary information page. All submitted files should be properly labelled so that they directly relate to the video files content. This should be within a maximum size of 50 MB.

Submission check list

The following list will be useful during the final checking of a manuscript prior to sending it to the journal for review. Please consult the Author Guidelines for further details of any item.

- One author has been designated as the corresponding author with contact details:
  - E-mail address.
  - Full postal address.
  - Telephone and fax numbers.
- All necessary files have been sent, and contain:
  - All figures are given separately in PDF, SVG, JPEG of PNG format.
  - Caption for figures is included at the end of the text.

  - All tables (including title, description, footnotes) are included in the text and large tables have been given separately as CSV.
  - The reference list has been given in XML, RIS, zotero.splite or BIB file format.
- Further considerations
  - Abstract does not exceed about 250 words.
  - Manuscript has been 'spell-checked' and 'grammar-checked'.
  - References are in the required format.
  - All references mentioned in the reference list are cited in the text, and vice versa.
  - Bibliographic data for all cited material has been provided.
  - Permission has been obtained for use of copyrighted material from other sources (including the Web).
  - A PDF document generated from the word processor used is submitted.

After Acceptance

Use of the Digital Object Identifier The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

Proofs, Reprints and Copyright The corresponding author will receive an electronic proof of the article and have an opportunity to review editorial changes and to double-check accuracy of content, tables, and statistics before publication. A list of any necessary corrections should be sent by email to the managing editor within a week of proof receipt to avoid unnecessary delays in the publication of the article. Alterations, other than essential corrections to the text of the article, should not be made at this stage. Manuscripts are accepted for publication on the understanding that exclusive copyright is assigned to Xjenza. However, this does not limit the freedom of the author(s) to use material in the articles in any other published works.

Xjenza Online: Science Journal of the Malta Chamber of Scientists
www.xjenza.org

Conference proceedings

8th Mediterranean Neuroscience Society Conference 2022 Croatia MNS2022

Welcome Message

Dear Colleagues,

On behalf of the Local Organizing Committee and the Croatian Neuroscience Society, it is my great pleasure to warmly welcome you all to the 8th Mediterranean Neuroscience Society (MNS) Conference 2022, in the magnificent city of Dubrovnik, Croatia.

This conference will bring together neuroscientists from the Mediterranean countries but also EU and worldwide international experts at the forefront of basic, clinical, and translational neuroscience.

The President of MNS, Giuseppe Di Giovanni, I, and the other members of the scientific and the local organizing committees have worked hard to organize a successful meeting, both scientifically and socially. Despite many obstacles and the postponement of the conference, the MNS2022 program is exceptional. It includes seven plenary lectures, more than 50 symposia, as well as over 50 poster presentations that will further stimulate face-to-face interactions.

One of the primary goals of the MNS2022 is to introduce and foster students at doctoral and postdoctoral levels, allowing them to share their research experiences and ideas in a vibrant but friendly environment. We are confident that the conference will refresh friendships and scientific collaborations among our research and academic institutions and also ignite new and exciting ones. Thank you for all your commitments and efforts made in preparing, sharing, and presenting your innovative and valuable research findings at this meeting. We also thank all our partners and sponsors for their support in these challenging times.

On behalf of the Local Organizing Committee, I wish you all much success with your presentations and forming new collaborations. I welcome you to enjoy a stimulating atmosphere in the early Croatian summer on the beautiful Adriatic coast.

Yours Sincerely,

CROATIAN SOCIETY FOR NEUROSCIENCE

Goran Šimić
Croatian Institute for Brain Research,
University of Zagreb Medical School
President of the Local Organizing Committee

Mediterranean Neuroscience Society (MNS)

The MNS has been created to support and help strengthen all initiatives that bring together Mediterranean neuroscientists.

The previously successfully held Mediterranean Conferences of Neuroscience were organized in Montpellier in 1997, Marrakech in 2006, Alexandria in 2009, Istanbul in 2012, Pula – Sardinia in 2015, St. Julian – Malta in 2017, and Marrakech again in 2019. The aforementioned MNS conferences gathered scientists from all Mediterranean countries and offered a rich program with lectures, symposia, poster sessions, and social events. These meetings have proved to be highly beneficial, not only for the scientific exchanges but also in terms of training opportunities for students and young researchers. Research on brain function in health and disease is among the priorities for today's societies, and several indicators put the Mediterranean research area among strategic issues for the European Union (EU).

Many South-North collaborations and networks have emerged in recent years through bilateral and multi-lateral actions, supported by the EU or by international and national actions, whether for setting up teaching curricula (Tempus programs) or building human potential (Horizon programs).

Objectives of the MNS

The MNS works towards three main objectives:

- Strengthen exchanges between Mediterranean neuroscientists;
- Promote education in the neurosciences and increase public awareness of progress made;
- Sustain the Mediterranean Neuroscience Conference;
- To reach these objectives, the MNS's policy is to work in close cooperation with existing national and international Neuroscience Societies.

MNS Council members

ORGANIZED UNDER THE AUSPICES AND SUPPORT OF

L-Università ta' Malta
Faculty of Medicine & Surgery

Local Organizing Committee

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Mirta BOBAN		Croatia
Anja BUKOVAC		Coratia
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Liana Fattore	Past-President	Italy
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Ali JAHANSHAHI	Treasurer	Netherlands
Patrick VUILLEZ	Council Member	France
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Patrizia CAMPO-LONGO	Council Member	Italy
Khalid EL ALLALI	Council Member	Malta
Fatiha CHIGR	Council Member	Malta

Secretariat of the 8th MNS Meeting 2022

Maja Orsag
conTres
maja@contres.hr

Information for Speakers and Chairpersons

The role of the chairpersons is to monitor speaking and discussion times and to lead the discussions. Chairpersons control the switch between presentations. Each presentation is 20 min followed by 5 min Q/A section.

Use a presentation in the 16:9 format. The Chairperson is responsible to collect all the presentations of their symposium. It is advisable that the Chairpersons use their own PC in which the presentations of the single speakers are saved for the Symposium. All speakers must submit their presentations to the Chairperson and Secretary at info@medneuroscisociety.org before the 28th of May.

Multimedia Considerations and Slide Preparation

Presenters: Make your presentations compatible with on-site audio/visual specifications.

All screens in Dubrovnik will be **16:9** widescreen format.

Before Travelling (Recommended)

It is highly recommended to send your presentation before the 28th of May by email to your chairperson/s and cc info@medneuroscisociety.org specifying in the SUBJECT SYMPOSIUM NUMBER AND SYMPOSIUM PRESENTATION (e.g. S33.2 Symposium n 32 presentation n 2).

For the Chairpersons:

Please note you are responsible for collecting all the presentations of your Symposium in a file on a USB memory stick and loading it on one of the Conference computers in the Conference Room before the start of the session. Another option is to use their own personal PCs with all the presentations saved.

Please note that the conference computers in the session halls are being supplied with Office 2020.

If combining video films with PowerPoint, please make sure to check it with your chairperson before the start of the session. Alternatively, you may supply your own laptop computer. In such a case please be aware if it has a VGA socket for external signal or take with you VGA to HDMI adapter.

Important note for Macintosh users

In order to use MAC presentations, you may use your own Macintosh laptop computer. In such a case please confirm you provide it with a VGA adaptor for external signal.

POSTER INFORMATION

Poster Presentations

Whole-day poster presentations will take place in the Poster Area from Monday, May 30, 11:10 – 11:40 h and 16:55 – 17:25 h and Tuesday May 31, 11:10 – 11:40 h and 16:55 – 17:25 h. Authors are requested to be in attendance at their poster for discussion, as scheduled below:

Monday, May 30
11:10 – 11:40 h and 16:55 – 17:25 h **Poster session**
Tuesday, May 31
11:10 – 11:40 h and 16:55 – 17:25 h **Poster session**

Please find your board number by locating your abstract on the programme book. You should display your poster on the board number assigned to you.

Poster boards are 2 meters high and 1 meter wide (portrait format).

Posters can be affixed by double-sided adhesive tape, available at the Poster Assistance desk onsite. Posters should be mounted at 08:00 a.m. Removal: Posters can be removed on Tuesday afternoon, after 17:30 h. The organizers cannot be responsible for posters not being removed by the above-stated time.

PROGRAMME

Sunday, May 29th 2022

10:00–20:00
Registration

17:30–18:00
Welcome to MNS Meeting
Goran Šimić (MNS2022 President), Tracy Bale (IBRO President), Jean-Antoine Girault (FENS President), Bayram Yilmaz (Secretary-General FEPS) and Giuseppe Di Giovanni (MNS President)

18:00–18:50
PLENARY LECTURE #1
Tracy Bale (IBRO President): "Extracellular vesicles as systemic stress signals important to the brain"
Chair: Liana Fattore

19.00–20.00
ALBA Network: Science and Networking Session
Christina Dalla: "Sex and gender aspects of neuropsychiatric research" Moderator: Željka Krsnik

20.00–22.00
ALBA Network Reception

Monday, May 30th 2022

08.00–18.00
Registration

08.30–09.20
PLENARY LECTURE #2
Laszlo Zaborszky (Center for Molecular and Behavioral Neuroscience, Rutgers, The State University of New Jersey, Newark, USA): "Forebrain Cholinergic System: From Anatomy to Function and Dysfunction"
Chair: Goran Šimić

09.30–11.10
Symposia 1–6

S1
"Synaptic communication in health and disease: from single molecule to network"
Chair: Laurent Groc

Laurent Groc (University of Bordeaux, France): "Physiological and pathological membrane crosstalk of NMDA and dopamine receptors"

Fang Liu (Toronto, Canada): "The glucocorticoid receptor–FKBP51 complex contributes to fear conditioning and posttraumatic stress disorder"

Eric Hanse (Gothenburg, Sweden): "Cerebrospinal fluid promotes maturation of human iPSC-derived neurons and acutely modulates synaptic and neuronal function"

Yuji Ikegaya (Hongo, Bunkyo-ku, Tokyo, Japan): "Synaptic modulation and plasticity during hippocampal synchrony"

S2
"Cellular and molecular mechanisms regulating persistent changes in reward-related behaviors"
Chair: Matt Lattal

Matt Lattal (Department of Behavioral Neuroscience, Oregon Health & Science University Portland, OR USA): "Persistent changes in motivation and reward following acute trauma"

Elizabeth A. Heller (Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, PA, USA): "Persistent epigenetic regulation of novel targets across cocaine abstinence"

Marcelo A. Wood (Department of Neurobiology & Behavior, University of California Irvine): "Epigenetic

mechanisms in the medial habenula underlying reinstatement of drug-seeking behavior"

Iva Zovkić (University of Toronto Mississauga, Mississauga, ON, Canada): "An emerging role for histone variants in behavioral regulation"

S3
"Novel Mechanisms by which Life Experiences across the Lifespan Change Neural Function and Behavior"
Chair: Gretchen Neigh

Kerry Ressler (Harvard Medical School, Belmont, MA, USA): "Translating Across Circuits and Genetics Toward Progress in Understanding the Biology of Trauma-Related Disorders"

Tanja Jovanovic (Wayne State University, Detroit, MI, USA): "Trauma exposure across generations: how maternal trauma exposure and PTSD impacts the neurobiology of her children"

Vasiliki Michopoulous (Emory University, Atlanta, GA, USA): "Trauma exposure across the lifespan increases risk for adverse behavioral and physiological health outcomes in pregnant persons"

Gretchen Neigh (Virginia Commonwealth University, Richmond, VA, USA): "Developmental experiences cause longterm changes in mitochondrial function in synapses"

S4
"The brain as a target for endocrine-disrupting chemicals"
Chairs: Matthieu Keller, Thierry Charlier

Sakina Mhaouty Kodja (Universite Pierre et Marie Curie, France): "Effects of exposure to low doses of plasticizers on cognitive behaviors in male mice"

Anne Simone Parent (Universite de Liege, Belgium): "Neuroendocrine disruption of puberty and reproduction"

Marilena Marraudino (Torino University, Italy): "Genistein: a new Metabolism Disrupting Chemical"

Anne Claire Binter (ISGlobal, Spain): "Prenatal exposure to environmental pollutants and neurodevelopment: results from two European birth cohorts"

S5
"Contribution of early-life stress to the development of psychiatric disorders"
Chairs: Desmedt Aline, Koehl Muriel

Gal Richter-Levin (Haifa, Israel): "Juvenile stress modulation of stress vulnerability and resilience in adulthood"

Archana Kolikil (Nijmegen, the Netherlands): "Effects of early-life stress on the quality of pup-dam interaction"

Desmedt Aline (Bordeaux, France): "Modeling adaptive versus maladaptive (PTSD-like) fear memory: Identification of contextual amnesia as a cause of PTSD-like hypermnesia"

Mohamed-Lyès Kaci (Bordeaux, France): "Prenatal stress increases vulnerability to PTSD-like memory"

S6
"Integrated neuromodulation in subcortical circuits for perception and reward"
Chairs: Rosario Moratalla, Raffaella Tonini

Raffaella Tonini (Italian Institute of Technology, Genova, Italy): "Neuromodulated plasticity in the noradrenergic locus coeruleus"

François Georges (University of Bordeaux, CNRS "Locus coeruleus wake-up dopamine neurons during environmental novelty"

Gilad Silberberg (Karolinska Institutet, Stockholm, Sweden): "Regulation of sensory responses by motor activity in the healthy and Parkinsonian striatum"

Adrian Sanz-MagrRosario (Instituto Cajal (CSIC) Madrid, Spain): : "Non-motor co-morbidities ferikain early stages of Parkinson´s Disease"

11.10–11.40
Coffee break and Poster Presentation

11.40–13.40
Symposia 7–11

S7
"New insights in the hypothalamic circuitry regulating energy metabolism: physiological and pathophysiological implications"
Chairs: Carole Rovère, Nicolas Chartrel

Sophie Steculorum (Max Planck Institute for Metabolism Research, Cologne, Germany): "Neurocircuits of food sensory perception"

Marie Picot (Université de Rouen, Normandie Université, Mont-Saint-Aignan, France): "Central regulation of glycemia by insulin involves the 26RFa neuronal network"

Ophélia Le Thuc (Division of Metabolic Diseases, TUM, Munich, Germany): "The role of mitochondrial function in astrocytes in the neuroendocrine control of metabolism"

Alexandre Benani (Université Bourgogne Franche-Comté, Dijon, France): "Toward a link between neuroglial plasticity and satiety"

Céline Cansell (Université Côte d'Azur, Valbonne, France): "Dietary fat exacerbates post-prandial hypothalamic inflammation involving GFAP-positive cells and microglia in male mice" (Video recording)

S8
"Glia-neuron glutamatergic interactions in health and disease"
Chairs: Yuriy Pankratov, Christian Henneberger

Robert Zorec (Ljubljana, Slovenia): "Vesicle Dynamics and Fusion Pore Regulation"

Christian Henneberger (Bonn, Germany): "Activity-dependent supply of NMDA receptor co-agonists in the hippocampus"

Justin Lee (Daejeon, Korea): "Best1-mediated tonic release of astrocytic D-serine in modulation NMDAR tone and cognitive flexibility"

Yuriy Pankratov (Coventry, UK): "Role for vesicular and non-vesicular glutamatergic gliotransmission in regulation of synaptic plasticity and working memory"

S9
"Why do we overeat? Unravelling the neuronal mechanisms underlying uncontrolled food intake"
Chair: Yonatan Kupchik

Paul Kenny (New York, USA): "A brain aversion network that drives addiction-like overeating in obesity"

Robyn Mary Brown (Melbourne, Australia): "Why do women overeat? Characterizing a model of 'emotional' binge eating in female mice"

Yonatan Kupchik (Israel): "Innate clues in the ventral pallidum for the susceptibility to overeat"

Stephanie Borgland (Calgary, Canada): "Why do we eat too much? How palatable diets change the orbitofrontal cortex and valuation of food rewards"

Serge Luquet (Paris, France): "Nutritional lipids act on dopamine receptor type 2 (DRD2)-expressing neurons to gate dopamine-associated behaviours"

S10
"Using multiscale approaches to uncover the role of the superior parietal lobule in humans and non-human primates"
Chair: Michela Gamberini

Nicola Palomero-Gallagher (Jülich, Germany): "Cyto- and receptor architectonic organization of the macaque and human superior parietal lobule"

Michela Gamberini (Bologna, Italy): "Anatomo-functional organization of the macaque superior parietal lobule"

Sabrina Pitzalis (Roma, Italy): "Functional specialization of the human dorso-medial parietal cortex"

Marco Davare (Uxbridge, UK): "The role of posterior parietal cortex in defining motor commands for reaching movements"

Ferdinand Binkofski (Aachen, Germany): "Somatosensory function and dysfunction of the superior parietal lobule. Tactile agnosia and tactile apraxia"

S11
"New perspectives on endocannabinoid signaling modulation of synaptic functions in physiological and pathological conditions"
Chair: Roberto Colangeli

Benjamin Barti (Budapest, Hungary): "STORM super-resolution imaging of cannabinoid signaling"

Roberto Colangeli (Ancona, Italy): "Endocannabinoid signaling deficiency drives emotional and cognitive comorbidities in epilepsy"

Miriam Melis (Monserrato, Italy): "Prenatal THC and polymodal activation of endocannabinoid signaling at dopamine neurons"

Haley Vecchiarelli (Victoria, Canada): "Microglia in stress, colitis and Cannabis exposure: interactions with the (endo)cannabinoid system"

11:40–13:40
Oral Communications (O1–O5)

O1 Alexander K. Converse (Madison, Wisconsin, USA): "Positron emission tomography neuroimaging of glucose metabolism in the rodent Pink1-/- Parkinson Disease model"

O2 Davor Virag (Zagreb, Croatia): "Diurnal and nocturnal locomotor patterns during recovery may predict the development of motor impairment in the 6-hydroxydopamine-induced rat model of Parkinson's disease"

O3 Maryann N. Krasko (Madison, Wisconsin, USA): "Early-Stage Parkinson Disease: dysphagia, gastrointestinal dysfunction, and pathology in the Pink1-/- rat model"

O4 Jan Homolak (Zagreb, Croatia): "Can fecal properties warn us about developing Parkinson's disease? Preliminary results from the nested case-control study in the 6-hydroxydopamine-induced rat model of Parkinson's disease"

O5 Pavlina Pavlidi (Athens, Greece): "PEERS — An Open Science 'Platform for the Exchange of Experimental Research Standards' in Neuroscience and Biomedical Research"

13:40–14:40
LUNCH

14:40–15:15
SYMPOSIA 12-16

S12
"Multi-level analyses of acute stress: from basic research to clinical translation"
Chair: Johannes Bohacek

Maurizio Popoli (Milan, Italy): "Dynamic dissection of short- and long-term response to acute stress: a matter of resilience or vulnerability"

Marloes Henckens (Nijmegen, Netherlands): "Neural activity and network connectivity associated with inter-individual differences in trauma susceptibility"

Johannes Bohacek (Zurich, Switzerland): "Chasing stress down a multi-omic rabbit hole"

Talma Hendler (Tel Aviv, Israel): "Self-neuromodulation targeting limbic activity for alleviating emotion-dysregulation in neuropsychiatric patients"

S13
"The Physiology, Function, and Pathology of the Claustrum"
Chairs: Gilad Silberberg, Ami Citri

Anna Terem (The Hebrew University): "A claustro-frontal dopamine-driven circuit essential for contextual association of reward"

Adam M. Packer (University of Oxford): "Input and output connectivity mapping reveals integrating properties of corticoclaustral and intraclaustral circuits"

Alan Carleton (University of Geneva): "The claustrum-medial prefrontal cortex network controls cognitive flexibility"

Roberto de la Torre-Martínez (Stockholm, Sweden): "Claustrum projections to the Anterior Cingulate Cortex are layer and cell-type dependent"

S14
"Molecular pathways and circuitry mechanisms in Autism Spectrum Disorder and Obsessive Compulsive Disorder: preclinical and clinical evidence"
Chairs: Claudio D'Addario, Viviana Trezza

Antonia Manduca (Dept. Science, Roma Tre University): "The endocannabinoid system as a novel target for autism spectrum disorder"

Claudio D'Addario (University of Teramo, Italy): "Exploring epigenetic mechanisms in Obsessive Compulsive Disorder, preliminary data on a possible interplay with microbiota modulation"

Fulvio D'Acquisto (Rohempton University, UK): "Immuno-moodulin: a novel biomarker and therapeutic target for OCD and related disorders"

Vincenzo Micale (University of Catania, Italy): "Preclinical models of neurodevelopmental disorders: Focus on current evidence for the discovery of novel therapeutic targets"

S15
"Parkinson's Disease is not only dopamine or motor dysfunctions"
Chairs: Micaela Morelli, Eduardo Tolosa

Eduardo Tolosa (University of Barcelona, Barcelona, Spain): "Neural substrates of non motor symptoms of Parkinson disease"

Véronique Sgambato (University of Lyon, France): "The role of serotonin on neuropsychiatric signs in Parkinson's disease"

Nina Vardjan (University of Ljubljana, Zaloska, Slovenia): "Astroglial contribution to neurodegeneration: focus on noradrenergic hypothesis"

Marina Pizzi (University of Brescia, Italy): "Non motor symptoms and synucleinopathy are associated with c-Rel deficiency in Parkinson's disease"

S16
"Recent advances in the understanding of pain and associated comorbidities"
Chairs: Jacques Noël, Jérôme Busserolles

Rebecca Seal (Pittsburgh, USA): "Cross species transcriptomic analysis accelerates insights into the spinal dorsal horn circuitry for persistent pain and the development of novel gene therapies"

Sandrine Geranton (University College London, UK): "Epigenetics, stress and chronic pain"

Jacques Noël (Université Côte d'Azur, France): "Lysophosphatidylcholine in the serum of obese mice fed with high-fat diet activates Acid-Sensing Ion Channel 3 to sensitize DRG neurons and induce heat pain hypersensitivity"

Jérôme Busserolles (Auvergne University, Clermont-Ferrand, France): "TREK-1 channels as pharmacological targets for analgesic drugs in cancer situation"

16.55–17.25
Coffee break and Poster Presentation

17.25–17.25
Symposia 17–21

S17
"Thalamocortical interactions in health and disease"
Chairs: Magor L. Lörincz, Nathalie Leresche

Nathalie Leresche (Université, Paris, France): "Centrally expressed Cav3.2 T-type calcium channel is critical for the initiation and maintenance of neuropathic pain"

Magor L. Lörincz (University of Szeged, Hungary): "State dependent thalamic activity on various timescales"

Stephane Charpier (Sorbonne Université, Paris): "Cortex and Thalamus: The Dangerous Liaisons"

Ferenc Mátyás (Research Centre for Natural Sciences, Budapest, Hungary): "The role of the thalamoamygdalar routes in associative learning"

László Acsady (Institute of Experimental Medicine, Budapest, Hungary): "On the variability of thalamic computational units"

S18
"Microbiome News and Views"
Chair: Illana Gozes

Markus M. Heimesaat (Berlin, Germany): "Gut microbiota and Pituitary adenylate cyclase-activating polypeptide (PACAP) – lessons learned from murine infection and inflammation models"

Anna Kiryk (Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland): "Metabolic, gut microbiota composition and behavioral changes induced by altered fat-to-sugar ratio upon a dietary challenge"

Illana Gozes (Sackler Faculty of Medicine, Sagol School of Neuroscience and Adams Super Center for Brain Studies, Tel Aviv University, Israel): "A cross-talk between the microbiome and the brain: the ADNP autism syndrome and therapeutic development as a case study"

S19
"Understanding the role of GPCR heteroreceptor complexes and their adaptor proteins in the neuronal networks of the brain in health and mental disorders"
Chairs: Dasiel O. Borroto-Escuela, Patrizia Ambrogini

Kjell Fuxe (Stockholm, Sweden): "GPCR heteroreceptor complexes and their adaptor proteins give new integrative mechanisms that may go wrong in Parkinson´s disease, schizophrenia and cocaine addiction"

Fang Liu (Toronto, Canada): "D2-DISC1 protein complexes and their relevance for schizophrenia"

Ramon Fores-Pons (Malaga, SPAIN): "On the balance of D2R-MOR and D4R-MOR in the dorsal and ventral striatum. Putative link to morphine dependence and addiction"

Dasiel O. Borroto-Escuela (Stockholm, Sweden): "On the role of GPCR heteroreceptor complexes neuromodulation of the Claustrum"

Patrizia Ambrogini (Urbino, ITALY): "5-HT1A-FGFR1 heteroreceptor complexes and their allosteric receptor-receptor interactions in the hippocampus. Relevance for major depression and its treatment"

S20
"Drug addiction: From circuits to molecules"
Chair: Rami Yaka

Yonatan Kupchik (Israel): "The role of different ventral pallidal projection neurons in abstinence from cocaine"

Ana João Rodrigues (Portugal): "Distinct (but not necessarily opposing) roles of nucleus accumbens D1- and D2-neurons in behavior"

Miriam Melis (Cagliari, Italy): "Mesolimbic dopamine dysregulation as a signature of aberrant salience attribution imposed by prenatal THC exposure"

Claire Thornton (UK): "The impact of cocaine exposure on mitochondrial dynamics"

Rami Yaka (Israel): "Molecular mechanism underlying the action of Zeta Inhibitory Peptide as memory eraser"

S21
"Sex differences in the neurobiology of Motivated Behaviors"
Chairs: Mohamed Kabbaj, Zuoxin Wang

Marcello Wood (University of California Irvine, USA): "Sex differences in an epigenetic feedback mechanism underlying effects of exercise in memory formation"

Florian Duclot (Florida State University, USA): "Transcriptomic regulations associated with individual differences in paternal care in prairie voles"

Stefania Maccari (North University of Lille, France): "Early maternal care at the core of the sex-dimorphic intergenerational transmission of the maladaptive response to stress in the perinatally stressed rats"

Xin-Yun Lu (Medical College of Georgia, Augusta University, Georgia, USA): "Exon-specific histone modifications of hippocampal Bdnf underlie individual variations and sex differences in stress susceptibility"

Mary Kay Lobo (University of Maryland, School of Medicine, Baltimore, USA): "Converging circuit and molecular mechanisms with opioid and stress exposure"

17:25–19:25
Oral Communications (O6–O10)

O6 Sanchez Clara (Valbonne, France): "Effect of lipid nature on microglial reactivity, neuroinflammation and cognitive disorders associated with obesity"

O7 D. Holcman (Paris, France): "Nanoscale molecular organization in dendritic spines regulates calcium storage and depletion"

O8 Pastor Jennyfer (Tel-Aviv, Israel): "Effects of IGF1 on excitability of sensory nociceptive dorsal root ganglia neurons"

O9 Nagesh C. Shanbhag (Lund, Sweden): "Curious case of impaired glymphatic pathways in a gyrencephalic brain"

O10 Anna Terem (Jerusalem, Israel): "The role of the claustrum in opiate versus psychostimulant preference - the differences do matter!"

19:30–20:30
PLENARY LECTURE #3
Jean-Antoine Girault (FENS President, Institut du Fer à Moulin, Sorbonne University, Paris): "Signaling and gene regulation in striatal projection neurons: function and dysfunction in neurological and psychiatric disorders"
Chair: Liana Fattore

20:30
Welcome Drink

Tuesday, May 31st 2022

10.00–18.00
Registration

08.30–09.20
PLENARY LECTURE #4
George Paxinos (School of Medical Sciences, UNSW Sydney, Australia): "Is the Brain the Right Size?" Chair: Christina Dalla

09.30–11.10
Symposia 22–27

S22
"New insights on endocannabinoid regulation of fear memory dynamics: from bench to bedside"
Chair: Maria Morena

Maria Morena (Calgary, Canada): "Endocannabinoid system and regulation of stress-effects on fear memory processes"

Andrew Holmes (Rockville, MD, USA): "Endocannabinoid circuit modulation of aversive memory"

Rebecca Shansky (Boston, MA, USA): "TRPV1 signaling as a mediator of sex-dependent fear generalization"

Leah Mayo (Linköping, Sweden): "The endocannabinoid system as a target for stress-related psychiatric disorders: evidence from healthy and clinical human populations"

S23
"Sex differences in motivated behaviors and their regulation by stress"
Chair: Debra Bangasser

Jill Becker (Michigan, USA): "Sex differences in the role of GPER-1 in motivated behaviors"

Jill Turner (Kentucky, USA): "Microglial contributions to nicotine dependence"

Deena M. Walker (Oregon, USA): "Adolescent social stress reprograms sex-specific cocaine induced behavior and transcription in the adult medial amygdala"

Debra Bangasser (Temple University, USA): "Effects of early life adversity on steroid hormones and motivated behaviors"

S24
"Vulnerabilities for psychopathologies and neurodegeneration: sensitive ages, mechanisms and targets"
Chairs: Aniko Korosi, Annamaria Cattaneo

Sandrine Thuret (London, UK): "Adult Hippocampal Neurogenesis in Major Depressive Disorder and Alzheimer's Disease: A potential converging mechanism"

Aniko Korosi (Amsterdam, The Netherlands): "Effects of early-life stress on memory and mood, a role for inflammation and nutrition"

Annamaria Cattaneo (Milan, Italy): "Inflammatory markers as early biological alterations of vulnerability associated with early life stress exposures"

Sarah Nicolas (Cork, Ireland): "Inflammatory stressors, memory and mood across the lifespan: hippocampal neurogenesis and microbiota-gut-brain axis as key mediators"

S25
"The contribution of V-ATPase to neurosecretion"
Chair: Nicolas Vitale

Nicolas Vitale (Strasbourg, France): "V-ATPase regulates the synthesis of fusogenic lipids at the exocytotic sites"

Julia Preobraschenski (Goettingen, Germany): "The role of the V-ATPase in synaptic vesicle filling with neurotransmitter"

Jurgen Klingauf (Muenster, Germany): "Assembly/disassembly of presynaptic V-ATPase regulates neurotransmitter release"

Oussama El-Far (Marseille, France): "The V-ATPase V0c /V0d interplay modulates V0c interaction with the SNARE complex and exocytosis"

S26
"Translational medicine for neurodegenerative pathologies: endogenous and natural molecules from human brain through Drosophila to cerebral organoids"
Chair: Andrea Diana

Maja Jazvinscak Jembrek (Zagreb, Croatia): "Neuroprotective potential of flavonols against oxidative stress-mediated injury"

Andrea Diana (Cagliari, Italy): "Effects of phytotherapic and human derived extracts on functional and morphological parameters in Drosophila mutants as Parkinson's disease models"

Goran Šimić (Zagreb, Croatia): "Therapeutic strategies for attenuation of imminent inflammation in Alzheimer's disease"

S27
"Neuropeptide modulation of pain transmission"
Chair: Marc Landry

Mai Iwasaki, Arthur Lefevre, Valery Grinevich, Alexandre Charlet (Institute of Cellular and Integrative Neurosciences, Strasbourg, France): "Deciphering the cellular basis of oxytocinergic control of pain associated disorders"

A. Gargouri, I. Kacem, R. Gouider (Razi University Hospital Tunisia): "Migraine: Calcitonin gene-related peptide implications and novel medications"

Marc Landry (University of Bordeaux, Institute of Neurodegenerative Diseases, Bordeaux, France): "Analgesic properties of the relaxin peptide family"

11:10–11:40
Coffee break and Poster Presentation

11:40–13:40
Symposia 28–32

S28
"Tuning the brain: neuromodulation for neurological and psychiatric diseases"
Chair: Salvatore Galati

Alain Kaelin-Lang (Lugano, Switzerland): "DBS for dystonia and related movement disorders: efficacy and mechanisms of action"

Veronica Ghiglieri (Rome, Italy): "Recovery of corticostriatal synaptic plasticity by transcranial magnetic stimulation in experimental parkinsonisms"

Salvatore Galati (Lugano, Switzerland): "Sleeping brain rhythms tune dyskinesias"

Alessandro Stefani (Rome, Italy): "Deep Brain Stimulation in Parkinson's disease patients and experimental disease models: scenes from a marriage?"

Graziella Madeo (Padua, Italy): "Brain stimulation for treating addictions: clinical outcomes and follow-up"

S29
"Dopamine Related Disorders: new insight and therapeutic prospectives"
Chair: Damiana Leo

Damiana Leo (University of Mons, Belgium): "DBS for dystonia and related movement disorders: efficacy and mechanisms of action"

Stefano Espinoza (Istituto Italiano di Tecnologia, IIT, Genoa, Italy): "Dopamine Transporter Knock-out Rats an innovative animal model for dopamine related diseas"

Massimiliano Caiazzo (Utrecht University, Netherlands/University of Naples "Federico II", Italy): "Neuronal hemoglobin induces loss of dopaminergic neurons in mouse *substantia nigra*, cognitive deficits and cleavage of endogenous α-synuclein"

Lucia Caffino (Department of Pharmacological and Biomolecular Sciences, University of Milan): "Deletion of dopamine transporter alters glutamate homeostasis in rat striatum"

Federica Bono (Università degli Studi di Brescia, Brescia Italy): "The role of dopamine receptors and their alterations in neurodegeneration"

S30
"Tryptophan, Serotonin, and Kynurenine Metabolites: Neurodevelopmental Building Blocks with Long-Lasting Impacts"
Chair: Ana Pocivavsek

Jodi Pawluski (Rennes, France): "Perinatal Serotonin and Maternal Mental Illness: Selective Serotonin Reuptake Inhibitors in Offspring - Neurobehavioral Outcomes"

Ana Pocivavsek (Columbia, USA): "Modeling Kynurenic Acid Elevation in Rodents during Development: Implications for Cognition and Psychiatric Illness"

Sarah Beggiato (Chieti/Italy and Ferrara/Italy): "Long-lasting kynurenine pathway alterations triggered by the exposure to THC in critical phases of brain maturation"

Stefano Comai (Milano, Italy): "Emotional Changes During Pregnancy and Postpartum: Role of the Tryptophan to Kynurenine Degradation, Inflammation and Stress"

Sophie Erhardt (Stockholm, Sweden): "Neuroinflammation and Tryptophan Degradation - Associations between Kynurenine Metabolites and Psychiatric Symptoms"

S31
"Exploring new therapeutic targets to treat

neurodevelopmental diseases: from synapse to behavior"
Chair: Antonia Manduca

Barbara Bardoni (Valbonne, France): "Modulation of cAMP and cGMP in therapeutic approaches for ASD"

Erica Zamberletti (Varese, Italy): "Targeting matrix metalloproteinase and inflammatory dysfunctions in autism spectrum disorder"

Maria Bove (Foggia, Italy): "N-acetylcysteine decreases stereotyped repertoire, anxiety-like behavior and neuroinflammation in a mouse model of ASD-like dysfunctions"

Annamaria Tartaglione (Rome, Italy): "Investigating the contribution of microbiota to ASD-like phenotype in the maternal immune activation mouse model: insights for novel therapeutic approaches"

S32
"Plant-derived versus endogenous cannabinoids in the burning brain: the root of all evil, or a panacea?"
Chairs: Katarzyna Starowicz, Giuseppe Di Giovanni

Luongo Livio (University of Campania "L. Vanvitelli", Naples, Italy): "endocannabinoids and microglia changes in a model of stroke-induced neuropathic pain: possible intervention with a palmitoylethanolamide/luteolin combination"

Tatina Pinto Morais, Vincenzo Crunelli, Giuseppe Di Giovanni (Cardiff University, Cardiff, UK): "Role of Cannabinoids in Absence Epilepsy"

Mauro Maccarrone, Lucia Scipioni, Marina Fava, Niccolò Pellegrini, Francesca Ciaramellano, Sergio Oddi and Alessandro Leuti (University of L'Aquila, L'Aquila, Italy): "The intersection between endocannabinoid signaling and resolution of inflammation in Alzheimer's disease"

Katarzyna Starowicz (Krakow, Poland): "Network analysis to disentangle cannabidiol pharmacology in complex diseases: focus on neuropathic component of osteoarthritis"

13:40–14:40
LUNCH

14:40–16:20
Symposia 33–38

S33
"Exploration into Future Targets for Addictions Pharmacotherapy"
Chair: Umberto Spampinato

Silvana Gaetani (Rome, Italy): "Effects of acylethanolamides on 'food addiction': from the modulation of compulsive eating to the mitigation of withdrawal symptoms"

John Neumaier (Seattle, WA, USA): "RiboTag-Seq Reveals a Compensatory cAMP Responsive Gene Network in Striatal Microglia induced by Morphine Withdrawal"

Umberto Spampinato (Bordeaux, France): "Central serotonin2B receptor blockade inhibits cocaine-induced hyperlocomotion: role of medial prefrontal cortex dopamine release"

S34
"The mesopontine tegmentum: a key crossroad for the modulation of physio-pathological behaviors"
Chair: Jacques Barik

Juan Mena Segovia (Rutgers University Newark, USA): "Neuronal substrates of behavioral inhibition in the PPN"

Kristi Kohlmeier (University of Copenhagen, Danemark): "Prenatal nicotine exposure is associated with cellular and synaptic changes in the laterodorsal tegmental nucleus which are likely to play a role in the high risk of motivation and attention disorders when exposed to nicotine during gestation"

Jacques Barik (Côte d'Azur University, France): "Role of the laterodorsal tegmental nucleus in defensive behaviors"

Ana João Rodrigues (University of Minho, Portugal) "Role of laterodorsal tegmentum to nucleus accumbens inputs in reinforcement"

S35
"Current Progress of Research on Neurodegenerative Diseases"
Chairs: Ahmad R. Bassiouny, James O. Olopade

James O. Olopade (University of Ibadan, Nigeria): "Let the brain get the best from the plant: An approach to neurophytotheraphy in relatively low resource settings"

Nermeen Zakaria Abuelezz (Misr University for Science and Technology, Egypt): "MicroRNAs as epigenetic orchestrator of inflammation in Alzheimer's disease: Reflections from an Egyptian population study"

Ahmad R. Bassiouny (Alexandria University, Egypt): "Parkinson Disease, the challenge of early diagnosis and prevention"

Amira Zaky (Alexandria University, Egypt): "Nano-curcumin Halts Pain-associated Neuroinflammation"

S36
"The Stressed brain: from humans to translational models of neuropsychiatric diseases"
Chairs: Nuno Sousa, Ioannis Sotiropoulos

Mohammed R. Milad (NYU School of Medicine, USA): "Impact of estradiol variance on the neural circuit of fear extinction: implications to psychopathology"

Katerina Antoniou (University of Ioannina, Ioannina, Greece): "An evaluation of cannabinoids' detrimental and therapeutic effects in experimental psychosis"

Ioannis Sotiropoulos (University of Minho, Portugal): "Chronic Stress & Exosomes: key players in progression and diagnosis of Alzheimer's disease"

Luisa Alexandra Meireles Pinto (University of Minho, Portugal): "Adult astrogliogenesis as a key mechanism underlying the pathophysiology of stress-induced depression"

S37
"Defining the stress response of the brain, adrenal, and other organs at the molecular, cellular and tissue levels"
Chair: Youssef Anouar

Y. Anouar (INSERM U1239, University of Rouen, France): "SELENOT modulates oxidative/ER stress responses in chromaffin cells in adrenal medulla and dopaminergic neurons in CNS"

L. Eiden (NIMH-IRP, Bethesda, USA): "PACAP, an emergency response neuropeptide acting at multiple levels to regulate stress"

A. Zaky (Alexandria University, Egypt): "Protective effect of blocking Redox factor-1 activity during pain signaling"

Nathalie C. Guérineau (University of Montpellier, France): "Stress-induced functional adaptive changes in the adrenal medullary tissue"

S38
"Role of gut-brain axis on the etiopathogenesis of mood disorders"
Chairs: Luigia Trabace, Giuseppina Mattace Raso

Lorena Coretti (University of Malta, Msida, Malta): "Gut microbiota alteration linked to anxiety-like behavior in a mouse model harboring a gain-of-function mutation associated with autism"

Adriano Lama (University of Naples, Italy) "Gut-brain axis: palmitoylethanolamide, a PPAR-α agonist, counteracts obesity-induced mood disorders"

Maria Grazia Morgese (University of Foggia, Foggia, Italy): "Dysfunction of the immune system in the pathogenesis of depression: role of n-3 PUFA deficiency"

Brian Harvey (North-West University Potchefstroom, South Africa): "Natural compulsive-like behavior in an animal model of OCD is associated with altered gut microbiota composition: Implications for comorbid anxiety and mood disorders"

16:20–17:20
Coffee break and Poster Presentation

17:20–18:35
Oral Communications (O10–O26)

O11-O13

O11 Arianna Mazzoli (Naples, Italy): "Fructose Removal from the Diet Reverses Inflammation, Mitochondrial Dysfunction, and oxidative Stress in Hippocampus"

O12 Klaus G. Petry (Bordeaux, France): " selection, NGS and bioinformatics of phage displayed peptide repertoires to define experimentally functional protein domains in inflammatory neurodegeneration"

O13 Ana Knezović (Zagreb, Croatia): "From determining brain insulin resistance in a sporadic Alzheimer's disease model to exploring the region-dependent effect of intranasal insulin"

O14-O16

O14 Asaid Khateb (Haifa, Israel): "Concept preactivation improves visual word processing in spoken and literary Arabic: A behavioral and event-related potential study using a picture-word matching task"

O15 Jorge F. Mejias (Amsterdam, the Netherlands): "Fluid functional hierarchies for multisensory integration in a large-scale computational model of the mouse brain"

O16 Silvia Mandillo (Rome, Italy): "Improving biomedical research by automated behavior monitoring in the animal home-cage — COST Action TEATIME CA20135"

O17-O19

O17 Željka Korade (Omaha, Nebraska, USA): "Disruption of brain sterol biosynthesis by commonly used prescription medications"

O18 Károly Mirnics (Omaha, Nebraska, USA): "Interaction of genetics, pregnancy, and medications on the developing brain"

O19 Liubov S. Kalinichenko (Erlangen, Germany): "Neutral sphingomyelinase determines the comorbidity trias of alcohol abuse, major depression and bone defects"

O20-O22

O20 Ozge Selin Cevik (Mersin, Turkey): "What doesn't kill you makes you stronger: increased memory function in maternally separated rats without effects of environmental enrichment"

O21 Ozge Selin Cevik (Mersin, Turkey): "Environmental enrichment as a strategy to encounter social isolation stress: attenuates memory impairment in stressed male rats"

O22 Stefania Schiavone (Foggia, Italy): "Social isolation induces anxiety-like behaviors in adult rats: relation to neuroendocrine and neurochemical dysfunctions"

O23-O24

O23 Sandra Jurado (Alicante, Spain): "Oxytocinergic modulation of synaptic function: Implications for neurodevelopment and aging"

O24 Blin Nicolas (Bordeaux, France): "Title: Successful cognitive aging relies on healthy adult born dentate neurons"

O25-O26

O25 Ali Jahanshahi (Maastricht, the Netherlands): "High frequency stimulation of the subthalamic nucleus: linking mood and motor effects at the level of the basal ganglia and 5-HT system"

O26 Rohan de Silva (London, UK): "MIR-NAT: A paired antisense long non-coding RNA gene regulates tau translation "

18:40–19:30
PLENARY LECTURE #5
Fiorenzo Conti (SIF President - Università Politecnica delle Marche, Ancona): "Glutamate transporter GLT-1: a novel localization for a novel function"
Chair: Giuseppe Di Giovanni

19:30–19:50
Poster prizes/Travel Grants/Honorary Memberships Awards
Chairs: Goran Šimić, Giuseppe Di Giovanni, Liana Fattore, Christina Dalla

19:50–20:40
MNS General Assembly
Chairs: Goran Šimić, Giuseppe Di Giovanni, Ali Jahanshahi, Liana Fattore, Christina Dalla

Wednesday, June 1st 2022

08.30–09.20
PLENARY LECTURE #6
Ivana Delalle (Brown University, Boston University, and German Center for Neurodegenerative Diseases): "MicroRNAs as Diagnostic and Prognostic Biomarker of Alzheimer's Disease"
Chair: Goran Šimić

09.30–11.10
Symposia 39–43

S39
"Deciphering the intricate glial response in aging and neurodegenerative disorders: from cellular changes to therapeutics"
Chairs: Caterina Scuderi, Erika Gyengesi

Caterina Scuderi (SAPIENZA University of Rome, Rome, Italy): "What differentiates an aged astrocyte from an Alzheimer's one? Looking for cellular differences for the development of new therapies"

Laura Ferraiuolo (Sheffield Institute of Translational Neuroscience, University of Sheffield, Sheffield, England): "Directly converted astrocytes retain the ageing features of the donor fibroblasts and elucidate the astrocytic contribution to human CNS health and disease"

Mariagrazia Grilli (University of Piemonte Orientale, Novara, Italy): "Glia and Neural Cell Stem cross-talk in aging and neurodegeneration"

Erika Gyengesi: "The contribution of glial reactivity in aging and neurodegenerative disorders: from cellular modifications to possible therapeutic approaches"

S40
"There's a time to make a change: how early exposure to drugs of abuse or to environmental challenges may affect the mesocorticolimbic pathway"
Chair: Carla Cannizzaro

Alba García-Baos (University Pompeu Fabra, Barcelona, Spain): "Cannabinoids modulate cognitive deficits induced by prenatal alcohol exposure in mice"

Steven Laviolette (The University of Western Ontario, London, Ontario, Canada): "Pre-natal Cannabinoid Exposure Leads to Long-Term Abnormalities in Brain Omega-3 Fatty Acid Levels and Sex-Dependent Schizophrenia-like Dysregulation of the Mesocorticolimbic Circuitry"

Mercè Correa (Universitat Jaume I, Castelló de la Plana, Spain): "Mild maternal separation in mice of both sexes affects the dopaminergic system and has an impact in adulthood on vigor to approach or to escape motivational stimuli"

Anna Brancato (University of Palermo, Italy): "Beyond the booze fun: binge alcohol drinking during adolescence alters dopamine and glutamate homeostasis in the nucleus accumbens and jeopardizes social resilience in rats"

S41
"Brain circuits and astroglia: unveiling causative interactions"
Chair: Dmitri Rusakov

Nathalie Rouach (College de France, Paris, France): "Astrocytes close the critical period plasticity in the visual system"

Gertrudis Perea (Cajal Institute, Madrid, Spain): "Accurate interplay between GABAergic signaling and astrocytes in prefrontal cortex improves decision-making"

Janosch Heller (Royal College of Surgeons in Ireland, Dublin, Ireland): "MicroRNA control of astrocytes in epilepsy"

Dmitri Rusakov (University College London, UK): "Long-term potentiation and inter-synaptic cross-talk"

S42
"Novel Psychoactive Substances (NPS): new exciting findings"
Chairs: Aviv Weinstein, Sabrine Bilel

Sabrine Bilel (Ferrara, Italy): "Pharmacotoxicological effects of fentanyls in the mouse: *in vitro* and *in vivo* pharmacokinetic and pharmacodynamic studies"

Aviv Weinstein (Ariel University, Israel): "The effects of synthetic cannabinoids on executive function and the brain"

Charalampos Brakatselos (Ioannina, Greece): "Repeated ketamine induces a regionally specific plasticity dysregulation and behavioral alterations related to schizophrenia. The impact of Cannabidiol administration"

S43
"Sex & Genes & Stress: Probing these factors in rodents models for a better understanding of psychiatric disorders"
Chairs: Anna Y. Yotova, David A. Slattery

Pavlina Pavlidi, Nikolaos Kokras, Christina Dalla (National and Kapodistrian University of Athens, Greece): "Sex differences in depression and anxiety: focus on neuroestrogen's receptor GPER1"

Anna Y. Yotova (University Hospital Frankfurt / Institute of Cell Biology and Neuroscience, Faculty of Biological Sciences, Goethe University Frankfurt, Germany): "Sex & Genes & Inflammation: Effects of prenatal immune challenge on phenotype and synaptic protein composition before birth and in adulthood"

David A. Slattery (University Hospital Frankfurt, Germany): "Insulin signalling — A Trojan Horse of mental disorders"

11:10–11:30
Coffee break

11:30–13:30
Symposia 44–49

S44
"Social behavior and social brain: from physiology to pathology"
Chairs: Laetitia Davidovic, Julie Le Merrer

Fabrice de Chaumont (Paris, France): "Complexity and dynamics of social behaviors in rodents"

Francesco Papaleo (Genova, Italy): "Circuits of Emotion Discrimination"

Alessandro Gozzi (Rovereto, Italy): "Oxytocin and the rodent social brain: a network-level perspective"

Julie Le Merrer (Tours, France): "Social behavior and striatum: reward matters"

Laetitia Davidovic (Valbonne, France): "Microbial metabolites, gut microbiota and social behavior"

S45
"Novel insights into physiology and pathology of autophagy in neuronal maintenance"
Chairs: Graziella Cappelletti, Antonella Scorziello

Diego Medina (Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy): "Lysosomal Signaling: The role of lysosomal calcium"

Nektarios Tavernarakis (Med. School Univ. of Crete and Foundation for Research and Tech., Heraklion, Crete, Greece): "Mechanisms of mitochondrial turnover in neuronal physiology and pathology during ageing"

Agnese Secondo (Federico II University of Naples, Italy): "Emerging role of lysosomal calcium store as the hub of autophagy and neuroprotection in ALS models"

Mattia Volta (Institute for Biomedicine, Eurac Research, Bolzano, Italy): "Lysosomal dysfunction in Parkinson's disease: the role of the small GTPase Rit2"

Maria Josè Sisalli (Federico II University of Naples, Italy): "Balancing mitophagy and mitochondrial biogenesis to maintain energy metabolism is required for the neuroprotection induced by ischemic brain preconditioning"

S46
"From pathophysiology to therapeutic strategies of Alzheimer's disease: novel insights from experimental models and patient studies"
Chair: Dubravka Svob Strac

Dubravka Svob Strac (Zagreb, Croatia): "Studying therapeutic potential of neurosteroids and neurotrophins in Alzheimer disease: an *in vitro* approach"

Dóra Zelena (Budapest, Hungary): "Phenotypic characterization of the triple transgenic animal model of Alzheimer's disorder, translational considerations"

Gordana Nedic Erjavec (Zagreb, Croatia): "Genetic biomarkers of Alzheimer's disease"

Alja Videtic Paska (Ljubljana, Slovenia): "DNA methylation of candidate genes in Alzheimer's disease"

Matea Nikolac Perkovic (Zagreb, Croatia): "Metabolic profiling of Alzheimer's disease: potential in biomarker discovery and early detection of Alzheimer's dementia"

S47
"Synaptic plasticity in epilepsy: from synapses to circuits"
Chairs: Giuseppe Di Giovanni, Sandra H. Vaz

Ana Maria Sebastião (University of Lisbon, Portugal): Synaptic plasticity in epilepsy: the Janus face of adenosine

Gian Michele Ratto (NEST, Istituto Nanoscienze CNR and Scuola Normale Superiore, Pisa, Italy): "Modeling of focal cortical dysplasia: where the normal brain meets a mutation"

Graham Collingridge (University of Bristol): "Glutamate receptors and synaptic plasticity in health and disease"

Eleonora Palma (Università di Roma Sapienza): "Dissecting the basic epileptogenic mechanisms in neurodevelopmental disorders"

Antonella Casamassa (School of Medicine, University of Naples "Federico II", Naples, Italy): "In brain post-ischemic plasticity, Na^+/Ca^{2+} EXCHANGER 1 and Ascl1 interact in microglia-dependent astrocyte differentiation"

S48
"Sex differences, immune and steroid effects in the brain: implications for neuropsychiatric disorders and their treatment"
Chair: Christina Dalla

Georgia E. Hodes (Virginia, USA): "Of Mice and Wo/Men: Translating sex differences in cytokine responses between treatment resistant depression and animal models"

Nikolaos Kokras (Athens, Greece): "Sex differences in antidepressant response: The role of the HPA axis"

Jordan Marrocco (New York, USA): "Epigenetic targets of oral corticosterone in the dorsal and ventral hippocampus"

Harris Alexopoulos (Athens, Greece): "Stiff Person Syndrome: Pathophysiology and sex differences"

S49
"Neuropathologies, Neuroprotection and Innovative Therapies"
Chairs: Olfa Masmoudi-Kouki, Taoufik Ghrairi

Imen Kacem and Riadh Guider University of Tunis El Manar, Tunisia): "Amyotrophic Lateral Sclerosis a model of neurodegenerative disease"

Taoufik Ghrairi (University of Tunis El Manar, Tunisia): "In vitro evaluation of the effect of cumin and thym essential oils on H2O2- induced cytotoxicity"

Olfa Masmoudi (University of Tunis El Manar, Tunisia): "Cytoprotective and neurotrophic effects of OctaDecaNeuropeptide (ODN) in *in vitro* and *in vivo* models of neurodegenerative diseases"

Lucio Annunziato (University of Naples, Italy): "The epigenetic and transcriptional factors HDAC4, HDAC5, dream and GATA3/KM5T2A complex regulate NCX3 expression contributing to ischemic neuroprotection"

13:30–14:30
LUNCH

14:30–15:30
Workshop on Publishing
"How To Get a Paper Published, Read & Cited" Elsevier
Giuseppe Di Giovanni
Philippe De Deurwaerdere

15:30–17:10
Symposia 50–54

S50
"Neuropeptidergic impact in cognition and metabolism"
Chairs: Francisco E. Olucha-Bordonau, Ángel Núñez-Molina

Ángel Núñez-Molina (Universidad Autónoma de Madrid, Spain): "Modulation of cortical activity by IGF-I through cholinergic basal forebrain neurons"

Francisco E. Olucha Bordonau (Universitat Jaume I, Castellón, Spain): "The relaxin 3-nucleus incertus projections to the medial septum in triggering hippocampal activity"

Miguel Garzón (Universidad Autónoma de Madrid, Spain): "Hypocretin targeting of pontine neural networks governing REM sleep"

Georgina Cano (University of Pittsburgh, USA): "Role of Urocortin-1 from Edinger-Westphal nucleus in thermoregulation and adipose tissue metabolism"

S51
"Risk and protective factors in drug use and vulnerability to addiction"
Chairs: Liana Fattore, Maria Antonietta de Luca

Maria Antonietta De Luca (University of Cagliari, Italy): "Age- and sex-related vulnerability in the use of novel psychoactive substances: preclinical data on cannabinoids, phenethylamines, and cathinones"

John D. Salamone (University of Connecticut, Storrs, USA): "Effort-related effects of atypical dopamine transport inhibitors"

Jaanus Harro (University of Tartu, Estonia): "Sensitivity in rats and humans to psychostimulants: Relationship with reward sensitivity vs positive affect"

Liana Fattore (CNR Institute of Neuroscience, Italy): "Impact of repeated exposure to hormonal contraceptives during adolescence on cannabinoid-induced behavior in female rats"

S52
"Exposure to chronodisruptive environment impacts neuroendocrine functions"
Chair: Patrick Vuillez

Virginie Laurent-Gydé (University of Strasbourg, Strasbourg, France): "Inappropriate exposure to blue enriched light affects behavior in mice. How is it relevant to humans?"

Valérie Simonneaux (INCI, Strasbourg, France): "A chronodisruptive ligh/dark cycle markedly impairs the central regulation of female fertility"

Andries Kalsbeek (Netherlands Institute for Neuroscience, Amsterdam, Netherlands): "Can well-timed exercise repair the chronodisruptive effects of mis-timed feeding?"

Henrik Oster (Institut of Neurobioloy, Lübeck, Germany): "Circadian appetite regulation — a tale of two clocks"

S53
"Rapid Acting Antidepressants — Not only NMDAR antagonism"
Chairs: Robert Zorec, Natalie Rasgon

Maurizio Popoli (Milano, Italy): "New mechanisms of ketamine action in acute and chronic stress models of psychopathology"

Robert Zorec (Ljubljana, Slovenia): "Astrocyte Specific Remodeling of Plasmalemmal Cholesterol Composition by Ketamine: a New Mechanism of Antidepressant Action"

Mark Rasenick (Chicago, USA): "A cellular approach to the mechanism of rapid-acting antidepressants: NMDAR independence and cAMP dependence"

Natalie Rasgon (California, USA): "Cellular and metabolic predictors of antidepressant response in major depression"

S54
"Proteostasis at the Cellular and Organismal Levels"
Chair: Ehud Cohen

Serena Carra: "Protein quality control of biomolecular condensates: implications for Amyotrophic Lateral Sclerosis and Frontotemporal degeneration"

Ritwick Sawarkar: "Mechanisms of transcriptional response to protein misfolding"

Anat Ben-Zvi: "Gonadotropin-releasing hormone receptor related 2 (gnrr-2) regulates somatic proteostasis in Caenorhabditis elegans"

Ehud Cohen: "Deciphering the proteostasis response to dissimilar proteotoxic challenges"

17:10–17:30
Coffee break

17:30–19:10
Symposia 55–58

S55
"Postdoctoral research symposium on stress"
Chairs: Patrizia Campolongo, Giulia Federica Mancini

Patrizia Campolongo (Sapienza University of Rome, Rome, Italy): "Bridging the preclinical-clinical boundary in stress research"

Eva Viho (Leiden University Medical Center, Leiden, Netherlands): "Stress hormones in Angelman syndrome: insights from single-cell transcriptomics and protein interaction in mouse hippocampus"

Giulia Federica Mancini (Santa Lucia Foundation, Rome, Italy): "Long-term effects of early-life adverse events: the role of sex differences"

Sebastiano Alfio Torrisi: "The arousal-based individual screening model: a step toward a better understanding of sex differences in PTSD susceptibility and resilience"

S56
"Understanding Brain Cholesterol homeostasis: from Basic Mechanisms to the Effects of Environmental and Nutritional factors"
Chairs: Luisa Cigliano, Valentina Pallottini

Frank W. Pfrieger ((INCI) CNRS, France): "Cholesterol metabolism and neurodegeneration: Niemann-Pick type C as case in point"

Aleksandra Mladenovic (University of Belgrade, Belgrade): "Brain cholesterol and dietary interventions — friends or enemies"

Marco Segatto (University of Molise, Italy): "Modulation of cholesterol biosynthetic pathway in the brain: effects on behavior and potential interference by exogenous compounds"

Luisa Cigliano (University of Naples Federico II, Italy): "Unraveling the link between Brain Cholesterol Homeostasis and Beta Amyloid Metabolism – focus on the impact of a western diet"

S57
"The role of cyclic AMP signalling in astrocyte function"
Chairs: Anja Teschemacher, Nina Vardjan

Anemari Horvat (University of Ljubljana, Ljubljana, Slovenia): "Distinct dynamics of astroglial Ca^{2+} and cAMP signaling and regulation of aerobic glycolysis"

Sergey Kasparov, Alexander V. Gourine (University College London, London, UK) "cAMP-mediated signalling controls lactate release by astrocytes"

Hajime Hirase (University of Copenhagen, Copenhagen; Denmark): "Second messenger signaling expressed in cortical astrocytes during fear conditioning learning"

Ryuta Koyama (The University of Tokyo, Tokyo, Japan): "Optogenetic manipulation of astrocytic cAMP to modulate memory"

S58
"The circadian clock and the sensory, integratory and executive parts of the nervous system: a keys for health"
Chair: Paul Pevet

Ruud M. Buijs (Instituto Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico): "Suprachiasmatic Nucleus-Arcuate Nucleus Axis: Interaction Between Time and Metabolism"

Andries Kalsbeek (University of Amsterdam, Amsterdam, Netherlands): "Can voluntary exercise shift the muscle clock?"

Carolina Escobar (Faculty of Medicine, UNAM, Mexico): "Scheduled feeding prevents circadian disruption, loss of homeostasis and disease"

Hugh D. Piggins (Faculty of Life Sciences, University of Bristol, Bristol, UK): "Timed daily exercise remodels circadian rhythms"

20:00–22:00
Social Dinner

Thursday, June 2nd 2022

08.30–09.20
PLENARY LECTURE #7
Ira Milošević (Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK): "Improving neurotransmission in the failing brain" Chair: Patrizia Campolongo

09.30–11.10
Symposia 59–62

S59
"Astrocyte roles in brain function and dysfunction"
Chairs: Eleanora Aronica, Rhein Parri

Sandra Henriques Vaz (Lisbon, Portugal): "Astrocytic derived adenosine is implicated on BDNF effect upon hippocampal LTP"

Rhein Parri (Birmingham, UK): "The role of astrocytes in cortical plasticity"

Giorgio Carmignoto (Padova, Italy): "Astrocyte control of excitation to Ventral Tegmental Area dopaminergic neurons affects dopamine-dependent behaviors"

Eleanora Aronica (Netherlands): "The role of astrocyte-mediated inflammatory processes in epileptogenesis"

Antonella Casamassa (Naples, Italy): "In brain post-ischemic plasticity, Na^+/Ca^{2+} exchanger 1 and Ascl1 interact in microglia-dependent astrocyte differentiation"

S60
"Learning from lorcaserin lesson: is there still a future for 5-HT2C receptor development and therapeutic pharmacology?"
Chairs: G. Di Giovanni, P. De Deurwaerdère

Butler Jasmine: "The deletion of SNORD115 in mice merely alters 5-HT2C receptor functions but destabilizes monoaminergic neurons activity in a manner opposite to 5-HT2C agonists"

Philippe De Deurwaerdere (France): "Lorcaserin and other 5-HT2C agonism-based strategies: searching beyond the dopaminergic systems"

Tatiana Pinto Morais (Malta): "5-HT2CR positive allosteric modulator CYD-1-79 as antiabsence epilepsy treatment"

S61
"Sensorimotor Integration and Control at the Apic: Empirical and Modeling perspectives"
Chairs: Matteo Filippini, Ivilin Stoianov

Matteo Filippini (Bologna, Italy): "Decoding sensorimotor information from the posterior parietal cortex and neuroprosthetic applications"

Ivilin Stoianov (Padova, Italy): "Model-based Analysis of Sensorimotor Control in the PPC"

Pablo Lanillos (Nijmegen,the Netherlands): "Deep active inference for predictive sensorimotor control"

Frauke Heins (Münster, Germany): "Implicit and latent motor learning in the oculomotor system and its perceptual consequences"

Ben Hamed Suliann (Lyon, France): "Rhythmic attentional processes and functional hierarchy of vigilance and attention in the prefrontal cortex"

S62
"Protein aggregation spreading and functional alterations in neurodegeneration"
Chairs: Fran Borovečki, Tiago Outerio

Karen Duff (London, UK): "Mechanisms and functional consequences of the spread of tauopathy"

Fran Borovecki (Zagreb, Croatia): "Genomic mechanisms regulating protein clearance in neurodegenerative diseases"

Chiara Zurzolo (Paris, France): "Role of Tunelling Nanotubes in the spreading of neurodegenerative diseases, and more"

Tiago Outeiro (Goettingen, Germany): "Release and uptake of proteins associated with neurodegenerative diseases: similarities and differences"

11:30–11:50
Coffee break

11:50–12:20
Conclusion

POSTERS

Note to poster presenters: All presenters must be present on 31st May 2022 (Tuesday) from 16:20-17:20 for discussion.

P1
"Dopamine D2 Receptors regulate spines in Striatal indirect-pathway neuron"

Alberquilla S., Merino-Serrais P., Camacho L., Martín E.D., DeFelipe J., Moratalla R.

P2
"Polymorphisms within serotonin receptor genes are associated with genetic, cerebrospinal fluid and neuropsychological biomarkers of Alzheimer's disease"

Mirjana Babić Leko, Matea Nikolac Perković, Ena Španić, Dubravka Švob Štrac, Nikolina Pleić, Željka Vogrinc, Ivana Gunjača, Nataša Klepac, Fran Borovečki, Nela Pivac, Tatijana Zemunik, Patrick R. Hof, Goran Šimić

P3
"The association of TSH and thyroid hormones with APOE genotype"

Mirjana Babić Leko, Nikolina Pleić, Ivana Gunjača, Vesela Torlak, Ante Punda, Goran Šimić, Ozern Polašek, Tatijana Zemunik

P4
"Three different methods confirmed the association of macro and microelements with cerebrospinal fluid biomarkers of Alzheimer's disease"

Matej Mihelčić, Mirjana Babić Leko, Jasna Jurasović, Matea Nikolac Perković, Ena Španić, Ankica Sekovanić, Tatjana Orct, Klara Zubčić, Lea Langer Horvat, Nikolina Pleić, Spomenka Kiđemet-Piskač, Željka Vogrinc, Nela Pivac, Fran Borovečki, Patrick R. Hof, Goran Šimić

P5
"Gastrointestinal redox homeostasis and cognitive performance in the mature adult and middle-aged Tg2576"

Ana Babić Perhoč, Jan Homolak, Ana Knezović, Jelena Osmanović Barilar, Melita Šalković-Petrišić

P6
"Plastic adaptive changes induced by chronic M-channel activation in hippocampal neurons"

Lior Bar, Lia Shalom, Asher Peretz, Shira Burg, Bernard Attali

P7

"Glymphatic function in Parkinson's disease"

Roberta Battistella, Arpine Sokratian, Chenchen Liu, M. Angela Cenci, Andrew West, Iben Lundgaard

P8

"Effects of the 5-HT2A receptor agonist TCB-2 on the neurochemistry of monoamines and amino acid neurotransmitters in the mouse striatum"

Jasmine Butler, De Deurwaerdère Philippe

P9

"The deletion of SNORD115, a potential regulator of 5-HT2C receptor expression, promotes cortico-subcortical imbalance of monoaminergic transmission in mice"

Jasmine Butler, Marty Virginie, Coutens Basile, Oumaima Chargui, Abdeslam Chagraoui, De Deurwaerdère Philippe, Guiard P. Bruno, Cavaillé Jérôme

P10

"Evaluation of procognitive activity of 5-HT1A biased ligand and muscarinic ligands in an animal model of schizophrenia"

Paulina Cieslik, Joanna M. Wieronska

P11

"Identification of a neuronal population in the hypothalamus, expressing 26RFa and orexins, involved in the regulation of glucose homeostasis"

Mélodie Devère, Yamina Cherifi, Saloua Takhlidjt, Arnaud Arabo, Julie Maucotel, Alexandre Bénani, Emmanuelle Nedelec, Benjamin Lefranc, Jérôme Leprince, Gaëtan Prevost, Nicolas Chartrel, Marie Picot

P12

"Xenapses grown on micropatterned thin films for tailored cryo-FIB milling and cryo-electron tomography of synaptic exocytic and endocytic structures"

Junxiu Duan, Ulrike Keller, Sai Krishnan, Yaroslav Tsytsyura, Nataliya Glyvuk, Jürgen Klingauf

P13

"The impact of APE-1 redox inhibition on regulation of the dopaminergic neurons' pathway during inflammatory pain condition"

Eman Khaled, Mayssaa M. Wahby, Ahmad Bassiouny, Marc Landry, Amira Zaky

P14

"Deranged central oxytocinergic signaling in pre-clinical models of obesity and hedonic feeding"

Barbara Eramo, Marzia Friuli, Maria Vittoria Micioni Di Bonaventura, Emanuela Micioni Di Bonaventura, Carlo Cifani, Silvana Gaetani, Adele Romano

P15

"Astrocytes exert negative modulation on hippocampal neuron excitability"

Sara Expósito, Samuel Alberquilla, Rosario Moratalla, Alfonso Araque, Eduardo Martín

P16

"Early life social experiences and dysregulation of the brain reward system: age- and sex-dependent interactions"

Jessica Bratzu, Maria Ciscato, Augusta Pisanu, Patrizia Porcu, Fabrizio Sanna, Liana Fattore

P17

"Morphological and functional characterization of human microglia in transient structures of the developing brain"

David Menassa, Janja Kopić, Alisa Junaković, Željka Krsnik, Ivica Kostović

P18

"Influence of acrylamide supplementation on the population of PACAP-like immunoreactive intramural neurons of the duodenum in the pig"

Aleksandra Karpiesiuk, Katarzyna Palus

P19

"Shutdown of NHE1 is the primary event at presynapses upon chemically induced ischemia to avoid neurotoxicity"

Tim Cebulla, Vera Kästingschäfer, Martin Kahms, Jürgen Klingauf

P20

"Lamotrigine rescues the attenuating effect of intracerebroventricular Aβ1-42 infusion on spontaneous theta rhythms in anesthetized rats"

Paulina Kazmierska-Grebowska, Renata Bocian, Jacek Grębowski, Maciej Studzian

P21

"DNase Treatment Prevents Cerebrospinal Fluid Block in Early Experimental Pneumococcal Meningitis"

Marios Kritsilis, Chiara Pavan, Anna L. R. Xavier, Marta Ramos, Jane Fisher, Adam Linder, Peter Bentzer, Maiken Nedergaard, Iben Lundgaard

P22

"Early compartmentalization and laminar rhythm of future projection neuron markers during the human early cortical plate stage"

Janja Kopić, Alisa Junaković, Mladen Roko Rašin, Ivica Kostović, Željka Krsnik

P23

"Suicidal behaviour and epigenetics: changes in expression of algorithm predicted miRNA"

Katarina Kouter, Urban Ališ, Tomaž Zupanc, Alja Videtič Paska

P24

"Modulation of oxytocin signalling by immunoglobulin G in stress-related disorders"

Henning Værøy, Emilie Lahaye, Christophe Dubessy, Magalie Benard, Marion Nicol, Saloua Takhlidjt, Serguei O. Fetissov

P25

"Executive functioning and Language in primary progressive aphasia"

Laurent Lefebvre, Sandrine Basaglia-Pappas, Isabelle Simoes Loureiro

P26

"Study of the Reelin effect in cellular models of Parkinson's disease"

Vania Macías-Calvio, Jean Gruenberg, Aurélien Roux, María Paz Marzolo

P27

"Modulation of Cricopharyngeal Quiescence During Swallowing in Healthy Normal Humans"

Timothy M. McCulloch, Michelle R. Ciucci

P28

"Differential interspecies posttranscriptional regulation of Nkx2-1 expression in the adult mammalian subthalamic nucleus"

Tila Medenica, Ema Bokulić, Goran Sedmak

P29

"Effects of cannabidiol on amphetamine and ketamine-induced behavioral profile"

Asprogerakas Michail-Zois, Brakatselos Charalampos, Ntoulas George, Tsarna Olga, Petros S. Tzimas, Eleftherios A. Petrakis, Maria Halabalaki, Leandros A. Skaltsounis, Polissidis Alexia, Antoniou Katerina

P30

"Western diet may trigger Alzheimer's disease by insulin signaling impairment"

Anna Mietelska-Porowska, Justyna Domańska, Andrew Want, Angelika Więckowska-Gacek, Dominik Chutorański, Maciej Koperski, Urszula Wojda

P31

"Mild Traumatic Brain Injury increases mitochondrial calcium levels and upregulates mitochondrial Na^+/Ca^{2+} Exchanger"

Rodrigo G. Mira, Waldo Cerpa

P32

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PLENARY LECTURES

THE IBRO PLENARY LECTURE

Extracellular Vesicles as Systemic Stress Signals Important to the Brain

KE Morrison, AF Stenson, R Marx-Rattner , S Carter, V Michopoulos, CF Gillespie, A Powers, W Huang, MA Kane, T Jovanovic, and TL Bale

Exposure to traumatic events and adversity during specific windows of development is a risk factor for negative physical and mental health outcomes, but the underlying mechanisms that perpetuate these lasting effects or our ability to identify at-risk populations are not known. Extracellular vesicles (EVs) are a novel signaling mechanism involved in numerous developmental and maturational processes. The EV protein and sncRNA cargo is significantly altered by stress and trauma experience and can impact the course and rate of fetal neurodevelopment and maturational life stages including adolescence. We investigated the impact and timing of trauma experienced during key developmental windows of childhood, adolescence, or adulthood on adult health outcomes and associated biomarkers, including EVs, in a cohort of adult women as part of the Grady Trauma Project. Our results found that significant changes in fear potentiated startle related to PTSD risk were uniquely observed when trauma had been experienced during adolescence. In an unbiased proteomics assessment, we identified a novel and robust EV signature comprised of a significant number of keratin-related proteins encoded in a 17q21 gene cluster and related to Merkel cells. To examine mechanisms relevant to these cells and timing of trauma exposure, we also developed a mouse model in which multimodal sensory stress experienced during puberty produced similar changes in EV proteins associated with the corresponding mouse keratin I gene cluster, 11qD, and increased adult fear-potentiated startle responses and freezing behaviors. Taken together, these results support EVs as novel biomarkers and potential stress signals relevant to neuropsychiatric disease risk. Specifically, tactile or sensory-based stress exposure during key developmental periods may increase sensitivity of novel aspects of stress circuitry.

Forebrain Cholinergic System: From Anatomy to Function and Dysfunction

Laszlo Zaborszky[1]

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Basal forebrain (BF) cholinergic neurons provide the cortex with acetylcholine. Despite the long-established involvement in sensory processing, attention, and memory, the mechanisms by which cholinergic signaling regulates cognitive processes remains elusive. Anatomical studies in the mid-1980s lumped together cholinergic neurons as part of the 'diffuse cortical projection systems'. Recent studies revealed that the cholinergic projection is not diffuse, but instead is organized into cortical target-specific groups of cholinergic neurons which receive specific combinations of inputs (Gielow and Zaborszky, 2017; Zaborszky and Gombkoto, 2018).
Our studies in rodents, using in silico anatomical reconstruction of the cholinergic forebrain (SFN Abstract, 2021) and large-scale recording in behaving animals link activity in anatomically defined circuits to specific cognitive operations (Gombkoto et al., 2021). Neuropathological studies suggest that the BF cholinergic system is affected in Alzheimer's disease (AD), although controversy as to how pathology in the BF relates to cognitive symptoms remains unresolved (Schmitz and Zaborszky, 2021). We developed a postmortem 3D map of the cholinergic space in humans (Zaborszky et al., 2008). In collaboration with Cantero's group (Cantero et al., 2010; 2017; 2019), it was found that patients with MCI exhibit volume reduction in the cholinergic space that is correlated with atrophy of its cortical targets as well as with tau and Aβ in CSF. Establishing functional subdivisions of the human cholinergic space and their relations to cortical networks using resting state analysis (Yuan et al., 2019) opened up investigations to monitor the progression of AD, PD and related neurodegenerative diseases (Oswal et al., 2020, *Brain*; Chu et al., 2022, *Neurology*).
Supported by NIH/NINDS grants 23945 and RF123945-28.

THE FENS PLENARY LECTURE

Signaling and Gene Regulation in Striatal Projection Neurons: Function and Dysfunction in Neurological and Psychiatric Disorders

Jean-Antoine Girault[1]

[1] *Institut du Fer à Moulin, UMR-S 1270 INSERM & Sorbonne University, Paris, France*

The basal ganglia circuits are crucial for many important and partly overlapping functions including movement, reward processing, procedural learning, and motivation. Their dysfunction results in multiple pathological conditions including but not limited to addiction, Parkinson's disease, L-DOPA-induced dyskinesia, Huntington's disease, and some forms of hereditary dystonia. The main

entry structure of the basal ganglia is the striatum comprising the caudate, putamen and nucleus accumbens, which receive convergent inputs from the cerebral cortex and thalamus. The very dense dopaminergic innervation regulates the striatal information processing and its plasticity. Understanding how dopamine controls signaling in striatal projection neurons (SPNs) is a major objective investigated by many laboratories including ours. SPNs are characterized by the expression of a set of signaling proteins that distinguishes them from other neuronal types. SPNs are divided into several populations, which display key differences depending on their anatomical connections and the dopamine receptors they express. We have investigated the dorso-ventral regional differences in translated genes between these populations, leading to the identification of novel striatal modulators such as transcription factors and prostaglandin E2. We have also examined the underlying epigenetic differences in DNA modification between SPN populations. Regulation of gene networks in SPNs provides information on long-lasting effects of operant learning and cocaine actions and provides clues on the mechanisms of procedural learning.

Is the Brain the Right Size?

George Paxinos[1]

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Our brain is the riverbed that holds and channels our stream of consciousness (Koch, 2012). It is moulded by family and culture. Experience sculpts our character from the genetic material we are granted as Phidias sculpted Apollo from a block of Parian marble. Alzheimer's disease will pay an unwelcome visit to many of us at end of life. It will disrupt the internal structure of our neurons and we will be living evidence the mind is the product of the brain and has no influence on it. Which one of us would not like to discard our depression, anxieties, obsessions, compulsions, our unrequited love? It seems the puppet is free only in as much as it loves its strings (Harris, 2012). Paxinos will speak on the neuroscience behind A River Divided, a novel in the environmental genre that broke a record in the time it took him to complete–21 years. He will speak of the neuroscience principles on the formation of heroes of the novel, giving a historical account of the origin of ideas of the mind, the soul, free will and consciousness.

Glutamate transporter GLT-1: a novel localization for a novel function

Fiorenzo Conti[1]

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Glutamate, the main excitatory neurotransmitter in the cerebral cortex, mediates classical point-to-point synaptic transmission but also spills out of the synaptic cleft of active excitatory synapses to enter that of neighboring synapses (spill in), thereby exerting modulating effects at farther sites. The distance between terminals, the morphology of the extracellular space, and the presence of interposed astrocytic processes (with the capacity to remove extracellular glutamate and act as barriers for diffusion) are some of the most important physical constraints determining the extent to which spillover can take place and lead to crosstalk among synapses.
At cortical excitatory synapses, glutamate spill out is closely regulated by high-affinity astrocytic plasma membrane transporter GLT-1, in line with its predominant perisynaptic localization (with peaks at 100-150 and 50-100 nm from the AZ edge). In an early confocal study, we showed that in cerebral cortex a fraction of synaptic GLT-1 is also localized at inhibitory GABAergic synapses, and here, using quantitative electron microscopy, we showed that the density of GLT-1-coding gold particles is highest in the extrasynaptic portion of perisynaptic astrocytic processes (PAPs), with a concentration peak at 510 nm. We therefore hypothesized that GLT-1 positive PAPs surrounding inhibitory synapses prevents glutamate escaped from adjacent excitatory synapses from binding to glutamate receptors located on GABAergic axon terminals (spill in). Here, using quantitative electron microscopy, we also showed that in cerebral cortex GLT-1 located extrasynaptically at inhibitory GABAergic synapses modulates interneuron-pyramidal cell transmission by activation of group III metabotropic glutamate receptors, thus regulating pyramidal neurons excitability.

MicroRNAs as Diagnostic and Prognostic Biomarker of Alzheimer's Disease

Ivana Delalle[1], Jan K. Blusztajn[1], Andre Fischer[1]

[1] *Brown University, Boston University, and German Center for Neurodegenerative Diseases*

Changes in cognitive function develop slowly over time so that Alzheimer Disease (AD) patients are diagnosed at an advanced stage of molecular pathology. The failure to diagnose AD at an early stage of molecular pathology is the major reason why causative treatments fail in clinical trials. Thus, there is an urgent need for biomarkers detecting individuals at risk for developing AD to allow for earlier interventions. Despite the development of blood biomarkers to detect AD-associated beta-amyloid or Tau pathology, the challenges remain because AD is characterized by dysregulated gene expression triggered by genetic and environmental risk factors. Genome-environment interactions are orchestrated by epigenetic processes that include

microRNAs which regulate gene-expression, proteostasis, and are linked to cognition. However, the interpretation of the current reports on the changes of microRNA expression in AD is hampered by small sample size and lack of mechanistic insights preventing the consideration of microRNAs as a biomarker detecting individuals at risk for developing AD. The combination of biospecimens from large, multinational cross-sectional and longitudinal studies is poised to overcome these limitations. We hypothesize that the circulating microRNAome includes biomarkers that can be used to diagnose AD, identify those individuals with mild cognitive impairment (MCI) who will develop AD, and inform about AD- associated pathological alterations in the brain. This hypothesis is supported by our recent discovery of a 3-microRNA signature, miR-181a-5p, miR-148-3p, and miR-146a-5p, in blood and cerebrospinal fluid able to identify MCI individuals and, when measured in blood, detect those at risk for converting to AD.

Improving Neurotransmission in the Failing Brain

Ira Milosevic[1]

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Exocytosis, a process of vital importance for (neuro)endocrine and neuronal cells, is controlled by a set of both positive and negative regulators. While promotors of exocytosis are well studied, negative regulators are poorly understood. In parallel with the characterisation of the proteinaceous machinery, the lipid requirements for the SNARE-mediated vesicle exocytosis arose. Lipids are the core components of the fusing membranes, thus changes in their composition, abundance or localization promptly modify the intrinsic fusogenic properties of membranes. Lipids also activate and recruit proteins to the local environments where exocytosis happens. We have previously reported a key lipid involved in spatial and temporal regulation of exocytosis – phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2). We have now discovered that PI(4,5)P2 engages a small SNARE protein amisyn (STXBP6) to negatively regulate exocytosis. Amisyn is a vertebrate-specific competitor of synaptobrevin-2/VAMP-2, an essential player in exocytosis (PMID: 32467162). This is a poorly studied protein despite several studies reported the occurrence of amisyn mutations in diabetes, autism spectrum disorders and cancer. We found that amisyn contains a pleckstrin homology domain that mediates its transient association with the plasma membrane by binding to phospholipid PI(4,5)P2. We further generated an amisyn mutant mouse line, which revealed amisyn's role in the regulation of synaptic vesicle pools and release probability at the presynaptic site. The detailed characterisation of amisyn's functions in exocytosis, neurotransmission and behaviour using cellular and knock-out mouse models will be discussed.

SYMPOSIA

S1 "Synaptic communication in health and disease: from single molecule to network"

Chair: Laurent Groc

S1.1
Physiological and pathological membrane crosstalk of NMDA and dopamine receptors

Laurent Groc[1]
[1] *Interdisciplinary Institute for Neuroscience, CNRS, University of Bordeaux, Bordeaux, France*

Understanding the cellular and molecular organization of the synaptic transmission have been, and is still, a key challenge in brain science. Indeed, synaptic transmission is at the basis of neuronal network functions and its plastic capacity sustains most our cognitive abilities. On the contrary, a deficit in synaptic transmission is believed to play central role in the etiology of neuropsychiatric disorders. Yet, recent advances in the field that has strongly revigorated our canonical view of synaptic transmission and its regulation. Here, I will describe how single molecule imaging have profoundly changed our understanding of synaptic transmission both in health and brain disease, focusing on the glutamatergic NMDA receptor and its environment during synaptic maturation and in models of psychosis.

S1.2
The glucocorticoid receptor–FKBP51 complex contributes to fear conditioning and posttraumatic stress disorder

Haiyin Li[1], Ping Su[1], Terence K.Y. Lai[1], Anlong Jiang[1], Jing Liu[1], Dongxu Zhai[1], Charlie T.G. Campbell[1], Frankie H.F. Lee[1], WeiDong Yong[2], Suvercha Pasricha[1,3], Shupeng Li[1,3], Albert H.C. Wong[1,3,4] Kerry J. Ressler[5], and Fang Liu[1,3,4,6]
[1] *Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada;* [2] *Comparative Medical Center, Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China;* [3] *Department of Psychiatry;* [4] *Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada;* [5] *McLean Hospital, Harvard Medical School, Belmont, Massachusetts, USA;* [6] *Department of Physiology, University of Toronto, Toronto, Ontario, Canada*

Posttraumatic stress disorder (PTSD) can develop after exposure to severe psychological trauma, leaving patients with disabling anxiety, nights, and flashbacks. Current treatments are only partially effective, and development of better treatments is hampered by limited knowledge of molecular mechanisms underlying PTSD. We have discovered that the glucocorticoid receptor (GR) and FK506 binding protein 51 (FKBP51) form a protein complex that is elevated in PTSD patients compared with unaffected control subjects, subjects exposed to trauma without PTSD, and patients with major depressive disorder (MDD). The GR-FKBP51 complex is also elevated in fear-conditioned mice, an aversive learning paradigm that models some aspects of PTSD. Both PTSD patients and fear-conditioned mice had decreased GR phosphorylation, decreased nuclear GR, and lower expression of 14-3-3ε, a gene regulated by GR. We created a peptide that disrupts GR-FKBP51 binding and reverses behavioral and molecular changes induced by fear conditioning. This peptide reduces freezing time and increases GR phosphorylation, GR-FKBP52 binding, GR nuclear translocation, and 14-3-3ε expression in fear-conditioned mice. These experiments demonstrate a molecular mechanism contributing to PTSD and suggest that the GR-FKBP51 complex may be a diagnostic biomarker and a potential therapeutic target for preventing or treating PTSD.

S1.3
Cerebrospinal fluid promotes maturation of human iPSC-derived neurons and acutely modulates synaptic and neuronal function

Eric Hanse[1]
[1] *Gothenburg University, Gothenburg, Sweden*

The cerebrospinal fluid (CSF) may be viewed as the natural extracellular medium for brain cells. We have tested to expose rat hippocampal slices and iPSC-derived human cortical 3-D aggregates to human CSF and compared the effect to an artificial CSF with exactly matched ion concentrations. Human CSF increased excitatory and inhibitory synaptic transmission, neuronal excitability and network synchronization. In hippocampal slices human CSF induced gamma oscillations and in human cortical 3-D aggregates human CSF increased the synchronization of spontaneous network activity. We have also tested to replace standard culture media with human CSF when culturing iPSC-derived human cortical cultures. This switch resulted in a faster maturation in terms of development of synchronous network activity in the human cultures. Our results demonstrate that human CSF contains neuroactive substances that promote synchronous network activity.

S1.4

Synaptic modulation and plasticity during hippocampal synchrony

Yuji Ikegaya[1]
[1] *Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan*

The excitation-to-inhibition ratio in ongoing neuronal activity of various brain areas, including the hippocampus, is homeostatically balanced over time. We recently discovered that mouse hippocampal sharp wave/ripple oscillations serve as intrinsic events that trigger long-lasting synaptic depression and contribute to a day-night neural activity balance. More specifically, silencing of sharp-wave ripples during slow-wave states prevented the spontaneous down-regulation of net synaptic weights and impaired the learning of new memories. The synaptic down-regulation was dependent on the N-methyl-d-aspartate receptor and selective for a specific input pathway. Our findings are consistent with the role of slow-wave states in refining memory engrams by removing recent memory-irrelevant neuronal activity. In this presentation, I explain our findings with the research backgrounds and will try to hypothetically extend their significance to a clinical dimension.

S2 "Cellular and molecular mechanisms regulating persistent changes in reward-related behaviors"

Chairs: Matt Lattal

S2.1

Persistent changes in motivation and reward following acute trauma

Matt Lattal[1]
[1] *Department of Behavioral Neuroscience, Oregon Health & Science University Portland, USA*

A common finding from research on memory and drugs of abuse is that salient experiences cause changes in behavior that persist long after the experience. In the case of memory, a single traumatic event can lead to changes in anxiety, motivation, and substance abuse months after trauma. In the case of drugs of abuse, drug-seeking behavior relapses even after long periods of abstinence. Trauma or exposure to drugs of abuse, such as cocaine or alcohol, can cause long-term changes in the neural circuitry regulating reward, motivation, and memory processes through dysregulation of various molecular mechanisms, including epigenetic regulation of activity-dependent gene expression. I will begin with an overview of the problem of persistent changes in neurobiological function and behavior, and how similar mechanisms operate as a consequence of exposure to trauma and to drugs of abuse. Data from several experiments in our lab will be reviewed that show persistent changes in motivated behaviors after exposure to an acutely traumatic experience. These changes are caused by activation of the basolateral amygdala and they can be reversed through modulation of behavior (via extinction) and epigenetic mechanisms (via histone deacetylase 3). Implications of these findings for understanding the basic neurobiology of PTSD and substance abuse will be discussed.

S2.2

Persistent epigenetic regulation of novel targets across cocaine abstinence

Marco D. Carpenter[1], Elizabeth A. Heller[1]
[1] *Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, PA, USA*

Cocaine addiction is characterized by compulsive drug seeking and high vulnerability to relapse even after prolonged abstinence. A major focus of the field of addiction research has therefore been to identify stable, cocaine-induced neuroadaptations occurring in brain reward circuits. Transcriptional changes are known to persist throughout abstinence, yet the underlying molecular mechanisms of such persistence remain elusive. Given that histone posttranslational modifications (hPTMs) confer long-lasting changes in gene expression necessary for stable cellular phenotypes, histone modifications acquired during abstinence may explain how individual genes "remember" prior drug exposure.
We recently performed transcriptomic analysis of gene expression at early (1-day) and late (28-day) abstinence following cocaine self-administration in mice. We discovered that the transcription factor, Nr4a1 (nuclear receptor subfamily 4), is activated in early cocaine abstinence but persistently regulates hPTMs at target genes at late abstinence, including Cartpt (cocaine and amphetamine regulated transcript). Specifically, we find that in late abstinence, Nr4a1 is stably enriched at Cartpt, coincident with deenrichment of the repressive histone modification H3K27me3. CRISPR activation of Nr4a1 in the nucleus accumbens (NAc) recapitulates the epigenetic regulation of Cartpt and represses cocaine seeking behavior during late abstinence. The significance of this finding is strengthened by the utility of therapeutic agents that regulate Nr4a1 and block mouse cocaine self-administration, underscoring the potential of this novel target gene in combating drug relapse, and reversing the cycle of chronic addiction.

S2.3

Epigenetic mechanisms in the medial habenula underlying reinstatement of drug-seeking behavior

Jessica Childs[1], Marcelo A. Wood[1]
[1]*Department of Neurobiology & Behavior, University of California Irvine*

Drugs of abuse, such as cocaine, cause long-term changes in the neural circuitry regulating reward, motivation, and memory processes through dysregulation of various molecular mechanisms, including epigenetic regulation of activity-dependent gene expression. Underlying drug-induced changes to neural circuit function are the molecular mechanisms regulating activity-dependent gene expression. Of note, histone acetyltransferases and histone deacetylases (HDACs), powerful epigenetic regulators of gene expression, are dysregulated following both acute and chronic cocaine exposure and are linked to cocaine-induced changes in neural circuit function. We investigated HDAC3-mediated regulation of Nr4a2/Nurr1 in the medial habenula, an understudied pathway in cocaine-associated behaviors. NR4A2, a transcription factor critical in cocaine-associated behaviors and necessary for MHb development, is enriched in the cholinergic cell-population of the MHb; yet, the role of NR4A2 within the MHb in the adult brain remains elusive. Using a combination of cell-type specific approaches, we found that choline acetyltransferase (ChAT) expressing cells in the MHb are sufficient to drive reinstatement behavior in both a conditioned place preference task as well as a self-administration task. In addition, we have found that the HDAC3 target gene, Nr4a2, in the ChAT cells of the MHb is necessary for reinstatement. Current studies are focused on understanding how NR4A2 regulates physiological properties of the ChAT cells using single nuclei RNAseq (snRNAseq). Overall, these findings demonstrate that a very small population of specific cells of the ventral MHb are critical for driving relapse-like behavior, and that the mechanism involves HDAC3/NR4A2-dependent gene regulation.ounterbalance the aberrant circuit activity in Tourette syndrome.

S2.4

An emerging role for histone variants in behavioral regulation

Iva Zovkic[1]
[1]*Department of Psychology, University of Toronto Mississauga, Mississauga, ON, Canada*

Epigenetic modifications have an established role in learning and memory, but a role for histone variants in behavioral regulation was only recently uncovered. I will discuss emerging evidence for opposing actions of individual histone variants in memory, whereby histone H2A.Z suppresses and histone macroH2A1 promotes memory formation. Their effects on memory will be discussed in the context of transcriptional changes in the mouse hippocampus and related to sex differences in Alzheimer's disease and age-related memory decline

S3 "Novel Mechanisms by which Life Experiences across the Lifespan Change Neural Function and Behavior"

Chair: Gretchen Neigh

S3.1

Translating Across Circuits and Genetics Toward Progress in Understanding the Biology of Trauma-Related Disorders

Kerry J. Ressler[1]
[1]*McLean Hospital, Harvard Medical School, Boston, Massachusetts, USA*

Trauma-related disorders are common and disabling, and they significantly increase risk for suicide and other causes of morbidity and mortality. However, there is tremendous potential for translational neuroscience to advance our understanding of these disorders, leading to novel and powerful interventions and even to preventing their initial development. This overview examines the general circuits and processes thought to underlie trauma disorders, including PTSD, along with the promise of translational research. It then examines some of the data-driven "next-generation" approaches that are needed for discovery and understanding but that do not always fit neatly into established models. From one perspective, these disorders offer among the most tractable problems in psychiatry, with a great deal of accumulated understanding, across species, of neurocircuit, behavioral, and, increasingly, genetic mechanisms, of how dysregulation of fear and threat processes contributes to trauma-related disorders. One example is the progressively sophisticated understanding of how extinction underlies the exposure therapy component of cognitive-behavioral therapy approaches, which are ubiquitously used across trauma-, anxiety- and fear-related disorders. However, it is also critical to examine gaps in our understanding between reasonably well-replicated examples of successful translation, areas of significant deficits in knowledge, and the role of large-scale data-driven approaches in future progress and discovery. Although a tremendous amount of progress is still needed, translational approaches to understanding, treating, and even preventing trauma-related disorders offer great opportunities for successfully bridging neuroscience discovery to clinical practice.

S3.2

Trauma exposure across generations: how maternal trauma exposure and PTSD impacts the neurobiology of her children

Tanja Jovanovic[1]
[1]*Wayne State University, Department of Psychiatry and Behavioral Neurosciences, Detroit, Michigan*

Trauma exposure has long-lasting consequences for the victims as well as the children of victims. Intergenerational transmission of trauma has been shown in several cohorts, including Holocaust survivors and refugee populations. Animal models have indicated that epigenetic mechanisms may account for some of these effects. On the other hand, human studies suggest that parenting behavior can contribute to both negative and positive outcomes in children. In addition, maternal psychopathology, such as posttraumatic stress disorder (PTSD) or depression can also directly impact her offspring. In our work, we have observed that maternal experiences of childhood trauma, including physical and emotional abuse, increase physiological biomarkers of anxiety in her children. Children of abused mothers had higher startle responses, even after controlling for their own trauma exposure. Most recently, we have found that maternal childhood trauma also impairs safety learning and neural connectivity between limbic and prefrontal brain regions. In this talk, we will review these recent findings from fear-potentiated startle and functional neuroimaging, as well as potential mechanisms of transmission, including parenting behavior. Further, we will describe parental buffering effects, in which warm parenting provides protection from threat-related responses in children. We found that fear conditioning and amygdala reactivity to fearful faces is associated with the child's own exposure to trauma, yet is reduced in children of warm mothers. These data show potential family-based intervention approaches to attenuate the intergenerational effects of trauma.

S3.3

Trauma exposure across the lifespan increases risk for adverse behavioral and physiological health outcomes in pregnant persons

Vasiliki Michopoulos[1]
[1]*Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, Georgia*

Trauma exposure across the lifespan is associated with increased risk for adverse behavioral health outcomes, including depression and posttraumatic stress disorder (PTSD). While significant sex differences in risk for stress-related adverse outcomes, few studies have focused on characterizing the influence of trauma exposure on risk for adverse behavioral and physiological health outcomes specifically in pregnant persons. To mitigate the risk of adverse trauma-related parental conditions and the intergenerational transmission of risk of trauma in offspring, studies are necessary to better understand mechanisms underlying risk for adverse gestational health outcomes, especially in populations suffering from significant health inequities. In this talk, we will highlight data collected from women recruited from primary care and obstetrics and gynecology (OBGYN) clinics at Grady Memorial Hospital in Atlanta, GA. We will discuss the high rates of lifetime trauma exposure, and concomitant high rates of PTSD and depression symptoms, as we all as the lack of disclosure of past psychiatric diagnoses with prenatal treatment providers. We will also show data showing that hyperarousal symptoms of PTSD and increased psychophysiological hyperarousal are greater in trauma-exposed pregnant than non-pregnant premenopausal persons. Finally, we will show data from a sample of first-trimester, pregnant Black persons highlighting the impact of trauma exposure on symptoms of anxiety, depression, PTSD, and emotion dysregulation. Overall, these data indicate that trauma exposure increases risk for adverse behavioral and physiological health outcomes in pregnant persons and underscores the need for trauma-informed care and interventions to reduce health inequities in at-risk communities.

S3.4

Developmental experiences cause long-term changes in mitochondrial function in synapses.

Gretchen N. Neigh[1]
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Neuropsychiatric disorders often include a history of developmental stress. Alterations in cerebral metabolic activity may underlie this relationship. These mechanistic questions can be difficult to disentangle in human subjects, creating a need for animal models that demonstrate related behavioral ethograms that can be assessed on a more invasive level. A model of chronic stress during adolescent development produces sustained changes in behavior as well as alterations in physiology. Adolescent stress sex-specifically alters expression of glucose transporters in the brain, suggesting that there could be further alterations in metabolism. In addition, chronic adolescent stress alters the neuroinflammatory response to immune challenge. Given the existing knowledge regarding the impact of chronic stress on synaptic architecture and inflammation, the current study assessed the impact of chronic adolescent stress and chronic low-level inflammation on behavior and synaptosomal metabolism. Data collected demonstrate that a history of chronic stress increases anxiety-like and alters memory performance. Syn-

aptosomal respiration is also altered in a sex-specific manner following chronic stress and chronic inflammation. In summary, these results suggest that while metrics of inflammation and reactive oxygen are disrupted in males following chronic stress and chronic LPS, only the combined condition is sufficient to alter synaptosomal respiration. Conversely, females demonstrate profound shifts in synaptosomal mitochondrial function with a history of chronic inflammation. These data highlight that differential mechanisms are likely in play between the sexes and suggest influence of life experiences on mitochondrial function in the synapses.

S4 "The brain as a target for endocrine-disrupting chemicals"

Chairs: Matthieu Keller, Thierry Charlier

S4.1
Effects of exposure to low doses of plasticizers on cognitive behaviors in male mice

Suzanne Ducroq[1], Sakina Mhaouty-Kodja[1]
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Phthalates are among the most frequently detected organic pollutants in the environment. Di-(2-ethylexyl)phthalate (DEHP), the most abundant of this family, is used in the manufacture and processing of plastic products. We have previously shown that adult exposure of male mice to environmental doses of DEHP alters reproductive behaviors, probably through a down-regulation of the neural androgen receptor (AR). The present study aimed to assess the effects of adult exposure to DEHP alone or in a phthalate mixture on the hippocampus, another androgen-sensitive brain area. The few studies addressing the effects of adult exposure to phthalates on learning and memory all used high doses, which were much more higher than the estimated environmental exposure. Adult male mice were orally exposed to DEHP alone at 5 $\mu/kg/d$, in the range of the environmental exposure, 50 $\mu/kg/d$, the tolerable daily intake dose, or to DEHP in an environmental phthalate mixture. The control group was exposed to the vehicle. Males were then analyzed for learning and memory (spatial memory, temporal order memory, novel object recognition) and general behaviors such as locomotor activity and anxiety-related behavior. At the cellular and molecular levels, structural and functional neuroplasticity was analyzed as well as the expression levels of AR and estrogen receptors (ER). These data were compared with those obtained from transgenic mouse models lacking these receptors in the nervous system. The obtained results will be presented and discussed in the light of literature on phthalates.

S4.2
Neuroendocrine disruption of puberty and reproduction

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Onset of puberty strongly depends on organizational processes taking place during the fetal and early postnatal life. Therefore, exposure to environmental pollutants such as endocrine disrupting chemicals during critical periods of development can result in delayed/advanced puberty and long-term reproductive consequences. Endocrine disrupting chemicals (EDCs) are a rising concern for public health due to their ubiquitous presence as complex mixtures affecting development throughout generations. Rodent and ovine studies indicate a possible role of fetal and neonatal exposure to EDCs, along the concept of early origin of health and disease. Such effects involve neuroendocrine mechanisms at the level of the hypothalamus where homeostasis of reproduction is programmed and regulated. We have shown that neonatal exposure to the ubiquitous endocrine disruptor Bisphenol A (BPA) leads to opposing dose-dependent effects on the neuroendocrine control of puberty in the female rat. In particular, a very low and environmentally relevant dose of BPA delayed neuroendocrine reproductive maturation through increased inhibitory GABAergic neurotransmission. More recently, we have focused on the effects of a complex mixture of estrogenic and anti-androgenic compounds on the hypothalamic control of puberty and reproduction. Female rats (F0 generation) were orally exposed to a mixture of 14 anti-androgenic and estrogenic EDCs or corn oil for 2 weeks before and throughout gestation and until weaning. The doses represented human exposure. While F2 and F3 females showed delayed vaginal opening, decreased percentage of regular estrous cycles and decreased GnRH interpulse interval, no such changes were detected in F1 animals. These reproductive phenotypes were associated with alterations in both transcriptional and histone posttranslational modifications of hypothalamic genes involved in reproductive competence and behavior like kisspeptin (Kiss1), oxytocin (Oxt), estrogen receptor (Esr1) and glutamate receptor (Grin2d). Concomitant with a decrease in transcriptional activity, we observed either a decrease of active histone marks for

Esr1 and Oxt promoter regions, an increase of repressive histone modifications for Grin2d, Th and Nr3c1 promoter regions or both for the Kiss1 promoter. Our data shows that gestational and lactational exposure to environmentally relevant EDCs transgenerationally affects sexual development throughout epigenetic reprogramming of the hypothalamus.

S4.3

Genistein: a new Metabolism Disrupting Chemical

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The danger to human health of synthetic contaminants in food, such as pesticides, is widely known and a subject of debate even among non-specialists. Much less known are the obesogens, a sub-group of endocrine disrupting chemicals (EDCs), associated with some molecules of natural origin, such as phytoestrogens, including genistein (GEN).

Genistein is produced by many plants, and is highly present in Leguminosae species in particular in soybeans, for this reason soy is now recognized as a hormonally active component of food whose large use is raising concern. GEN by binding estrogen receptors can alter both the functional processes that depend on them (for example, reproduction and energy metabolism) and the development of the neuroendocrine circuits that regulate these activities. In a our study we showed that early postnatal exposure to GEN, in a dose comparable to exposure level in babies fed with soy-based formula, determines an obesogenic phenotype only in adult female mice and a long-term sex specific effects on different hypothalamic neural circuits related to the control of food intake. More recently, we are investigating the sexually dimorphic predisposition to obesity in adult caused by the exposure to GEN at an early stage of life, and, in particular, the role of different estrogen receptors.

The alteration of these nervous circuits could be at the root of some problems (constantly growing in our society) that are found in the human field, such as the predisposition to obesity in children fed with soy-milk. Furthermore, the GEN effect during development may be due to epigenetic modifications in the offspring.

S4.4

Prenatal exposure to environmental pollutants and neurodevelopment: results from two European birth cohorts

Anne-Claire Binter[1]

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Background: More than 5000 chemicals are currently being produced on a large scale. Numerous chemicals end up directly in the environment, and reach the general population via consumer and food products. Most of these chemicals are nonpersistent and, consequently after exposure, rapidly metabolized and excreted. However, results from biomonitoring studies have shown that humans, in particular pregnant women, are continuously exposed to chemicals. Prenatal exposure to environmental pollutants such as organic solvents, phthalates, phenols, and pesticides has been suggested to impair cognitive development. Evidence is needed from longitudinal birth cohorts to understand their impact on child neurodevelopment across time.

Methods: The PELAGIE cohort and the Generation R study are two prospective birth cohorts established in 2002 in Brittany (France) and Rotterdam (the Netherlands), respectively. Women were recruited in early pregnancy (nearly 3,500 and 10,000 women, respectively). Chemical were measured in maternal urines, collected during pregnancy. Neurodevelopment was assessed at age 2, 6, and 10 years using neuropsychological tests and magnetic resonance imaging.

Results: Prenatal exposure to organic solvents, pesticides, were associated with lower cognitive scores, and higher risk of behavioral disorders. Some chemicals, in particular organophosphate insecticides, were associated with altered brain structures and function but not with altered maternal thyroid function.

Conclusions: Prospective birth cohorts have well suited designs for studying the early effects of exposure to chemical pollutants. Future research should investigate the potential mediating effects of brain outcomes and hormone metabolisms.

S5 "Contribution of early-life stress to the development of psychiatric disorders"

Chairs: Desmedt Aline, Koehl Muriel

S5.1
Juvenile stress modulation of stress vulnerability and resilience in adulthood

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The exposure to stress early in life is considered a risk factor that can increase the vulnerability to developing psychopathologies later in life. However, the exact early life period of exposure makes a difference with regards to the profile of the outcome. We focus on the post-weaning, pre-pubertal or juvenile period since it is a period which best resembles human childhood. We could demonstrate that, similar to humans, exposure of rodents to juvenile stress indeed increases the probability of developing psychopathologies, if exposed to trauma later in life.
However, even when combined with the background of exposure to juvenile stress, not all individuals exposed to trauma develop pathology. Employing a 'Behavioral Profiling' analysis approach we developed we could demonstrate that some of the neural mechanisms activated by trauma or juvenile stress are not related to the developing pathology, but rather to establishing resilience.
The results indicate first, that stress resilience is an active process. Secondly, if resilience requires the activation of mechanisms of resilience, then pathology may result not only from the activation of mechanisms of pathology, but also from the failure to activate mechanisms of stress resilience.
The exposure to juvenile stress may thus increase vulnerability by compromising the ability to activate mechanisms of stress resilience.

S5.2
Effects of early-life stress on the quality of pup-dam interaction

Archana Ashokan[1], Jorine Geertsema[2], Aniko Korosi[2], Marloes Henckens[1], and Judith Homberg[1]
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Experiences in early-life leave significant impact on the physical and emotional health of all mammalian species. In mammals, one of the most common sources of early-life stress is the unpredictable and fragmented nature of parental signals in the environment. Challenging environments constituting stressors burden primary caregivers (mothers in most species) with stress leading to disturbances in maternal care which may result in long-lasting alternations in the brain, behaviour and physiology of the offspring. In this study we focussed on the quality of maternal care affecting offspring's brain-gut axis development. During early-life, stress was induced in nursing mice and their respective litters through adverse housing conditions characterised by limited bedding and nesting. Through this paradigm, we assessed unpredictability in maternal care through behavioural observations. Stressed animals showed steady rise in unpredictable maternal care which significantly increased only during the last day of stress-treatment. Other physiological parameters such as body weight and stress hormonal pattern in the form of corticosterone measures were also assessed to validate the effect of stress in both dams and offspring. Stress had a significant effect is altering the body weights of stressed offspring however their corticosterone profile was unaffected. Previous studies suggest an important role of bacterial colonization of the intestine during postnatal development in shaping immune and endocrine responses in growing animals. One of the early potential microbial sources colonizing the intestine could be mother's milk. Therefore, it could also serve as a putative precursor for colonizing the gut of the offspring. Stress could be a potent factor for inducing dysbiosis in the commensal microbiome housed by dams and thereby affecting the overall quality of breastmilk. In this study, we also hypothesise presence of stress-induced alternations in the breast milk microbiome of nursing mothers which in turn may play a role in influencing gut functions such as permeability and inflammation along with maternal-care behaviour pattern. These factors together could putatively contribute in shaping discrete aspects of brain neurochemistry and the HPA axis in offspring.

S5.3
Modeling adaptive versus maladaptive (PTSD-like) fear memory:Identification of contextual amnesia as a cause of PTSD-like hypermnesia

Desmedt Aline[1]
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Post-traumatic stress disorder (PTSD), which is developed by a subpopulation of victims of traumatic events (≈ 30 %), is characterized by a paradoxical memory alteration with emotional hypermnesia for some salient trauma-related cues and declarative/contextual amnesia. A major issue to be solved is to know what are the risk

and resilience factors for the development of this stress-related psychiatric disorder. Some clinical studies strongly suggest that contextual amnesia, and thus the underlying hippocampal dysfunction, might be responsible for the formation and persistence of PTSD-related intrusive hypermnesia. Yet, so far the absence of animal model for such maladaptive fear memory made it impossible to test this causality between contextual amnesia and hypermnesia.
Using the first animal model that precisely recapitulates the two memory components of PTSD and distinguishes maladaptive (PTSD-like) from adaptive fear memory, we demonstrated that (i) contextual amnesia can cause PTSD-like hypermnesia, and that (ii) treating this amnesia durably prevents, and even cures, PTSD-like hypermnesia. More precisely, promoting the hippocampus-dependent contextual memory of the trauma, either by (i) an optogenetic stimulation of the hippocampus, (ii) a cognitive-behavioral or (iii) pharmacological approach (brexpiprazole administration), induces a long-lasting suppression of the erratic hypermnesia, and thus prevents/treats PTSD-like memory.
These findings identify contextual amnesia and the underlying hippocampal hypofunction as a cause of PTSD-like memory, and the stimulation of the hippocampal function as a resilience factor. Therefore, they call therapeutic approaches of PTSD to turn to trauma (re)contextualization and the underlying hippocampal mechanisms.

S5.4
Prenatal stress increases vulnerability to PTSD-like memory

Mohamed-Lyès Kaci[1], Chloe Bouarab[2], Djoher Nora Abrous[1], Aline Desmedt[2] and Muriel Koehl[1]
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Life events in childhood, experienced as early as during in utero life, play a pivotal role in shaping adult behavior, and studies have shown that exposure to prenatal stress (PS) could constitute a developmental risk factor for psychiatric disorders, with behavioral features reminiscent to those of post-traumatic stress disorder (PTSD).
One of the cardinal feature of PTSD is a paradoxical pattern of memory with both emotional hypermnesia and contextual amnesia. Furthermore, it has recently been proposed that alteration in contextual pattern separation, which depends on adult neurogenesis, could contribute to this abnormal memory profile.
Altogether, this led us to examine the impact of PS in mice in a fear paradigm allowing to evidence PTSD-associated memory disturbances, and to analyze the contribution of adult neurogenesis in the PS-induced phenotype. We used optogenetics to target and activate 6-weeks old newborn neurons when the mice were exposed to the fear paradigm in a specific context. We then measured the effects of this stimulation on freezing behavior when the mice were re-exposed to the conditioning context or to a neutral context. We report that PS mice exhibit a PTSD-like aberrant memory profile after conditioning, while control mice develop a normal fear memory. Activating adult born neurons prevents this PTSD-like memory in PS mice while it has no effect in control mice. In conclusion these results indicate that PS alters trauma contextualization, hence increasing the risk of developing a PTSD-like memory, and that acting on adult-born neurons activity could help restoring some of the induced impairments.

S6 "Integrated neuromodulation in subcortical circuits for perception and reward"

Chairs: Rosario Moratalla, Raffaella Tonini

S6.1
Neuromodulated plasticity in the noradrenergic locus coeruleus

Raffaella Tonini[1], Andrea Locarno[1], Ieva Misevičiūtė[1], Dan Covey[2], François Georges[3], Joseph F. Cheer[2]
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Incentive stimuli and environmental stressors are encoded at the level of the prefrontal cortex (PFC) circuits, which send their glutamatergic excitatory projections to several neuromodulatory regions, including the Locus Coeruleus (LC), the major source of norepinephrine (NE) for the entire forebrain. Despite the potential implications for NE-mediated regulation of action control and for the etiology of stress-related neuropsychiatric conditions, it remains to be explored how LC neuronal activity is shaped by impinging PFC inputs (PFC→LC) to affect behavior, and whether these inputs are modulated by in-vivo experience. Raffaella Tonini will present recent evidence suggesting a role for a direct PFC→LC connection in learning and retrieval of contextual memory associations and provide mechanistic insights into how this connection undergoes plasticity secondary to in-vivo experiences. She

will also discuss how local changes in the synaptic strength at PFC→LC connection may affect NE release back to the cortex, ultimately pointing at the PFC→LC synapse as key node of a PFC-LC interconnected loop.

S6.2

Locus coeruleus wake-up dopamine neurons during environmental novelty and control cocaine-triggered plasticity

François Georges[1], Giulia R. Fois[1], Karl Y. Bosque-Cordero[2], Rafael Vazquez-Torres[3], Cristina Miliano[4], Solal Chaquet[1], Xavier Nogues[5], Carlos A. Jimenez-Rivera[3], Stéphanie Caille[6]

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A key feature of human and animal brain is to handle novelty. Anything that is new, different or unusual exerts an attractive power, catches our attention and triggers exploration. Exploring a novel context (spatial novelty) is essential for the species survival, and has been proposed to increase motivation, facilitate reward processing, and potentiate cocaine consumption. Different brain circuits are activated by novelty, but three specific brain regions seems critical for this spatial novelty detection network: the noradrenergic neurons originating from the locus coeuruleus (LC), the dopaminergic neurons from the ventral tegmental area (VTA) and the hippocampus. However, how spatial novelty can interfere with the reward system and control cocaine impact on VTA dopamine neuron plasticity and associated-behavior is not well understood yet. Here we investigate how novelty induced by a switch of context trigger changes in electrophysiological properties of VTA dopamine neurons and the role of novel environment to trigger cocaine-evoked plasticity in dopamine neurons. We combined *in vitro* and *in vivo* electrophysiological approaches to uncover the early cellular targets of cocaine in the mesolimbic dopamine system and the consequent adaptations at the circuit and behavioral level. We found that the novelty exposure is necessary for cocaine-induced effects on VTA dopaminergic neurons activity and that this effect is due to the exploration of a novel environment and is not supported by a stress-effect during novelty exposure. Our data also reveal the key role of LC to the cocaine-induced effects on VTA dopamine neurons during exposition in a new context.

S6.3

Regulation of sensory responses by motor activity in the healthy and Parkinsonian striatum

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The striatum is the main input structure of the basal ganglia and is involved in various motor functions such as motor learning, planning, and execution. Dysfunction in striatal circuits underlies several diseases and disorders, the most common of which is Parkinson's disease (PD). The striatum is also involved in sensory processing of tactile, auditory, and visual inputs, which are also impaired in PD. We have previously shown that the striatum integrates sensory responses in mice, delivered as bilateral whisker deflections. Moreover, these sensory responses were impaired in dopamine-depleted mice, using the 6OHDA mouse model for PD. Here we wanted to understand how sensory integration is modulated by motor activity. We delivered tactile sensory stimuli by briefly deflecting the ipsi- and contralateral whiskers of mice during quiescent periods and while mice were actively whisking. Our results show significant modulation of sensory responses by the whisking, both in the amplitudes and temporal properties of the responses. In Parkinsonian mice, the whisking pattern and sensory integration were both altered. Our results highlight the role of striatum in sensory processes and suggest that both sensory and motor functions are impaired in PD.

S6.4

Non-motor co-morbidities in early stages of Parkinson´s Disease

Adrián Sanz-Magro[1], Noelia Granado[1], Mónica Gómez-Benito[1], Manuel Márquez-Rivera[1], Rosario Moratalla[1]

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Parkinson´s disease (PD) is the most prevalent motor neurodegenerative disease, affecting more than 7 million of people in the world. In recent years, growing evidence shows that, beyond motor alterations, PD is a multisystemic disease that curse with a great variety of non-motor symptoms that precede the onset of motor signs, like gastrointestinal abnormalities, sleep disturbances or emotional alterations. During last years, co-morbid anxiety and depression in PD get special attention. Both are present in 40-60% of PD patients and boost severe parkinsonian symptoms, worsening the quality of life and the expec-

ted outcome of the patients. Although it is known that motor impairments are caused by the death of dopaminergic neurons of the nigrostriatal pathway, anatomical and molecular mechanisms underlaying anxiety and depression remains unclear. Therefore, to determine the alterations underlying these symptoms is very relevance. To determine the timing of the appearance of the symptoms as well as the pathological, anatomical and biochemical changes that correlate with the co-morbid non-motor symptoms in PD we used well established PD mice models, based on the lack of dopaminergic neurons, such as the aphakia mice, or based in the progressive aggregation of the alpha-synuclein protein, main component of Lewy Bodies detected in PD patients. We had used different behavioural tests to determine anxiety and depressive signs in our models, accompanied by complete histological and biochemical analysis to determine pathological changes and synaptic alterations in different brain nuclei. Funded by European Commission ref 848002 and by MICIN-PID2019-111693RB100.

S7 "New insights in the hypothalamic circuitry regulating energy metabolism: physiological and pathophysiological implications"

Chairs: Carole Rovére, Nicolas Chartrel

S7.1
Neurocircuits of food sensory perception

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Food sensory perception has recently emerged as a potent regulator of specialized feeding circuits by rapidly reversing the neuronal activity state of key feeding-regulatory neurons. Exposure to food cues inhibits neurons promoting feeding and activates the ones decreasing it. However, the resulting behavioral outputs and the underlying neuronal principles remain poorly understood. We investigated the feeding-regulatory role of projections from the olfactory bulb to hypothalamic and non-hypothalamic regions. I will discuss our results uncovering sensory pathways that integrate food odors to control food intake.

S7.2
Central regulation of glycaemia by insulin involves the 26RFa neuronal network

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26RFa (QRFP) is a biologically active peptide that regulates glucose homeostasis by acting as an incretin and by increasing insulin sensitivity at the periphery. 26RFa is also produced by a neuronal population localized in the hypothalamus. As it is now well accepted that the hypothalamus is also involved in the control of glucose homeostasis, we investigated whether 26RFa may play a role in the hypothalamic regulation of glucose homeostasis. Our data indicate that a central injection of 26RFa induces a robust antihyperglycemic effect, similar to that observed peripherally, associated with an increase of insulin production by the pancreatic islets. To understand the mechanisms underlying this new role of the central 26RFa/GPR103 peptidergic system, we examined its relationship with central insulin signaling. We found that insulin strongly stimulates 26RFa expression and secretion by the hypothalamus. RNAscope experiments revealed that neurons expressing 26RFa in the lateral hypothalamic area and the ventromedial hypothalamic nucleus also express the insulin receptor and that insulin induces the expression of 26RFa in these neurons. Concurrently, we show that the central antihyperglycemic effect of insulin is abolished in presence of a 26RFa receptor (GPR103) antagonist as well as in mice deficient for 26RFa. Finally, our data indicate that the hypothalamic 26RFa neurons are not involved in the central inhibitory effect of insulin on hepatic glucose production, but mediate the central effects of the hormone on its own peripheral production. Together, these data led us to identify a novel actor of the hypothalamic regulation of glucose homeostasis, the 26RFa/GPR103 system and we provide the evidence that this neuronal peptidergic system is a key relay for the central regulation of glucose metabolism by insulin.

S7.3
The role of mitochondrial function in astrocytes in the neuroendocrine control of metabolism

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The mammal brain is an organ of which the energy costs are high, and where most of the energy is used at the synaptic level to ensure information encoding and propagation of neuronal impulses. Mitochondria are the powerhouses of the cell that can modulate their efficiency to respond to cellular energy requirements by dynamically adjusting their size, shape, location and/or connectivity to further meet energy demands of the local circuits. Yet, neurons are not the only actors at the synapse: non neuronal components, such as some associated astrocytes, also participate in the assembly and function of synapses. The coherence between neuronal and astrocytic cellular bioenergetics is crucial to enable adequate brain function — including circuits entailed in regulating metabolism. In fact, recent insights revealed that mitochondrially-derived energy defects in astrocytes translate to a dysfunctional neuronal circuits and resulting in aberrant metabolic control, associated with obesity. However, the mechanisms by which the mitochondrial function of astrocytes, play a key role in supporting the functionality of hypothalamic circuits to participate in the control of the systemic energy metabolism deserve further investigation. To address this question, we have generated series of cell- and region-specific loss-of-function mouse models to target mitochondria-dependent bioenergetic processes specifically in astrocytes. Until now, our observations support that astrocytes control the activation of hypothalamic hunger circuits via mitochondrial Uncoupling Protein 2 (UCP2) in order to adjust feeding behavior. Accordingly, the ablation of UCP2 in astrocytes aggravates the insults to metabolic health associated with the consumption of a hypercaloric diet. Overall, our findings indicate that mitochondrial function in astrocytes is important to engage suitable hypothalamic responses and adjust the activity of hypothalamic NPY (neuropeptide Y) neurons to achieve homeostatic regulation of feeding behavior.

S7.4

Toward a link between neuroglial plasticity and satiety

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Mechanistic studies in rodents clearly evidenced state-dependent plasticity in neuronal circuits that control food intake. In recent works, we show that firing activity of anorexigenic POMC neurons located in the hypothalamus is increased after a standard healthy meal. Postprandial hyperactivity of POMC neurons relies on synaptic plasticity that engages pre-synaptic mechanisms, which does not involve structural remodeling of synapses but retraction of astrocytic coverage. These findings indicate that neuroglial plasticity within the melanocortin system happens at the time scale of meal. Further chemogenetic studies suggest that postprandial neuroglial plasticity is involved in the short-term regulation of food intake. Interestingly, all these effects are lost with a high-fat meal. By contrast, high fat meal initiates microglial changes that could constitute another mean for a fast and accurate control of food intake.

S7.5

Dietary fat exacerbates post-prandial hypothalamic inflammation involving GFAP-positive cells and microglia in male mice

Céline Cansell[1], Katharina Stobbe[1], Clara Sanchez[1], Ophélia Le Thuc[1], Coralie-Anne Mosser[2], Selma Ben-Fradj[3], Joris Leredde[1], Cynthia Lebeaupin[1], Delphine Debayle[1], Lucile Fleuriot[1], Frédéric Brau[1], Nadège Devaux[1], Alexandre Benani[3], Etienne Audinat[4], Nicolas Blondeau[1], Jean-Louis Nahon[1], Carole Rovère[1]

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In humans, obesity is associated with brain inflammation, glial reactivity, and immune cells infiltration. Studies in rodents have shown that glial reactivity occurs within 24 hours of high-fat diet (HFD) consumption, long before obesity development, and takes place mainly in the hypothalamus (HT), a crucial brain structure for controlling body weight. Here, we sought to characterize the postprandial HT inflammatory response to 1, 3 and 6 hours of exposure to either a standard diet or HFD. HFD exposure increased gene expression of astrocyte and microglial markers (GFAP and Iba1 respectively) compared to standard treated mice and induced morphological modifications of microglial cells in HT. This remodeling was associated with higher expression of inflammatory genes and differential regulation of hypothalamic neuropeptides involved in energy balance regulation. DREADD and PLX5622 technologies, used to modulate GFAP-positive or microglial cells activity, respectively, showed that both glial cell types are involved in hypothalamic post-prandial inflammation, with their own specific kinetics and reactiveness to ingested foods. Thus, recurrent exacerbated post-prandial inflammation in the brain might promote obesity and needs to be characterized to address this worldwide crisis.

S8 "Glia-neuron glutamatergic interactions in health and disease"

Chairs: Yuriy Pankratov, Christian Henneberger

S8.1
Vesicle Dynamics and Fusion Pore Regulation

Robert Zorec[1]
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Eukaryotic exocytotic vesicles merge with the plasmalemma, thus forming an intermediate, termed the membrane fusion-pore. Current hypothesis holds that the fusion-pore, once established, enters a stable, dynamically regulated state, with diameters from subnanometers to several tens of nanometers. These pores can then undergo either reversible constriction-closure to limit vesicle discharge, or full widening (full fusion exocytosis), to facilitate vesicle discharge. Fusion-pore closure and widening was shown to involve proteins, consistent with the first proposal that the fusion-pore is a proteinaceous structure in 1990 by Almers and Tse. While the fusion-pore was also modelled to be exclusively made of lipidis already in 1992 by the group of Julio Fernandez, it is more likely to be a mixture, made of proteolipids. In this lecture the results obtained by using high resolution cell-attached membrane capacitance recording to study unitary exo-and endocytotic events and super-resolution microscopies to monitor the discharge from a single vesicle in pituitary cells, gliocrine astrocytes and fibroblasts, will present the role of proteins, in particular SNAREs and those regulating SNARE complex formation, and cholesterol at the post-fusion stage. **S8.2**

Activity-dependent supply of NMDA receptor co-agonists in the hippocampus

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Glutamate receptors of the NMDA subtype (NMDARs) require the binding of glutamate and of a co-agonist, D-serine or glycine, and depolarization to open. Previous work of ourselves and others indicates that astrocytes control the supply of D-serine in an activity-dependent manner and in turn NMDAR-dependent synaptic long-term potentiation. This implies that also NMDAR-dependent supra-linear integration is controlled by astrocytes. We found that exogenous D-serine reduces the threshold of dendritic spikes, a hallmark of supra-linear dendritic integration, and increases their amplitude at CA1 pyramidal cells in acute slices. This was also triggered by pyramidal cell population activity, which involved astrocytic endocannabinoid receptors (CB1Rs), astrocytic Ca^{2+} signaling and an increase in extracellular D-serine levels. Interestingly, pyramidal cell activity in the theta range was particularly effective in activating this signaling cascade. Thus, theta activity engages a positive feedback loop via astrocytes that promotes dendritic spiking. Importantly, disrupting this feedback loop by conditional deletion of CB1Rs from astrocytes impaired object location memory and reversal learning. These observations raised the question if supply of the co-agonist glycine is also controlled in an activity-dependent manner. A novel optical glycine sensor (GlyFS) enabled us to optically probe the mechanisms that control extracellular glycine concentrations in the CA1 region of the hippocampus. Interestingly, we found that stimuli that are widely used to induce long-term potentiation and depression of synaptic transmission also increased the extracellular glycine concentration, which involved glycine transporters. These results demonstrate that supply of both NMDAR co-agonists is controlled by distinct patterns of neuronal activity.

S8.3
Best1-mediated tonic release of astrocytic D-serine in modulation NMDAR tone and cognitive flexibility

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NMDA receptor (NMDAR) hypofunction has been implicated in several psychiatric disorders with impairment of cognitive flexibility. However, the molecular mechanism of how NMDAR hypofunction with decreased NMDAR tone causes the impairment of cognitive flexibility has been minimally understood. Furthermore, it has been unclear whether hippocampal astrocytes regulate NMDAR tone and cognitive flexibility. We employed cell type–specific genetic manipulations, ex vivo electrophysiological recordings, sniffer patch recordings, cutting-edge biosensor for norepinephrine, and behavioral assays to investigate whether astrocytes can regulate NMDAR tone by releasing D-serine and glutamate. Subsequently, we further investigated the role of NMDAR tone in heterosynaptic long-term depression, metaplasticity, and cognitive flexibility. We found that hippocampal astrocytes regulate NMDAR tone via BEST1-mediated corelease of D-serine and glutamate. Best1 knockout mice exhibited reduced NMDAR tone and impairments of homosynaptic and a1

adrenergic receptor–dependent heterosynaptic long-term depression, which leads to defects in metaplasticity and cognitive flexibility. These impairments in Best1 knockout mice can be rescued by hippocampal astrocyte-specific BEST1 expression or enhanced NMDAR tone through D-serine supplement. D-serine injection in Best1 knockout mice during initial learning rescues subsequent reversal learning. These findings indicate that NMDAR tone during initial learning is important for subsequent learning, and hippocampal NMDAR tone regulated by astrocytic BEST1 is critical for heterosynaptic long-term depression, metaplasticity, and cognitive flexibility.

S8.4
Role for vesicular and non-vesicular glutamatergic gliotransmission in regulation of synaptic plasticity and working memory

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Astrocytes are an active element of brain signalling, capable of release of small molecule gliotransmitters by vesicular and channel-mediated mechanisms. However, specific physiological roles of astroglial exocytosis of glutamate and D-Serine remain controversial. Our data demonstrate that cortical astrocytes can release glutamate and D-Serine by combination of SNARE-dependent exocytosis and non-vesicular mechanisms dependent on TREK-1 and Best1 channels. Astrocyte-derived glutamate and D-serine elicited complex multicomponent phasic response in neocortical pyramidal neurons, which is mediated by extra-synaptic GluN2B receptors. Impairment of either pathway of gliotransmission (in the TREK1 KO, Best-1 KO or dnSNARE mice) strongly affected the NMDAR-dependent long-term synaptic plasticity in the hippocampus and neocortex. Moreover, impairment of astroglial exocytosis in dnSNARE mice led to the deficit in the spatial working memory which was rescued by environmental enrichment. These results demonstrate that synergism between vesicular and non-vesicular gliotransmission is crucial for astrocyte-neuron communication and astroglia-driven regulation of synaptic plasticity and memory. Our data also show that age-related decline in the glutamatergic gliotransmission contributes to the dysfunction of synaptic transmission in physiological ageing and Alzheimer's disease.

S9 "Why do we overeat? Unravelling the neuronal mechanisms underlying uncontrolled food intake"

Chair: Yonatan Kupchik

S9.1
A brain aversion network that drives addiction-like overeating in obesity

Paul J. Kenny[1], Richard M. O'Connor[1], Victor P. Mathis[1], Paul M. Johnson[2], Maria V. Micioni Di Bonaventura[1], W. Matthew Howe[1], Alexandra G. DiFeliceantonio[1], Kavya Devarakonda[1], Sara Klein[1], Austin Hake[1], Stephanie P.B. Caligiuri[1], Alexander C.W. Smith[1], Vanessa E. Lehmann[1], Kristin G. Beaumont[3], Masago Ishikawa[1]
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Many overweight individuals compulsively overeat despite negative health and social consequences. Neurobiological underpinnings of compulsive overeating are poorly understood. We found that obese rats or mice with access to a cafeteria-style diet compulsively overate, reflected by persistent consumption in a threatening environment. Using single cell RNA sequencing, we found that obesity induced transcriptional plasticity in lateral hypothalamic cells, particularly glutamatergic (LHGlu) neurons. Using virus-expressed barcodes and RNA sequencing to map brain-wide single cell connectivity of LH neurons revelated their projections to lateral habenula and other aversion-related brain sites. Electrophysiological recordings demonstrated that LHGlu cells that project to habenula (LHGlu-LHb neurons) were hypofunctional in obese animals. Using *in vivo* calcium imaging, we found that LHGlu-LHb neural activity was reduced in lean animals upon encountering food, the magnitude of reduction being proportional to the hedonic value of the food. In obese animals, only hedonic energy-dense food reduced LHGlu-LHb neural activity. Chemogenetic silencing of LHGlu-LHb neurons rendered food consumption resistant to threatening environmental stimuli. iDISCO-based whole-brain mapping of LHGlu neurons synaptic contacts in lean and obese mice revealed obesity-associated deficits in connectivity with the median raphe nucleus (MRn). Lesion of MRn neurons that received synaptic input from LH rendered food consumption resistant to threatening environmental stimuli. Together, these findings suggest that LHGlu-LHb

neurons, through interactions with the MRn, link the value of foraged food items with the risk associated with their consumption, a process profoundly perturbed in obese animals. Hence, abnormalities in LHGlu-LHb-MRn circuit function may explain the compulsive eating that defines obesity.

S9.2

Why do woman overeat? Characterizing a model of 'emotional' binge eating in female mice

Robyn Mary Brown[1,2] Roberta Goncalves Anversa[1,2], Erin Jane Campbell[1], Sarah Sulaiman Ch'ng[1], Andrew John Lawrence[1,2]

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Overeating of highly palatable food is a major contributing factor to obesity and related health complications. For women in particular, negative emotions such as stress, frustration, anxiety, and loneliness have been shown to strongly influence eating behaviour and bingeing episodes. Despite this knowledge there is a paucity of research investigating the neurobiology underlying emotional and stress related bingeing, particularly in female subjects. This is primarily due to a lack of suitable animal models and the historical focus of neuroscientific studies on male subjects. Dr Brown will describe a model of emotional stress-induced binge eating she has developed in mice that does not depend on caloric restriction, a behaviour that she has observed specifically in female mice. This behaviour is not oestrogen-dependent as it is not impacted by ovariectomy. Dr Brown will describe the neural correlates and putative networks driving this behaviour with a focus on the insular cortex.

S9.3

Innate clues in the ventral pallidum for the susceptibility to overeat

Yonatan M. Kupchik[1]

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Even though the global average body weight is constantly increasing, not all individuals develop obesity. Why some individuals are more susceptible than others to overeat and become obese is not yet known but it had been suggested that the susceptibility to overeat palatable food is embedded in certain parts of the reward circuitry. In my talk I will present data suggesting that the ventral pallidum (VP), a main structure in the reward circuitry, plays a role in making some more prone to overeat palatable food than others. I will show that in a group of mice fed on high-fat-high-sugar diet, those that gained the most weight showed reduced excitability of VP neurons and a tendency of the inhibitory input to the VP to potentiate upon repeated activation. Moreover, we found the synaptic potentiation of inhibitory input to the VP to exist also in mice fed on chow but that showed the highest level of palatable-food-seeking in an operant task. This suggests that the potentiation of inhibitory input to the VP might be part of the mechanism turning an individual more susceptible to overeat palatable food. Taken together, our data suggests that the susceptibility to overeat palatable food may be encoded, at least in part, by increased inhibition on VP activity.

S9.4

Why do we eat too much? How palatable diets change the orbitofrontal cortex and valuation of food rewards

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The lateral orbitofrontal cortex (lOFC) receives sensory information about food and integrates these signals with expected outcomes to guide future actions, and thus may play a key role in a distributed network of neural circuits that regulate feeding behaviour. Here, we will present evidence for a novel role of the lOFC in the cognitive control of feeding behaviour in obesity. Using patch clamp electrophysiology, obese mice exhibited suppressed inhibitory synaptic transmission and disinhibition of lOFC pyramidal neurons. These effects were due to altered astrocyte function resulting in increased extrasynaptic glutamate action at mGluR5 receptors leading to an endocannabinoid-mediated suppression of inhibition. Using inhibitory DREADDS expressed in GABAergic neurons, we found that, similar to obese mice, disinhibition of lOFC pyramidal neurons lead to impaired reward devaluation. We used optogenetic and pharmacological strategies to boost GABAergic tone and restore excitability in the lOFC and this restored goal directed behaviour. Taken together, these results suggest that obesogenic diets disrupt astrocyte function to influence synaptic transmission in the OFC, which may influence cognitive and emotional processing of the value representation leading to overeating associated with obesity.

S9.5
Nutritional lipids act on dopamine receptor type 2 (DRD2)-expressing neurons to gate dopamine-associated behaviours

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The release of dopamine (DA) within the reward circuit is instrumental to encode the reinforcing/rewarding aspects of feeding. This circuit is also the substrate by which drugs of abuse exert their addictive actions. In the reward circuit, DA-producing and dopaminoceptive neurons specifically express the lipoprotein lipase (LPL), an enzyme able to hydrolyze the dietary form of lipids, namely the triglycerides (TG), suggesting that circulating TG might modulate the activity of dopaminergic and dopaminoceptive neurons. By using *in vivo* central TG delivery, which mimics post-prandial increase of TG specifically in the brain, we have discovered that circulating TG act directly onto DA-D2 (DRD2) receptors expressing neurons modulating the reinforcing and motivational values of feeding. In particular, we have demonstrated that this mechanism depends on the integrity of the LPL in the reward circuit, and is blunted in conditions of high circulating TG which is known to be associated with obesity. We now have new results revealing that: 1) in humans, the neural responses to food cues show a significant correlation between post-prandial increases in TG and Drd2/Taq1 genetic polymorphism and 2) in rodents, central TG-sensing exert a bias modulatory action on the activity of DRD2-expressing neurons. These results suggest that TG-sensing in the reward circuit could be involved in the rewarding aspects of food and the compulsive/addictive action of highly palatable diet.

S10 "Using multiscale approaches to uncover the role of the superior parietal lobule in humans and non-human primates"

Chair: Michela Gamberini

S10.1
Cyto- and receptor architectonic organization of the macaque and human superior parietal lobule

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The macaque superior parietal lobule (SPL) is composed of 7 cytoarchitectonically distinct areas: PE and PEc on the lateral surface of the hemisphere, PEci and PGm on its medial aspect, and areas V6, V6Av, and V6Ad on its posterior portion. Furthermore, three subdivisions can be identified within PE (medial PEm, rostrolateral PEla, and caudolateral PElp) based on differences in receptor densities. The human SPL encompasses at least 7 cyto- and receptor architectonically distinct areas: areas 5L and 7PC on the lateral surface of the hemisphere, areas 7A and 7P on the dorsal aspect, as well as areas 5Ci, 5M, and 7M on the mesial surface. The most posterior aspect of the human SPL has not yet been mapped. These detailed parcellation schemes finally enable the definition of homologous SPL areas in the human and macaque brains based on similarities in topology, cytoarchitecture and receptor densities. Such homologies would represent

a breakthrough in cross-species studies aiming to unravel the structural-functional relationships in the primate SPL, since to date this endeavor has been hampered by Brodmann's much simpler parcellation scheme of the macaque brain, together with his view that the largest portion of macaque area 7 was located on the inferior parietal lobule.

S10.2

Anatomo-functional organization of the macaque superior parietal lobule

Michela Gamberini[1], Lauretta Passarelli[1], Patrizia Fattori[1], Claudio Galletti[1]

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The macaque superior parietal lobule (SPL) is almost totally occupied by Brodmann's area 5, but functionally it shows a clear heterogeneity. Its anterior part (area PE) hosts somatic information, while the most posterior part, in the depth of the parieto-occipital sulcus, hosts visual information (area V6). Area PE is likely involved in preparation/execution of limb movements, area V6 in analysis of visual motion. The areas located in between (PEc and V6A) host both visual and somatic information, as well as motor signals related to limb movements (lower and upper limbs area PEc, only upper limbs area V6A). Both areas are involved in sensorimotor coordination, likely in control of locomotion and of limbs interaction with environment area PEc, and in visual guidance of reach-to-grasp movements area V6A. The above described functional results and suggestions were confirmed by neuronal networks revealed by tracer injections. Both cortical and subcortical afferents to SPL strongly support the specific sensory and motor roles of different areas that compose it. The picture resulting from these data is that SPL contains three functional sectors: a somatic one anteriorly (area PE), a visual one posteriorly (area V6), and a bimodal one in between (areas PEc and V6A). This organization is the same of that of human SPL, with somatic Brodmann's areas 5 anteriorly, visual area 19 posteriorly, and bimodal area 7 in between.

S10.3

Functional specialization of the human dorsomedial parietal cortex

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According to recent models of visuo-spatial processing, the medial parieto-occipital cortex is a crucial node of the dorsal visual stream. Monkey evidence suggests that the cortex hidden into the parieto-occipital sulcus contains regions (V6+, V6Av and V6Ad) known to process visual motion and visuomotor (arm-reaching relevant) information, while anterior to the POs, the exposed surface of the superior parietal lobule contains regions (as the PEc) processing somatomotor information from upper and lower limbs. In humans, these areas have been mapped recently thanks to neuroimaging methods such as wide-field retinotopy, task-evoked activity and resting-state functional connectivity. Like in macaque, human V6 is a retinotopic motion area, while V6Av and V6Ad respond to hand pointing movements and PEc responds preferentially to leg movements and foot pointing and also to optic flow. In addition, human V6, V6Av, V6Ad and PEc show distinct patterns of cortical connections which are consistent with those showed by the anatomical tracing studies in the corresponding monkey areas. Our findings demonstrate a gradient of functional specialization and cortical connections from the human POs to the anterior precuneus, with more posterior regions dedicated to the analysis of visual attributes useful for spatial navigation, and more anterior regions devoted to integrate visual and somatic spatial information from both limbs, relevant for goal-directed action, as reaching and locomotion.e encoded, at least in part, by increased inhibition on VP activity.

S10.4

The role of posterior parietal cortex in defining motor commands for reaching movements

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Visually-guided hand movements require processing of sensory information about the target to be reached and transformation of these target visual coordinates into a hand-centered motor command. The amount of visual information available appears thus critical in this sensorimotor transformation process. It is known that longer durations of target visual fixation lead to better movement performance in a series of conditions (e.g. quiet eye). However, the sensorimotor mechanisms underlying this behavioural observation are largely unknown. Here we used transcranial magnetic stimulation (TMS) in healthy volunteers (n=24) performing a wrist step-tracking task to probe direction-specific motor plans generated in the primary motor cortex (M1) before actual movement initiation, hence before any corrective visual feedback could

update the motor command online. We simultaneously collected motor evoked potentials (MEPs) in 4 different forearm muscles whose pulling vectors directly corresponded to 4 different target directions. After normalisation of MEP amplitudes, differences in corticospinal excitability across muscles would therefore be indicative of direction-related motor plans in M1. Interestingly, we found that normalised MEP amplitudes across all 4 muscles were significantly different from each other when the target was presented for 200 ms (all $p < 0.027$) compared to 50 ms (all $p > 0.05$). Importantly, this effect of visual information availability on the motor plan definition was abolished after TMS-induced virtual lesion of the middle, but not anterior intraparietal sulcus, areas defined using MNI coordinates. These findings shed new light on the role of posterior parietal cortex in mediating highly defined motor plans through processing of visual information.

S10.5
Somatosensory function and dysfunction of the superior parietal lobule. Tactile agnosia and tactile apraxia

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In the light of anatomical and electrophysiological studies in animals and of lesion and neuroimaging studies in humans, the caudal part of the superior parietal lobule (SPL), area PEc, is known to be engaged in the processing of visual information, whereas the rostral part, area PE, processes somatosensory information. In recent years the combination of different neuroimaging methods yielded increasing information about the role of SPL in sensory guided actions. Along these lines I will present a meta-analysis of human fMRI studies in which we could identify four bilateral parietal foci, the more posterior of which show greater lateralization for contralateral visual stimulation than more anterior ones. Furthermore, the more anterior foci show greater lateralization for the use of the contralateral hand than the more posterior ones. These activation foci are organized along a posterior-anterior gradient of visual-to-somatic information integration. On the basis of novel high resolution Diffusion Tensor Tractography (DTI) I will demonstrate that this functional architecture of the SPL is mirrored by the patterns of anatomical connectivity. In my talk I will further show that human area PE is engaged in the processing of complex somatosensory-motor information, and that its lesion is related to a clinical condition of tactile apraxia in the contralateral hand. A related clinical condition, tactile agnosia, stems from lesions in the contralateral rostral PE and the adjacent primary sensory areas.

S12 "Multi-level analyses of acute stress: from basic research to clinical translation"

Chair: Johannes Bohacek

S12.1
Dynamic dissection of short- and long-term response to acute stress: a matter of resilience or vulnerability

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Stress is a primary risk factor for stress-related brain disorders. Evidence from preclinical models and clinical studies of stress-related disorders (depression, anxiety, PTSD, etc.) have revealed an array of structural, functional and behavioral maladaptive changes, whereby adverse environmental factors shape the brain. Although many preclinical studies use chronic stress protocols, long-term changes are also induced by acute exposure to traumatic stress, opening a path to identify determinants of resilient versus susceptible stress responses. A limitation of chronic stress models is that generally they assess the modifications at one terminal endpoint, making it difficult to understand how changes develop over time. As acute stress may induce long-term changes similar to those induced by chronic stress (e.g., sustained dendritic atrophy), a new longitudinal stress protocol has been developed, allowing to distinguish resilient/vulnerable animals by measuring anhedonic behavior as early as 24 hours after acute stress exposure, and to identify targets for rapid-acting drugs. By measuring various read-outs in the two animal groups, this approach is used to identify biomarkers of resilience versus vulnerability. This protocol represents a simpler alternative to classical chronic stress protocols to study pathophysiology of psychiatric disorders and test novel pharmacological approaches.

S12.2
Neural activity and network connectivity associated with inter-individual differences in trauma susceptibility

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Understanding the biological basis of individual differences in stress susceptibility is key to gain improved insight

into stress-related disorders like post-traumatic stress disorder (PTSD). From the clinical perspective it is now increasingly recognized that PTSD involves aberrant activity and intra and inter-network connectivity of large-scale functional brain networks; i.e., the salience (SN), default mode (DMN) and executive control (ECN) network. Here, we implemented a preclinical rodent model for PTSD to investigate whether deviations in network activity and connectivity are also detected in susceptible mice, and if so, when these develop. Following trauma exposure, trauma susceptible vs. resilient mice were identified using behavioral phenotyping and - in two independent cohorts - peri- and post-trauma brain-wide activity was compared, by tagging neuronal activity in living mice by the use of the ArcTRAP transgenic mouse line. Immunolabeling-enabled three-dimensional imaging of solvent-cleared organs (iDISCO+) was used to unbiasedly identify brains regions that displayed differential activity and SN, DMN and lateral cortical network (LCN, the rodent homologue of the ECN) connectivity. Results implicated increased activity of sensory and memory-related regions, including the retrosplenial cortex and subiculum during trauma processing in susceptible vs. resilient mice. The relative increase in activity of the retrosplenial cortex and subiculum in susceptible mice remained present under resting conditions after trauma, accompanied by increased orbitofrontal activation. Furthermore, susceptible mice showed increased correlations between the DMN and LCN peri-trauma, as well as increased resting DMN-SN and SN-SN connectivity post-trauma. These results indicate a) important homologies in network deviations in PTSD patients and susceptible mice, indicating the fitness of mouse models to study underlying neurobiology, and 2) that aberrant network activity and connectivity peri-trauma is predictive of later symptom development.

S12.3

Chasing stress down a multi-omic rabbit hole

Johannes Bohacek[1]

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The genome-wide molecular changes in response to chronic stress have been intensively studied, as chronic stress is a major risk factor for neuropsychiatric disorders. Much less is known about the genome-wide response to acute stress, although the border between acute and chronic stress is diffuse, and acute stressors constitute the building blocks of chronic stress. A successful stress response must rapidly provide energy resources to meet situational demands, but it must also efficiently terminate the stress response, to prevent allostatic overload that would cause wear and tear on tissues, exhaustion and disease. Here we follow the molecular cascades triggered by an acute, brief swim stress challenge across all molecular levels (from protein phosphorylation to transcription and translation) using multi-omic screening techniques down to the level of cell types and single cells. On each molecular level we track the changes across several time points from peak to termination of the response. The result is a first-of-its-kind atlas of the acute stress response. We find that the stress response starts with a very broad wave of uninhibited molecular activity, which is then tightly regulated towards translation, letting only very few protein-level changes emerge at the end. We argue that our work characterizes the healthy stress response and lays the groundwork for identifying pathological "breaking points" where the tightly regulated stress responses can go awry and lead to disease.

S12.4

Self-neuromodulation targeting limbic activity for alleviating emotion-dysregulation in neuropsychiatric patients

Talma Hendler[1], Naomi Fine[2], Ayelet Or-Borichev[3], Guy Gurevitch[4]

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We present evidence from two randomized control trials in two neuropsychiatric disorders of emotion dysregulation known to be induced or worsened by life-stress and mediated by heightened limbic activity; Post Traumatic Stress Disorder (PTSD) and Chronic pain. To target limbic activity in a non-invasive manner we utilized self-neuromodulation closed-loop reinforcement learning procedure, known as NeuroFeedback (NF). To reliably probe deeply located limbic activity in a scalable manner, we utilized a computational model of EEG signal inspired by simultaneously acquired amygdala-BOLD signal (Amygdala-related Electrical Fingerprint;Amyg-EFP) that has been successfully validated in the context of healthy participants and individuals under chronic stress. The current study aimed to investigate the clinical utility as an add-on treatment and the neural targeting of repeated ses-

sions of Amyg-EFP down-regulation via NF (Amg-EFP-NF) in women patients suffering from moderate-severe symptoms of emotion dysregulation. In trial-1, 47 women with Fibromyalgia (FM) were randomized to Amyg-EFP-NF (n=21), sham-NF (n=13), or treatment-as-usual (TAU; n=13) and in trial-2, 55 women with complex PTSD (cPTSD) exposed to repeated sexual abuse related trauma, were randomized to Amyg-EFP-NF augmented to intensive trauma related behavioral therapy (ITBT ,n=40), or maintaining ITBT (n=15). Pre and-post treatment, and at 3 follow-up measurements patients provided self-reports of related symptoms and underwent one session of Amygdala-fMRI-NF aimed to unveil the neural modification effect. Results from the FM study showed that pain related symptoms were robustly alleviated following treatment only in the test-NF group (time∗group $p < 0.001$) and that subjective reports on fatigue and other physical complains were improved in the test and sham-NF groups but not in the TAU group (time∗group $p < 0.003$; $p < 0.05$), evident even more robustly in one year follow-up measurement. Correspondingly, in trial-2 cPTSD symptoms improvement was demonstrated in NF augmentation compared to ITBT alone (time∗group $p < 0.054$) and was sustained 6 months post-treatment (time∗group $p = 0.07$). In both studies, demonstrating transferability, amygdala BOLD down-regulation following treatment was highly correlated to Amyg-EFP down-regulation during treatment for the patients in the test-NF group only (FM; r=0.63, $p < 0.004$, cPTSD; $r = 0.35$, $p < 0.05$). These findings strongly suggest that repeated training of down regulating amygdala related electrical signal through self-neuromodulation can alleviate emotion dysregulation symptoms related symptoms transdiagnostically. IMportnatly, fMRI results further support the involvement of the amygdala activity in training effect. Together these findings opens an exciting horizon for mechanism inspired brain-guided psychiatric treatments.

S13 "The Physiology, Function, and Pathology of the Claustrum"

Chairs: Gilad Silberberg, Ami Citri

S13.1
A claustro-frontal dopamine-driven circuit essential for contextual association of reward

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The claustrum is a small nucleus, exhibiting vast reciprocal connectivity with cortical, subcortical and midbrain regions. Recent studies, including ours, implicate the claustrum in salience detection and attention. We develop an iterative functional investigation of the claustrum, guided by quantitative spatial transcriptional analysis. Using this approach, we identify a circuit involving dopamine-receptor expressing claustral neurons projecting to frontal cortex necessary for context association of reward. Moreover, claustral dopamine system is recruited by cocaine and has essential role in drug sensitization. Applying chemo- and opto- genetic manipulation of increasingly specified claustral subpopulations, we identify a role for a defined network of claustrum neurons in the acquisition of contextual cocaine reward and de novo context reinforcement. Our results identifies a role for a dopamine-driven claustro-frontal neural circuit in the attribution of incentive salience, allocating contextual attention to reward-related cues.

S13.2
Input and output connectivity mapping reveals integrating properties of corticoclaustral and intraclaustral circuits

Adam M. Packer[1], Andrew M. Shelton[1], David K. Oliver[1], Joachim S. Grimstvedt[1], Jake A. Swann, Ishaan Kapoor[1], Simon N. Williams[1], Caitlin A. Ashcroft[1], Clifford G. Kentros[1], Menno P. Witter[1], Simon J. Butt[1]
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The claustrum is highly interconnected with many structures in the brain, but our knowledge of the organizing principles governing its vast connectivity remains incomplete. The present study investigates the architecture of circuits between the claustrum and neocortex and within the claustrum itself. Immunohistochemistry, retrograde tracing, *in vitro* whole-cell patch-clamp electrophysiology, dual-color optogenetic circuit mapping, and *in vivo* calcium imaging of neural activity were used to assess whether claustrum neurons combine inputs from multiple cortical areas and what impact claustrum neurons have on the cortex. We determined that individual claustrum neurons frequently integrate inputs from more than one cortical site, most commonly between regions of

the frontal cortex. Additionally, we found that neurons in the claustrum receive inputs from an array of sensory and associative cortical areas, albeit to a lesser extent. Retrograde labeling further indicated that input integration from frontal cortical regions depends on the output target of claustrum neurons. Optogenetic mapping revealed that intraclaustral connectivity was far more frequent than previously reported in coronal slices, particularly among neurons that did not share the same output target. Finally, claustrum axons recorded during *in vivo* calcium imaging displayed clear sensory responsiveness and an integration of sensory-related inputs that was transmitted to downstream cortical targets. Our findings shed light on the organizing principles of claustrum connectivity, demonstrating a clear relationship between cortical projections, local claustral connectivity, and claustral outputs.

S13.3

The claustrum-medial prefrontal cortex network controls cognitive flexibility

Alan Carleton[1], Leon Fodoulian[1,2], Olivier Gschwend[2*], Chieko Huber[1,2*], Sophie Mutel[1,2*], Rodrigo F. Salazar[1*], Roberta Leone[1,2], Jean-Rodolphe Renfer[1,2], Kazadi Ekundayo[2], Ivan Rodriguez[2]

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In various psychiatric disorders, prefrontal cortex dysfunction is thought to induce cognitive deficits. Here we studied how the claustrum (CLA), a nucleus sharing dense reciprocal connections with the cortex, may contribute to cognitive impairments. We molecularly characterized CLA neurons using single cell RNA sequencing and used a Cre-driver transgenic mouse line to specifically study CLA glutamatergic projection neurons. We show that CLA projection neurons exert a direct excitatory input on medial prefrontal cortex (mPFC) neurons. Furthermore, specific ensembles of CLA and of mPFC neurons are activated during a task requiring cognitive flexibility such as attentional set-shifting (i.e. the ability to shift attention towards newly relevant stimulus-reward associations while disengaging from irrelevant ones. Perturbing the recruitment of specific CLA assemblies through opto/chemogenetic manipulations impairs the activation of mPFC ensembles and alters cognitive flexibility. Our results emphasize a potential role of the CLA-mPFC network in cognitive dysfunctions observed in some mental disorders.

S13.4

Claustrum projections to the Anterior Cingulate Cortex are layer and cell-type dependent

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The claustrum (CLA) is an enigmatic subcortical brain structure, wedged between the lateral striatum and the insula. One of its striking hallmarks is the extensive excitatory connectivity it forms with numerous cortical areas. This unique synaptic organization has led to passionate debates over how the CLA contributes to cortical information processing and brain function in general. Experimental and theoretical studies have suggested the involvement of CLA in novelty coding, attention, sensorimotor integration, stress, and consciousness. Underpinning all these behavioral phenotypes is how the CLA specifically targets the cortex. Here, we focused on the cortical targets of CLA at the anterior cingulate cortex (ACC). We used a combination of *in vivo* multiunit recordings in awake mice, simultaneous ex vivo paired whole-cell patch-clamp recordings, optogenetics, and pharmacology, to investigate which cortical layers and cell types in the ACC were targeted by different types of CLA neurons. We report that CLA projections target all layers of the ACC with monosynaptic excitatory input, however, the synaptic connectivity patterns is layer and cell-type specific. Moreover, synaptic connectivity also depended on the type of presynaptic CLA population. This study shows that the functional connectivity between CLA and ACC follows intricate organizing principles, reflecting the types and topography of interconnected neurons.

S14 "Molecular pathways and circuitry mechanisms in Autism Spectrum Disorder and Obsessive Compulsive Disorder: preclinical and clinical evidence"

Chairs: Claudio D'Addario, Viviana Trezza

S14.1
THE ENDOCANNABINOID SYSTEM AS A NOVEL TARGET FOR AUTISM SPECTRUM DISORDER

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Fragile X syndrome (FXS) is the most frequent inherited cause of mental retardation and the leading genetic cause autism spectrum disorder (ASD). No effective and specific treatments are yet available for FXS, and none of the off-label medications prescribed to FXS patients selectively ameliorates their deficits. Different lines of evidence support the involvement of the endocannabinoid system in the pathogenesis of FXS since endocannabinoids are key modulators of several traits altered in FXS patients and cannabinoid drugs can normalize some behavioral, biochemical and electrophysiological changes displayed by FMRP-deficient mice. The aim of the present work was to test the involvement of the endocannabinoid system in FXS using the Fmr1-$^{\Delta}$exon 8 rat, a novel animal model for FXS generated by zinc-finger nuclease (ZFN) methodologies, whose behavioral repertoire has just been characterized. We found that in the course of development, Fmr1-^{Delta}exon 8 rats showed core FXS-like traits, confirming the face validity of this animal model of FXS. At the neurochemical level, Fmr1-$^{\Delta}$exon 8 rats showed changes in endocannabinoids levels in multiple brain regions. Interestingly, both systemic and intracranial pharmacological manipulation of endocannabinoid neurotransmission rescued the cognitive and social dysfunctions displayed by Fmr1-^{Delta}exon 8 rats. Altogether, these findings shed light on the role of the endocannabinoid system in the first rat model of FXS and provide an alternative pharmacological target to simultaneously ameliorate the symptomatology of the disease in the core cognitive and social domains.

S14.2
Exploring epigenetic mechanisms in Obsessive Compulsive Disorder, preliminary data on a possible interplay with microbiota modulation

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Obsessive-Compulsive Disorder (OCD) is a prevalent and severe clinical condition. Although robust evidence suggests a genetic component in its etiopathogenesis, the causes of the disorder are still not completely understood. In order to provide further knowledge, it is of relevance for instance to study how genes interact with environmental risk factors, thought to be mediated by epigenetic mechanisms. Moreover, microbial metabolites of diet can also be epigenetic modulator and the role of human gut microbiome in psychiatry has gained interest with preclinical evidence shown also for OCD. We here report preliminary data on altered levels in DNA methylation at oxytocin receptor gene promoter analyzed in saliva samples from OCD subjects when compared to healthy controls. Among the different phyla analyzed, we also observed selective higher levels of actinobacteria in the saliva of OCD subjects and, interestingly, directly correlated with the alterations of the epigenetic mark. To our knowledge, these are the first data suggesting an interplay between microbiota modulation and epigenetic mechanisms opening new avenues for the understanding of disease trajectories and for the development of new therapies.

S14.3
Immuno-moodulin: a novel biomarker and therapeutic target for OCD and related disorders

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The research in the field of psychiatric disorders has seen an enormous expansion over the last few years - not just in the amount of knowledge that has been produced but also in the ways we look at the roots of the problem. The expansion has been, in the literal sense, physical as we

now consider biological systems "outside" the brain as key contributors to or modulators of mental disorders. One of these systems is the immune system. Several mental disorders have been associated with changes in the number and functions of immune cells with OCD, PANS and PANDAS being among the best examples of what are now being called immunopsychiatric diseases.
We have recently identified a new protein modulator of repetitive anxiety behaviour in experimental mice. We called this protein Immuno-moodulin (Imood) as it is produced by T lymphocytes. More specifically, we have identified Imood in the T lymphocytes of mice that are highly susceptible to immune disorders. Interestingly, we found that the levels of Imood are also very high in blood cells of OCD.
When T lymphocytes become activated, they release Imood in circulation. We have generated a unique set of antibodies that bind to Imood and block its effects on the brain. Administration of these antibodies to mice cause a significant reduction in their level of anxiety and changes the localisation of T lymphocytes in the body. Current investigations are exploring how the administration of Imood blocking antibodies changes the expression of genes that regulate anxiety and repetitive behaviour in the brain. The results of these studies might shed new light on the links between the brain and the immune system and might open up a much needed discussion on new venues to treat psychiatric diseases.

S14.4
Preclinical models of neurodevelopmental disorders: Focus on current evidence for the discovery of novel therapeutic targets.

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Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by altered social communication and interaction, associated with stereotyped and repetitive behaviours. ASD often co-occurs with mental health disorders, including obsessive compulsive disorder (OCD), which is characterized by repeated obsessional thoughts and compulsive acts. Interestingly, it occurs with greater frequency in persons with ASD than in general population. The pathophysiological mechanisms (i.e., genetic, anatomic and neurobiological alterations) underling these psychiatric conditions are still not fully elucidated, limiting the therapeutic efficacy of currently available therapies. Here, we first discuss the concepts of construct, face and predictive validity in animal models of ASD or OCD. Then, we discuss how ASD or OCD relevant behavioural phenotypes can be mimicked in rodents, providing examples of different rodent models widely used and validated in the preclinical research. Finally, we discuss how these findings may ultimately help to develop new treatment strategies for ASD and other related disorders.

S15 "Parkinson's Disease is not only dopamine or motor dysfunctions"

Chairs: Micaela Morelli, Eduardo Tolosa

S15.1
Neural substrates of non motor symptoms of Parkinson disease

Eduardo Tolosa[1]
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Parkinson disease is more than a disease of the nigrostriatal dopaminergic system and currently non motor symptoms such as pain or sleep problems are recognized as part of the disease related symptoms that are unrelated to dopamienrgic dysfunction. In my presentation I shall discuss the clinical impact of the most prominent disease related non motor symptoms (sleep disturbances, dysautonomia, pain and cognitive changes) and their anatomo-functional bases. Particular empahsis will be placed on the early premotor no motor symptoms since recognition of these early features that predate classic motor symptoms will be important as effective neuroprotective therapy becomes available.

S15.2
The role of serotonin on neuropsychiatric signs in Parkinson's disease

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Parkinson's disease (PD) is a complex disorder with both motor and non-motor symptoms. Besides the dopaminergic neuronal loss, serotonergic neurons from the raphe nuclei also degenerate in PD. The aim of our research was to investigate the causal role of this 5-HT lesion, besides the DA one, on neuropsychiatric symptoms in PD. For that purpose, we developed a macaque model exhibiting a double lesion using MDMA (3,4-methylenedioxy-N-methamphetamine) and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and used multiple approaches (multimodal imaging, behavior and histology) to characterize it. In this talk, I will present the impact of each lesion on neuropsychiatric-like symptoms and more particularly discuss about the involvement of the serotonergic system. I will also discuss clinical stud-

ies indicating that the lesion of the serotonergic system underlies neuropsychiatric signs in parkinsonian patients.

S15.3

Astroglial contribution to neurodegeneration: focus on noradrenergic hypothesis

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Neurons from the noradrenergic nucleus locus coeruleus (LC) play a key neuromodulatory role in the brain. They project axons to the most brain areas and release noradrenaline from their numerous axonal varicosities triggering global excitation by volume transmission. Noradrenaline preferentially activates astrocytes, homeostatic neuroglial cells, enriched with adrenergic receptors. Astroglial adrenergic activation triggers intracellular signals by second messengers Ca^{2+} and/or cAMP, which control astroglial homeostatic functions, including maintenance of brain metabolism. Activation of adrenergic receptors in astrocytes augments aerobic glycolysis and the production of lactate, an important energy fuel that supports neuronal functions, including learning and memory formation. In most neurodegenerative diseases (e.g. Parkinson's and Alzheimer's diseases) one of the first areas undergoing degeneration is the LC. Moreover, altered expression of brain adrenergic receptors has been linked to neurodegeneration, suggesting that impairment of the noradrenergic function represents one of the defining factors of disease progression. Deficits in noradrenergic function may act via altered astroglial function and consequently through dysregulated brain metabolism, exacerbating cognitive abnormalities. By measuring lipid and glucose metabolism in living astrocytes using fluorescent sensors and microscopy, we have recently demonstrated that astroglial adrenergic receptor expression and signaling as well as lipid and glucose metabolism and lactate release are dysregulated in stressed astrocytes that form intracellular protein (e. g. TDP-43) inclusions, a hallmark of neurodegenerative diseases. This may suggest that astroglial capacity to homeostatically support neurons is impaired and that astrocytes most likely contribute to the onset and progression of neurodegeneration, representing a novel target to treat neurodegeneration.

S15.4

Non motor sympthoms and synucleinopathy are associated with c-Rel deficiency in Parkinson's disease

Marina Pizziy[1], Edoardo Parrella[1], Vanessa Porrini[1], Marina Benarese[1], Annamaria Lanzillotta[1], Gaia Faustini[1], Arianna Bellucci[1], Francesca Longhena[1], Giulia Abate[1], Daniela Uberti[1]
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Parkinson's disease (PD) patients manifest a prodromal syndrome that includes olfactory and gastrointestinal dysfunctions years before the frank degeneration of nigrostriatal neurons and appearance of motor symptoms. According to the Braak staging, the onset of non-motor and motor symptoms relates to progressive ascendant diffusion of α-synuclein pathology in the brain.

We recently described that NF-κB/c-Rel deficient mice develop a progressive Parkinson's disease-like phenotype recapitulating both prodromal and motor symptoms as well as neuropathological features in brain regions and nigrostriatal degeneration.

From 2 months of age, c-rel-/- mice display intestinal constipation and olfactory impairment. At 2 months, c-rel-/- mice exhibit α-synuclein accumulation in the colon. Moreover, they develop an age-dependent deposition of fibrillary α-synuclein that, starting at 5 months from the olfactory bulbs, dorsal motor nucleus of vagus and locus coeruleus, reached the *substantia nigra* at 12 months. At this age, the α-synuclein pathology associates with a drop of dopamine transporter in the striatum that anticipates by 6 months the axonal degeneration. These findings support that misregulation of c-Rel protein may lead to Parkinson's disease. With the aim to study c-Rel activity in PD, we found that c-Rel DNA-binding was significantly lower either in post-mortem substantia nigra or peripheral blood mononuclear cells of sporadic PD cases when compared to healthy controls. The findings reinforce the notion that PD is characterized by reduced NF-$\varkappa$B/c-Rel activity. Furthermore, they support that reduced c-Rel DNA-binding could potentially constitute a novel biomarker for Parkinson's disease diagnosis

S16 "Recent advances in the understanding of pain and associated comorbidities"

Chairs: Jacques Noël, Jérôme Busserolles

S16.1
Cross species transcriptomic analysis accelerates insights into the spinal dorsal horn circuitry for persistent pain and the development of novel gene therapies.

Rebecca Seal[1]
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The spinal dorsal horn transforms incoming somatosensory information and transmits it supraspinally to generate modality-specific sensory percepts. Understanding precisely how neurons in this region process somatosensory information in rodents and higher-order species, such as primates, has been hampered by the incomplete identification of individual cell types. In this presentation, I will describe our latest work in which we generated a comprehensive classification scheme for molecularly defined cell types across species-from mouse to primate. To do this we performed single nucleus RNA and ATAC-Seq of the Rhesus macaque dorsal horn and compare to mouse. I will also present our work on spinal dorsal horn circuits important for mechanical allodynia and how the deeper understanding of the cellular and molecular organization is illuminating the pathways and mechanisms as well as allowing for the development of novel gene therapies to treat mechanical pain.

S16.2
Epigenetics, stress and chronic pain

S. M. Géranton[1], M. Maiarù, R. Acton[1], C. G. Bell[1]
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We have recently shown that genetic deletion and pharmacological blockade of the stress regulator FKBP51 alleviate chronic pain states in mice. Importantly, a significant body of work from MacLean and colleagues suggest that genetic variants of *FKBP5* alter pain sensitivity after trauma such as car crash and sexual assault, supporting the idea that FKBP51 drives persistent pain states in humans. Early-life trauma can lead to a decrease in *FKBP5* DNA methylation, an epigenetic change that primes *FKBP5* for hyper-responsiveness and increases the susceptibility to post-traumatic stress disorder (PTSD) in adulthood. We believe that similar processes could underlie the vulnerability to chronic pain. Here, we explored the possibility that long-lasting changes in *FKBP5* DNA methylation could occur following injury or early life adversity, which could respectively maintain persistent pain states and increase the susceptibility to chronic pain. Overall, we found that injury-induced changes in *FKBP5* DNA methylation are unlikely to maintain persistent pain states or to increase the susceptibility to chronic pain. However, early life stress exposure leads to long-term changes in *FKBP5* DNA methylation that could promote the susceptibility to chronic pain in later life.

S16.3
Lysophosphatidylcholine in the serum of obese mice fed with high-fat diet activates Acid-Sensing Ion Channel 3 to sensitize DRG neurons and induce heat pain hypersensitivity

Noël Jacques[1*], Negm Ahmed[1], Stobbe Katharina[2], Fleuriot Lucile[2], Debayle Delphine[2], Deval Emmanuel[1], Lingueglia Eric[1], Rovere Carole[2]
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Diet induced obesity is one of the major causes of obesity worldwide, which affects 13% of the adult population. Obesity is correlated to chronic pain regardless of other components of the metabolic syndrome and type 2 diabetes. Our study focuses on investigating the effect of obesity on peripheral sensory neurons activity and pain perception, followed by deciphering the underlying cellular and molecular mechanisms that involve Acid-Sensing Ion Channel 3 (ASIC3). We show that heat sensitive C-fibers from mice made obese by consumption of a high-fat diet exhibit an increased activity during baseline and upon heating. Obese mice show long-lasting heat pain hypersensitivity once obesity is well established, while mechanical sensitivity is not affected. We show that, in our experimental feeding conditions, the serum of obese mice is enriched with lysophosphatidylcholine species (LPC16:0, LPC18:0 and LPC18:1), which activate ASIC3 channels and increased peripheral neuron excitability. Genetic deletion and in vivo pharmacological inhibition of ASIC3, with the toxin APETx2, protects and rescues mice from obesity-induced thermal hypersensitivity. Our results identify ASIC3 channels in dorsal root ganglion (DRG) neurons and circulating LPC species that activate them as a mechanism contributing to heat pain hypersensitivity associated with high-fat diet induced obesity.

S16.4

TREK-1 channels as pharmacological targets for analgesic drugs in cancer situation

Jérôme Busserolles[1,2], Vanessa Pereira[1,2], Sylvain Lamoine[1,2], Mélissa Cuménal[1,2], Laura Poupon[1,2], Stéphane Lolignier[1,2], Youssef Aissouni[1,2], David Balayssac[1,2], Sylvie Ducki[3], Alain Eschalier[1,2], Emmanuel Bourinet[4]

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The TREK-1 channel is a member of the two-pore domain K^+ (K2P) channels family with background activity. It is expressed in sensory neurons, particularly in nociceptors, and is also broadly distributed in the central nervous system. We have previously demonstrated the role of this channel in polymodal pain perception and its contribution in morphine-induced analgesia in mice. The TREK1 potassium channel is activated downstream of μ receptor and involved in the antinociceptive activity of morphine but not in its adverse effects. Bypassing the μ opioid receptor to directly activate TREK1 could therefore be a safer analgesic strategy. Activating TREK-1, using the non-selective activator Riluzole, exerts analgesic effect in cancer-linked pain situations, namely oxaliplatin-induced neuropathic pain and bone cancer pain in mice. Hence, riluzole's analgesic effect is lost when TREK-1 is genetically or pharmacologically deleted in these cancer situations. Moreover, riluzole induces a TREK-1 dependent antiproliferative effect in human cancer cells and slows down cancer proliferation in cancer mice models.

S17 "Thalamocortical interactions in health and disease"

Chairs: Magor L. Lőrincz, Nathalie Leresche

S17.1

Centrally expressed Cav3.2 T-type calcium channel is critical for the initiation and maintenance of neuropathic pain

Nathalie Leresche[1]

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Cav3.2 T-type calcium channel is a major molecular actor of neuropathic pain in peripheral sensory neurons, but its involvement at the supra-spinal level is almost unknown. The Anterior Pretectum (APT) is a hub of connectivity of the somatosensory system involved in pain perception. In particular APT neurons exert a powerful inhibitory control on higher-order thalamic nuclei. We show that Cav3.2 channels are expressed in a sub-population of APT GABAergic neurons co-expressing parvalbumin (PV). In these PV-expressing neurons, Cav3.2 channels contribute to a high frequency bursting activity, which is increased in the spare nerve injury model of neuropathy. Specific deletion of Cav3.2 channels in APT neurons reduced both the initiation and maintenance of mechanical and cold allodynia. These data are the first direct demonstration that centrally expressed Cav3.2 channels also play a fundamental role in pain pathophysiology.

S17.2

State dependent thalamic activity on various timescales

Magor L. Lőrincz[1]

[1] *University of Szeged, Szeged, Hungary*

The thalamocortical system generates various spontaneous activity patterns in the absence of sensory inputs including rhythmic activities during wakefulness, sleep and epilepsy. Here I will highlight various thalamocortical network mechanism related to the generation, maintenance and termination of various physiological and pathological network oscillations in the thalamocortical system including the state dependence of first order thalamic spontaneous activity, intrinsic and synaptic mechanisms of seizure generation and higher order thalamic mechanisms of seizure generalization.

S17.3

Cortex and Thalamus: The Dangerous Liaisons

Stéphane Charpier[1]

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Absence seizures, a form of non-convulsive epileptic fits that provoke a breakdown in conscious processes, are known to originate from deleterious interactions between neocortex and thalamus. Because these two structures are intricate through bidirectional connections, determining the site of initiation of paroxysmal activity within the cortico-thalamic loop has become a classical "egg-and-hen" problem for both neurophysiologists and clinicians. While the thalamic hypothesis has dominated the debates for a long time, an increasing amount of clinical and experimental data suggest that spike-and-wave discharges (SWDs), the electrical hallmark of absence seizures, are rather triggered in a neocortical zone: the so-called "cortical focus". Specifically, multisite electrophysiological recordings in rodent models of absence epilepsy indicate

that SWDs are initiated in the somatosensory cortex then invade larger neocortical and thalamic territories, causing widespread paroxysmal oscillations. Further multi-scale explorations led to the identification of a population of pyramidal neurons, located in the deep layers of the cortical focus, endowed with a set of potentially pro-epileptic properties. This includes: an excessive membrane depolarization, an elevated firing rate and an augmented intrinsic excitability. Moreover, the time-to-time instability of intrinsic excitability and sensory responsiveness of ictogenic neurons in the course of the seizure could account – at least in part – for the main symptom of absences: a lack of conscious perceptual experience. Many aspects of the tumultuous relations between cortex and thalamus still remain mysterious, in particular the very initial neuronal changes precipitating the local initiation of paroxysms and the mechanisms responsible for seizure termination. This will be discussed.

S17.4
The role of the thalamoamygdalar routes in associative learning

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Behavioural responses to environmental stimuli like a threat are evolutionarily adaptive actions mediated by the amygdala. It relies on the perception of external, sensory cues and internal arousal-related signals. These signals can be processed by distinct thalamic nuclei and transferred to the amygdala. By integrating behavioural, in vivo electrophysiological, anatomical and optogenetic approaches in mice, we investigate how the arousal-coding midline and the fear-associated multisensory lateral thalamic inputs can shape the individual intra-amygdalar networks. Currently, a serial information flow travelling through a single amygdala route (lateral amygdala → basolateral amygdala → central amygdala → subcortical centres) is widely accepted mediating motor and/or autonomic actions, in which thalamic signals are predicted to latch on. Based on our unpublished observations and the contradictions in the literature data, we challenge this view and propose the existence of multiple and segregated intra-amygdalar circuits driven by individual thalamic inputs. Our research is to clarify the complexity of the thalamo-amygdalar communication and broaden our understanding about amygdala-mediated adaptive and maladaptive brain functions.

S17.5
On the variability of thalamic computational units

László Acsády[1]
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Inputs to thalamus display perplexing heterogeneity in source, transmitter and the complexity of axon terminals. Almost the entire neuraxis provides excitatory and/or inhibitory terminals to the thalamus. The structure of both glutamatergic and GABAergic inputs varies from simple unisynaptic to highly complex multisynaptic terminals. Variable bouton structures support neurotransmission with different kinetics. Since the majority of thalamic inputs are confined only to a portion of the structure the emerging picture is that inputs can be integrated in many distinct ways in different thalamic territories. As a consequence, unlike in modular networks (like striatum, cerebellum or hippocampus) no canonical thalamic module can be defined. The reason for this unique complexity is presently unclear but the lack of canonical input organization in the thalamus certainly limits the opportunity of generalizing thalamic transfer function between territories. Deciphering the role of thalamus requires the understanding of the diversity in thalamic input integration in each region.

S18 "Microbiome News and Views"

Chair: Illana Gozes

S18.1
Gut microbiota and Pituitary adenylate cyclase-activating polypetide (PACAP) — lessons learnt from murine infection and inflammation models

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Pituitary adenylate cyclase-activating polypeptide (PACAP) constitutes a neuropeptide that is widely distributed in the host exerting essential cytoprotective properties, whereas PACAP$^{-/-}$ mice display increased susceptibility to distinct immunopathological conditions. The orchestrated interplay between the gut microbiota and the host is pivotal in immune homeostasis and resistance to disease. In order to assess potential PACAP dependent gut microbial perturbations we performed a comprehensive survey of the intestinal microbiota composition in PACAP$^{-/-}$ and wildtype mice starting 2 weeks post-partum until 18 months of age applying quantitative culture-independent techniques. Fecal enterobacteria

and enterococci were lower in PACAP$^{-/-}$ than wildtype mice aged 1 month and $\geq$6 months, respectively. Strikingly, health-beneficial bifidobacteria were virtually absent in the intestines of PACAP$^{-/-}$ mice, even when still breast-fed. Furthermore, wildtype mice were perorally subjected to high or low dose Toxoplasma gondii in order to induce peracute or subacute ileitis, respectively, and treated intraperitoneally with synthetic PACAP. As compared to placebo controls, PACAP treatment was not only accompanied with less distinct pro-inflammatory immunopathological responses in intestinal, extra-intestinal and even systemic compartments, but also with less distinct gut microbiota shifts characterized by higher ileal numbers of bifidobacteria and lactobacilli. We conclude i.) that PACAP deficiency is accompanied by distinct changes in gut microbiota composition with virtually absent bifidobacteria as a major hallmark that might be linked to increased susceptibility to disease and furthermore, ii.) that synthetic PACAP treatment dampens murine ileitis and iii.) that this anti-inflammatory effect is accompanied with higher intestinal loads of probiotic bacteria including bifidobacteria and lactobacilli.

S18.2

Metabolic, gut microbiota composition and behavioral changes induced by altered fat-to- sugar ratio upon a dietary challenge

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Carbohydrates and fats serve as the body's main source of energy. We hypothesized that combination of these two macronutrients in the right ratio is crucial for proper metabolic function, microbiome composition and behavior.
To investigate the effects of diets with different carbohydrate-to-fat ratios, C57Bl/6 mice were fed standard chow diet (STAND), high sugar diet/Western diet (HSD), high fat diet (HFD), or ketogenic diet (KD) for eight weeks. After only one week, mice in HSD and HFD groups gained significantly more weight compared to STAND group, indicating that carbohydrate-to-fat ratio affects the kinetics of weight gain in mice. However, all mice consumed the same amount of calories over week. Possible reason was elevated non-fasting blood glucose level in HSD group, which may have influenced energy storage in adipose tissue. HFD and HSD diets had a high glycemic load due to their high sugar content. When combined with high amounts of saturated fat, they cause excessive fat gain. Therefore, no/low carbohydrate KD diet does not induce an insulin peak, which prevents fat sequestration in adipose tissue and results in increased energy expenditure.
Diets strongly effected composition of gut microbiota. High sugar and fat diets reduced microbiome diversity which may disturb host energy homeostasis and lead to obesity.
Furthermore, HSD and HFD may have contributed to cognitive decline in mice. Complex learning task involving spatial and procedural memory in the IntelliCage was used. Mice fed HSD and HFD showed poorer rule-based learning, suggesting that these diets may negatively affect learning of difficult tasks.

S18.3

A cross-talk between the microbiome and the brain: the ADNP autism syndrome and therapeutic development as a case study

Illana Gozes[1], Gidon Karmon[1], Oxana Kapitansky[1], Alexandra Lobyntseva[1], Eliezer Giladi[1], Stefan Bereswill[2], Markus M. Heimesaat[2]
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The microbiome literature has surged up in recent years, as it is tightly connected with our well-being. Signatures for brain disorders have been searched for, and as such autism has been connected to changes in the gut microbiota composition. Here, we focus on one of the single gene de novo mutation autism and intellectual disability, namely the activity-dependent neuroprotective protein (ADNP) syndrome. We have discovered ADNP over 20 years ago and we have later shown that it is essential for the development of the brain and the hematopoietic system. Regulating hundreds of genes, ADNP is of critical function in ADNP syndrome patients. We asked if in mouse models mimicking the ADNP syndrome there is a change in the microbiota composition, and if this change can be corrected by treatment with the ADNP fragment (eight amino acids), replacement drug treatment, NAP. Our results discovered a microbiota signature in our Adnp haploinsufficient mouse model, indicating correlation with behavior and correction by NAP treatment. Dramatic sexual differences were observed, necessitating gender separation and evaluation. Our recent results in a CRISP-Cas9, Adnp-mutated mouse model, harboring a highly prevalent human ADNP mutation also showed marked sex differences, genotype associated deficiencies and correction by NAP treatment. Interestingly,

both models show a change in the *Bifidobacterium genus (BIF)* coupled with NAP corrective effects in agreement with our previous findings, with increased probiotic commensal bifidobacterial loads in the ileal lumen of NAP-treated inflamed mice displaying dampened inflammatory responses.

S19 "Understanding the role of GPCR heteroreceptor complexes and their adaptor proteins in the neuronal networks of the brain in health and mental disorders"

Chairs: Dasiel O. Borroto-Escuela, Patrizia Ambrogini

S19.1
GPCR heteroreceptor complexes and their adaptor proteins give new integrative mechanisms that may go wrong in Parkinson's disease, schizophrenia and cocaine use disorder

Kjell Fuxe[1], Patrizia Ambrogini[2], Karolina Wydra[3], Sarah Beggiato[4], Manuel Narvaez[5], Malgorzata Frankowska[3], Luca Ferraro[4], Malgorzata Filip[3], Dasiel Borroto-Escuela[1]
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The concept of allosteric receptor-receptor interactions in which GPCR homo-and heteroreceptor complexes, in which they physically interact with each other and adaptor proteins, provides a new dimension to molecular integration in the CNS. Interactions through allosteric mechanisms dynamically alter recognition, pharmacology, signaling and trafficking of the receptor protomers that include e.g. also ionotropic receptors and receptor tyrosine kinases. Allosteric mechanisms come together with phosphorylation and dephosphorylation mechanisms to optimize the molecular integration of dynamic receptor complexes in the synaptic and extra-synaptic membranes necessary for CNS function and especially for learning and memory. It may involve the reorganization of homo-heteroreceptor complexes into novel transient synaptic receptor complexes, representing a short-term memory that can become consolidated into stabilized synaptic receptor complexes (molecular engram) forming a long-term memory. It may involve the binding of soluble molecules, derived from the transient molecular engram, to transcription factors modifying their transcriptional activity into forming novel adaptor proteins. By binding to the novel transient heteroreceptor complex these novel adaptor proteins can stabilize this complex in various ways leading to the formation of a long-term memory. A2AR-D2R heterocomplexes are implicated in Parkinson's disease. These complexes can become reorganized upon chronic treatment with levodopa in Parkinson's disease leading to wearing off of the therapeutic actions. Multiple A2AR-D2R heterocomplexes in the ventral striatal-pallidal GABA neurons instead play a role in schizophrenia through the allosteric inhibition produced by A2AR activation of the D2R protomer function. A2AR-D2R complexes in this pathway also play a significant role in cocaine and morphine use disorders.

S19.2
D2-DISC1 protein complexes and their relevance for schizophrenia

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Current antipsychotic drugs primarily target dopamine D2 receptors (D2Rs), in conjunction with other receptors such as those for serotonin. However, these drugs have serious side effects such as extrapyramidal symptoms (EPS) and diabetes. Identifying a specific D2R signaling pathway that could be targeted for antipsychotic effects, without inducing EPS, would be a significant improvement in the treatment of schizophrenia. We report here that the D2R forms a protein complex with Disrupted in Schizophrenia 1 (DISC1) that facilitates D2R-

mediated glycogen synthase kinase (GSK)-3 signaling and inhibits agonist-induced D2R internalization. D2R-DISC1 complex levels are increased in conjunction with decreased GSK-3α/β (Ser21/9) phosphorylation in both postmortem brain tissue from schizophrenia patients and in Disc1-L100P mutant mice, an animal model with behavioral abnormalities related to schizophrenia. Administration of an interfering peptide that disrupts the D2R-DISC1 complex successfully reverses behaviors relevant to schizophrenia but does not induce catalepsy, a strong predictor of EPS in humans.

S19.3

On the balance of D2R-MOR and D4R-MOR in the dorsal and ventral striatum. Putative link to morphine dependence and addiction.

Ramon Fores-Pons[1], 2, Manuel Narvaez[1], Lakshmi Vasudevan[3], Minerva Crespo-Ramirez[4], Alicia Rivera[5], Miguel Perez de la Mora[4], Christophe Stove[3], Kjell Fuxe[2] and Dasiel O. Borroto-Escuela[2]

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The widespread distribution of heteroreceptor complexes with allosteric receptor-receptor interactions in the CNS represents a novel integrative molecular mechanism in the plasma membrane of neurons and glial cells. It was proposed that they form the molecular basis for learning and short-and long-term memories. This is also true for drug memories formed during the development of substance use disorders like morphine and cocaine use disorders. Herein, we discuss and propose how an increase in opioid heteroreceptor complexes, containing MOR-DOR, MOR-D4R and MOR-D2R, and their balance with each other and A2AR-D2R complexes in the striatal-pallidal enkephalin positive GABA antireward neurons, may represent markers for development of morphine use disorders. We suggest that increased formation of MOR-DOR complexes takes place in the striatal-pallidal enkephalin positive GABA antireward neurons after chronic morphine treatment in part through recruitment of MOR from the MOR-D2R and/or MOR-D4R complexes due to the possibility that MOR upon morphine treatment can develop a higher affinity for DOR. As a result, increased numbers of D2R monomers/homomers in these neurons become free to interact with the A2ARs found in high densities within such neurons. Increased numbers of A2AR-D2R heteroreceptor complexes are formed and contribute to enhanced firing of these antireward neurons due to loss of inhibitory D2R protomer signaling which finally leads to the development of morphine use disorder. Altogether, we propose that these altered complexes could be pharmacological target to modulate the reward and the development of substance use disorders.

S19.4

On the role of GPCR heteroreceptor complexes neuromodulation of the Claustrum

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G protein-coupled receptors (GPCRs) modulate the synaptic glutamate and GABA transmission of the claustrum. Our work focused on the transmitter-receptor relationships in the claustral catecholamine system and receptor-receptor interactions between kappa opioid receptors (KOR), dopamine receptor (D1R, D2R and D4R) and SomatostatinR2 (SSTR2) in claustrum. Methods used involved immunohistochemistry and in situ proximity ligation assay (PLA) using confocal microscopy. Double immunolabeling studies on D1R and tyrosine hydroxylase (TH) immunoreactivities (IR) demonstrated that D1R IR existed in almost all claustral and endopiriform nucleus nerve cell bodies, known as glutamate projection neurons, and D2R and D4R IR in large numbers of nerve cell bodies of the claustrum and endopiriform nucleus. However, only a low to moderate density of TH IR nerve terminals was observed in the endopiriform nucleus versus de few scattered TH IR terminals found in the claustrum. These results indicated that dopamine transmission in the rat operated via long distance dopamine volume transmission in the rat claustrum and endopiriform nucleus to modulate claustral-sensory cortical glutamate transmission. Large numbers of these glutamate projection neurons also expressed KOR and SSTR2 which formed KOR-SSTR2 together with D2R heteroreceptor complexes. The findings indicate that the sensory cortical glutamate drive on the glutamate claustral-cortical projection neurons is modulated by GPCRs and their receptor complexes located in the plasma membrane of these glutamate projection neurons. This can give the sensory cortical regions significant help in deciding on the salience to be given to various incoming sensory stimuli.

S19.5

5-HT1A-FGFR1 heteroreceptor complexes and their allosteric receptor-receptor interactions in the hippocampus. Relevance for major depression and its treatment.

Patrizia Ambrogini[1], Davide Lattanzi[1], Marica Pagliarini[1], Stefano Sartini[1], Riccardo Cuppini[1], Kjell Fuxe[2], Dasiel Oscar Borroto-Escuela[2]

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Major depression (MD) is one of the most devastating illnesses, and current therapies are limited. One of the emerging concepts in MD is that disturbances in the integrative allosteric receptor–receptor interactions in specific serotonin 5-HT1A heteroreceptor complexes may contribute to causing major depression and become novel targets for its treatment. Disruption and/or dysfunction in the 5-HT1A-FGFR1 heteroreceptor complexes in the raphe-hippocampal serotonin neuron systems has been demonstrated to participate to the development of MD, by modulating neuron excitability. Indeed, neurophysiological studies in our group have provided evidence that in Sprague-Dawley rats FGFR1 agonists substantially reduce the 5-HT1A receptor-induced opening of the GIRK channels in the 5-HT1AR positive pyramidal glutamate neuron cell bodies of the CA1 and CA2 fields of the dorsal hippocampus. The putative molecular mechanism is an antagonistic allosteric interaction in the 5-HT1AR-FGFR1 complex through which the agonist-activated FGFR1 protomer induces a conformational change in the 5-HT1AR protomer, reducing its ability to open GIRK channels. This mechanism is probably also in operation in the 5-HT1A auto-receptor-FGFR1 complex in the midbrain raphe neurons. These results open new possibilities to develop other rapid antidepressant drugs similar to ketamine, namely brain permeable FGFR1 agonists, which have, besides trophic actions, also the ability to rapidly reduce the 5-HT1A auto-receptor signaling in the ascending serotonin neurons from the midbrain. Such drugs should also contribute to development of rapid antidepressant effects of serotonin selective reuptake inhibitors.

S20 "Drug addiction: From circuits to molecules"

Chair: Rami Yaka

S20.1

The role of different ventral pallidal projection neurons in abstinence from cocaine

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The ventral pallidum (VP) is a central hub in the reward circuitry receiving mainly GABAergic inputs from the nucleus accumbens (NAc) and projecting to a variety of brain regions within and outside of the basal ganglia. Most research of the role of the VP in reward and addiction treats the VP as a uniform structure without differentiating between different cell populations. Recent studies reveal that different genetically-defined neuronal populations of the VP (i.e. glutamatergic neurons, Npas1-expressing neurons, parvalbumin-expressing neurons) have different influence on reward seeking but it is not yet known whether VP neurons that project to different targets have different roles in reward seeking and addiction. In my talk I will present recent data showing that different projections of the VP, even of the same cell type, may have different and even opposite roles in drug reward. I will show that inhibiting a specific VP projection can increase drug reward while inhibiting a different projection can decrease drug reward. I will also show that after cocaine exposure and abstinence the same neuronal type can show strengthening or weakening of its synapses depending on the target of that neuron. This work shows that the role of the VP in encoding drug reward depends on the projection target and future research should take this information into account when manipulating or recording from VP neurons.

S20.2

Distinct (but not necessarily opposing) roles of nucleus accumbens D1- and D2-neurons in behavior

Ana João Rodrigues[1]

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The nucleus accumbens (NAc) is a key player in reward-related behaviors and in addiction. NAc privileged anatomical position, integrating information from cortical and limbic structures, allows to convey pertinent motivational information, directing behavior. NAc medium spiny neurons (MSNs), segregated into those that express dopamine receptor D1 or D2, have received particular attention because drugs of abuse elicit long-lasting synaptic and molecular changes in these neuronal populations.

D1-MSNs have been associated with positive reinforcement and reward, whereas D2-MSNs neurons are associated with negative reinforcement and aversion. Yet, recent studies, including from our team, questioned this functional dichotomy.

We will show that by differentially controlling the activation pattern of either type of nucleus accumbens MSNs,

one can trigger both reward and aversion. Brief optical activation of either population elicits positive reinforcement, whereas prolonged activation induces aversion. This bidirectional effect was associated with distinct electrophysiological effects in downstream regions, namely the VTA and the ventral pallidum. Importantly, the effects of brief and prolonged D1- or D2-MSN stimulation were different in the context of cocaine conditioning, suggesting a differential contribution of these neuronal populations in cocaine reinforcement.
We will further show that even for the same type of MSN, distinct subpopulations exist that respond differently to reward.
Our data suggests that additional studies are needed to better dissect the role of each MSN population in behavior.

S20.3
Mesolimbic dopamine dysregulation as a signature of aberrant salience attribution imposed by prenatal THC exposure

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Cannabis is the illicit drug most widely used by pregnant women worldwide. Its growing acceptance and legalization have markedly increased the risks of child psychopathology, including psychotic-like experiences, which lowers the age of onset for a first psychotic episode. As the majority of patients with schizophrenia go through a premorbid condition long before this occurs, understanding neurobiological underpinnings of the prodromal stage of the disease is critical to improving illness trajectories and therapeutic outcomes. We have previously shown that male rat offspring prenatally exposed to Δ9-tetrahydrocannabinol (THC), a rat model of prenatal cannabinoid exposure (PCE), exhibit extensive molecular and synaptic changes in dopaminergic neurons of the ventral tegmental area (VTA), converging on a hyperdopaminergic state. This leads to a silent psychotic-like endophenotype that is unmasked by a single exposure to THC. Here, we further characterized the VTA dopamine neuron and sensorimotor gating functions of PCE rats exposed to acute stress or a challenge of the D2 receptor agonist apomorphine, by using in vivo single-unit extracellular recordings and Prepulse Inhibition (PPI) analyses. At pre-puberty, PCE male rat offspring display a reduced population activity of VTA dopamine neurons in vivo, the majority of which are tonically active. PCE male progeny also exhibit enhanced sensitivity to dopamine D2 (DAD2) receptor activation and a vulnerability to acute stress, which is associated with compromised sensorimotor gating functions. This data extends our knowledge of the multifaceted sequelae imposed by PCE in the mesolimbic dopamine system of male pre-adolescent rats, which renders a neural substrate highly susceptible to subsequent challenges that may trigger psychotic-like outcomes.

S20.4
The impact of cocaine exposure on mitochondrial dynamics

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The incidence of cocaine abuse is increasing especially in the UK where the rates are among the highest in Europe. In addition to its role as a psychostimulant, cocaine has profound effect on brain energy metabolism, altering glycolysis and impairing oxidative phosphorylation. Cocaine exposure alters metabolic gene expression and protein networks in brain regions including the prefrontal cortex, the ventral tegmental area and the nucleus accumbens. Furthermore, indirect cocaine exposure in utero is reported to impair the brain metabolic profile of the offspring. The goal of this talk is to highlight how exposure to cocaine alters mitochondrial function, examining effects on mitochondrial fission and fusion as well as biogenesis and mitophagy. Using *in vitro* techniques we have determined that these molecular effects are cell-type specific, depending on, for example, whether the exposure was direct or indirect. In vivo, the impact of acute and chronic cocaine paradigms on mitochondria dynamics are also investigated. Overall, the consequences of cocaine-mediated mitochondrial dysfunction include impaired bioenergetics, oxidative stress and cell death. As such, therapies maintaining mitochondrial functional integrity may hold promise in mitigating cocaine pathology and addiction.

S20.5
Molecular mechanism underlying the action of Zeta Inhibitory Peptide as memory eraser

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Upregulation of the glutamate type AMPA receptors (AMPARs) is one of the important factors that plays role in the mechanisms of formation and maintenance of long-term memory. Until recently, constitutively act-

ive protein kinase M-Zeta (PKMZ) believed to be essential and sufficient factor that drives AMPARs to the synaptic membrane and prevents their endocytosis. Zeta Inhibitory Peptide (ZIP) is a short peptide that mimics the regulatory site of PKMZ and originally synthetized as PKMZ inhibitor. Recent findings show that the activity of ZIP preserved even in the absence of PKMZ via unknown mechanism. In addition, scrambled ZIP (scrZIP), which contains the same amino acids as ZIP, but in a random sequence, has shown to act similar to ZIP. We hypothesized that mechanism of action of ZIP is independent of PKMZ (fully or partly) and may involve direct effects on AMPARs that are independent of PKMZ. We found that ZIP induces redistribution of the AMPAR-GluA1 in HEK293 cells and primary cortical neurons, and decreases AMPAR-mediated currents in the nucleus accumbens (NAc). These effects were mimicked by free arginine or by a modified ZIP in which all but the arginine residues were replaced by alanine. Redistribution was blocked by a peptidase-resistant version of ZIP and by treatment with the nitric oxide (NO)-synthase inhibitor L-NAME. ZIP increased GluA1-S831 phosphorylation and ZIP-induced redistribution was blocked by nitrosyl-mutant GluA1-C875S or serine-mutant GluA1-S831A. Introducing the cleavable arginine-alanine peptide into the NAc attenuated expression of cocaine-conditioned reward. Together, these results suggest that ZIP may act as an arginine donor, facilitating NO-dependent downregulation of AMPARs, thereby attenuating learning and memory.

S21 "Sex differences in the neurobiology of Motivated Behaviors"

Chairs: Mohamed Kabbaj, Zuoxin Wang

S21.1
Sex differences in an epigenetic feedback mechanism underlying effects of exercise in memory formation

Marcelo A. Wood[1], Ashley Keiser[1]
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It is clear world wide that aging populations will have a significant impact on health systems considering 16-20% of current individuals over 65 years of age are predicted to become cognitively impaired. In addition to age, another major risk factor for dementia is sedentary behavior, which unlike aging is the top modifiable risk factor for Alzheimer's disease (AD). We and others have shown that exercise has numerous benefits for brain health, including learning and memory. One key molecular mechanism underlying normal learning and memory is epigenetic regulation of gene expression. In the past decade, our studies and numerous others have demonstrated that dysregulation of epigenetic mechanisms leads to cognitive impairment throughout the lifespan, and conversely, ameliorating the dysregulation improves cognition. The epigenome represents a signal transduction platform that is capable of encoding experience (e.g. exercise) and current metabolic states (because nearly every epigenetic modification is a metabolite) to establish stable changes in cell function that lead to long-term changes in behavior. Understanding the interplay between exercise, epigenetics and metabolism may reveal novel insight into age-related memory processes and new approaches to ameliorating cognitive decline in AD. We have identified a molecular feedback loop involving specific histone modifications, metabolic mechanisms affecting histone modification, and gene expression required for memory formation. This epigenetic feedback loop is modulated by exercise, becomes dysregulated in the aging brain, and may have features that are sex-specific.

S21.2
Transcriptomic regulations associated with individual differences in paternal care in prairie voles

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Early life experiences, including parental care, shape an individual's response to its environment in adulthood and represent a critical risk factor for a variety of neuropsychiatric disorders. Although the involvement of maternal care is well-documented, it is important to recognize that fathers also display paternal care towards their young. Surprisingly, however, we know relatively little about the neurobiology of paternal behaviors. The socially monogamous prairie vole (Microtus ochrogaster) has emerged as a useful model for the study of complex social behaviors including paternal care, as both mothers and fathers care for their offspring. Interestingly, some sexually-naive males spontaneously exhibit paternal behaviors when exposed to pups (Paternal), whereas others show aggression (Attackers), highlighting individual differences in the expression of paternal behaviors in prairie voles. To identify the underlying molecular mechanisms, we conducted an unbiased analysis of the transcriptomic profiles by RNA sequencing in the medial preoptic area (MPOA), lateral septum (LS), and nucleus accumbens (NAc) of Paternal and At-

tackers males, alongside fathers, and mothers. Overall, between-structures differences in gene expression vastly exceeded between-phenotypes differences, highlighting a distinct transcriptome in each structure. Nevertheless, we found structure-specific differences in gene expression between phenotypes, revealing gene-sets associated with cohabitation with an opposite-sex partner in the NAc, sex differences in the MPOA, and individual differences in paternal behaviors within sexually-naive males in the LS. Furthermore, these sets of genes were related to distinct biological pathways. Altogether, these observations uncover novel sets of candidate genes associated with paternal behaviors in prairie voles.

S21.3

Early maternal care at the core of the sex-dimorphic intergenerational transmission of the maladaptive response to stress in the perinatally stressed rats

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The programming of brain development and behavioral responses is shaped by a complex interaction between genes and environment and stressful events occurring during prenatal and early post-natal life (e.g. perinatal period) alter the programming of the developmental trajectory of the offspring. We have shown that exposure to perinatal stress (PRS) in rats induces long-term alterations that are predicted by the reduced maternal behavior as a consequence of gestational stress. We examined the intergenerational effect of PRS by mating first-generation (F1) PRS female rats with naïve males and exploring the phenotype of F1 and F2 offspring. The risk-taking behavior associated with stress/ anti-stress neurobiological alterations observed in the PRS model (F1) persisted in the second-generation (F2), despite the fact that the offspring was not directly exposed to stress in utero. Both F1 and F2 generations also displayed prolonged corticosterone response to stress, increased BDNF levels, reduced mGlu2/3 receptor expression, and lower synaptic proteins expression in the hippocampus. The phenotype of F1 and F2 offspring was associated with reduced maternal behavior of both mothers (F1) and grandmothers (F0). Because of the well known role of the maternal care on inducing epigenetic transmissible effects to the second generation, we then focused on epigenetic modifications induced by maternal care and behavior and we identified differential gene expression patterns transmitted across F1 and F2 generations and key canonical pathways via IPA analysis involved in glutamatergic synaptic transmission, in the balance between stress and anti-stress systems and in protein post-translational glycosylation. Methylation of MR and BDNF genes was increased and decrease respectively by the grandmother's stress in both F1 and F2 generation. Carbetocin post-partum treatment inducing increased maternal care reversed the long term effects induced by PRS in the offspring indicating a crucial role played by the maternal care in the imprinting of the HPA axis of the offspring. Overall, epigenetic mechanisms lie at the core of the synaptic and neuroendocrine changes induced by perinatal stress and are transmitted intergenerationally via maternal behavior. These puts in highlight epigenetic programming of the response to stress in the offspring depending on maternal care.

S21.4

Exon-specific histone modifications of hippocampal Bdnf underlie individual variations and sex differences in stress susceptibility

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Chronic stress can cause depression in susceptible individuals, however, the underlying mechanisms remain elusive. Chronic unpredictable stress (CUS) and chronic social defeat stress (CSDS) are two widely used animal models to induce behavioral deficits. We investigated exon-specific expression of brain-derived neurotrophic factor (Bdnf) and histone modifications at individual Bdnf promoters in the hippocampus following CUS and CSDS. CUS downregulated Bdnf mRNA expression in the hippocampus of susceptible, but not resilient, mice, with sex differences in exon-specific expression patterns associated with histone acetylation and methylation at individual promoters. CSDS also decreased hippocampal Bdnf expression but showed no difference between susceptible and resilient subgroups. Furthermore, while female mice were more sensitive than male mice to CUS, male mice exhibited more persistent behavioral phenotypes than female mice. These results suggest that expression of exon-specific Bdnf transcripts in the hippocampus may contribute to sex and individual differences in stress susceptibility.

S21.5

Converging circuit and molecular mechanisms with opioid and stress exposure

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Prolonged abstinence from opioids or stress exposure both cause negative affective outcomes. Use of the synthetic opioids, fentanyl, is on the rise causing a major societal health issue including deadly outcomes by overdose. Despite these synergistic behavioral states in stress exposure and prolonged opioid abstinence there is limited research into overlapping neurobiological mechanisms. Previously we demonstrated that repeated social stress leads to reduced dendritic complexity in nucleus accumbens (NAc) dopamine receptor 1 (D1)-medium spiny neurons (MSNs). To investigate behavioral and MSN subtype specific adaptations in fentanyl abstinence, we established a paradigm where mice underwent 5 days of fentanyl (10ug/ml) in their drinking water or water for control conditions followed by 10 days of abstinence. We observed enhanced stress susceptible behavior in fentanyl abstinent males. Fentanyl abstinent mice of both sexes display enhanced anxiety-like and reduced social preference behaviors. Accompanying these negative behavioral states, we observe reduced D1-MSN dendritic complexity in both sexes. To uncover molecular mediators of these structural changes we performed RNA-seq on mRNA from D1-MSNs and from D2 receptor expressing MSNs. D1-MSNs display more differentially enriched genes in fentanyl abstinent mice compared to controls. Network analysis identified 11 cell subtype modules associated with fentanyl, 9 D1-MSN modules and 2 D2-MSN modules. Many modules included molecules related to dendritic structure and plasticity. These findings have implications for understanding the neurobiological mechanisms underlying negative behavioral states, in both sexes, that can trigger opioid intake in individuals suffering from chronic and relapsing opioid use disorder.

S22 "New insights on endocannabinoid regulation of fear memory dynamics: from bench to bedside"

Chair: Maria Morena

S22.1

Endocannabinoid system and regulation of stress-effects on fear memory processes

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Stress has a profound impact on memory functions and neuromodulatory systems activated by stress, such as endocannabinoids, are crucial regulators of stress-related behavioral responses and fear memory processes. Accumulating evidence indicates that acute stress alters endocannabinoid brain levels and synaptic plasticity within different fear-related brain regions, including the amygdala and hippocampus, which play a central role in modulating fear memory function. Altered fear memory processing represents the hallmark symptom of Post-Traumatic Stress Disorder (PTSD), as PTSD patients present over-consolidation and excessive recall of traumatic memory and are resistant to fear extinction, among other symptoms. Findings will be presented on how endocannabinoids modulate different phases and types of fear memory in limbic brain regions and how stress can influence these mechanisms, at the synaptic and behavioural level. Collectively, findings presented here help to elucidate the neural underpinnings of the fine-tuned regulation of limbic neurocircuitry involved in modulating the impact of stress on fear memory processes, thus facilitating the discovery of novel endocannabinoid-based therapeutic interventions for the treatment of memory alterations associated with PTSD.

S22.2

Endocannabinoid circuit modulation of aversive memory

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The endocannabinoid (eCB) system is a focus of preclinical and clinical research because of its purported role in multiple behavioral functions and neuropsychiatric disease states, including anxiety disorders and other conditions resulting from aberrant responses to stress. Intriguingly, components of the eCB system that offer potential druggable targets for new anxiolytic medications, including selectively amplifying eCBs recruitment by interfering with eCB-degradation, via fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) – both of which manipulations have been linked to reductions in anxiety-like behaviors in rodents and variation in human anxiety symptoms. However, while there is evidence that these effects are produced by modifying activity in prefrontal cortical and amygdalar regions, the precise neural circuit basis of eCBs effects on therapeutically relevant behaviors such as fear extinction remains unclear. This presentation will discuss potential approaches to using circuit-based preclinical research to identify tractable paths to developing novel compounds that could prove

useful for treating trauma-related and anxiety disorders.

S22.3
TRPV1 signaling as a mediator of sex-dependent fear generalization

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Abstract main text: Women are twice as likely as men to develop Post-Traumatic Stress Disorder (PTSD) after a trauma, but the neurobiological basis for this discrepancy is poorly understood. One hallmark symptom of PTSD is a re-experiencing of the trauma in safe situations, a "generalization" phenomenon that can be studied using preclinical rodent models like Pavlovian fear conditioning. We are currently investigating the role of endocannabinoids in modulating fear generalization in both male and female rats. First, we found that auditory fear conditioning itself induced a selective increase in hippocampal AEA levels in female rats, but not males. Next, we found that systemic pharmacological blockade of the endocannabinoid CB1 receptor during fear conditioning produced robust context generalization in female rats, but not males. We were then able to block this effect by co-administering an antagonist to the transient receptor potential vanilloid 1 (TRPV1), a cation channel that can be bound by AEA. These intriguing preliminary data suggest that sex-specific behavioral effects of CB1 blockade may be due to AEA actions at TRPV1. We are following up this behavioral work with investigations into sex differences into TRPV1 membrane trafficking and presynaptic CB1 expression at amygdala-projecting hippocampal neurons, a circuit likely to be involved in fear generalization.

S22.4
The endocannabinoid system as a target for stress-related psychiatric disorders: evidence from healthy and clinical human populations

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The endocannabinoid system is proposed to function as a stress buffer, mitigating the negative consequences of stress. Targeting the endocannabinoid system also promotes the extinction of fear memories in animal models. Thus, modulating endocannabinoid function may serve as a novel treatment approach in trauma-related psychiatric disorders such as post-traumatic stress disorder (PTSD). In a series of studies, we have begun to characterize the role of endogenous cannabinoid signaling in stress and affective processing in humans, with the long-term goal of determining whether the endocannabinoid system constitutes a novel pharmacotherapeutic target for PTSD. We have found that elevated levels of the endogenous cannabinoid ligand anandamide are associated with greater recall of fear extinction, reduced stress reactivity, and enhanced regulation of negative affect in healthy humans. We subsequently assessed the individual and additive effects of childhood trauma exposure and substance use disorder (SUD) development on endocannabinoid levels and related stress and affective processing. Preliminary analysis suggests that elevated anandamide in some trauma-exposed individuals may protect against subsequent SUD development, as well as impairments in affective processing. Finally, we are currently testing whether augmenting endocannabinoid signaling together with internet-delivered prolonged exposure therapy can improve symptoms in a PTSD population. Together, this work provides novel insights into endocannabinoid function in humans and its potential therapeutic utility in clinical populations.

S23 "Sex differences in motivated behaviors and their regulation by stress"

Chair: Debra Bangasser

S23.1
Sex differences in the role of GPER-1 in motivated behaviors

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Females exhibit a greater response to psychomotor stimulants than males due to the gonadal hormone estradiol (E2). E2 enhances drug-seeking and the rewarding properties of cocaine for females, but the role of E2 in male drug-seeking is not well understood. E2 binds to one of three types of E2 receptors (ER)s: alpha (α), beta (β), or G-protein receptor-1 (GPER-1). Most of what we know about the sites and mechanisms of actions of E2 is from work on ERα and ERβ. Recent work has found that GPER-1 is also important for behavior in males and females. In males, we find that activation of G-protein coupled E2 receptor 1 (GPER1), via administration of ICI 182,780 or the GPER-1 agonist G1, attenuated conditioned place preference for 10mg/kg cocaine, while inhibition of GPER1, via G15, enhanced preference at a 5mg/kg cocaine dose. Similarly, GPER1 activation, via G1, prevented males from forming a preference for 0.1%

saccharin versus plain water. In a second study, we investigated the contribution of GPER1, on drug-seeking via administration of G1 into the dorsolateral striatum (DLS) of female and male rats. We find that G1 treated females had a significantly greater breaking point than control treated females. While prior G1 treatment did not alter extinction rates, G1 treated females did have greater drug-induced reinstatement (10mg/kg cocaine (i.p.). However, there was no effect of intra-DLS G1 treatment on males' breaking points, rates of extinction or drug-induced reinstatement. These data suggest that GPER-1 differentially regulates motivation for cocaine in males and females.

S23.2
Microglial contributions to nicotine dependence.

Dr. Jill R Turner[1]
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Smoking is the largest preventable cause of death and disease in the United States. However, <5% of quit attempts are successful, underscoring the urgent need for novel therapeutics. Microglia are one untapped therapeutic target. While previous studies have shown that microglia mediate both inflammatory responses in the brain and brain plasticity, little is known regarding their role in nicotine dependence and withdrawal phenotypes. In this presentation, we will present evidence of dramatic alterations in microglial morphology during nicotine withdrawal, which co-occur with pro-inflammatory signaling and anxiogenic behaviors. Additionally, we observe that pharmacological microglial depletion during withdrawal prevented these effects. Of particular interest, we see female-specific alterations in the neuroinflammatory responses across the mesocorticolimbic network, suggesting an important opportunity for application of precision medicine in treatment of women with tobacco use disorder. More broadly, these results define differential effects of nicotine and withdrawal on inflammatory signaling in the brain, laying the groundwork for development of future smoking cessation therapeutics.

S23.3
Adolescent social stress reprograms sex-specific cocaine induced behavior and transcription in the adult medial amygdala.

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Sex differences in reward-associated behaviors are necessary for the perpetuation of many species. Such behaviors emerge during the adolescent period, a developmental window associated with increased vulnerability to psychiatric disorders, including substance use disorder, in humans. Previously, we have shown that adolescent social isolation disrupts sex-specific reward- and stress-related behaviors and the transcriptional response to cocaine throughout the reward circuitry. Through integration of gene co-expression analysis and other bioinformatic approaches we identified the thyroid hormone binding protein, crystalline mu (Crym), as a sex-specific upstream regulator of the transcriptional alterations induced by cocaine. Using viral mediated gene transfer to overexpress Crym in the adult medial amygdala, we not only recapitulated the behavioral effects of adolescent stress but replicated the sex-specific transcriptional profiles altered by adolescent stress. These data suggest that disruption of thyroid hormone signaling within the medial amygdala can open a window of plasticity for reprogramming sex-specific behaviors. Currently, we are expanding on these studies to investigate the epigenetic mechanisms by which thyroid hormone signaling might program the sex-specific response to stress and cocaine response in the medial amygdala with the overall goal of identifying specific molecular targets for substance use disorder in both males and females.

S23.4
Effects of early life adversity on steroid hormones and motivated behaviors

Debra Bangasser[1], Samantha Eck[1], Jamie Palmer[1], Evelyn Ordoñes Sanchez[1], Rachel Carpenter[1], Drew Peterson[1], Reza Karbalaei[1], Stan Floresco[2], Benjamin Garcia[3], Mathieu Wimmer[1]
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Early life stress that is not overwhelming can have an "inoculating" effect that promotes the development of resilience in adulthood, but the mechanisms underlying stress inoculation are unknown. Here we used the limited bedding and nesting (LBN) model—where rat dams and pups during the pups' first week of life are exposed to a low resource environment—to assess how this manipulation affects adult hormones and behaviors. We first tested whether LBN altered adult gonadal hormones. There was no effect of the LBN manipulation of testosterone, but LBN increased plasma estradiol levels in males. Estradiol in males is important for sex behavior and we found that LBN exposed males were better than controls at male reproductive behaviors, a change that may be adaptive for living in an adverse environment. Next, we extended these studies to assess addiction-related behaviors. In the delayed discounting task, LBN males more often chose the larger/delayed reward, indicating reduced impulsive

choice. LBN did not alter choice in delayed discounting in female rats. We next gave LBN-exposed rats access to morphine self-administration. LBN males took less morphine and had a lower breakpoint on a progressive ratio schedule than control males. Again, LBN females were not affected. We then assessed changes in gene expression and histone modifications in the nucleus accumbens (NAc), a region implicated in impulsivity and addiction. LBN caused sex-specific alterations in transcription. Using a genome-wide screen of histone post-translational modifications, we found that LBN significantly altered 1 mark in females as compared to 3 marks in males. Future studies will determine which epigenetic modifiers and histone modifications critically contribute to regulating LBN-derived changes in gene expression and behavior. Importantly, identifying factors underlying stress inoculation may reveal novel treatments options for patients that promote resilience.

S24 "Vulnerabilities for psychopathologies and neurodegeneration: sensitive ages, mechanisms and targets"

Chairs: Aniko Korosi, Annamaria Cattaneo

S24.1
Adult Hippocampal Neurogenesis in Major Depressive Disorder and Alzheimer's Disease: A potential converging mechanism

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Alzheimer's Disease (AD) and Major Depressive Disorder (MDD) are two of the most common mental health disorders and are clinically correlated while reciprocally elevating the risk for one another. AD patients are more likely to develop depressive symptoms, and impaired cognition is a common symptom of both disorders. New neurons in the hippocampus are generated throughout life and hippocampal neurogenesis is important for establishing novel memories and mood regulation. Adult hippocampal neurogenesis (AHN) is altered in both MDD and AD. In this talk we will present data and new approaches using patients' serum and human hippocampal progenitor cells to investigate the impact of MDD, cognitive decline and AD on human neurogenesis and highlight how health exposures and lifestyle3 modulate and mitigate altered neurogenesis.

S24.2
Long-term effects of early-life stress on cognition and emotional functions: a synergistic action of stress, inflammation and nutrition

Aniko Korosi[1]
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Early-life stress (ES) is associated with increased vulnerability to cognitive impairments later in life. We investigate the role of a synergistic effect of stress, metabolic factors, nutrition and the neuroimmune system in this early-life induced programming. We use an established model of chronic ES and expose mice to limited nesting and bedding material during first postnatal week and study the lasting brain structural and functional effects under basal and challenged conditions (i.e. LPS, amyloid accumulation (in Alzheimer's disease transgenic mice) and exercise). We focus on cognitive and emotional functions and various forms of brain plasticity including neurogenesis and microglia and study the biochemical and molecular underpinnings (i.e. brain gene/protein expression profile, epigenetic mechanisms and lipid profiles. Given the high nutritional demand during development, we propose that early nutrition is critical for programming of brain and body. We focus on essential micronutrients and fatty acids and propose that an early dietary intervention with these nutrients protect against ES-induced functional deficits. We show that ES leads to cognitive and emotional impairments associated with reduced hippocampal neurogenesis at basal conditions as well as in response to exercise, primed microglia with exaggerated response to LPS or amyloid accumulation. With an early dietary intervention with micronutrient or fatty acid we were able to (at least partly) prevent ES-induced cognitive and emotional decline, associated with modulation of microglia and neurogenesis. These studies give new insights for the development of targeted dietary interventions for vulnerable populations.

S24.3
Inflammatory markers as early biological alterations of vulnerability associated with early life stress exposures

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Early life stress, especially when experienced during the first period of life, affects the brain developmental trajectories leading to an enhanced vulnerability for stress-related psychiatric disorders later in life. Although both clinical and preclinical studies clearly support this associ-

ation, the biological pathways deregulated by such exposure, and the effects in shaping the neurodevelopmental trajectories, have so far been poorly investigated. During my talk I will show data on how inflammatory related markers and mechanisms represent an early biological vulnerability signatures associated with an early exposure to stress. By focusing the attention on the prefrontal cortex, an area that we have previously shown to be highly sensitive to PNS exposure, we performed both candidate genes analyses (pro-inflammatory cytokines and microglia related markers) and also a transcriptomic approach in rats exposed or not to prenatal stress (PNS) and sacrificed at different postnatal days (PNDs 21, 40, 62). Our main aim was to establish whether PNS exposure could also affect the neurodevelopmental trajectories in order to identify the most critical temporal window. We observed that PNS adolescent rats showed a pro-inflammatory profile that was observed both in term of pro-inflammatory cytokines, and microglia activation and also in term of network analyses. This pro-inflammatory status in adolescence was then prevented in PNS animals that received Lurasidone. Finally, I will show data on saliva measurements in cohorts of adolescence exposed to early adversities. Overall, I will discuss the role of inflammation and inflammatory biomarkers as potential useful biomarkers as early biological markers of vulnerability.

S24.4
Inflammatory stressors, memory and mood across the lifespan: hippocampal neurogenesis and microbiota-gut-brain axis as key mediators

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The hippocampus has a central role in memory and mood, and is particularly vulnerable to inflammatory stressors due to its high density of pro-inflammatory cytokine receptors. Chronic stress is a well-known instigator of neuroinflammation, mood and memory impairment. Dysregulation of adult hippocampal neurogenesis (the birth of new neurons) in response to inflammatory stress contributes to the emotional and cognitive impairment evident in neurodegenerative and psychiatric disorders. Conversely, physical exercise is a positive modulator of adult hippocampal neurogenesis, emotion and cognition. Adolescence is a critical period for maturation of the hippocampal circuitry, while during older age hippocampal neuronal function declines. Thus, both of these periods of the lifespan may be sensitive to neurogenesis regulators such as inflammatory stress and exercise. This study examined the impact of chronic neuroinflammation and physical exercise during adolescence and adulthood on hippocampal neurogenesis and associated behavioural tasks. Adult and adolescent cohorts of male rats were injected with a lentivirus overexpressing the pro-inflammatory cytokine IL-1β into the hippocampus. In separate experiments, cohorts of adolescent, adult and older-aged rats were housed with/without access to a running wheel. Performance was assessed in hippocampal neurogenesis-associated tasks and hippocampal tissue was analysed for neurogenesis. We examined the role of the microbiota-gut-brain axis in exercise-induced changes in inflammation, AHN neurogenesis and behaviour. Results show that chronic inflammation and exercise have differential effects on hippocampal neurogenesis and associated memory and mood at different times of the lifespan and that the microbiota-gut-brain axis may be an important regulator of these changes.

S25 "The contribution of V-ATPase to neurosecretion"

Chair: Nicolas Vitale

S25.1
V-ATPase regulates the synthesis of fusogenic lipids at the exocytotic sites

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Despite increasing evidence that lipids play key cellular functions and are involved in an increasing number of human diseases, little information is available on their exact function. This is especially the case in neurosecretion that relies on the fusion of specific membrane organelle with the plasma membrane for which relatively little attention has been paid to the necessary role of lipids. However recent pioneer studies have established the importance of lipid compartmentalization at the exocytotic sites and validated the contribution of fusogenic lipids such as phosphatidic acid (PA) for membrane fusion. Nevertheless, the mechanisms allowing the regulation of the fine dynamics of these key lipids during neurosecretion remains poorly understood. The V-ATPase is involved both in vesicle loading in neurotransmitters and vesicle fusion seems to represent an ideal candidate to regulate the fusogenic status of secretory vesicles according to their replenishment state. Indeed, the V1 and V0 subdomains were shown to dissociate during stimulation allowing subunits of the vesicular V0 to interact with different proteins of the secretory machinery. We show here that V0a1 interacts with the exchange factor ARNO and promotes ac-

tivation of the GTPase Arf6 during exocytosis in neuroendocrine cells. Interfering with the V0a1-ARNO interaction prevented phospholipase D (PLD) activation, phosphatididic acid synthesis during exocytosis, and altered the kinetic parameters of individual fusion events. Altogether these data suggest that V1 dissociation from V0 could represent the signal that triggers the activation of the ARNO-Arf6-PLD1 pathway and promotes PA synthesis needed for efficient exocytosis in neuroendocrine cells.

S25.2

The role of the V-ATPase in synaptic vesicle filling with neurotransmitter

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The proton pumping vacuolar-type-ATPase (V-ATPase) complex is a key player in neurotransmitter (NT) loading of synaptic vesicles (SVs). It provides the energy required to fill an SV with more than 2000 neurotransmitter molecules by pumping protons into the SV lumen, thus, generating a proton electrochemical gradient ($\triangle\mu H^+$) across the vesicle membrane to which NT transport is ultimately coupled. $\triangle\mu H^+$ consists of the proton gradient ($\triangle$pH) and the membrane potential ($\triangle\psi$) component, which contribute to NT loading to different extents depending on the NT charge and compensatory ion fluxes associated with each individual NT transport mechanism. Despite its essential role in SV filling, the regulatory parameters and the precise contribution of the V-ATPase to the bioenergetics of NT transport, in particular for the major excitatory NT glutamate and the major inhibitory NT GABA, are still unclear. Beyond that, the precise role of additional physiologically relevant ions such as Cl^-, K^+ and Na^+ in $\triangle\mu H^+$ formation remains elusive. Using a reconstituted system containing the purified transporter (VGLUT1 and VGAT) and a bacterial ATPase reconstituted in liposomes together with hybrid vesicles and isolated synaptic vesicles we provide novel insights into how the V-ATPase is regulated and how glutamate and GABA uptake is coupled to $\triangle\mu H^+$ and additional ions to efficiently fill SVs with NT.

S25.3

Assembly/disassembly of presynaptic V-ATPase regulates neurotransmitter release

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The vacuolar H^+-ATPase (V-ATPase) is a multisubunit molecular motor consisting of a membrane-bound V0 sector for proton translocation and a cytosolic V1 complex for ATP hydrolysis. In synaptic vesicles (SV) it provides a proton-motive force necessary for neurotransmitter refilling. Proteomic data indicated a very low copy number per SV suggesting a precise control of V-ATPase activity. However, the molecular mechanisms are unknown. We performed fluorescence recovery after photobleaching (FRAP) of various GFP-tagged subunits of the V-ATPase at presynaptic boutons. We found that during resting conditions the cytosolic V1 domain only transiently interacts with the V0 membrane sector. However, neuronal activity and dissipation of the luminal acidic pH of SVs strongly shifted the binding equilibrium towards V0/V1 assembly. Direct imaging of V-ATPase exo- and endocytosis revealed a small (<10%) but significant fraction of the V0 sector in the bouton membrane. Moreover, FRAP experiments showed that the specific inhibitor Salicylihalamide blocks ATPase activity by locking it in the assembled state irrespective of the luminal pH. Intriguingly, presence of V1 strongly reduces SV release probability in a frequency-dependent manner, maybe simply by steric hindrance of docking and priming. We uncovered a hitherto unknown assembly/disassembly cycle of the SV V-ATPase during the SV exo-endocytosis cycle that helps lowering the energy requirements by keeping V-ATPase activity to a minimum and warrants fusion of only fully filled and acidified SVs.

S25.4

The V-ATPase V0c /V0d interplay modulates V0c interaction with the SNARE complex and exocytosis

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The vacuolar proton pump (V-ATPase) is a multisubunit complex composed of two distinct non-covalently-associated sectors. The cytosolic V1 sector hydrolyses ATP, providing the energy for the V0 membrane sector to translocate protons into the vesicle lumen. The proton gradient is then used by vesicular transporters to load synaptic vesicles with specific neurotransmitters. In fully loaded synaptic vesicles, V1 is thought to dissociate from

V0 and leave this free membrane embedded sector as a marker of fully loaded synaptic vesicles. In addition to the primary role of the V-ATPase in vesicle loading, subunits of the V0 membrane sector regulate SNARE-mediated membrane fusion downstream of synaptic vesicle acidification. V0a and V0c, two membrane subunits of the V0 sector have been shown to interact with SNARE proteins and their photo-inactivation rapidly impairs synaptic transmission. We recently addressed the importance of V0d in modulating neurotransmission. This subunit is a peripheral component of the V0 sector that strongly interacts with V0a and V0c and is crucial for the canonic proton transfer activity of the V-ATPase. Our investigations show that V0d interaction with V0c modulates its availability for interaction with SNARE proteins. Consequently, overexpression of V0d modulates various parameters of single exocytotic events in chromaffin cells and V0d injection in superior cervical ganglion neurons modulates neurotransmission.

S26 "Translational medicine for neurodegenerative pathologies: endogenous and natural molecules from human brain through Drosophila to cerebral organoids"

Chair: Andrea Diana

S26.1
Neuroprotective potential of flavonols against oxidative stress-mediated injury

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The last talk by Dr Maja Jazvinšćak Jembrek will be directed towards clarifying the neuroprotective efficacy of the flavonols quercetin and myricetin against oxidative stress (OS) - mediated injury, a condition that is commonly associated with neurodegeneration. OS in Alzheimer´s disease has been linked to the impairment of copper homeostasis. Via the Fenton chemistry copper may trigger generation of extremely dangerous hydroxyl radicals and induce oxidative damage of cellular macromolecules. Polyphenolic phytochemicals, including flavonols, are generally appreciated as a promising and safe adjuvant therapeutic option in neuroprotection based on their antioxidative activities, metal-chelating properties, and ability to regulate redox-sensitive signalling pathways. Results performed in P19 neuronal cells by Dr Jazvinšćak Jembrek indicate that the neuroprotective effects of quercetin are determined by the severity and the type of oxidative injury. In copper-induced OS, quercetin improved viability of moderately damaged neurons by preventing free radical accumulation and downstream apoptotic changes. At the molecular level, quercetin attenuated copper-induced increase of p53 upregulated modulator of apoptosis (PUMA) expression, reduced levels of nucleoside diphosphate kinase NME1 and modulated activity of ERK1/2 and PI3K/Akt signalling pathways. In severely injured neurons, quercetin acted prooxidatively and exacerbated harmful effects of copper. On the other hand, in hydrogen peroxide-induced OS, only beneficial effects of quercetin were observed. Effects of myricetin against copper-induced OS were studied in neuroblastoma SH-SY5Y cells. Myricetin demonstrated prooxidative effects, reduced viability, modulated expression of pro-apoptotic and anti-apoptotic proteins, and affected cell surface and nanomechanical properties of SH-SY5Y cells. The obtained results are relevant in the context of considering polyphenolic phytochemicals as a possible adjuvant therapy in neuroprotection, particularly in conditions accompanied with metal dyshomeostasis.

S26.2
Effects of phytotherapic and human derived extracts on functional and morphological parameters in Drosophila mutants as Parkinson's disease models

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The fruit fly, Drosophila melanogaster, with leucine-rich repeat kinase 2 mutants (LRRK2) loss-of-function in the WD40 domain, has been indicated as ideal organism for sharp insights into corresponding human behaviour, possibly contributing to define some physiopathologic features of Parkinson's disease (PD) in both genetic and sporadic forms. As matter of fact, mutations in the LRRK2 gene are the most frequent cause of familial PD and, from a clinical point of view, mutant LRRK2-PD patients seem to have similar phenotypes compared to sporadic patients. Using the above Drosophila mutant, experiments performed with Withania somnifera (a plant growing spontaneously also in the Mediterranean area) have provided the favourite background, with respect to its anti-inflammatory properties, to further test human dialyzable leukocyte extracts (DLE) in order to verify the ability to transfer antigen-specific molecules for the activity of various immune components, including pro- and anti-inflammatory cytokines. The overall results showed that the molecular components of the human blood derived extracts dramatically impact functional parameters, namely locomotor and climbing activities, muscle electrophysiological response to stimuli, well overlapping with mi-

tochondria integrity, protection from oxidative stress and anti-inflammatory cascade. Finally, it will be illustrated, to what extent some anatomical structures were responsible for restored functions in parkinsonian-like mutant flies as resulted from the topographical correlation between improved performances in locomotor ability and the rise in number of dopaminergic neurons found in specific areas of LRRK2 mutant brains.

S26.3
Therapeutic strategies for attenuation of imminent inflammation in Alzheimer's disease

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As microglia-derived exosomes containing short tau fibrils activate the NLRP3 inflammasome in neighboring cells and accelerate neurofibrillary propagation, microglial dysfunction can be envisioned as causal for neuronal degeneration in Alzheimer's disease (AD). In the first part of my talk, I will report some of the recent results from our lab regarding NLRP1, ASC, gasdermin, caspase-6, and LRP1 protein expression in the hippocampal formation postmortem brain tissue from AD and cognitively healthy controls (HC), their correlation with neuropathological changes, and potential role in early AD pathogenesis. In the second part of my talk, I will try to integrate and interpret recent insights in the field and suggest strategies for attenuation of inflammation in AD. One possibility is to measure levels of plasma microglia-derived exosomes and characterize their cargo proteins in subjects suspected of cognitive and behavioral impairment due to AD. Another possibility is the generation of human-induced pluripotent stem cells from dermal fibroblasts of AD subjects, and their *in vitro* differentiation into neural precursor cells/neurons and hematopoietic progenitor cells/microglia. These cells enable the evaluation of omics differences in microglia from AD and HC. They can be also co-cultivated with NPC-derived neurons. Such an approach would also allow experimenting with various strategies to revert induced proinflammatory phenotype using NLRP3 and cathepsin-B inhibitors, non-steroidal anti-inflammatory drugs, and immune selective anti-inflammatory derivatives. Moreover, by preventing exosome biogenesis and secretion (e.g. by using neticonazole and tipifarnib), AD responders can be selected. The overarching aim of all of these efforts is to predict the extent of neuroinflammation in time, thus enabling personalized anti-inflammatory and anti-exosome (the use of blood-brain barrier crossing nanobodies) treatment.

S27 "Neuropeptide modulation of pain transmission"

Chair: Marc Landry

S27.1
Deciphering the cellular basis of oxytocinergic control of pain associated disorders

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In the recent years, we finely characterized the contribution of parvocellular oxytocin (OT) neurons to analgesia: a tiny population of them simultaneously control magnocellular OT neurons activity to induce OT blood release, and directly project to spinal cord to inhibit wide-dynamic-range (WDR neurons), therefore promoting analgesia. However, additional OT-mediated analgesic pathways are currently unknown. We hypothesized that the periaqueductal gray (PAG), which plays a key role in the modulation of nociceptive input through descending pathways, could be involved in OT-induced analgesia. Using viral approaches and a new transgenic rat line (OTR-IRES-Cre) generated with CRISPR/Cas9, we found OTR-expressing neurons and OT fibers in the PAG. In vivo electrophysiology showed that optogenetically-evoked axonal OT release in the PAG resulted in an overall long-lasting increase of PAG neuronal activity, linked to an indirect suppression of spinal cord neurons activity. Intriguingly, we found no overlap between the PAG and spinal cord OT projections suggesting two anatomically segregated networks. These results highlight a new pathway for OT-induced analgesia and pave the way to a better understanding of the complex analgesic action of the neuropeptide.

S27.2
Migraine: Calcitonin gene-related peptide implications and novel medications

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Migraine is a common disabling neurovascular primary headache disorder. Many factors have been implicated in the pathogenesis of it, such as activation of the tri-

geminovascular system, dysfunction of cerebral blood vessels, circulating vasoactive substances, and neuropeptides like calcitonin gene-related peptide (CGRP). These neuropeptides may take part in neurogenic inflammation of the intracranial vasculature and peripheral and central sensitization of the trigeminal system. In this presentation we will provide an overview of migraine pathophysiology, with an emphasis on the role of calcitonin gene-related peptide (CGRP) and discuss the different therapeutic approaches involving migraine-related neuropeptides in the acute and prophylactic treatment of migraine headache.

S27.3
Analgesic properties of the relaxin peptide family

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Chronic pain, often accompanied by anxiety and depression, is a global scourge. The modulation of pain by neuropeptides is well established at the spinal level. However, little data is available on neuropeptide role on pain in the brain. The relaxin family comprises the neuropeptides relaxin and relaxin-3. Relaxin is widely expressed in various organs including the central nervous system (CNS) and has antifibrotic properties. In contrast, relaxin-3 is neuron-specific and exhibits anxiolytic and antidepressant effects. Relaxin and relaxin-3 signaling is mediated by the G protein-coupled receptors RXFP1 and RXFP3, respectively. Because of the prominent expression of these receptors in pain processing areas of the brain, we aimed at studying the possible pain modulatory effects of relaxin and relaxin-3 by using pharmacological, behavioural and anatomical approaches in a mouse model of persistent inflammatory pain obtained by the injection of Complete Freud´s Adjuvant in the hind paw. We have studied the sensory and affective components of pain and our results show that both the relaxin-3/RXFP3 and relaxin/RXFP1 systems have transient analgesic effects in inflammatory pain. We further identified the neurochemical phenotype of RXFP1/RXFP3-expressing neurons and proposed that the sites of action of these peptide systems include cortical (cingulate cortex, claustrum) and subcortical (amygdala) regions that regulate descending pathways and sensory integration in the spinal cord. Interestingly, the analgesic effects depend on the pain modalities (mechanical vs thermal) that were investigated. Our data highlight a novel role for this peptide family and suggest their therapeutic potential in persistent pain conditions.

S28 "Tuning the brain: neuromodulation for neurological and psychiatric diseases"

Chair: Salvatore Galati

S28.1
DBS for dystonia and related movement disorders: efficacy and mechanisms of action

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Even though globus pallidus DBS is nowadays a standard therapy for treating severe dystonia in humans, its mechanism of action is still unclear. Improvement in dystonic symptoms under DBS takes usually several months and after DBS discontinuation, clinical benefits can still be observed for several days. Overall, mechanism of action in dystonia seems to rely on DBS induced plastical changes in sensorimotor networks. We will review the most recent evidences shedding light on this complex DBS mechanism of action in dystonia.

S28.2
Recovery of corticostriatal synaptic plasticity by transcranial magnetic stimulation in experimental parkinsonisms

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In Parkinson's disease (PD) therapy, current treatments are not able to arrest the progression of neurodegenerative events, and the risk of developing L-Dopa-induced side effects is still not predictable. Novel therapeutic approaches that combine pharmacological and non-pharmacological early interventions may engage intrinsic compensative mechanisms and improve subjects' response to dopamine replacement therapies with limited side effects. Animal models of PD have helped demonstrate that basal ganglia alterations are associated with loss of synaptic plasticity and that identifying the mechanisms underlying the response to treatments can help find new strategies to optimize therapeutic outcomes. In this talk, I will present recent electrophysiological, behavioral and morphological

evidence of the possible mechanisms underlying transcranial magnetic stimulation (TMS)-induced beneficial effects on the corticostriatal functions in a rat model of PD with distinct degrees of dopamine denervation and under chronic treatment with L-Dopa, modeling L-Dopa-induced dyskinesia (LID). The objective is to provide a basic knowledge of the effects of different stimulation patterns, with the final goal to promote a critical discussion on data obtained in animal models to improve the design of translational research studies in a multidisciplinary view.

S28.3
Sleeping brain rhythms tune dyskinesias

Ninfa Amato[1], Serena Caverzasio[1], Claudio Staedler[1], Alain Kaelin-Lang[1], Salvatore Galati[1]
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The role of sleep in the regulation of homeostatic synaptic plasticity is widely recognized. The amount of slow wave activity during slow wave sleep (SWS-SWA), which is mainly produced in the first part of the night and gradually decreases throughout the night, represents the main electrophysiological marker, as well as a contributor, of the homeostatic process regulating brain plasticity. An alteration of synaptic plasticity has been proposed to be at the root of several movement disorders. In this perspective, we investigated, in previous studies, the amount of SWS-SWA, and its behavior throughout the night in Parkinson's disease patients, with and without levodopa-induced dyskinesia and in dystonic patients, and observed alterations in this mechanism. Specifically, these patients presented a lower amount of SWS-SWA, which showed a different topography compared to control subjects and which remained quite stable across the night. We believe that the nature of the association between SWS-SWA alterations and the appearance of these disorders, could be causative or at least facilitative. Clarify this link may encourage the development of new therapies based on SWA-enhancing interventions.

S28.4
Deep Brain Stimulation in Parkinson's disease patients and experimental disease models: scenes from a marriage?

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The history of deep brain stimulation (DBS) as effective therapy for Parkinson's disease (PD) patients should represent a paradigmatic example of an efficient cross-talk between behavioral results obtained in mammalian disease models and clinical evidence collected in humans. However, despite the success achieved by DBS into the subthalamic nucleus of primates rendered parkinsonian by MPTP intoxication, several findings collected in rodent's neurotoxic model promoted dogmatic visions and wrong research directions. Although small, dopamine-deprived, mammals share, with PD patients, some neurophysiological hallmarks as counterpart of akinesia, namely beta band increase and cortical-basal ganglia synchronization, several divergences emerged when considering routine rat 6-OHDA paradigm. The role of glutamate revealed negligible in humans during transition to ON-state (in other words, suppression of subthalamic glutamate does not play a key therapeutic player). Besides, a tonic release of dopamine, inferred by experiments under stimulation in rodents, were not replicated in humans. For other pitfalls, harbored in routine rodent's models, consider that small mammal's settings a) do not mimic the full spectrum of motor and non-motor disabilities experienced in humans; b) reproduce an extremely advance neurodegeneration and fail to provide a progressive assessment of the discrete changes correlated to different stages of a progressive disease; c) describe a "pure" dopamine depletion (not affecting other systems notoriously critical in some parkinsonian phenotypes, i.e. noradrenergic and cholinergic deficits). Here, we examine those successes and these contradictions, to endeavor where to shift the tiller of renovated DBS-oriented research.

S28.5
Brain stimulation for treating addictions: clinical outcomes and follow-up

Graziella Madeo[1]
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Recently non-invasive brain stimulation (NIBS) techniques, including transcranial magnetic stimulation (TMS) have offered the promise for neural circuit-based treatments for addictions, including Cocaine Use Disorders (CUDs). Evidence from both preclinical and clinical studies suggest that repetitive TMS impacts on neural activity modulating the neuroadaptative mechanisms underlying the addicted brain. We provide an integrated view of evidence highlighting the mechanisms of TMS induced effects on modulating the maladaptive brain circuitry of addiction. Then, we review the clinical findings suggesting rTMS as an effective interventional tool for the treatment of CUDs.

S29 "Dopamine Related Disorders: new insight and therapeutic prospectives"

Chair: Damiana Leo

S29.1
Dopamine Transporter Knock-out Rats an innovative animal model for dopamine related diseases

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Here, we present a newly developed strain of rats in which the gene encoding the dopamine transporter (DAT) has been disrupted (Dopamine Transporter Knockout rats [DAT-KO rats]). DAT-KO rats display functional hyperdopaminergia accompanied by pronounced spontaneous locomotor hyperactivity. Hyperactivity of DAT-KO rats can be counteracted by amphetamine, methylphenidate, and a few other compounds exerting inhibitory action on dopamine-dependent hyperactivity. DAT-KO rats also demonstrate cognitive deficits in working memory and sensorimotor gating tests, less propensity to develop compulsive behaviors, and strong dysregulation in frontostriatal BDNF function. These observations highlight the key role of DAT in the control of brain dopaminergic transmission. DAT-KO rats could provide a novel translational model for human diseases involving aberrant dopamine functions such as Attention Deficit with Hyperkinetic disorders, Parkinson's disease and partly bipolar disorders.

S29.2
Neuronal hemoglobin induces loss of dopaminergic neurons in mouse substantia nigra, cognitive deficits and cleavage of endogenous α-synuclein.

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Parkinson's disease (PD) presents the selective loss of A9 dopaminergic (DA) neurons of Substantia Nigra pars compacta (SNpc) and the presence of intracellular aggregates called Lewy bodies. α-synuclein (α-syn) species truncated at the carboxy terminal (C-terminal) accumulate in pathological inclusions and promote α-syn aggregation and toxicity. Hemoglobin (Hb) is the major oxygen carrier protein in erythrocytes. In addition, Hb is expressed in A9 DA neurons where it influences mitochondrial activity. Hb overexpression increases cells' vulnerability in a neurochemical model of PD *in vitro* and forms cytoplasmic and nucleolar aggregates upon short-term overexpression in mouse SNpc. In this study, α and β-globin chains were co-expressed in DA cells of SNpc *in vivo* upon stereotaxic injections of an Adeno-Associated Virus isotype 9 (AAV9) and in DA iMN9D cells *in vitro*. Long-term Hb over-expression in SNpc induced the loss of about 50% of DA neurons, a mild motor impairment and deficits in recognition and spatial working memory. Hb triggered the formation of endogenous α-synuclein C-terminal truncated species. Similar α-syn fragments were found *in vitro* in DA iMN9D cells over-expressing α and β- globins when treated with pre-formed α-syn fibrils. Our study positions Hb as a relevant player in PD pathogenesis for its ability to trigger DA cells' loss *in vivo* and the formation of C-terminal α-synuclein fragments.

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S29.3
Cell reprogramming approaches for the generation of dopaminergic *in vitro* neural systems

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The understanding of neurodegenerative diseases is strongly hindered by the limited physiological relevance of the animal models that are not able to reproduce the sensitivity and limited regenerative capacity of the human nervous system. On the other side we have the chance to study human neurons only as single cell population in a cell culture dish. Therefore our goal is to generate complex *in vitro* human neural systems that can simulate the functionality of neuronal pathways and their interactions with different neural populations such as astrocytes, microglia and oligodendrocytes. The achievement of human neural models with higher degree of complexity will be instrumental to understand and characterize the early steps of neurodegenerative diseases such as Parkinson's

disease (PD). This approach can eventually lead to the identification of new early diagnostic and therapeutic targets and therefore to a new powerful tool to perform drug screening approaches. To this aim we are devising a variety of experimental approaches to generate advanced human neural *in vitro* models by means of bioengineering and cell reprogramming. The combination of these experimental efforts will possibly contribute to the generation of an *in vitro* model of nigrostriatal pathway that could be used as a platform for PD studies.

S29.4

Deletion of dopamine transporter alters glutamate homeostasis in rat striatum

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Dopamine and glutamate interact in striatum influencing neural excitability and promoting synaptic plasticity. The main ionotropic glutamate receptors, NMDA and AMPA, colocalize with striatal dopaminergic receptors in the postsynaptic MS neurons, where they regulate motor function and spatial memory. However, little is known regarding the molecular mechanisms underlying the crosstalk between dopamine and glutamate. The major aim of our work was to evaluate the effect of DAT deletion on the expression of critical determinants of the glutamate synapse in striatum and its role in the electrophysiological transmission. To this end, we analyzed the expression of glutamate system determinants in specific subcellular fractions and pre- and post-synaptic electrophysiological transmission in the striatum of DAT knockout rats (DAT-KO). We found that DAT deletion has reduced the stabilization of the main subunit of both NMDA and AMPA glutamate receptors at the post-synaptic density, promoting their lateral trafficking in extra-synaptic sites. Accordingly, we found reduced expression of the main glutamatergic scaffolding proteins (PSD-95, SAP-102 and SAP-97), which normally target and anchor glutamate receptors into the synaptic membrane of the dendritic spine. Interestingly, such reduced retention of glutamate receptors in the membrane was accompanied by an impairment in both LTP and LTD post-synaptic transmission in the striatum of DAT-KO rats. In conclusion, our data show that increased extracellular levels of DA has reorganized the glutamate synapse in the rat striatum destabilizing glutamate neurotransmission, an effect that might serve as critical neurobiological substrate for vulnerability to dopamine-related disorders.

S29.5

The role of dopamine receptors and their alterations in neurodegeneration

Federica Bono[1], Veronica Mutti[1], Paola Devoto[2], Silvia Bolognin[3], Jens C. Schwamborn[3], Cristina Missale[1], Chiara Fiorentini[1]

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Personalized medicine is a concept very suitable for Parkinson's disease (PD), a neurodegenerative disease that includes a highly heterogeneous group of patients. Understanding the basis of the large diversity of phenotypes with appropriate clinical, imaging, and biochemical measures is an important step to guide therapy toward its greatest precision and safety. Alongside these key features, the chance to investigate with the induced pluripotent stem cell (iPSCs) technology PD patient-derived dopamine neurons (DAn) at the molecular level, can make a strong contribution not only for clarifying pathogenic mechanisms underlying neurodegeneration, but also for developing the most appropriate therapeutic approach for each PD patient and patient subgroups. On these bases, we recently investigated the characteristics of DAn derived from iPSCs obtained from two PD patients harboring the G2019S LRRK2 mutation. The data obtained in our studies showed that DAn differentiated from G2019S LRRK2-derived iPSCs are resistant to the neurotrophic effects of dopamine D2 and D3 receptor (D2R/D3R) agonists and show significant alterations of D2R/D3R signaling. Moreover, analysis of synaptic function demonstrated a remarkable dysregulation of receptor mechanisms controlling DA release, suggesting that G2019S mutation significantly impacts on the trafficking and function of key receptors controlling DAn function. More recently, we also found that astrocytes carrying the G2019S mutation were characterized by reduced D2R localization at the plasma membrane. Together, our results may indicate that, an abnormal expression or activity of these receptors could represent an early, pre-degenerative event in patients carrying LRKK2 mutation with various consequence that likely contribute to make DAn more vulnerable.

S30 "Tryptophan, Serotonin, and Kynurenine Metabolites: Neurodevelopmental Building Blocks with Long-Lasting Impacts"

Chair: Ana Pocivavsek

S30.1
Perinatal Serotonin and Maternal Mental Illness: Selective Serotonin Reuptake Inhibitors in Offspring - Neurobehavioral Outcomes

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Selective serotonin reuptake inhibitor (SSRI) medications are one of the first lines of treatment for maternal affective disorders and are prescribed to up to 10% of pregnant women. Concern has been raised about how perinatal exposure to these medications affect offspring neurobehavioral outcomes due to their impact on the developing serotonergic system. In addition, how these medications act on the maternal brain to treat perinatal mental illnesses remains to be determined. The aim of our work over the past few years has been to take a two generational approach by investigating effects of SSRIs on neurobehavioral outcomes in both the mother and offspring. In the mother research is showing that the effects of SSRI medications on the maternal hippocampus differ with reproductive state, eg. pregnancy or postpartum in addition to the normative changes in hippocampal plasticity that occur with motherhood. In the offspring, our research shows that perinatal exposure to SSRIs, when using a model of maternal depression via gestational stress, prevents the negative effect of maternal stress on depressive-like behavior, sibling play and has minimal effects on anxiety. We also show that the effects of altering the serotonergic system in development are often sexually differentiated in terms of hippocampal plasticity and behavioral outcomes. Our next steps are to understand how maternal care and maternal affective state may interplay with SSRI treatment to alter the maternal gut-brain axis as a target for future research and treatments. Together, these results further characterize the role of perinatal SSRIs and maternal affective state on the mother and developing offspring and point to areas of much needed future research.

S30.2
Modeling Kynurenic Acid Elevation in Rodents during Development: Implications for Cognition and Psychiatric Illness

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Dysfunction in the kynurenine pathway (KP) has been implicated in the pathology of psychotic illnesses like schizophrenia (SZ). The KP metabolite kynurenic acid (KYNA) has been linked to cognitive impairments in SZ and may also contribute to sleep disturbances in patients. To understand the role of KYNA in SZ etiology, we developed an experimental system in rats (Pocivavsek et al., *Psychopharm.*, 2014) where kynurenine (kyn; 100 mg/day) is fed to pregnant dams from embryonic day (ED) 15 to ED 22 (control: ECon; kyn-treated: EKyn) to elevate fetal brain KYNA. As sleep disturbances can often aggravate illness severity for SZ patients and plausible hypotheses suggest a connection with cognitive deficits, we are investigating the interplay between KYNA, sleep, and cognition. We presently focused on investigating differences in a sex-dependent manner when evaluating a) KP metabolism b) learning and memory, and c) sleep-wake patterns using electroencephalogram and electromyogram telemetry. Our data demonstrate that continuous elevation of KYNA levels during neurodevelopment is sufficient to cause long-lasting effects reminiscent of SZ in adult male offspring (increased brain KYNA, impaired learning, sleep disruption) and more subtle impairments in adult female offspring (no increase in brain KYNA, minor learning deficits, hyperarousal). In conclusion, the identified sex differences further support our prenatal kynurenine treatment in rats as an attractive tool to study the role of the KP in the pathophysiology of schizophrenia. Reducing KYNA with a brain-penetrable kynurenine aminotransferase II inhibitor is being investigated as a plausible therapeutic strategy to overcome behavioral phenotypes.

S30.3
Long-lasting kynurenine pathway alterations triggered by the exposure to THC in critical phases of brain maturation

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Cannabis remains one of the most widely used illicit drugs during pregnancy and adolescence. The main psychoactive component of marijuana ($\triangle^9$-tetrahydrocannabinol, THC) is correlated with untoward physiological effects on brain maturation. Neurobehavi-

oral and cognitive impairments have been reported in individuals exposed to cannabinoids during gestational and/or adolescent periods. Interestingly, the deleterious effects of prenatal cannabis use are similar to those observed in adult rats prenatally exposed to (L)-kynurenine, the direct bioprecursor of the neuroactive metabolite kynurenic acid (KYNA). We therefore investigated whether alterations in KYNA levels and/or kynurenine pathway (KP) metabolism in the rat brain might play a role in the long-term consequences of prenatal or adolescent cannabinoid exposure. Compared to controls, extracellular basal KYNA levels were higher, and basal glutamate levels were lower, in the prefrontal cortex (mPFC) of prenatally THC-exposed rats [5 mg/kg, p.o.; from gestational day (GD)5 through GD20]. These rats also showed abnormal short-term memory. Following an additional acute challenge with a low dose of kynurenine (5 mg/kg i.p.) in adulthood, the increase in extracellular KYNA levels in the mPFC was more pronounced in in prenatally THC-exposed rats. Increased mPFC extracellular basal KYNA levels, cognitive disfunctions and alterations in KP metabolism were also observed in adult rats treated with THC during the adolescence [increasing doses of THC twice a day (PND 35–45)]. In the translational realm, these experiments raise the prospect of prevention of KYNA neosynthesis as a promising novel approach to combat some of the detrimental long-term effects of prenatal and adolescent cannabis use.

S30.4
Emotional Changes During Pregnancy and Post-partum: Role of the Tryptophan to Kynurenine Degradation, Inflammation and Stress

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Depression and anxiety symptoms are highly prevalent among women during pregnancy and post-partum. Growing evidence indicates an enhanced metabolism of tryptophan (Trp) into kynurenine (Kyn) due to increased inflammation and/or stress to be among the possible underlying neurobiological mechanisms. However, it is still unclear the complex interplay among inflammation, stress, and the degradation of Trp into Kyn, and their relationship with longitudinal changes in anxiety and depressive symptoms during the perinatal period. We thus examined a cohort of 110 healthy women at 34–36 gestational weeks for salivary cortisol and 97 for the serum levels of interleukin 6 (IL-6), Trp and Kyn. The participants were also assessed with the Edinburgh Postnatal Depression Scale (EPDS) and the State Trait Anxiety Inventory subscale (STAI-S) at 34–36 gestational weeks, delivery, 3 and 12 months postpartum. We observed that Trp levels and the Kyn/Trp ratio at 34–36 gestational weeks moderate the association between IL-6 levels and depressive symptoms during the perinatal and the post-partum period. No interactions were seen between Trp and Kyn biomarkers and cortisol on depressive symptoms. Notably, these associations were not significant for the trajectory of anxiety symptoms during the perinatal and the post-partum period. These data collected in a low-risk cohort indicate the involvement of the Trp to Kyn pathway and inflammation in the course of depressive but not anxiety symptoms in women during pregnancy and the post-natal period until one-year post-partum, adding novel insights on the mechanisms regulating mood and emotions during pregnancy and after delivery.

S30.5
Neuroinflammation and Tryptophan Degradation—Associations between Kynurenine Metabolites and Psychiatric Symptoms

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Mounting evidence points to the involvement of neuroinflammation in psychosis and cognition. Elevated levels of the pro-inflammatory cytokine interleukin (IL)-1β have been reported in both schizophrenia and bipolar disorder. This cytokine also induces the kynurenine pathway of tryptophan degradation and patients with schizophrenia and bipolar disorder display elevated cerebrospinal fluid (CSF) concentrations of kynurenic acid (KYNA), an endogenous antagonist of N-methyl-D-aspartate (NMDA) and alpha7 nicotinic receptors. In this presentation, data showing elevated brain KYNA concentrations in patients with schizophrenia and patients with bipolar disorder and how KYNA controls dopaminergic neurotransmission will be discussed. We will show that KYNA relates to psychotic symptoms and cognitive impairments and how the kynurenine pathway is highly inducible by immune activation. Pre-clinical results suggest that reduced synthesis of KYNA, by inhibition of kynurenine aminotransferase (KAT) II, is a novel target for psychosis and may improve cognitive performance in schizophrenia. Here, we show that blockade of KAT II also decreases rat midbrain dopamine firing.

S31 "Exploring new therapeutic targets to treat neurodevelopmental diseases: from synapse to behavior "

Chair: Antonia Manduca

S31.1
Modulation of cAMP and cGMP in therapeutic approaches for ASD

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and a leading cause of autism. It is due to the silencing of the FMR1 gene coding for an RNA-binding protein, FMRP, which modulates translation of a subset of synaptic proteins. To date no specific treatment is available for this disorder. To better understand the pathophysiology of FXS, we searched for target mRNAs of FMRP by a CLIP (Cross-Link UV Immunoprecipitation) assay in brain cortex and hippocampus of 13 day old mice (when FMRP reaches its highest expression and there is a peak in synaptogenesis). Among the targets we identified, we focused our attention on those involved in the homeostasis of cAMP and cGMP. We showed that Phosphodiesterase 2A (Pde2a) mRNA is a prominent target of FMRP. PDE2A is an enzyme involved in the degradation of both cAMP and cGMP, two second messengers at the crossroad of many signaling pathways in neurons. It is the only PDE located in docked synaptic vesicles and it is highly expressed in brain regions involved in FXS pathology. Mutants in the PDE2A gene have been identified in patients affected by intellectual disability. PDE2A abundance and activity are increased in Fmr1-KO neurons in cortex and hippocampus. Consequently, the abundance of cAMP and cGMP is reduced in the mouse Fmr1-KO hippocampus and cortex. Consistently, blockade of PDE2A with its powerful and specific inhibitor, BAY 60-7550, rescues multiple *in vitro*, *ex-vivo* and *in vitro* FXS phenotypes. In addition, Recently, we found an increased activity of PDE2A in the brain of Valproic Acid (VPA)-exposed rats, that are a model of environmental ASD. Remarkably, treating VPA-rats with BA607550 reverted socio-cognitive deficits characterizing these animals at infancy, adolescence and adult life. This suggest that PDE2A can be a therapeutic target not only for FXS but also for other models of DBD.

S31.2
Targeting matrix metalloproteinase and inflammatory dysfunctions in autism spectrum disorder

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Matrix metalloproteinases (MMPs) play crucial roles in normal brain development as well as in a number of key pathological processes including neuroinflammation. Substrates of MMPs have important implications for synaptogenesis, synaptic plasticity and long-term potentiation. Animal studies have documented the presence of MMP-9 and MMP-2 in the brain, which are mainly secreted by glial cells due to different triggers. Here, we explored the involvement of MMP-2 and MMP-9 activity in the pathogenesis of ASD-like signs in an animal model of ASD based on prenatal valproic acid (VPA) exposure in rats, by investigating their possible role in the regulation of microglia-neuron communication via CX3CL1 signaling. MMP-2 and MMP-9 activity was significantly upregulated in the hippocampus of rats prenatally exposed to VPA. Prenatal VPA exposure significantly downregulated the expression of CX3CR1 receptors on microglia cells, leading to persistent microglia activation within this brain region. The administration of a selective MMP-2 and MMP-9 inhibitor (5 mg/kg/day, P34–38) attenuated social behavior deficits and compulsive behavior, and seemed to ameliorate short-term memory deficits in the prenatal VPA model. Inhibition of MMP-2 and MMP-9 proteolytic activity through SB3CT administration reduced microglia activation in VPA-exposed animals. Ongoing analysis are aimed at dissecting the downstream consequences of MMP-2 and MMP-9 inhibition on 1) the CX3CL1/CX3CR1 communication system and 2) synaptic abnormalities including spine density and morphology. These data suggest that inhibition of MMP-2 and MMP-9 proteolytic activity could represent a promising approach to relieve ASD symptoms by restoring tonic microglia-neuron signaling through the CX3CL1/CX3CR1 axis.

S31.3
N-acetylcysteine decreases stereotyped repertoire, anxiety-like behaviour and neuroinflammation in a mouse model of Autism Spectrum Disorders-like dysfunctions

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Deficits of social interactions and stereotyped behaviours are commonly considered as Autism Spectrum Disorders (ASD) core symptoms. Currently, limited therapeutic interventions are available for treating the het-

erogeneous ASD symptoms. Recently, it has been shown that the administration of the antioxidant compound N-acetylcysteine (NAC), precursor of the glutathione enzyme, improved different psychiatric-like symptoms. We have previously demonstrated that early postnatal ketamine administration in mice is able to resemble ASD typical behavioural dysfunctions, such as repetitive and stereotyped repertoire, social impairments and anxiety-like behaviour. Here, in our ASD-like mouse model, we supplemented drinking water with NAC, from weaning until adulthood. To investigate NAC effects on behavioural, neurochemical and biomolecular ASD-like dysfunctions, we carried out a 4-days behavioural tests battery, together with the quantification of excitatory-inhibitory neurotransmitters and neuroinflammatory biomarkers. Our results showed that NAC supplementation in ketamine-treated mice decreased stereotyped and anxiety-like behaviours, without affecting social interactions. In addition, we found a decrease in hippocampal glutamate levels in ketamine-treated mice with NAC administration compared to the ketamine ones, but no differences were retrieved in GABA levels and GAD67 expression levels between the two experimental groups. As regarding neuroinflammation, there was an enhancement in kynurenine levels, together with TNF-α and NF-$\varkappa$B expression levels in ketamine-treated mice compared to controls, while NAC supplementation significantly reduced those increases. In conclusion, long lasting NAC administration was able to revert ketamine-induced stereotyped and anxiety-like behaviours, together with neuroinflammation, without affecting sociability. This opens new perspectives to implement an early approach for targeting the different ASD symptoms.

S31.4

Investigating the contribution of microbiota to ASD-like phenotype in the maternal immune activation mouse model: insights for novel therapeutic approaches

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Autism Spectrum Disorder (ASD) is a sex-biased neurodevelopmental disorder (4:1 male to female ratio) characterized by persistent deficits in social communication and interaction and restricted-repetitive patterns of behavior, interests or activities. In addition, gastrointestinal symptoms and an altered microbiota are common comorbidities in ASD. Immune system impairments such as higher peripheral levels of pro-inflammatory cytokines as well as signs of neuroinflammation (i.e. increased markers of reactive microglia and astrocytes) have been also reported in ASD. Despite the evidence that gut- and immune system-related peripheral abnormalities have a direct impact on CNS functions, the link between microbiota, neuroinflammatory state and behavioral alterations has not been explored so far in ASD. We use the maternal immune activation (MIA) mouse model, based on robust epidemiological evidence linking maternal infection during pregnancy to increased autism risk in children, to answer to two key questions. First, is prenatal or early postnatal microbiota critical to ASD-like phenotype (microbiota, neuroinflammation and behavior alterations)? Second, does the administration of the short-chain fatty acid butyrate in lactation modify or revert the ASD-like phenotype induced by MIA? The use of both male and female offspring in the experimental design allow us to verify if ASD-like behavioral phenotype is paralleled by sex-dependent alterations in neuroinflammatory mediators and microbiota composition, accounting for the male prevalence of ASD. Data collected could support the development of microbiota-targeted therapeutic interventions with the potential to modulate neuroinflammation and ameliorate behavioral deficits in ASD.

S32 "Plant-derived versus endogenous cannabinoids in the burning brain: the root of all evil, or a panacea? "

Chairs: Katarzyna Starowicz, Giuseppe Di Giovanni

S32.1

Endocannabinoids and microglia changes in a model of stroke-induced neuropathic pain: possible intervention with a palmitoylethanolamide/luteolin combination

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Central post-stroke pain (CPSP), including thalamic syndrome, is one of the most serious sequelae that can occur after a cerebrovascular accident involving any tract of central somatosensory system. The persistent, and often refractory, painful sensation can be a major problem that affects the quality of life of patients. The pharmacological treatment is still modest since the mechanisms at

its basis are still poorly understood CPSP is characterized by spontaneous and evoked pain, with typical manifestations of neuropathic pain such as hyperalgesia and allodynia. Clinical evidence strongly suggests a dysfunction in central pain pathways as an important pathophysiological factor in the development of CPSP, but the accurate underlying mechanisms remain poorly understood We used a CPSP mouse model in order to clarify the pathophysiology of this syndrome through *in vivo* microdialysis and electrophysiology. This model is based on a unilateral hemorrhagic stroke of the thalamic ventral posterolateral nucleus-VPL (whose lesion typically causes central post-stroke pain in humans) by microinjection of collagenase IV. Preliminary behavioral data showed that the sensory changes in this model are comparable to the sensory abnormalities observed in human patients suffering from CPSP. Moreover, we observed a long-term development of depressive-like behavior, similarly to other chronic pain conditions. The establishment of a neuroinflammatory condition in the surroundings of the hemorrhagic lesion involves the activation of astrocyte and microglia and the functional damage of the residual neurons mediated by those cells. This process seems to have a crucial role in supporting neuronal hyperexcitability in thalamocortical circuits and in the onset and maintenance of CPSP. Similar phenomena could happen for the cognitive and affective component of the syndrome, considering the important thalamus role in the transmission of the emotional content of sensation and pain perceptions. In this context, the modulation of endocannabinoid system by endocannabinoid-like substances, such as palmitoylethanolamide (PEA) and its derivates, can improve pain and pain-related behaviors. These results suggest that the pharmacological manipulation of the endocannabinoid system, given its neuro-immuno-modulatory role, may represent a new therapeutic target to support current therapeutic approaches in CPSP management.

S32.2
Role of Cannabinoids in Absence Epilepsy

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The use of medical/recreational marijuana and its legal market size are on the rise worldwide, including in the UK. Medical Marijuana has potential benefits for different diseases, but the lack of biomedical research and its popularity based on anecdotal evidence poses a risk to society. For instance, medical use of cannabis and derived cannabinoids show promising results in severe paediatric epilepsies. However, cannabinoids acting on the endogenous cannabinoid system can aggravate different types of seizures.Here we have clarified how the cannabinoids affect absence seizure, the most common childhood epilepsy. The failure of first and second monotherapy with anti-absence drugs in 25% of children with absence seizures and the high rate of comorbidity, including attention-deficit-hyperactivity-disorders and learning/memory impairment (which persist in seizure-free children), demand novel therapeutic approaches and the cannabinoid system may be a promising target. Using cutting-edge in vivo and *in vitro* techniques, we have investigated the effect of drugs that increase the concentration of endogenous cannabinoids in absence seizures GAERS model by blocking key catabolic enzymes. Moreover, we have characterized the effect of exogenous cannabinoids in this absence seizure model. Our preliminary data indicate a complex role of exogenous and endocannabinoids in controlling absence seizures. Since endocannabinoid modulators with an excellent safety record in humans are already available, our data may identify new targets that in the medium-term lead to a novel treatment for absence and their comorbidity.

S32.3
The Intersection Between Endocannabinoid Signaling and Resolution of Inflammation In Alzheimer's Disease

Mauro Maccarrone[1,2], Lucia Scipioni[1,2], Marina Fava[2,3], Niccolò Pellegrini[4], Francesca Ciaramellano[2,5], Sergio Oddi[2,5,3] and Alessandro Leuti[2,4]
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Specialized pro-resolving mediators (SPMs) are a novel class of ω-3 and ω-6 derived lipids that orchestrate resolution of inflammation, thus avoiding collateral tissue damage due to aberrant immune responses. Although SPMs are considered the main executioners of this process, other bioactive lipids like endocannabinoids (eCBs) can exert pro-resolving-like actions. Recent evidence suggests that SPMs and eCBs communicate and share molecular targets to coordinate immune regulation; however, their functional cross-talk remains largely unknown in both health and disease. In line with this, recent studies have

linked neuroinflammatory-related changes in Alzheimer's disease (AD) to an impaired resolution (Leuti et al., 2020). Here, we sought to investigatewhether eCB administration or FAAH inhibition could modulate metabolic enzymes and target receptors of SPMs during the resolution of neuroinflammation. Primary human macrophages were chronically treated with anandamide (AEA) or the FAAH inhibitor URB597, then resolution-related functional readouts (i.e., efferocytosis and SPMs production), expression of SPM receptors and metabolic enzymes and immunophenotypical markers (CD80, CD54, CD206, CD163) were measured as compared to vehicle-treated macrophages. In addition, endogenous levels of the main SPMs and expression of SPM receptors and metabolic enzymes were measured in the hippocampus and prefrontal cortex of Tg2576 mice—a murine model of amyloidosis-induced cognitive decline—upon chronic treatment with palmitoylethanolamide (PEA) and URB597. AEA treatment of human macrophages: i) enhanced efferocytosis in a GPR18-dependent manner, ii) modulated two pivotal enzymes involved in SPM metabolism—namely 5-lipoxigenase (5-LOX) and 15-prostaglandine dehydrogenase (15-PGDH), and iii) induced the synthesis of SPMs such as RvD1, RvD2, MaR1, and LXA4 in these cells. Furthermore, URB597 and PEA treatment resulted, in mice, in a reduced expression of SPM receptors (e.g., GPR18, GPR32, ALX, ChemR23, LGR6, and GPR37) and inactivating enzymes (15-PGDH), as well as it enhanced the expression of 5-LOX and promoted pro-resolving-like changes in the production of pro-inflammatory lipids in the hippocampus and prefrontal cortex of WT mice, with respect to Tg2576 littermates. Pharmacological modulation of the eCB tone—achieved by either direct administration of AEA/PEA or inhibition of the hydrolase FAAH—improves neuroprotection in AD by activating pro-resolving pathways.

S32.4
Network analysis to disentangle cannabidiol pharmacology in complex diseases: focus on neuropathic component of osteoarthritis

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Systems pharmacology employs computational and mathematical methods to study the network of interactions a drug may have within complex biological pathways. These tools are well suited for research on multitarget drugs, such as natural compounds, in diseases with complex etiologies, such as osteoarthritis (OA). The aim of the present study was to analyse the publicly available data in order to assess therapeutic potential of CBD in OA. Molecular targets of CBD were established through literature search. Genes associated with osteoarthritis and neuropathic pain were obtained through Open Targets Platform. Computational approach involved Venn analysis, protein-protein interactions and functional enrichment, performed with STRING and KEGG databases. Pain was assessed with kinetic weight bearing, Von Frey and Hargreaves tests. Molecular changes were characterised in cartilage and spinal cord by RT-qPCR. Open Targets Platform provided 970 and 2472 genes associated with neuropathic pain and OA, respectively. Among 60 distinct molecular targets of CBD, we have revealed receptors, which activation may result in either beneficial or detrimental effects on OA patients. CBD was able to restore impaired weight bearing, however produced thermal hyperalgesia in Hargreaves test. A key role of PPARγ in mediating the therapeutic potential of CBD was revealed, whereas upregulation of multiple transient receptor potential channels demasked CBD-induced heat hyperalgesia. Our findings pave the way for novel CBD-based therapy with improved therapeutic potential but also encourage the use of bioinformatic tools to predict the mechanism of action of CBD in different conditions.

S33 "Exploration into Future Targets for Addictions Pharmacotherapy"

Chair: Umberto Spampinato

S33.1
Effects of acylethanolamides on "food addiction": from the modulation of compulsive eating to the mitigation of withdrawal symptoms

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Although no clear consensus has yet emerged on the validity of the concept of "food addiction", a large body of experimental observations is pointing to common underlying neural mechanisms between drug addiction and aberrant eating patterns involving compulsive overeating. Such patterns are usually triggered by calorie-dense high palatable food (HPF) and often cause overweight and obesity. Identifying overlapping brain systems involved in regulating the motivational properties of palatable food and drugs of abuse might facilitate the development of effective therapeutic strategies that reduce problematic overeating and drug use. A large body of experimental evidence is pointing to the regulatory roles of acylethanolamides in the brain and their potential use as novel

pharmacological targets for the treatment of binge eating disorders and overfeeding. In our study we investigated the effects of oleoylethanolamide and of the pharmacological inhibition of its degrading enzyme, fatty acid amide hydrolase (FAAH), in two different model of compulsive eating: i) an intermittent HPF model in female rats, in which binge eating is triggered by acute mild stress exposure and history of food restriction/refeeding; ii) a chronic HPF model of obesity, in which the prolonged abstinence from a cafeteria-like palatable diet is able to produce behavioral alterations in male rats. In both models we demonstrated that either pharmacological strategy is able to normalize rat behavior and improve the neurochemical alterations induced by HPF exposure/abstinence, thus suggesting that acylethanolamides might be involved in "food addiction" and might represent an interesting novel target for the treatment of binge eating disorders or compulsive overfeeding.

S33.2

RiboTag-Seq Reveals a Compensatory cAMP Responsive Gene Network in Striatal Microglia induced by Morphine Withdrawal

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Microglia have recently been implicated in dependence to opioids. To investigate this directly, we used RNA sequencing of the "translatome"—ribosome associated RNAs from striatal microglia (RiboTag-Seq)—after the induction of morphine tolerance and then the precipitation of withdrawal by naloxone. The RNA sequencing data from individual male and female mice was analyzed using differential expression of individual genes, gene set enrichment analysis, and WCGNA with over-representation analysis. We detected large, inverse changes in RNA translation following opioid tolerance and withdrawal, and bioinformatics analysis revealed an intriguing upregulation of cAMP-associated genes with tolerance that are involved in microglial motility, morphology, and interactions with neurons. Three-dimensional histological reconstruction of microglia revealed no substantial changes in process branching and termination following opioid tolerance although cAMP effects on microglia filopodia and motility under multiphoton microscopy are ongoing. Direct activation of Gi/o-coupled DREADD receptors in microglia, rather than mimicking the effects of morphine and mitigating withdrawal, exacerbated the signs of opioid withdrawal. Together these indicate that opioid tolerance shifts the engagement of cAMP signaling in microglia and that rapid reversals in these changes occur after naloxone administration that contribute immediately to the signs of opioid withdrawal.

S33.3

Central serotonin$_{2B}$ receptor blockade inhibits cocaine-induced hyperlocomotion: role of medial prefrontal cortex dopamine release

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serotonin$_{2B}$ receptor (5-HT$_{2B}$R) antagonists inhibit cocaine-induced hyperlocomotion independently of changes of accumbal dopamine (DA) release. Given the relationship between accumbal DA activity and locomotion, and the inhibitory role of medial prefrontal cortex (mPFC) DA on subcortical DA neurotransmission and DA-dependent behaviors, the suppressive effect of 5-HT$_{2B}$R antagonists on cocaine-induced hyperlocomotion may result from an activation of mPFC DA outflow which would subsequently inhibit accumbal DA neurotransmission. Here, combining neurochemical, behavioral and cellular approaches in rats, we tested this hypothesis using two selective 5-HT$_{2B}$R antagonists, RS 127445 and LY 266097. The intraperitoneal (i.p.) administration of RS 127445 (0.16 mg/kg) or LY 266097 (0.63 mg/kg) potentiated cocaine (10 mg/kg, i.p.)-induced mPFC DA outflow. The suppressant effect of RS 127445 on cocaine-induced hyperlocomotion was no longer observed in rats with local 6-OHDA lesions in the mPFC. Also, RS 127445 blocked cocaine-induced changes of accumbal glycogen synthase kinase (GSK) 3β phosphorylation, a postsynaptic cellular marker of DA neurotransmission. Finally, in keeping with the location of 5-HT$_{2B}$Rs on GABAergic interneurons in the dorsal raphe nucleus (DRN), the intra-DRN administration of the GABA$_A$R antagonist bicuculline (100 µM or 0.1 µg/0.2 µl) prevented the effect of RS 127445 on cocaine-induced mPFC DA outflow as well as on cocaine-induced hyperlocomotion and GSK3β phosphorylation. These results show that DRN 5-HT$_{2B}$R blockade suppresses cocaine-induced hyperlocomotion by potentiation of cocaine-induced DA outflow in the mPFC and the subsequent inhibition of accumbal DA neurotransmission.

S34 "The mesopontine tegmentum: a key crossroad for the modulation of physio-pathological behaviors"

Chair: Jacques Barik

S34.1
Neuronal substrates of behavioral inhibition in the PPN

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The pedunculopontine nucleus (PPN) is composed of three neurochemically-defined neuronal subtypes: cholinergic, glutamatergic and GABAergic. Each of these neuronal groups have a distinctive connectivity pattern and maintain a close relationship with the basal ganglia. Most remarkably, we found that cholinergic and glutamatergic neurons project to the striatum and preferentially target interneurons. Optogenetic experiments revealed excitatory responses in different classes of striatal interneurons that in turn inhibit striatal projection neurons, therefore effectively blocking the striatal output through a disynaptic mechanism. In addition, recent evidence demonstrates that PPN neurons are capable of stopping motor actions by means of activating descending glutamatergic projections that target the spinal cord, or ascending GABAergic projections that target the basal ganglia. The conclusions arising from these experiments clash with the traditional view of the PPN as part of functional systems that typically elicit behavioral activation, such as the reticular activating system or the mesencephalic locomotor region. One such example is the modulatory role of PPN cholinergic and glutamatergic neurons over midbrain dopamine neurons during reinforcement learning. Given its key position as an interface between cortex, basal ganglia and spinal cord, it is possible that different subtypes of PPN neurons act in coordination to initiate certain actions while blocking other competing or outdated behavioral strategies. In my talk I will discuss the integrative role of the PPN in behavioral selection.

S34.2
Prenatal nicotine exposure is associated with cellular and synaptic changes in the laterodorsal tegmental nucleus which are likely to play a role in the high risk of motivation and attention disorders when exposed to nicotine during gestation

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As we cycle between the states of wakefulness and sleep, a bilateral cholinergic nucleus in the pontine brain stem, the laterodorsal tegmentum (LDT), plays a critical role in control of salience processing, attention, arousal, and electrophysiological signatures of the sub- and microstates of sleep. Disorders involving abnormal alterations in behavioral and motivated states, such as drug dependence likely involve dysfunctions in LDT signaling. In addition, as the LDT exhibits connectivity with the thalamus, and mesocortical circuits, as well as receives input from the prefrontal cortex, a role for the LDT in cognitive symptoms characterizing attention deficit hyperactivity disorder (ADHD) including impulsivity, inflexibility, and dysfunctions of attention is suggested. Prenatal nicotine exposure (PNE) is associated with a higher risk for later life development of drug dependence and ADHD, suggesting alteration in development of brain regions involved in these behaviors. PNE has been shown to alter glutamate and cholinergic signaling within the LDT. As glutamate and acetylcholine are major excitatory mediators, these alterations would likely alter excitatory output to target regions in limbic motivational circuits and to thalamic and cortical networks mediating executive control. Further, PNE alters neuronal development and transmission within prefrontal cortex and limbic areas, which send input to the LDT, which would compound effects of differential processing within the PNE LDT. When taken together, alterations in cholinergic and glutamatergic signaling seen in the LDT are likely to play a role in negative behavioral outcomes seen in PNE individuals, including a heightened risk of drug dependence and ADHD behaviors.

S34.3
Role of the laterodorsal tegmental nucleus in defensive behaviours

Loïc Broussot[1,2], Thomas Contesse[1,2], Renan Costa-Campos[1,2], Hugo Fofo[1,2], Thomas Lorivel[1,2], Sebastian P. Fernandez[1,2], Jacques Barik[1,2]
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Stress is a key motor of adaptation. Whenever a living organism is presented with an environmental stressful stimulus such as a threat, it activates dedicated cerebral circuitries to select the most adaptive response among a diverse repertoire of conserved defensive behaviors, which have been shaped by natural selection. In terms of behavioral outputs, defensive behaviors range from passive strategies such as freezing to active fight-or-flight responses, and the switch between these passive/active modes is essential for behavioral flexibility. Freezing is cardinal in stress-coping processes as it corresponds to a

state of hypervigilance, enabling decision-making and consequently building the most pertinent behavioral strategy. Although freezing has relevance for the etiology of threat-related disorder such as PTSD, panic attacks and social phobias, the underpinning neuronal circuits and cellular substrates are far from being understood. A large body of evidence indicates that cerebral structures such as the periaqueductal gray, the hypothalamus, or the amygdaloid complex play a major role in the detection, integration and response to threats in both rodents and humans. Yet, in light of the impact of stress on the brain, stress-coping is likely to recruit key modulatory brain networks, which could shape the freezing response. Although primarily studied for its role in reward-oriented behaviours, the laterodorsal tegmental nucleus (LDTg) has been recently shown to convey stress-related information. The LDTg is a heterogeneous nucleus located in the brainstem, receives limbic inputs and responds to somatosensory, visual and auditory stimuli. Here, we will present novel findings challenging the role of the LDTg in modulating freezing.

S34.4

Role of laterodorsal tegmentum to nucleus accumbens inputs in reinforcement

Ana João Rodrigues[1]
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Pharmacological, lesion, and optogenetic studies have involved the laterodorsal tegmentum (LDT) in reward processing and reinforcement. The LDT sends inputs to the VTA, regulating activity of midbrain dopamine neurons. Consequently, LDT indirectly impacts dopamine release in the nucleus accumbens (NAc), a key brain region in reward-related behaviors. However, LDT effects in reward-related behaviors go beyond direct control of VTA, since anatomical evidence showed that it sends direct projections to the NAc. In this seminar, we will focus on the role of the LDT-VTA/NAc triad in behavior. In a two-choice instrumental task, optical activation of LDT terminals in the VTA shifts preference to a laser-paired reward in comparison to an otherwise equal reward. In a progressive ratio task, LDT-VTA activation boosts motivation. The opposite was observed with LDT-VTA inhibition experiments. Optical activation of LDT-VTA inputs was associated with increased recruitment of NAc D1-neurons; whereas in inhibition experiments, D2-neurons appear to be preferentially recruited. Regarding LDT-NAc circuit, we will show that the majority of inputs are cholinergic, but there is also GABAergic and glutamatergic innervation. Specific activation of LDT-NAc cholinergic inputs (but not glutamatergic or GABAergic) is sufficient to shift preference, increase motivation, and drive positive reinforcement. LDT-NAc optical activation effects appeared to be mostly mediated by D1-MSNs. These results provide evidence that the LDT-VTA/NAc triad is an important player in motivated behaviors and reinforcement, and emphasizes the importance of additional studies to dissect how the LDT integrates reward information and signals through the VTA and NAc to drive reward-related behaviors.

S35 "Current Progress of Research on Neurodegenerative Diseases"

Chairs: Ahmad R. Bassiouny, James O. Olopade

S35.1

Let the brain get the best from the plant: An approach to neurophytotheraphy in relatively low resource settings

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A huge population of Africans still depends on herbal preparations either singly or in combination with western medicine. This has however proven to be of great scientific benefits as many neuroscience researchers on the continent concentrate on the investigations of these plants based on folklore abilities or explore them on the possibilities of treatment for various neurodegenerative diseases. While novel compounds can be discovered from plants with direct modulatory effects on the brain, the compounds elucidated from plants can be further reconfigured chemically to produce more potent drugs from them. Many of the science in Africa from literature show far more concentration on use of direct plant extracts and the reporting of subsequent behavioral alterations, and histological changes that results in the brain. Recently however, with more collaborations and investments in science on the continent, some researchers have performed extractions, fractionalization, and characterization of active compounds from plants and compared neurotherapeutic effects of the crude, fractions and pure compounds. Such experiments portend a great future for African neuroscience through best scientific practices, continuous collaboration and increased capacity of equipment and personnel. In this workshop, I shall be discussing on our experience with 3 plants, Grewia, Spondias and Moringa and their neurotherapeutic properties, and the huge potentials that lie ahead in the treatment of neurodegenerative diseases.

S35.2

MicroRNAs as epigenetic orchestrators of inflammation in Alzheimer's disease: Reflections from an Egyptian population study

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Alzheimer's disease (AD) is the most common neurodegenerative disorder worldwide and Egypt is one of the highest ten affected countries in the Mediterranean region. Unfortunately, accurate, non-invasive and affordable diagnosis is still lacking. AD pathophysiology involves chronic inflammation status. The critical role of inflammation mediators in microglial activation and neuronal Amyloid ($A\beta$) peptides and phosphorylated Tau misfoldings is continuously reported. Interestingly, increasing evidence imply that peripheral TNF-α level can also modulate AD progression, and high levels of inflammatory cytokines are detected in serum of AD patients. To this end, miRNAs are stable, established regulators of inflammatory molecules. They are also involved in regulating target genes that contribute to AD progression. Hence, circulating miRNAs and inflammation mediators can present promising diagnostic AD markers. However, rare studies explored the relation between circulating miRNAs and inflammatory cytokines in Egyptian AD affected patients. So in this study, we aimed to explore the differential expression of a selected miRNA panel in serum of AD patients. Secondly, we investigated the possible correlation between the measured miRNAs and serum TNF-α as possible aiding diagnostic markers for AD disease.

S35.3

Parkinson Disease, the challenge of early diagnosis and prevention

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Parkinson's disease (PD) is a by the disturbing dopaminergic cycle of the nerve cells of substantia nigra and currently incurable neurodegenerative movement disorder. Precise and timely diagnosis of Parkinson's disease is challenging, especially the pathology starts up to a decade before symptoms are severe enough to allow a diagnosis using current criteria. Artificial Intelligence (AI) specifically machine learning has recently dominated healthcare, particularly in medical imaging and there are attempts to precisely diagnose PD especially using Machine learning (ML). Machine learning is a subset of AI which allows a machine to automatically learn from past data without programming explicitly. It is getting tremendous attention considered a panacea for neurodegenerative diseases such as learning complex data patterns. It can provide various assessments for the diagnosis of PD using different deep learning techniques such as human gait information, changes in EEG dynamics which may represent early signs of cortical dysfunction, which have potential use as biomarkers of PD in the early stage. Using combined multimodal (imaging and clinical) data in these applications may further enhance PD diagnosis and early detection. We anticipate that machine-learning techniques will further help improve early detection of PD, and help detect PD at pre-motor stage to make it possible for early treatments. Conclusion, the AI through machine learning algorithms and routinely gathered assessments are vital components for the diagnosis of early PD by strictly applying scientific validation, clinical evaluation using data describing motion of upper and lower extremities, and using of big data configuration.

S35.4

Nano-curcumin Halts Pain-associated Neuroinflammation

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Inflammatory pain is triggered by tissue damage and is often accompanied by the accumulation of endogenous factors released from activated nociceptors, associated with the generation of free radicals that cause oxidative stress. The natural product curcumin has been used as a therapeutic agent in traditional Indian medicine. Curcumin has been tested as an anti-inflammatory agent for treatment for many diseases. This compound is insoluble in water which limits its bioavailability, however, Nano-curcumin (nCUR) has shown much less hydrophobicity than Curcumin with higher water solubility. Sprague Dawley rat models have aided in our understanding of the pathophysiological mechanisms of inflammation induced by peripheral injection of formalin and the neuroprotective effect of nanocurcumin. In this research we performed behavioural, histological, biochemical and molecular analyses to evaluate the antinociceptive and anti-inflammatory effects of nano-curcumin. We also assessed the expression of level of APE1 protein. Behavior test showed antinociceptive effects on nCUR -treated group as pain sensitization has decreased in this group, compared to formalin-induced one. Electron microscopy confirmed the change of cell organelles' structure and organization in formalin-treated group and showed great recovery from neuroin-

flammation in the nanocurcumin-treated group. NCUR treatment showed a significant decrease in inflammation mediators, pro-inflammatory cytokines, oxidative stress indices and an increased level of APE1 expression versus induced group. In conclusion, from the results of this investigation we propose nCUR as effective neuroprotective agent, in part, by modulating APE1/Ref-1 and regulates signaling pathways. Further studies are still required to elucidate the possible mechanism.

S36 "The Stressed brain: from humans to translational models of neuropsychiatric diseases"

Chairs: Nuno Sousa, Ioannis Sotiropoulos

S36.1
Impact of estradiol variance on the neural circuits of fear extinction: implications to psychopathology

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Fluctuations in endogenous estrogens modulate fear extinction, but the influence of exogenous estradiol is less studied. We use a well-established classical conditioning paradigm and functional MRI to study the interactions between estrogens and neural mechanisms of fear extinction in women. Specifically for this symposium, I will present data from a study in which we examined the impact of estradiol administration on fear extinction-induced brain activation, functional connectivity (FC), and resting-state in healthy women. Our focus was on whether estradiol administration in oral contraceptive (OC) users exhibit similar neural modulation as in naturally cycling (NC) women. Our sample consisted of 90 healthy women (57 OC group, 33 NC group). All participants were fear conditioned on day 1 and randomized (double-blind) to take either estradiol or placebo pill prior to extinction learning on day 2. Extinction memory retention was assessed on day 3. Skin conductance responses (SCR) and blood-oxygenated-level-dependent (BOLD) signals were collected. The influence of estradiol administration on resting-state, task-based activations, and FC was assessed. Our results show that estradiol facilitated extinction memory retention and significantly modulated the neural signature associated with fear extinction learning and memory. Estradiol administration induced a broad impact on multiple neural networks, including the default mode and the somatomotor networks. The impact of estradiol on these networks during extinction memory retention was mediated by post-extinction learning resting-state FC. I will show some data revealing some differences between NC and OC groups regarding estradiol-induced neural modulation patterns. The data from my talk will support a significant impact of estradiol on distributed neural networks associated with emotional learning and memory consolidation. Findings also provide novel insights into the distinct impact of estradiol on neural circuits depending on the current use of oral contraceptives. I will end my talk with a discussion about the potential use of estradiol administration as an adjunct to current exposure-based therapies for anxiety and fear-based disorders.

S36.2
An evaluation of cannabinoids' detrimental and therapeutic effects in experimental psychosis

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Evidence suggests an involvement of cannabinoids in psychosis and schizophrenia, but further research is needed to clarify this relationship in terms of symptomatology, pathophysiology, and respective treatment. According to our results, cannabinoids modulate basal or evoked behavioral output along with dopaminergic/glutamatergic activity in a regionally dependent manner. Moreover, escalating low-dose $\triangle^9$-tetrahydrocannabinol (THC) during adolescence disrupts motor and cognitive function, leading to long-lasting changes to neuroplasticity and neurogenesis processes in adulthood. At a translational level, these findings demonstrate a region-specific vulnerability while lacking a tangible psychosis-like profile induced by high doses of THC in adolescence. On the other hand, our most recent findings have shown that cannabidiol (CBD), a non-addictive constituent of cannabis, attenuates the psychotogenic profile of ketamine administration. These results, based on experimental approaches that mirror the symptomatology, pathophysiology, and pharmaceutical intervention of schizophrenia, suggest a complex and heterogeneous role of cannabinoids in behavioral and underlying neurobiological profiles and establish their use in modelling psychosis and schizophrenia and screening their antipsychotic potential.

S36.3
Chronic Stress & Exosomes: key players in progression and diagnosis of Alzheimer's disease

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Alzheimer's disease (AD), the leading cause of dementia, affects more than 40 million people worldwide with an estimated annual cost >$600 billion, or 1% of global GDP.

Despite the significant progress of the understanding of its neurobiological underpinnings, AD remains a complex disease with no effective treatment and poorly understood risk factors. There is an urgent need for clarification of AD precipitating factors and novel biomarkers that will aid disease early diagnosis and prognosis. Our research work focuses on the understanding of the deleterious effects of chronic stress as a risk factor for Alzheimer's disease (AD) and the role of exosomes (small extracellular vesicles), which have been suggested to contribute to the spread of brain pathology in AD and also emerge as a breakthrough biomarker tool that will serve in early diagnosis, prognosis and overall monitoring of the disease progression. Our studies in experimental animals show the aggravating role of chronic stress in AD neuropathology through the overproduction and accumulation of amyloid peptide β (Aβ) and pathological forms of Tau protein which cause structural and functional brain damage (e.g. synapse loss, atrophy, and neuronal dysfunction) as well memory impairment. We have also recently demonstrated that exposure to chronic stress or high levels of the main stress hormones, glucocorticoids (GC), dysregulate and inhibits endolysosomal pathway and autophagy leading to Tau protein accumulation and secretion via exosomes contributing to the propagation of AD brain pathology. Given that in modern lifestyles, individuals are increasingly exposed to high-stress load, it is clear that understanding the mechanistic interactions between chronic stress and the etiopathogenesis of AD will contribute substantially to both the diagnosis and treatment of the disease.

S36.4
Adult astrogliogenesis as a key mechanism underlying the pathophysiology of stress-induced depression

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Post-natal neuro and glio-plasticity is largely driven by the transduction of environmental stimuli into essential neuroadaptations. Neuro- glio-plastic maladaptations often result in the manifestation of pathological traits, from which depressive behavior is a paradigmatic example. We are investigating the pathological basis of both physiological and behavioral impairments and their potential epigenetic and molecular determinants. It is also our aim to study how depression and antidepressant drugs can modulate epigenetic patterns in key limbic areas and how this impact in the transduction of their effects. In this talk I will focus on the mechanistic link between neuro- and glio-plasticity and depression, taking into account the dynamic spatio-temporal events that define plasticity and the dichotomy between dorsal and ventral hippocampus. Moreover, we will show how glial-restricted precursor cells (GRPs) are able to modulate neuronal networks and behavior in the adult brain hippocampus. Our results highlight GRPs as a promising therapeutic approach for specific behavioral domains known to be affected by mood disorders, such as depression. Altogether, we intend to dissect the molecular cascade leading to neuron-glia/behavioral dysfunction to gain insights into the underpinnings of susceptibility and resilience to depression.

S37 "Defining the stress response of the brain, adrenal, and other organs at the molecular, cellular and tissue levels"

Chair: Youssef Anouar

S37.1
SELENOT modulates oxidative/ER stress responses in chromaffin cells in adrenal medulla and dopaminergic neurons in CNS

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Oxidative stress is central to the pathogenesis of Parkinson's disease (PD), but the mechanisms involved in the control of this stress in dopaminergic neurons have not been fully elucidated. We demonstrated that selenoprotein T (SELENOT), a new thioredoxin-like protein of the ER identified in chromaffin cells, has a potent oxidoreductase activity which is essential for embryonic development and dopaminergic neuron survival and function. Analysis of human brain samples showed that SELENOT is highly expressed in the striatum of PD patients compared to controls. Conditional disruption of the SELENOT gene in the mouse brain provoked a reduction in the size and dopamine content of the striatum. Treatment with a Parkinson's disease-inducing neurotoxin such as 1-methyl-1-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or rotenone triggered SELENOT expression in the nigrostriatal pathway of wild-type mice, but provoked rapid and severe parkinsonian-like motor defects in conditional brain SELENOT-deficient mice. Based on these findings, we designed a small peptide named PSELT as a potential

mimic of SELENOT active site to test its activity in PD animal models. PSELT proved to be efficient in protecting dopaminergic neurons *in vitro* and in vivo and could improve motor skills in animal models of PD. PSELT is cell penetrating and acts through activation of the transcription factor EZH2 to promote dopaminergic neuron survival. Our results uncover the role of SELENOT as a neuroprotective enzyme and propose PSELT as a new therapeutic candidate for treatment of PD.

S37.2

PACAP, an emergency response neuropeptide acting at multiple levels to regulate stress

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Stress responses, triggered by molecular, cellular and environmental perturbogens, are mobilized within cells and organisms to cope with intrusions on the basal state. PACAP (pituitary adenylate cyclase-activating polypeptide) is a neuropeptide that mediates stress responses at all three levels, to mediate cellular protection, neuroendocrine activation, and behavioral responses to threat. In the peripheral nervous system, PACAP is a primary neurotransmitter at sympathetic and sympathoadrenal synapses, sustaining catecholamine release and biosynthesis during prolonged systemic or psychogenic stress through induction of catecholamine biosynthetic enzymes and catecholamine release via elevation of both calcium and cyclic AMP. PACAP acts, at synapses not yet fully characterized within the brain, to boost CRH mRNA production which sustains the ability of the hypothalamopituitary adrenal (HPA) axis to enhance cortisol/corticosterone (CORT) secretion from the adrenal cortex. PACAP is also required, within a circuit arising in the parabrachial nucleus of the brain stem and projecting to the extended amygdala, for the expression of behavioral responses to psychogenic stress. Stress is accompanied by activation of the immediate-early gene (IEG) Fos at both loci in CNS, and both stress responding and Fos activation are abrogated in PACAP-deficient mice. In addition to Fos activation, PACAP and other neuropeptides control the induction of additional IEGs, including Egr1/Zif268, the latter via cAMP activation of the. neuroendocrine-specific guanine nucleotide exchange factor RapGEF2. Understanding of pleiotrophic signaling by PACAP, through its receptor PAC1, provides insight into how a single GPCR can shape molecular, cellular and organ responses to stress through multiple, cell-specific, signaling pathways.

S37.3

Protective effect of blocking Redox factor-1 activity during pain signaling

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Inflammatory pain is sophisticated condition which implicate many key signaling components of the CNS. APE1/Ref-1 is one of the crucial, multifunctional cellular modulator that is highly expressed in the CNS. Hence, in the current study we extended our previous investigation on the possible implication of the redox activity function of the pleotropic APE1/Ref-1 protein in formalin-induced inflammatory pain. The processing of inflammatory pain signals from periphery (injection of 50µl formalin in rat hind paw) to the spinal cord was assessed at molecular level in the presence and absence of co-administration of the selective redox activity inhibitor, E3330. The results indicated that the co-administration of the chemical compound E3330, significantly ameliorated the projection of key pro-inflammatory cytokines from spinal cord tissue (NF-KB, IL-1β, IL-6, TNFα, and its receptor as well as iNOS expression) versus the induced group. The protective effect of E3330 was further confirmed by electron microscopic analysis as a supporting evidence which confirmed the E3330 positive enhancement effect on Golgi apparatus, mitochondrial cisternae and myelin sheaths preservation superior formalin-induced group. In conclusion, redox activity is considered promising future target for therapeutic development and further investigations are still required to pinpoint the exact mechanism.

S37.4

Stress-induced functional adaptive changes in the adrenal medullary tissue

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In mammals, catecholamine secretion from adrenal chromaffin cells is a key event helping the organism to cope with stressful situations. Adrenomedullary stimulus-secretion coupling relies on both a neurogenic command arising from the splanchnic nerve terminals synapsing onto chromaffin cells and a local gap junction-mediated intercellular communication between chromaffin cells. Chromaffin cell excitability, cholinergic neurotransmission and gap junctional communication are remodeled in stressed rats. Cold exposure (5 days, 4°C) induces an increase in action potential frequency in chromaffin cells. The

frequency of the spontaneous excitatory post-synaptic currents is alco increased in cold-stressed animals. Interestingly, the nature of nicotinic cholinergic receptors (nAChRs) involved in synaptic transmission differs between unstressed and stressed animals. Whilst α3 nAChRs are the main contributing channels in control rats, α9-containing nAChRs dominantly contribute to synaptic currents and acetylcholine-induced currents in rats exposed to cold. Consistently, expression levels of α9 nAChR transcript and protein are overexpressed in stressed rats. Gap junction-dependent intercellular communication between chromaffin cells is also enhanced in response to stress. This correlates with the appearance of a robust electrical coupling, allowing action potentials to propagate between cells. This is associated with an increased expression of two main connexins expressed in chromaffin cells, Cx36 and Cx43. It is noteworthy that a stress-triggered upregulation of gap junctional coupling is similarly observed in mice. Collectively, these results show that the adrenomedullary tissue remodels in response to a physiological stress and that chromaffin cell stimulus-secretion coupling undergoes functional adaptation to generate an appropriate secretory behaviour to cope with stress.

S38 "Role of gut-brain axis on the etiopathogenesis of mood disorders"

Chairs: Luigia Trabace, Giuseppina Mattace Raso

S38.1
Gut microbiota alteration linked to anxiety-like behavior in a mouse model harboring Kir4.1-R18Q gain-of-function mutation associated with autism

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Dysbiotic profiles of the gut microbiota (GM) have been described in several psychiatric conditions and their potential to impact brain function is largely under investigation in Autism Spectrum Disorders (ASD). In a cohort of children characterized by Autism-Epilepsy phenotype new variants in the *KCNJ10* gene encoding for the inwardly-rectifying K^+ channel, Kir4.1, such as R18Q, V84M and R348H that resulted in gain-of-function of the channel, have been identified. To further assess the pathophysiological relevance of these variants, we generated a mutant rodent model of the disease (Kir4.1-R18Q) using CRISPR-Cas9 technology. Patch-clamp recordings and Western blot analyses on cultured cortical astrocytes showed that Kir4.1-R18Q mice derived cells possess increases in Kir4.1 current density and protein. Significant abnormalities in tests employed to assess Kir4.1-R18Q mice's level of anxiety and autistic-like behavior have been detected. Kir4.1-R18Q mice showed a shift in the overall GM structure with taxonomic adaptations also reported in other studies exploring the role of GM in mood disorders and autism. Specifically, we found a decrease of butyrate-producing bacteria along with an increase in genera containing opportunistic pathogens such as Odoribacter and *Parasutterella*. Our data indicate that genetically-induced enhancement of Kir4.1 expression alters GM and behavior phenotype, advising Kir4.1-R18Q mice as a valid animal model to study the vicious circle of gut-brain axis related to neurodevelopmental diseases. Furthermore, the association of genetic risk factors with specific microbiota profiles may represent an ideal approach to establish the differential diagnosis and to develop precision medicine and prevention in the complex pathophysiology of ASD.

S38.2
Gut-brain axis: palmitoylethanolamide, a PPAR-α agonist, counteracts obesity-induced mood disorders

Adriano Lama[1], Claudio Pirozzi[1], Chiara Annunziata[1], Federica Comella[1], Rosaria Meli[1], Giuseppina Mattace Raso[1]

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Obesity and mood disorders have become prevalent during the last years, especially during COVID-19 pandemic, representing public health problems. The pathogenic mechanisms of this comorbidity are multiple but low-grade inflammatory state and dysbiosis induced by lipid overload could represent the starting point. Indeed, peripheral pro-inflammatory cytokines reach the hypothalamus, the main regulator of food intake, triggering microglial and astrocytic activation and the following neuroinflammation. The onset of these deleterious events affects other connected brain areas, such as mesolimbic system which regulates motivation and reward, inducing mood alterations. Palmitoylethanolamide (PEA) has proven to be a multi-target compound, whose metabolic and central effects have been associated to activation of peroxisome proliferator activated receptor (PPAR)-α. Here, the focus was set on the capability of PEA in limiting obesity-induced mood disorders.

We used a consolidated animal model of high-fat diet (HFD)-induced obesity, where male C57Bl/6J mice were fed with HFD for 12 weeks and then treated with an ultra-micronized formulation of PEA (um-PEA) for 7 weeks. We demonstrated that um-PEA limited mood alterations of obese mice by behavioral tests, increasing their responsiveness and effort to escape from adverse states, improving self-care and hedonic behavior, reducing thigmotaxis, and improving cognitive functions. The improvement of behavioral features by PEA was associated with the modulation of monoamine pathways in different brain areas, the stimulation of synaptic plasticity and neurogenesis, and the counteraction of HFD-induced neuroinflammation. Taken together, um-PEA represents a multifunctional compound useful to limit complex disorders, where the role of the gut-brain axis is crucial.

S38.3
Dysfunction of the immune system in the pathogenesis of depression: role of n-3 PUFA deficiency

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It is now well recognized the undisputed benefit that correct eating habits as well as the presence in the diet of certain macronutrients plays a fundamental role in the correct functioning of our central nervous system. Among the various mechanisms underlying this, the study of reciprocal gut-brain communication has laid the foundation for understanding the impact of nutrients on brain disorders. Reduced dietary n-3 polyunsaturated fatty acids (PUFA) consumption has been associated with the development of depressive symptoms. Indeed, we have previously found that lifelong exposure to n-3 PUFA deficient diet in female and male rats leads to depressive-like symptoms in early adulthood. In this study, we also focused our attention on adolescence and plain adulthood periods. Our findings strongly suggest that the lack of n-3 PUFA during developmental period was an important risk factor for evoking depressive-like behaviors, quantified by forced swimming and sucrose preference tests. In addition, we found that n-3 PUFA deficiency led to depressive tryptophan shift toward kynurenine (KYN) production as consequence of indolamine-2,3-dioxygenase activation driven by stress response hyper-activation. The perpetuating of such dietary deficiency caused everlasting high KYN levels and a pseudoinflammation prompting to innate immune activation underlined by overexpression of central toll like receptors type 2 and 4. Such pseudoinflammatory state in turn was accompanied by increased Aβ oligomer production and by lower serotonin amount.

S38.4
Natural compulsive-like behavior in an animal model of OCD is associated with altered gut microbiota composition: Implications for comorbid anxiety and mood disorders

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Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts and repetitive behaviors, with compulsivity related anxiety that is context-specific. Available treatment is suboptimal, while anxiolytics are ineffective. Certain OCD phenotypes may be more prone to developing anxiety, e.g. harm avoidance or contamination OCD. Chronic anxiety states can progress to major depression. A disordered gut-brain axis (GBA) has been advocated to play a causal role in psychiatric illness. While definitive evidence for gut dysbiosis in OCD is lacking, case reports suggest that the introduction of Bifidobacterium and Lactobacillus can improve symptoms of anxiety, depression and OCD. The deer mouse (DM) has robust predictive and face validity for OCD, including motor stereotypies and excessive nest building, the latter a security/safety motivated behavior. High stereotypic DM display disordered frontal cortical redox, suggesting a redox-inflammation - stereotypy association. DM also present with significant differences in gut microbiota in large nest builders, with genera in large (security motivated) nest builders associated with pro-inflammatory properties (Desulfovermiculus, Aestuariispira, Peptococcus and Holdemanella) while genera in normal nest builders are associated with anti-inflammatory properties (Prevotella and Anaeroplasma). This suggests a causal role for redox-inflammation and a disordered GBA in anxiety-related behavior in DM and possibly OCD. Excessive nest building in DM is expressed at the cost of other functions and regarded as a naturalistic maladaptation. Large nest building suggests bolstered anxiety driven security motivation, a typical manifestation in harm avoidance OCD, viz. safety (excessive checking) and contamination (excessive washing). Thus, OCD may co-present with anxiety and predict later mood disorders.

S39 "Deciphering the intricate glial response in aging and neurodegenerative disorders: from cellular changes to therapeutics"

Chairs: Caterina Scuderi, Erika Gyengesi

S39.1
What differentiates an aged astrocyte from an Alzheimer's one? Looking for cellular differences for the development of new therapies

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Old age is the main risk factor for sporadic Alzheimer's disease (AD). Histopathologically, AD is characterized by peculiar cellular modifications that occur well in advance of the clinical symptoms. These are neuronal loss, the formations of neurofibrillary tangles, and deposition of beta-amyloid peptides in senile plaques. Besides aberrant proteins deposits, alterations of both glia morphology and activities have been observed. Among glial cells, astrocytes emerge as central elements in Alzheimer's disease etiology or progression, mainly because of their ability to maintain brain homeostasis at all levels of organization. In AD, both astrocytic reactivity and atrophy have been identified. These responses are considered pathological, and both contribute to the perturbation of brain homeostasis leading to neuronal damage and cell death. Are these alterations due to AD or are they a consequence of aging? To answer this question, we studied the expression of specific astrocytic and microglial structural and functional proteins in different preclinical models of AD, testing the effects of several compounds such as cannabidiol (the main non-psychoactive component of Cannabis sativa) and palmitoylethanolamide (an endogenous lipid compound). Our data show the presence of varied astrocytic responses that depend on the model used and the stage of the pathology. Moreover, the results of MRI/MRS experiments performed to evaluate brain metabolism in young and adult 3xTg-AD mice suggest that aging, rather than AD progression, importantly affects mice cerebral metabolism. In our experimental conditions, astrocytes appeared the most vulnerable cells, whose structure and functions were profoundly modified. Our data open novel perspectives in the field of astrocyte functions in health and disease, suggesting their potential as pharmacological targets.

S39.2
Directly converted astrocytes retain the ageing features of the donor fibroblasts and elucidate the astrocytic contribution to human CNS health and disease

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Astrocytes are highly specialised cells, responsible for CNS homeostasis and neuronal activity. Lack of human *in vitro* systems able to recapitulate the functional changes affecting astrocytes during ageing represents a major limitation to studying mechanisms and potential therapies aiming to preserve neuronal health. Here we show that induced astrocytes from fibroblasts donors in their childhood or adulthood display age-related transcriptional differences and functionally diverge in a spectrum of age-associated features also involved in neurodegenerative disorders. Astrocytes from older donors display lower response to oxidative stress with consequent accumulation of cellular reactive oxygen species, impaired nucleocytoplasmic transport and higher levels of DNA damage. Remarkably, we also show an age-related differential response of induced Astrocytes in their ability to support neurons in co-culture upon pro-inflammatory stimuli. These results show that induced Astrocytes are a renewable, readily available resource of human glia that retain the age-related features of the donor fibroblasts, making them a unique and valuable model to interrogate human astrocyte function over time in human CNS health and disease.

S39.3
Glia and Neural Cell Stem cross-talk in aging and neurodegeneration

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Adult neurogenesis (aNG) occurs constitutively in discrete brain regions such as the dentate gyrus (DG), the subventricular zone and the hypothalamus. It is currently believed that the intrinsic structural plasticity of the adult neurogenic process allows the brain to face and adapt to the continuously changing external and internal environment throughout the entire lifespan. In particular, adult hippocampal neurogenesis (ahNG) has attracted growing interest due to its involvement in cognition, memory, and emotional behavior. On the other hand, it has been proposed that deregulated ahNG may play a role in cognitive impairment and mood alterations associated with aging and neurodegenerative disorders. Adult neurogenesis requires the coordinated interplay between different cell types within the specialized microenvironment of the neurogenic niche. We will share and discuss recent data supporting an important role of glial cells in the modu-

lation of aNG under both physiological and pathological conditions. Particularly, focus will be devoted on: i) the role of astrocytes and their secretome as active contributors in the balance between quiescence and self-renewal of Neural Stem Cells (NSC), in the regulation of their differentiation programs as well as in the survival/integration of newborn neurons; ii) the relevance of dysregulated astrocyte-NSC cross-talk in selected pathophysiological conditions; iii) the possibility that a better understanding of astrocyte-NSC cross-talk alterations may disclose novel pharmacological strategies in aging and in neurodegenerative disorders.

S39.4

The contribution of glial reactivity in aging and neurodegenerative disorders: from cellular modifications to possible therapeutic approaches

Erika Gyengesi[1], Rashmi Gamage[1], Ilaria Rossetti[1], Ingrid Wagnon[1], Ryan Childs[1], Garry Niedermayer[2], Gerald Münch[1]

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Chronic neuroinflammation is a promising therapeutic target in many neurodegenerative and age-related brain disorders. In this study, we investigated two highly bioavailable curcumin preparations, Longvida® (LC) and Meriva® (MC) for their anti-inflammatory properties, using the GFAP-IL6 mouse model. We hypothesized that the highly bioavailable curcumin, as a potent cytokine-suppressive anti-inflammatory drug, will decrease microglial and astroglial activation, and consequently improve motor and cognitive functions. GFAP-IL6 and wild type mice were fed with LC and MC for 1 and 6 months, respectively. LC fed mice were tested on the elevated walking beam, Rotarod, Barnes maze and Novel object recognition tests before all the mice were sacrificed. Immunohistological staining for microglia and astrocytes were carried out and stereological analysis was completed for all groups. Short term MC oral administration lead to a dose-dependent reduction in neuroinflammatory markers. Moreover, MC decreased the number of activated microglia and astroglia, as well as changed the microglial morphology from activated to resting state. Long term LC treatment led to a significant decrease in the number of microglia in the hippocampus and cerebellum and in turn, led to significant improvement of both motor and cognitive function. Both short- and long-term consumption of modified curcumin preparations significantly downregulated microglial activation GFAP-IL6 mice. Spatial memory and recognition memory improvements were also found in mice fed with LC in comparison to control counterparts. Our results promise potential therapeutic applications of both Longvida® and Meriva® curcumin against brain inflammation and associated cognitive and motor decline.

S40 "There's a time to make a change: how early exposure to drugs of abuse or to environmental challenges may affect the mesocorticolimbic pathway"

Chair: Carla Cannizzaro

S40.1

Cannabinoids modulate cognitive deficits induced by prenatal alcohol exposure in mice

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Alcohol exposure during development can produce physical, mental and behavioural disabilities. Several molecular mechanisms might underly teratogenesis induced by alcohol, including alterations of endocannabinoids signaling. Moreover, the phytocannabinoid cannabidiol has arisen as an anti-inflammatory agent that might be useful for the treatment of neuropsychiatric disorders. In this study, we focus on the modulatory effects of the endocannabinoid system to restore the cognitive deficits produced by prenatal and postnatal alcohol exposure in mice, and on the possible mechanisms of these effects. Additionally, we assessed the effects of cannabidiol on cognitive deficits produced by early alcohol exposure. For that, pregnant C57Bl/6 female mice were exposed to an experimental protocol of "drinking-in-the-dark" test from gestation to weaning. Offspring was treated with cannabidiol from post-natal day (PD) 25 until PD34. A second group of mice was treated with fatty acid amide hydrolase (FAAH) inhibitor URB597 during 10 consecutive days, starting at PD25. Finally, we evaluate the neurobehavioural performance of the adult offspring at PD60 employing a battery of cognitive tests, including the novel object recognition, novel object location and reference memory tasks. Furthermore, we analyzed long-term pro-inflammatory and apoptotic markers within the prefrontal cortex and hippocampus. Our findings show that cannabidiol treatment and FAAH inhibition during critical periods of development ameliorate cognitive deficits observed in the foetal alcoholic spectrum disorder-like mouse model. Moreover, cannabidiol restores the levels of neuroinflammatory markers in the discrete brain areas. Consequently,

the manipulation of endocannabinoid system might be a potential target to counteract certain impairments of cognitive domain during critical developmental periods.

S40.2

Pre-natal Cannabinoid Exposure Leads to Long-Term Abnormalities in Brain Omega-3 Fatty Acid Levels and Sex-Dependent Schizophrenia-like Dysregulation of the Mesocorticolimbic Circuitry

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Deficiencies in Omega-3 and arachidonic fatty acids in mesocorticolimbic brain circuits and neurodevelopmental exposure to cannabinoids, are both linked to increased risk of mental health disorders, including schizophrenia, anxiety and depression. Dietary interventions with omega-3 supplementation are reported to reduce the transition to psychosis in clinical populations at high risk for schizophrenia. These pathological fatty acid phenotypes are associated with deficits in synaptic efficiency and neuronal modelling. In addition, cannabinoids can modulate Omega-3 and arachidonic acid (AA) signaling. Using a rodent model of pre-natal delta-9-tetrahydrocannibinol (THC) exposure, we combined in vivo neuronal electrophysiology, behavioural modelling of schizophrenia-like affective and cognitive phenotypes and matrix-assisted laser deionization imaging (MALDI) to measure expression levels of the Omega-3 fatty acid (DHA) and associated signaling pathways, including glycerophospholipids, in various brain regions. We report that pre-natal THC exposure causes a substantial loss of DHA and AA in various mesocorticolimbic structures. In addition, we observed several sex-dependent differences in male vs female offspring in terms of schizophrenia-like neuronal, molecular and behavioural endophenotypes. Finally, pre-natal THC exposure led to profound, sex-dependent disturbances in resting neuronal activity phenotypes in the ventral tegmental area, prefrontal cortex and hippocampus. This presentation will report on these findings and the results of a maternal dietary intervention with Omega-3 fatty-acid rich diet on the phenotypic outcomes of THC-exposed offspring. Our findings demonstrate that pre-natal THC exposure can induce profound dysregulation of neural Omega-3 fatty and AA levels which may predispose offspring to long-term mesocorticolimbic dysregulation and increased neuropsychiatric vulnerability.

S40.3

Mild maternal separation in mice of both sexes affects the dopaminergic system and has an impact in adulthood on vigor to approach or to escape motivational stimuli

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Early-life stress affects brain development and can lead to psychiatric disorders, such as depression, later in life. Little is known about the effect of early-life stress on motivational processes such as effort-based decision-making. Mesolimbic dopamine (DA) regulates activation and effort in motivated behaviors. Stress changes DA systems. Maternal Separation (MS) could act as an early-life stressor depending on its duration and intensity. Using CD1 male and female mice, we evaluated the impact of early but mild MS (PND3-5, 90 min each day), on selection of effortful responses in adulthood under positive or aversive conditions. In a three-choice-T-maze task, engagement in effortful activities such as running in a wheel (RW) versus sedentary eating sweet pellets was evaluated, and in a forced swim task (FST), time dedicated to vigorously escape versus passively floating was measured. In both sexes, MS mice spent more time in the RW, and climbing in the FST, showing an increase in relative preferences for activity-based reinforcers, and persistence in vigorous escaping from aversive contexts compared to non-separated mice. Thus, mild early-life stress potentiates effortful behaviors independently of the emotional valence of the situation. In adulthood, after administering tetrabenazine (TBZ), a VMAT-2 blocker that depletes DA, only males showed anergia: reduced time in the RW, increased time eating in the T-maze, and reduced climbing and increased immobility in the FST. MS increased cerebral dopamine neurotrophic factor (CDNF) in accumbens only among females, suggesting that this neurotrophic factor may protect mesolimbic DA regulated functions.

S40.4

Beyond the booze fun: binge alcohol drinking during adolescence alters dopamine and glutamate homeostasis in the nucleus accumbens and jeopardizes social resilience in rats

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Binge alcohol drinking is increasingly common among adolescents and repeated alcohol withdrawals may negatively impact on the underdeveloped neural substrates that process reward and stress response. As socially stressful events pose an additional challenge for brain regions key to reward processing, such as the nucleus accumbens (NAc), this research explored the consequences of binge alcohol drinking during adolescence on affective behaviour and social stress coping during withdrawal, in addition to dopamine- and glutamate-related neuroplasticity in the NAc. Adolescent male rats underwent a three-week binge-like alcohol—or water—exposure, and assessed for hedonic response, in the social preference- and sucrose consumption test, and anxiety-like behaviour, in the novelty suppressed feeding test; moreover, rats underwent repeated social stress in the resident-intruder paradigm and evaluated for defensive coping strategy. Pre- and postsynaptic markers of dopamine- and glutamate signaling in the NAc, as well as serum corticosterone level, were evaluated by immunofluorescence, gene expression and ELISA. Our results show that binge alcohol exposure during adolescence altered social preference, sucrose consumption and anxiety-like behaviour during early- and late withdrawal, with dynamic rearrangements of dopamine- and glutamate signaling in the NAc. In rats exposed to social stress, binge alcohol exposure increased passive coping, induced an abnormal stress response, with opposite effects on stress-induced dopamine and glutamate-related neuroplasticity in the NAc. Binge alcohol drinking during adolescence induced long-term consequences on affective and social resilience, with perturbation of the NAc microcircuits that may constitute a locus minoris resistentiae for stress- induced pathologies in early adulthood.

S41 "Brain circuits and astroglia: unveiling causative interactions"

Chair: Dmitri Rusakov

S41.1
Astrocytes close the critical period plasticity in the visual system

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Critical developmental periods are periods of early postnatal development during which neuronal networks are highly plastic and sensitive to experience. Termination of these periods of intense plasticity is associated with settling of neuronal circuits, allowing for efficient information processing. Yet, the cellular processes defining the timing of these developmental periods remain unclear. Here, I will present data showing that astrocytes contribute to the closure of the critical period in the mouse visual cortex via an unconventional signaling pathway controlling the maturation of interneurons. These data indicate that astrocytes play an essential role in the experience-dependent plasticity of brain developing circuits, and point to a novel cellular targets to treat neurological disorders involving defects in the closure of critical periods.

S41.2
Accurate interplay between GABAergic signaling and astrocytes in prefrontal cortex improves decision-making

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Interneurons and GABAergic activity play are fundamental for precise control of brain networks coordination and animal behavior. Astrocytes have relevant roles in synaptic transmission and plasticity by sensing synaptically released neurotransmitters, including GABA. However, the GABAergic control of astrocyte-neuron communication in brain circuits and its behavioral outcome are still poorly defined. Therefore, we will discuss recent data showing how GABAergic signaling in astrocytes enables the temporally accurate excitation/inhibition balance in prefrontal cortical circuits, driving correct animal performance. As result, we will propose the existence of functional GABAergic units established between cortical interneurons and astrocytes, which tune the prefrontal cortex operation modes that dictate goal-directed behaviors.

S41.3
MicroRNA control of astrocytes in epilepsy

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Epilepsy is one the most common neurological diseases; affecting more than 70 million people worldwide – more than 6 million in Europe alone. At least 30% of people with epilepsy do not respond to commonly available anti-epileptic drugs. A universal hallmark of epileptic tissue is astrocyte dysfunction which has received little attention as a therapeutic target. Astrocytes play an active role in shaping and maintaining neuronal circuits. Molecular signal exchange between astrocytes and synapses occurs in a highly heterogeneous microenvironment. The molecular machinery for microRNA-controlled translation is present locally within astrocyte processes that surround synapses throughout the brain. MicroRNA function is widely disrupted in the epileptic brain and targeting microRNAs in neurons alleviates seizures in epilepsy. We tested a novel strategy for seizure-suppressive or disease-modifying actions that specifically target astrocytes to prevent excessive network excitation and thus seizure generation. We employed super-resolution single molecule localisation microscopy of hippocampal brain tissue to assess astrocyte morphology in healthy and epileptic brain. Super-resolution microscopy can circumvent the optical diffraction limit and offers ease of use and flexibility not seen in electron microscopy. We isolated astrocyte processes in the vicinity of synapses and analysed the microRNAs present. In future work, we will target candidate microRNAs to influence astrocyte morphology, and increase local translation of neurotransmitter and ion channels in astrocytic processes. In turn, this will allow the clearing of excess glutamate and potassium from the synaptic cleft and hence prevents synchronous neuronal discharges that generate seizures.

S41.4
Long-term potentiation and inter-synaptic cross-talk

Dmitri A. Rusakov[1]
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Cell-cell excitatory transmission in central circuits depends on rapid uptake of glutamate by high-affinity transporters expressed in perisynaptic astroglial processes (PAPs). Memory formation in the brain relies on remodelling of synapses, but whether the morphology and glutamate buffering capacity of PAPs remains are also affected remains poorly understood. This long-standing question has been a challenge because the nanoscopic dimensions of PAPs are beyond the diffraction limit of traditional optical microscopy. We applied microscopy methods that are independent of light diffraction to find that a classical mechanism of synaptic memory, long-term potentiation (LTP), prompts PAP shrinkage and withdrawal away from potentiated synapses. Patch-clamp electrophysiology combined with optical glutamate sensors (iGluSnFR) and three-colour 3D dSTORM super-resolution imaging in acute hippocampal slices reveal that LTP induction thus initiate retreat of perisynaptic astroglial glutamate transporters GLT-1, boosting glutamate spillover and NMDA receptor-mediated inter-synaptic cross-talk. The LTP-triggered PAP withdrawal can also be triggered by the whisker-stimulation induced LTP in the barrel cortex in vivo. In more recent experiments in awake animals, we also detect increased glutamate escape following LTP induction, using a novel multiplexed imaging method that enables tracking synaptic efficacy changes and glutamate escape at individual synapses. These findings uncover mechanisms by which inducing a memory trace alters signal integration rules in the astroglial microenvironment of excitatory synapses.

S42 "Novel Psychoactive Substances (NPS): new exciting findings"

Chairs: Aviv Weinstein, Sabrine Bilel

S42.1
Pharmacotoxicological effects of fentanyls in the mouse: *in vitro* and *in vivo* pharmacokinetic and pharmacodynamic studies

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[1] *Department of Translational Medicine, Section of Legal Medicine and LTTA Centre, University of Ferrara, Ferrara, Italy;* [2] *Collaborative Center for the Italian National Early Warning System, Department of Anti-Drug Policies, Presidency of the Council of Ministers, Italy*

Novel Synthetic Opioids is a growing class of new psychoactive substances mostly consisting of analogues of fentanyl that have caused numerous overdose and fatalities worldwide. The analogues of fentanyl that has been recently seized are usually generated by a modification of fentanyl's propionyl chain. Data on the pharmacology of these compounds are limited. The aim of our study is to investigate the *in vitro* and *in vivo* pharmacodynamic profile of Acrylfentanyl, Ocfentanyl and Furanylfentanyl compared with Fentanyl. *In vitro* results revealed that all Fentanyl derivatives were able to activate the mu opioid receptor in a concentration dependent manner. In calcium mobilization assay, compounds were able to elicit maximal effects similar to that of dermorphin, with the exception of Furanylfentanyl that displayed lower max-

imal effects. In the BRET G-protein assay, all compounds mimicked the maximal effects of dermorphin on G-protein. While, Fentanyl, Acrylfentanyl, and Ocfentanyl behaved as partial agonists for the β-arrestin-2 pathway in comparison with dermorphin whereas Furanylfentanyl was inactive on β-arrestin-2. *In vivo*, all the compounds impaired sensorimotor, motor and cardiorespiratory parameters of the mice. The present study demonstrates that Acrylfentanyl, Ocfentanyl and Furanylfentanyl behave similarly to Fentanyl as mu opioid agonists. In difference to Fentanyl and the two other compound tested, Furanylfentanyl acts as a partial agonist at mu opioid receptors, it's inactive on β-arrestin-2 recruitment and shows lower efficacy in most of the behavioral tests. These data reveal the high risk of use of these compounds and prove the relation between the chemical structure and the pharmaco-toxicology of the fentanyl analogs.

S42.2

The effects of synthetic cannabinoids on executive function and the brain

Aviv Weinstein[1]

[1] *Department of Behavioral Science, Ariel University, Ariel, Israel*

The aims of our studies were to investigate the effects of chronic use of synthetic cannabinoids on the brain's structure and function, cognitive and emotional function and schizotypal personality disorder and personality. Synthetic cannabinoid users have exhibited overall smaller grey matter volume than control participants, and in specific regions: insula, the inferior frontal gyrus, the anterior cingulate cortex and the precuneus. These brain regions are rich with cannabinoid CB1-receptors and are associated with addictive behaviors, cannabis use and abstinence. Secondly, SC users were less accurate and showed longer reaction times on the 2-back and 1-back task than control participants. On the high working memory load, control participants showed additional activation in both the parahippocampal gyrus and the precuneus, areas associated with the default mode network. We have further found impairments in mental flexibility (WCST task), impulsivity (Go No Go task) and response to emotional words (Stroop) in SC users. Furthermore, SC users were more depressed, had higher scores of schizotypal personality disorder and were more introverted, neurotic and less conscientious on the big five questionnaire compared with regular cannabis users and control participants. In conclusion, these findings may have major implications for our understanding of the long-term consequences of synthetic cannabis on cognitive and brain function. We currently run a study using F-DOPA in PET MR to assess dopamine function and neural networks in SC users. We have also started a study using dTMS to treat chronic SC users and we plan to present preliminary results of both studies.

S42.3

Repeated ketamine induces a regionally specific plasticity dysregulation and behavioral alterations related to schizophrenia. The impact of Cannabidiol administration.

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Repeated ketamine (KET) administration has been used as an animal model of schizophrenia, while the neurobiological underpinnings are poorly understood. Cannabidiol (CBD), a non-addictive phytocannabinoid has been reported to present antipsychotic potential, but the mechanisms involved are still unknown. This study aims to investigate specific behavioral, neurochemical, and neurobiological aspects related to schizophrenia, emphasizing on plasticity processes induced by repeated KET and to explore the potential mitigating role of CBD. Sprague-Dawley rats underwent a 10-day-long treatment of 30 mg/kg/day KET, followed by a 5-day long treatment with 10 mg/kg/day of CBD. Subsequently, rats underwent amphetamine challenge on the open field, novel object recognition, social interaction, and pre-pulse inhibition behavioral tests. Glutamatergic activity has been estimated in the prefrontal cortex, dorsal, and ventral hippocampus of treated rats, using HPLC-ED. Additionally, neuroplasticity markers were estimated in the abovementioned regions using immunoblots, and Golgi-stained ventral-CA1 pyramidal neurons underwent morphological analyses. KET affected positive-, cognitive-, and negative-like behavioral indices. Subsequent analyses revealed a differentiated profile of glutamatergic function and neuroplasticity marker's expression in the cortex versus hippocampi, an effect that CBD partially mitigates. Moreover, KET affected dendritic morphology, while CBD restored this effect. KET induced a schizophrenia-related bio-phenotype in terms of behavior, neurochemical, and neurobiological analyses. CBD ameliorated the behavioral aspects of this schizophrenia-like profile while modulated the neurochemical alterations and the neurobiological underpinnings of the bio-phenotype in a differentiated manner in the cortex versus hippocampi. Our findings characterize further the schizophrenia-like bio-phenotype induced by KET, and en-

rich our understanding on CBD's antipsychotic potential.

S43 "Sex & Genes & Stress: Probing these factors in rodents models for a better understanding of psychiatric disorders"

Chairs: Anna Y. Yotova, David A. Slattery

S43.1
Sex differences in the role of GPER-1 in motivated behaviors

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Affective disorders pose a major burden in modern western societies and women are twice as vulnerable as men. Recent findings link rapid neuroestrogen signaling with depression/anxiety and the newly-identified G protein-coupled estrogen receptor 1 (GPER1). Furthermore, it appears that the unique rapid antidepressant action of the glutamatergic agent, ketamine, shares striking similarities with the neuroestrogen-mediated GPER1 rapid signaling. Therefore, our group aims to understand the role of GPER1, which could reveal novel therapeutic pathways for the faster and better treatment of mood disorders in men and women. In a recent experiment, adult male and female Wistar rats received acutely either vehicle, a GPER1 agonist (G1) or antagonist (G15), fluoxetine, ketamine or the combination of the aforementioned treatments. All animals were subjected to the Open field (OF), Light/Dark test (L/D test), Novelty suppressed feeding test (NSFT), and Forced swim test. Results of this ongoing study, reveal that G15 blocks ketamine's effects in center entries during OF and in the latency to consume the presented food during NSFT only in males. Similarly, G15 blocks G1's effect in the number of transitions between the two compartments in the L/D test in males. G1+ketamine had a synergistic effect and decreased the latency to consume the presented food in males. Sex differences were also identified as before. Our findings may lead to the identification of a novel target, whose pharmacological agonism could improve the quality of life for millions of patients worldwide.

S43.2
Sex & Genes & Inflammation: Effects of prenatal immune challenge on phenotype and synaptic protein composition before birth and in adulthood

Anna Y. Yotova[1]
[1]*Department of Psychiatry, Psychosomatic Medicine, and Psychotherapy, University Hospital Frankfurt, Germany / Institute of Cell Biology and Neuroscience, Faculty of Biological Sciences, Goethe University Frankfurt, Germany*

Environmental and genetic influences have been repeatedly identified as risk factors for multiple neuropsychiatric developmental disorders (NDDs). Here, I will show our work utilising the maternal immune activation (MIA) mouse model, mimicking viral infection during early pregnancy, and its sex-dependent effects on NDD-relevant behaviours of adult mice. Furthermore, I will present novel insights by comparing the synaptic proteome of MIA offspring before birth and in adult hippocampi, concentrating again on sex differences. Furthermore, I will give an overview of neuromorphological effects of MIA in cortical cell culture from embryos and in situ in brain regions of adults of both sexes. Ongoing investigations combining MIA and transgenic models of developmental regulator genes should expand our understanding of the role of genetic and environmental risks, and their interplay in NDDs of interest.

S43.3
Insulin signalling — A Trojan Horse of mental disorders

David A. Slattery[1]
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In this talk, I will discuss the core concept of the PRIME EU study (https://prime-study.eu/) of insulin signalling as a key mechanism underlying the multimorbidity of major mental and somatic illnesses. It is well known that aberrant insulin signalling causes high health and socioeconomic burden through its role in diabetes, metabolic syndrome, and obesity. We posit that the impact of 'insulinopathies' is still largely underestimated, since insulin multimorbidity also extends to the brain, where altered insulin signalling appears to be implicated in dementias such as Alzheimer disease and in mental illnesses characterized by compulsivity, especially obsessive compulsive disorder and autism. During the talk, I will discuss how insulin multimorbidity evolves throughout life, necessitating a lifespan approach and a multidisciplinary team. Thereafter, I will discuss a number of the approaches and findings from the study, plus those from the literature, that are addressing this issue. I will focus on findings from both sexes of the animal models that we are using across the consortium and report our findings to date, as well as report on some of our other recent findings that explore the mechanisms through which insulin signalling leads to mental disorders (comorbid or not with somatic disorders).

S44 "Social behavior and social brain: from physiology to pathology"

Chairs: Laetitia Davidovic, Julie Le Merrer

S44.1
Complexity and dynamics of social behaviors in rodents

Fabrice de Chaumont[1], Elodie Ey[1,2], Thomas Bourgeron[1]
[1]*Human genetics and cognitive functions, Institut Pasteur, Université de Paris, paris, France;* [2]*FPhysiopathology of aneuploidy, gene dosage effect and Down syndrome, CNRS, IGBMC, Illkirch, France*

Social interactions and communication are key behaviors in the life of animals. Indeed, animals interact socially to regulate major functions such as reproduction, inter-individual coordination and protection from predators. Despite the broad use of mice as models for neuropsychiatric disorders, the knowledge on their social communication system is still fragmented. We here document their spontaneous social behavior in same-sex groups. We challenged the communication system by studying both wild-type mice and mice mutated in Shank3, a synaptic protein associated with autism spectrum disorder. For that purpose, we used a real-time method for behavioral analysis of mice housed in groups gathering computer vision, machine learning and Triggered-RFID identification to track and monitor animals over several days in enriched environments. This system—Live Mouse Tracker (LMT)—extracts a thorough list of individual and collective behavioral traits and provides a unique phenotypic profile for each animal. Recordings of ultrasonic vocalizations were synchronized with this system to document multiple modes of communication. LMT is open source, open hardware, enables closed loop experiment and we provide python libraries to extend the analysis to custom needs. In this study, we observed sex-related differences in the amount of social interactions, but also in the usage and structure of ultrasonic vocalizations. We also demonstrated that synchronizing the different modalities of communication allowed to refine the behavioral description. Finally, mice mutated for Shank3 displayed social communication abnormalities which did not appear in classical protocols, suggesting that studying spontaneous behavior complements classical behavioral phenotyping.

S44.2
Circuits of Emotion Discrimination

Francesco Papaleo[1]
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Abstract main text: Recognition of other's emotions influences the way social animals interact and adapt to the environment. Here, we will show how using a combination of anatomical, genetic, and chemogenetic approaches, we were able to demonstrate the contribution of selective endogenous OXT circuits in the ability of mice to discriminate conspecifics based on their emotional states. Furthermore, starting from the knowledge that emotion recognition abilities might rely on an intact cortical neuronal excitatory and inhibitory balance, here we will show the implication of prefrontal cortex (PFC) circuits in mediating such socio-cognitive behaviors. In particular, optogenetic manipulations reveal a double dissociation between the role of PFC interneurons in social cognition. Inhibition of PFC somatostatin (SOM+), but not of parvalbumin (PV+) interneurons, abolishes emotion discrimination. Accordingly, as visualized by in vivo single cell microendoscopic Ca2+ imaging, an increased synchronous activity of PFC SOM+ interneurons, guiding inhibition of pyramidal neurons, is associated with emotion discrimination. Our findings provide new insights into the neurobiological mechanisms of emotion recognition, in physiological and pathological conditions.

S44.3
Oxytocin and the rodent social brain: a network-level perspective

Alessandro Gozzi[1]
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Endogenous release of the neuropeptide oxytocin (OXT) modulates socio-affective behavior. However, the brain-wide functional networks engaged by this neurohormone remain undetermined. In my talk I will summarize research carried out in my lab aimed to explore the large-scale substrates modulated by OXT in the mouse brain. Specifically, I will show how functional magnetic resonance imaging (fMRI) is exquisitely sensitive to the effects of OXT in this species, both in terms of direct regional activation as well as in terms of interaction between areas (i.e. "functional connectivity"). I will next illustrate how the combined use of chemogenetics and fMRI (chemo-fMRI) permits to map the topography and dynamics of large scale circuitry engaged by endogenous OXT release. Collectively, our findings show that both exogeneous OXT administration (via intranasal dosing) and endogenous release (via DREADD-induced stimulation of OXT-releasing neurons) recruit key substrates of the rodent social brain, with a prominent cross talk between prefrontal cortico-limbic regions and hypothalamic areas involved in the control socio-affective behavior. These res-

ults shed light on the large-scale circuitry modulated by OXT in the mammalian brain.

S44.4

Social behavior and striatum: reward matters

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Social interactions are experienced as pleasurable, which in turn facilitates their occurrence. Consistent with this, the so-called "social brain" widely overlaps with the brain reward circuit. Within this circuit, the nucleus accumbens (NAc) works as a hub structure and plays a unique role in reward processing and approach. Accumulating evidence suggest that the NAc is a key substrate for modulating social behavior. However, the respective contributions of the two main neuronal populations in the NAc, Striatal Projection Neurons (SPNs), bearing either D1R or D2R dopamine receptors, remains elusive. D1R and D2R SPNs play contrasted roles in modulating reward, with the former (direct SPNs: dSPNs) proposed to drive pro-reward/approach responses and the latter (indirect SPNs: iSPNs) considered as inhibiting these responses. We previously evidenced that chronic facilitation of mGlu4 glutamate receptor activity, known to put a brake on iSPN activity, relieves social deficit in the Oprm1 null mouse model of autism. Here we tested the hypothesis that excessive iSPN activity may compromise social reward. We first explored the respective roles of D1R and D2R SPN of the NAc in driving social behavior by selectively ablating each of these neuronal populations. We then used pharmacological tools to rescue behavior in ablated mice and transcriptome analysis to assess striatal physiology. Finally, we mimicked excessive iSPN activation using optogenetics. This study allowed us to identify the respective roles of NAc D1R and D2R SPNs in driving social motivation, with exciting perspectives for the treatment of pathologies such as autism, schizophrenia or depression.

S44.5

Microbial metabolites, gut microbiota and social behavior

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Perturbations of the microbiota-gut-brain axis have been identified in autism spectrum disorders (ASD). Notably, changes in microbiota composition and fecal, serum or urine levels of microbial metabolites are associated with ASD. Also, germ-free rodents, devoid of microbiota, exhibit social behavior deficits. This underlines that microbial signals influence neurodevelopment and social behaviors programming. Yet, the underlying mediators and mechanisms remain unclear. We hypothesised that metabolites produced by the gut microbiota contribute to ASD core symptoms, including social behavior deficits. We focused on p-Cresol, a microbial metabolite described as abnormally elevated in the urine of ASD patients. We showed that chronic treatment of mice with p-Cresol induces autistic-like behaviours, and notable deficits in social behaviour. Social deficits were associated with decreased activity of central dopamine neurons involved in the social reward circuit. Further, p-Cresol modified the relative abundance of specific bacterial taxa which associated with the severity of autistic behaviors. In addition, social behavior deficits were transferrable from p-Cresol-treated mice to control mice by fecal matter transfer. We also show that the microbiota of mice recipient of p-Cresol-induced microbiota endogenously produces more p-Cresol. In contrast, the microbiota from control mice rescued social interactions, dopamine neurons excitability and decreased p-Cresol levels when transplanted to p-Cresol-treated mice. The microbial metabolite p-Cresol induces social behavior deficits in mice via a gut microbiota-dependent mechanism. Our study paves

the way for therapeutic interventions targeting the production of p-Cresol by gut bacteria to treat patients with ASD.

S45 "Novel insights into physiology and pathology of autophagy in neuronal maintenance"

Chairs: Graziella Cappelletti, Antonella Scorziello

S45.1
Lysosomal Signaling: The role of lysosomal calcium

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Lysosomes are intracellular organelles deputed to the degradation of macromolecules and damaged organelles. Recent evidence has shown that lysosomal biogenesis and autophagy are transcriptionally regulated by a gene network and by its master gene TFEB, which regulates the expression of lysosomal and autophagy genes. TFEB activity responds to environmental cues and is regulated by mTORC1-mediated phosphorylation, which occurs on the lysosomal surface). We discovered that calcineurin, a Ca^{2+}-modulated phosphatase, de-phosphorylates TFEB thus promoting its nuclear translocation. Interestingly, we also found that calcineurin is activated by a lysosomal calcium signaling mechanism mediated by the lysosomal calcium channel mucolipin 1 (MCOLN1). Together these results revealed, for the first time, the presence of lysosome-to-nucleus signaling mechanisms and changed the view of the lysosome from a "suicide bag" to a dynamic organelle that responds to environmental cues. The identification of global transcriptional regulation of lysosomal function was exploited by us first and then by other groups, to boost lysosomal function in mouse models of a variety of disease conditions. We found that the overexpression of TFEB on promotes the clearance of pathologic lysosomal storage in vitro and in vivo. Therefore, the possibility of modulating lysosomal function by acting in the TFEB network may lead to a novel therapeutic strategy with potential applicability to more than 50 LSDs. We are currently testing this possibility in our high content screening laboratory. Some of these studies resulted in the repurposing of drugs that regulates TFEB and reduce storage in LSDs.

S45.2
Mechanisms of mitochondrial turnover in neuronal physiology and pathology during ageing

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Mitochondria, the main energy hub of the cell, are highly dynamic organelles, playing essential roles in fundamental cellular processes. Mitochondrial function impinges on several signalling pathways modulating cellular metabolism, cell survival and healthspan. Maintenance of mitochondrial function and energy homeostasis requires both generation of newly synthesized and elimination of dysfunctional mitochondria. Impaired mitochondrial function and excessive mitochondrial content are major characteristics of ageing and several human pathophysiological conditions, highlighting the pivotal role of the coordination between mitochondrial biogenesis and mitophagy. However, the cellular and molecular underpinnings of mitochondrial mass homeostasis remain obscure.We found that DCT-1, the Caenorhabditis elegans homolog of mammalian BNIP3 and BNIP3L/NIX, is a key mediator of mitophagy promoting longevity under stress. DCT-1 acts downstream of the PINK-1-PDR-1/Parkin pathway and is ubiquitinated upon mitophagy-inducing conditions to mediate the removal of damaged mitochondria. Accumulation of damaged mitochondria triggers SKN-1 activation, which initiates a bipartite retrograde signaling pathway stimulating the coordinated induction of both mitochondrial biogenesis and mitophagy genes.Taken together, our results unravel a homeostatic feedback loop that allows cells to adjust their mitochondrial population in response to environmental and intracellular cues. Age-dependent decline of mitophagy both inhibits removal of dysfunctional or superfluous mitochondria and impairs mitochondrial biogenesis resulting in progressive mitochondrial accretion and consequently, deterioration of cell function.

S45.3
Emerging role of lysosome and its ionic machinery as a hub of neuroprotection in ALS models

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Amyotrophic lateral sclerosis (ALS) is a rare neurological disease characterized by neurodegeneration, pro-

gressive voluntary muscle wasting and death. Cellular clearance mechanisms, including the autophagy-lysosome pathway, as well as the alteration of calcium (Ca^{2+}) homeostasis may largely contribute to motor neuron demise in ALS. This suggests that autophagy-lysosome pathway may be considered as a new therapeutic target for the treatment of ALS-associated neurodegeneration. In this respect, lysosomal Ca^{2+} dysregulation has emerged as an important pathomechanism leading to neuronal loss in ALS as part of the much more complex dysfunctional Ca^{2+} signaling. One of the most important proteins involved in the regulation of autophagy is the lysosomal Ca^{2+} channel Mucolipin TRP channel 1 (TRPML1), whose activation triggers autophagy signaling cascade. Of note, we showed that TRPML1 function was downregulated in preclinical models of ALS/Parkinson-dementia complex and in ALS transgenic mice. This may determine autophagy impairment accompanied by lysosomal Ca^{2+} dyshomeostasis. Pharmacological stimulation of TRPML1 either by endogenous or synthetic agonists prevented L-BMAA-induced neuronal death and ER-stress in primary and clonal motor neurons as well as the accumulation of the autophagy-related proteins p62/SQSTM1 and LC3-II. Interestingly, administration of the endogenous agonist of TRPML1 in a protected formulation increased the survival rate of ALS mice as well as their motor performances. Collectively, the selective stimulation of TRPML1 lysosomal channel might represent a new promising route to prevent or, at least, delay neurodegeneration in ALS via an autophagy boosting effect.

S45.4

Lysosomal dysfunction in Parkinson's disease: the role of the small GTPase Rit2

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In Parkinson's disease (PD) misfolded alpha-synuclein (aSyn) accumulates in the substantia nigra, where dopamine (DA) neurons are progressively lost. The mechanisms underlying aSyn pathology are still unclear but hypothesized to involve the autophagy-lysosome pathway (ALP). LRRK2 mutations cause familial and sporadic PD, hyperactivate kinase activity and its pharmacological inhibition reduces pS129-aSyn inclusions. Our previous study showed accumulation of pS129-aSyn and dysregulation of lysosomal biology in neuroblastoma cells stably expressing G2019S-LRRK2, both restored by pharmacological LRRK2 kinase inhibition. The novel PD risk factor *RIT2* is downregulated in our G2019S-LRRK2 expressing cells, in DA neurons microdissected from PD patient midbrains and in DA neurons differentiated from A53T-aSyn iPSCs. Rit2 overexpression in G2019S-LRRK2 cells diminished pS129-aSyn inclusions, increased lysosome number and promoted proteolytic function, phenocopying pharmacological LRRK2 kinase inhibition. Rit2 and LRRK2 interacted in these cells with LRRK2 showing reduced kinase activity. We virally overexpressed FLex-Rit2 in DAT-Cre mice, yielding selective expression in DA neurons. This conferred protection against DA neuron loss and aSyn neuropathology, elicited by AAV-A53T-aSyn. Furthermore, Rit2 overexpression prevented the A53T-aSyn-dependent increase of LRRK2 kinase activity in vivo. Lastly, we asked if Rit2 played a physiological role in the ALP and used SH-SY5Y cells carrying a CRISPR-Cas9-mediated deletion of the *RIT2* gene. These cells display accumulation of autophagosomes, reduction of lysosome number and reduced proteolytic activity.
Our data indicate that Rit2 inhibits overactive LRRK2 to ameliorate ALP and counteract aSyn neuropathology. Further, Rit2 physiologically modulates lysosome biology. Targeting Rit2 could represent a novel therapeutic strategy in familial and idiopathic PD.

S45.5

Balancing Mitophagy and Mitochondrial Biogensis to maintain energy Metabolism is required for the Neuroprotection induced by ischemic Brain preconditioning

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Mitochondrial quality control is crucial for the homeostasis of the mitochondrial network. The balance between mitophagy and biogenesis is needed to prevent the cerebral ischemia induced cell death. Ischemic preconditioning (IPC) represents an adaptation mechanism of CNS, that increased tolerance to the lethal cerebral ischemia. It has been demonstrated that hypoxia-induced Siah2-E3 ligase activation influences mitochondrial dynamics promoting the degradation of mitochondrial proteins. Therefore, we investigated the role of Siah2 in the IPC- induced neuroprotection in an *in vitro* model of IPC. To this aim, cortical neurons were exposed to 30-min oxygen and glucose deprivation (OGD, sublethal insult) followed by 3hrs OGD plus reoxygenation (lethal insult). Our results reveal that the mitochondrial depolarization induced by hypoxia activates Siah2 at mitochondrial level and increases LC3-II protein expression, an effect counteracted by the reoxygenation phase. By contrast, hypoxia reduces the expres-

sion of PGC1-alpha, a marker of mitochondrial biogenesis, whereas its expression was increased after reoxygenation thus improving mitochondrial membrane potential, mitochondrial calcium content, and mitochondrial morphology, and leading to the neuroprective effect of ischemic preconditioning. Collectively, these findings indicate that the balance between mitophagy and mitochondrial biogenesis due to the activation of the Siah2–E3 ligase is involved in IPC-induced neuroprotection.

S46 "From pathophysiology to therapetic strategies of Alzheimer disease: novel insights from experimental models and patient studies"

Chair: Dubravka Svob Strac

S46.1
Studying therapeutic potential of neurosteroids and neurotrophins in Alzheimer disease: an in vitro approach

Dubravka Svob Strac[1], Barbara Vuic[1], Marcela Konjevod[1], Lucija Tudor1, Nedic Erjavec Gordana[1], Matea Nikolac Perkovic[1], Julija Erhardt[2], Nela Pivac[1]
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Alzheimer disease (AD) has become a major public health concern, due to increasing aging of world's population. Therefore, recent multidisciplinary research have focused on the AD pathophysiology, specific biomarkers, and new therapeutic options for its prevention and treatment. Various in vitro approaches have been developed in order to provide deeper insights into molecular mechanisms related to the etiology and pathogenesis of AD, as well as to investigate the new potential therapeutics. Some of these approaches have been used to investigate neurosteroid dehydroepiandrosterone (DHEA) and neurotrophin brain derived neurotrophic factor (BDNF), which are involved in many important brain functions, including neuronal plasticity and survival, cognition and behavior, demonstrating preventive and therapeutic potential in AD. As in vitro AD model, we have used primary C57BL/6 mouse neuronal culture treated with A-oligomers, which are toxic and identified as a cause of AD neuropathology. In the experiments, we have applied A42 isoform, most commonly associated with AD. Structural characterization of Aβ-oligomer preparations has been conducted using atomic force microscopy, whereas oligomer toxicity has been tested in cell culture by monitoring cell viability. After optimizing the dose and duration of the treatment, cellular and molecular mechanisms of DHEA and BDNF protective action are investigated in vitro using analyses of cell viability, apoptosis, oxidative stress and selected signalling pathways. The results contribute to the improved understanding of DHEA and BDNF actions and mechanisms of their therapeutic potential, as well as in expanded knowledge about the neurobiological basis of complex cellular and molecular pathophysiology of AD.

S46.2
Phenotypic characterization of the triple transgenic animal model of Alzheimer's disorder, translational considerations

Dóra Zelena[1], Eszter Sipos[1], Bibiána Török[1], Csilla Lea Fazekas[1], Tiago Chaves[1], Pedro Correia[1], Adrienn Szabó[1]
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Alzheimer's disease (AD) is a progressive neurodegenerative disorder whose most distinctive symptom is the cognitive decline. Preclinical studies with animal models play crucial role since the disease remains incurable to this day. The main aim of our study was to characterize the triple transgenic mouse model of AD (3xTg-AD). Locomotion is required for almost all tests, therefore first we measured motor-activity and found reduce locomotion in open-field, but normal motor-coordination in rotarod. Further, we examined if enhanced anxiety might be in the background and confirmed than 3xTg-AD mice froze more to fox-odor presentation reflecting enhanced innate fear. When we used highly motivating factors (as social stimulus in social discrimination or water in Morris Water Maze test) we confirmed the cognitive decline of our mice-line. However, during tests based upon food motivation (operant conditioning, pellet retrieval) the 3xTg-AD mice performed even better, suggesting an over-activated food-drive. Indeed, in a metabolic cage we confirmed round-o-clock higher food and water intake and decreased physical activity of 3-Tg-AD mice in comparison to controls. Our data are in line with human observations about increased anxiety co-morbidity in AD patient and draw attention to metabolic considerations, which might highly influence the outcome of behavioural test. When new drugs are tested in this model careful, planning is necessary in selecting the appropriate behavioural test.

S46.3
Genetic biomarkers of Alzheimer's disease

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Alzheimer's disease (AD), as a predominant form of dementia, is a complex and heterogeneous, severe neurodegenerative disorder with different genetic background characterizing different types of the disease. Some rare cases of early-onset familial Alzheimer's diseases (EOAD) are caused by mutations in genes coding for presenilin 1 and 2, while multifactorial late-onset Alzheimer's disease (LOAD) is associated with more than 20 genetic risk loci, whereas the apolipoprotein E ε4 represents a major genetic risk factor for LOAD. Beside the 'standard' genes directly involved in the AD pathology, there are many additional genetic risk loci involved in the LOAD pathology or associated with the characteristic symptoms of the disease, although their exact contribution is still not clear. There are indices of association between brain derived neurotrophic factor (BDNF) and catechol-O-methyltransferase (COMT) genes' variants and psychotic symptoms in AD. Other genes, such as monoamine oxidase B (MAOB) and dopamine β-hydroxylase (DBH) genes, also involved in dopaminergic neurotransmission, as well as genes coding for interleukins, are associated with cerebrospinal fluid AD biomarkers including total and phosphorylated tau proteins and amyloid-β42. The use of genetic biomarkers of Alzheimer's disease in monitoring the development, treatment response, and prognosis of the disease is promising, but still far away from the clinical application.

S46.4
DNA methylation of candidate genes in Alzheimer's disease

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Alzheimer's disease (AD) is a slow, irreversible, but progressive, complex and multifactorial neurodegenerative disorder. Main risk factors for AD are older age, genetic predisposition, gender, cardiovascular factors and presence of the mild cognitive impairment (MCI). MCI is characterized by mild changes and disruptions in mental abilities such as memory, the ability to think and to remember. MCI might lead to AD, since a great percent of subjects with MCI (50 % - 65 %) later develop some form of dementia, especially AD. At present, clinical diagnosis of (probable) AD is established thorough a combination of clinical symptoms, cognitive screening tests, detailed neuropsychological testing and imaging techniques. Tests based on molecular-genetic biology analysis are only entering the routine clinical practice, but are, as are other clinical tests, relevant only after the disease has already made considerable progress. In our study we used latest contemporary methods (next generation sequencing, droplet digital PCR) to determine methylation status of AD candidate genes, catechol-O-methyl transferase and brain-derived neurotrophic factor, in blood-based liquid biopsy samples and circulating cell-free DNA (cfDNA) from plasma in clinically well-defined AD patients and subjects with MCI. Determining the differences of white blood cells methylation status and methylation cfDNA, as a pool of DNA from distant tissues, could lead to identification of peripheral markers, which reflect broader picture of the organ status, including the status of otherwise unobtainable tissue, like the brain.

S46.5
Metabolic profiling of Alzheimer's disease: potential in biomarker discovery and early detection of Alzheimer's dementia

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Alzheimer's dementia (AD) is a growing public health problem, which is often missed or diagnosed too late. A lot of new evidence suggests that pathological processes associated with dementia can manifest themselves, not only in the central nervous system, but also at the periphery. Metabolomics is one of the newest "omics" approaches that enables detection of endogenous metabolite levels, which represent the end point of all biochemical reactions, and might be used as a rather sensitive measure of overall

health status. The aim of this study was to apply LC-MS and GC-MS based untargeted metabolomics approach to investigate the metabolic profile of patients with AD and compare it with metabolic profiles of subjects diagnosed with mild cognitive impairment (MCI) and healthy subjects. Study included plasma samples from AD patients (N=40), subjects with MCI (N=40) and healthy controls (N=40). The results suggested altered lipid, amino acid and energy metabolism (glycolysis, tricarboxylic acid cycle, β-oxidation of lipids, gluconeogenesis, ketogenesis). Observed changes in phospholipid and sphingolipid concentrations could indicate destabilization of membranes in AD. Metabolic alterations related to the biosynthesis of different neurotransmitters, urea cycle, metabolism of purines, polyamines and bile acids were also detected. Therefore, this study proposes metabolomics as a promising novel approach for advancing the current knowledge of AD pathogenesis and aetiology, and highlights the possible benefit from this approach in discovering the novel blood-based biomarkers for the diagnosis, prognosis, and therapy follow-up in AD patients.

S47 "Synaptic plasticity in epilepsy: from synapses to circuits"

Chairs: Giuseppe Di Giovanni, Sandra H. Vaz

S47.1
Synaptic plasticity in epilepsy: the Janus face of adenosine

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Adenosine is an endogenous anticonvulsant. ATP, released by neurons and astrocytes, is extracellularly metabolized into adenosine. Adenosine is taken up through equilibrative transporters, the inward gradient being maintained by adenosine kinase (ADK), which phosphorylates intracellular adenosine into AMP. When ADK levels are pathologically increased, the resulting extracellular adenosine deficiency translates into increased susceptibility to seizures. Surprisingly ADK deficiency in human patients (OMIM:614300) also leads to seizures. We demonstrated that ADK activity, besides influencing the basal tone of extracellular adenosine and the corresponding A1R-dependent tonic inhibition, modulates the adenosine A2AR-dependent facilitatory effects of BDNF on hippocampal synaptic transmission and plasticity (Diogenes et al., 2014). To identify the mechanism that leads to seizures in a situation where enhanced extracellular levels are expected (ADK deficiency), we used a mouse model with a brain-wide deletion of ADK (Adkbrain), which develops a progressive stress-induced seizure phenotype (Sandau et al., 2016). By performing pharmacological, biochemical, and electrophysiological assays we could conclude that these mice possess enhanced adenosine levels around synapses, but lower levels of the inhibitory A1R. LTP was enhanced in the mutants, this being dependent on excitatory A2AR and BDNF-TrkB signaling. Accordingly, reducing adenosine A2AR activity in Adkbrain mice attenuated seizure risk. Altogether the data show that either pathologically increased or decreased levels of extracellular adenosine may lead to increased susceptibility to seizures, and that this is due to dysregulated A1R/A2AR control upon synaptic plasticity and BDNF signaling.

S47.2
Modeling of focal cortical dysplasia: where the normal brain meets a mutation

Gian Michele Ratto[1], Didi Lamers[1], Silvia Landi[1], Gabriele Nardi[1], Enrico Pracucci[1], Riccardo Parra[1], Teresa Tommasini[1], Francesco Trovato[1] [1]*NEST, Istituto Nanoscienze CNR and Scuola Normale Superiore, Pisa, Italy*

Genetic mosaicism, a condition in which an organ includes cells with different genotypes, is frequently present in monogenic diseases of the central nervous system due to the random inactivation of the X-chromosome (for X-linked pathologies), or to somatic mutations affecting a subset of neurons. Examples of such diseases associated to severe encephalopathies are Rett Syndrome, focal cortical dysplasia and the clustering epilepsy due to PCDH19 mosaicism. The comprehension of the mechanisms of these diseases and of the cell-autonomous effects of specific mutations, requires the generation of sparse mosaic models, where the genotype of each neuron is univocally identified by the expression of a fluorescent protein in vivo.

In this talk I will review a dual-color reporter system (Trovato et al, 2020) that, when transduced in a floxed mouse line for a target gene, leads to the creation of tunable mosaics. Intravital two-photon microscopy can reveal the genotype of each transduced neuron by imaging the binary expression of a different fluorescent protein. Furthermore, by the combined expression of a variant of the genetically encoded Calcium sensor GCaAMP6f, we can study activity at the level of individual genotyped neurons and dendrites. This allows the observation of the behavior of interspersed mutant and wild-type neurons and their reciprocal interactions.

We demonstrate the generation of a knock-out mosaic of the autism/epilepsy related genes PTEN and PCDH19 and their anatomical phenotype in the mouse cortex. Fi-

nally, we image activity in resting state of neurons and dendrites of the two genetically distinct neuronal populations.

S47.3
Glutamate receptors and synaptic plasticity in health and disease

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One important function of GABA-R mediated synaptic transmission is to limit the synaptic activation of NMDARs. Of physiological significance, brief periods of high frequency stimulation are able to depress this inhibition to facilitate the synaptic activation of NMDARs. This transient depression of GABA-mediated inhibition operates most effectively at the theta frequency due to the kinetics of GABA-B autoreceptors (Davies et al, 1991 Nature PMID: 1847993). Any process that upsets this powerful regulatory mechanism can predispose the circuit to epileptiform activity. Therefor understanding how GABA-inhibition is regulated during neuronal activity and how GABA-mediated inhibition influences the synaptic activation of NMDARs is relevant to both learning and memory and epilepsy. In this presentation, I will describe (i) how GABA-mediated inhibition may be regulated by neuronal activity and (ii) some of the ways by which GABA-mediated synaptic inhibition can influence NMDAR mediated synaptic plasticity, which in turn results in long-lasting changes in AMPAR-mediated synaptic transmission.

S47.4
Dissecting the basic epileptogenic mechanisms in neurodevelopmental disorders

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Many authors found a delay in the normal development of the GABAergic system in different neurodevelopmental disorders. In particular, a less hyperpolarizing action of GABA currents has been identified as a typical feature of the immature brain. In addition, syndromes that are caused by different mutations (such as Rett syndrome and tuberous sclerosis complex-TSC or focal cortical dysplasia-FCD) or chromosomal alterations (such as Angelman and Down syndrome - DS) can share similar patterns of brain immaturity. In most of the cases, these alterations also involve GABAergic transmission, thus inducing an excitation/inhibition imbalance that can explain, at least in part, the high incidence of epilepsy in these patients.
Indeed, in many neurodevelopmental syndromes some clues regarding a probable GABAergic dysfunction have already been found: for instance, there is an alteration of GABAARs subunits in Angelman syndrome and an immature GABAergic electrophysiological function both in TSC and FCD Furthermore, a crucial dysfunction of KCC2 (one of the two main chloride cotransporters involved in GABAergic function) has been investigated in Rett syndrome and many other similar findings have been reported for neurodevelopmental pathologies such as Fragile X (FRA-X), and Dravet syndrome. Furthermore, there is a clear link between GABAergic dysfunction and cognitive decline in different forms of neurodevelopment diseases. In addition, AMPA glutamate receptors undergo a change in their subunit composition during development, being the GluA2 subunit upregulated compared to GluA1 in mature brain.
Beyond the aforementioned physiological results, the concept of GABAA receptors (GABAARs) as key factors in neurodevelopmental diseases has been confirmed by a study that demonstrated the efficacy of bumetanide (a drug that by acting on NKCC1 chloride transporters and modifying chloride equilibrium, can modulate GABAARs function) on restoring hippocampus-dependent memory in a DS mouse model.
The GABAergic alterations could contribute to explain the link between neurodevelopmental diseases and epilepsy since the importance of GABAARs in the onset and recurrence of seizures is well-known and supported by a huge amount of scientific literature even if a full electrophysiological characterization of "human" GABAARs in these diseases is still to be obtained. Here, I will focus the attention on recent studies of the GABAARs and AMPA function in neurodevelopmental syndromes involving human tissues and few well-validated animal models of diseases.
I would like to shift the focus to another point of view that could lead to the development of therapeutic approaches tailored on specific "neurodevelopmental targets" able not only to act on the symptoms of these patients, but also on the physiopathological alterations that are their cause, eventually slowing down or preventing the progression of the pathology itself, and the related cognitive decline.

S47.5
In brain post-ischemic plasticity, Na^+/Ca^{2+} EXCHANGER 1 and Ascl1 interact in microglia-dependent astrocyte differentiation

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The intricate glia interaction occurring after stroke is strongly dependent by the maintenance of intraglial ionic homeostasis. Among the several ionic channels and transporters, the plasmamembrane Na^+/Ca^{2+} exchanger (NCX) represents a good candidate in maintaining astroglial Na+ and Ca2+ homeostasis.
Here, using a combined in vitro, in vivo and ex vivo experimental strategy we evaluated whether activated microglia may influence the morphological and the transcriptional plasticity of post-ischemic astrocytes. Astrocyte plasticity was monitored by the expression of the transcription factor Acheate-scute like 1 (Ascl1), which plays a central role in the commitment of astrocytes towards the neuronal lineage. Furthermore, we explored the implication of NCX1 expression and activity in mediating Ascl1-dependent post-ischemic astrocyte remodeling.
We demonstrated that: (a) in astrocytes co-cultured with microglia the exposure to oxygen and glucose deprivation followed by 7 days of reoxygenation promoted from one side a strong increase of the protective M2 microglia and from the other side induced a prevalence of bipolar astrocytes overexpressing Ascl1 and NCX1, whereas this did not occur in monocultured astrocytes; (b) the reoxygenation of anoxic astrocytes with the M2 microglia-derived conditioned medium strongly elicited the astrocytic co-expression of Ascl1 and NCX1; (c) Ascl1 expression in anoxic astrocytes was dependent by NCX1 since its silencing prevented Ascl1 expression both in in vitro and in post-ischemic ex vivo experimental conditions.
Collectively, the results of our study support the idea that, after brain ischemia, astrocyte-microglia crosstalk can influence astrocytic morphology and its Ascl1 expression. This phenomenon is strictly dependent on ischemia-induced increase of NCX1 which in turn induces Ascl1 overexpression possibly through astrocytic Ca^{2+} elevation.

S48 "Sex differences, immune and steroid effects in the brain: implications for neuropsychiatric disorders and their treatment"

Chair: Christina Dalla

S48.1
Of Mice and Wo/Men: Translating sex differences in cytokine responses between treatment resistant depression and animal models

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There is a bi-directional relationship between the immune system and major depressive disorder (MDD). Little is known about mechanisms contributing to the higher incidence of inflammatory and stress-related illness in females. We used multiplex ELISA to quantify plasma cytokine protein expression regulated by treatment resistant and non-treatment resistant depression in men and women compared to age matched (21-55 years) healthy controls. To test the ability of mouse stress models to recapitulate the cytokine changes found in depressed individuals we examined circulating levels of cytokines for male and female mice exposed to 6-day variable stress and 28-day variable stress. Additional studies examined cytokine levels following 6 days of variable stress in four-core genotype mice which allow dissociation of genetic sex from gonadal sex. We found there are sex differences in the peripheral immune response to MDD or stress that transcend species. Women with treatment resistant MDD have a sex specific profile of T-cell related immune response suggestive of an autoimmune disease. Women with treatment resistant depression and men that are not treatment resistant show activation of cytokines released by the innate immune system. Rodent stress paradigms also produced a similar pattern for their regulation of peripheral cytokines. Sex differences in immune profiles were highly dependent on genetic sex although we did find some effects of gonadal sex in a subset of cytokines. These data demonstrate that segregation by sex and treatment resistant status are important for understanding the impact of depression or stress on cytokine profiles in humans and rodents.

S48.2
Sex differences in antidepressant response: The role of the HPA axis

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Depression, an emerging cause of disability among western societies presents interesting sex differences in epidemiology, symptom presentation and treatment. Similarly, there is abundant evidence of sex differences in various experimental models of depression. Despite research, the neurobiology of sex differences in depression remains partially understood, but stress-related abnormal

activation or regulation of the hypothalamous-pituitary-adrenals (HPA) axis is thought to be an important contributing factor and in the past compounds targeting the HPA axis were unsuccessfully tested as candidate antidepressants. Given the involvement of the HPA axis in the stress response, sex differences in cortisol and corticosterone are of particular interest for clinical and preclinical research respectively. Previous research showed that in preclinical studies, fluctuations in serum corticosterone correlate with the male and less with the female behavioural response. This suggests a different modality or level of HPA axis involvement in the stress response between the two sexes, possibly involving an additional estrogenic regulation of HPA axis. Considering such experimental findings, it may be that sex differences have contributed to the failure of novel HPA axis-based drugs in clinical trials. Recent findings from our group and others showed that neuroestrogens are involved in mood regulation and we propose that rapid neuroestrogens signaling, and the newly-identified G protein-coupled estrogen receptor 1 (GPER1), may be involved in mood regulation, HPA axis regulation and antidepressant response.

S48.3

Epigenetic targets of oral corticosterone in the dorsal and ventral hippocampus

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Circulating glucocorticoids induce gene expression change that are brain-region dependent, particularly in cortico-limbic structures. To date, no studies have investigated region-specific genomic differences in hippocampal subregions, namely the dorsal (dHPC) and ventral (vHPC) hippocampus, in preclinical models exposed to exogenous glucocorticoids. Chronic oral corticosterone (CORT) in mouse is a pharmacological approach that blunts the response to stress, increases affective behavior, and induces genomic changes in the HPC of wildtype (WT) mice and mice heterozygous for the gene coding for brain-derived neurotrophic factor Val66Met (hMet), a variant associated with genetic susceptibility to stress. Using RNA-sequencing, we investigated the genomic signatures of oral CORT in the dHPC and vHPC of WT and hMet male and female mice, to examine sex and genotype differences in response to oral CORT. Males under CORT showed lower glycemia and increased anxiety- and depression-like behavior compared to females that showed instead opposite affective behavior in response to CORT. Rank-rank-hypergeometric overlap (RRHO) was used to identify genes from a continuous gradient of significancy that were concordant across groups and showed that CORT-induced differentially expressed genes (DEGs) in WT and hMet converged in the dHPC of both sexes, while in the vHPC, DEGs converged in males and diverged in females. The vHPC showed a higher number of DEGs compared to the dHPC and exhibited sex differences related to glucocorticoid receptor (GR) binding genes and epigenetic modifiers. Methyl-DNA-immunoprecipitation in the vHPC revealed differential methylation of the exons 1C and 1F of the GR gene (Nr3c1) in hMet females. Together we report behavioral and endocrinological sex differences in response to CORT, as well as sex- and genotype-specific epigenetic signatures that differ in the dHPC and vHPC.

S48.4

Stiff Person Syndrome: Pathophysiology and sex differences

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Stiff Person Syndrome (SPS) is a sporadic, rare neurological disorder affecting mostly women, which can be manifested as paraneoplastic or idiopathic. It is a disorder associated with several different autoantibodies (GAD, Glycine receptor, amphiphysin and gephyrin), which target antigens predominantly expressed in the inhibitory synapses of the central nervous system. In the idiopathic variant, a few immune-modulating therapies such as intravenous immunoglobulin (IVIg) and plasmapheresis significantly improve symptoms, which strongly support the view that the disorder is antibody-mediated. A strong genetic association has been documented with several DQb1 and DRb1 MHC class-II alleles, although no single predominant allele(s) has been identified. Despite all the recent progress, it is still not fully understood how the autoantibodies might cause disease and whether any genes beyond the MHC complex may contribute to disease pathogenesis. We suggest that anti-GAD antibodies, despite their strong association with SPS are not pathogenic but rather a marker of an ongoing autoimmune activation. Further,

we will present epidemiological data on sex differences and discuss how a newly identified genetic link might provide clues to SPS pathophysiology.

S49 "Neuropathologies, Neuroprotection and Innovative Therapies "

Chairs: Olfa Masmoudi-Kouki, Taoufik Ghrairi

S49.1
Amyotrophic Lateral Sclerosis a model of neurodegenerative Disease

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Amyotrophic Lateral Sclerosis (ALS) is a progressive, motoneuron disease manifested by loss of control over voluntary muscles, which leads to death between 1 to 5 years after diagnosis. Currently, mechanisms of neurodegeneration of ALS are multiple and there is no effective treatment. Familial and sporadic forms of ALS share several key cellular pathologies, including Neuromuscular Junction disruption, perturbations in axonal transport, formation of toxic protein aggregates and loss of motoneuron (MN) in the spinal cord and cortex. ALS is characterized by marked inter-individual variability in susceptibility, spectrum and outcomes. Thus, ALS mirrors any complex disease trait resulting from dynamic interactions between environmental factors, and genetic causes acting on a susceptible polygenic host background. Recent years has seen dramatic advances leading to the discovery of genetic risk factors for such fatal illnesses, including the determinants of neurology degeneration genetic factors. Therefore, with the increasing recognition of phenotypic heterogeneity in ALS and the overlap between ALS and other neurodegenerative diseases, the importance of identifying new genetic markers has re-emerged. According to our recent study among Tunisian ALS patients we found that compared to data from the literature; ALS appears to have a slower progression a better prognosis and younger age specific for bulbar onset among Tunisian population.

S49.2
In vitro evaluation of the effect of cumin and thym essential oils on H_2O_2- induced cytotoxicity

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Free radicals generated during metabolic processes are involved in the progression of many diseases including neurodegenerative diseases. Antioxidant systems normally neutralize these free radicals and thus prevent the body from this damage. However, in unusual circumstances, when the production of free radicals is excessive or the antioxidant system is compromised, they exhibit various degenerative effects. Subsequently, supplementation with exogenous antioxidants would be essential. Recently, the use of essential oils is attracting more attention because they contribute significantly to the prevention and treatment of various diseases. By using nervous cell lines (N2a) treated by H_20_2 inducing an oxidative stress, our objective was to determine whether the cytotoxic effects of H202 were attenuated by essential oils (cumin and thym). The *in vitro* cytoprotective activity of essential oils was determined using the FDA and MTT assays to evaluate the impact on cell growth and cell viability. GC/MS analysis of cumin EO showed a richness in the monoterpene fraction predominated by cuminaldehyde (42.019%) with fairly high contents of ɣ-terpinene, β-pinene and p-cymene. *In vitro* assay showed that cumin EO remains cytotoxic in the absence and/or presence of H_2O_2 while exerting a pro-oxidant effect by positive control of all the key steps of the process of induction of oxidative stress. On the other hand, pretreatment with thyme EO promoted the survival of N2a cultured cells under acute oxidative stress induced by H_2O_2. This neuroprotective effect of thyme essence involves inhibition of overproduction of reactive oxygen species, lipid peroxidation and increased expression of catalase and superoxide dismutase.

S49.3
Cytoprotective and neurotrophic effects of OctaDecaNeuropeptide (ODN) in in vitro and in vivo models of neurodegenerative diseases

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Octadecaneuropeptide (ODN) and its precursor diazepam-binding inhibitor (DBI) are peptides belonging to the family of endozepines which are exclusively produced by astroglial cells in the central nervous system of mammals, and their release is regulated by stress signals and neuroactive compounds. There is now compelling evidence that the gliopeptide ODN protects cultured neurons and astrocytes from apoptotic cell death induced by various neurotoxic agents. ODN, at very low concentrations (in the subpicomolar range), has been shown to rescue neurons and glial cells from neurotoxicity induced by several substances such as H_2O_2, 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). ODN also exerts a strong protective effect against oxidative stress-induced apoptosis on cultured neurons and astrocytes. ODN acts by preventing i) the accumulation and overproduction of intracellular reactive oxygen species (ROS), ii) the depletion of glutathione (GSH) levels, and iii) the decrease of the expression and activity of the antioxidant enzymes provoked by oxidative stress. In vivo, ODN causes a very strong neuroprotective action against neuronal degeneration in a mouse model of Parkinson's disease. This neuroprotective activity of ODN is based on its capacity to reduce inflammation, apoptosis, and oxidative stress. The protective effects of ODN are mediated through its metabotropic receptor. This receptor activates a transduction cascade of second messengers to stimulate protein kinase A (PKA), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) signaling pathways, which in turn inhibits the expression of proapoptotic factor Bax and the mitochondrial apoptotic pathway. The antiapoptotic and neurotrophic properties of ODN, including its antioxidant, antiapoptotic, and prodifferentiating effects, suggest that this gliopeptide and some of its selective and stable derivatives may have therapeutic value for the treatment of some neurodegenerative diseases.

S49.4

The Epigenetic and Transcriptional Factors HDAC4, HDAC5, DREAM and GATA3/KM5T2A Complex Regulate NCX3 Expression Contributing to Ischemic Neuroprotection

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NCX3 (Na^+-Ca^{2+} exchanger 3) plays a relevant role in stroke; indeed its pharmacological blockade or its genetic ablation exacerbates brain ischemic damage, whereas its upregulation takes part in the neuroprotection elicited by ischemic preconditioning. To identify an effective strategy to induce an overexpression of NCX3, we examined transcription factors and epigenetic mechanisms potentially involved in *NCX3* gene regulation.

The histone deacetylases (HDACs)-dependent mechanisms regulating gene transcription of the Na^+/Ca^+ exchanger isoform 3 (ncx3) after stroke are still unknown. Overexpression or knocking-down of HDAC4/HDAC5 down-regulates or increases, respectively, NCX3 mRNA and protein. Likewise, MC1568 (class IIa HDACs inhibitor), but not MS-275 (class I HDACs inhibitor) increased NCX3 promoter activity, gene and protein expression. Furthermore, HDAC4 and HDAC5 physically interacted with the transcription factor downstream regulatory element antagonist modulator (DREAM). As MC1568, DREAM knocking-down prevented HDAC4 and HDAC5 recruitment to the ncx3 promoter. Importantly, DREAM, HDAC4, and HDAC5 recruitment to the ncx3 gene was increased in the temporoparietal cortex of rats subjected to transient middle cerebral artery occlusion (tMCAO), with a consequent histone-deacetylation of ncx3 promoter. Conversely, the tMCAO-induced NCX3 reduction was prevented by intracerebroventricular injection of siDREAM, siHDAC4, and siHDAC5. Notably, MC1568 prevented oxygen glucose deprivation plus reoxygenation and tMCAO-induced neuronal damage, whereas its neuroprotective effect was abolished by ncx3 knockdown. Among the putative transcription factors sharing a consensus sequence on the ncx3 brain promoter region, GATA3 was the only able to up-regulate ncx3. Interestingly, GATA3 physically interacted with KMT2A, and their overexpression or knocking-down increased or downregulated NCX3 mRNA and protein, respectively. Notably, site-direct mutagenesis of GATA site on ncx3 brain promoter region counteracted GATA3 and KMT2A binding on *NCX3* gene. More importantly, we found that in the perischemic cortical regions of preconditioned rats GATA3 recruited KMT2A and the complex H3K4-3me (trimethylated lysine-4 of histone-3) on ncx3 brain promoter region, thus reducing transient middle cerebral artery occlusion–induced damage. Consistently, in vivo silencing of either GATA3 or KMT2A prevented NCX3 upregulation and consequently the neuroprotective effect of preconditioning stimulus. The involvement of GATA3/KMT2A complex in neuroprotection elicited by ischemic preconditioning was further confirmed by in vitro experiments in which the knocking-down of GATA3 and KMT2A reverted the neuroprotection induced by

NCX3 overexpression in cortical neurons exposed to anoxic preconditioning followed by oxygen and glucose deprivation plus reoxygenation.
Collectively, we found that: (1) DREAM/HDAC4/HDAC5 complex epigenetically down-regulates ncx3 gene transcription after stroke, and (2) pharmacological inhibition of class IIa HDACs reduces stroke-induced neurodetrimental effects. In addition, our results revealed that GATA3/KMT2A complex epigenetically activates *NCX3* gene transcription during ischemic preconditioning

S50 "Neuropeptidergic impact in cognition and metabolism"

Chairs: Francisco E. Olucha-Bordonau, Ángel Núñez-Molina

S50.1
Modulation of cortical activity by IGF-I through cholinergic basal forebrain neurons

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It has been demonstrated that insulin-like growth factor-I (IGF-I) can be a potent stimulator of neuronal activity, participating in numerous brain processes. Here, we show that IGF-I may increase cortical activity by action on cholinergic basal forebrain (BF) neurons. We studied the effect of IGF-I in neurons of the horizontal diagonal band of Broca (HDB) in mice. Local injection of IGF-I in the HDB nucleus increased their neuronal activity and induced fast oscillatory activity in the electrocorticogram (ECoG). Furthermore, IGF-I facilitated tactile responses in the primary somatosensory cortex elicited by whisker stimulation. Specifically, IGF-I increased the activity of optogenetically-identified cholinergic neurons, suggesting that most of the IGF-I-induced excitatory effects were mediated by activation of these type of neurons. Accordingly, the long-lasting excitatory effects of IGF-I on cortical neurons were blocked by atropine. Furthermore, BF and cortical responses to IGF-I were recorded in young ($\leq$ 6 months old) and old ($\geq$20-month-old) mice. We observed that excitatory effects of IGF-I decreased in old mice. Effects of aging were partially ameliorated by chronic IGF-I treatment to old mice. In conclusion, we demonstrated that cortical activation induced by IGF-I was partly due to excitation of cholinergic neurons in the BF. Present findings also indicate that reduced IGF-I activity in old animals may participate in the age-associated decline of cognitive functions during aging.

S50.2
The relaxin 3-nucleus incertus projections to the medial septum in triggering hippocampal activity

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Arousal depends, in part, on triggering projections arising from subcortical structures. The nucleus incertus (NI) in the pontine tegmentum is a tiny structure that contains GABAergic neurons some of them also producing the neuropeptide relaxin3 (RLN3). Extensive literature has highlighted the role of relaxin3 as a chain of overlapped ascending projections including the dorsal and median raphe, the supramammillary nucleus the medial septum and the entorhinal-hippocampal system. These projections are able to modulate hippocampal theta rhythm and regulate some of its related functions including spatial navigation, spatial working memory and social recognition. The NI also projects to specific areas of the extended amygdala which may regulate hippocampus-amygdala interactions specially in process related to anxiety and social interactions. Double injections of tracers in the temporal lobe areas (which included the hippocampus and the entorhinal cortex) on one side and in the medial septum on the other side reveal a scattered number of collateralization which indicates that discrete areas of the nucleus incertus are involved in specific functions over specific areas of the hippocampus or medial septum. Finally, we observed that the projections from the NI to the medial septum abruptly appears at the P17 postnatal day, just before weaning when the animal starts its autonomous life.

S50.3
Hypocretin targeting of pontine neural networks governing REM sleep

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The hypocretinergic system is linked to pathogenesis of narcolepsy type 1 (NT1), a sleep disorder associated to autoimmune destruction of hypothalamic hypocretin (Hcrt) neurons. NT1 patients have very low Hcrt levels

in cerebrospinal fluid (CSF), excessive daytime hypersomnolence and loss of REM sleep control. Additionally, they also display episodes of muscle atonia though being awake (cataplexy attacks). Further manifestations are episodes of SOREMs (sleep onset REM) i.e. REM sleep entering directly from wakefulness without preceding NREM sleep, and hallucinations mimicking dream activity in transitions between wakefulness and sleep. The pontine tegmentum is a key region in sleep mechanisms. Through cholinergic selective stimulation, we showed that the ventral region of the oral pontine tegmentum (vRPO) acts to generate REM sleep, while the dorsal region (DOPT) facilitates the appearance of wakefulness with muscle tone suppression. Hcrt neurons target vRPO and DOPT, and vRPO and DOPT exert a feedback control over the hypothalamus through GABA and noradrenaline, respectively. Functionally, there is a differential hypothalamic Hcrt modulation on vRPO and DOPT. Thus, Hcrt in DOPT promotes wakefulness, whereas in vRPO produces a specific GABA-mediated REM sleep suppression. Therefore, hypothalamic Hcrt neurons in physiological conditions would be inhibiting REM generation mechanisms in vRPO. In NT1, the removal of this inhibition by degeneration of Hcrt neurons would produce REM attacks (SOREMs) and/or partial facilitation of REM sleep features. In contrast, the failure of Hcrt signaling in DOPT would determine the excessive daytime hypersomnolence typically expressed in NT1.

S50.4

Role of Urocortin-1 from Edinger-Westphal nucleus in thermoregulation and adipose tissue metabolism.

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Centrally projecting Edinger-Westphal nucleus (cpEW), which is unrelated to the classic preganglionic parasympathetic group involved in pupilloconstriction, can modulate thermoregulation and adipose tissue metabolism. The cpEW is the main source of urocortin-1, a potent anorexigenic neuropeptide that belongs to the corticotropin-releasing factor (CRF) family and projects extensively throughout the brain. Brown adipose tissue (BAT) regulates heat production to maintain body temperature, whereas white adipose tissue (WAT) serves as an energy reserve. Modulation of BAT and WAT activity is exerted via central control of their sympathetic innervation. Viral transsynaptic tracing showed that urocortin-1 neurons are part of the circuit that coordinates BAT and WAT activities simultaneously in rodents. In a model of diet-induced obesity, urocortin-1 neurons involved in WAT control were decreased in obese-resistant rats respect to obese and controls, suggesting that changes in urocortin-1 expression are linked to these phenotypes. Injection of urocortin-1 in raphe pallidus, which contains presympathetic neurons controlling BAT thermogenesis, increased BAT temperature and nerve activity. Stimuli that challenge the metabolic status, such as cold and fasting, activated urocortin-1 neurons as well as afferent hypocretin/orexin neurons labeled by retrograde tracing from cpEW. Hypocretin/orexin and urocortin-1 neurons, both involved in feeding and thermoregulation, are reciprocally innervated. Relaxin-3 neurons, which promote food intake, receive urocortin-1 projections and express CRF receptors, suggesting a possible interaction to exert opposite effects on feeding behavior. Urocortin-1 is involved in energy and metabolic control via modulation of sympathetic outflow to adipose tissues and interactions with other systems also involved, such as hypocretin/orexin and relaxin-3.

S51 "Risk and protective factors in drug use and vulnerability to addiction"

Chairs: Liana Fattore, Maria Antonietta de Luca

S51.1

Age- and sex-related vulnerability in the use of novel psychoactive substances: preclinical data on cannabinoids, phenethylamines, and cathinones

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Novel Psychoactive Substances (NPS) are a broad variety of drugs not regulated by present legislation. The advent of NPS has contributed to the appearance and growth of a new 'drug scenario' characterized by an increased number of drug users among youth and the consumption of drugs with unknown effects or safety profiles. Preclinical and clinical findings have shown that at lower doses NPS may produce effects comparable to those of illicit psychoactive drugs, such as Cannabis, heroin, cocaine and MDMA, however, with more severe consequences. To date, more than 900 NPS have been identified; the first wave of NPS came to Europe in the early 2000s in the form of synthetic cannabinoids followed by synthetic cathinones and phenethylamines. In order to characterized the influence of age and sex on the pharmaco-toxicological

effects of NPS, here we performed in vivo preclinical studies on three selected NPS, namely 5F-MDMB-PICA (synthetic cannabinoid), 2-Cl-4,5- MDMA (phenethylamine), and MDPHP (synthetic cathinone). Therefore, by in vivo microdialysis, we evaluated the effects of 2-Cl-4,5-MDMA (1-5 mg/kg iv) and MDPHP (0.1-0.5 mg/kg iv) on dopaminergic (DA) and serotonergic (5-HT) transmissions in the nucleus accumbens (NAc) shell and core, and the medial prefrontal cortex (mPFC) of male and female adolescent and adult rats. Preliminary results showed that 2-Cl-4,5-MDMA and MDPHP significantly increased NAc shell DA and 5-HT transmission of adult and adolescent male rats with adolescents being more sensitive to the lower doses. This vulnerability was confirmed after the treatment with 5F-MDMB-PICA (0.01 mg/kg ip) that stimulated NAc shell DA of adolescent, but not adult, male mice. Moreover, we observed that adolescent mice acquired 5F-MDMB-PICA intravenous self-administration (IVSA) at a lower dose (2.5 ug/kg/inf) compared with that of the prototypical synthetic cannabinoid JWH-018 (7.5 ug/kg/inf), thus confirming the increased abuse liability of the newer NPS. Notably, 5F-MDMB-PICA IVSA during adolescence induced remarkable changes in the adult behavior such as an increased propensity for aggressive behavior together with a lower social interaction than control mice. Taking together, findings from these different studies highlight the alarming age-related consequences of the use of NPS. Evaluation of sex differences is in progress.

S51.2

Effort-related effects of atypical dopamine transport inhibitors

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People with depression, Parkinson's disease, schizophrenia, and other psychiatric disorders suffer from fatigue, anergia, avolition, apathy, and other motivational dysfunctions, which can be highly treatment resistant. Animal tasks have been developed to measure effort-related choice, offering the option of high effort actions leading to more valued reinforcers vs. low effort/low reward activities. Such tasks are useful for preclinical studies related to drug development. A low effort bias can be induced in male and female rats by injection of the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ), which induces depressive symptoms in people. Suppression of lever pressing is also induced by injections of pro-inflammatory cytokines, which provide an inflammatory challenge. These deficits can be reversed by drugs that are known dopamine transport (DAT) inhibitors, including lisdexamfetamine, methylphenidate, and GBR-12909. Because many drugs that block DAT act as major stimulants and produce undesirable side effects, there is a need to develop and characterize novel atypical DAT inhibitors with unique neurochemical profiles. Recent studies have shown that novel atypical DAT inhibitors, including modafinil analogs, also can restore motivational function, and increase selection of high-effort activities involving physical effort. These compounds include modafinil, CE-123, CE-158, CT-005404, JJC8-088, and others. Drugs that stimulate serotonin transmission are not effective in this regard. It is possible that this research will identify new avenues for drug treatment of effort-related motivational symptoms in humans, including apathy, anergia, and COVID-related fatigue.

S51.3

Sensitivity in rats and humans to psychostimulants: Relationship with reward sensitivity vs positive affect

Jaanus Harro[1], Margus Kanarik[1], Evelyn Kiive[2], Kadri Kõiv[3], Karita Laugus[1], Denis Matrov[3], Katre Sakala[4,5,6], Aleksander Pulver[5], Marten Vares[3], Ruth Shimmo[5], Toomas Veidebaum[6]

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Inter-individual differences sensitivity to the effects of intoxicants as well as the development of addiction have been attributed to sensitivity to rewards. What exactly constitutes reward sensitivity in neural terms is not clear, possibly because 'reward' is an imprecise construct that often is extended to the experience of positive affect. In animal studies, the approaches under the reward sensitivity term are manifold. We have shown that rats with high sucrose intake are more sensitive to amphetamine and more vulnerable to amphetamine sensitization if previously chronically stressed but the effect of amphetamine is mitigated by stress in animals with low inherent positive affect as expressed in 50-kHz ultrasonic vocalization. Within a single experiment, chronic stress again reduced the rewarding effect of amphetamine to the highest degree in

animals with high sucrose intake and low positive affect. In humans, reward sensitivity can be parsed into striving towards multiple rewards (Openess to Rewards) and fixation to a specific reward (Insatiability by Reward) that are differently associated with positive affect and ADHD symptoms. Analysis of the data of the longitudinal Estonian Children Personality Behaviour and Health Study (www.ecpbhs.ee) revealed that while sedative psychoactive drug use was associated selectively with Insatiability to Reward, psychostimulant use had an additional association with Openness to Rewards. However, positive affect was not related to use of either type of psychoactive substances. Conclusively, psychostimulant use and effect have separate associations with distinct aspects of reward sensitivity, and positive affectivity has a limited direct role.

S51.4
Impact of repeated exposure to hormonal contraceptives during adolescence on cannabinoid-induced behavior in female rats

Liana Fattore[1], Augusta Pisanu[1], Patrizia Porcu[1]
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Cannabis is still the most used drug worldwide, with a number of adolescent female users that has gradually increased over the last decade. Hormonal contraceptives (HC) continue to be the most commonly used form of prescription contraceptives used by adolescents in many countries, and evidence is mixed regarding any increased health risk for the concomitant use of drugs of abuse. HC block ovulation by reducing the levels of estradiol and progesterone, two hormones that within the brain modulate emotional states, cognitive processes and reward. We have previously demonstrated that chronic treatment with HC induces anxiety, reduces social behavior and sex motivation and affects memory processes in female rats. In this study we tested the hypothesis that long-term adolescent treatment with ethinyl estradiol (EE, 0.030 mg) plus levonorgestrel (LNG, 0.125 mg), two of the most widely used steroids in the HC pill, may interfere with the behavioral effects induced by the cannabinoid CB1 receptor agonist WIN55,212-2 (WIN) in female rats. Specifically, we evaluated the effects of a repeated intravenous administration of WIN at the dose of 12.5 µg/kg/0.1ml, known to activate the brain reward system, on (i) motor activity, (ii) emotional reactivity, (iii) social behavior, (iv) cognitive functions and (v) plasma levels of estrogen and progesterone of HC-exposed and vehicle-exposed (control) females. Translated at the human level, our findings contribute to verify the hypothesis that young women using HC are differently vulnerable to cannabis-induced behavioral effects and that cannabis alters the emotional states and cognitive functions of adolescents using HC.

S52 "Exposure to chronodisruptive environment impacts neuroendocrine functions"

Chair: Patrick Vuillez

S52.1
Inappropriate exposure to blue enriched light affects behavior in mice. How is it relevant to humans?

Virginie Laurent-Gydé[1]
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Light is considered the most important "zeitgeber" of living organisms (day/night cycle, seasonal variations, reproduction. . .) playing an essential role as synchronizer between the environment, internal physiology and behaviour. Inappropriate chronic use of blue light-emitting devices disrupt sleep and circadian rhythms, both of which can influence alertness, mood, cognition and behaviour and potentially lead to enhanced impulsivity and impaired recognition of social cues, components of uncontrolled aggression. The non-visual information is mediated by a melanopsinergic pathway (intrinsically photosensitive ganglion cells (ipRGC) sensitive to short wavelength blue light, 460-480 nm), projecting from the retina to the hypothalamic suprachiasmatic nuclei (SCN). Besides the regulation of circadian rhythms ipRGCs also projects to nuclei involved in the emotional regulation and aggression system, a neural circuitry which is common interspecies including humans.
We have set up a protocol to mimic human exposure to blue light at night and controlling the SCN pathway in order to test the direct effects of light on retina and the brain. We have demonstrated that monoaminooxydase A KO (catecholamines catabolism) and C3H mice (rod and cone less model) chronically exposed to warm white -enriched in blue- light at an inappropriate timing (during the day for a nocturnal animal) display changed anxiety and aggressive behaviors compared to their counterparts exposed to warm white light. Our data seem to confirm that artificial blue light acts on mammalian brain, a question that has become a dominant health issue (ANSES report 2019).

S52.2

A chronodisruptive ligh/dark cycle markedly impairs the central regulation of female fertility

Valérie Simonneaux[1]
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In female mammals, cycles in reproductive function depend both on the biological clock synchronized to the light/dark cycle, and a balance between the negative and positive feedbacks of estradiol. In women, studies report that chronodisruptive environments such as shiftwork, may impair fertility and gestational success. The objective of this study was assess the effect of chronodiruption in female mice. Mice exposed to a single 10 h-phase shift exhibit a minor and transient alteration in the timing of LH surge and robustness of estrous cyclicity. By contrast, mice exposed to chronic shifts (successive rotations of 10 h-phase advances/10 h-phase delays), exhibited a severely impaired reproductive activity illustrated by a full inhibtion of the LH surge and a two time reduced number of pups.

S52.3

Can well-timed exercise repair the chronodisruptive effects of mis-timed feeding?

Andries Kalsbeek[1]
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Shift-work is associated with negative health effects such as obesity and type 2 diabetes. The most obvious disrupted behavior in shift-workers is the sleep-wake rhythm, as they are working and thus awake and active during nighttime, the natural resting period. We used time-restricted running (TRR; i.e. voluntary, but timed access to a running wheel) as an animal model to mimic this "activity during the natural resting or active period" aspect of shift-work. Rats could either run ad libitum, only during their natural active period (=dark) or during the natural inactive (=light) period. Timing of exercise influenced peripheral clock-gene expression in a tissue- and gene-dependent manner with exercise during the natural inactive phase dampening the day/night differences and exercise during the natural active phase strengthening the day/night difference. Therefore, exercise when timed appropriately, might be a tool to reduce the negative health effects of shift-work.

S52.4

Circadian appetite regulation — a tale of two clocks

Henrik Oster[1]
[1]*Institut of Neurobioloy, Lübeck, Germany*

Energy intake and expenditure are regulated by metabolic control centres of the central nervous system. A homeostatic circuit in the hypothalamus regulates meal intake in response to energetic demands while hedonic circuits of the limbic system may override homeostatic set points and promote overeating on energy-dense, palatable foods. We have developed paradigms to analyse the role of the circadian clock system in these two aspects of appetite regulation. We identified pathways of central clock resetting in mice and a circadian dopaminergic system that drives hedonic appetite in particular during the early rest phase. Our data may provide an inroad into targeting circadian aspects of hedonic overconsumption in an environment of abundance.

S53 "Rapid Acting Antidepressants — Not only NMDAR antagonism"

Chairs: Robert Zorec, Natalie Rasgon

S53.1

New mechanisms of ketamine action in acute and chronic stress models of psychopathology

Maurizio Popoli[1]
[1]*Department of Pharmaceutical Sciences, University of Milano, Milano, Italy*

Administration of subanesthetic ketamine (10 mg/kg) to rats vulnerable to chronic mild stress rescued anhedonic behavior, impairment of basal glutamate release, BDNF mRNA dendritic trafficking and dendritic atrophy in hippocampus. Therefore, ketamine in just 24 hours was able to rescue depressed-like behavior and related cellular/molecular changes due to chronic stress. Regarding acute stress, a single ketamine injection blocked the typical stress-induced enhancement of depolarization-evoked glutamate release in prefrontal cortex (PFC), if administered either 24 hours before or 6 hours after footshock (FS) stress. Ketamine administered 6 hours after acute FS stress rescued the prolonged enhancement of glutamate release (24 hours). Ketamine also blocked the increase of sEPSCs peak amplitude and dendritic retraction in PFC. On the behavioral level, ketamine did not rescue depressed- (anhedonia) or anxious-like behavior, but instead facilitated extinction of contextual fear memory, which is implicated in PTSD. Altogether, the data combined from our chronic and acute stress studies suggest that ketamine, rather than just inducing a general activation of glutamatergic synapses in corticolimbic areas, exerts a modulatory homeostatic effect on glutamatergic transmission, stabilizing glutamate dysfunction induced by either acute or chronic stress. Indeed, when synapses are hypofunctional (after chronic stress) ketamine restores glutamate release to control levels while, when glutamate

release is enhanced by acute stress, it dampens glutamate efflux, thus stabilizing glutamatergic transmission. Our results, besides pointing at new mechanisms in the antidepressant effect of ketamine, concur to encourage the study of this drug as an innovative therapeutic strategy to be administered shortly after the traumatic experience for inhibiting fear memory consolidation in PTSD.

S53.2

Astrocyte Specific Remodeling of Plasmalemmal Cholesterol Composition by Ketamine: a New Mechanism of Antidepressant Action

Robert Zorec[1]

[1]*Institute of Pathophysiology, University of Ljubljana, Medical Faculty, Ljubljana, Slovenia*

Ketamine is an antidepressant with rapid therapeutic onset and long-lasting effect, although the underlying mechanism(s) remain unknown. Using FRET-based nanosensors we found that ketamine increases [cAMP]i in astrocytes. Membrane capacitance recordings, however, reveal fundamentally distinct mechanisms of effects of ketamine and [cAMP]i on vesicular secretion: a rise in [cAMP]i facilitated, whereas ketamine inhibited exocytosis. The inhibition of exocytosis is associated with a ketamine-induced cholesterol redistribution in the plasmalemma in astrocytes, but neither in fibroblasts nor in PC 12 cells. This novel mechanism posits that ketamine affects density and distribution of cholesterol in the astrocytic plasmalemma, consequently modulating a host of processes, including the release of growth factors, that may contribute to ketamine's rapid antidepressant action.

S53.3

A cellular approach to the mechanism of rapid-acting antidepressants: NMDAR independence and cAMP dependence

Mark Rasenick[1]

[1]*Jesse Brown VAMC, University of Illinois College of Medicine, Chicago, USA*

All antidepressants examined thus far, including "atypical" compounds such as HDAC6 inhibitors, dissociative anesthetics like ketamine, and psychedelics like psilocin, increase cAMP by translocating the G protein Gsalpha from cholesterol-rich lipid rafts to non-raft membrane regions, where they activate adenylyl cyclase. This antidepressant-induced, sustained increase in cAMP leads to activation of several genes, including the neurotrophic factor, BDNF (brain-derived neurotrophic factor). Recent studies reveal that Gsalpha becomes depalmitoylated (loses its lipid modification) and dissociates from membrane tubulin (the protein anchoring Gsalpha in lipid rafts) after antidepressants concentrate, slowly, in lipid rafts. Furthermore, while the putative targets of these drugs (NMDA receptors for ketamine and serotonin 2A receptors for LSD and psilocybin) are not coupled to the activation of adenlylyl cyclase and increased cAMP, the drugs do increase cAMP, and achieve this along a significantly faster timescale than traditional antidepressants. Recent human studies suggest the biomarker potential of the above for personalized depression treatment.

S53.4

Cellular and metabolic predictors of antidepressant response in major depression

Natalie Rasgon[1]

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Among patients with major depression, increased inflammatory markers at baseline may predict an antidepressant response. Reducing inflammation may augment response to psychotropic medications. Few studies have investigated an association between Leukocyte Telomere Length (LTL) and therapeutic response in depression, reporting mixed results. No studies assessed LTL and treatment response with PPAR-ɣ agonists. While there are many newer rapidly acting antidepressant agents becoming more available on the market, the treatment response is either short-lived or still lags behind the time-to-action of an anti-depressant. We postulate that there are allostatic load biomarkers (like metabolic dysfunction oxidative stress) that might predict anti-depressant response. (1) LTL as a predictor of anti-depressant response to PPAR-ɣ agonist in patients with unremitted depression. (2) the correlation between LTL and insulin resistance (IR) status. We aimed to assess LTL as a predictor of antidepressant response to Pioglitazone in groups of insulin resistant and insulin-sensitive subjects using surrogate markers of IR. Medically stable men and women (n = 42) ages 23–71 with non-remitted depression participated in double-blind placebo-controlled add-on of Pioglitazone to treatment-as-usual. Oral glucose tolerance tests were administered at baseline and at 12 weeks. At baseline, no differences in LTL were detected by depression severity, duration or chronicity. LTL was also not significantly different between insulin-resistant and insulin-sensitive subjects. Subjects with longer telomeres exhibited greater declines in depression severity in the active arm, but not in a placebo arm. LTL also predicted improvement in insulin sensitivity in the group overall and did not differ between the active and placebo arm. LTL may emerge as a viable predictor of antidepressant response. An association between insulin sensitization and LTL regardless of the baseline IR status points to potential role of LTL

as a non-specific moderator of metabolic improvement in these patients. The utilization of biomarkers of oxidative stress or similar aging (LTL) can be further validated in novel rapidly acting anti-depressant agents to assess their accuracy.

S54 "Proteostasis at the Cellular and Organismal Levels"

Chair: Ehud Cohen

S54.1
Protein quality control of biomolecular condensates: implications for Amyotrophic Lateral Sclerosis and Frontotemporal degeneration

Serena Carra[1], Laura Mediani[1], Francesco Antoniani[1], Marco Cimino[1], Jonathan Vinet[1], Jared Sterneckert[2], Simon Alberti[3]
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Protein folding is essential for life and is maintained by molecular chaperones and degradation systems, which together compose the Protein-Quality-Control (PQC) system. Proteostasis imbalances are associated with aging and disease. In particular, proteostasis dysfunction, impaired stress granule (SG) dynamics, defective nucleocytoplasmic trafficking and nucleolar stress are emerging themes in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal degeneration (FTD). Yet, how these processes are linked and influence each other's is only partly understood. Defective ribosomal products (DRiPs) result from premature translation termination, damaged mRNAs, DNA mutations and include translation products generated outside of protein-coding regions by RAN translation, such as C9orf72-dipeptide repeats (DPRs). DRiPs are cleared by the PQC. Here we will discuss how misfolded proteins and DRiPs can accumulate inside SGs, PML bodies and nucleoli promoting their conversion into an aggregated-state. Similar to DRiPs, DPRs and nonstop proteins that are translated from nonstop mRNAs accumulate inside nucleoli. Nonstop proteins are ubiquitylated by the Ribosome-associated-Quality-Control (RQC) protein LTN1 for proteasome-mediated degradation. By enhancing nucleolar retention of nonstop proteins, LTN1 impairment disrupted nucleoli. Since loss of LTN1 function results in proteotoxicity and promotes neuronal dysfunction, it will be important to address to what extent nucleolar accumulation of nonstop proteins contributes to ALS/FTD.
In summary, our data highlight an intricate connection between protein misfolding, PQC, RQC and biomolecular condensates, with important implications for cell dysfunction and disease.

S54.2
Transcriptional downregulation during proteotoxic stress and neurodegeneration

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Neurodegeneration typically involves collapse of chaperone capacity leading to an increase in proteotoxic stress. We uncovered that proteotoxic stress causes a large-scale transcriptional attenuation affecting genes involved in metabolism and protein biosynthesis, presumably to divert cellular resources to stress response. Investigations into mechanism underlying transcriptional attenuation led us to discover a novel stress-induced nuclear condensate formed by a transcriptional regulator called NELF (Negative Elongation Factor). Deletion of intrinsically disordered region of NELF allowed us to uncouple stress from transcriptional downregulation. Evidence suggests that transcriptional attenuation is necessary for cellular survival under proteotoxic stress conditions.

S54.3
Gonadotropin-releasing hormone receptor related 2 (gnrr-2) regulates somatic proteostasis in *Caenorhabditis elegans*

Anat Ben-Zvi[1], Mor Kishner[1], Alexandra Polonsky[1], Libat Habaz[1]
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The cellular proteome is tightly regulated by cellular quality control machineries that assure proper protein homeostasis (proteostasis). In *Caenorhabditis elegans*, quality control networks are down regulated cell-nonautonomously by the gonadal longevity pathway or metabolic signaling at the onset of reproduction. However, how signals are mediated between the gonad and the somatic tissues is not known. Gonadotropin-releasing hormone (GnRH)-like signaling functions in the interplay between development and reproduction and have conserved roles in the regulation of reproduction, metabolism and stress. We, therefore, asked whether GnRH-like signaling are involved in proteostasis collapse at the onset of reproduction. For this, we examined whether *C. elegans* orthologues of GnRH receptors modulate heat shock

survival during adulthood. We find that *gnrr-2* is required for proteostasis remodeling in different somatic tissues at the transition to adulthood. We show that *gnrr-2* functions downstream of the gonad in the gonadal-longevity pathway by activating DAF-16. This activation is required for *gnrr-2*-depenednt modulation of vitellogenin expression levels and thus reproduction. Taken together, our data suggest, that *gnrr-2* play a role in mediating the cross-talk between the reproduction system and the soma in regulating systematic proteostasis.

S54.4
Deciphering the proteostasis response to dissimilar proteotoxic challenges

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The "proteostasis network" (PN) is composed of various mechanisms that act in concert to maintain the integrity of the proteome. Early in life, the PN efficiently maintains proteostasis however, as the organism ages, subsets of aggregation-prone proteins challenge PN, form insoluble aggregates and in some cases, underlie the development of neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD). How the PN responds to dissimilar challenges and how these responses are regulated across the organism are unanswered questions. Employing nematodes that either express the HD-causing, abnormally long poly-glutamine (polyQ) stretches or the AD-causing peptide Aβ, we found that while Torsin chaperones protect the animal from polyQ, they aggravate Aβ toxicity. These opposing effects were observed regardless whether the aggregative proteins were expressed in neurons or muscles cells. To explore this regulatory mechanism we compared the transcriptomes of tor RNAi-treated worms that express Aβ to these of polyQ expressing animals, asking which genes respond in opposing manners in the two strains. Among other genes we found that a subset of neuropeptides are upregulated in polyQ worms and downregulated in Aβ worms. We further discovered that the insulin/IGF signaling cascade, and its downstream transcription factor SKN-1/NRF, play instrumental roles in the orchestration of the PN responses to distinct proteotoxic challenges. Our results show that the PN differentially responds to dissimilar proteotoxic challenges, show that specific neuropeptides are involved in the regulation of the proteostasis across tissues, and suggest that future therapies for different neurodegenerative maladies should be specifically tailored.

S55"Postdoctoral research symposium on stress"

Chairs: Patrizia Campolongo, Giulia Federica Mancini

S55.1
Bridging the preclinical-clinical boundary in stress research

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In this introductory talk to the symposium centered on novel important tiles in the stress research all presented by Post-Doctoral Research Fellows, I will offer a perspective on a productive translational research approach in studies of stress-related mental disorders. Stress research is more and more standing out as a field that illuminate mechanisms of susceptibility and of resilience. I will briefly discuss approaches, both traditional and innovative, that have the potential to make a substantial difference in the field, with the final aim to inspire young researchers for their future and brilliant journey in the intriguing rebus of stress research.

S55.2
Stress hormones in Angelman syndrome: insights from single-cell transcriptomics and protein interaction in mouse hippocampus

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Angelman syndrome (AS) is a neurodevelopmental disorder caused by the loss of function in the maternal allele of Ube3a which codes for the ubiquitin protein ligase E3A (also known as E6-AP). The paternal allele of Ube3a is silenced in neuronal cells, therefore neuronal cells are deprived of functional UBE3A in AS. Anxiety

and stress-related symptoms are often observed in AS patients. Moreover, mouse models for AS (Ube3a-/+) display a similar phenotype associated with anxiety-like behavior, increased plasma levels of glucocorticoids, as well as hippocampal synaptic malfunction and learning deficiency. Glucocorticoids (GCs) are stress hormones and powerful modulators of brain function. The hippocampus is a prominent GC target, as it particularly expresses the nuclear glucocorticoid receptor (GR). GR acts as a ligand-dependent transcription factor and relies on a complex and specific interactome to regulate gene expression in a context-specific manner. Previous studies suggested that UBE3A was a GR transcriptional coregulator and/or regulated GR by targeting the protein for ubiquitination and proteasomal degradation. We hypothesized that neuronal GR signaling is disrupted by the absence of UBE3A in AS mouse hippocampus.
We investigated the UBE3A-GR interaction, evaluating gene expression in the AS mouse hippocampus after chronic exposure to GCs using RNA sequencing (RNA-seq). The results showed that AS mice had a partially altered gene expression profile in response to GCs compared to WT mice. This suggests that UBE3A absence in neuronal cells specifically can change the outcome of GR signaling in the whole mouse hippocampus. We used publicly available single-cell sequencing data (scRNA-seq) to further guide the interpretation of our bulk RNAseq results. scRNA-seq data confirmed that GR and its downstream target gene network show a very heterogenous basal expression throughout hippocampal cell types, which likely predicted cell type-specific responsiveness to GCs. In addition, results on co-expression between GR and transcriptional coregulators such as UBE3A supported the hypothesis of cell type-specific transcriptional GR regulation. Our results indicate cell-type specificity of GR transcriptional interactome and supports its relevance in the pathological context of AS for which the underlying biological dysfunction is neuronal-specific. Altogether, our results allow the identification of a subset of GR-mediated pathways responsible for stress maladaptation in AS and offer potential therapeutic strategies via selective and cell-specific manipulation of GR signaling in neuronal cells.

S55.3

Long-term effects of early-life adverse events: the role of sex differences

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Exposure to stress represents a well-known risk factor for psychiatric diseases. However, the timing of life stress may be important in determining its long-term outcomes. Growing evidence has demonstrated that experiencing early-life adverse events, especially in the prenatal and adolescent periods, can interfere with neurodevelopmental trajectories, which may result in altered vulnerability to stress-related disorders later in life. Literature data suggest that women present a greater risk to develop psychiatric diseases than men, and this seems to be influenced by the effects of sex hormones on the stress-response system. However, the mechanisms underlying these gender differences remain unclear due to the paucity of both clinical and preclinical studies carried out in female subjects. Therefore, in this talk I will discuss how early-life adverse events might produce different stress-responses in male and female adult rats. In particular, I will present data demonstrating that early-life stressors (prenatal stress or repeated brief social isolation stress during early-adolescence) induced behavioral alterations on emotionality and cognitive functions in the long-term and that these effects are sex divergent. Thus, our findings are relevant to future research aimed not only at investigating sex-differences in the neurobiology of stress-related disorders, but also at evaluating pharmacological interventions to treat long-term alterations induced by early-life stressful events.

S55.4

The arousal-based individual screening model: a step toward a better understanding of sex differences in PTSD susceptibility and resilience

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Available animal models for the study of stress-related disorders such as post- traumatic stress disorder (PTSD) have provided important findings. However, several reports have demanded the development of more effective and translational animal models for studying PTSD. In particular, a major limitation of this research field is the lack of effective animal models that include female rodents. This indeed does not corroborate the human literature showing that traumatized women are significantly more likely to develop PTSD compared to men. In an attempt to address these challenges, we have recently developed a novel animal model called arousal-based individual screening (AIS) model. To design this model, we combined the traumatization of C57BL/6J mice, with an individual profiling approach consisting of long-term z-normalization of change in post-trauma acoustic startle reactivity. Through the AIS model, we provide evidence that an inbreed population of adult mice subjected to 24

hours of restraint stress can be segregated in susceptible and resilient subpopulations. The AIS model has the advantage of being able to model the chronicity of multiple PTSD symptoms. Indeed, susceptible male mice exhibit multiple PTSD-like phenotypes, resembling different PTSD symptoms, up to 75 days post-trauma. Intriguingly, our preliminary data show that the AIS model is in fact more effective by enrolling C57BL/6J female mice, which are more susceptible and exhibit even more robust PTSD-like phenotypes compared to male susceptible mice. From a translational perspective, these preliminary results are highly relevant. Indeed, preclinical studies have shown that stress-induced PTSD-like phenotypes in female rodents are generally much weaker and significantly different from those observed in male rodents. Thus, the AIS model, being able to model key features of PTSD, is a unique translational tool that can be used for studying the unclear sex-biased neurobiology of PTSD as well as for identifying new potential treatments.

S56"Understanding Brain Cholesterol homeostasis: from Basic Mechanisms to the Effects of Environmental and Nutritional factors"

Chairs: Luisa Cigliano, Valentina Pallottini

S56.1
Cholesterol metabolism and neurodegeneration: Niemann-Pick type C as case in point

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Cholesterol is a key component of cells in the central nervous system featuring highly specialized structures and signaling processes that depend on cholesterol-rich membranes. This implies that defects in cholesterol homeostasis cause havoc in the brain. A prime example is Niemann-Pick type C disease. This rare autosomal-recessive lysosomal storage disorder is provoked by defects in NPC1 or NPC2, which mediate collectively the exit of lipoprotein-derived cholesterol from the endosomal-lysosomal system. Patients present a wide range of disease onset, neurovisceral symptoms and life spans. Based on our previous studies, we used the retinae of NPC-deficient mice to test our working hypothesis that neurons depend on cholesterol delivered by glial cells. We observed layer-specific pathologic changes in the retina of NPC1-deficient mice and the presence of lamellar inclusions in neurons, which represent the ultrastructural correlate of cholesterol accumulation in neurons. We showed that intravitreal injections of beta-cyclodextrin, a drug that has been tested in clinical trials with NPC patients, cause release of these inclusions from neurons and their uptake by glial cells. This neuron-glia collaboration may protect neurons from cholesterol overload. Currently, we determine the molecular pathways that determine the degree of neuronal vulnerability to NPC1 deficiency. Uncovering these pathways may provide new therapeutic targets to treat this ultimately fatal disease. In my presentation I will summarize current findings and provide an outlook.

S56.2
Brain cholesterol and dietary interventions — friends or enemies

Aleksandra Mladenovic[1], Kosara Smiljanic[1], Milica Prvulovic[1], Smilja Todorovic[1], Milka Perovic[1], Selma Kanazir[1]
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Cholesterol is an essential component of synapses, representing 30% of all the lipids in the brain. Maintaining the brain cholesterol homeostasis is an important prerequisite for the proper brain functioning. The majority of brain cholesterol is synthesized *in situ*, as cholesterol does not pass the blood–brain barrier (BBB). Cholesterol homeostasis is accomplished through a sophisticated regulation of synthesis, transport, and elimination. Disturbance of these processes underlies numerous brain disorders, like AD, PD, MS, etc.

Dietary restriction (DR), one of the most promising anti-aging environmental interventions has been shown to have significant impact on brain cholesterol metabolism. Here we summarized the data about the impact of various DR on brain cholesterol, its precursors and metabolites, as well on the key players involved in cholesterol synthesis and catabolism. We examined the effects of various dietary regimes in the rat cortex, hippocampus and cerebellum by varying the onset, duration, percent and type of restricted feeding. We also followed changes in cholesterol homeostasis in the periphery, in the liver and serum.

Although cholesterol metabolism on the periphery and in the brain is separated by the BBB, it seems that dietary restriction could influence cholesterol brain level and metabolism. We have shown that most positive impact in preserving cholesterol homeostasis and counteracting age-related changes has the lifelong moderate dietary restriction. In addition, although cholesterol is ubiquitously distributed throughout the brain, we showed that dietary restriction led to the specific spatiotemporal pattern of changes in the cholesterol homeostasis.

S56.3

Modulation of cholesterol biosynthetic pathway in the brain: effects on behavior and potential interference by exogenous compounds.

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The cholesterol biosynthetic pathway, also known as mevalonate (MVA) pathway, is crucial for most eukaryotic cells. The key and rate-limiting enzyme of this metabolic process, the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), plays a pivotal role in brain physiology since it leads to the production of cholesterol and non-sterol isoprenoids that are vital for a wide range of neuronal functions. Experimental evidence highlights that MVA pathway is differently modulated in each brain region, and is critically involved in the regulation of emotional reactivity and cognitive processes. Importantly, any exogenous compound able to cross the blood brain barrier, ranging from drugs to pollutants, may affect the expression and the activation of proteins belonging to MVA pathway, with important consequences for the maintenance of brain physiology.

S56.4

Unraveling the link between Brain Cholesterol Homeostasis and Beta Amyloid Metabolism — focus on the impact of a western diet

Luisa Cigliano[3*],Maria Stefania Spagnuolo[1], Valentina Pallottini[2], Arianna Mazzoli[3], Martina Nazzaro[3], Lucia Iannotta[3], Claudia Tonini[2], Marcus Ståhlman[4], Raffaella Crescenzo[3], Susanna Iossa[3]

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Why is there a higher incidence of neurodegenerative diseases such as Alzheimer's disease in Westernized countries? Unhealthy nutrition is known to influence cerebral physiology, but the specific effect of western diets on brain cholesterol homeostasis, particularly at middle age, is not fully clarified. Cholesterol homeostasis is crucial for brain structure and function. Given the link between brain cholesterol dysregulation, beta amyloid production and Alzheimer's disease onset, our investigations evaluated whether typical western diets rich in fat and/or sugar affects the protein network implicated in cholesterol synthesis and shuttling between glial cells and neurons, as well as crucial markers of beta amyloid metabolism.
Aging rats were fed a high fat-high fructose (HFF) or a control diet for 4 weeks. Inflammatory markers and cholesterol levels significantly increased in hippocampus of treated rats, and these results were associated to significant alterations of key players of brain cholesterol metabolism. Indeed, a higher activation of 3-hydroxy 3-methylglutaryl coenzyme-A reductase, coupled with lower levels of Apolipoprotein E, LXR-beta, and lipoproteins receptors was measured in hippocampus from HFF rats. These alterations were associated with brain changes preluding to the development of Alzheimer's disease. We will discuss further emerging data on the impact of western diets on brain cholesterol dysmetabolism, as well the putative beneficial effect of nutritional factors such as probiotics.

S57"The role of cyclic AMP signalling in astrocyte function"

Chairs: Anja Teschemacher, Nina Vardjan

S57.1

Distinct dynamics of astroglial Ca2+ and cAMP signaling and regulation of aerobic glycolysis

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Astrocytes, highly heterogeneous neuroglial cells in form and function, are important regulators of brain energy metabolism, which is impaired in many neuropathologies. In contrast to oxidative neurons, astrocytes are considered mainly glycolytic cells. In response to extracellular stimuli (*e.g.*, noradrenaline, ATP, lactate), astrocytes, through the activation of plasma membrane receptors coupled to Ca^{2+} and cAMP signaling pathways, upregulate glucose uptake, glycogenolysis and aerobic glycolysis, resulting in L-lactate production. Released from astrocytes, extracellular L-lactate can be taken up by neurons and used as an energy substrate (astrocyte-neuron lactate shuttle) or act as a signal affecting cell energy and redox state. Contribution of astroglial Ca^{2+} and cAMP signals in the upregulation of glucose metabolism in astrocytes is poorly understood. Our studies revealed that upon receptor-mediated stimulation of astrocytes, Ca^{2+} and cAMP signals exhibit distinct temporal properties; Ca2+ signals are fast and transient, whereas cAMP signals

are 10-fold slower and persistent. Contrary to the previous view that glycogenolysis and aerobic glycolysis are primarily mediated by cAMP in astrocytes, our studies revealed that Ca^{2+} signals represent a robust trigger of augmented aerobic glycolysis in astrocytes and that cAMP only aids to the Ca^{2+}-driven increase in aerobic glycolysis. We also show that Ca^{2+}-driven aerobic glycolysis in astrocytes depends on the availability of extracellular D-glucose and the glycogen shunt activity. The results open new avenues to explore whether astroglial Ca^{2+} signals, mediating L-lactate production, signaling and delivery to neurons, are dysregulated and contribute to neuropathologies with impaired brain metabolism.

S57.2

Brain cholesterol and dietary interventions — friends or enemies

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The functional role of cAMP-mediated signalling in astrocytes is not fully understood. The presentation will focus on the mechanisms that mediate the neuronal activity-dependent elevations in cAMP in neighboring astrocytes leading to the release of lactate. The data will be presented suggesting that increased neuronal activity is associated with the release of ATP which induces cAMP responses in astrocytes. cAMP increases glycogenolysis and glycolysis in astrocytes leading to the enhanced production and release of lactate to fuel the neuronal activity. It is hypothesized that this new signalling mechanism involving astroglial cAMP is responsible for on-demand metabolic support of the neuronal activity.

S57.3

Second messenger signaling expressed in cortical astrocytes during fear conditioning learning

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Several lines of evidence support that activation of astrocytic G protein-coupled receptors (GPCRs) leads to the secretion of molecules that modulate synaptic plasticity. However, how astrocytic GPCR activation occurs during learning has yet to be addressed. We performed dual-color simultaneous imaging of Ca^{2+} and cAMP, the two representative second messengers of GPCRs, in behaving mice and found that found that Ca^{2+} response and cAMP responses have distinct dynamics. Optogenetic stimulation of noradrenergic axons in the cortex resulted in elevations Ca^{2+} and cAMP in astrocytes. cAMP elevation, however, required longer stimulation to be detected by the Pink Flamindo cAMP probe. In addition to prominent astrocytic Ca^{2+} elevations, cAMP elevation in the cortex was elevated during fear conditioning learning via the beta-1 adrenergic receptor. Our results suggest that astrocytic GPCR second messengers are activated according to the vigilance state of the animal. Currently, we are attempting to activate Gs signaling selectively in astrocytes using a transgenic mouse that express the OptoB2AR optogenetic GPCR in mice.

S57.4

Optogenetic manipulation of astrocytic cAMP to modulate memory

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Astrocytes play essential roles in synaptic plasticity and memory formation. Previous studies have mainly focused on Ca^{2+} signaling in astrocytes as underlying mechanisms. Thus, despite that astrocytes express multiple receptors which transduce cyclic AMP (cAMP)-mediated cellular signals, the involvement of astrocytic cAMP in synaptic plasticity and memory formation is undetermined. To answer this question, we developed an optogenetic approach to manipulate the intracellular cAMP levels specifically in astrocytes in vivo. We developed a transgenic mouse line in which astrocytes express photoactivated adenylyl cyclase (PAC) which converts ATP to cAMP in response to blue light. We found that increase in local astrocytic cAMP induces c-Fos expression in surrounding neurons. In addition, astrocytic cAMP increase induced long-term potentiation (LTP) in hippocampal slices. Furthermore, optogenetic increase of astrocytic cAMP in the hippocampus during memory formation or retention modulated memory differently. We have also shown that astrocytic cAMP facilitates synaptic plasticity through astrocyte-neuron lactate shuttle (ANLS) and NMDA receptor activation. Thus, our findings suggest that astrocytic cAMP signaling modulates synaptic plasticity and memory. This study further provides a new perspective for studying astrocytic functions in the brain.

S58 "The circadian clock and the sensory, integratory and executive parts of the nervous system: a keys for health"

Chair: Paul Pevet

S58.1

Suprachiasmatic Nucleus-Arcuate Nucleus Axis: Interaction Between Time and Metabolism

Buijs Ruud M.[1], Soto-Tinoco Eva[1], Rodríguez-Cortés Beatriz[1], Hurtado-Alvarado Gabriela[1], Martínez-Gómez Ricardo[1], Santacruz Esteban[1], Méndez-Hernández Rebeca[1]

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Several anatomical studies have revealed reciprocal connections between the Suprachiasmatic Nucleus (SCN) and the Arcuate nucleus (ARC). After obtaining evidence of circadian variations in neuronal activity in the ARC and activity change in the SCN after intravenous glucose injections, we have studied the importance of these reciprocal connections. First, disruption of SCN-ARC interaction using Halasz knife cuts resulted in a loss in circadian rhythm in activity, temperature, and corticosterone, indicating paramount importance of this interaction for circadian physiology. Second, the SCN induced rhythm in α-MSH neuronal activity was essential for the daily changes in body temperature. A circadian controlled rhythmic release of SCN Vasopressin (VP) and α-MSH in the medial preoptic area is essential for the correct timing of the temperature dip early in the sleep period. Next, the ARC appeared to be necessary for the negative feedback of corticosterone to regulate the circadian variation in its circulating levels. Here we will pay special attention to our recent studies showing that the SCN controls glucose penetration from the circulation into the ARC. VP release onto tanycytes late at night increases glucose transporter GLUT1 expression in tanycytes, leading to increased glucose concentration in the ARC. This glucose increase in the ARC drives down circulating glucose, whereas application of VP-antagonists or GLUT1 transporter blockers prevents glucose entrance into the ARC. Thus, peripheral glucose levels remain high. Altogether, these studies provide evidence for SCN-ARC interaction as an essential mechanism to adjust and control circulating glucose and corticosterone levels, both necessary for metabolic control.

S58.2

Can voluntary exercise shift the muscle clock?

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Many metabolic problems in our current society are at least partly explained by misalignment of different clock systems in our body, most severe problems being experienced by shift workers. It is still not clear, however, which factor is (most) responsible for these problems, i.e. disturbed sleep/wake or rest/activity rhythms, changed eating patterns, light at night, or a combination of these factors? In a series of experiments we investigated the metabolic consequences of light and feeding at the wrong time of day, i.e. in rats during night or day, respectively. These experiments revealed the primary problem seems to be a desynchronization of the different peripheral clocks. Whereas the liver clock nicely adapts to the new feeding time, the muscle clock becomes arrhythmic and the brown adipose tissue clock shows a partial phase shift and reduced amplitude. The varying degrees of adaptation of the different peripheral clocks likely results in a non-optimal alignment of different metabolic processes, such as glucose production and glucose uptake. Therefore, we wondered if, contrary to feeding, voluntary wheel running would be able to shift the muscle clock.

Male rats were provided with ad lib access to a running wheel for 2 weeks. At the end of this acquisition period they ran 4 km/day, mostly during the dark phase. Next, wheel access was limited to a 10h period in the light- or dark phase. Controls had no (sedentary) or unrestricted access to a wheel. After 4 weeks of time-restricted running, dark- and unrestricted runners still ran ∼3 km/day. After a strong initial decrease for 2 days, the light-restricted group increased running again, with total running activity stabilizing at ∼1.5 km/day after 4 weeks. All animals with access to a running wheel showed a decrease in adiposity compared to sedentary controls, but light-restricted runners showed the smallest effect. Comparing dark- and light-restricted animals running the same cumulative distance revealed that this diminished effect was due to both the reduced amount of running as well as its timing. Muscle clock gene rhythms are currently being analysed.

Male Wistar rats perform voluntary exercise in a running wheel during their regular sleep period, and the beneficial effects of exercise are determined both by quantity and timing.

S58.3

Scheduled feeding prevents circadian disruption, loss of homeostasis and disease

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Daily circadian rhythms are synchronized by environmental signals, from which the light-dark cycle, feeding schedules and activity patterns provide time signals to the biological clock. A coordinated function of the circadian system requires that the main synchronizing signal are coupled in time, resulting in a coherent time reference for the biological clock. Exposure to light at night, shifted feeding and activity schedules are conditions that lead to disruption of the circadian function. In this presentation we will present several experimental models that explore the consequences of circadian disruption similar to jet-lag, shift work and light at night. We have shown that rats exposed to such conditions exhibit affected metabolism, inflammatory response and depression-like behavior. With these models we tested the use of restricted and scheduled feeding as a strategy to restore and/or prevent circadian disruption. We used regular rodent food as well as palatable food. Both types of food when scheduled in phase with the expected activity phase restores and aligned circadian rhythms. This condition also influences in a positive manner metabolism and behavior. Contrasting feeding schedules aligned with the expected rest phase exerted adverse effects on the circadian function and consequently on homeostasis and behavior. We show that this effect is achieved by directly modifying the activity of the suprachiasmatic nucleus, the biological clock. Thus, we emphasize the need of maintaining a restricted time window for food intake in temporal coordination with the activity phase and the light-dark cycle.

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S58.4

Scheduled feeding prevents circadian disruption, loss of homeostasis and disease

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Intrinsic daily rhythms in physiology and behavior are generated by internal circadian clocks and the synchronization of these clocks to the external world. The suprachiasmatic nucleus (SCN) of the hypothalamus functions as the dominant circadian clock and is entrained by daily variation in light (photic cues) as well as by arousal-promoting stimuli (non-photic cues) such as social interactions and sleep deprivation. Clock cells of the SCN coordinate using vasoactive intestinal polypeptide as an intercellular signal. Mice lacking type 2 VIP receptor ($Vipr2^{-/-}$) do not express 24h rhythms in behavior and do not entrain to light. Using the non-photic cue of scheduled voluntary exercise (SVE) in a running wheel (6h/day every 24h for 21-24 days), we found that $Vipr2^{-/-}$ animals rapidly entrain to this stimulus, with SCN clock cell synchrony improved and most mice now capable of expressing 24h rhythms in behavior when the SVE regimen ended. Unexpectedly SVE reduced $Vipr2^{-/-}$ SCN neuronal activity and altered GABAergic activity. $Vipr2^{+/+}$ mice also responded to SVE, but typically required >35 days to achieve entrainment. The behavioral effects of SVE in $Vipr2^{-/-}$ animals were 'dose-dependent', as 1h/day of wheel-running for 21 days or 6h/day for 8 days were much less effective at promoting 24h rhythms. Further, when 6h/day of SVE was presented every 25h, $Vipr2^{-/-}$ synchronized to the time of wheel availability but resorted to 24h rhythms when this program was completed. These findings suggest that scheduled physical exercise is a useful intervention to restore daily rhythms in physiology and behavior.

S59 "Astrocyte roles in brain function and dysfunction"

Chair: Eleanora Aronica, Rhein Parri

S59.1

Astrocytic derived adenosine is implicated on BDNF effect upon hippocampal LTP

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Astrocytes are key cellular partners to neurons, playing an important role in multiple processes in the brain. Astrocytes are not only supportive cells with homeostatic functions, but also play a role in information processing, by responding to neuronal synaptic activity with Ca^{2+} elevations that may induce the release of gliotransmitters,

which in turn modulate neuronal excitability and synaptic plasticity. Hippocampal long-term potentiation (LTP) is a sustained enhancement of excitatory synaptic strength believed to underlie learning and memory processes, and it has been described that astrocytes regulate synaptic transmission and play a role in shaping LTP, specifically, through the release of gliotransmitters, such as glutamate, ATP, and D-serine. Other very important molecule for the modulation of LTP is brain-derived neurotrophic factor (BDNF), a neurotrophin involved in the development and protection of different neuronal populations. BDNF has a facilitatory action upon hippocampal LTP, being this action dependent on the adenosine A_{2A} receptor (A_{2A} R) activation. Thus, we evaluated 1) the involvement of astrocytes upon the modulatory effect of BDNF upon LTP, 2) the involvement of adenosine (and A_{2A} R) on this process and 3) the role of adenosine receptors activation on calcium signaling mediated by astrocytes. Our findings suggest that BDNF effect upon synaptic plasticity is under the control of astrocytes. These results further highlight the role of astrocytes in the CNS but, more importantly, the role of astrocytes on the glial–neuron communication involving synaptic plasticity modulation by neurotrophins.

S59.2

The role of astrocytes in cortical plasticity

Rheinallt Parri[1]

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Mice explore the environment using their whiskers. Action potentials in sensory afferents triggered by whisker deflections are ultimately transmitted to somatotopically organised populations of cells in the primary somatosensory cortex known as the barrel cortex. Alterations in whisker experience may induce plastic changes in neurons of the barrel cortex—Experience-Dependent Plasticity (EDP). Much is known about the synaptic mechanisms underlying these changes however, comparatively little is known about the role of astrocytes in these processes. This talk will describe work aimed at determining the role of astrocytes and astrocyte calcium signaling in these processes. Using whisker deprivation paradigms together with models of genetic modifications targetting astrocyte calcium pathways such as $IP3R2^{-/-}$ mice and AAV transfection revealed astrocyte roles in Hebbian synaptic long term depression and potentiation. Astrocytic $[Ca^{2+}]i$ signaling is therefore important in several forms of synaptic and experience-dependent plasticity mechanisms in neocortex.

S59.3

Astrocyte control of excitation to Ventral Tegmental Area dopaminergic neurons affects dopamine-dependent behaviors

Giorgio Carmignoto[1]

[1]*University of Padova, Padova, Italy*

Glutamatergic synapses in the Ventral Tegmental Area (VTA) modulate the burst firing mode of dopamine neurons and their phasic dopamine release at target regions. These processes encode key behavioral responses, including locomotor activity, learning and motivated-behaviors. We found that VTA astrocytes respond to dopamine neuron bursts with Ca^{2+} elevations mediated by activation of endocannabinoid CB1 and dopamine D2 receptors. This astrocyte activation is followed by a long-lasting potentiation of the glutamatergic input to adjacent dopamine neurons that depends on presynaptic metabotropic glutamate receptors possibly activated by astrocytic glutamate. We also found that chemogenetic in vivo activation of VTA astrocytes increases the burst firing of dopamine neurons and enhances locomotor activity. Our data support a key role of astrocytes in the modulation of VTA dopamine neuron activity that encodes dopamine-dependent functions.

S59.4

microRNAs: key regulators of astrocyte mediated inflammation in CNS Pathologies

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The mounting evidence obtained during the past decade has emphasized the critical role of astrocytes in the pathophysiological processes implicated in a large spectrum of genetic and acquired forms of epilepsies. In both experimental and human epileptic tissues astrocytes undergo complex changes in their physiological properties, including the activation of inflammatory pathways, which can alter glio-neuronal communication, contributing to seizure precipitation, recurrence and associated comorbidities. In this context, understanding which of the molecular mechanisms are crucially involved in the regulation of glio-neuronal interactions under pathological conditions associated with seizure development is important to get more insight into the role of astrocytes in epilepsy. Accumulating experimental evidence suggests that proinflammatory molecules can alter glio-neuronal communications contributing to the generation of seizures and seizure-related

neuronal damage. In particular, both in vitro and in vivo data point to the role of astrocytes as both major source and target of epileptogenic inflammatory signaling. In this context, understanding the astroglial inflammatory response occurring in epileptic brain tissue may provide new strategies for targeting astrocyte-mediated epileptogenesis. The role of small regulatory molecules (microRNAs) involved in the regulation of specific pathways (such as the interleukin-1 receptor/Toll-like receptor pathway) and acting as key players of the astrocyte-mediated inflammation and oxidative stress will be addressed. Both clinical observations in drug-resistant human epilepsies and experimental findings in clinically relevant models will be discussed and elaborated, highlighting specific astrocyte-mediated inflammatory pathways as potential targets for antiepileptic, disease-modifying therapeutic strategies.

S59.5
In brain post-ischemic plasticity, Na^+/Ca^{2+} exchanger 1 and Ascl1 interact in microglia-dependent astrocyte differentiation

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The intricate glia interaction occurring after stroke is strongly dependent by the maintenance of intraglial ionic homeostasis. Among the several ionic channels and transporters, the plasmamembrane Na^+/Ca^{2+} exchanger (NCX) represents a good candidate in maintaining astroglial Na^+ and Ca^{2+} homeostasis.
Here, using a combined in vitro, in vivo and ex vivo experimental strategy we evaluated whether activated microglia may influence the morphological and the transcriptional plasticity of post-ischemic astrocytes. Astrocyte plasticity was monitored by the expression of the transcription factor Acheate-scute like 1 (Ascl1), which plays a central role in the commitment of astrocytes towards the neuronal lineage. Furthermore, we explored the implication of NCX1 expression and activity in mediating Ascl1-dependent post-ischemic astrocyte remodeling.
We demonstrated that: (a) in astrocytes co-cultured with microglia the exposure to oxygen and glucose deprivation followed by 7 days of reoxygenation promoted from one side a strong increase of the protective M2 microglia and from the other side induced a prevalence of bipolar astrocytes overexpressing Ascl1 and NCX1, whereas this did not occur in monocultured astrocytes; (b) the reoxygenation of anoxic astrocytes with the M2 microglia-derived conditioned medium strongly elicited the astrocytic co-expression of Ascl1 and NCX1; (c) Ascl1 expression in anoxic astrocytes was dependent by NCX1 since its silencing prevented Ascl1 expression both in in vitro and in post-ischemic ex vivo experimental conditions.
Collectively, the results of our study support the idea that, after brain ischemia, astrocyte-microglia crosstalk can influence astrocytic morphology and its Ascl1 expression. This phenomenon is strictly dependent on ischemia-induced increase of NCX1 which in turn induces Ascl1 overexpression possibly through astrocytic Ca^{2+} elevation.

S60 "Learning from lorcaserin lesson: is there still a future for 5-HT2C receptor development and therapeutic pharmacology?"

Chairs: G. Di Giovanni, P. De Deurwaerdère

S60.1
The deletion of SNORD115 in mice merely alters 5-HT2C receptor functions but destabilizes monoaminergic neurons activity in a manner opposite to 5-HT2C agonists

Butler Jasmine[1], Marty Virginie[2], Coutens Basile[3], Hebras Jade[2], Personnaz Jean[4], Mercier Pascale[5], Krogh Nicolai[6], Nielsen Henrik[6], Aguirrebengoa Marion[7], Seitz Hervé[8], Pradère Jean-Philippe[4], De Deurwaerdère Philippe[1], Guiard Bruno[3], Cavaillé Jérôme[1]
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Serotonin2C receptor (5-HT2CR) agonists are a target of choice in the treatment of obesity and addiction to cite a few. Lorcaserin has been the only therapeutic option that has reached FDA approval. The widespread expression of the 5-HT2CRs in the brain and its ability to

alter the activity of neurobiological networks at rest are some of the main concerns. The other concerns regard the knowledge of the numerous, molecular regulatory mechanisms including the non-coding RNAs like SNORD115, editing/splicing of the mRNA, and level of expression. We report herein the consequences of the deletion of the SNORD115 in mice on the physiology of the mice with some focus on food intake, locomotor activity, and anxiety for behaviors and monoamines function. The deletion of SNORD115 that was supposed to dramatically alter the editing and expression of the receptor led to very few changes of 5-HT2CR mRNA editing and expression across the brain of mutant mice. The deletion did not modulate food intake, or basal and cocaine-stimulated locomotor activity, or anxiety in general. Yet, the monoaminergic function across the brain was slightly modified, marked by a reduction of tissue levels of homovanillic acid in the orbito/prefrontal cortices (presumably a reduction of dopamine tone), associated with an increase in the electrical activity of ventral tegmental area dopaminergic neurons and dorsal raphe nucleus 5-HT neurons. The changes reported would correspond to lower responsiveness of 5-HT2CRs, perhaps those located in the cortex. Indeed, the pattern of effects in rats that we can evaluate after the administration of agonists including lorcaserin are different and sometimes opposite on the function of monoamines.

S60.2

Lorcaserin and other 5-HT2C agonism-based strategies: searching beyond the dopaminergic systems

Philippe De Deurwaerdère[1], Giuseppe Di Giovanni[2]
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Serotonin2C receptor (5-HT2CR) is an interesting pharmacological target in the treatment of numerous neuropsychiatric diseases including obesity, addiction, depression, or schizophrenia. The use of the agonist lorcaserin in the treatment of obesity validated the strategy but its withdrawal from the market for suspicion of cancer willingly addressed issues on the exact mechanisms triggered by these drugs in the central nervous system. The purpose of this talk is to present in-house data to consider multiple actions of 5-HT2CR agonists beyond mesolimbic dopaminergic neurons. While lorcaserin and other agonists inhibit the electrical activity of ventral tegmental area, but not substantia nigra dopaminergic neurons, the data become less clear when looking at the extracellular levels of dopamine (DA) in the nucleus accumbens, the striatum, or the prefrontal cortex. The ability of 5-HT2CRs to regulate the electrical activity of dopaminergic neurons is not the solely contribution in their ability to regulate central dopaminergic transmission. A widespread analysis of DA and metabolites tissue content in 29 rat brain areas revealed that the agonists WAY-1639099 and lorcaserin (0.3 or 3 mg/kg, i.p.) induced dose-dependent modifications of DA neurochemical parameters in a few and discrete brain regions. However, the correlations of DA tissue content and the index of turnover in saline-treated rats are reduced in 5-HT2CRs agonists-treated rats whereas the correlations on serotonergic and noradrenergic markers across the brain regions tended to be augmented. Beyond monoaminergic regulatory influences, 5-HT2CRs have been shown to control the electrophysiological response of the basal ganglia to cortical stimulations and more particularly the responses involving the subthalamic nucleus.

S60.3

5-HT2CR positive allosteric modulator CYD-1-79 as antiabsence epilepsy treatment

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Absence seizures (ASs) are the hallmark of childhood/juvenile absence epilepsy. Monotherapy with first-line anti-absence drugs only controls ASs in 70% of patients, indicating the need for novel therapeutic targets. Since lorcaserin, a serotonin 2C receptor (5-HT2CR) agonist known to be able to modulate ASs in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), has been withdrawn from the market because a high dose increases the risk of some cancers, we investigated the anti-epileptic effect of CYD-1-79, a positive 5-HT2CRs allosteric modulator. CYD-1-79 was administered on its own and co-administered with a low dose of lorcaserin (1 mg/kg), which was ineffective on its own. GAERS rats were implanted with fronto-parietal EEG electrodes under general anesthesia, and their ASs were later recorded under freely moving conditions before and after intraperitoneal administration of lorcaserin 1 mg/kg, CYD-1-79 0.3, 1, 3, 10 mg/kg and their combination CYD 3 mg/kg + lorcaserin 1 mg/kg. The CYD-1-79 dose-dependently suppressed ASs for one hour. CYD-1-79 co-administered with a low dose of lorcaserin does not have an additive effect on CYD-1-79 administration on its own.

In summary, our data confirm that 5-HT acting on 5-HT2CRs negatively controls the expression of experimental ASs, indicating that a 5-HT2CRs PAM might be a potential novel anti-absence treatment.

S61 "Sensorimotor Integration and Control at the Apic: Empirical and Modeling perspectives"

Chairs: Matteo Filippini, Ivilin Stoianov

S61.1
Decoding sensorimotor information from the posterior parietal cortex and neuroprosthetic applications

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Despite the well recognized role of the posterior parietal cortex (PPC) in processing sensory information to guide action, the differential encoding properties of this dynamic processing, as operated by different PPC brain areas, are scarcely known. Within the monkey's PPC, the superior parietal lobule hosts areas V6A, PEc, and PE included in the dorso-medial visual stream that is specialized in planning and guiding reaching movements. To investigate how the information is processed in these areas, we trained two macaque monkeys to perform a delayed reaching task towards 9 positions (distributed on 3 different depth and direction levels) in the 3D peripersonal space. The activity of single cells was recorded from V6A, PEc, PE and fed to convolutional neural networks that exploited the temporal structure of neuronal activation patterns to reconstruct the target positions reached by the monkey. We found that data from the most caudal V6A and PEc areas outperformed PE area in the spatial position recognition. In all areas, decoding accuracies started to increase at the time the target to reach was instructed to the monkey, and reached a plateau at movement onset. The results support a dynamic encoding of the different phases and properties of the reaching movement differentially distributed over a network of interconnected areas. This study may have implications in the perspective of novel neuroprosthetic devices based on the decoding of these rich signals for faithfully carrying out patient's intentions.

S61.2
Model-based Analysis of Sensorimotor Control in the PPC

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During goal-directed actions, the brain processes sensory and motor information to dexterously guide movements toward targets. The Posterior Parietal Cortex is known to integrate exteroceptive and proprioceptive signals and compute sensorimotor transformations to dynamically guide ongoing actions, but details of the underlying neural coding and computations in that structure are only partially known. For example, in reach-to-grasp actions, spatiotopic coding of environment and body is assumed to be necessary for interactions, but motor control operates in proprioceptive domains. We investigated this question with a novel model-based analysis of neural activity in the PPC during the planning and execution of sensorimotor tasks. The analysis is based on the Bayesian brain hypothesis, which views neural computations as aiming to deliver optimal behavior in an uncertain world through predictive coding and minimization of surprise. In this view, perception accumulates sensory evidence to improve its estimate of the latent states of the world, by generating exteroceptive sensory predictions and updating its estimates to reduce prediction errors. In turn, motor control further minimizes exteroceptive surprise by computing muscle commands that minimize proprioceptive prediction errors. This view is embraced in several theories of perception and action, including Predictive Coding and Active Inference, and makes alternative predictions about the type of information content and processing in the brain. We discuss how the neural signal from the PPC can be better interpreted in light of these computational theories and how this approach could be applied to improve neuroprosthetic devices and intelligent human-aiding agents.

S61.3
Deep active inference for predictive sensorimotor control

Pablo Lanillos[1]

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Perception and action are intimately related. Contemporary sensorimotor control models, such as active inference, suggest that the action system drives the body to a state that minimizes sensory surprise with the predicted or desired state. A strong forecast of such models is that

involuntary actions would arise to reduce the prediction error, especially in conflicting situations. Here I describe a novel computational model based on deep active inference, which deals with high-dimensional sensory inputs (Pixel-AIF), that permits validating these sensorimotor effects on virtual reality agents and robots, and compare behavioral predictions with results observed in humans. To illustrate the power of our method, I first describe how the model can replicate the rubber-hand illusion perceptual drift dynamics (proprioceptive and visual). Second, I show how, both humans and artificial agents, exert involuntary movements to reduce body prediction errors. According to the model, humans may adapt their bodies to match the expected location according to other (visual) sensory input. Furthermore, I discuss the scalability of the method to model, within a computational level, large-scale body perception and action.

S61.4

Implicit and latent motor learning in the oculomotor system and its perceptual consequences

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Saccadic eye movements are often imprecise and result in an error between expected and actual retinal target location after the saccade. Such a mismatch between predicted and actual sensory consequence of an eye movement can be induced in the laboratory by an intra-saccadic shift of the saccade target either in or against saccade direction that typically goes unnoticed due to saccadic suppression. Repeated experience of the resulting error leads to changes in saccade amplitude, to reduce the error, and concomitant changes in apparent visual location. We investigated the relationship between these two plastic processes in a series of experiments. Following a recent paradigm of inhibition of saccadic adaptation, our participants inhibited the adjustment of saccade amplitude to the post-saccadic error and nevertheless perceived a visual probe presented near the saccade target to be shifted in direction of the target error. The location percept of the target itself also shifted and diverged from the executed saccade. Our findings indicate a trans-saccadic association between pre- and post-saccadic visual target positions that is learned independently from saccade amplitude changes. This associative learning may be important for maintaining our sense of spatial stability of the visual world across saccades.

S61.5

Rhythmic attentional processes and functional hierarchy of vigilance and attention in the prefrontal cortex

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Attention corresponds to the cognitive process whereby important sensory information is selected for enhanced processing, while irrelevant information, away from the attentional locus, is suppressed. The prefrontal cortex plays a central role in the control of attention. In my presentation, I will apply machine learning methods to monkey prefrontal cortical activity to track the spatial locus of attention in real time and I will provide evidence for rhythmic spatial attention exploration by this prefrontal attentional spotlight in the alpha (7-12Hz) frequency range, impacting both sensory encoding and behavioral reports. While these oscillations are task-independent, I will describe how their spatial unfoldment flexibly adjusts to the ongoing behavioral demands, organizing alternations of exploration and exploitation epochs. I will then use dimensionality reduction methods to further our understanding of prefrontal mixed-selectivity. I will first show that prefrontal attentional coding coexists with other time-varying task-related information such as task expectancy and motor preparation. I will then discuss how dynamic within trial prefrontal attentional coding also coexists with slower fluctuations in neuronal processes, both at the scale of a few second and at the scale of several minutes. I will show that behavior is best accounted for by a precise understanding of the contribution of each of these prefrontal information. I will conclude by proposing a hierarchical model of vigilance to attention states in the prefrontal cortex, that controls sensory processing in downstream areas and overt behavioral performance.

S62 "Protein aggregation spreading and functional alterations in neurodegeneration"

Chairs: Fran Borovečki, Tiago Outerio

S62.1

Mechanisms and functional consequences of the spread of tauopathy

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Pathology composed of abnormal tau protein is a com-

mon feature of neurodegenerative diseases. Tau pathology (tauopathy) is one of the two hallmark pathologies in Alzheimer's disease and it is the main pathology in frontotemporal lobe dementia linked to chromosome 17 (FTD-tau). The distribution of pathological tau in the brain of patients with AD is highly predictable, and as disease worsens, it spreads transynaptically from initial regions of vulnerability. Mechanisms by which abnormal tau accumulates within neurons, how tau transfers between cells and the consequences of pathology development will be discussed.

S62.2

Genomic mechanisms regulating protein clearance in neurodegenerative diseases

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Accumulation of misfolded proteins in the brain represents a pathological hallmark of neurodegenerative diseases, suggesting that inadequate clearance of aggregation-prone proteins plays an important role in the disease pathogenesis. The synucleinopathies, including Parkinson's disease (PD) and dementia with Lewy bodies (LBD), are a group of neurodegenerative disorders characterized by the accumulation and aggregation of a-synuclein (aSyn). Studies on the rare inherited forms of PD caused by mutations in the aSyn gene have highlighted disturbed aSyn clearance through the autophagy-lysosomal pathway (ALP) as a key mechanism leading to PD/LBD. Furthermore, several rare inherited disorders caused by mutations in the lysosomal genes show parkinsonian-like phenotype and accumulation of aSyn, providing additional evidence for the role of lysosomal dysfunction in the pathogenesis of synucleinopathies. Genomic variants in the genes regulating ALP have been implicated in the development of PD, suggesting a potential role for transcriptional and post-transcriptional mechanisms in promoting neurodegeneration. Additionally, genetic variants in 3' UTR which can affect miRNA activity and consequently change the translation process, have also been implicated in promoting PD pathology. In our previous studies we have utilized the next generation sequencing approach from whole blood samples to identify genetic variants in exonic, intronic and 3' UTR region of ALP genes in patients with PD. The results of our studies showed increased occurrence of specific variants in the PD population. These findings indicate possible role of 3' UTR variants in genes related to the ALS, leading to increased risk of PD. Further studies will be needed to gain a more profound insight regarding their role in PD development, which will help to assess the role and impact of post-transcriptional regulation on disease pathology.

S62.3

Role of Tunelling Nanotubes in the spreading of neurodegenerative diseases, and more

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Tunneling nanotubes (TNTs) are actin-based cellular connections that allow the transport of different cellular components between cells. They were described for the first time in a cell line in culture 15 years ago, and now they are recognized as an important mechanism of cell-to-cell communication. Since their discovery, the structure and function of TNTs have been characterized in several cell types, including neurons and astrocytes. Under homeostatic conditions, TNTs transport different vesicular cargoes and entire organelles like mitochondria and lysosomes. However, they can be hijacked by different pathogens and amyloid proteins involved in neurodegenerative diseases, such as Parkinson´s (PD) Alzheimer's (AD). We have previously demonstrated that both alpha-synuclein and Tau aggregates, respectively the hallmark of PD and AD, can be spread from one cell to another via TNTs. We have proposed that this is a key mechanism for the progression of the disease and for the spreading of the pathology to the whole brain. In my talk I will address the similarities and differences between TNT-mediated diffusion of these two types of aggregates, in order to identify common pathways leading to neurodegeneration, and assess the likelihood of TNT in vivo.

S62.4

Release and uptake of proteins associated with neurodegenerative diseases: similarities and differences

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The misfolding and aggregation of disease-related proteins is a common hallmark among several neurodegenerative diseases. This includes alpha-synuclein (aSyn) in synucleinopathies, tau in tauopathies, and huntingtin (Htt) in Huntington's disease. Recent studies demonstrated that these proteins can be transferred from cell-to-cell and seed pathology throughout the brain, contributing for

disease progression and neurodegeneration.

Several mechanisms have been proposed for the spreading of aSyn, tau and Htt. However, it is not clear what is the relative contribution of each of the possible mechanisms for the spreading of the different proteins. To address this, we are performing a systematic assessment of the release of aSyn, Htt and tau (i) in free form, (ii) via the misfolding-associated protein secretion (MAPS) pathway, that uses USP19 to export aberrant cytosolic proteins, (iii) in extracellular vesicles (EVs), as ectosomes and exosomes, and (iv) and via tunneling nanotubes (TNTs).

Our results show that aSyn, tau and Htt are secreted to the cell media at different levels. Furthermore, co-expression with USP19 slightly increases their secretion to the cell media. Interestingly, aSyn and tau are present in higher levels in ectosomes than in exosomes, while 25QHtt and 103QHtt are present in identical levels. The EVs can be further internalized in primary neuronal cultures. Finally, CAD cells transfer different proteins to neighbouring cells via TNTs.

Our findings suggest that care must be taken when considering the targeting of spreading of pathology in different neurodegenerative diseases.

ORAL PRESENTATIONS

O1

Positron emission tomography neuroimaging of glucose metabolism in the rodent *Pink1-/-* Parkinson Disease model

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To better understand the neurobiology of communication deficits in Parkinson Disease (PD), we imaged an index of cerebral glucose metabolism in the Pink1-/- rat model*. Adult wild type (n=7) and *Pink1-/-* (n=12) Long Evans rats were imaged with high resolution positron emission tomography (PET) and the glucose analog [^{18}F]fluorodeoxyglucose (FDG). Three parameters of ultrasonic vocalization (USV), length, power, and peak frequency, were measured within a week prior to PET scanning. Preliminary analysis of these data yielded a number of interesting findings. First, FDG uptake was examined in three regions chosen a *priori* for their relevance to the noradrenergic system: brainstem, thalamus, and medial prefrontal cortex (mPFC). *Pink1-/-* rats exhibited lower FDG uptake in thalamus, and across all rats, thalamus FDG correlated positively with brainstem FDG. Additionally, mPFC FDG correlated positively with USV call length. Subsequently, whole brain exploratory analysis revealed several regions with group differences in FDG uptake and others where FDG correlated with behavior. Two regions exhibited both reduced FDG in *Pink1-/-* and correlations with behavior. Namely, stria terminalis FDG correlated positively with USV power and FDG in brachium of the superior colliculus correlated positively with USV peak frequency. Further analysis and interpretation of these findings is in progress. Future longitudinal studies will examine the effects of behavioral and pharmacologic treatments relevant to PD on PET and behavioral measures in this rat model.

O2

Diurnal and nocturnal locomotor patterns during recovery may predict the development of motor impairment in the 6-hydroxydopamine-induced rat model of Parkinson's disease

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The Parkinson's disease rat model produced by intrastriatal injection of low doses of 6-hydroxydopamine (6-OHDA) is an indispensable tool for studying the preclinical stages of the disease, but eventual development of the characteristic phenotype is highly unpredictable. We aimed to examine whether early changes in spontaneous home cage motor activity can be used to predict eventual development of motor dysfunction on the standard rotarod performance test. Adult male Wistar rats had 6-OHDA (8 µg) or vehicle (CTR) applied into striata bilaterally ($n_{6\text{-OHDA}}$=20, n_{CTR}=10) and were subjected to the rotarod test at 14, 28, 35 and 60 days after treatment. Baseline spontaneous motor activity was recorded for 4 days preceding the treatment, and for the following 7 days using MIROSLAV (Multicage InfraRed Open-Source Locomotor Activity eValuator), a novel home cage-mounted system based on passive infrared sensors. Data analysis was performed in R. Compared to their baseline activity levels, animals that developed a motor deficit at the 60 day rotarod test showed markedly reduced activity during both diurnal and nocturnal phases of the first 3 days, as opposed to the unsuccessful models, which demonstrated an increase in both diurnal and nocturnal activity. These effects largely dissipated at 7 days post-op. The vehicle-treated animals demonstrated increased diurnal, and decreased nocturnal activity. Preliminary MIROSLAV data indicates that 6-hydroxydopamine could have distinct effects on the animals' motor patterns during recovery, with opposing effects that seem to predict subsequent development of motor dysfunction.

O3

Early-Stage Parkinson Disease: dysphagia, gastrointestinal dysfunction, and pathology in the *Pink1-/-* rat model

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Parkinson disease (PD) is a whole-body neurodegenerative disorder. Early motor and non-motor signs like dys-

phagia and constipation may serve as potential markers; however, because they are non-specific and age-related, they often go unreported. As such, how dysphagia and gastrointestinal dysfunction manifest in early-stage PD is not well understood. Furthermore, the transcription levels of mRNA of pathologic markers, including levels of α-synuclein and proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6), are not well defined in early PD. We used a well-established early-onset genetic *Pink1-/-* rat model to study swallow and gastrointestinal dysfunction. Fifteen *Pink1-/-* and 15 wildtype (WT) controls were tested at 4 and 6 months of age, representing early-stage PD. Videofluoroscopic swallow and gastrointestinal studies were completed—mastication rate (cycles/sec), bolus speed (mm/sec), GI motility, and fecal number and weight (g) were analyzed. Two- and three-way mixed model ANOVAs showed that, compared to WT controls, *Pink1-/-* rats have slower mastication rate ($p < 0.001$), slower bolus speed ($p < 0.001$), fewer contents within the colon ($p < 0.01$), a lower fecal pellet count, and higher fecal pellet weight ($p < 0.01$). Results demonstrate that oropharyngeal swallowing and GI dysfunction occur in *Pink1-/-* rats at an age analogous to early-stage PD. PCR comparing transcription levels of mRNA for α-synuclein, TNF-α, IL-1β, and IL-6 in the colon, and immunofluorescence for localization to the enteric nervous system among rat groups is ongoing and preliminary results will be presented. This work is foundational for the advancement of identification and treatment of PD.

O4

Can fecal properties warn us about developing Parkinson's disease? Preliminary results from the nested case-control study in the 6-hydroxydopamine-induced rat model of Parkinson's disease

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Gastrointestinal dyshomeostasis precedes the development of motor symptoms of Parkinson's disease (PD) suggesting that the gastrointestinal system may be i) involved in the etiopathogenesis; ii) an invaluable source of (non-invasive) biomarkers of PD in the early (reversible) phase. The aim was to explore whether morphometric, metabolic, and redox fecal features can be used to predict the development of motor symptoms in the rat model of PD. 3-month-old male Wistar rats received bilateral intrastriatal 6-hydroxydopamine (2µl; 8µg in 0.02% ascorbic acid; N=20), while the rest received vehicle (CTR;N=10). Motor performance assessment (rotarod test) and 24-hour fecal pellet collection were repeated 3x during the 9-week-follow-up. Based on final time-point motor performance 6-hydroxydopamine-treated animals were defined as either cases (i.e. successful PD model;O+) or the controls (O-). 24-hour fecal pellets were dried, scanned, weighed, and ground. Fecal lipids were analyzed by chloroform-methanol extraction followed by Sudan black lipid blotting (SBLB). Total antioxidant capacity was analyzed by nitrocellulose redox permanganometry (NRP) and the reduction of the 2,2'-Azinobis(3-Ethylbenzthiazoline-6-Sulfonate) cation radical (ABTS), H_2O_2 dissociation potential, and the effect of the fecal extract on catalase activity was assessed using Hadwan's assay. O+ had lower fecal reductive capacity (NRP, ABTS) and mucins, and greater lipid content in comparison with O- already after 2 weeks. Fecal H_2O_2 dissociation potential was lower in O+ and the same effect was replicated by incubation of samples with exogenous catalase. O+ produced fewer fecal pellets with lower water content. Fecal pellets may be a valuable predictor of gastrointestinal redox, metabolic, and motor dyshomeostasis present already in the very early post-induction period in the rat model of PD.

O6

Effect of lipid nature on microglial reactivity, neuroinflammation and cognitive disorders associated with obesity

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Obesity is a serious public health problem. It is associated with "low-grade" systemic inflammation and many studies are devoted to understand the mechanisms causing obesity. Some of them showed that deregulation in the brain could be responsible for this syndrome. In addition to the peripheral inflammation, a local hypothalamic inflammation was found in obese animals fed a high fat diet (HFD), leading to eating disorders and sometimes cognitive disorders as anxiety. Indeed, certain lipids are responsible for this inflammation in a dependent manner of the quality of their fatty acids. Polyunsaturated fatty

acid (PUFA) can be Omega 6 (ω6) or Omega 3 (ω3) and the balance between them is really essential for the organism functioning. At the cellular level, an excess of nutrients leads to activation of astrocytes and microglia which have a preventive role at first but can become harmful in the long term. The purpose of this study was to characterize the impact of a HFD enriched in PUFA in the obesity development, the neuroinflammation associated and the possible cognitive disorders. To do this, we designed many HFD enriched in vegetal oil (Rapeseed, Soybean/Corn and Sunflower diets) with different ω6/ω3 ratios. We fed mice over 20 weeks with these HFD and we characterized obesity development, neuroinflammation and behavior of mice. We showed that all HFD induce a strong weight gain associated with hyperleptinemia, hyperglycemia and deregulated glucose homeostasis. However, only the Sunflower diet induces neuroinflammation in hypothalamus associated with microglial reactivity and in hippocampus associated with anxiety-like behavior.

O7

Nanoscale molecular organization in dendritic spines regulates calcium storage and depletion

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Nanoscale molecular organization describes the specific location of key molecular players necessary to perform a subcellular function, such as fast trafficking, local ATP production by endoplasmic reticulum-mitochondria complex (ER-mitochondria complex), or spontaneous activity in neurons or astrocytes. We will present here the molecular organization required for slow and fast calcium transients ($<$10 ms) in dendritic spines, that are critical components of neuronal synapses. The presence of a spine apparatus (SA), which is an extension of the smooth ER, a calcium-induced calcium release (CICR) is triggered at the base of the spine by the fastest calcium ions arriving at a Ryanodyne receptor (RyR). The mechanism relies on the asymmetric distributions of RyRs and sarco/ER calcium-ATPase (SERCA) pumps that we predict using a computational model and further confirm in culture and slice hippocampal neurons. The spine apparatus (SA) can also regulate the slow calcium dynamics when calcium release events are depleting the SA reservoir rapidly, yet the next cycle of signaling requires its replenishment. How spines achieve this replenishment without triggering calcium involves the store-operated calcium entry pathway during spontaneous calcium transients. To conclude, we identified two main conditions for SA replenishment without depletion: a small amplitude and a slow timescale for calcium influx, and a close proximity between SA and plasma membranes. Thereby, spine nanoscale organization separates SA replenishment from depletion.

O8

Effects of IGF1 on excitability of sensory nociceptive dorsal root ganglia neurons

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Sensory dorsal root ganglia (DRG) nociceptive neurons convey pain signals from the peripheral to the central DRG terminals and project to the CNS. They express various receptors and ion channels, essential players of neuronal excitability. Nociceptive DRGs express TRPV1, a ligand-gated nonselective cation channel, which triggers painful stimuli. Insulin-like growth factor-1 (IGF-1) is a peptide widely distributed in tissues, including nociceptive DRG, that plays a crucial role in growth and have neuroprotective effects mediated by its receptor IGF-1R. Little is known about the role of IGF1 on DRG excitability. Our aim is to examine the role of IGF-1 on DRG excitability and its possible interactions with TRPV1 channels. Using whole-cell patch-clamp recordings, we showed that acute application of IGF-1 on DRG neurons triggers hyper-excitability by inducing spontaneous firing and depolarization of the membrane. Surprisingly, acute exposure to IGF-1 produced a biphasic effect on spikes evoked by capsaicin-induced TRPV1 activation. Upon co-application of IGF-1 and capsaicin, an increase in firing was observed, followed by a profound inhibition of the spikes, compared to the firing evoked by capsaicin alone. Voltage-clamp recordings of DRG showed that the inward current evoked by capsaicin alone was transiently increased by co-application of IGF-1 and capsaicin and was then potently decreased. Upon chronic exposure of DRG with IGF-1, we observed a sensitization of TRV1 by capsaicin resulting in an increased firing. Our ongoing work attempts to decipher the complex mechanisms involved in IGF-1 in DRG excitability.

O9

Curious case of impaired glymphatic pathways in a gyrencephalic brain

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In the brain, perivascular spaces in the brain are key channels surrounding the arteries and veins and contain cerebrospinal fluid (CSF). The CSF flow in these spaces contributes to the clearance of solutes and constitutes a key part of the brain's solute clearance system called the glymphatic system (GS). However, the foundational science of the GS is based on rodent studies. CSF penetration into the brain via perivascular pathways, a hallmark of glymphatic function, was seen throughout the gyrencephalic brain, validating the conservation of the GS in a large mammal. Accidentally, during our novel glymphatic investigations, we encountered an idiopathic subdural hematoma (SDH) altering the glymphatic pathways globally. Upon undergoing intracisternal infusion of a fluorescent tracer under general anesthesia to delineate CSF pathways, the pig was euthanized at the end of 3h of tracer circulation. During brain isolation, a hematoma beneath the dura was evident overlying fronto-parietal brain surface. Interestingly, CSF tracer distribution was markedly reduced on dorsal, lateral and ventral surfaces of the brain when compared with a control pig that was infused with the same tracer. Furthermore, regional distribution of tracer along the interhemispheric fissure, lateral fissure and hippocampus was 4-5-fold reduced in comparison with the control pig. We report the first case of impaired glymphatic pathway due to an idiopathic SDH in a pig. This accidental finding of globally impaired glymphatic function sheds light on a novel consequence of SDH, which may play a role in the enhanced cognitive decline seen in elderly presenting with chronic SDH.

O10

The role of the claustrum in opiate versus psychostimulant preference – the differences do matter!

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The claustrum is a small nucleus exhibiting vast reciprocal connectivity with cortical, subcortical and midbrain regions. The claustrum has been recognized as a major hub of neuromodulatory action in the brain, uniquely enriched in expression of receptors for many classes of neuromodulators, and receiving inputs from multiple neuromodulatory structures. In a recent study (Terem et al., 2020) we identified a role for a dopamine-receptor expressing population of frontal-projecting claustral neurons in the attribution of incentive salience, allocating contextual attention to reward-related cues. Motivated by our observations regarding the role of claustral projection neurons in cocaine preference, we were intrigued to address their role in response to other drugs of abuse, primarily the highly addictive opiate, fentanyl. We found recruitment of claustral neurons projecting to frontal cortex after exposure fentanyl, as assayed by c-fos induction. We established an oral fentanyl self-administration setup, where mice were allowed to self-administer fentanyl while group-housed in their home-cages. In this setup we found that constitutive inhibition of frontal-projecting claustral neurons led mice to consume more fentanyl and exhibit prolonged bouts of fentanyl consumption. In order understand the roles of frontal-projecting claustral neurons (i.e. AAC/OFC), we recorded Ca^{+2} signals from these specific populations while mice had the opportunity to consume fentanyl. Our photometry recordings revealed a unique signature of activity in both population of claustral neurons while mice received reward. These experiments provide the first implication of the claustro-frontal circuit in regulating fentanyl consumption, supporting novel approaches to limit the development of opiate addiction.

O11

Fructose Removal from the Diet Reverses Inflammation, Mitochondrial Dysfunction, and oxidative Stress in Hippocampus

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Young age is often characterized by high consumption of processed foods and fruit juices rich in fructose, which, besides inducing a tendency to become overweight, can promote alterations in brain function. The aim of this study was therefore to (a) clarify brain effects resulting from fructose consumption in juvenile age, a critical phase for brain development, and (b) verify whether these alterations can be rescued after removing fructose from the diet. Young rats were fed a fructose-rich or control diet for 3 weeks. Fructose-fed rats were then fed a control diet for a further 3 weeks. We evaluated mitochondrial bioenergetics by high-resolution respirometry in the hippocampus, a brain area that is critically involved in learning and memory. Glucose transporter-5, fructose and uric acid levels, oxidative status, and inflammatory and syn-

aptic markers were investigated by Western blotting and spectrophotometric or enzyme-linked immunosorbent assays. A short-term fructose-rich diet induced mitochondrial dysfunction and oxidative stress, associated with an increased concentration of inflammatory markers and decreased Neurofilament-M and post- synaptic density protein 95. These alterations, except for increases in haptoglobin and nitrotyrosine, were recovered by returning to a control diet. Overall, our results point to the dangerous effects of excessive consumption of fructose in young age but also highlight the effect of partial recovery by switching back to a control diet.

O12

In vivo selection, NGS and bioinformatics of phage displayed peptide repertoires to define experimentally functional protein domains in inflammatory neurodegeneration

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In previous works we have characterized inflammatory brain lesions affecting the neurovascular unit in both human Multiple sclerosis (MS) and its experimental autoimmune encephalomyelitis (EAE) model by *in vivo* MR bioimaging developments (1,2). In more recent *in vivo* phage display selections in EAE, we identified peptide ligands to pathological neuroinflammation lesions entangled by non-affected CNS tissue (3,4). By molecular and structural proteomics, we characterized some of the molecular targets of these peptides at the inflammatory blood brain barrier (5). Then to identify, within massive NGS targeting peptide repertoires, the potentially mimicked interactive proteins, we developed new bioinformatics (6). I will present the application of the various generated modules in a strategy to define functional protein domains in neuroinflammation. By aligning the selected 270,612 EAE specific phage-peptides (derived from 3) to the human proteome, massive peptide clusters were mapping with proteins. Being mimicked by peptides, the domains of these proteins are potential interactive binding candidates in neuroinflammation. Quantitative and functional interactive ranking of all the mimicked proteins and domains allowed focusing on candidates of interest. Among the most relevant proteins, one presented several domains being internal repeats. In addition, the same protein presented an unique single mimicked peptide sequence. BLAST analysis revealed that this single protein sequence is conserved among vertebrates including fish, and to a minor degree in arthropods and in some bacteria. Histochemical binding studies using the synthetized mimicked protein domain revealed labeling of the vasculature in brain tissue of MS and Alzheimer patients and their experimental models. In the Zebra fish model, vasculature labeling was observed during early development. In adult Zebra fish the caudal fin regeneration is blocked by administration of the synthetized protein domain indicating its antagonistic effect in angiogenesis. Studies with human U87 cancer cells in mouse brain tumor and *in vitro* angiogenesis models confirmed binding specificity to angiogenic vasculature. Altogether these data indicate that our bioinformatics of massive peptide selections allows defining new functional protein domains. In the present example the identified protein domain plays a role in injured adult CNS vasculature and tissue repair, which hence is the main failure in neurodegenerative diseases such as MS.

O13

From determining brain insulin resistance in a sporadic Alzheimer's disease model to exploring the region-dependent effect of intranasal insulin

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Impaired response to insulin has been linked to many neurodegenerative disorders like Alzheimer's disease (AD). In line with this finding, an animal model of sporadic AD has been developed by intracerebroventricular (icv) administration of streptozotocin (STZ), which given peripherally causes insulin resistance. Brain insulin resistance is defined in literature as poor signaling of insulin receptors, reduced insulin levels in the brain and/or reduced trafficking of insulin into the brain and other, so far unknown processes. Can we really consider the level of insulin in the brain as an indicator of insulin resistance and can we acknowledge insulin resistance based solely on changed protein levels and activity of the insulin receptor signaling cascade? To explore the possible presence of brain insulin resistance in the STZ-icv model, we measured neuronal activity (c-fos levels) after intranasal insulin administration that enables the delivery of insulin to the brain with the relative absence of systemic uptake and related peripheral side effects. On account of the unexplored diverse insulin role in the brain and mechanism of its beneficial

effect on cognition, we wanted to explore the effect of acute IN insulin administration on peripheral metabolic and central glutamatergic and metabolic parameters in cognitively normal rats in comparison to rats with cognitive deficit (STZ-icv rat model of sAD). STZ and insulin brain region-specifically altered the levels and activity of proteins involved in cell metabolism and glutamate signaling. Insulin did not produce a systemic response, while central changes found after IN insulin in STZ-icv rats suggest insulin sensitivity of hippocampal and cortical regions (temporal). Altered metabolic parameters in hypothalamus of STZ-icv rats were not normalized by IN insulin, indicating possible insulin insensitivity. Brain insulin sensitivity depends on the affected brain region and presence of metabolic dysfunction.

O14

Concept pre-activation improves visual word processing in spoken and literary Arabic: A behavioral and event-related potential study using a picture-word matching task

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Diglossia in the Arabic language refers to the use of two varieties of the same language: Literary Arabic (LA) and Spoken Arabic (SA). Behavioral studies on Arabic using auditorily presented words have shown that SA words were processed faster than LA ones. In contrast, when presented visually, LA words were shown to be processed faster than SA ones. Semantic priming studies have shown that words are processed faster when preceded by a semantically related (SR) prime than by an unrelated (SU) one. Event-related potential (ERP) analyses have shown that SU relative to SR words enhances the N400 component. This study examined whether the activation of a concept by an image followed immediately either by printed SA and LA words will facilitate the processing of SA words. The N400 component elicited by LA and SA words was analyzed during a picture-word matching task. Behaviorally, independent of language variety, SR words ($M = 702$ ms) were processed faster than SU words ($M = 756$ ms). No difference was found between LA-SR and SA-SR words, but LA-SU words were processed faster than SA-SU ones. Analysis of the N400 amplitude showed larger N400 for SU words than for SR words, but with no effect of language variety. However, analysis of the N400 latency based on difference waves showed an earlier peak for LA than for SA. These results indicate that priming by the image have improved the visual recognition of LA-SR and SA-SR words to the extent that difference between the two varieties disappeared for the image-related words.

O15

Fluid functional hierarchies for multisensory integration in a large-scale computational model of the mouse brain

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The efficient integration of information from different sensory modalities, or multisensory integration (MSI), is one of the most salient features of perception. It is not yet clear which brain areas contribute most prominently to MSI, as limitations in electrophysiological recordings restrict the conclusions to simultaneous recordings of a few areas at most, and the variability across different sensory modalities is context-dependent and hard to quantify. Our study presents a detailed computational model, constrained by advanced anatomical connectivity data, to identify relevant MSI areas in the mouse brain. Our simulations of this large-scale brain network revealed the existence of a novel functional hierarchy for crossmodal integration, with brain areas at the top of the hierarchy integrating multisensory signals most efficiently. Our model also predicted that the position of a given area in such a hierarchy is highly fluid and depends several factors, including stimulus strength, environmental conditions, and current brain state. For example, we observe that the set of areas integrating visuotactile stimuli changes depending on the level of background visual input—therefore experiments with different light conditions will deliver different results on which areas perform MSI. We determined that the origin of such hierarchical dynamics is the structural heterogeneity of the network, and extended our results to macaque cortical networks. Our work provides a compelling explanation as of why it is not possible to identify unique MSI areas even for a well-defined multisensory task, and proposes that MSI circuits are highly context-dependent.

O16
Improving biomedical research by automated behavior monitoring in the animal home-cage—COST Action TEATIME CA20135

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COST Actions promote interdisciplinary networking and cooperation among researchers and innovators across Europe on a specific topic (www.cost.eu). The Action TEATIME aims to develop and use automated home-cage monitoring technologies, combining experts in mouse behavior, laboratory animal science and data science, to critically and transparently assess the potential of these technologies, to develop user guidelines and standard operating procedures and to identify needs for further technological development, including analysis of big data. The Action will also contribute to building capacities for adoption of these technologies by holding workshops, laboratory rotations and disseminating knowledge.

Developing refined experimental conditions can substantially improve lab animal welfare and importantly, enhance the translational value and data reproducibility. Novel and emerging technologies allow 24/7 collection of behavioral data in undisturbed mice, minimizing the impact of stressors, such as human interaction and testing in novel arenas, which are known to influence data collection and animal welfare. In addition to promoting welfare, home-cage monitoring can improve preclinical bio-medical research, advance higher success rates of translation, and may further provide valuable insights into other types of pathologies and genetic alterations. In this presentation, examples will be given on the use of home-cage monitoring systems to screen for phenotypes of neurodegenerative disease mouse models.

O17
Disruption of brain sterol biosynthesis by commonly used prescription medications

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Cholesterol is an essential precursor for various biologically important molecules. It also plays an integral role in maintaining cell membrane structure and function. ~25% of the body's total cholesterol resides in the brain. The brain fully relies on de novo sterol synthesis as the blood-brain barrier prevents the uptake of cholesterol from the circulation. Importantly, our studies show that neurons express all the genes encoding cholesterol biosynthesis enzymes, and during development neuronal cholesterol biosynthesis is indispensable. Mutations in sterol enzymes lead to several neurodevelopmental disorders. Smith-Lemli-Opitz Syndrome (SLOS) is an autosomal recessive disorder caused by mutations in DHCR7 (the last enzyme in the cholesterol biosynthesis pathway), and SLOS transgenic mouse models recapitulate molecular and biochemical changes seen in SLOS patients. SLOS is characterized by markedly decreased cholesterol and desmosterol levels in the brain, and highly elevated 7-DHC levels. 7-DHC, the immediate precursor of cholesterol, is the most oxidizable lipid molecule known to date leading to over a dozen oxidation products. Buildup of 7-DHC-derived oxysterols results in gene expression changes, affects neuronal signaling and leads to morphological alterations. Human population studies suggest that first-trimester exposure to DHCR7 inhibitors result in outcomes like those of known teratogens. Notably, many currently used, commonly prescribed medications are DHCR7 inhibitors, including both psychotropic medications and beta-blockers. Based on our findings we recommend that medications that increase 7-DHC levels should not be prescribed during pregnancy, as they might interfere with the intrauterine brain development of the child.

O18
Interaction of genetics, pregnancy, and medications on the developing brain

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Cholesterol is essential for life. Dysfunction of the cholesterol biosynthesis leads or contributes to a number of neurodevelopmental and neurodegenerative disorders. The last step in the cholesterol biosynthesis pathway is conversion of 7-dehydrocholesterol (7-DHC) to cholesterol by the 7-dehyrocholesterol reductase (DHCR7) enzyme. DHCR7 inhibition leads to reduced levels of cholesterol and desmosterol (DES) and accumulation of their immediate precursors, 7-DHC and 7-dehyrodesmosterol (7-DHD). 7-DHC and 7-DHD are the most reactive lipids known to date. 7-DHC is toxic during embryonic development, and DHCR7 inhibitors during pregnancy are considered teratogens. As the blood-brain barrier (BBB) prevents passage of cholesterol from the rest of body to the central nervous system, the brain fully relies on its own cholesterol biosynthesis. However, a signific-

ant number of medications with sterol biosynthesis inhibiting side effects cross BBB – including haloperidol, aripiprazole, cariprazine, fluoxetine, trazodone and amiodarone, and others. This is particularly pronounced when both the mother and the offspring carry the Dhcr7$^{+/-}$ genotype. Studies of human dermal fibroblasts from individuals who carry DCHR7$^{+/-}$ single allele mutations suggest that the same *gene*medication* interaction also occurs in humans. This suggests that the 1-3% of individuals with the DHCR7$^{+/-}$ genotype might be at increased risk of adverse outcomes when taking medications with sterol-inhibiting side effects. Understanding the interaction between *maternal genotype*fetal genotype*developmental stage*medication* interaction is essential. We recommend that medications that increase 7-DHC levels should not be prescribed during pregnancy before assessment of DHCR7 genotype of the parents—and perhaps not prescribed at all to individuals who are DCHR7$^{+/-}$ carriers.

O19

Neutral sphingomyelinase determines the comorbidity trias of alcohol abuse, major depression and bone defects

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Mental disorders, such as depression and alcohol abuse, possess high comorbidity with peripheral diseases. Shared pathogenic pathways might determine these comorbidities. The major components of membranes, ceramides, control the comorbidity between alcohol abuse and depression. We observed that neutral sphingomyelinase (NSM) determining ceramide synthesis contributes to the comorbidity trias of alcohol abuse, depression and bone defects. A genetic association analysis in 456,693 volunteers found associations of SMPD3 haplotypes coding for NSM with alcohol consumption, anxiety and depressive symptoms, and bone mineralisation. Functional analysis in female heterozygous NSM knockout mice (fro) confirmed these findings. Fro mice possessed reduced alcohol consumption and depression/anxiety-like behaviour compared to wild type controls. Voluntary alcohol drinking reversed the low-depression phenotype in fro mice, probably by affecting monoaminergic system functioning. Alcohol altered the extracellular levels of dopamine and serotonin, expression of their receptors and transporters, and affected serotonin uptake in synaptosomes in a genotype-specific manner. NSM also controlled bone–brain communication by enhancing signalling of osteocalcin, an inductor of bone mineralisation, in fro mice. Osteocalcin administration independently supressed alcohol consumption and reduced depressive behaviour in a way similar to NSM effects. Altogether, we identified a single gene source, which interlink disorders of a mental–physical comorbidity trias of alcohol abuse—depression/anxiety—bone disorder. Targeting NSM and osteocalcin signalling may, thus, provide a new systems approach in the treatment of a mental–physical co-morbidity trias.

O20

What doesn't kill you makes you stronger: increased memory function in maternally separated rats without effects of environmental enrichment

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Maternal separation is a detrimental postnatal influence, whereas environmental enrichment is a therapeutic and protective agent. It is unclear if long-term environmental enrichment can compensate for the effects of maternal separation stress. We examined how environmental enrichment affects memory functions, and related gene expressions (Grin2a, Grin2b, BDNF, and cFos) in the hippocampus in maternally separated rats. There are six groups in this study: control (C), maternal separation+standard cage (MS), maternal separation+enriched environment (MSE), and enriched environment (E), maternal separation that decapitated at postnatal 21 (MS21) and standard cage that decapitated at postnatal21 (STD21). The maternal separation applied for 21 days (between 09:00 am 12:00 am). Enriched (E,MSE) or standard cage environment rats (MS,C) spent PN (22-55) days in either enriched or standard cages. Learning and memory performance were determined with the Morris test. The expression levels of genes were measured by the RT-PCR method. Results showed that MS increased memory performance ($p < 0.05$), but it did not change gene expression levels. Enrichment did not change the memory performance and related gene expression levels. MSE group increased their memory performance ($p < 0.05$) and gene expression level did not change. Grin2a, Grin2b, and BDNF gene expression level increased in the MS21 group ($p < 0.05$). Maternal separation increased memory performance. Increased gene expression levels in 21 days maternal separated group became disappeared in the MS group. Our results also suggest that

any gene expression changes are short-lived. Future studies should use decapitation groups at PN21 for all manipulations to examine gene expression.

O21

Environmental enrichment as a strategy to encounter social isolation stress: attenuates memory impairment in stressed male rats

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Early social isolation (SI) produces behavioral and cognitive abnormalities. Conversely, environmental enrichment (EE) offers beneficial effects on brain plasticity and development. This study was designed to examine how environmental enrichment affects memory functions and related gene expressions such as Grin2a, Grin2b, BDNF, and cFos in the hippocampus in socially isolated rats.

Wistar albino male rats (n=40) were separated into the five groups: standard cage (SC), SI, EE, SI+SC, and SI+EE group. For each group, eight rats were housed, either grouped or isolated, in a standard or 3-week enriched environment, respectively. Morris Water Maze Test (MWMT) was used for measuring the learning and memory function. The expression levels of genes were measured by the RT-PCR method.

Results showed that environmental enrichment increased memory performance in the socially isolated group ($p < 0.05$). BDNF expression level was down regulated in EE and SI+SC compared to the SC group (respectively; $p = 0.012$; $p = 0.011$). Grin2a, Grin2b, mTOR and Cdk5 expression levels did not change between groups significantly ($p > 0.05$).

Social isolation impaired memory performance while environmental enrichment has beneficial effects on memory in socially isolated rats. Environmental enrichment alone was insufficient to cause alterations in memory performance. The therapeutic effects of environmental enrichment became strengthened while applying together with stress protocol. SI seemed to be the reason for increasing in BDNF expression level.

O22

Social isolation induces anxiety-like behaviors in adult rats: relation to neuroendocrine and neurochemical dysfunctions

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Subjects suffering from psychosis frequently experience anxiety. However, mechanisms underlying this comorbidity remain still unclear. The social isolation rearing represents a reliable experimental tool to mimic psychotic-like symptoms in rodents and to investigate mechanisms leading to the development of an anxiety-like state following the exposure to such a psychosocial condition. Here, we investigated whether neurochemical and neuroendocrine dysfunctions were involved in the development of anxiety-like behaviors in adult rats exposed to social isolation from post-natal (PND) day 21 to PND 70. In the elevated zero maze test, isolated (ISO) rats showed a significant reduction in the time spent in the open arms, as well as an increase in the time spent in the closed arms, compared to control (GRP) rats. Isolation-induced anxiety-like behavior was accompanied by decreased plasmatic oxytocin, prolactin, ghrelin and melatonin levels, whereas plasmatic amount of Neuropeptide S was not altered. Social isolation also caused a significant reduction of noradrenaline, serotonin (5-HT) and GABA levels in the amygdala of ISO animals compared to GRP, whereas an increase of 5-HT turnover and glutamate levels was detected in the same brain region. Furthermore, plasmatic amount of 5-HT and its transporter (SERT) were significantly reduced following social isolation. This was accompanied by elevations of plasmatic kynurenine levels, while no significant changes in 5-HIAA levels were observed. Taken together, our data provide novel insights in the neurobiological alterations underlying the comorbidity between psychosis and anxiety, opening new perspectives for multi-target therapies acting on both neurochemical and neuroendocrine pathways.

O23

Oxytocinergic modulation of synaptic function: Implications for neurodevelopment and aging

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The oxytocinergic system regulates vital homeostatic functions as well as complex behaviors like social interaction, as such the dysregulation of this system has been

implicated in neurological disorders characterized by social deficits. Despite its important neuromodulatory action, many details regarding oxytocinergic circuit formation and oxytocin (OXT) release in the Central Nervous System remain unknown. Our laboratory has implemented a multidisciplinary approach combining novel genetic tagging and imaging methods to identify OXT vesicle dynamics, light-sheet ultraresolution imaging and iDISCO+ clarification for 3D circuit reconstruction, electrophysiology and behavior to advance our current understanding of oxytocinergic neuromodulation from neurodevelopmental specification to the alterations underlying social deficits characteristics of various neurodevelopmental and neurodegenerative disorders.

Our findings have revealed the expression of unconventional SNARE proteins in hypothalamic oxytocinergic neurons, and the existence of distinct OXT vesicle pools which are differentially mobilized in response to neuronal stimulation, an overlooked feature which may be relevant for behavior fine tuning. Furthermore, we have analyzed the formation of the oxytocinergic circuit and its alterations in an animal model of Rett´s syndrome, as well as during natural and pathological aging. 3D hypothalamic circuit reconstructions indicate a profound remodeling of the oxytocinergic system during early postnatal stages that involves a shift of neuropeptide expression, which could be impaired during pathological conditions. Our studies provide new fundamental information for understanding oxytocinergic neuromodulation in the brain and its plastic properties to orchestrate different aspects of social behavior.

O24

Successful cognitive aging relies on healthy adult born dentate neurons

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The progressive decline of memory associated with aging is variable between individuals; some retain good memory performances while others suffer substantial loss of memory abilities. Adult neurogenesis in the dentate gyrus plays an essential role in learning and memory and represents a good candidate for the resilience/vulnerability to cognitive aging as animals with preserved memory abilities show higher levels of neurogenesis at old age. In this project, we aim to determine the role of adult dentate granule neurons (adu-DGNs) born throughout adult life in the development of memory deficits with age. First, we showed using the immediate early gene Zif268 as a proxy for neuronal activity that adu-DGNs are less responsive to the learning task in old aged impaired rats (Vulnerable) compared to the aged rats with preserved memory (Resilient). Next, we aimed to understand the mechanisms involved in such differences in responsiveness of adu-DGNs. We investigated possible alterations in their morphology and/or cellular homeostasis when animals were middle-age, to detect early signs of dysfunction that could lead to memory loss. To do so, the dendritic complexity, mitochondrial network and cellular senescence were investigated. We showed that adu-DGNs display similar morphological characteristics between populations and no sign of cellular senescence. However, we observed in the vulnerable population an impairment of their mitochondrial network in a specific sub-dendritic compartment. Memory deficits observable at old age are linked to a decrease of adu-DGNs reactivity in response to learning that could be related to an early alteration of their metabolism starting at middle-age.

O25

High frequency stimulation of the subthalamic nucleus: linking mood and motor effects at the level of the basal ganglia and 5-HT system

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a neurosurgical procedure commonly used for the management of severe movement disability in advanced Parkinson's disease (PD), but some patients experience debilitating psychiatric effects that have an unknown neural origin. Here we use animal models to uncover effects of DBS of the STN on relay stations such as the lateral habenula nucleus (LHb), a fast emerging controller of motivational and emotive behaviors, and a major source of input to 5-HT neurons in the dorsal raphe nucleus (DRN). STN stimulation at clinical parameters, consistently modulated the firing of the majority of LHb neurons tested. LHb neurons projecting to the DRN were identified using antidromic activation, and were also modulated by STN stimulation. Juxtacellular labelling confirmed that STN-responsive neurons were LHb glutamatergic neurons. We identified a behavioral correlate of the neurophysiological effects of STN stimulation. Thus, STN stimulation induced a behaviorally selective decrease in food and sucrose intake, consistent with a

reduced motivational state. Moreover, the use of neurotoxic lesions demonstrated that these STN-evoked responses were dependent on both the LHb and 5 HT. Collectively, the present data demonstrate that DBS of the STN influences the LHb and its pathway to the midbrain 5-HT system to generate decreases in motivational outputs. Therefore, the impact of the STN on a major controller of motivational and emotive behaviors offers an unexpected route by which STN stimulation might evoke psychiatric effects in patients with PD.

O26

MIR-NAT: A paired antisense long non-coding RNA gene regulates tau translation

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Neuronal and glial fibrillar tau pathology defines the tauopathies, a large group of progressive neurodegenerative disorders of old age, including Alzheimer's disease (AD). The MAPT gene which codes for tau resides on chromosome 17q, in a region with a large (~900bp) inversion polymorphism causing evolution of two non-recombining haplotypes, H1 and H2 of which the H1 haplotype is a significant risk factor for the four-repeat tauopathies, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) as well as Parkinson's disease (PD). Mutations in MAPT cause familial frontotemporal lobar dementia with tau pathology (FTLD-tau). We identified a long non-coding RNA (lncRNA) gene, MAPT-AS1 that overlaps in antisense with the MAPT promoter, expressing multiple splice variants (natural antisense transcripts, NATs). All these NATs share a distal 3' exon with an embedded transposable element of the class of mammalian interspersed repeats (MIR) thus, MIR-NAT. With knock-down of the endogenous MAPT-AS1 gene in iPSC-derived neurons and overexpression in a neuroblastoma cell line, we demonstrated that the tau MIR-NAT represses tau translation by complementarity-based hindrance of ribosomal recruitment of the 5'-untranslated region of MAPT mRNA. We also identified over 1200 further MIR-NAT genes paired with protein coding genes, with a particular preference for genes of intrinsically disordered proteins (IDPs) including those important for brain function and disease. This suggests that MIR-NATs present an extra layer required for the tight regulation of homeostasis of these proteins.

POSTER PRESENTATIONS

P1
Dopamine D2 Receptors regulate spines in Striatal indirect-pathway neurons

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Dopamine transmission is involved in the maintenance of the structural plasticity of direct and indirect pathway striatal projection neurons (d-SPNs and i-SPNs, respectively). The lack of dopamine in Parkinson's disease produces synaptic remodeling in both types of SPNs, reducing the length of the dendritic arbor and spine density and increasing the intrinsic excitability. However, the specific role of the D2 receptor (D2R) is unknown. To explore the specific role of D2R in the synaptic remodeling of SPNs, we used knockout D2R mice (D2R-/-) and wild-type mice crossed with tom- enhanced red fluorescent protein (tom) to identify d-SPNs and i- SPNs. Corticostriatal slices were used for reconstruction of the dendritic arbors after Lucifer yellow intracellular injection and for whole-cell recordings in naïve and parkinsonian mice treated with saline or levodopa. The genetic inactivation of D2R reduces the spine density in i-SPNs, which also increases their spiking.

P2
Polymorphisms within serotonin receptor genes are associated with genetic, cerebrospinal fluid and neuropsychological biomarkers of Alzheimer's disease

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Decrease in serotonergic transmission throughout the brain is among the earliest pathological changes in Alzheimer's disease (AD). Serotonergic receptors are also affected in AD. Polymorphisms in genes for serotonin (5HT) receptors were mostly associated with behavioural and psychological symptoms of dementia (BPSD). In this study we aimed to test if individuals carrying different genotypes in 5HTR1B rs13212041, 5HTR2A rs6313 (T102C), 5HTR2C rs3813929 (-795C/T) and 5HTR6 rs1805054 (C267T) polymorphisms have higher risk for development of AD. Study included 115 AD patients and 53 mild cognitive impairment patients with determined cerebrospinal fluid (CSF) AD biomarkers, neuropsychological tests, and apolipoprotein E (APOE) haplotype and 2701 cognitively healthy individuals with determined APOE haplotype. All four analysed polymorphisms of serotonin receptor genes showed the association with either genetic, CSF or neuropsychological biomarkers of AD. Thus, these polymorphisms deserve further investigation as potential genetic biomarkers and therapeutic targets for AD.

P3
The association of TSH and thyroid hormones with *APOE* genotype

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The scope of this study was to investigate if *APOE* (apolipoprotein E) genotype affects thyroid stimulating hormone (TSH) and thyroid hormone levels. *APOE* is the main genetic risk factor for development of sporadic Alzheimer's disease (AD) (with $\varepsilon 4$, $\varepsilon 2$ and $\varepsilon 3$ as risk, protective and the most common allele, respectively). A recent study showed the association between serum TSH levels and AD pathology, with TSH levels being positively correlated and fT4 levels negatively correlated with cereb-

ral amyloid β burden. However, the other study showed that higher thyroid function (with lower TSH levels and higher fT3 levels) was associated with greater annual hippocampal volume loss. Additionally, it was shown that *APOE* ε4 genotype is the risk factor for foetal iodine deficiency syndrome. In fact, *APOE* protein possesses a thyroid hormone binding domain and triiodothyronine (T3) can affect *APOE* gene expression. In this study, we included 2701 cognitively healthy individuals with determined *APOE* haplotype, TSH and thyroid hormone levels (fT3, fT4). We found no significant change in TSH and thyroid hormone levels between carriers of different *APOE* genotype. However, after subgroup analysis (according to the age and gender), we observed a significant decrease in fT3 levels in carriers of *APOE* ε4 risk allele ($p = 0.039$; in males younger than 65 years). Interestingly, in the individuals older than 65 years carrying protective *APOE* ε2 allele, we also observed a decrease in fT3 ($p = 0.034$) and fT4 levels ($p = 0.012$). In males older than 65 years carrying risk *APOE* ε4 allele we observed the decrease in TSH levels ($p = 0.003$). Our results did not depict the clear relationship between thyroid hormones and *APOE* genotype since conflicting results were observed in older and younger participants. However, these results indicate that the possible involvement of TSH and thyroid hormones in AD pathology deserves further investigation.

P4

Three different methods confirmed the association of macro and microelements with cerebrospinal fluid biomarkers of Alzheimer's disease

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The homeostasis of metals is altered in the brain of Alzheimer's disease (AD) patients. It was proposed that changes in metal homeostasis are related to AD pathology. Additionally, metals that are not present in the brain under normal circumstances (such as mercury, lead and cadmium) were associated with AD pathogenesis. The aim of this study was to test if macro and microelements (Li, B, Na, Mg, Al, S, K, Ca, Cr, Fe, Co, Mn, Ni, Cu, Zn, As, Se, Sr, Mo, Cd, Ba, Tl, Pb, and Hg) measured in cerebrospinal fluid (CSF) and plasma of patients with dementia are associated with CSF biomarkers of AD. CSF AD biomarkers reflect pathological changes in AD brain, while the involvement of different metals in AD pathogenesis is still the matter of debate. Macro and microelements were determined by inductively coupled plasma mass spectroscopy (ICP-MS), while CSF biomarkers were measured by enzyme-linked immunosorbent assays (ELISA). Macro and microelements were measured in CSF of 194 subjects and in plasma of 144 subjects (study included overall 125 AD patients, 50 patients with mild cognitive disorder and 19 healthy controls). We used three different statistical methods to test the association of macro and microelements with CSF biomarkers of AD. All three methods (simple correlation and two machine learning algorithms; redescription mining and principal component analysis [PCA]) demonstrated the association of macro and microelements with CSF biomarkers of AD. Possible explanations for association of macro and microelements with CSF biomarkers of AD await elucidation of their environmental sources or detection of their release from brain tissue due to cell death. Also, these results should be further validated on larger cohorts.

P5

Gastrointestinal redox homeostasis and cognitive performance in the mature adult and middle-aged Tg2576

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The gastrointestinal tract and the central nervous system are intricately connected and gut dysbiosis is a significant factor in the pathogenesis of neurodegenerat-

ive disorders like Alzheimer's disease. In the fAD model Tg2576, gut dysfunction was found to precede deposition of the pathological cerebral Aβ. We aimed to further assess changes in gastrointestinal redox homeostasis with respect to cognitive performance of Tg2576-mice. Tg2576-mice (20x aged 7M-mature adult; 20x aged 12M-middle-aged) and respective wild-types were used. Cognitive performance was defined as a principal component-derived composite of variables of the Morris Water Maze test. Anxiety-like behaviour was assessed with Open field. Redox homeostasis was evaluated in samples of mice' duodenum, using the ABTS, ORAC, nitrocellulose-permanganometry (NRP), TBARS, low molecular weight thiols (LMWH) content, protein sulfhydryl-SH content, peroxidase and catalase activity assays. Mature adult Tg2576-mice showed no obvious cognitive deficit, with a slight reduction detected in ABTS, NRP, GSH and SH content, but no change in other redox measures. In the middle-aged Tg2576 with developed cognitive deficit, the activity of catalases and peroxidases was decreased, while NRP and ORAC indicated a pro-oxidative shift in redox balance. Interestingly, ABTS and LMWH were increased. In both Tg2576 cohorts, intestinal redox homeostasis was a poor predictor of cognitive performance and hippocampal Aβ and hyperphosphorylated tau content, but was associated with other behavioural patterns; contributors to the nucleophilic arm of redox homostasis predicted anxiety-related behaviour in the open field test. In conclusion, redox dyshomeostasis occurs before cognitive deficits in Tg2576 mice, but seems to poorly predict cognitive performance and hippocampal Aβ and hTau. Gut redox equilibrium appears to be associated to anxiety-related behaviour in mature adult Tg2576 mice. Further investigation is warranted to prove an association of these biological phenomena.

P6

Plastic adaptive changes induced by chronic M-channel activation in hippocampal neurons

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In response to alterations in neuronal activity, neurons use various mechanisms of homeostatic plasticity to maintain excitability at a certain set point. M-channels are voltage-gated potassium channels that play a crucial role in regulating neuronal excitability. We previously showed that in cultured hippocampal excitatory neurons, acute exposure to the M-channel blocker XE991 increased intrinsic excitability and spontaneous firing rate. However, chronic XE991 treatment leads to adaptative compensations, triggering intrinsic and synaptic homeostatic plasticity at different timescales. This plastic adaptation does not occur in hippocampal inhibitory neurons. In this study, we examined whether the homeostatic plasticity induced by M-channel modulation was bidirectional by investigating the acute and chronic effect of the M-channel opener retigabine on hippocampal neuronal excitability, using whole-cell patch-clamp recordings. Acute Retigabine exposure decreased excitability in both excitatory and inhibitory neurons by increasing the threshold current for firing and decreasing the spontaneous firing rate. However, chronic retigabine treatment (24 hours) led to homeostatic adaptation of the threshold current and spontaneous firing rate in excitatory neurons. In contrast, in inhibitory neurons, adaptation of the threshold current occurred only after 48 hours, while homeostatic normalization of the spontaneous firing rate did not occur at all. Our results indicate that excitatory and inhibitory hippocampal neurons differ in their adaptation to chronic alterations in neuronal excitability induced by M-channel activation and inhibition. The homeostatic changes are bidirectional but not symmetric in terms of kinetics and mechanisms.

P7

Glymphatic function in Parkinson´s disease

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Recent studies in Lewy body diseases including Parkinson's disease (PD) and dementia with Lewy bodies show the strong presence of α-synuclein (α-syn) seeding and fibril-templating activity in cerebrospinal fluid (CSF). Glymphatic system (GS) is involved in the clearance of peptides from the brain through the exchange of CSF and interstitial fluid, mediated by the water channel aquaporin 4 (AQP4). Interestingly, GS is impaired in Alzheimer´s disease, and is involved in the clearance of amyloid-beta from the brain. However, how the GS is affected in PD and its role in the removal from the brain of amyloidogenic

α-syn has not been established yet. Here we investigated whether the GS is impaired in parkinsonian mice or mice exposed to pre-formed mouse α-syn fibrils (mPFFs). We injected fluorescent tracers in the CSF at the cisterna magna (CM) to track its distribution in the brain and periphery in 6-hydroxydopamine (6-OHDA) lesioned mice and in mice exposed to mPFFs. Our results show the importance of glymphatic clearance of pathological α-syn injected in the brain which followed glymphatic pathways. Our results showed a trend towards decreased CSF influx in the brain of 6-OHDA mice, suggesting that neurodegeneration has a negative impact on GS. mPFFs injected mice showed similar cognitive performance to aCSF mice, but their motor performance on the rotarod was significantly impaired. No differences between aCSF and mPFFs injected mice were detected in GS function, but in aCSF mice a correlation was found between motor performance and GS function, which was lost in mPFFs mice.

P8

Effects of the 5-HT2A receptor agonist TCB-2 on the neurochemistry of monoamines and amino acid neurotransmitters in the mouse striatum

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TCB-2 is a preferential 5-HT2A receptor (5-HT2AR) agonist that induces classical signs of serotonergic hallucinogenic drugs in rodents. These drugs modulate neurotransmitter contents in various brain regions but it is unclear if the responses are homogenous inside a brain region. The striatum has distinct functional territories allowing us to address 1) the neurochemical effects of TCB-2 within two territories, here the ventromedial and ventrolateral striatum, and 2) the connection of the neurotransmitter content between the two regions using correlative analyses. Tissue levels of monoamines [dopamine (DA), noradrenaline (NA), serotonin (5-HT)], their metabolites, and amino acids neurotransmitters (aspartate, glutamate, glycine, GABA) were measured using HPLC coupled to electrochemical detection in the striatum of male C57Bl6/J mice one hour after the intraperitoneal injection of TCB-2 (0.3, 3, 10 mg/kg). TCB-2 did not alter the striatal levels of amino acid neurotransmitters, NA, tended to enhance DA (mainly ventrolateral), and increased 5-HT content at the highest dose. TCB-2 dose-dependently and robustly reduced the 5-hydroxyindoleacetic acid/5-HT and 3-methoxytyramine/DA ratios in both regions. The 5-HT2AR antagonist MDL100907 (0.2 mg/kg, 15 minutes before 3 mg/kg TCB-2) counteracted the effect of TCB-2 on 3-methoxytyramine/DA only. The strong correlative link reported for the neurotransmitter contents between the ventrolateral and the ventromedial striatum in control animals was reduced or suppressed in TCB-2-treated mice. In conclusion, TCB-2 homogeneously inhibits in the two striatum the DA and 5-HT metabolisms involving or not 5-HT2ARs, respectively, and disrupts the correlative links for all neurotransmitter contents between the two striatum.

P9

The deletion of SNORD115, a potential regulator of 5-HT2C receptor expression, promotes cortico-subcortical imbalance of monoaminergic transmission in mice

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The neuronal-specific SNORD115 has gathered interest because its deficiency may contribute to both the pathophysiology of Prader-Willi syndrome (PWS) and the post-transcriptional regulation of the expression of the mRNA encoding the serotonin (htr2c) receptors. Yet, SNORD115-KO mice do not resume the main symptoms of PWS while subtle altered A-to-I RNA editing of htr2c mRNAs were reported. Htr2c receptors are linked to the regulation of the activity of monoaminergic neurons, implying that the deletion of SNORD115 could indirectly alter monoaminergic systems function. The results showed that SNORD115 was normally expressed in both monoaminergic and non-monoaminergic cells of the ventral tegmental area (VTA) and the dorsal raphe nucleus (DRN) containing the cell bodies of dopaminergic and serotonergic neurons, respectively. The measurement of the tissue level of monoamines and metabolites revealed very few differences except that the content of homovanil-

lic acid - a metabolite of dopamine - was decreased in the orbitofrontal and prefrontal cortex of SNORD115-KO mice. This effect was associated with a few changes of correlative maps of monoamine tissue content across the 12 sampled brain regions. Using *in vivo* single cell extracellular recordings, we reported that the firing rate of VTA dopaminergic neurons and DRN serotonergic neurons was significantly increased in SNORD115-KO mice. The deletion of SNORD115 did not modify binge eating, compulsive behavior, nor the conditioned place preference and locomotor hyperactivity induced by cocaine. In conclusion, specific deletion of SNORD115 genes remodels central monoaminergic circuits to an extent that would not be observable among the core symptoms of PWS.

P10

Evaluation of procognitive activity of 5-HT1A biased ligand and muscarinic ligands in an animal model of schizophrenia

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The most treatment-resistant domain of schizophrenia symptoms are cognitive disturbances, which include memory and attention deficits Activation of receptors expressed in brain regions that are critical for cognitive functioning could have the potential to reverse cognitive symptoms. Both muscarinic and serotonergic receptors are implicated in the regulation of cognitive processes. Recently it was shown that modulation of 5-HT1A (F15599), M1 (VU0357017), M4 (VU0152100) and M5 (VU0238429) receptors reversed deficits in working memory in animal model of schizophrenia. Thus, we aimed to assess the activity of aforementioned ligands alone or in combination in another cognitive domain - spatial memory. Male CD-1 mice were used to assess the efficacy of combined administration of 5-HT1A and muscarinic ligands in Morris water maze. Mice were trained for 5 consecutive days and on the 6th day the test session was performed. The drugs were administered 30 min before MK-801, which was administered 30 min each day before the training to impair learning and memory. F15599 as well as muscarinic ligands reversed MK-801-induced disruptions in several parameters measured during the test trial. Based on the results of the dose-dependency studies following combinations were then tested: top doses together, ineffective doses together and top+ineffective dose. Tested combinations of ligands reversed a number of parameters, but not all combinations with muscarinic receptors ligands were active in this test. Our results suggest that concomitant activation of 5-HT1A and muscarinic receptors has limited potential to reverse schizophrenia-related cognitive symptoms.

P11

Identification of a neuronal population in the hypothalamus, expressing 26RFa and orexins, involved in the regulation of glucose homeostasis

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26RFa (QRFP) is a biologically active peptide that regulates glucose homeostasis by exerting an incretin effect at the periphery in parallel to a robust central antihyperglycemic effect. These two actions are associated with an increase of insulin production by the pancreatic islets. In addition, it was found that central 26RFa is a key relay of the central insulin action allowing the regulation of glucose homeostasis. In order to decipher the involvement of the hypothalamic 26RFa neurons in the regulation of glucose homeostasis, we investigated in the present study, the effect of an activation of the 26RFa-expressing neurons in the hypothalamus by a chemogenetic approach, the Designer Receptor Exclusively Activated by Designer Drugs (DREADD), in 26RFa deficient and 26RFa-expressing mice. Our data indicate that the stimulation of 26RFa neurons in 26RFa-expressing mice potentiates the hyperglycaemia induced by an intraperitoneal injection of glucose. Moreover, this stimulation also triggers the hepatic glucose production and the insulin production by the pancreatic islets. The same results were obtained in 26RFa deficient mice and consequently exempt the implication of 26RFa in this reduction of glucose tolerance. Interestingly, double labelling RNAscope experiment revealed that the 26RFa neurons localized in the lateral hypothalamus aera also express the neuropeptides orexins. To con-

clude, the present data reveal for the first time that the 26RFa/orexin neurons of the lateral hypothalamic aera are involved in the central regulation of glucose homeostasis by decreasing glucose tolerance. This reduced glucose tolerance may be due to orexins but not to 26RFa.

P12

Xenapses grown on micropatterned thin films for tailored cryo-FIB milling and cryo-electron tomography of synaptic exocytic and endocytic structures

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For studying quantitative aspects of synaptic exo- and endocytosis by live-cell microscopy at the molecular level, we have developed cultured 'xenapses', TIRFM-amenable purely presynaptic boutons on a host substrate. These are formed by murine hippocampal neurons cultured on micropatterned glass coverslips, which have been functionalized with synaptogenic cell adhesion proteins. Xenapses, however, should be also ideally suited for high-resolution correlative cryo-electron microscopy, because they are thin, lack the electron-dense postsynaptic densities, and can be grown in a targeted fashion for directed focused ion beam (FIB) milling. Here we developed ultrathin glass films (1.5 nm SiO2) that can be lifted on holey carbon films on TEM grids. Xenapses are developed on these ultrathin films within a few days. Their functionality was confirmed by live-cell calcium and pHluorin imaging experiments. Xenapses expressing the endogenously expressed pH-sensitive exo-endocytosis probe pHluorin show the same tight and synchronous action potential vesicle fusion coupling as their counterparts growing on glass coverslips. Xenapses, cryo-fixed by plunge freezing, displayed well-preserved ultrastructure, with large numbers of synaptic vesicles at or near the pre-synaptic membrane. Our results indicate that structure and function of xenapses grown on ultrathin films do not differ from their counterparts on glass coverslips.

P13

The impact of APE-1 redox inhibition on regulation of the dopaminergic neurons' pathway during inflammatory pain condition

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Apurinic/Apyrimidinic Endonuclease 1/Redox Effector-1, APE1/Ref-1 functions as a negative regulator of inflammatory response via several mechanisms in neuronal cells. APE1's redox activity stimulates the DNA-binding activity of several transcription factors, including NF-κB, AP-1, HIF-1α, and STAT3. We investigated targeting the APE1 redox activity that might influence the neurotransmitters and related receptors by intradermal injection of E3330 (selective redox inhibitor of APE1) in formalin-induced inflammatory pain model in rats as a means of studying and potentially combating neuroinflammation. Accumulating evidence has shown that dopamine systems in the brain are also involved in the central regulation of chronic pain. Most importantly, descending dopaminergic pathways play an important role in pain modulation. Therefore, we tested the effect of APE1 redox activity on the regulation of dopaminergic signaling pathway. We determined the index of pain through behavioral tests after peripheral induction of formalin (50µl in the dorsal surface of hindpaw). Interestingly, our data point to a decreased nuclear accumulation of APE1 mRNA expression, changed its distribution in the inflamed group as compared to the sham group (i.e. reduced IL-6 expression), and alleviated pain, as assessed by measuring the paw edema. In support to our results, the study of Pacheco, 2017 reported that high-dopamine levels promote the stimulation of low affinity dopamine receptors including, DRD1, DRD2 and DRD4, inducing anti-inflammatory effect in microglia, while low dopamine levels selectively stimulate high-affinity dopamine receptors including, DRD3 and DRD5, triggering inflammation. In conclusion, inhibition of the reduction-oxidation function of APE1 by E3330 compound might constitute a novel approach for treating inflammatory pain through modulating the level of dopamine and the affinity of its D5R and D2R receptors inside spinal cord. Therefore, further investigation is needed toward this approach.

P14

Deranged central oxytocinergic signaling in preclinical models of obesity and hedonic feeding

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The conventional view of homeostatic regulation of

body-weight has been expanded to include also non-homeostatic processes. Oxytocinergic system is implicated in various processes, including eating and metabolism, involving activation of brain areas belonging to both homeostatic and non-homeostatic circuits. The endogenous-acylethanolamides, like oleoylethanolamide (OEA), play biological functions from regulation of food-intake to mood-tone. An interplay between oxytocinergic-system and OEA in modulation of both homeostatic and non-homeostatic circuits has been demonstrated. By using rat-models of obesity and hedonic-feeding: 1 rat-model of diet-induced-obesity based on exposure to a high-fat-diet or low-fat-diet; 2 female-rat-model of binge-eating based on cycles of intermittent food restriction/refeeding and palatable-food consumption, followed by 15-minute-exposure to palatable-food sight and smell (frustration-stress); 3 rat-model of diet-induced-obesity based on hedonic-overfeeding, induced by exposure to a cafeteria-diet and abstinence from it, we evaluate first whether rat-models show an altered central-oxytocinergic-neurotransmission and then whether an increase of acylethanolamides-tone might affect such signal, through immunohistochemistry and in-situ-hybridization analyses in selected brain-areas (including medial-prefrontal-cortex, caudate-putamen and nucleus-accumbens). Endogenous-acylethanolamides-tone was stimulated by peripherally-administering OEA 10 mg/kg i.p. (models 1-2) and the fatty-acid-amide-hydrolase (FAAH, enzyme involved in acylethanolamides-catabolism) inhibitor, PF-3845 10 mg/kg s.c. (model 3). Our results reveal an alteration of oxytocinergic-system in all models analyzed, affecting both oxytocin and oxytocin-receptor expression. Surprisingly, the increasing endogenous-acylethanolamides-tone modulates such transmission, suggesting that the modulation of central-oxytocinergic-signaling by increasing acylethanolamides-tone might represent one of the mechanisms that coordinate energy balance at crossroads between homeostatic and non-homeostatic mechanisms, opening the way to new pharmacological target for obesity and aberrant-eating-behaviors' treatment.

P15

Astrocytes exert negative modulation on hippocampal neuron excitability

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Neuronal firing is the essential element of neuronal networks as action potentials are the end product of synaptic integration. Therefore, neurons adjust their intrinsic membrane excitability to maintain the firing rate within their own optimal operational range. A principal homeostatic factor of neuronal excitability in the mammalian hippocampus is the postburst afterhyperpolarization (AHP). AHP exerts a negative control predominantly through a Ca^{2+} dependant K^+ current that contributes to the slow AHP (sIAHP) responsible for the spike-frequency adaptation, and can be dynamically influenced by neuronal modulators. Astrocytes are cellular elements involved in information processing in the nervous system. However, little is known about the direct effect of astrocyte signalling on neuronal intrinsic properties. To address this issue, we used electrophysiological and Ca^{2+} imaging techniques in mouse hippocampal slices, as well as chemogenetic, electric and optogenetic stimulation of astrocytes and/or GABAergic interneurons. We saw that chemogenetic stimulation of astrocytes with Clozapine-N-oxide (CNO) in CA1 hippocampal region decreases pyramidal neuron excitability through increasing sIAHP and the reduction of action potential firing. Both effects were blocked by using specific adenosine 1 receptor antagonist. Next, we used high frequency stimulation and optogenetic protocols to specifically stimulate hippocampal interneurons. Thus, we found that GABA released from interneurons activates astrocytic GABAB receptors. Consequently, astrocytes release ATP/adenosine, which acts on pyramidal neurons A1 receptors increasing sIAHP and reducing neuronal excitability. Present results uncover the role of astrocytes in the regulation of neuronal intrinsic properties and reveal a novel mechanism involved in network dysfunctions and brain disorders related with neuronal hyperexcitability.

P16

Early life social experiences and dysregulation of the brain reward system: age- and sex-dependent interactions

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Early life environmental factors are critical for future wellbeing and development of appropriate social and cognitive skills. Exposure to a socially impoverished/socially enriched environment during the early stages of postnatal life may increase/decrease the salience of rewarding stimuli by facilitating/attenuating the risk of dysregulation of the brain reward system. The Communal Nesting (CN) paradigm is a form of pre-weaning environment enrichment in which three female mice are mated with the same male, gestate and rear their litters together until weaning.

The Early Social Isolation (ESI) paradigm is an environmental manipulation consisting in a 30-min period of social isolation from both mother and peers during the 3rd postnatal week. In this study we trained adolescent and adult male and female rats reared at the different condition (SH, CN, SH+ESI, CN+ESI) to self-administered palatable food under a continuous and progressive reinforcement schedules. Results showed that CN rats took longer to acquire operant behavior and showed lower food intake than SH animals, with ESI leading to a steeper curve in adulthood. In general, SH-CTRL males showed higher food self-administration than corresponding females under FR-1 protocol, with ESI increasing the responding for food in SH adolescent females, but not males, and CN reverting ESI-induced effect. Under PR protocol, sex differences were more evident, as SH-ESI females showed a higher breaking point than SH-ESI males, and CN prevented the effect of ESI in both sexes. These findings indicate for the first time that an early life socially enriched condition, like the CN condition, exerts a "protective" effect toward early stress-induced behaviors related to reward and motivation.

P17

Morphological and functional characterization of human microglia in transient structures of the developing brain

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Prenatal human brain develops via dynamic progressive and reorganization processes of histogenetic events. Transient structures enable the development of specific and unique morphology and connectivity pathways of the human cortical and subcortical structures. Microglial morphology varies in transient layers of the future neocortex and transitional structures during brain development. To date, the role of microglia in morphogenetic events during human brain development remains underexplored. Differences in microglial morphology are likely coupled with a specific function serving the purpose of shaping the neurodevelopmental landscape. Therefore, a proper characterization of morphological microglial states is required in areas of neurogenetic importance. In this study, we aimed to analyze different phenotypes of microglia in transient, human characteristic structures during the period of their existence and gradual disappearance. We expect to unravel the possible role of microglia in these particular processes of transient structures which are important for further cortical and connectivity development.

P18

Influence of acrylamide supplementation on the population of PACAP-like immunoreactive intramural neurons of the duodenum in the pig

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Acrylamide is a compound found in heat-treated food products, such as French fries, chips and corn flakes. Pituitary adenylate cyclase-activating polypeptide and exerts a cytoprotective effect. The aim of the study was to assess the effect of acrylamide intoxication on the population of PACAP-like immunoreactive (LI) intramural neurons located in the porcine duodenum. The research was carried out on 15 gilts of the Danish breed. Animals were divided into 3 groups: C- receiving empty gelatin capsules, E1- receiving low dose of acrylamide (0.5 μg/kg of body weight) and E2- receiving high dose of acrylamide (5 μg/kg of body weight) for 28 days each morning. After the supplementation period, all animals were euthanized and the duodenal fragments were collected. Then, frozen sections were subjected to double immunofluorescence staining using primary antibodies (Hu C/D (pan-neuronal marker) and PACAP) and appropriate secondary antibodies (Alexa Fluor 488 and 546). Acrylamide supplementation evoked changes in the number of PACAP-LI neurons in the duodenum. A high dose of acrylamide increased population of PACAP-LI neurons in the myenteric plexus (from 28.27±1.45% to 54.37±1.97%), in the outer submucous plexus (from 23.4±3.03 to 47.42±4.19%) and in the inner submucous plexus (from 21.59±2.42 to 54.88±6.24%). While low dose of acrylamide increased the number of PACAP-positive neurons only in the myenteric plexus (to 38.91±4.5%). The results suggest the participation of PACAP in the protection of ENS neurons against the harmful effects of acrylamide in the porcine duodenum.

P19

Shutdown of NHE1 is the primary event at presynapses upon chemically induced ischemia to avoid neurotoxicity

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Pre- and postsynaptic mechanisms consume up to 55% of the total ATP used on action potentials. Here, we systematically analyzed the relative ATP demand of action potential generation and presynaptic processes such as exocytosis, release site clearance, Ca^{2+} clearance, endocytosis and SV reformation/refilling in primary hippocampal neurons. We found that chemical interference with ATP production does not affect the excitability of neurons immediately and that with respect to the synaptic vesicle cycle ATP depletion manifests earliest on the process of compensatory endocytosis. However, surprisingly we observed that ATP depletion causes an immediate shutdown of the sodium-proton-antiporter 1 (NHE1-transporter) leading to a block of cytosolic realkalinization upon stimulation-induced acidification. Furthermore, the impaired endocytosis phenotype upon ATP depletion can be mimicked by pharmacological block of NHE1 function and can be rescued by optogenetic restoration of the intracellular pH using the light-driven proton pump Arch3. We therefore hypothesize that impaired endocytosis is only a secondary consequence of ATP depletion while block of the NHE1 transporter is the primary effect leading to pronounced and sustained intracellular acidification. In this way, Na+ toxicity is avoided by block of NHE1 mediated Na^+ influx, but at the expense of intracellular pH and synaptic vesicle recycling.

P20

Lamotrigine rescues the attenuating effect of intracerebroventricular Aβ1-42 infusion on spontaneous theta rhythms in anesthetized rats

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Theta rhythms are involved in sensorimotor integration, movement planning, and memory formation and involves a specific interplay between ionic and synaptic mechanisms. Disruptions of theta rhythms are present in individuals with various disorders, including Alzheimer's disease (AD). HCN channels are theta modulators, and several medications such as Lamotrigine are known to enhance their activity. In AD pathology, Aβ, a peptide synthesized in the neuron and secreted extracellularly, is believed to be among the most pathological factors leading to neurodegeneration, membrane disruption, and synaptic dysfunction. To date very few electrophysiological studies have attempted to characterize oscillatory activity in animal models of AD. Hence our goal was to characterize the direct effect of Aβ1-42 intracerebroventricular (icv) administration on hippocampal theta rhythms *in vivo*. To this end the frequency, power, and amplitude of spectra changes after 7,14 and 21 days from icv Aβ1-42 infusion was studied. All experiment were monitored by a Local Ethical Commission. Male Wistar rats (300–350 g) were divided randomly into three experimental groups: naive group, vehicle injected group, Aβ1-42 injected group and Aβ scramble group. Additionally, we investigated how lamotrigine would affect hippocampal theta rhythms in anaesthetized rats previously centrally infused with Aβ1-42. Our results indicate that: 1 / Aβ1-42 injections resulted in a significant reduction of theta rhythm amplitude and power after 7,14, and 21 days from injection, 2/ vehicle and scramble injections had no effect on the spontaneous hippocampal EEG activity, 3/ LTG intrahippocampal injections in Aβ1-42 treated animals increased the level of theta synchrony.

P21

DNase Treatment Prevents Cerebrospinal Fluid Block in Early Experimental Pneumococcal Meningitis

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Streptococcus pneumoniae is the leading cause of bacterial meningitis. Brain edema is a major cause of morbidity in S. pneumoniae meningitis. We hypothesized that neutrophil extracellular traps (NETs) disrupt cerebrospinal fluid (CSF) transport by the glymphatic system and contribute to edema formation in S. pneumoniae meningitis. We used DNase I treatment to disrupt NETs and then assessed glymphatic function by cisterna magna injections of CSF tracers in a rat model of S. pneumoniae meningitis. We showed that both CSF influx into the brain parenchyma and CSF drainage to the cervical lymph nodes were reduced in the rat model of S. pneumoniae meningitis. Degrading NETs by DNase treatment restored glymphatic transport and eliminated the increase in brain weight

of rats. In contrast, first-line antibiotic treatment had no effect on restoring CSF dynamics. This study suggests that CSF accumulation is responsible for cerebral edema formation and identifies the glymphatic system and NETs as possible new treatment targets in S. pneumoniae meningitis.

P22

Early compartmentalization and laminar rhythm of future projection neuron markers during the human early cortical plate stage

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The precise coordination of differential gene expression involved in fundamental neurogenetic and histogenetic processes is essential for development of the human fetal brain. Corticogenesis relies upon precise timing and location of cell proliferation and migration, followed by neuronal differentiation and molecular identity attaining. Furthermore, the correct establishment of the future six-layered human neocortex depends on the appearance of transient compartments and accurate developmental program during the first condensation of cortical plate (CP). Importantly, future projection neurons need to obtain the exact laminar position in order to mature and specify for their role. In this study, we aimed to monitor the early expression pattern of projection neuron markers, i.e. future cortical layer-specific markers (CELF1, TBR1, CTIP2, TLE4) during the development of early cortical plate. In order to reveal laminar shifts and molecular specification of major classes of neurons, we performed immunofluorescence (IF) of these markers on prenatal postmortem human brain tissue. Moreover, we used additional markers (Ki67, PAX6, TBR2) to track stages of cell differentiation during the early cortical plate period. Our results showed that projection neuron markers are expressed during early cortical plate stage, suggesting their involvement in neurogenetic processes responsible for establishment of six-layered human cerebral cortex.

P23

Suicidal behaviour and epigenetics: changes in expression of algorithm predicted miRNA

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Suicide is multifactorial and polygenic phenotype, affected by environmental and genetic factors. Epigenetic mechanisms have already been associated with suicidal behaviour. The effect of noncoding RNA however has been relatively neglected in psychiatric research compared to DNA methylation and histone modification. To overcome limitations of candidate miRNA and whole genome sequencing approaches, we created an in silico analysis algorithm that would help select the best suitable miRNAs that target the most interesting genes associated with suicidality. We used five publicly available databases/web algorithms and six preselected candidate genes, which had emerged as promising candidates in the context of suicide research through previous research (*SLC6A4, HTR1A, BDNF, NR3C1, ZNF714, and NRIP3*). Based on prediction algorithm we have chosen miRNAs that are targeting regulation of the genes listed, and are at the same time being expressed in the brain. The highest ranking scores were obtained for hsa-miR-4516, hsa-miR-3135b, hsa-miR-124-3p, hsa-miR-129-5p, hsa-miR-27b-3p, hsa-miR-381-3p, hsa-miR-4286. Expression of these miRNAs was investigated in brain (Brodmann area 10) of 40 suicide completers and controls, and hsa-miR-4516 and hsa-miR-381-3p showed trend for statistical significance. As miRNA can influence the expression of genes that they target, we next investigated the expression of miRNA target genes. *NR3C1* expression was lower in suicide completers compared to controls, which is in accordance with available literature results. To determine miRNAs most suitable for further suicidality research, more studies, combining in silico analysis and wet lab experiments should be performed.

P24

Modulation of oxytocin signalling by immunoglobulin G in stress-related disorders

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Oxytocin (OT) is a 9 amino acid hypothalamic neuropeptide which activates its receptor (OT-R) triggering intracellular Ca^{2+} release and internalization. OT plays a major role in promoting social interaction, and deficient OT signalling is linked with stress-related disorders, as aggressiveness. OT-reactive immunoglobulin (Ig) were found in human plasma, correlating with behavioural traits, without knowing if they may modulate OT signalling. We compared IgG biological activity from two groups, control and "aggressive", using HEK 293 cells lines expressing human OT-R. Ca^{2+} secretion was assayed using fluorimetry after a 3 minutes incubation with OT (10-7M) or individuals Ig (10-7M) preincubated with OT overnight. In the same way, OT-R coupled with GFP internalization was followed during 30 minutes with confocal microscopy. OT induced a typical Ca^{2+} releasing with a fast increase and slow decrease kinetics and OT-R internalisation. IgG/OTproceeded differently: they also triggered a fast increase of Ca^{2+} liberation with a similar amplitude, but it is followed by a faster return to the baseline. The total Ca^{2+} secretion, as measured by the area under curve, was decreased by about 50% ($p < 0,0001$) compared to OT kinetics, and weaker in aggressive group vs. control ($p < 0,0001$). Internalisation occurs after 5 minutes incubation with OT or IgG/OT, with a slower dynamic for the aggressive group. The present data show that IgG/OTactivate OT-R with different kinetics than neuropeptide alone, suggesting that Ig may play a role in OT signalling. The possible relevance of their implication in stress-related disorders remains to be studied.

P25

Executive functioning and Language in primary progressive aphasia

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Our goal was to describe the language and executive profiles of the three variants of primary progressive aphasia (PPA). We also compared the APP profiles to an Alzheimer's disease patients (AD) group and a healthy matched group. We recruited 68 PPA (22 nonfluent/agrammatic (nf/avPPA), 25 semantic (svPPA), 21 logopenic (lvPPA)), 32 AD, 41 age-matched healthy controls. Materials. Participants underwent a language and executive functions (EF) assessment: discourse, confrontation naming, repetition, reading, auditory/visuospatial span tasks, Trail Making Test, Stroop test, tower of London and verbal/design fluency. Scores on measures differed significantly in PPA and AD groups relative to healthy controls. Only repetition, auditory/visuospatial span tasks and design fluency testing was preserved in svPPA and visuospatial forward span in lvPPA. A principal component analysis regrouped all language and executive tests onto one factor for controls, but not for PPA and AD groups. Dysexecutive difficulties are observed at the onset of the disease in the three variants of PPA. This breakdown appears to be more important than what it was expected according to diagnostic criteria of Gorno-Tempini et al. (2011). SvPPA is the less dysexecutive variant. The interrelationship between language and EF is less important in patients than in controls. Although language deficits remain the core symptoms, executive dysfunction is observed at the early stages of PPAs, even though it has been described to remain relatively unaffected and is currently excluded from diagnostic criteria; the relationship between language and EF seem to weaken with the disease.

P26

Study of the Reelin effect in cellular models of Parkinson's disease

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Parkinson's disease (PD) is a critical neurodegenerative disease that significantly impacts worldwide health systems. PD has a genetic and environmental predisposition. The disease is composed of motor and non-motor symptoms, mainly triggered by the aggregation of alpha-synuclein that induces the degeneration of dopaminergic neurons in the Substantia Nigra. Moreover, it was found that mutations in the gene encoding for the retromer subunit Vps35 are found among late-onset forms of PD. Reelin is a secreted glycoprotein crucial for developing of the nervous system, especially the dopaminergic system. Reelin has been associated with neuronal survival in adult animals, synaptic plasticity, learning, and memory. We hypothesize that reelin has a neuroprotective effect in cellular models of Parkinson's disease, ameliorating the cellular damage. Methods: To induce the aggregation of alpha-synuclein, neuron-like MN9D, and SH-SY5Y cells were either treated with i) the pesticide rotenone or transfected with ii) the retromer mutant Vps35 D620N or with iii) the alpha-synuclein mutant A53T. In each case, cells were also treated with reelin or mock-conditioned medium. Results: rotenone-treated MN9D cells show higher neurite integrity after reelin treatment when compared to controls.

Based on this, we expect that reelin will also improve cell survival and neurite integrity after alpha-synuclein aggregation induced by Vps35 D620N or alpha-synuclein A53T. Conclusions: reelin has a neuroprotective effect in PD cellular models, reducing the cellular damage caused by the aggregation of alpha-synuclein. Perspectives: it is expected to evaluate how reelin performs its neuroprotective role.

P27

Modulation of Cricopharyngeal Quiescence During Swallowing in Healthy Normal Humans

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Neural control of swallowing is complex. The upper esophageal sphincter (UES) opens during swallowing due to bolus pressure, movement of the larynx, and quiescence of muscle activity. These muscle fibers integrate multiple modulatory signals, are tonically active during non-swallowing tasks, and completely relax during bolus transit. We have found that duration of UES opening is determined by bolus volume during single and this likely changes when drinking continuously. Yes, the contribution of muscle quiescence to duration of UES opening has not been measured. Here, we tested the hypotheses that duration of quiescence of muscle activity is affected by volume during single swallows and sequential swallows. We used intramuscular electromyography (EMG) and high-resolution manometry to evaluate muscle activity related to UES opening in 9 subjects (20- 43 years, 6 male). Good quality UES EMG data were obtained in 4 subjects, allowing for the evaluation of 179 swallows across 8 types of swallows: saliva, 2cc, 5cc, 10cc, 20cc, effortful 5cc effortful 10 cc, and sequential swallowing). There were no significant differences in duration of muscle quiescence as a function of bolus volume. We found shorter duration during sequential swallows, likely because there is continuous laryngeal/pharyngeal activity and swallow apnea without a 'reset' during this task. Importantly, timing of muscle quiescence within the UES during swallowing is a relatively preserved swallow reflex response. Further work will explore other swallowing parameters that adjust to this pre-programed timing of UES quiescence.

P28

Differential interspecies posttranscriptional regulation of Nkx2-1 expression in the adult mammalian subthalamic nucleus

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Subthalamic nucleus (STN) is a basal ganglia structure, clinically important as a target in the treatment for Parkinson's disease. Nkx2-1 is a transcription factor and, in the forebrain, a marker of neurons derived from medial ganglionic eminence (MGE) and hypothalamic basal plate. Nkx2-1 is widely expressed in the subcortical forebrain, especially in the hypothalamus and the basal ganglia such as globus pallidus and striatum. STN is the most underexplored basal ganglia structure and its basic cytochemistry is still not fully described, neither in rodent models, nor in humans. The aim of this research is to investigate the expression of Nkx2-1 in the adult mouse, rat, and human STN. We used immunofluorescence and RNAscope to determine the expression of both Nkx2-1 mRNA and protein on adult FFPE mouse, rat, and human coronal brain slices containing STN. We reveal that the Nkx2-1 mRNA is present in all species' STN, while Nkx2-1 protein is expressed only in the rat and human STN. The conclusion is that the Nkx2-1 mRNA is not translated into protein in the mouse STN, and this is a case of species-dependent posttranscriptional regulation of gene expression. The question remains what the functional significance of this finding is and why are the rat and human STN more similar in this parameter, when while looking at evolutionary relationships, this is expected from mouse and rat.

P29

Effects of cannabidiol on amphetamine and ketamine-induced behavioral profile

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Acute administration of d-amphetamine (d-amp) or ketamine (ket) in rats represents a behavioral model that simulates psychosis-like behavior. On the other hand, cannabidiol (CBD) is a non-addictive component of cannabis, known for its anti-psychotic potential. Studies have shown that CBD exerts a modulatory role on the behavioral profile induced by d-amp or ket but overall, these findings related to CBD antipsychotic effects on d-amp or ket-induced psychosis are inconsistent. Therefore, in this study we evaluated the role of CBD on psychosis-related behavioral indices induced by acute d-amp or ket administration. Adult male Sprague-Dawley rats were used to evaluate motor activity using the open field paradigm and sensorimotor gating using Prepulse inhibition (PPI). The rats treated with amp or ket exhibited a stimulated motor profile and disrupted PPI. Interestingly, CBD differentially modulated the ket-induced and d-amp-induced profile especially in terms of motor activity. Our findings provide novel insights regarding d-amp- and ket-induced psychosis-related behaviors, while enriching our understanding of CBD's pharmacological properties.

P30

Western diet may trigger Alzheimer's disease by insulin signaling impairment

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Western diet (WD) is a type of nourishment based on ultra-processed foods, rich in simple sugars and saturated fats. Long-term consumption of WD lead to disruption of insulin signaling and the development of insulin resistance. Insulin resistance is one of considered risk factors for Alzheimer's disease (AD). The aim of this study was to verify the hypothesis that WD can trigger the initiation and propagation of major neuropathological features of AD - amyloid-β (Aβ) plaques and neurofibrillary tangles. To this aim, male C57BL/6J mice were fed WD or standard diet (CTR) from 3 months of age and analyzed at 4-, 8-, 12-, and 16-months of age. The effects of WD on the levels of the insulin signaling pathway components: p-IRS-1(Ser616), p-Akt(473), p-GSK-3β(Ser9) and on AD biomarkers: p-Tau(Thr231) and APP/Aβ levels were analyzed in the entorhinal cortex and hippocampus. Entorhinal cortex proved to be more sensitive to WD-dependent insulin impairments than the hippocampus: analysis in the entorhinal cortex revealed an increase in p-IRS-1(Ser616) levels, indicating the development of insulin resistance under the WD. Moreover, a change in the localization of p-Tau(Thr231) in cellular compartments from fibers to nerve cell bodies indicated a progressive tauopathy. We also observed an age-dependent decrease in APP protein levels correlating with the appearance of Aβ peptides under the WD. Obtained results suggest that the WD diet, by inducing abnormalities in the brain insulin signaling, promotes the development of AD, and may be considered as a significant, modifiable AD trigger.

P31

Mild Traumatic Brain Injury increases mitochondrial calcium levels and upregulates mitochondrial Na^+/Ca^{2+} Exchanger

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Traumatic brain injury (TBI) is brain damage due to external forces, and repeated mild TBI is a known risk factor in developing neurodegenerative diseases. It is well established that glutamate levels increase after TBI, and our group has shown that NMDA receptors redistribute from synaptic to extrasynaptic sites. *In vitro* studies have indicated that calcium influx through extrasynaptic NMDA receptors leads to mitochondrial calcium overload and dysfunction. In this study, we wanted to evaluate mitochondrial calcium levels and handling capacity changes after mTBI. We used a model of repeated mTBI in mice consisting of the direct hit of a steel ball accelerated by gravity. After 24 h, we isolated hippocampal mitochondria, excluding presynaptic mitochondria contained in synaptosomes. We observed that mTBI induces a decrease in mitochondrial membrane potential and elevated intramitochondrial calcium levels, indicating mitochondrial damage. We also observed increased calcium retention capacity with any changes in calcium uptake at the conditions measured. At the protein level, we observed increased NCLX protein levels in total hippocampal lysates as well as in mitochondrial fractions. Thus, we believe that mTBI leads to mitochondrial calcium overload, but rapidly hippocampal cells upregulate NCLX as a compensatory mechanism. Our results suggest that NCLX could be upregulated in response to acute neuropathology, but it remains to be elucidated the transcriptional regulators

of NCLX that govern how mitochondria respond to acute injury in the hippocampus.

P32

Bacterial peptidoglycan-sensing molecules are expressed in the mouse hypothalamus during specific temporal windows of postnatal development

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Pattern-recognition receptors that recognize conserved microbial molecular signatures such as bacterial surface molecules (e.g., peptidoglycans, PGN) have emerged as potential regulators of gut microbiota-brain interactions. PGN-sensing molecules are highly expressed in various brain regions underlying cognitive functions, like prefrontal cortex and hippocampus, during postnatal life. Moreover, the absence of PGN-recognition protein 2 (Pglyrp2) leads to abnormal social development in mice. The hypothalamus is a key brain region involved in the regulation of social behavior, mainly through the production of the neuropeptides oxytocin (Oxt) and vasopressin (Avp). However, little is known about the expression of PGN-sensing molecules in the hypothalamus. Using expression-profiling techniques, we found that two families of PRRs that specifically detect PGN [i.e., PGN-recognition proteins (Pglyrp1-4) and NOD-like receptors (Nod1 and Nod2)] and the PGN transporter PepT1 were highly expressed in the hypothalamus during specific temporal windows of postnatal development in C57BL/6J mice. Specifically, the gene expression levels of Pglyrp2, Nod2 and PepT1 were significantly higher during the first few days of life, thereafter, decreasing to adult levels. In contrast, Nod1 and Pglyrp1 mRNA levels were significantly lower during the first postnatal week than in adults, after which they increased to peak levels at postnatal days 14 and 21, respectively. Interestingly, we did not find any significant sex differences in their expression levels. In addition, there was an age-dependent increase in Oxt and Avp mRNA levels. These findings suggest that the gut microbiota, via the central activation of PGN-sensing molecules, could influence the development and function of the hypothalamus.

P32

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P33

Inhibitory transcranial magnetic stimulation reduces side effects of L-Dopa in parkinsonian rats

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Dopamine replacement therapy with levodopa (L-Dopa) represents the mainstay of Parkinson's disease (PD) therapy. Oral pulsatile administration exerts an initial good effect in controlling motor aspects of the disease, but long-term chronic treatments are associated with wearing-off and the development of dyskinesia. In experimental models, dyskinetic behavior in response to L-Dopa is associated with an impairment in corticostriatal bidirectional synaptic plasticity with alterations of NMDA receptor subunits ratio and post-synaptic density composition. In the last decades, an inhibitory stimulation protocol such as the continuous Theta Burst Stimulation (cTBS) has been widely used as a possible treatment for both PD and hyperkinetic movement disorders. This study explored the therapeutic effects of a two-week chronic cTBS and L-Dopa co-treatment in a late symptomatic animal model of PD. To this aim, 6-OHDA-fully-lesioned rats were subjected to *in vivo* co-treatment, and synaptic depotentiation of spiny projection neurons of the dorsolateral striatum was investigated ex vivo with electrophysiological techniques. Abnormal Involuntary Movements was scored to test the antidyskinetic effect of cTBS. Flow cytometry analysis was performed to evaluate the levels of pro- and anti-inflammatory cytokines in the cerebrospinal fluid (CSF) of the treated animals. Electrophysiological recordings from corticostriatal slices in parkinsonian animals showed that co-treatment prevented NMDAR-dependent plastic abnormalities and reduced the incidence and the intensity of dyskinetic behaviors. In the CSF of animals treated with cTBS, pro-inflammatory cytokines were reduced, while anti-inflammatory Interleukin 10 was significantly increased. Our results provide a piece of evidence that noninvasive stimulation may protect corticostriatal synapses from the side effects of pharmacological PD therapy, confirming its anti-inflammatory potential.

P34

Cannabinoid-NMDA receptor heteromers as new therapeutic targets to combat Alzheimer's disease

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Both cannabinoid receptors CB1R and CB2R, are considered as target to afford neuroprotection, and N-methyl-D-aspartate (NMDA) ionotropic glutamate receptors, which are key in mediating excitatory neurotransmission, are expressed in both neurons and glia. As NMDA receptors are the target of current medication in Alzheimer's disease patients and with the aim of finding neuromodulators of their actions that could provide benefits in dementia, we hypothesized that cannabinoids could modulate NMDA function. In a heterologous system, we identified CB_1-NMDA and CB_2-NMDA complexes with a particular heteromer print consisting of impairment by cannabinoids of NMDA receptor function. The print was detected in activated primary microglia treated with lipopolysaccharide and interferon-α and also in neuronal primary cultures. On the one hand, CB_2R activation blunted NMDA receptor-mediated signaling in primary hippocampal neurons from $APP_{Sw/Ind}$ mice. Furthermore, imaging studies showed that in brain slices and in primary cells (microglia or neurons) from $APP_{Sw/Ind}$ mice, there was a marked overexpression of macromolecular CB_2-NMDA receptor complexes thus becoming a tool to modulate excessive glutamate input by cannabinoids. The results indicate a negative cross-talk in CB_1-NMDA and also CB_2-NMDA complexes signaling. Moreover, the expression of the CB_2-NMDA receptor heteromers increases in both microglia and neurons from the $APP_{Sw/Ind}$ transgenic mice, compared with levels in samples from age-matched control mice.

P35

Cognitive impairment and alterations in glutamatergic function of Fmr1 knock out rats, an animal model of the Fragile X Syndrome

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Fragile X Syndrome (FXS) the most common single gene cause of autism (ASD) and intellectual disabilities, caused by the lack or deficiency of the FMRP protein. This lack leads to dysregulation of synaptic plasticity and cognitive deficits. Glutamate, the main excitatory neurotransmitter, plays a vital role in cognitive and neuroplastic processes. In the present study we evaluated the cognitive profile of Fmr1KO and wildtype (WT) rats using specific behavioral paradigms while in parallel glutamate alterations were assessed in distinct brain regions. Adult male Fmr1 KO and WT littermates were used. Motor activity and habituation were evaluated using the open field paradigm. Indices of spatial and recognition memory were assessed using the Object Location task (OLT) and Object Recognition task (ORT). NMDA and AMPA subunits protein expression were evaluated in the prefrontal cortex (PFC) and Hippocampus (HIPP) using Western blot analyses. In parallel, glutamate tissue levels were estimated in the above-mentioned brain regions using HPLC-ED. KO rats were hyperactive while they exhibited impaired indices of behavioral habituation, spatial and recognition memory. In parallel, KO rats exhibited a differentiated glutamatergic profile with comparison to WT rats as reflected by the cortical increase and hippocampal decrease in NR2B subunit protein expression of KO rats as compared to WT counterparts. These alterations were enriched by specific alterations in glutamate tissue levels. Based on our findings, a stimulated motor profile and cognitive impairments along with glutamatergic region-specific alterations were found in Fmr1KO rats. These results indicate an impaired cognitive function and dysregulated plasticity-related processes in Fmr1KO rats, furthering our understanding of pathophysiologies potentially related to FXS and ASD.

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Changes of insulin signaling in transgenic mice model od Alzheimer disease is reversed by galactose treatment

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The Tg2576 model is one of the well characterized mouse models of Alzheimer disease (AD) and widely used to investigate the efficacy of new therapies. Literature data showed changes in the brain energy metabolism before amyloid β plaques burdened brain and galactose showed potential therapeutic effect in this model. Therefore, we aimed to investigate involvement of hippocampal (HPC) insulin signaling cascade proteins in development and progression of learning and memory deficit in transgenic Tg2576 model and therapeutic potential of oral galactose. Adult male B6; SJL-Tg(APPSWE)2576Kha transgenic (TG) mice and wild types (WT) aged 5 (5M) and 10 (10M) months were used in experiments. Oral galactose therapy was given to half of WT (WT+G) and half of TG (TG+G) group for 2 months (200mg/kg/day), while others received tap water ad libitum. Before sacrifice, behavioral tests were done to assess learning and memory deficit and the expression of insulin receptor substrate total and phosphorylated (IRS, pIRS), phosphatidylinositol 3-kinase (PI3K), cyclin-dependent kinase 5 (CDK5), tau and phosphorylated tau (ptau) was measured by Western blot in HPC. Data were analyzed by Kruskal-Wallis and Mann-Whitney *U*-test ($p < 0,05$). There were no changes in expression of PI3K and CDK5 in HPC in younger and older transgenic mouse model of AD. The decrement in p/t IRS and p/t tau ratio were seen only in older mice and the galactose treatment reversed it to the levels of control. The potential therapeutic impact of galactose seems to be connected to maintaining of energy balance and depend on the age and stage at which AD occurs.

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Glyphosate-induced alterations in the vasoactive intestinal peptide- like immunoreactive enteric nervous system neurons in the porcine ileum

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Vasoactive intestinal peptide (VIP) is an inhibitory neurotransmitter well-known for its neuroprotective properties. Glyphosate-based herbicides have been one of the most intensively used pollutants worldwide and food products containing glyphosate are an essential component of human and animal diets. The goal of present experiment was to evaluate the effect of glyphosate supplementation on the population of the VIP-like immunoreactive (LI) enteric neurons in the porcine ileum. 15 sexually immature gilts divided on 3 groups (5 pigs in each) were used: C- control, G1- receiving low dose of glyphosate (0.05 mg/kg bw/day), G2- receiving a high

dose of glyphosate (0.5 mg/kg/day). All pigs received capsules (empty or with low or high doses of glyphosate) for a period of 28 days. After this period all gilts were euthanized and fragments of ileum was collected and fixed. Frozen sections were then subjected to the procedure of double immunofluorescent staining.

Glyphosate supplementation increased the number of neurons showing immunoreactivity towards VIP. In both experimental groups (G1 and G2) enhanced population of VIP-positive enteric neurons were noted in each kind of intramural plexuses. In the myenteric plexus (MP) an increase from 12.63±0.71% to 20.38±1.54% in G1 group and to 32.93±1.43% in the G2 group was observed, in the outer submucous plexus (OSP) from 13.18±0.70% to 21.34±2.22% and to 40.43±1.10%, in the inner submucous plexus (ISP)) from 12.21±1.07% to 21.87±1.14% and 40.54±1.31%, respectively. Obtained results suggest the participation of VIP in neuronal protection and/or recovery processes within the GI tract in response to glyphosate intoxication.

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Altered Wnt/β-catenin signaling shows oncogenic effect and promotes astrocytoma progression

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Wnt signaling is a major cellular pathway responsible for development and cancer. Its transcriptional response is mediated through β-catenin and cofactors TCF/LEF. We investigated changes of key components of Wnt pathway in human astrocytomas of different malignancy grades. PCR/LOH and methylation-specific PCR were used for genetic and epigenetic analyses while immunohistochemistry and semi-quantitative score for protein expressions. All positive signaling regulators – β-catenin, TCF1, LEF1 and GSK3β, showed upregulation. The immunostaining revealed the prevalence of β-catenin's active unphosphorylated form ($rs = 0.634$, $p < 0.001$) and TCF1 and LEF1 expression significantly increased with grades ($P = 0.001$). A positive correlation was established between expressions of DVL3 and both TCF1 ($P = 0.020$) and LEF1 ($P = 0.006$) suggesting their joint involvement in malignant progression. The negative regulators of the pathway – APC, AXIN1, DKK1, DKK3, SFRP1, SFRP3 and SFRP4, were mainly downregulated. AXIN1 was downregulated in 31% of glioblastomas and 22% of astrocytomas. Changes of APC gene were found in 44.44% of samples which also showed higher H-score for β-catenin ($P = 0.038$). Additionally, promoter methylation of DKK1, DKK3, SFRP1, SFRP4 and GSK3β genes was found in 38%, 43%, 32%, 16% and 18% of samples, respectively. SFRP1 gene was significantly epigenetically silenced in glioblastomas ($P = 0.042$) compared to lower grades. However, both SFRP3 and SFRP4 cytoplasmic expressions increased in higher grades. A positive correlation between methylated DKK3 and the expression of active pGSK3β-Y216 ($P = 0.011$) was also established. In conclusion, the results of this study indicate the activation of the pathway in astrocytoma and emphasize the importance of methylation for the regulation of Wnt signaling.

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Cannabinoids in absence epilepsy: a health risk, a new seizure treatment, or both?

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The use of medical/recreational marijuana and its legal market size are on the rise worldwide. Medical marijuana has potential benefits for different diseases, but the lack of biomedical research and its popularity based on anecdotal evidence poses a risk to society. For instance, the medical use of cannabis and derived cannabinoids show promising results in severe paediatric epilepsies. However, cannabinoids acting on the endogenous cannabinoid system can aggravate different types of seizures. Here we have studied how the cannabinoids affect absence seizures (ASs), the most common childhood epilepsy. The failure of first and second monotherapy with anti-absence drugs in 30% of children with ASs and the high rate of comorbidity, including attention and learning/memory impairments (which persist in seizure-free children), demand novel therapeutic approaches and the cannabinoid system may be a promising target. Using *in vivo* techniques in freely moving Genetic Absence Epilepsy Rats from Strasbourg, an absence seizure model with strong face-, construct- and content-

validity, we have investigated the effect of endogenous and exogenous cannabinoids on these non-convulsive seizures. WIN55 (1,3, 5 mg/kg), a synthetic cannabinoid, dose-dependently exacerbated ASs, an effect that is blocked by pre-administration of AM251 (2mg/kg), an inverse agonist at the CB1 cannabinoid receptor. In contrast, cannabidiol (CBD) at 50, 100, 200 mg/kg had no effect on GAERS ASs when injected ip in both acute and subchronic (7 days) treatments. The block of FAHH (Fatty acid amide hydrolase), the catabolic enzyme of the endocannabinoid anandamide, by PF-04457845 did not affect ASs when administered ip (1 mg/kg) both acutely and subchronically (7 days) but decreased ASs when injected directly(30ng) in the ventrobasal thalamus, one of the key brain regions for AS expression. Thus, our preliminary data indicate a complex role of exogenous and endocannabinoids in controlling ASs. Since endocannabinoid modulators, with an excellent safety record in humans, are already available, our data may identify new targets that in the medium-term lead to a novel treatment for ASs.

P40

Adaptor Protein-mediated Release Site Clearance during Compensatory Endocytosis

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Synaptic vesicles (SVs) are released at active zones (AZ), and SV constituents are retrieved by compensatory endocytosis at distinct sites outside the AZ, the peri-active zone (periAZ). For repeated neurotransmission sorting of SV components from the AZ to the periAZ, so-called release site clearance (RSC), is necessary. Although various mechanisms of RSC have been proposed, involving passive diffusion and active chaperoning of SV components, the small size of vertebrate synaptic boutons near the diffraction limit has hampered direct observation of the spatio-temporal dynamics of RSC. We used 'xenapses', purely presynaptic boutons directly formed on micropatterned and functionalized coverslips, to overcome this limitation. Xenapses provide an advantage over conventional cultures owing to their size, TIRF amenability and the absence of apposed post-synapses, rendering them better suited for super-resolution microscopy. The presence of distinct AZ and periAZ in xenapses was exploited to study sorting of one of the most abundant SV components, Synaptobrevin2 (Syb2) by its cargo-specific adaptor, AP180. Combining super-resolution, TIR-FRAP and live TIRF microscopy, we revealed a population of AP180 stably enriched at the periAZ at rest. Upon stimulation, free AP180 from the cytosol translocates first to the AZ, and later along with exocytosed Syb2 to the periAZ. This AP180-mediated RSC is abolished in AP180 mutants with reduced affinity for Syb2. These data confirm previous biochemical data and corroborate the notion of AP180 as an important RSC factor. Our xenaptic system provides a platform for visualizing molecular events during RSC and exo-endocytosis coupling.

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Effects Of Environmental Enrichment On Modulation Of Behavior And Hippocampal Neuroplasticity In Huntington Disease Model Yac128

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Huntington's disease (HD) is a neurodegenerative genetic disorder characterized by cognitive, motor, and psychiatric disturbance. Evidence has suggested that some of these deficits may be related to hippocampal dysfunction. We used the YAC128 mouse model of HD to perform a temporal characterization of behavioral dysfunction and to seek the effects of environmental enrichment (EE). Male and female wild-type (WT) and YAC128 mice were evaluated at early (3-4 months) and late (11-13 months) symptomatic phases for mood, motor and cognitive alterations. Another cohort of animals was exposed to EE for 60 days (2-4 months), after that, behavioral tests were performed. Hippocampal dentate gyrus cell proliferation and neuronal differentiation were evaluated by immunohistochemistry. Early and late symptomatic YAC128 mice exhibited depressive-like behavior and motor deficits compared with their WT littermates. Both WT and YAC128 mice, at 12 months of age, showed motor deficits compared to their respective younger WT and YAC128 counterparts. In addition, YAC128 mice exhibited cognitive deficits in the late symptomatic stage. Exposure to EE in the early symptomatic stage reversed the YAC128's depressive-like behavior to WT's level and improved cognitive YAC128 performance compared to YAC128 mice in the control environment. EE increased cell proliferation in the WT and neuronal differentiation in WT and YAC128 mice and decreased cell proliferation in the YAC128 mice. YAC128 mice presented behavioral changes over time. EE could improve HD symptoms and modulate hippocampal neurogenesis. EE may play a potential therapeutic role in the treatment of HD.

P42

Mapping of neuroinflammation-induced hypoxia in the spinal cord using optoacoustic imaging

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The principal feature of multiple sclerosis (MS) is an overactive immune system; however, recent studies suggest that other factors such as metabolic changes and oxygen deficiency in the CNS could play important roles. In our present study, we investigated the changes in oxygenation and analyzed the vascular perfusion of the spinal cord in the experimental autoimmune encephalomyelitis (EAE) rodent model of MS. We performed multispectral optoacoustic tomography (MSOT) of the lumbar spinal cord of EAE mice to measure oxygenation in real time. In addition, mice were transcardially perfused with lectin to label the vasculature and their spinal columns were optically cleared, followed by light sheet fluorescence microscopy (LSFM). To analyze the angioarchitecture of the intact spinal cord, we used VesSAP, a novel deep learning-based framework. In EAE mice, the spinal cord had lower oxygen saturation and hemoglobin concentration compared to healthy mice, indicating compromised perfusion of the spine. Oxygen administration reversed hypoxia in the spinal cord of EAE mice in general, while interestingly the ventral region remained hypoxic. Additionally, we report a reduction in length and complexity of the perfused vascular network in EAE. Our results point at a potential occlusion of part of the vasculature in the lower spinal cord, which hinders perfusion and could cause the decrease in blood flow and the hypoxia in the CNS that we have observed in EAE. We also introduce optoacoustic imaging as a tractable technique with the potential to further decipher the role of hypoxia in EAE and to monitor it in MS patients.

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Evolutionary novel genes in neurodevelopmental disorders

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Neurodevelopmental disorders (NDDs) are an umbrella term describing various central nervous system development conditions. Here we present 26-year-old male and 51-year-old female patients demonstrating typical features of NDDs, including undeveloped speech, intellectual disability, epilepsy, and behavioral disorder associated with distinct facial characteristics. Custom chromosomal microarray in both cases detected a copy number loss in chromosome 15q13.2 encompassing the *ARHGAP11B* gene. *ARHGAP11B* gene belongs to a group of genes that evolved specifically in the human lineage, and recent findings suggest it has a crucial function in the evolutionary expansion of the neocortex. To elucidate the *ARHGAP11B* prenatal spatiotemporal expression pattern and its potential role in neurogenetic events during human corticogenesis, we performed immunofluorescence (IF) of diverse neuronal markers on the midfetal postmortem human brain tissue. Our results showed *ARHGAP11B* immunoreactive neurons in the marginal zone, cortical plate, and the subplate of the midfetal cortex, as well as its colocalization with markers of projecting neurons placed in the deep cortical layers. Our findings support a need for the *ARHGAP11B* gene to be investigated as a substantial risk gene underlying NDDs. *Acknowledgments: This work was supported in parts by the Croatian Ministry of Science Education and Sport (LB); Business Innovation Croatian Agency – Croatian Institute for Technology BICRO-HIT (FB). The research was co-financed by the Scientific Centre of Excellence for Basic, Clinical, and Translational Neuroscience.*

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Characterization of motor function in mice: Meta-analysis on CatWalk XT system output

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Gait is an important behavior to evaluate when studying mouse models of motor dysfunction (e.g. Parkinson's disease), pain rodent models (e.g. Sciatic nerve injury), and general central nervous system dysfunction mouse models (e.g. Traumatic brain injury). In the last two decades, automated systems were developed with specialized software that measure hundreds of gait parameters simultaneously, adding new types of information (e.g. temporal) over the traditional ink and paper method, while reducing the possibility of human error. However, when investigating hundreds of parameters importance and relevance of each parameter are not always clear. The Noldus CatWalk XT Automated Gait Analysis system has been commercially available since 2006, with over 350 systems installed worldwide, used in over 2000 publications, making the CatWalk one of the most widely implemented automated gait analysis systems today. The result is large amounts of information from a large number of mouse models, created in the same basic system. There is great potential in combining information from multiple studies with animals from different genetic backgrounds and disease models. The goal is to produce a single gait analysis database of different models.

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Interactions between trait sensitivity to performance feedback and compulsive alcohol drinking in rats

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In this study, we investigated the theoretical claim that sensitivity to negative and positive performance feedback, measured as a stable and enduring cognitive trait, can interact with vulnerability to the development of compulsive alcohol drinking in rats. The animals were trained and tested in a series of 10 probabilistic reversal learning sessions, and based on the results of this screening, each rat was classified as insensitive or sensitive to negative and positive feedback. Subsequently, the animals have been tested in the "intermittent alcohol access two-bottle choice" and in the "instrumental second-order chained schedule of the alcohol reinforcement" tasks. Finally, we measured how trait sensitivity to feedback affects the extinction of alcohol-seeking and the reinstatement of this behavior following a period of abstinence. The results of our study demonstrated, for the first time, that trait sensitivity to feedback might determine the vulnerability of rats to the development of compulsive alcohol seeking and the propensity to extinguish alcohol-seeking behaviors following termination of alcohol availability. They also suggest that this trait could be considered as a cognitive biomarker of vulnerability to the development of addiction.

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Use of medical cannabis by patients with fibromyalgia in Malta after cannabis legalization

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Fibromyalgia is a chronic health condition that is characterized by widespread musculoskeletal pain commonly comorbid with other symptoms such as mood disturbance, insomnia, fatigue, and cognitive problems. Due to the multi-faceted nature of this condition, treatment of Fibromyalgia has had limited success, and this underlines a need for alternative therapies. The cannabis plant has been used for healing for millennia, and recently more evidence is indicating a role for cannabis in modern medicine Past studies show that Fibromyalgia patients with a number of comorbidities respond more favorably to central-acting therapies, such as cannabis. In this study, 15 Fibromyalgia patients were asked to self-report the severity of their Fibromyalgia and co-morbid symptoms before, 1 month and 3 months after starting medical cannabis therapy. Seven validated questionnaires were used to classify the patients' condition within the following domains: pain intensity, sleep quality, anxiety levels, fatigue, pain self-efficacy, quality of life and functionality. The patients were also asked to characterize their medical cannabis use, and finally questioned on societal attitudes towards medical cannabis use and its effect on patients and their families, notably after the recent legalization of recreational cannabis in Malta. The results show a significant global improvement within the timeframe studied with minimal adverse effects, indicating that medical cannabis therapy shows promise in the treatment of Fibromyalgia. Nevertheless, as this was a self-reported study, more work in this field is needed to shed light on the suitability of this novel therapy.

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Neuroprotective effect of the nutraceutical Dehydrozingerone and its symmetric Dimer in a Drosophila model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the selective loss of dopaminergic neurons and motor impairment. Mutations in Leucine-rich repeat kinase 2 (LRRK2) locus, contributes to genetic forms of PD. The fruit fly *Drosophila melanogaster* (Dm) carrying the mutation LRRK2 loss-of-function, is an *in vivo* model of PD that develops motor impairment and is a valid tool to test novel therapeutic approaches to the disease. Dehydrozingerone (DHZ), is a compound with anti-inflammatory and antioxidant properties. For these reasons could have a potential to act on neurodegenerative disorders. We tested the DHZ and its Dimer (DHZ-DIM) in the LRRK2-Dm PD model, by assessing changes in climbing behavior and in brain dopaminergic neurons. Mutant and wild type flies received DHZ and its Dimer at the dose of 0.5 and 1mM, for 14 and 21 days of treatment. Both molecules only at the dose of 1mM improved climbing behavior at 14 days with respect to controls whereas after 21 days of treatment a recovery of the motor disability was found only with DHZ-DIM. Both compounds at 1 mM significantly prevented the loss of dopaminergic neurons in all posterior clusters involved in locomotion and arousal, at 14 of treatment whereas, at 21 days, a significant prevention of dopaminergic neuron loss was observed only with the DHZ-DIM treatment. Our data indicate that the DHZ-DIM exert a more potent neuroprotective effect with respect to the monomer in the PD model, prompting further investigation of these compounds in rodent models of PD.

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Effect of pharmacological and environmental interventions on pathological anxiety and associated neuro-inflammatory dysbalance

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Neuroinflammation is discussed to play a role in specific subgroups of different psychiatric disorders. We have previously shown that a mouse model of trait-anxiety (HAB) displays enhanced microglial-density and phagocytic-activity in key regions of anxiety-circuits in comparison to normal anxiety controls (NAB). Using minocycline we now provided proof of principle evidence that reducing microglia activation within the dentate gyrus (DG) attenuated enhanced-anxiety in HABs. In addition to this pharmacological intervention, we investigated the effect of "positive-stimuli", which have the advantage of exerting no or negligible side-effects, and indeed have been shown to attenuate inflammation in humans. We aimed to reveal whether environmental-enrichment (EE) as a "positive intervention" would be sufficient to modulate inflammation in high anxiety HABs. We now show that EE can also attenuate enhanced-anxiety when presented during adulthood, complimenting our previous observations of such EE effects in early development. Using immunohistochemistry, we found that EE-induced anxiolysis was associated with attenuation of enhanced microglial-density in the DG and medial-prefrontal cortex. Furthermore, EE also reduced phagocytic-activity of microglia within the DG. Hence, successful attenuation of trait-anxiety by EE was associated with normalization of part of the identified neuro-inflammatory imbalances. Together with the pharmacological findings, these results indicate that beneficial environmental cues can partly mimic anti-inflammatory effects of minocycline in individuals predisposed to trait-anxiety. Recently, we also found sex differences in microglial-expression, microglial-morphology as well as synaptic-pruning pathways in the DG of HABs compared to NABs and we are currently investigating whether and how these contribute to the EE-induced anxiolytic-like effect. Taken together, pharmacological or environmental microglial inhibition could serve as useful treatment strategy in hyperanxious individuals with altered neuroinflammatory system.

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Analysis of ASC protein levels in CSF and plasma of mild cognitive impairment and Alzheimer's disease subjects

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Many recent studies confirmed importance of the NLRP3 and NLRP1 inflammasome activation in the pathogenesis of Alzheimer's disease (AD). Apoptosis-associated speck-like protein (ASC) has a key role in assembling inflammasome complex as it couples danger-signal sensors and procaspase-1. We aimed to compare CSF and plasma concentrations of ASC protein in AD, mild cognitive impairment (MCI), and cognitively normal controls, and to correlate them with subjects' age, Mini-Mental State Examination (MMSE) score, and core CSF biomarkers of AD (levels of Aβ1-42, total tau [t-tau], and tau phosphorylated at epitope 181 [$p-tau181$]). Concentrations of ASC were measured in 127 AD, 78 MCI, and 39 control CSF samples and 82 AD, 33 MCI, and 9 control plasma samples using ELISA. Compared to controls, the ASC levels in CSF were significantly higher in the AD and MCI group, whereas differences in plasma levels did not reach significance. CSF levels of ASC protein also positively correlated with the age of the subjects and the concentrations of t-tau and p-tau181. Therefore, we concluded that the ASC level in CSF, but not in plasma, could be a useful biomarker of both tau pathology and inflammasome activation in AD.

P50

T-pattern analysis and transition matrices for the study of the behavioral abnormalities of a mouse model of Tourette's syndrome

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The transgenic D1CT-7 mouse is one of the best-characterized animal models of Tourette's syndrome (TS), exhibiting spontaneous tic, like Head-Body Twitches (HBT) and deficits in sensorimotor gating. This study is aimed at evaluating the behavioral dynamics of these mutants and their potential relevance to TS. The behavior of D1CT-7 and Wild Type littermates was firstly assessed by considering frequencies and durations. To detect recurrent real-time behavioral sequences, the multivariate T-pattern analysis was employed. Analyses of transition probabilities among behaviors further provided an overall picture of the behavioral dynamics. T-patterns and transition matrices revealed in D1CT-7 mice clearcut hyperactivity compared to controls, with a lower behavioral organization and a marked shift from cautious sniffing toward locomotion. Moreover, the behavioral patterns of the transgenic mice were pervasively disturbed by intrusive tic, like HBT leading to a marked fragmentation of the behavior. Novel exposure to the open field test provoked a transient inhibitory control over the disrupting phenotype. The results of this study show that the D1CT-7 mouse model is subjected to a behavioral fragmentation, with repercussions going beyond the simple tic, like phenomenon. These phenotypes are strikingly akin to behavioral problems observed in patients with TS and further validate the power of this model in summarizing pivotal behavioral aspects of TS.

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Moderate perinatal hypoxia causes permanent reorganization of the hippocampal perineuronal nets and interneurons network in rat

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The study investigates the possibility, extent, and persistence of structural or connectivity changes in the rat hippocampus after moderate perinatal hypoxia. The distribution, qualitative and quantitative changes in parvalbumin-positive neurons (PV) and the perineuronal nets (PNN) were researched. For this purpose, 18 Wistar Han (RccHan: WIST) rat pups were randomly subjected to hypoxia (partial pressure of oxygen-pO_2 73 mmHg; atmosphere pressure-p^{ATM} 350 mmHg) or normoxia (pO_2

159 mmHg; p^{ATM} 760 mmHg) for two hours at the first postnatal day. At the age of 3.5 months, the rats were sacrificed, their brains were isolated and used for immunohistochemistry and analysis of PV and PNN of the hippocampi (bregma: levels -2.92 mm; -3.36 mm; -4.56 mm) using OlympusBX60 and Neurolucida 10 software. Qualitative analysis revealed differences in the co-expression pattern of PNNs' constituents (aggrecan, versican, and neurocan) and differences in PNN and PV areal/layer distribution between hypoxia and normoxia groups. Quantitative analysis revealed a significantly higher density of PNN and PV, especially in the CA1 area of the hippocampus of mature animals subjected perinatally to hypoxia. These results align with the changes in behavior such as significant hyperactivity and a slower pace of learning in rats after perinatal hypoxia, published previously by our group. Further research is needed to disclose the underlying sequence of molecular events and the injury-plasticity relations that lead to the permanent hippocampal and behavioral alteration in rats after moderate perinatal hypoxia.

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Determination of genotype distributions of ApoE among Slovenian patients with Alzheimer's disease, mild cognitive impairment and subjective cognitive decline

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Brain diseases represent the most important health problem in European societies. In Slovenia it represents 7% of the gross domestic product. Among neurodegenerative disorders Alzheimer's disease (AD) is the most common. Clinical diagnosis of (probable) AD is established through a combination of clinical symptoms, cognitive screening tests (MMSE, MoCA), detailed neuropsychological testing and imaging techniques. Given the rapid progress in the field of AD biomarkers and correlation between the genetic code and disease, it would make sense to develop tests that would base on the investigation of polymorphisms of selected genes disease, and can provide diagnosis before the full symptoms develop. The only gene, currently used for predicting the possibility of the development of AD, is the apolipoprotein E (ApoE). The carriers of homozygous E4/E4 genotype have a 5-fold higher risk of developing the disease. Since the ApoE genotype distributions differ among different ethnic groups, we analyzed them for the first time on Slovenian patients with AD, mild cognitive impairment (MCI), subjective cognitive decline (SCD) subjects, and controls. Analysis of over 600 subjects showed the E4/E4 genotype is the most frequent in the AD patients (14%), and was statistically different to MCI (1.8%; $P<4.4x10-9$), while it was completely absent in the SCD and control group. Statistical analyses to associate particular ApoE genotype and biochemical blood markers with the clinical diagnosis are in progress. The results will provide a new insight in clinical diagnostic value of ApoE genotype for AD in the Slovenian population.

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Evaluation of procognitive activity of mixed administration of NO releasers and muscarinic receptor activators, VU0357017 and VU0152100, in the novel object recognition test

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The most treatment-resistant domain of schizophrenia symptoms are cognitive disturbances. NO donors may induce procognitive effects in animal models, however their action is burdened with variety of adverse effects. On the other hand muscarinic receptors M1 and M4 were shown to play a role in learning and memory processes, and their activators, VU0357017 and VU0152100 reversed cognitive deficits induced by the administration of tool compounds (scopolamine or MK-801). The aim of the present studies was to investigate if muscarinic receptor activators can enhance the activity of NO releasers. Slow and fast NO releasers, DETANoNoate and spermineNoNoate were used. The compounds were administered together with VU0357017 or VU0152100 and the activity of the combinations was investigated in the novel object recognition test. The following pairs of ligands were investigated:DETANoNoate+VU0357017 or VU0152100, spermineNoNoate + VU0357017 or VU0152100. The drugs were administered at the following schedule: combination of active doses, combinations of inactive doses and combinations of intermediate doses. Our results indicate that the administration of NoNoates in combinations may have synergistic effects as the combined administration of the compounds in subeffective doses or intermediate doses

induced the same effects as that observed for each compound administered alone at the top dose. Therefore, the treatment with the subeffective doses of both compounds together could improve cognitive decline associated with mental disorders and may be less burdened with the risk to induce adverse effects than the treatment with the high doses of drugs.

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Characterization of human Tau protein expressed in yeast

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Alzheimer's disease (AD) is a common neurodegenerative disorder associated with accumulation of Tau protein aggregates in neurons of the affected brain regions and the consequent neuronal death. Despite a vast number of studies, the causes of tau protein aggregation and toxicity are still largely unclear. Considering that the main risk factor for the onset of AD is aging, and that the ability of a cell to maintain protein homeostasis decreases with aging, impaired protein quality control pathways are considered a possible factor in the development of AD. In order to take advantage of the power of yeast genetics in identifying modifiers of Tau protein aggregation, we expressed human Tau protein in a cell model, yeast *Saccharomyces cerevisiae*. To study the factors affecting Tau oligomerization, which is considered an early step in Tau pathology, we used luminescent reporter NanoBiT in which protein-protein interaction results in the complementation of the luciferase NanoLuc. We expressed Tau-NanoBiT fusion constructs in a wild-type strain, mutants with impaired protein quality control pathways and mutants reported to have increased Tau phosphorylation and increased levels of sarkosyl-insoluble Tau, and measured reporter activation. Further, we examined Tau intracellular localization by fusing it with a fluorescent protein and tested how this is affected by chronological aging.

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