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# 4 Basal ganglia, drug addiction and the neuroscience of maladaptive habits

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## Abstract

*The mammalian brain has developed memory systems mediating rigid, yet evolutionarily adaptive patterns of responding to invariant environmental stimuli and internal demands. Such memory systems promote the recall of specific response templates and the execution of inflexible actions to liberate buffering capacity for performing conscious, explicit cognitive processing. The dopamine-innervated neostriatum is central to the ability to learn such consistent associations between stimuli and actions implicitly. Controlled by their outcome when initially learned, actions succumb through iteration*

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*to the influence of triggering stimuli and progressively detach themselves from the pleasurable results originally produced, thereby becoming pervasive habits. This might be the case for drug-seeking and drug-taking behaviours, actions learned in part through dopamine-dependent drug-induced reinforcement when the drug is first experienced. With extended drug use, however, drug-seeking actions might become conditioned to, and triggered by, specific exteroceptive stimuli and/or affective states, gradually becoming irrepressible forms of responding. We will review neuroanatomical, neuropharmacological and behavioural evidence suggesting that the basal ganglia play a prominent role in the shaping of drug addiction, here regarded as a pathological modification of otherwise adaptive habit learning systems mediated by the basal ganglia.*

# Introduction

The basal ganglia have long been recognised as central to the pathophysiology of movement disorders. The early discoveries at the turn of the 20$^{th}$ century revealing motor disturbances in patients with damage to the basal ganglia [1,2], and many later breakthroughs, were the key in the formation of this opinion. Disorders such as Parkinson's disease –a progressive neurodegenerative disorder caused by gradual loss of dopamine input to the striatum– and Tourette syndrome –a neurodegenerative condition involving reduced caudate volumes in both children and adults– are associated with basal ganglia abnormalities. Such pathologies compromise the coherent activity of the basal ganglia and allied thalamocortical loop pathways and impair motor function as a result. The basal ganglia were first considered as a simple funnel system through which cortically born information accessed brainstem motor nuclei. This perspective was based on the notion that there was convergence of information from distinct cortical areas upon basal ganglia structures, which, in turn, resulted in unitary output, composed of mixed functional modalities. However, modern theories regard the basal ganglia as a complex multi-channel system through which not only motor but also sensory and limbic information flows, becomes modified and is subsequently redistributed to the neocortex by way of thalamocortical afferents [3,4]. Thus, rather than a funnel, the striatum and associated basal ganglia nuclei began to be considered as "a multilaned throughway for separate streams of influence..." [5]. The striatum, the main recipient of inputs from the cortical mantle, appears to have multiple representations at the level of the pallidum and the substantia nigra. The three functional modalities (sensorimotor, associative and limbic) of the striatum are processed through segregated channels maintaining the specific topography of the corticostriate projection. This basic organisational scheme seems to apply to the various re-entrant, parallel circuits linking cortex, basal ganglia and

thalamus [4,6,7]. Such novel conceptualization of the basal ganglia, derived from fine grain neuroanatomical and physiological analysis, fuelled speculation on the potential role of the basal ganglia in functions other than motor processing, including learning, memory and motivated behaviour.

In addition to the anatomical analysis of the basal ganglia circuitry, pioneering experimental studies on the phenomenology of human basal ganglia pathology and behavioural evidence accrued in experimental animals has documented a wide implication for the basal ganglia in adaptive non-motor behaviour. Studies in animals with lesions to the striatum (neostriatum in the rat and caudate and putamen nuclei in nonhuman primates) demonstrated impairments in non-motor tasks including alternation performance, resistance to extinction and conditioned avoidance [e.g. 8,9,10,11,12,13]. Since those first studies, experimental evidence has been gathered from a variety of sources including among others electrophysiological recordings, lesion and inactivation studies, and neuropsychological and neuroimaging data supporting the basal ganglia as a key substrate for implicit memory function, a cognitive adaptation different but not totally alien from the memory systems residing in the medial temporal lobe.

Drug addiction is a multi-faceted process that involves the acquisition of drug-seeking and drug-taking behaviours, their maintenance, and their eventual extinction and reinstatement. Drug addiction is a disease of the brain characterized by difficulties in limiting drug intake, patterned and sequential compulsive behaviours including recurring thoughts and actions, strong resistance to extinction in the face of declarative knowledge of the adverse consequences for the addict's own health, and relapse. Drugs are notorious for their ability to modify the activity of dopamine-modulated systems implicated in learning and memory function. We propose in the following account that drug addiction is a special case of maladaptive learning mediated by the basal ganglia and we will review experimental evidence in animals and humans to support this hypothesis.

# Overview of the neuroanatomy of the neostriatum and allied thalamocortical pathways

## General anatomical considerations

The concept of basal ganglia refers to a number of intimately interrelated subcortical structures, including the striatum, the pallidum, the subthalamic nucleus and the midbrain dopamine (DA) system as main components. The chief input structure of the basal ganglia is the striatum, which receives massive projections from the entire cortical mantle and from monoaminergic neurotransmitter systems in the midbrain.

First, representing the input stage of the system, the striatum displays a complex modular ordering of afferent/efferent projections and neurochemical

systems, reflected in a multilevel functional organisation [14,15]. The first organisational level is determined by the pattern of striatal dopaminergic projections that originate in the mesencephalon. There is at least a crude topographical relationship between the area of origin of the dopaminergic projection and the region innervated in the striatum. A second level of organisation in the striatum is determined by the orderly pattern of termination of the corticostriate projections. There is a clear topographical delineation such that restricted areas of the cortex project to distinct territories in the striatum. A third organisational principle is imposed by the neurochemical compartmental organisation of the striatum into patch and matrix compartments. Last, the fourth level of functional ordering is determined by the segregation of striatal outputs to the substantia nigra/pallidal complex (substantia nigra/entopeduncular complex in the rat) and to the external segment of the globus pallidus through direct and indirect striatofugal pathways.

Two crucial aspects of the organisation of the corticostriate projections is that they are somatotopically organised and topographically distributed [16], such that there is a point-to-point transfer of information between the cortex and the striatum and that specific portions of the cortex project to circumscribed striatal zones with relatively little overlap from adjacent, generally interconnected cortical areas. The segregated pattern of projection of the corticostriate pathways led to a tripartite subdivision of the striatum, namely the sensorimotor, the associative and the limbic territories[ 17,18]. The *sensorimotor territory* includes the postcommissural dorsolateral neostriatum and receives projections from primary motor and sensorimotor cortices. The *associative territory* comprises large portions of the dorsal neostriatum with the exception of its dorsolateral aspect and receives innervation from association cortices in the frontal, temporal and parietal lobes. Last, the *limbic territory* includes the nucleus accumbens, the olfactory tubercle, and the most ventral and anterior parts of the neostriatum and receives strong input from limbic and paralimbic cortices, amygdala and hippocampus. In former subdivisions of the striatum, emphasis had already been placed on the classical distinction between a ventromedial limbic and dorsolateral non-limbic domain [19,20]. Such anatomical observations strongly suggested that different sectors of the striatum could be contributing differentially to behaviour, on the one hand, and that the functions of the striatum could be more complex than previously envisaged, on the other.

## The patch-matrix organization

The pattern of distribution of neurotransmitters and neuropeptides reflects the complexity and heterogeneity of the striatum. Neurons in the striatum are segregated into patch and matrix compartments. This patch-matrix

organisation was initially demonstrated with μ-opiate receptor binding [21], acetylcholinesterase histochemistry [22], and subsequently with other neurochemical markers, including those for neurotransmitter systems like dopamine, serotonin and GABA, and those for neuropeptides such as enkephalin, substance P, somatostatin and dynorphin. The patch-matrix organisation is particularly evident in the dorsal striatum. However, the patches and the matrix, as they are defined in the dorsal striatum, have not been recognised as a distinct feature of the ventral striatum [23]. The patches, or striosomes [22], are characterised by more detectable levels of D1 receptors, M1 cholinergic receptors, dynorphin and neurotensin, whereas the extrastriosomal matrix is richer in dopamine D2 receptor binding and dopamine uptake sites, choline uptake sites, acetylcholinesterase, enkephalin and somatostatin [24]. One of the most reliable markers of patches and matrix compartments in the neostriatum is the labelling of patches with dense opiate-receptor binding. These are aligned with patches of weak calcium-binding protein (calbindin-$D_{28kDa}$) immunoreactivity. Conversely, parts of neostriatum with weak naloxone binding and strong calbindin immunoreactivity are regarded as matrix. The patch-matrix organisation of the striatum is intimately related not only to the specific pattern of termination of striatal afferents, but also to the ordering of striatal output pathways. Virtually all afferent systems of the striatum adhere to the patch-matrix organisation, a rule by which the striatum is able to channel these inputs into specific neurochemical environments. Initially, it became apparent that prefrontal and limbic cortices display a preference for patches, whereas sensorimotor, parietal and occipital cortices show a tendency to innervate the matrix compartment. However, the distribution of the inputs from cortical areas to the striatum is not strictly categorised into patch and matrix. For example, it was shown that corticostriate projections from the frontal insular cortex preferentially innervate the patches dorsally and the matrix ventrally [25], suggesting a systematic dorso-ventral realignment of cortical inputs. Moreover, the distribution of cortical inputs to the striatum was subsequently proposed to depend upon the lamina of origin in the cortex such that corticostriate neurons in deep, infragranular layers of the cortex projected to the patches and those in superficial, supragranular layers innervated the matrix compartment [14,15]. Adding considerable complexity, the appreciation that some corticostriate projections have a patchy distribution in the matrix led to the term “matrisomes” [24], suggesting a modular organisation of the matrix compartment itself. The neostriatum also receives extensive input from the thalamus. This input mainly originates in the intralaminar and the midline nuclei, and from specific relay nuclei, such as the ventral anterior, ventral lateral and pulvinar nuclei [see 26]. Thalamostriatal input, as well as mesencephalic dopaminergic afferents, conform to the patch-matrix organisation of the striatum, such that the patch compartment that receives

input from deep cortical laminae is avoided by midline and intralaminar thalamic nuclei and is innervated by the most ventral areas of the substantia nigra. On the contrary, the portions of matrix compartment receiving input from the superficial layers of the cortex are targeted by intralaminar and midline thalamic nuclei and by dopamine cell groups in the ventral tegmental area, the retrorubral area and the dorsal substantia nigra. This dissociation suggests the presence of different mesostriatal and thalamostriatal neurochemical systems in the patch and matrix compartments of the striatum.

The functional significance of the patch-matrix organisation of the striatum is not completely understood. The clustered, compartmental arrangement of neurons in the striatum was conceptualised as a channelling mechanism that maintained the segregation of cortical input/output [27,15], through basal ganglia-thalamocortical channels. Further, the patch-matrix organisation has been related to limbic and non-limbic functions of the striatum. The matrix is preferentially innervated by the sensorimotor cortex, whereas the patches receive input from areas affiliated with the limbic system, such as the amygdala and the prelimbic cortex [24,14]. However, this dissociation is not categorical and only reflects the relative weight of cortical afferents to either compartment.

# Basal ganglia, striatal activity and habit learning

## Functional definitions of goal-directed actions and habits

In an attempt to exclude "non-scientific" concepts from the analysis of instrumental behaviour, some learning theorists of the 20$^{th}$ century reduced the importance of the consequences of the behaviour in driving subsequent responding. Within this framework, goal-directed actions were interpreted in terms of stimulus-response (S-R) bonds which are simply strengthened or weakened by the result of the action (positive reinforcement or punishment) [28,29,30]. Thus, according to this interpretation, the delivery of reward reinforces the associative connection between the triggering stimulus and the response. Such mechanistic two-process models of instrumental conditioning were challenged by other conceptions of instrumental conditioning which incorporated sophisticated elements such as internal representations and intentionality. Such interpretations of instrumental conditioning emphasized the control of action by a representation of the outcome as a goal [31,32], and not by antecedent stimuli. Within this context, behaviour was said to be goal-directed if it involved a twin representation of the contingency between action and outcome and a representation of the outcome as a goal. The implications of such different conceptions in terms of which underlying cognitive processes mediate instrumental behaviour are significant. If an animal is given the opportunity to self-administer cocaine or morphine by pressing a lever, it will

readily do so. Its behaviour is said to be goal-directed because the animal is aware of the relationship between the action and the outcome (lever press followed by a pleasurable internal state produced by the drug) and because the animal wants the outcome to occur. Such response-outcome association implies, therefore, declarative, explicit knowledge of the relationship between instrumental actions and their consequences. By contrast, the behaviour is said to be stimulus-bound if the animal responds on the lever because it has learned an association between the lever and the action. Such association gains strength through drug reinforcement. In this regard, the behaviour requires no explicit knowledge and is simply a reflection of a procedural, mechanical course of action. These actions are referred to as habits because subsequent changes in the value of the reinforcer (in this case, the drug) generally fail to affect responding.

There is ample evidence to support that animal behaviour is driven by both action-outcome and stimulus-response associations. Research over the past decades showed that animals encode action-outcome relationships, driving their behaviour according to the anticipated consequences of their actions. Assays have been developed to manipulate both the value of the reinforcer (reinforcer devaluation) and the action-outcome contingency (contingency degradation). Such tests allow the decision as to whether behaviour is goal-directed or stimulus-driven. For example, drug reinforcement can be devalued by pairing drug infusions with shock [33]. Introducing free rewards in a non-contingent fashion degrades action-outcome relationships [34,35]. For any given behaviour to be considered as goal-directed, it must be affected by reinforcer devaluation and contingency degradation. Conversely, the behaviour will be considered a habitual form of responding if it does persist under these conditions [36,37].

Can we reconcile the two opposing perspectives of instrumental conditioning? It has become apparent that two critical factors facilitate the acquisition of habits in experimental animals: overtraining and variable schedules of reinforcement. Indeed, extended training in instrumental tasks promotes stimulus-response bonds and habit formation [38,39]. Similarly, interval schedules of reinforcement, but no fixed ratio schedules, facilitate the emergence of **automatic** forms of responding [40], presumably because of the weaker response-outcome contingency associated with such schedules. Thus, both reiteration and unpredictability could make the progression from action-outcome strategies to stimulus-response habits possible, both by increasing the amenability for association between actions and antecedent stimuli or contexts, and by reducing the strength of the association between actions and consequences. Goal-directed actions and habits could thus be regarded as processes representing stages of the same learning continuum.

McDonald and White [41] proposed one of the most influential neurobiological accounts of learning and mnemonic function by dissociating

three subsystems within the brain. These different memory systems were postulated to have nodal points in the hippocampus, the amygdala and the neostriatum, and to be responsible for declarative, emotional and procedural memory, respectively. According to this and other similar conceptions [e.g. 42,43] the basal ganglia as a whole, and the neostriatum in particular, were regarded as central to the incremental acquisition of stimulus-response associations which form the basis of implicit, habit-building knowledge. Behavioural data supported the mediation of habit learning by the basal ganglia and the relative independence of habit learning from the memory functions that sustain the acquisition of hippocampal-based declarative knowledge, on the one hand, and of amygdala-based Pavlovian affective learning, on the other. Such independence is more hypothetical than real, however, as interactions between the subsystems are likely to occur both directly at the level of the neostriatum, which receives strong projections from the hippocampus and amygdala, and through the complex array of basal ganglia loop pathways spanning the telencephalon.

## Sensorimotor striatum and the learning of habits

Extensive evidence indicates that the neostriatum and affiliated basal ganglia structures are necessary for the incremental acquisition of stimulus-response associations or habits. Behavioural assays combined with lesions of the dorsolateral striatum provided strong evidence in favour of this hypothesis. Packard et al. [44] studied the behaviour of rats with lesions of the dorsolateral striatum using the 8-arm radial arm maze. In the win-shift version of the task, rats are required to retrieve food pellets placed in each of the eight arms of the maze in a single session carried out daily. Entries into arms previously visited within the session are scored as incorrect entries and are thought to represent errors of spatial working memory. The win-stay version of the task is essentially a visual discrimination task in which only four illuminated arms contain food pellets. The rats have to learn the relationship between the stimulus (light) and the response (arm entry). The win-stay task is devoid of spatial or working memory requirements and probably involves the acquisition of a stimulus-response habit. Sage and Knowlton [45] demonstrated that rats over trained in the win-stay version of the task continued to enter into the illuminated arms even when the food was subsequently devalued by pairing it with nauseating injections of lithium chloride. Analogous tasks were developed for the Morris water maze in which the location of the platform might be visible or might be located under the water. The rats locate the platform depending on visual or allocentric cues. The studies showed that the mnemonic function of the dorsolateral striatum and the hippocampus could be doubly dissociated on these tasks. Lesions of the dorsal striatum impaired the

acquisition of stimulus-response habits but not the ability to solve the spatial tasks, while lesions of the hippocampus produced the opposite pattern of results [44,41]. Further supporting a role for the striatum in habit learning, other tasks which probably require the formation of stimulus-response associations, including conditional visual [46] and auditory [47] discrimination learning and two-way active avoidance [48], were shown to be sensitive to lesions of the dorsal sector.

In addition to lesion studies, electrophysiological recordings from identified striatal neurons during the execution of behavioural tasks suggest the implication of the dorsal striatum in habit-based responding. Using multiunit recording and tetrode technology in a T-maze auditory discrimination task for food reinforcement, Jog et al. [49] demonstrated changes in the activity of neuronal ensembles in the dorsolateral striatum during the sensorimotor acquisition of stimulus-response learning, such that spike activity only incremented at the beginning and the end of the task as learning proceeded. This would be consistent with the gradual building of a task-dependent motor set that undergoes strengthening through positive reinforcement. Further, Barnes et al. [50] showed extensive re-organization of neuronal activity in the sensorimotor striatum during acquisition, extinction and re-training of the same procedural T-maze task. These observations strongly suggest that plastic and dynamic neuronal activity in the dorsolateral striatum is a correlate of habit-based learning.

Human data from neurologically affected patients also comes in support for the hypothesis that the dorsal striatum mediates the learning of habitual forms of responding, of non-motor tendencies and of knowledge in the absence of awareness.

Explicit memories dependent on the integrity of structures in the medial temporal lobe are acquired rapidly, often in the course of one trial or episode, and are flexible, for they are remembered consciously and applied readily to novel situations. Implicit memories are acquired slowly and gradually, generally in the course of many trials, and are stereotyped and rigid, as performance collapses when the rules of the task are modified. Such different memories are mediated by distinct neural substrates in the human brain [51,52]. For example, one of the tasks used to dissociate these abilities in humans is the probabilistic task, in which patients are required to guess, based on probability, which of two outcomes follows a particular stimulus presented in the trial. Stimuli and outcome are probabilistically linked and so it is difficult to learn the relationship explicitly. Amnesic patients show normal learning of the probabilistic task but show no declarative memory for the training episode. In turn, non-demented patients with Parkinson´s disease cannot learn the probabilistic task, but do remember the training episode [43]. Patients with Tourette´s syndrome also failed in a similar classification task involving weather prediction [53]. Moreover, patients with medial temporal

lobe dementia were abnormally slow in an object discrimination task in which subjects had to choose the reinforced object of a pair and explicitly remember the associations. However, they did eventually learn the object-reinforcement associations, though without any awareness or declarative knowledge, as patients could not describe the task, the objects or the instructions given [54]. Such findings were interpreted as evidence for an intact learning system that mediates implicit learning and operates independently of the medial temporal lobe system. Recent observations in patients with focal neurological damage point to the putamen nucleus, the human homolog of the rat dorsolateral striatum, as key anatomical substrate for such rule-based, implicit knowledge [55].

## Involvement of nigrostriatal dopamine in habit learning

As previously indicated, [56] showed that reinforcer devaluation following extensive training under interval schedules for sucrose reinforcement failed to affect instrumental responding in control rats, thereby suggesting habit formation, whereas responding was reduced by devaluation in rats with lesions of the dorsolateral striatum, thus suggesting preserved outcome expectancy in these rats. Therefore, instrumental behaviour continues to be under the control of the outcome after overtraining in the absence of the dorsolateral striatum. Physiological observations indicate that neurons in the dorsal striatum of the monkey increase their firing rates in response to reward-related signals after overtraining, and that such enhancement is blocked or attenuated by impairing dopamine transmission within this region [57]. Is neostriatal dopamine essential to habit formation? Faure et al. [58] compared the performance of control rats with that of rats with 6-hydroxydopamine lesions of the terminal projection to the dorsolateral striatum in tests of goal sensitivity after extended training in cued instrumental tasks. Control rats were insensitive to outcome devaluation, a fact consistent with the hypothesis that their behaviour had become habitual, whereas rats sustaining lesions were sensitive to goal devaluation, suggesting that they had been unable to develop a habit. Taken together, these findings suggest that nigrostriatal dopamine might play an enabling role on habit formation. Most drugs of abuse enhance dopaminergic function and produce long-term changes in dopamine-innervated areas. Can we therefore establish a relationship between long-term drug-taking, dopamine-modulated activity in the dorsal striatum, habit formation and drug addiction?

# Drug-taking and addiction: Goal-directedness or habit

## Drug addiction and the mesolimbic-accumbens pathways

Research over the last two decades has focused on the role of the ventral striatum and extended amygdala systems as potential substrates for the rewarding and addictive properties of abused drugs. By contrast, the

participation of the dorsal striatum has been overlooked, if not disregarded, until quite recently. Significant evidence showed that many drugs of abuse, as well natural reinforcers such as food, sex and social interactions, enhance dopamine neurotransmission in the mesolimbic dopamine system, most notably in the shell region of the nucleus accumbens. Such findings fuelled speculation that these pathways sub serve the reinforcing effects of addictive drugs and that they could play a central role in the shaping of drug addiction. Reinforcing this hypothesis, other behaviours, such as the so-called "natural addictions" –the compulsive abuse of natural reinforcers–, have been linked to abnormalities in these brain regions [59]. Furthermore, several recent publications reported that neuroadaptations in the ventral tegmental-nucleus accumbens dopamine axis might contribute to the development of stimulant sensitization, the progressively incremented psychomotor response evoked by repeated stimulant treatment [60,61,62,63]. Drug sensitization is one of the central elements of the theory of addiction proposed by Robinson and Berridge [64]. According to these researchers, repeated exposure to drugs produces incremented neuroadaptations in the mesolimbic system, which lead to enhanced psychomotor stimulation and, in parallel, elevated desire to consume the drug.

Other current and influential theories of addiction, including the hypothesis of dysregulation of reward and allostasis postulated by Koob and Le Moal [65], placed the emphasis on alterations of the mesolimbic dopamine system and associated striatal circuitry as a fundamental substrate upon which drugs of abuse act to induce the persistent behavioural modifications that phenotype addiction.

The central implication of the dopamine system innervating the ventral striatum in the effects of abused drugs is well substantiated at physiological and molecular levels. Several recent studies have focused on the influence of drugs of abuse on synaptic function, synaptic morphology and plasticity events in the ventral tegmental area and nucleus accumbens synapses. For example, Ungless et al. [66] reported that a single exposure to cocaine induced long-term potentiation of dopamine neurons in the ventral tegmental area. Processes of synaptic plasticity in the nucleus accumbens and dopaminergic midbrain have been shown to be significantly altered by the molecular actions of drugs other than cocaine, including amphetamine, opiates, nicotine and marijuana [63,67,68,69]. As well as persistent alterations in physiological responsiveness, drugs of abuse can induce lasting modifications in signal transduction pathways, early-gene response genes and protein synthesis. Psychomotor stimulants, opiates and ethanol produce changes in signal transmission in the projection areas of the mesolimbic and nigrostriatal dopamine pathways, which translate into cascades of biochemical reactions propagating from the membrane to the nucleus of the neurons. Such reactions lead to changes in the programming and expression of genes and to enduring modifications in cell

morphology and function. How stable are these changes? One of the chief mechanisms by which biochemical signals influence gene expression is through the regulation of transcription factors, proteins that bind specific regulatory elements of certain genes, thereby modifying their transcription. Amongst these genes, members of Fos/Jun and NGFI-A families of transcription factors have been the most studied in the context of drug administration [70-76]. Although the expression of these early response genes is rapid and transient following acute drug administration, recent studies identified stable and persistent gene isoforms. The transcription factor deltaFosB (35-37 kDa), a truncated form of the *fosB* gene, accumulates gradually in the brain in response to chronic exposure to psychomotor stimulants [75,77]. Accumulation of deltaFosB protein in the nucleus accumbens could induce differential sensitivity to addictive drugs.

The evidence implicating the mesolimbic dopamine pathway and the nucleus accumbens in the induction of drug effects, including psychomotor stimulation, reward and reinforcement, is compelling. Thus, it is likely that ventral striatal activation is essential at least during the initial stages of drug-seeking and drug-taking. Activation of nucleus accumbens neurons and mesoaccumbens dopamine are both important for reward procurement. Accumbens neurons show patterned discharges during operant responding for natural reinforcers such as food and water, as well as during training for cocaine self-administration, although either process might recruit different sets of neurons [78]. Consistently, Phillips et al. [79] reported some important findings. These authors showed enhanced subsecond changes in dopamine neurotransmission in the nucleus accumbens during key stages of cocaine self-administration. Increases in extracellular levels of dopamine were observed within seconds preceding the reinforced responses for cocaine that coincided temporally with the initiation of drug-seeking responses. Changes were also noted after response completion. More generally, single-unit recording studies demonstrated that dopamine neurons in the midbrain respond phasically to novel and unexpected reward, and signal error when predicted reward is omitted, thus promoting reinforcement-based learning in expert striatal neurons [80,81,82]. Therefore, nucleus accumbens dopamine might play a key part in the process of acquiring response-outcome associations that link drug-seeking, drug procurement and drug-induced reinforcement.

## A transition of changes from ventral to dorsal mediates habit learning

Recent research advances in the neuroscience of drug addiction suggest that a progression of changes from ventral-to-dorsal at striatal levels could mediate the addiction process. This exciting hypothesis has opened new avenues for unravelling the biological processes that promote addictive

behaviours. The development of addiction may not simply require the establishment of the aforementioned response-outcome associations that so firmly depend on the subjective consideration of the drug as a goal. Rather, addictive behaviours show remarkable resistance to extinction, even when mid-term and long-term consequences for the individual are notoriously prejudicial. Loss of control over drug intake, compulsion and relapse are central features of addiction. Consequently, the concept of substance addiction would harmonize with the notion of gradual consolidation of habit-based patterns of responding [83-88], patterns that build slowly through action-outcome learning and consolidate into stimulus-response learning. This hypothesis prompts a critical question. What is the nature of the stimuli that trigger drug-seeking in addicts? Are they only conditioned exteroceptive stimuli such as drug paraphernalia, locations where the drug was experienced or general stimuli classically conditioned to drug experiences? Alternatively, are feelings of discomfort, disphoria or depression typically associated with withdrawal also important as stimuli precipitating drug-seeking? These interoceptive feelings are probably just as significant in provoking drug-oriented responses and relapse. We have previously proposed that both exteroceptive and interoceptive stimuli can form stimulus-response bonds, recruiting the loop pathways in the sensorimotor striatum that ground habit-based knowledge [88]. Is there neurobiological and behavioural evidence to support the claim that drug addiction may indeed result from such subversion of adaptive memory systems? In other words, are the manifestations of impulse control deficits and of relapse after protracted abstinence from drugs the result of strengthened stimulus-response processes?

Several lines of evidence, including anatomical, neurochemical and behavioural observations come to support the idea that addiction could involve a transition from action-outcome responses to stimulus-bound, habitual behaviours and that a key element in such a process resides in the dorsal striatum. Haber et al. [89] studied the reciprocal projections between the striatum and dopamine cells in the midbrain of the monkey. These authors described a spiralling system connecting the shell of the nucleus accumbens with dopamine cells that innervated neurons in the core of the nucleus accumbens, which, in turn, projected to dopamine cells connecting with the dorsal striatum. Such hierarchical system could mediate dopamine-modulated transfer of synthesized information from ventral to dorsal structures within the striatum. In this fashion, motivational and emotional information processed in the extended amygdala systems would find a dopamine-dependent route to recruit and consolidate motor programs built and strengthened through reinforcement. Behavioral and neurochemical assays with drugs of addiction provided hints that such progression might in fact occur. Early-gene assays

demonstrated that repeated psychomotor stimulant treatment produced network-level adaptations in the dorsal striatum. Canales and Graybiel [76] showed that intermittent cocaine or amphetamine administration in rats induced lasting modifications in the activation of matrix neurons within the dorsal striatum. Repeated exposure to stimulants produced selective activation of striosome neurons, dampening the activation of neurons in the matrix. Further, the degree to which activation in the striosomes exceeded that in the matrix predicted the expression of sensitized motor responses. Such a phenomenon is dependent on the concurrent activation of dopamine receptors [90] and it is not readily apparent in the compartments of the nucleus accumbens [91]. This evidence critically indicated that repeated drug exposure re-organizes the activation of dorsal striatal neurons when challenges with the drug are experienced subsequently.

Models of drug self-administration have provided additional evidence pointing at the dorsal striatum as a substrate for habitual responding in the context of drug-seeking and drug-taking behaviours. Ito et al. [92] trained rats extensively in cocaine self-administration and paired reinforcement with a conditioned stimulus (light). These authors showed that the presentation of the conditioned stimulus in the absence of cocaine elevated extracellular concentrations of dopamine in the dorsal striatum, but not in the nucleus accumbens, suggesting that dorsal structures signal the occurrence of events that have become tightly linked with drug-seeking behaviours. Interestingly, comparing the brains of rhesus monkeys with varying degrees of experience in cocaine self-administration, Letchworth et al. [93] showed a progression of changes from ventral to dorsal within the striatum. These researchers used positron emission tomography to measure dopamine transporters sites at different locations and found a gradual accumulation in the sensorimotor striatum as training progressed. Critical observations have also been made in human addicts using neuroimaging techniques. Abnormal activation patterns have been found in the dorsal striatum of drug addicts [94], including a direct relationship between aberrant dopamine release in the dorsal striatum and the experience of drug craving [95]. Therefore, recent evidence, accumulated over the last few years, suggests a potential role for the dorsal striatum in the mediation of motor responses, conditioned responses and affective states associated with the long-term use of addictive drugs.

## Basal ganglia and neurobiology of relapse to drug-seeking

One of the essential characteristics typifying drug addiction is relapse. Activation of drug desire by internal and external stimuli holds a central

position in the recurring nature of substance use disorders [96-99]. One of the most salient features that occurs during withdrawal or abstinence from compulsive drug use is the ability of drug-associated environmental cues (e.g. drug-associated locations and paraphernalia) and unobservable internal states (e.g., disphoria, anxiety) to elicit drug desire. The systematic investigation of the impact of conditioned stimuli in experimental animals and of subjective craving in drug dependent humans has been performed mainly through studies of cue reactivity. Studies of cue reactivity have given rise to a number of theoretical models, most of which use the principles of classical conditioning to account for cue-elicited craving and reactivity [100-102].

Conditioned stimuli can play a key part both in on-going drug-seeking and drug-taking and in the triggering of craving and renewed desire for taking the drug. In abstinent cocaine addicts the presentation of stimuli previously associated with the use of cocaine produced both physiological arousal and strong self-reports of craving for the drug [103,104]. Conditioned responses of this nature have also been noted for drugs other than cocaine, including alcohol [97], opiates [105] and nicotine [106].

One of the most reliable and meaningful methods for studying the neurobiology of addiction and the mechanisms of relapse is the self-administration model. Animals such as rodents and monkeys will self-administer cocaine, alcohol and a variety of other psychoactive compounds if given the opportunity to do so [107,108]. This is typically performed in self-administration chambers where an operant response on a lever activates an infusion pump to deliver a measured amount of drug via a catheter implanted intravenously. In the case of alcohol self-administration, a number of additional methods have been used. The superiority of the self-administration method lies in the fact that reinforcement is given a response-contingent manner, such that rapid associations between the response and the outcome can be made. The self-administration procedures allow to model different aspects of the process, including the acquisition of responses, maintenance, extinction or abstinence (active or passive extinction) and reinstatement.

The vast majority of studies in the last two decades have explored the neural substrates underlying the acquisition and maintenance of drug-related responses but considerable focus has been aimed more recently at deciphering the mechanisms responsible for relapse to drug-seeking after discontinuation of drug self-administration. Drug discontinuation is typically done by exposing the animal to the context of drug self-administration (e.g., chambers, levers) but removing drug availability. As lever presses are no longer reinforced, drug responses extinguish. Three methods have been used to reinstate drug-seeking behaviour: conditioned cues (e.g., light or sound), priming injections of the drug (e.g., an injection of cocaine) and stress (e.g., footshock). All of these factors are known to induce craving and renew drug desire in detoxified human

subjects [109,110]. Extensive work has been performed over the last decade to identify the anatomical pathways and the neurotransmitter systems implicated in reinstatement of drug-seeking. Data derived from these studies suggested that the molecular events that mediate cue-, drug- and stress-induced reinstatement are not identical and that the anatomical circuits implicated are only partially overlapping. Several laboratories have characterized the cortico-basal ganglia loop pathways that mediate the acquisition, maintenance and reinstatement of drug-seeking. If we examine the research literature on reinstatement of drug-seeking, the nucleus accumbens, the prefrontal cortex and the mesolimbic dopamine pathways feature prominently as key common elements of the distributed circuitry that mediates relapse to various drugs of abuse [110]. Thus, only the ventral domains of the basal ganglia have been consistently implicated in relapse. By contrast, the putative role of the dorsal striatum in relapse to drug-seeking has been neglected until quite recently.

Concerning the potential role of the dorsal striatum and affiliated basal ganglia circuits in relapse, critical observations have been recently made by the group of Ronald E. See at the South Carolina Medical School. Using local inactivation procedures with baclofen and muscimol, this laboratory has shown that in rats that undergo forced abstinence in place of explicit extinction training, intact function of the dorsolateral striatum is required for robust cocaine-seeking at the time of reinstatement [111]. In abstinent rats, inactivation of the basolateral amygdala or the dorsolateral prefrontal cortex failed to block reinstatement of cocaine seeking. Further, Fuchs et al.[111] showed that within the dorsolateral striatum both dopamine D1 receptors and glutamate AMPA receptors participate in the reinstatement of drug-seeking responses. Interestingly, D1 and AMPA receptors are positively coupled to ERK (extracellularly regulated kinase) phosphorylation [112,113], and ERK has been postulated as a “coincidence detector” that transduces coordinate activation of dopamine and glutamate receptors into changes in gene expression [114]. Further, D1 receptors are expressed abundantly by striosome projection neurons of the dorsolateral striatum and repeated stimulant exposure enhances gene expression in this population of neurons [76]. Thus, the use of the abstinence model, which is superior to the active extinction model in terms of face validity, may provide new and exciting leads in the participation of the dorsal striatum in relapse to drug-seeking.

# Concluding remarks and future directions

The findings described in the foregoing section come at a time of growing interest within the addiction research field on the role of the dorsal striatum and allied thalamocortical pathways in habit learning. Compelling data has already accumulated from numerous sources pointing at the dorsal striatum as

an active participant in drug-induced sensitization, drug conditioning, craving and relapse to drug-seeking. Several novel observations in animals and humans have confirmed this possibility. In addition, concepts from learning theory, including the notions of stimulus-response learning, implicit knowledge and habit have been elegantly associated with patterned activity of basal ganglia circuits spanning through the dorsal striatum. Considered altogether, these novel observations and theoretical approximations constitute to date one the most interesting and heuristic corpus of data on the neurobiology of drug addiction, and one certainly worth exploring much further.

The basal ganglia nuclei are a dynamic set of structures exposed to heavy information trafficking, feedback and relay. The parallel nature of the basal ganglia circuits makes it essential to identify the anatomical structures that in concert with the dorsal striatum mediate the plastic events that lead up to the consolidation of drug-seeking behaviours and their reinstatement following discontinuation. Also, it will be critical to identify the neurochemical systems and transduction pathways responsible for such plasticity of neostriatal neurons. In the next few years, we can look forward to unravelling the participation of specific sectors of the medial prefrontal cortex, including prelimbic, infralimbic and cingulate cortices, in the transit from action-outcome responses to habit-based responding for drugs of abuse. Similarly, a more complete picture will emerge when activity in the basal ganglia projection areas of the neostriatum is examined, particularly in the substantia nigra and the globus pallidus and, by implication, in the thalamus. Moreover, within the dorsal striatum, the intricate patch-matrix organization probably hides new treasures to unwrap. Indeed, striosome neurons of the dorsal striatum are recipients of inputs from the limbic brain, including input from the medial prefrontal cortex and the amygdala, and directly control the firing of dopamine neurons in the midbrain. Thus, striosome neurons are centrally positioned to regulate the long-term effects of abused drugs.

Studies on human basal ganglia pathophysiology have focused for decades on the motor disturbances exhibited by patients with Parkinson’s disease, Tourette syndrome, Huntington’s chorea and several other neurodegenerative conditions affecting the integrity of the basal ganglia. We now know that the functions of the basal ganglia are much broader than previously thought. The activity of the basal ganglia appears to be necessary for the storage of memories that bind actions with consequences, stimuli and with previously reinforced actions. Action-outcome and stimulus-action strategies could represent ends of a continuum through which practice and iteration of actions promotes adaptive automatic performance independent of dedicated neural systems that mediate declarative learning. In this context, the basal ganglia could perform the vital task of translating reinforced goal-directed actions into invariant stimulus-bound

behaviours. One aspect that deserves future attention is to understand specifically how goal-directed behaviours become habits, and how these may become compulsive. Such understanding may throw new light on the neurobiology of addictive disorders and the role of the basal ganglia in adaptive behaviour.

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