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Review

Personality, Addiction, Dopamine: Insights from Parkinson's Disease

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In rare instances, patients with Parkinson's disease (PD) may become addicted to their own medication or develop behavioral addictions such as pathological gambling. This is surprising because PD patients typically have a very low incidence of drug abuse and display a personality type that is the polar opposite of the addictive personality. These rare addictive syndromes, which appear to result from excessive dopaminergic medication use, illustrate the link between dopamine, personality, and addiction. We describe the clinical phenomena and attempt to relate them to current models of learning and addiction. We conclude that persistently elevated dopaminergic stimulation promotes the development and maintenance of addictive behaviors.

Introduction

James Parkinson's essay on the shaking palsy notably described a movement disorder with "the senses and the intellect being uninjured"; however, Parkinson's disease (PD) also consists of cognitive, behavioral, and mood symptoms, which are now being recognized as a major source of disability. The movement disorder, which is due to dopamine deficiency in the motor subdivision of the striatum, responds well to the dopamine precursor levodopa and to dopamine agonists such as pramipexole and ropinirole. However, recently, a constellation of addictive syndromes has been noticed in certain patients: addiction to one's medications, compulsive behaviors, and behavioral addictions such as pathological gambling, compulsive shopping, or hypersexuality. These syndromes are side-effects of the medications used to treat PD and are now thought to be a consequence of excessive dopaminergic stimulation.

Addiction can be viewed as a disorder of decision making, learning, and motivation (Berke and Hyman, 2000), and dopamine acting on cortico-striatal neurons is normally involved in all of these phenomena. More specifically, the known role of dopamine in reward learning and reinforcement provides a mechanism by which the repeated use of addictive drugs can eventually become compulsive and habitual. Most addictive drugs release dopamine in the brain, and lesions of the dopamine system attenuate their reinforcing effects (Robbins and Everitt, 1999). Wise suggested that addictive drugs exert their reinforcing effects by acting on dopaminergic brain circuitry that normally processes natural rewards such as food and sex (Wise and Rompre, 1989).

Questions remain however. By what mechanism does dopamine promote learning and reinforcement? Is dopamine also involved in maintaining the addictive behavior in the face of negative consequences? Are there pre-existing abnormalities in the dopamine system that confer vulnerability to addiction, and is there such a thing as an addictive personality? What is the importance of sensitization (increased dopamine response to repeated drug administration) in human addiction? Although rare, the addictive syndromes in PD may help us answer these questions.

The Parkinsonian Personality

PD patients typically do not engage in impulsive or addictive behaviors. The notion of a parkinsonian personality was proposed as early as 1913 and appeared consistently in the psychoanalytical literature of the forties and fifties (Todes and Lees, 1985). Subsequently, controlled studies confirmed the existence of a personality described as rigid, introverted, and slow-tempered, and whose presence may precede the emergence of motor symptoms by a considerable duration (Todes and Lees, 1985). Another observation of interest was that PD patients tended not to smoke cigarettes or drink alcohol, a phenomenon thought to be a feature of the personality profile just described.

In parallel, other researchers described similar personality variants within the general population. Cloninger (1987) proposed the tridimensional personality model, one dimension of which is novelty seeking. Novelty seeking is described as a tendency to be aroused by and respond positively to appetitive or novel stimuli. High novelty-seeking individuals are impulsive, fickle, excitable, quick-tempered, and extravagant while their opposites are rigid, stoic, and slow-tempered. These latter traits are reminiscent of the parkinsonian personality, and, indeed, formal testing has demonstrated that PD patients score lower than matched controls on Cloninger's measure of novelty seeking (Menza et al., 1993). Several studies have linked high novelty-seeking temperament in the general population to drug addiction and impulse control disorders (ICD) such as pathological gambling (Kim and Grant, 2001). Cloninger hypothesized that novelty seeking was related to an elevated dopamine response to novel or rewarding stimuli, and human neuroimaging studies have confirmed a correlation between novelty seeking and dopamine release in response to stimulant drugs (Leyton et al., 2002). In a recent case-control study, low sensation-seeking scores (which correlate with novelty seeking) largely accounted

for reduced smoking and alcohol intake in PD (Evans et al., 2006a). Thus, reduced dopaminergic neurotransmission may be the link between the parkinsonian personality and a reduced risk of addiction in PD. Surprisingly, however, a small percentage of PD patients do develop addictive disorders, but only after the initiation of dopaminergic therapy.

Addictive Syndromes in Parkinson's Disease

Starting in the 1980s, case descriptions of apparent levodopa addiction were reported in the literature, and formal diagnostic criteria were proposed (Giovannoni et al., 2000). The clinical characteristics of these patients met accepted criteria for addiction: compulsive drug taking in excess of clinical requirements; intoxication similar to that seen with stimulant drugs like cocaine, and characterized by hypomania and impulsivity; persistent use despite social and personal difficulties caused by the drug; withdrawal symptoms such as dysphoria and anxiety following reductions in dosage; hoarding the drug or obtaining prescriptions from different physicians (Giovannoni et al., 2000).

Behavioral addictions have also been described in PD (Dodd et al., 2005; Driver-Dunckley et al., 2003; Pontone et al., 2006; Voon et al., 2007; Weintraub et al., 2006). The most common are pathological gambling, hypersexuality, compulsive shopping, and compulsive eating. In this review, we follow the taxonomy of the Diagnostic and Statistical Manual of Mental Disorders IV and refer to these as disorders of impulse control. There is, however, a movement toward grouping them closer to substance use disorders, as "behavioral addictions" (Potenza, 2006), as they share a conceptual resemblance to drug addiction in that individuals pursue an activity in a compulsive manner despite harmful consequences. ICD such as pathological gambling share many features with drug addiction, including clinical characteristics, risk factors, comorbidities, and neurobiology (Potenza, 2006).

Risk factors for the development of both medication addiction and ICD in PD are male sex, young age at the time of PD diagnosis, a premorbid history of drug or alcohol abuse, depression, and elevated scores on the personality measure of novelty seeking (Evans et al., 2005; Voon et al., 2007). Interestingly, these are also risk factors for drug addiction in the general population, suggesting that the PD patients who do develop addictions had a premorbid vulnerability.

Causal Role of Dopaminergic Medication

There is now evidence that the trigger for pathological gambling and other ICDs in PD is the administration of dopaminergic therapy, and especially of dopamine agonists. The first suggestion that dopamine agonists were specifically implicated was made by Driver-Dunckley et al. (2003) who, in a retrospective review of 1884 PD patients, identified nine cases of severe pathological gambling in patients receiving a dopamine agonist. None of the patients treated with levodopa alone (33% of the sample) reported pathological gambling, and seven of the nine who developed the problem did so within a month of a dopamine agonist dose increase. Dodd et al. (2005) supported these findings with a report of 11 PD patients with pathological gambling in whom the problem started soon after the initiation of a dopamine agonist (2 months or less in most patients) and ceased soon after its discontinuation, typically within a month. In reviewing the literature, they noted that, in all previous reports where full medication history was available, dopamine agonist use was present in cases of pathological gambling. A review of the Food and Drug Administration adverse events database identified dopamine agonists as a major correlate of pathological gambling (Szarfman et al., 2006). The most frequently identified medication was pramipexole: of 67 gambling reports in the database (not confined to PD), pramipexole was identified in 58% of cases. Two more recent studies using rigorous clinical evaluations confirmed that dopamine agonist use was predictive of developing an ICD in PD patients (Pontone et al., 2006; Weintraub et al., 2006). As in the initial case reports, patients treated with levodopa alone (40%–50% of patients) did not develop ICD.

The existence of a causal relationship between dopamine agonists and pathological gambling was initially questioned. First, there had also been reports of pathological gambling and compulsive sexuality with levodopa (in fact these were already described in the earliest days of levodopa therapy). Second, in the mid to late 1990s it was common in specialized movement disorders clinics to prescribe dopamine receptor agonists to younger patients with PD, the very group who would be most at risk of developing an ICD. Finally, early publications linking pramipexole to pathological gambling could have led to a reporting bias. However, recent reports have indeed confirmed a causative role for dopamine agonists. In a follow-up study of a previously reported cohort of PD patients with ICD, a reduction in dopamine agonist dose with a concomitant increase in levodopa dose, to achieve the same motor benefit, led to resolution of ICD symptoms (Mamikonyan et al., 2008). A review of all published case series to date concluded that 174 out of 177 reported PD patients with ICD were on a dopamine agonist (Gallagher et al., 2007). The causative role of dopaminergic stimulation is further supported by the fact that typical daily doses in these patients were very high and often higher than the recommended maximum. This review estimated that PD patients treated with agonists had an incidence of pathological gambling as high as 8%, compared to less than 1% in the general population. Finally, there have been recent reports of pathological gambling complicating the treatment of restless legs syndrome with dopamine agonists (Tippmann-Peikert et al., 2007).

Pathophysiological Mechanism of Addiction in Parkinson's Disease

Medication addiction and ICD are both associated with the presence of dyskinesias, involuntary movements that are due to excessive dopamine, and, as mentioned earlier, ICD symptoms abate after reductions in dopamine agonist medication. Thus, elevated dopamine neurotransmission appears to play a role in the occurrence of ICD.

Where in the brain is dopamine stimulation acting to promote addiction in PD patients? Sensorimotor, cognitive, and limbic regions of the striatum can be distinguished, based on their connections with cerebral cortex (Parent, 1990). The ventral striatum (VStr) receives input from limbic areas such as the hippocampus, amygdala, and orbitofrontal cortex, and is implicated in drug addiction (Robbins and Everitt, 1999). It is therefore possible that excessive limbic dopaminergic stimulation is involved in ICD.

Table 1. Possible Site of Striatal Dopamine Dysfunction Causing Different Motor and Cognitive Symptoms in Parkinson's Disease

Cortical Origin of the Cortico-Striatal Loop	Striatal Region	Effect of Low Dopamine	Effect of High Dopamine
primary motor	putamen	bradykinesia, clumsiness	dyskinesia
accessory motor	rostral putamen	akinesia	stereotypies, tics
limbic	ventral striatum	"parkinsonian personality," mental rigidity, neophobia	"addictive personality," impulsivity, novelty seeking, impaired reversal learning
prefrontal	caudate	dysexecutive syndrome, impaired planning (sequential actions to reach a goal), working memory, and cognitive flexibility	compulsive disorders, punding (excessive engagement in goal-directed behavior)

This model is of necessity overly simple as dopamine dysfunction also occurs in cortical areas in PD.

If this is the case, PD patients with relatively preserved ventral striatal dopamine projections at the time of initial treatment ought to have an increased risk of developing the syndromes described here. In non-PD populations, factors likely to be associated with elevated mesolimbic dopamine include young age, since dopamine nerve terminals are naturally lost with age (Frey et al., 1996), and novelty-seeking personality (Leyton et al., 2002), both of which are also risk factors for the addictive syndromes in PD.

In PD, dopamine neurons projecting to the VStr are less severely affected by the disease process (Kish et al., 1988). This raises the possibility that pharmacological restoration of dopamine neurotransmission in the motor striatum leads to overdosing of the limbic striatum, i.e., excessive dopamine receptor stimulation leading to adverse effects (Swainson et al., 2000). This hypothetical difference in baseline dopamine levels between the dorsal and ventral striatum likely accounts for the finding that levodopa improves performance on cognitive tasks involving the dorsal striatum, such as working memory and task-set switching, while causing deficits in tests of reversal learning and the Cambridge Gamble Test, which depend on the ventral striatum (Cools et al., 2001). Further evidence for the ventral overdose hypothesis is provided by functional magnetic resonance imaging (fMRI) studies in which the normal signal that arises in the VStr (nucleus accumbens) when subjects must reverse a previously learned response is abolished in PD patients treated with levodopa, in parallel with impaired task performance (Cools et al., 2007). The postulated effects of dopamine overdosing in the different subdivisions of the striatum are outlined in Table 1.

Another neurobiological factor that may contribute to mesolimbic overdosing is sensitization, which refers to an increased effect of stimulant drugs with repeated administration (Paulson and Robinson, 1995). Sensitized animals are more likely to self-administer drugs, and there is evidence that PD patients with addiction do express sensitization in the VStr. Evans et al. (2006b) used positron emission tomography to measure dopamine release in response to a single dose of levodopa in PD patients with and without medication addiction. Levodopa caused dopamine release in the motor striatum in both groups in equal measure; however, only the addicted group showed significant dopamine release in the VStr (Figure 1A), indicating sensitization. This finding is reminiscent of the dopaminergic response to amphetamine in healthy but high novelty-seeking young adults (Leyton et al., 2002) (Figure 1B). In both cases, dopamine release in the VStr correlated with reports of drug "wanting," supporting the link between mesolimbic dopamine and the potential for drug addiction. Sensitization to amphetamine has recently been demonstrated in humans using positron emission tomography (Boileau et al., 2006) and shown to be proportional to the novelty-seeking score as measured by Cloninger's personality questionnaire (Cloninger, 1987).

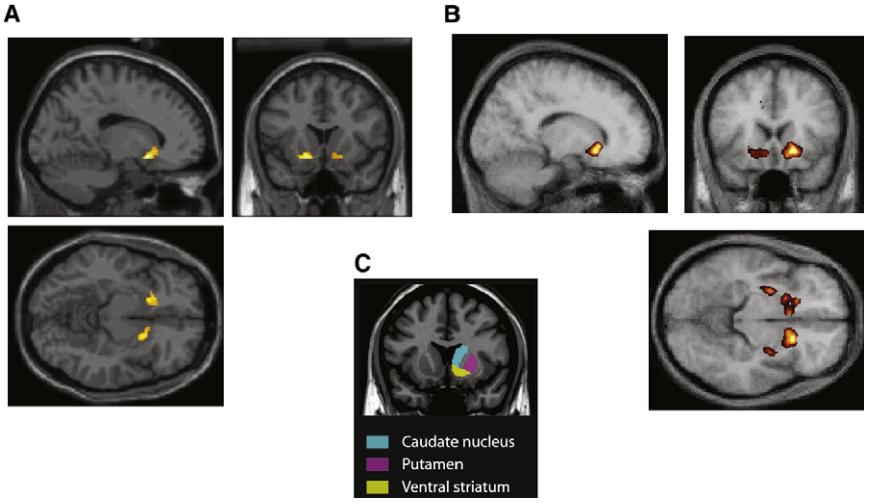

Figure 1. Dopamine Release Measured Using Positron Emission Tomography and [^{11}C]raclopride

The hot-metal t maps are superimposed on coregistered grayscale anatomical MRI images in Montreal Neurological Institute space.

(A) Area of significantly greater dopamine release in PD patients with addiction compared to patients without addiction in response to a single dose of levodopa (Evans et al., 2006b).

(B) Areas of amphetamine-induced dopamine release in healthy young volunteers (Leyton et al., 2002). In both cases, dopamine release was greater in high novelty-seeking subjects and correlated with drug wanting.

(C) Identification of the striatal structures.

The dopamine D3 receptor may play a role in sensitization and in the development of addictive syndromes in PD as it is primarily expressed in the limbic system, including the VStr, and is upregulated in response to levodopa treatment in animal models of PD (Bordet et al., 1997). D3 upregulation is also described in drug addicts at postmortem, and there is much evidence from animal and human studies linking D3 receptor stimulation to sensitization, drug addiction, and relapse. For example, in animals, D3 receptor agonists increase the motivation to obtain drugs when the cost is high and increase reactivity to environmental cues previously paired with the drug (Le Foll et al., 2005). D3 receptor partial agonists decrease cocaine-seeking on a second-order schedule of reinforcement (Pilla et al., 1999). Pramipexole has greater D3 agonist effects than other dopamine agonists or levodopa. Note however that early reports implicating pramipexole over other dopamine receptor agonists have not been confirmed in larger meta-analyses (Gallagher et al., 2007), and a specific role for D3 agonism in the syndromes described here therefore remains unproven.

Dopamine: Learning and Addiction

The striking clinical syndromes described in this review confirm the importance of dopamine neurotransmission in addiction but also raise certain questions that may force us to rethink our understanding of dopamine function in normal and abnormal motivated behaviors.

Dopamine is released in response to drugs of abuse and to nondrug rewards such as food or sex, or, in the case of humans, money. With time, dopamine neurons fire upon exposure to conditioned stimuli associated with these primary reinforcers (Schultz, 2006), and the resultant increase in dopamine levels plays a role in triggering a behavioral response. Increasing dopamine levels in the nucleus accumbens with direct amphetamine infusion augments responding reinforced solely by such conditioned stimuli acting as conditioned reinforcers (Taylor and Robbins, 1984), and accumbens dopamine release is both necessary and sufficient for the response to occur (Taylor and Robbins, 1986) or for conditioned approach to the stimuli (Nicola et al., 2005). Recent studies with in vivo voltammetry, which allows measurements of dopamine levels with great temporal resolution, convincingly demonstrate that the cue-induced dopamine response promotes the associated reward-seeking behavior (Cheer et al., 2007; Phillips et al., 2003). However, it is important to realize that this enhanced response to conditioned cues can be maladaptive; thus, in the studies by Taylor and Robbins (1984, 1986), the responding induced by intra-accumbens amphetamine occurred even in the absence of the goal and was perseverative in nature, possibly akin to the impaired reversal learning (Cools et al., 2007) and other forms of compulsive behavior induced by levodopa or dopamine agonists in Parkinson's disease.

Theories on the mechanism by which dopamine promotes reinforcement can be divided into two broad categories: (1) dopamine as a learning signal and (2) dopamine as an energizing or activating agent that assigns incentive value to stimuli and actions. The learning theories are based on the observation, now made repeatedly and using many different paradigms and measurement techniques, that phasic dopamine neuron firing strongly resembles a reward prediction error signal used in computer models of reinforcement learning (Montague et al., 1996; Schultz, 2006). In the computer models, the reward prediction error signal gradually optimizes behavior by changing the synaptic strengths of action selection neural networks. In the brain, dopamine acting on cortico-striatal synapses can affect long-term depression and potentiation (see below). Addiction, therefore, can be viewed as a form of aberrant learning resulting from persistently positive reward prediction (one might think of a gambler who always expects to win). The second group of theories takes into account evidence that dopamine also appears to have motivating and activating effects independent of learning. Here the emphasis is on dopamine enhancing reward-seeking behaviors by acting on arousal, attention, movement, and effort (Robbins and Everitt, 2007; Salamone et al., 2005). One example is the incentive salience hypothesis of Berridge and Robinson (1998), in which dopamine firing exaggerates the incentive properties of stimuli in the environment, turning them into "objects of desire."

The two models are not mutually exclusive. In learning paradigms, changes in phasic dopamine occur immediately prior to a reward-seeking action (such as pressing a lever for cocaine) and again once the reward is received (Phillips et al., 2003); thus, phasic dopamine could act as both a learning signal and an incentive signal. McClure et al. (2003) have attempted to reconcile the two models using a computational neuroscience approach in which the reward prediction error signal also biases neural activity in favor of actions or stimuli predictive of reward. In this scheme, dopamine not only encodes reward prediction error for the purpose of learning, but also encodes the expected future reward rate, which can be taken as equivalent to incentive salience (i.e., the incentive salience of a stimulus in the environment is equal to its reward prediction). Niv et al. (2007) take this idea further by proposing that dopaminergic stimulation is a running average of recent rewards, and hence an index of likely future rewards. This would explain why high dopamine neurotransmission (e.g., in agonist-treated PD patients) not only biases choices toward reward predicting actions or stimuli but also energizes and invigorates the individual: when expected rewards are high there is a high cost of doing nothing. If these models are correct, the PD patient on a dopamine agonist would have a persistently elevated expectation of rewards and would be biased and energized toward reward-predicting cues and behaviors associated with reward.

The conceptual link between learning models and addiction has received further support from recent human and animal studies examining naturally occurring variations in dopamine function. In humans, two polymorphisms that determine dopamine D2 receptor expression are associated with impulsivity and vulnerability to drug addiction, and both have been shown to influence performance in a probabilistic task that distinguishes positive from negative feedback learning. The TAQ-1A polymorphism modulates D2 receptor density in the striatum. The A1 allele, which is associated with lower expression of D2 receptors, is also associated with impulsivity, addiction, and compulsive behaviors including pathological gambling (Comings et al., 1996). Individuals with this allele are better at learning from positive feedback, but worse at learning from negative feedback, than individuals without the allele, and the two groups differ in their reward-related

response in the VStr during fMRI (Klein et al., 2007). Poorer learning from negative feedback was also reported for the C957T polymorphism of the D2 receptor gene, which is also associated with reduced expression of D2 receptors (Frank et al., 2007).

Similarly, spontaneously impulsive rats (based on their level of premature responding on a serial choice reaction time task) were found to have reduced D2/D3 receptor density in the VStr along with an increased propensity to self-administer cocaine (Dalley et al., 2007). Such rats also self-administer cocaine in a compulsive manner, as defined by the persistence of the behavior and its resistance to punishment by electric shock (Belin et al., 2008). Of especial significance, novelty seeking only predicted initiation of drug taking and enhanced susceptibility to the reinforcing effects of cocaine, but not the development of compulsive drug taking, which was predicted by impulsivity. This result suggests that we need carefully to discriminate measures of impulsivity (the tendency to respond prematurely in a risky manner without due consideration) and novelty seeking in humans, especially as the relevant scales often confound the two (e.g., Cloninger 1987).

Could impulsivity and addiction be, in part, explained by an inability to learn from negative feedback? Negative reward prediction errors (e.g., when an expected reward fails to arrive) are conveyed by pauses in dopamine neuron firing (Bayer et al., 2007). Persistent postsynaptic dopamine stimulation may therefore reduce the ability of these pauses to influence learning, accounting for the difficulty medicated PD patients have in negative feedback learning (Frank et al., 2004; Cools et al., 2007). As stated earlier, a consistent feature in the human (Frank et al., 2007; Klein et al., 2007) and animal (Belin et al., 2008) dopamine-related impulsive phenotypes described above is impaired negative feedback learning. (According to this model the gambler always expects to win because he does not learn from his losses.)

These theories are supported by recent findings on the cellular neurophysiology of striatal dopamine. A well-validated model of the cortico-striatal system divides it into a direct and an indirect pathway (Albin et al., 1989). The direct pathway contains dopamine D1 receptors and is involved in action selection, while the indirect pathway contains D2 receptors and subsumes response inhibition (Mink, 1996). Dopamine signaling also occurs in two modes: slow single bursts of dopamine neuron activity control tonic dopamine levels, which act via the D2 receptor, while phasic bursts lead to transient increases in synaptic dopamine that are several orders of magnitude greater, and act via the lower-affinity D1 receptor (Grace, 2008). Frank has proposed a model in which the phasic bursts that follow unexpected rewards promote positive reinforcement within the direct pathway, via the D1 receptor, while withheld rewards or punishments, by reducing tonic dopamine levels, lead to negative reinforcement via reduced D2 signaling in the indirect pathway (Cohen and Frank, 2008). Indeed, it has recently been shown that D1 stimulation and lack of D2 stimulation both promote long-term potentiation at the cortico-striatal synapses of the direct and indirect pathways, respectively (Shen et al., 2008). Thus, both tonic and phasic dopamine signaling likely shape striatal synaptic plasticity, whether normal (learning) or pathological (addiction). Persistent pharmacological stimulation of dopamine receptors, as occurs in medicated PD patients, could accelerate positive reinforcement learning and impair learning from punishments, in effect acting on both sides of the "addiction equation": increased engagement in reward-seeking behaviors and reduced ability to disengage in the face of negative consequences.

This bidirectional influence of dopamine on ventral striatal information processing has been demonstrated at the cellular and behavioral level in rats (Goto and Grace, 2005). D1 stimulation in the accumbens enhanced hippocampal afferents acting on accumbens output neurons, while favoring learning of a behavioral task. On the other hand, a lack of D2 stimulation enhanced prefrontal input to these same neurons, while favoring switching of a learned response after punishment. By contrast, D2 stimulation with a dopamine agonist prevented the prefrontal cortex from controlling behavior, leading to an inability to disengage from reward seeking in the face of negative feedback.

Theoretically, dopamine agonists in clinical use ought only to affect the indirect pathway, as they act on D2/D3 receptors but have no affinity for the D1 receptor (Seeman, 2007). This might suggest that they can impair negative reinforcement without affecting positive reinforcement. However, dopamine denervation of the striatum has been shown to lead to D3 receptor expression on D1-expressing neurons of the direct pathway (Bordet et al., 1997), which would make them sensitive to dopamine agonists.

Ventral Striatum and Impulsivity

All of these studies point in the same direction: dopamine acting in the VStr is related, in some way, to impulsivity and addiction. Although it is not clear how dopamine neurotransmission is affected in impulsive humans and animals, individuals with the TAQ-1A A1 allele appear to have increased dopamine synthesis rates (Laakso et al., 2005). One possibility, then, is that a heightened dopaminergic response to appetitive stimuli is a cause of impulsivity and vulnerability to addiction. In PD patients, levodopa increases behavioral measures of impulsivity (Cools et al., 2003), an effect probably mediated via the VStr (Cools et al., 2007), and, as stated earlier, PD patients who are addicted to their own medication appear to have an increased VStr response to levodopa (Evans et al., 2006b).

Recent human fMRI studies also link VStr function to impulsivity. Impulsive individuals tend to prefer immediate rewards to larger delayed rewards. Choosing an immediate reward is associated with greater activity in areas innervated by the mesolimbic dopamine system, including the VStr (McClure et al., 2004). In healthy individuals, a single dose of levodopa increases the VStr response to monetary gains (Pessiglione et al., 2006), and the VStr response to monetary gains correlates with a behavioral measure of impulsivity (Hariri et al., 2006).

However, recent data suggest that neural activity in the VStr is not a general marker of impulsivity. It may only appear to be so because of the way certain tasks are designed. In a paradigm in which individuals had to evaluate the desirability of a changing delayed reward compared to a fixed immediate reward, VStr activation (measured with fMRI) actually predicted choosing the delayed reward (Kable and Glimcher, 2007), suggesting that VStr activation is a measure of the expected value of a reward rather than an "impulsivity signal." In other words, in certain task designs, it may be that an expected value signal ends up looking like an impulsivity signal. This latter study is

perhaps more compatible with animal studies showing that lesions of the nucleus accumbens (core region) actually *induce* impulsivity in a delayed gratification paradigm, suggesting that the nucleus accumbens outflow normally exerts an inhibitory influence on impulsive behavior (Cardinal et al., 2001).

Challenges to Theories of Dopamine Function

An implicit feature of several theories of dopamine function is that phasic dopamine neuron firing conveys temporally specific information about discrete events and objects in the environment. In the learning theories, dopamine neuron bursts signal information regarding actual versus expected rewards at a point in time (Schultz, 2006). Similarly, in some of the behavioral activation theories, phasic dopamine plays a discriminative role with respect to stimuli in the environment that requires it to be restricted in time and space (however, see Berridge, 2007).

The challenge for these models is that PD patients treated with dopamine agonists likely have significantly impaired phasic dopamine neuron signaling. First, even at the early stages of the disease, there is a significant loss of dopamine neurons (estimated in the range of 50%–80%), and the surviving dopamine neurons exhibit greatly increased turnover of dopamine (Wilson et al., 1996), leaving the synaptic vesicles depleted of dopamine. Moreover, dopamine agonists greatly reduce dopamine firing: in animals, pramipexole completely silences dopamine neurons (Piercey et al., 1996), at least following acute administration. Thus, while dopamine agonists can restore tonic dopamine signaling, they may well abolish or significantly reduce phasic dopamine. The occurrence of addictive syndromes in patients treated with agonists raises the possibility that phasic dopamine is not necessary for the development or maintenance of addiction. PD patients, with persistently elevated tonic stimulation of postsynaptic dopamine receptors, are capable of reward learning (Frank et al., 2004) and of developing addictive behaviors. Moreover, although they may exhibit increased incentive salience attribution, they retain the ability to discriminate between stimuli. They do not view all stimuli in the environment as incentives.

Recent findings from brain self-stimulation paradigms, in which animals are trained to self-administer electrical stimulation via an electrode implanted in the medial forebrain bundle, also raise questions regarding the role of phasic dopamine signals in learning. It was initially thought that each electrical impulse stimulated dopamine release, as self-stimulation could be facilitated or abolished by enhancing or blocking dopamine transmission. However, this is not the case: in vivo voltammetry demonstrates that phasic accumbens dopamine release rapidly disappears with continuing self-stimulation (Garris et al., 1999). Thus, while a phasic dopamine response to stimulation may be necessary for task acquisition, it does not seem to be necessary for maintenance. Nonetheless, the rats must still be receiving reward information during self-stimulation since disconnecting the electrode rapidly abolishes responding. Therefore, the reward signal, at least during maintenance, cannot be conveyed by phasic dopamine. However, dopamine tone is elevated during self-stimulation, and higher tonic levels appear to correlate with the rewarding effect of each stimulation (Hernandez et al., 2006). The conclusion is that information regarding the spatial and temporal characteristics of rewards is not conveyed by dopamine neurons, but that dopamine tone enables and scales the transmission of this reward information to the efferent action-controlling stages of the circuit. These findings are consistent with several related views of dopamine function: that it promotes the allocation of effort (Niv et al., 2007; Salamone et al., 2005), potentiates responding for conditioned reinforcement (Everitt and Robbins, 2005; Hernandez et al., 2006; Phillips et al., 2003; Schultz, 2006), or sets the gain on incentive salience attribution (Berridge, 2007). Thus, dopamine deficiency in PD would not abolish the reward signal (explaining why reward learning can still occur) but would reduce the ability of reward estimation to trigger motivated behavior. Similarly, elevated tonic levels, in patients receiving high doses of dopamine agonist medication, would promote excessive reward seeking leading to addiction and impulsivity, but leave intact the ability to learn about and discriminate among different incentives.

Experiments in transgenic mice support this view. A dopamine-deficient mouse is capable of normal reward learning but appears to be impaired on measures of motivation to work for rewards (Robinson et al., 2005). A DAT knockdown mouse, which has persistently elevated striatal dopamine levels, displays normal learning but enhanced motivation to obtain sweet-tasting liquids (Pecina et al., 2003). This is not to deny the existence of reward prediction error in the brain, which is supported by a plethora of animal (Schultz, 2006) and human neuroimaging (O'Doherty et al., 2002) studies showing that the firing rate of dopamine neurons closely resembles the reward prediction error signal of computational neuroscience. The dopamine signal may not however be the actual or only learning signal (Berridge, 2007). There are multiple neural systems that can mediate learning, potentially allowing normal habit learning to occur in the absence of dopamine signaling. Indeed, imaging studies suggest that normal habit learning in PD patients may occur via recruitment of extrastriatal brain regions such as the hippocampus (Moody et al., 2004).

Finally, although most of the literature on addiction in PD has focused on mesolimbic dopamine, the dorsal striatum and frontal lobe may also play a role. Everitt and Robbins (2005) have proposed that addiction represents a shift in the response to cues from ventral to dorsal striatum, at which point the behavior becomes habitual (i.e., dominated by stimulus-response rather than action-outcome representations) and possibly even compulsive. This process is accelerated by sensitization (Nelson and Killcross, 2006), and possibly by chronic dopamine agonist treatment. It is interesting to speculate how the more severe DA loss in the dorsal striatum in PD might interact with D2 agonists in this context; one possibility is that the D2 receptors become supersensitive and thus promote compulsive responding when occupied by the D2 agonist. The second possibility is that these patients' behavior has more of the perseverative property associated with excess dopamine function in the VStr.

Impulsivity has also been conceptualized as an imbalance between an overactive mesolimbic (impulsive) system and an underactive prefrontal (inhibitory) system (Jentsch and Taylor, 1999; Robbins and Everitt, 1999). Frontal abnormalities have been identified by neuropsychological testing and neuroimaging in individuals addicted to a variety of drugs and in pathological gamblers, and they appear to contribute to addiction

maintenance and relapse (Goldstein and Volkow, 2002). Significantly, stereotyped behaviors, compulsions, impulsivity, hypersexuality, and even pathological gambling have been described in the frontal lobe variant of fronto-temporal dementia (Lo Coco and Nacci, 2004; Passant et al., 2005) in the absence of treatment with dopaminergic medications. Frontal lobe atrophy also occurs in PD (Burton et al., 2004), and impaired executive function is a hallmark of the disease. It would thus be informative to determine whether patients with addictive problems display frontal gray matter loss compared to nonaddicted PD patients.

Conclusion

The view that hyperdopaminergic function in the striatum is a risk factor for addiction has been challenged. An alternative theory, the ''reward deficiency'' hypothesis of addiction, holds that it is reduced mesolimbic dopamine function that predisposes individuals to addiction (Blum et al., 2000). There is evidence that impulsivity can also be due to low dopamine neurotransmission. For example, patients with attention deficit hyperactivity disorder hypothetically have low striatal dopamine, are impulsive, and have an elevated risk of addiction. Amphetamine reduces certain measures of impulsivity in rodents and individuals with attention deficit hyperactivity disorder (van Gaalen et al., 2006). The dopamine reuptake blocker methylphenidate, which increases tonic dopamine levels in the striatum, also attenuates risky betting on a laboratory gambling task in patients with attention deficit hyperactivity disorder (DeVito et al., 2008), and in patients with the frontal lobe variant of fronto-temporal dementia (Rahman et al., 2006). Note, however, that, in the healthy brain, dopamine levels are not simply high or low: for example, increased tonic dopamine levels can lead to reduced phasic responses (Grace, 2008). There are probably multiple biological pathways to addiction, although one must admit that the reward deficiency hypothesis appears to be directly falsified by the premorbid Parkinsonian personality syndrome and by the occurrence of addiction in PD patients when they are overdosed with dopaminergic medication. Chronically low levels of dopamine in untreated PD lead to low novelty-seeking personality and a reduced incidence of addiction, while dopaminergic replacement, probably coupled with mesolimbic sensitization, confers vulnerability to addiction and impulse control disorders. This suggests that, in the general population as well as in PD patients, factors that lead to enhanced striatal dopaminergic function, whether hereditary or acquired, represent a biological substrate of addictive propensity.

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