Compulsive Drug Use Linked to Sensitized Ventral Striatal Dopamine Transmission

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Objective: A small group of Parkinson's disease (PD) patients compulsively use dopaminergic drugs despite causing harmful social, psychological, and physical effects and fulfil core Diagnostic and Statistical Manual (of Mental Disorders) Fourth Edition criteria for substance dependence (dopamine dysregulation syndrome [DDS]). We aimed to evaluate levodopa-induced dopamine neurotransmission in the striatum of patients with DDS compared with PD control patients.

Methods: We used a two-scan positron emission tomography protocol to calculate the percentage change in 11C-raclopride binding potential from a baseline withdrawal (off drug) state to the binding potential after an oral dose of levodopa. We related the subjective effects of levodopa to the effects on endogenous dopamine release of a pharmacological challenge with levodopa in eight control PD patients and eight patients with DDS.

Results: PD patients with DDS exhibited enhanced levodopa-induced ventral striatal dopamine release compared with levodopa-treated patients with PD not compulsively taking dopaminergic drugs. The sensitized ventral striatal dopamine neurotransmission produced by levodopa in these individuals correlated with self-reported compulsive drug “wanting” but not “liking” and was related to heightened psychomotor activation (punding).

Interpretation: This provides evidence that links sensitization of ventral striatal circuitry in humans to compulsive drug use.

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Dopaminergic drug therapy is a highly effective symptomatic treatment for the motor disability of Parkinson's disease (PD). However, antiparkinson dopaminergic medications have the potential to be compulsively used by a small group of susceptible individuals with PD. These individuals typically request extra drugs and complain of developing tolerance to the effects of the drugs despite the external appearance of being well medicated and displaying disabling drug-induced abnormal involuntary movements (dyskinesias). This syndrome is called “dopamine dysregulation” (DDS), and many of these individuals fulfill core Diagnostic and Statistical Manual (of Mental Disorders) Fourth Edition diagnostic criteria for substance dependence due to the negative effects that their compulsive pattern of dopaminergic drug use has on social, psychological, and physical functioning (eg, marital breakdown, among others). In animal models, L-dopa and dopamine agonists appear to share some of the psychomotor activating properties of commonly abused drugs. It has been posited that the addictive liability of antiparkinson dopaminergic medications may be mediated by alterations in ventral striatal (VS) dopamine neurotransmission and related neural circuitry, a system that evolved to mediate aspects of “natural” rewards such as food, water, and sex.

Early experiences with high doses of L-dopa without peripheral dopa decarboxylase inhibition in PD and bipolar depressive disorder highlighted the frequent occurrence of neuropsychiatric disturbance, including hypomania, psychosis, insomnia, aggression, impulsive behavioral disturbances, and intermittent “mood spells” in which patients would develop sudden feelings of intense exhilaration. More recently, it has become apparent that dopaminergic medications may also potentiate the appearance of drug-responsive compulsive behaviors (pathological gambling, hypersexuality, and food bingeing) and the development of punding, a form of complex behavioral stereotypy. These drug-responsive behaviors frequently complicate DDS and may be implicated in a common neurobiological process.
The aim of this study was to evaluate L-dopa–induced dopamine neurotransmission in the VS of patients with DDS compared with PD control patients using molecular imaging with positron emission tomography (PET) and the dopamine D2/3 receptor ligand [11C]raclopride (RAC). We also aimed to examine whether the differences in L-dopa–induced endogenous dopamine release in DDS patients mediate the hedonic (ie, pleasurable, euphoric) effects of L-dopa (drug “liking”), or a subcomponent of reward termed incentive salience (drug “wanting”).

Patients and Methods
Eight nondemented patients with DDS and eight nondemented control PD patients (Table) gave written informed consent for protocols approved by local ethics committees. Permission to administer RAC was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom. Patients were asked to withhold all antiparkinson medication for 12 hours prior to scanning. We used a two-scan protocol to study the effects of the pharmacological challenge on endogenous dopamine levels that were estimated using percentage change in RAC binding potential (BP) relative to a baseline withdrawal (off drug) state. Each patient received two RAC-PET scans on separate mornings after overnight drug withdrawal: under baseline conditions and then after an oral dose of Sinemet-275 (L-dopa 250mg, carbidopa 25mg). The characteristics of the PET scanner are described elsewhere. Dynamic emission scans were initiated at the beginning of administration of a slow intravenous bolus of a mean 183MBq dose of RAC. Patients also had volumetric brain magnetic resonance imaging. Two methods of analysis were employed: (1) a region of interest (ROI) approach focusing on the VS and dorsal striatum; and (2) Statistical Parametric Mapping (SPM), allowing exploratory voxel-by-voxel group comparisons throughout the entire brain volume.

Region of Interest Analysis
Parametric images of RAC-BP for each patient were generated from the dynamic RAC scans using a BASIS function implementation of the simplified reference region compartmental model with the cerebellum as the reference tissue and were anatomically coregistered with their respective volumetric T1-weighted magnetic resonance imaging. Values of BP for caudate, putamen, and VS were obtained by defining on the coregistered magnetic resonance images ROIs that were subsequently applied to the parametric images similar to the method Leyton and colleagues reported, and averaged values of the right and left sides were calculated for each region. Percentage change in RAC-BP was calculated using the formula: 100 × [(value when “off” L-dopa) − (value when “on” L-dopa)] ÷ (value when “off” L-dopa). Percentage change in motor Unified Parkinson’s Disease Rating Scale (UPDRS) scores was calculated as follows: 100 × [(value when “off” L-dopa) − (value when “on” L-dopa)] ÷ (value when “off” L-dopa).

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control PD group</th>
<th>DDS PD group</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>60.0 (45–70) years</td>
<td>51.2 (42.5–61) years</td>
<td>−2.10 (p = 0.038)</td>
</tr>
<tr>
<td>Mean symptom duration (range)</td>
<td>12.1 (7–17) years</td>
<td>12.4 (5–20) years</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Mini-Mental Parkinson’s score (range)</td>
<td>29 (27–32)</td>
<td>28.6 (25–31)</td>
<td>NS</td>
</tr>
<tr>
<td>Motor UPDRS “off” medication score</td>
<td>37.1 (20–64)</td>
<td>52.7 (21–81)</td>
<td>0.71 (p = 0.721)</td>
</tr>
<tr>
<td>Motor UPDRS “on” L-dopa score</td>
<td>27.1 (10–43)</td>
<td>23.1 (8–59)</td>
<td>0.71 (p = 0.721)</td>
</tr>
<tr>
<td>Mean daily L-dopa equivalent dose (range)</td>
<td>848 (267–1,287)</td>
<td>1,517 (700–2,200)</td>
<td>−2.20 (p = 0.027)</td>
</tr>
</tbody>
</table>

Calculation of a daily L-dopa equivalent unit dose was based on theoretical equivalence to L-dopa similar to previous reports. PD = Parkinson’s disease; DDS = dopamine dysregulation syndrome; NS = not significant; UPDRS = Unified Parkinson’s Disease Rating Scale.
obtained in the “off” medication state) ∕ (prescan affect scores obtained in the “off” medication state) × 100. To control for the effects of scanning on affect, we obtained a summary measure by subtracting the percentage change in PA and NA during the “off” medication scan from the percentage change in PA and NA during the “on” L-dopa scan. Motor disability was assessed in a baseline “off” medication state with the UPDRS\textsuperscript{22} and then again immediately after the “on” drug L-dopa scan. Percentage change in motor UPDRS scores was calculated as follows: 100 × [(value when “off” L-dopa) − (value when “on” L-dopa)] ∕ (value when “off” L-dopa).

**Drug Effects Questionnaire**

After overnight medication withdrawal, patients underwent a challenge with L-dopa in a similar manner to the challenge conducted on the day of PET. Patients’ ratings of subjective L-dopa effects (drug “wanting” and drug “liking”) were evaluated using the Drug Effects Questionnaire.\textsuperscript{23} In the “on” state, patients rated drug effects on two 100mm visual analogue scales, anchored at 0 = “not at all” and 100 = “very much,” with two questions: “Do you like the effects you are feeling right now?” and “Do you want more of what you consumed, right now?” The patient’s reward responsivity, as measured by speeding of responses in the presence of a small monetary reward, was assessed using the Card Arranging Reward Responsivity Objective Test.\textsuperscript{24} Punding behaviors were rated by the examining physician,\textsuperscript{13} and patients completed questionnaires assessing novelty\textsuperscript{25} and fun-seeking\textsuperscript{26} personality traits. To minimize potentially confounding influences of stress during the PET scan on these assessments, we rated Drug Effects Questionnaire, punding, the Card Arranging Reward Responsivity Objective Test, and personality scores during a separate L-dopa challenge prior to undergoing PET scanning.

**Results**

Using a priori defined dorsal and VS ROIs, we found no significant differences in “off” drug RAC-BP between the PD groups (ROI RAC-BP mean values ± standard error of the mean: control PD caudate, 1.95 ± 0.1; putamen, 3.08 ± 0.2; VS, 2.01 ± 0.1; DDS caudate, 1.95 ± 0.1; putamen, 2.98 ± 0.1; VS, 2.07 ± 0.1; p ≥ 0.72). Following L-dopa administration, both groups showed significant decreases in all regional striatal RAC-BPs compared with the “off” drug scan. L-Dopa had an equal effect on percentage reduction in dorsal putaminal RAC-BP in control and DDS groups. In marked contrast, there was significantly greater generation of dopamine in ventral striatal regions (VS) in the DDS group (putamen: control 11.5 ± 3.3 vs DDS patients 11.6 ± 2.0; p = 0.88; VS: control 3.6 ± 1.5 vs DDS patients 14.4 ± 2.7; p = 0.003).

DDS patients were punders; p = 0.001). If the patients are divided along lines of punders versus non-punders, the percentage reduction of VS RAC-BP in punders was markedly higher (punders: 14.1 ± 2.4; non-

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*Fig 1. Effect of a single dose of L-dopa on percentage reduction in striatal 11C-raclopride (RAC) binding potential (mean ± standard error of the mean) in control Parkinson’s disease versus dopamine dysregulation syndrome (DDS) patients indicating a significantly greater generation of dopamine in ventral striatal regions (VS) in the DDS group (putamen: control 11.5 ± 3.3 vs DDS patients 11.6 ± 2.0: p = 0.88; VS: control 3.6 ± 1.5 vs DDS patients 14.4 ± 2.7; p = 0.003).*
nonpunders: 0.83 ± 2.1; Z-score = −3.23; \( p < 0.001 \); however, the dorsal striatal release was not different between the groups.

In the DDS group, l-dopa “wanting” was higher than in the control group and significantly correlated with l-dopa–induced dopamine levels in the VS (Fig 3A). In contrast, there was no significant association with l-dopa “liking” (see Fig 3B). We examined whether self-reported drug effects were related to daily medication intake and found a weak positive trend, although not significant, between daily dopaminergic drug intake and drug “wanting” (\( r_s = 0.627; \ p < 0.10; \ n = 8 \); conversely, “liking” was negatively correlated (\( r_s = −0.771; \ p = 0.025; \ n = 8 \)). In the “off” medication state, DDS patients had lower PA (\( t = −2.46; \ p = 0.027 \) and showed a trend toward a higher NA (\( t = 1.84; \ p = 0.087 \)) than control patients. Ratings of state affect “on” l-dopa were comparable between the groups (data not shown). We observed only a weak trend for an association between l-dopa–induced VS dopamine increases and change in PA (\( r_s = 0.690; \ p = 0.058; \ n = 8 \) and no association with change in NA. The relation between ratings of drug “wanting” and l-dopa–induced dopamine levels in the VS was only mildly weakened by partialling out the effects of changes in self-reported affect (\( r_s = 0.682; \ p = 0.092 \)). DDS patients also showed an increased willingness to work for a small financial reward “on” l-dopa (mean “reward responsivity” on Card Arranging Reward Responsivity Objective Test testing, 12.3% [8.8 standard deviation] for DDS patients vs −1.9% [8.8 standard deviation] for PD control patients; Z-score = −2.94; \( p = 0.003 \)). Reward responsivity correlated with punding severity (\( r_s = 0.873; \ p = 0.005; \ n = 8 \)).

UPDRS motor scores were comparable in control PD and DDS patient groups both in the “on” and “off” l-dopa states (see the Table). l-Dopa–induced increases in dopamine neurotransmission in the putamen positively correlated with percentage improvement in UPDRS across the two groups (\( r_s = 0.59; \ p = 0.017; \ N = 16 \), but did not correlate with l-dopa “wanting” or “liking.” Percentage change in UPDRS motor scores did not correlate with the percentage reduction in VS RAC-BP.

DDS patients had increased novelty-\(^{25}\) and fun-seeking\(^{26}\) traits (Behavioral Activation System (BAS) fun-seeking mean [range]: control patients, 9.5 [7–12]; DDS patients, 12.5 [8–16], Z-score = −2.34; \( p = 0.021 \); NS1-Exploratory Excitability mean [range]: control patients, 1.4 [0–3]; DDS patients, 2.6 [2–4]; Z-score = −2.14; \( p = 0.050 \)). Neither of these traits correlated with l-dopa–induced VS dopamine release.

**Discussion**

Using RAC PET, we demonstrate that there is enhanced or sensitized drug-induced VS dopamine neurotransmission in PD patients compulsively using dopaminergic drug therapy despite its adverse consequences. Basal levels of dopamine D2 receptor availability were comparable between the groups. Other clinical studies have linked compulsive drug use to reductions in striatal D2 receptor binding. However, in those individuals, the findings may be explained by past chronic drug exposure or possibly represent a premorbid susceptibility factor for compulsive drug use.\(^{27-28}\) In our study, the control group had been exposed to chronic intermittent dopaminergic drug regimens for a similar duration to DDS patients. Therefore, the sensitized VS dopamine response that we found in the DDS group would not be the result of drug exposure per se, but rather must be related to the development of a compulsive pattern of drug use.

Progressive augmentation of drug-induced VS dopamine release, measured after a period of drug withdrawal, is a consistently reported neuroadaptation associated with repeated psychostimulant drug administration in rodent microdialysis studies.\(^{14,15,29}\) Basal dopamine levels, however, remain largely unal-
tered. Some have proposed that compulsive drug seeking results from neuroadaptations that lead to persistent hypersensitivity (neural sensitization) of VS dopaminergic circuitry, a circuit that mediates certain aspects of reward.\textsuperscript{14,15}

In animals, expressions of drug-induced stereotypies are influenced by drug dose\textsuperscript{14,15,30} and are hypothesized to index the neuroadaptive changes that occur in the VS in response to compulsive drug self-administration, as the neural substrate that mediates drug-induced stereotypies overlaps with the neural substrate responsible for the rewarding effects of drugs.\textsuperscript{9,15}

In PD, drug-induced complex stereotyped behavior has been called punding. This behavior is characterized by an intense fascination with the repetitive manipulation, examination, cataloging, and endless sorting of common objects. The presence of punding and its severity has been reported to relate strongly to compulsive dopaminergic drug use and drug dose.\textsuperscript{15} Our results provide further evidence that punding may be homologous to drug-induced motor stereotypies in laboratory animals studies because we found that the VS dopamine levels that were generated after oral l-dopa ingestion were even more striking in punders than nonpunders.

DDS patients frequently demand more medication and quickly complain of tolerance to the beneficial effects of treatment. However, spiraling dopaminergic drug intake tends to worsen drug tolerance and lead to an increased frequency of distressing “off” (medication withdrawal) periods. We found that, in the DDS patients, enhanced l-dopa–induced dopamine neurotransmission in the VS positively correlated with l-dopa “wanting” but not l-dopa “liking.” Furthermore, drug “wanting” predicted levels of drug use in DDS patients. Moreover, with increasing dopamine neurotransmission there was an increasing dissociation between l-dopa “wanting” and its subjective pleasurable effects (l-dopa “liking”), potentially reflecting the concurrent development of tolerance. In these individuals, the hedonic impact of l-dopa, as measured by drug “liking,” was negatively related to the patients’ daily amount of l-dopa intake. Consequently, l-dopa “wanting” appears to be directly related to compulsive use of that drug, even when its effects become less pleasant. The dopaminergic VS and related circuitry is proposed to mediate a specific reward process called “wanting” or incentive salience.\textsuperscript{14,15} With repeated drug taking, brain reward systems mediating drug “wanting” become hypersensitive (sensitized) to drugs and drug-associated stimuli. At the same time, individuals are thought to become tolerant to the hedonic impact of drugs, thus drugs become compulsively “wanted” or craved even when the drug’s pleasurable effects become diminished. These conceptualizations of compulsive drug use (the Incentive Sensitization Theory) may be directly relevant to understanding compulsive use of dopaminergic drugs in PD patients with DDS. For instance, dopaminergic agonists have also been shown induce the neural and behavioral phenotypes induced by psychostimulant drugs.\textsuperscript{31}

Animal data investigating the behavioral effects of drug sensitization have found enhanced responding for natural reward–related stimuli such as sugar, food, and sex and conditioned stimuli for such rewards.\textsuperscript{32–34} By contrast, a proposed characteristic of human addiction is that responding for nondrug reinforcement decreases relative to that for drug reinforcement. It has been suggested that motivation for nondrug rewards may actually be decreased in humans,\textsuperscript{35} although there are anecdotal reports of hypersexuality in cocaine addicts\textsuperscript{15} and some substance-dependent individuals may be hyperresponsive to money rewards.\textsuperscript{36} The increased responsivity to nondrug (monetary) rewards that we found in DDS patients is consistent with clinical observations that link the dopaminergic drugs used in PD and DDS\textsuperscript{2} with other addictive behaviors such as hypersexuality and compulsive gambling.\textsuperscript{37,38} and it is relevant to the debate whether behavioral and chemical addictions share the same substrates. The correlation between punding severity and reward responsivity may reflect a relation between the reward-enhancing and stereotypical effects of psychomotor stimulant drugs\textsuperscript{39} or relate to a global increase in wanting for conditioned rewards.\textsuperscript{33}

A clear general relation exists between novelty–\textsuperscript{25} and fun-seeking\textsuperscript{26} personality traits and addiction proneness.\textsuperscript{40–42} These traits mediate biological responses to novelty\textsuperscript{43} and individual variability of drug-induced dopamine neurotransmission in the VS.\textsuperscript{19} In adolescence, high novelty seekers are more likely to experiment with drugs\textsuperscript{42} and develop harmful patterns of drug\textsuperscript{44} and alcohol use.\textsuperscript{40} In individuals with substance dependence, novelty-seeking traits also influence craving,\textsuperscript{45} vulnerability to relapse,\textsuperscript{46} and social influences on drug taking.\textsuperscript{47} Higher novelty-seeking traits independently predict the presence of DDS in PD.\textsuperscript{48} In this study, these trait scores did not correlate with l-dopa–induced VS dopamine release, suggesting they may be independent predisposing risk factors for DDS.

These findings offer a unique insight into how exposure to a drug, even for therapeutic purposes, can subvert brain reward systems and lead to enduring susceptibility to compulsively use a drug. Our findings may also be relevant to understanding the neurobiological processes that lead to other forms of addiction and to the development of management strategies for the disorder. For instance, the persistence of drug-induced neuroadaptive changes in many laboratory models suggests that once features of the syndrome are present, management can be difficult and relapse of the disorder common. Reduction in dopaminergic drug therapies can reduce the disability caused by the behavioral disorders associated with DDS. However, individuals may remain
sensitized to the drug’s rewarding effects, and in time, relapse may occur with smaller drug dosages. Identifying patients diagnosed with PD prospectively who may be vulnerable to developing a pattern of compulsive dopaminergic drug use may be a critical step in preventing the physical, social, and financial impact of DDS.

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References