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Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors

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ABSTRACT

Background: Parkinson disease (PD) patients treated with dopamine agonist therapy can develop maladaptive reward-driven behaviors, known as impulse control disorder (ICD). In this study, we assessed if ICD patients have evidence of motor-impulsivity.
Methods: We used the stop-signal task in a cohort of patients with and without active symptoms of ICD to evaluate motor-impulsivity. Of those with PD, 12 were diagnosed with ICD symptoms (PD-ICD) and were assessed before clinical reduction of dopamine agonist medication; 12 were without symptoms of ICD [PD-control] and taking equivalent dosages of dopamine agonist. Levodopa, if present, was maintained in both settings. Groups were similar in age, duration, and severity of motor symptoms, levodopa co-therapy, and total levodopa daily dose. All were tested in the dopamine agonist medicated and acutely withdrawn (24 h) state, in a counterbalanced manner. Primary outcome measures were mean reaction time to correct go trials (go reaction time), and mean stop-signal reaction time (SSRT).
Results: ICD patients produce faster SSRT than both Healthy Controls, and PD-Controls. Faster SSRT in ICD patients is apparent in both dopamine agonist medication states. Also, we show unique dopamine medication effects on Go Reaction time (GoRT). In dopamine agonist monotherapy patients, dopamine agonist administration speeds GoRT. Conversely, in those with levodopa co-therapy, dopamine agonist administration slows.
Discussion: PD patients with active ICD symptoms are significantly faster at stopping initiated motor actions, and this is not altered by acute dopamine agonist withdrawal. In addition, the effect of dopamine agonist on GoRT is strongly influenced by the presence or absence of levodopa, even though levodopa co-therapy does not appear to influence SSRT. We discuss these findings as they pertain to the multifaceted definition of 'impulsivity,' the lack of evidence for motor-impulsivity in PD-ICD, and dopamine effects on motor-control in PD.

1. Introduction

"Impulsivity" describes a pattern of hastily made decisions or behaviors (Evenden, 1999). The term itself invokes a negative connotation, although in certain circumstances, impulsive or spontaneous decisions can be quite functional (Dickman, 1990). From a cognitive and behavioral perspective, impulsivity invites some confusion, as it describes a heterogeneous set of behaviors that manifest in distinct contexts and over distinct timescales (Evenden, 1999). When recognized clinically, impulsivity is most often associated with maladaptive patterns of behavior. In recent years, a broad distinction has been made between 'motor' and 'motivational' impulsivity (Bari and Robbins, 2013), where motor impulsivity describes inappropriate motor reactions to immediate circumstances or stimulus events on a millisecond timescale, and 'motivational impulsivity' characterizes decisions that lack reflection, forethought, patience, and consideration of long-term consequences and reward contingencies (Bari and Robbins, 2013). In human and animal models, these two manifestations of impulsivity are linked to distinct neural mechanisms (Bechara, 2005; Kenner et al., 2010), and can be dissociated using germane cognitive tasks, thus providing a useful framework for classifying clinically observed forms of impulsive behavior.

Emergence of 'impulsive behaviors' as a consequence of medical therapy in Parkinson disease (PD) is most often attributed to pharmacologic manipulations of dopamine, which include the use of the dopamine precursor levodopa and dopamine receptor agonists (DAAg) (Weintraub et al., 2010). The administration of DAAg (and to a much

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lesser extent, levodopa) has been linked to the development of impulse control disorder (ICD) in approximately 15–20% of patients (Voon et al., 2006; Weintraub et al., 2010). ICD describes excessive interest and participation in certain reward-driven behaviors, expressed in shopping, gambling, eating, sex, and hobbies (Ahlskog, 2011). An understanding of the underlying neurocognitive processes that drive such marked behavioral changes is starting to emerge, but generally remains limited. Determining if ICD behaviors are linked to motor or motivational impulsivity would provide a significant advance in our understanding of the phenomenology of these behaviors. Some studies suggest that, compared to PD patients without ICD, individuals with a history of ICD prefer smaller immediate rewards over larger delayed rewards (i.e., show larger delay discounting effects) (Voon et al., 2010), and those with active ICD symptoms pursue riskier choices (Claassen et al., 2011). Neuroimaging studies highlight differences between patients with and without a history of ICD in mesocorticolimbic circuitry involved in risk decision-making, reward evaluation, and reward learning (Rao et al., 2010; van Eimeren et al., 2010; Voon et al., 2010; Ray et al., 2012). Thus, ICD may represent an emergence of maladaptive 'appetitive' behaviors stemming from dopamine-mediated effects on the mesocorticolimbic network.

Few investigations have studied the role of motor impulsivity in ICD patients. We recently investigated differences between PD patients with and without active symptoms of ICD, in the susceptibility to acting on prepotent motor impulses and the proficiency of inhibiting interference from these impulses (Wylie et al., 2012). Contrary to a motor impulsivity hypothesis, patients with active ICD showed a reduced tendency to act incorrectly on strong motor impulses compared to patients without ICD, irrespective of whether they performed under DAAg withdrawal or administration. Additionally, both groups showed similar proficiency in inhibiting interference from impulsive actions when tested withdrawn from DAAg and similar impairment to inhibitory control when tested On medication. These findings (Wylie et al., 2012) provide the motivation to determine if PD-ICD patients have an enhanced susceptibility to acting on motor impulses or reduced ability to inhibit strong motor impulses.

To further investigate the role of motor impulsivity in PD patients with active ICD, we studied the speed at which patients are able to stop already-initiated movements. The gold standard for measuring stopping control is the stop-signal task, which requires participants to make speeded choice reactions to 'go' stimuli, but stop reactions upon the infrequent and unpredictable occurrence of a 'stop' stimulus, presented within a few hundred milliseconds after the onset of a 'go' stimulus (Logan, 1994). The task measures the proficiency (i.e., latency) of interrupting or canceling the preparation of an initiated overt response. Prolonged stop signal reaction time (SSRT) is described in clinical populations characterized by impulsive behaviors and poor inhibitory control, including patients with attention-deficit hyperactivity disorder (Oosterlaan et al., 1998), substance abuse (Monterosso et al., 2005; Fillmore and Rush, 2002), obsessive–compulsive disorder (Krikorian et al., 2004), and schizophrenia (Badcock et al., 2002). More so, individuals rating high on impulsive traits also have longer SSRTs (Logan et al., 1997; van den Wildenberg and Christoffels, 2010); thus reduced motor control is directly associated with impulsive behavior.

Here we assessed performance on the stop-signal task in PD patients with active ICD, patients without ICD, and healthy matched controls. All PD patients were taking DAAg, and groups were carefully matched for disease duration, duration of DAAg use, dose of DAAg and levodopa, and motor symptom severity. To determine if the presence of DAAg was critical to stopping effects, the stop-signal task was competed on optimal dopaminergic medication, and after withdrawing selectively from DAAg. Consistent with previous findings, we predicted that PD patients would show slower SSRTs when compared to healthy controls (Gauggel et al., 2004). Support for the role of motor impulsivity in ICD was expected to manifest as exacerbated slowing of SSRT as compared to PD patients without ICD. Finally, we expected a role for DAAg in stopping control to be revealed by differences in stopping speed on versus temporarily withdrawn from DAAg medication.

2. Materials and methods

2.1. Participants

Study participants included 24 PD patients and 12 healthy controls. All PD patients met diagnostic criteria based on the UK Brain Bank, and were diagnosed by a Movement Disorder Neurologist (D.C.) (Hughes et al., 1992). All participants were formally screened for global cognitive impairment (Mini-Mental Status Examination, MMSE; (Folstein et al., 1975)) and depression (Center for Epidemiological Studies-Depression Scale, CESD; (Radloff, 1977)). Motor symptom severity in the On medication state was graded using the UPDRS part III motor score (Fahn et al., 1987). All dopamine medications were converted to levodopa daily dose equivalent (LEDD) using previously reported formulas (Weintraub et al., 2006). See Table 1 for participant details. All participants had normal or corrected-to-normal vision. Participants were screened to ensure that they did not have a history of any neurological condition other than PD, mood disorder such as major depression, history of bipolar affective disorder, schizophrenia, or other psychiatric condition with known effects on cognition, or an untreated or unstable medical condition known to interfere with cognition. Prior to study entry, all participants provided informed consent, which was compliant with standards of ethical conduct in human investigation as regulated by the institutional review board.

All PD patients were taking DAAg, and about half were taking concomitant levodopa therapy. Both patients and a family member completed the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's disease to screen for the presence or absence of active ICD behaviors (Weintraub et al., 2012). All patients were interviewed by a neurologist (D.C.) and a neuropsychologist (S.W.) to confirm the presence or absence of ICD symptoms based on published criteria (McElroy et al., 1994; American Psychiatric Association, 2000; Grant et al., 2004; Voon et al., 2006). For those meeting ICD criteria, we confirmed the emergence of ICD symptoms subsequent to DAAg initiation. Behaviors included excessive participation, and heightened interest in sexual behaviors (5/12), shopping or buying (5/12), eating (6/12), and time spent on a hobby (9/12). Most patients endorsed at least two of the behaviors (11/12) listed above, and 2 patients endorsed three or more behaviors. PD controls (PD-C) did not meet criteria for any ICD behaviors based on screening and interview, and closely matched age,

Table 1
Participant characteristics.

	HC ($n = 12$)	PD-ICD ($n = 12$)	PD-Control ($n = 12$)
Age (years)	58.5 (6.3)	59.4 (5.5)	60.8 (7.2)
Education (years)	15.3 (2.9)	17.1 (2.7)	16.3 (2.8)
Gender (male:female)	6:6	8:4	6:6
MMSE[a]	28 (1.7)	29 (1.6)	28.7 (1.6)
CES-Depression Score	7.0 (6.2)	11.8 (7.7)	8.7 (5)
Disease duration (years)	–	6.5 (4.7)	6.1 (3.8)
UPDRS motor score	–	15.9 (6.6)	15.7 (8.3)
Patients on DA agonist monotherapy	–	5	5
DA agonist duration (years)	–	3.4 (3)	2.7 (2)
Levodopa dose (mg)	–	408.2 (349.6)	319.7 (318.9)
DA agonist dose in LEDD (mg)	–	293.8 (167.4)	200.6 (116.8)
Total LEDD (mg)	–	618.7 (361.9)	520.3 (314.9)

Values represent mean scores with standard deviations reported in parentheses. Comparisons between Parkinson disease patients with ICD (PD-ICD) and PD patients without ICD (PD-Control) were not statistically significant ($p > 0.05$).
ICD = impulse control disorder; MMSE = mini-mental state examination; CES = Center for Epidemiological Studies; DA = dopamine; LEDD = levodopa equivalent daily dose.
[a] Healthy controls completed the Montreal Cognitive Assessment (MoCA) in place of the MMSE.