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Dopaminergic medication improves cognitive control under low cognitive demand in Parkinson's disease

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Abstract

Objective

Dopamine agonists are the main pharmacological intervention for the motor symptoms of Parkinson's disease (PD). However, dopaminergic medication has been associated with disinhibitory psychopathology in some patients. The aim of this study was to test the effect of dopaminergic medication on inhibitory control in patients with PD using the paced Random Number Generation task (RNG), which requires inhibition of pre-potent counting in series to produce a random sequence of numbers.

Methods

Twenty-three PD patients performed RNG on- and off-dopaminergic medication. Cognitive load was manipulated by performing RNG at faster (1Hz) and slower (0.5 Hz) rates. For RNG, two scores (CS1 and CS2) were derived – which are considered indices of more automatic and more controlled counting respectively.

Results

There were no main effects of medication on RNG performance. There was a significant main effect of cognitive load on CS1, with higher CS1 scores at the faster rate (p = <.01). A significant interaction effect between medication and rate (cognitive load) (p = .03) followed by post-hoc testing, revealed that CS2 scores were higher, on-medication, at the slower but not the faster rate.

Conclusions

Patients with PD displayed increased use of more controlled processing strategies on-medication at the slowest rate of RNG. Therefore, while dopaminergic medication has been associated with disinhibitory psychopathology, our results suggest that dopamine therapy may enhance some forms of inhibitory cognitive control in PD, but only there is sufficient time to engage controlled processing strategies.

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Keywords: Parkinson's disease, executive function, inhibition, impulsivity, random number generation, cognition

Public significance statement

- Dopamine medication did not influence the ability of patients with Parkinson's disease to inhibit habitual counting in ones, which is an automatic response during random number generation.
- When tested on medication, patients with Parkinson's disease were better able to engage more controlled processing strategies when performing random number generation at slower rates.
- Dopaminergic medication improves controlled processing when patients with Parkinson's disease have sufficient time to engage such processes.

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Dopaminergic medication improves cognitive control under low cognitive demand in Parkinson's disease

While Parkinson's disease (PD) has historically been thought of as a movement disorder, patients also experience non-motor symptoms, including psychiatric problems and cognitive deficits. PD-associated cognitive difficulties are often characterised by executive dysfunction, which can present as impaired attentional control, set-shifting, planning, and inhibitory control (Dirnberger & Jahanshahi, 2013).

The ability to inhibit pre-potent automatic responses is an important executive control component because it allows for the selection of potentially more appropriate actions. As such, impaired inhibitory control can give rise to pathological impulsivity. Various forms of impulsivity have been distinguished (Evenden, 1999) and studied in patients with PD. These include i) engaging in risky behaviours (e.g., Weintraub, David, Evans, Grant, & Stacy, 2015), ii) reflection impulsivity (e.g., Djamshidian et al., 2013), iii) deficits in motor inhibition (e.g., Obeso et al., 2011), and iv) impaired delayed gratification (e.g., Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010). While some of these types of disinhibition likely result from PD pathology, others have been thought to be caused by the dopaminergic therapy used to treat motor symptoms.

Inhibitory control can be assessed with the Random Number Generation (RNG) task. During RNG, participants are required to verbally produce random sequences of numbers, synchronised with an audible pacing stimulus. In order to produce a random sequence of numbers, an individual must inhibit the pre-potent response of counting in series (learned over years of practice), and instead engage controlled processing strategies to generate numbers randomly. This is thought to involve several cognitive control sub-processes including: holding the task instructions and requirements in working memory (e.g., select only numbers 1-9), accessing the concept of randomness itself from long-term memory (whatever that is for the

individual), integrating this information in working memory to perform the task, self-monitoring of performance, and supressing the automatic pre-potent response to count serially (i.e., 1-2-3) (Jahanshahi, Saleem, Ho, Dirnberger, & Fuller, 2006). One advantage to using RNG to assess cognitive control over other neuropsychological measures, is that automatic responding and efforts to engage in more controlled responding can be measured independently and at the same time. Quantitative analysis of the patterns of numbers produced generates two scores from the same response sequence, Count Score 1 and Count Score 2, which are used to infer the recruitment of more automatic and more controlled processing strategies, respectively (Jahanshahi, Dirnberger, Fuller, & Frith, 2000; Jahanshahi et al., 1998; Jahanshahi et al., 2006).

Random Number Generation is theoretically underpinned by The Network Modulation Model (Jahanshahi et al., 2000). This model proposes that inhibition of automatic counting in series during RNG is achieved via the modulatory influence of the left Dorsolateral Prefrontal Cortex (ldlPFC) over a number-associative network located in the superior temporal cortex, which represents numbers in an ordered serial fashion. The Network Modulation Model of RNG and the role of the ldlPFC is supported by evidence from both imaging and transcranial magnetic stimulation studies in patients with PD (Jahanshahi & Dirnberger, 1999; Jahanshahi et al., 2000). The proposed role of the ldlPFC in the Network Modulation Model of RNG is corroborated by its demonstrated involvement in other tasks that require top-down control of automatic processes in healthy participants, for example during the Stroop Task (Li et al., 2017; Vanderhasselt, De Raedt, & Baeken, 2009; Vanderhasselt, De Raedt, Baeken, Leyman, & D'Haenen, 2006)

The involvement of controlled and automatic processes in RNG can be further probed by manipulating the pace of RNG performance (paced RNG), and therefore the cognitive load. Dual Processing Theory (Schneider & Shiffrin, 1977) proposes that automatic information processing strategies are fast, engaged with little effort, robust to interference from other

cognitive processes, are difficult to suppress, and require little attentional processing. However, controlled processing strategies are slow, effortful, capacity-limited, and require larger amounts of directed attentional processing. When RNG is performed at faster rates, greater cognitive load is induced as there is less time to engage the controlled processes of selection and generation of numbers in a random fashion. As a result, the more automatic strategy for generating sequences of number (resulting in higher Count Score 1) will be employed, and the generated sequence of numbers will be less random.

We have repeatedly shown that patients with PD exhibit impaired RNG performance, with a greater tendency to count in series (as measured by Count Score 1), and producing less random sequences of numbers than healthy controls (Brown, Soliveri, & Jahanshahi, 1998; Dirnberger, Frith, & Jahanshahi, 2005; Obeso et al., 2011). Randomness during RNG is further impaired under conditions of higher cognitive load, as has also been observed during paced RNG performance at faster rates in healthy participants (Dirnberger & Jahanshahi, 2010). Patients with PD (Obeso et al., 2011). PD patients who have had deep brain stimulation of the subthalamic nucleus (Williams, Wilkinson, Limousin, & Jahanshahi, 2015), also exhibit larger deficits in inhibitory control than age-matched controls, and engage in more automatic and less random counting (higher Count Score 1) when performing RNG at faster and more demanding rates. Taken together, these results suggest that patients with PD experience impairments in inhibitory control which worsen under conditions of high cognitive load. Problems with cognitive control such as this, may underpin difficulties with impulsivity that some patients with PD experience, particularly during high-pressure conditions when important decisions need to be made quickly (Heiden, Heinz, & Romanczuk-Seiferth, 2017).

The effect of dopaminergic medication for PD on RNG performance has not yet been assessed. Therefore, the aim of this study was to use the RNG task to investigate whether dopaminergic medication affects the ability of PD patients to inhibit the pre-potent response of

counting in series during RNG. To that end, we compared patients' paced RNG performance 'on' and 'off' medication. Cognitive load was manipulated by including faster and slower paced conditions. A group of non-medicated healthy controls was included to see how patients' RNG performance compared to 'normal' performance both on- and off-medication. We hypothesised that patients would perform more poorly (i.e. produce less random responses) compared to healthy controls. We also hypothesised that responses would be less random at the faster rate of RNG (under greater cognitive load).

With respect to hypothesised medication effects, dopaminergic therapy for PD has been associated with both impaired and improved inhibitory control. The increased incidence of Impulse Control Disorders in PD patients taking dopaminergic therapy would suggest that dopaminergic medication induces or worsens impairments in inhibitory control (Weintraub et al., 2006). Conversely, the demonstrated association between dopamine depletion and impaired performance during tasks that require inhibitory control (e.g., set-shifting; Nagano-Saito et al., 2008) would suggest that dopamine agonists might ameliorate impulsivity in PD. Indeed, there is growing recognition for the complexity of the relationship between dopaminergic medication used to treat PD and inhibitory control, which likely depends on individual patient-factors such as disease severity and duration (Grall-Bronnec et al., 2018). Therefore, we had no specific predictions about the direction of effect of dopaminergic medication on RNG in patients with PD.

Methods

Participants

Twenty-three patients (16 male) with a clinical diagnosis of PD according to the Parkinson's Disease UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) were recruited from the Movement Disorders Clinics at The National Hospital for Neurology and Neurosurgery. All patients recruited to the study were taking prescribed dopaminergic

medication for the treatment of their PD (Levodopa). The Beck Depression Inventory (BDI; Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961) was used to screen for clinical depression (scores above 10) and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used to screen for cognitive impairment and dementia (scores below 26). A neurologist assessed on- and off-medication motor symptom severity using the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008), and disease stage using the Hoehn & Yahr Scale (H&Y; Hoehn & Yahr, 1967) . Twenty-three healthy controls (16 male) with no history of head injury, physical, neurological, psychiatric illness, or alcohol or drug abuse also participated. Participant demographic and clinical information is presented in Table 1.

The study inclusion criteria were absence of any major psychiatric disorder or cognitive impairment as measured by the MMSE, and no co-existing neurological disorder. None of the patients had undergone deep brain stimulation surgery. For healthy controls, the inclusion criteria were no history of head injury, physical, neurological, psychiatric illness, or alcohol or drug abuse (established by interview).

This study was approved by the Joint Ethics Committee of the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery. Informed, written consent was obtained from all participants.

Design and procedure

Patients performed the paced RNG task (Jahanshahi et al., 2006) twice; on- and off-medication on two different days, with the order counterbalanced. In the 'off state', patients had been instructed not to take their first dose of the day, and as such had been withdrawn from their long-acting dopaminergic medication for approximately 13 hours (M = 12.82, SD = 2.75). Healthy controls were not administered any dopaminergic medication but performed the task twice to control for the effects of repeated assessment and to provide control data for patients

in both medication conditions. Previous evidence shows that repeated performance of RNG does not alter the results as there are no learning or practice effects (Jahanshahi et al., 2006).

The Random Number Generation Task

During the RNG task (Jahanshahi et al., 2006), participants are instructed to verbally produce 100 random numbers between one and nine (inclusive), synchronising their responses with an audible pacing tone. To assist in the conceptualisation of randomness, participants were instructed to imagine selecting and replacing numbered balls from a hat, one at a time. Paced RNG was performed at two rates, with participants required to produce a random number in time with the audible pacing tone every one second (faster rate condition) or two seconds (slower rate condition). The order of these conditions was counterbalanced between participants. To familiarize themselves with the rate, participants listened to the pacing tone for eight seconds before starting RNG.

RNG performance was analysed by extracting seriation measurements from the number sequences that participants produced. Seriation has been identified as one of the main factors underlying human RNG (Ginsburg & Karpiuk, 1994), and has previously been reported as sensitive to load and treatment manipulation in patients with PD performing RNG (e.g., Williams et al., 2015). Two measures of seriation were obtained for each condition, from the same sequences of numbers generated: Count Score 1 (CS1) and Count Score 2 (CS2) (Spatt & Goldenberg, 1993). CS1 and CS2 are calculated from counting the number of times an individual consecutively counts up or down in steps of one or two (respectively) and squaring that value to give greater weight to longer runs. For example, in the series ‘1-2-3’, there are two consecutive steps up of one (CS1). Two squared equals four. Therefore, in this example, ‘1-2-3’ would yield a CS1 of 4. A longer run of ‘1-2-3-4’ would result in a CS1 of 9. All incidences of CS1 across the trial are summed to produce an overall CS1 score for that trial. Similarly, CS2 measures the number of times an individual consecutively counts up or down

in steps of two. For example, in the series '2-4-6' there are two steps up of two. Two squared equals four, so the CS2 score for this sequence would be four. CS2 scores for the whole trial are calculated by adding all the incidences of CS2 within that trial.

Counting in steps of one (CS1) is considered to be an overlearned strategy and is therefore thought to reflect the implementation of an automatic, pre-potent and learned tendency to generate numbers in series. Conversely, counting in steps of two (CS2) is thought to reflect an attempt to engage the central executive to suppress counting in steps of one, and therefore represents the employment of a more controlled number generation strategy (Jahanshahi et al., 1998; Jahanshahi et al., 2006). Therefore, both CS1 and CS2 were used to capture the recruitment of more automatic and more controlled counting strategies from the same number sequences produced during RNG.

Statistical analysis

Data were entered into SPSS and screened for normality using the Kolmogorov-Smirnov test. CS1 and CS2 scores were found to violate the assumption of normality ($p < .05$). However, ANOVA models are considered robust to violations of normality with equal group sizes (Tabachnick, 2001). Therefore, to assess for the effect of medication status on paced RNG performance, a mixed ANOVA was conducted with 'medication status' (on vs off), measure (CS1 vs CS2), and rate (faster vs slower) as the within-subjects factors and 'group' (patients vs controls) as the between-subjects factor. To compensate for the violation of normality in post-hoc testing, bootstrapped independent t-tests (1000 resamples) with confidence intervals were used to explore significant interaction effects, and bootstrapped Pearson's correlation coefficients (1000 resamples) with confidence intervals were employed in the exploratory correlational analysis. The Minimally Clinically Important Difference was calculated to assess whether any statistically significant medication effects might represent clinically meaningful changes.

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Results

Demographic and clinical characteristics of participants

Demographic and clinical characteristics of participants are presented in table 1. The two groups were matched in age, years in education, and MMSE scores. Neither group exhibited signs of dementia (MMSE scores below 24). Patients reported more severe depressive symptomology than healthy controls but, at group level, BDI scores did not exceed the clinical cut-off (above 10). Patient's mean H&Y score suggested that participants were in the relatively early stages of PD. Comparisons of the UPDRS on- and off-medication indicated that the patients' motor symptoms were improved by dopaminergic medication; $t(18) = -6.68$, $p = <.001$.

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Table 1

Demographic and clinical characteristics

	Patient			*Healthy Control*			
	M	*SD*	*Min-Max*	*M*	*SD*	*Min-Max*	*p*
Age	65.9	7.9	52-80	61.4	7.1	46-69	.051
Education	14.6	4.7	8-25	16.1	3.6	10-24	.233
MMSE	29.4	.66	28-30	29.1	1.2	25-30	.242
BDI	7.9	4.0	2-16	4.2	5.4	0-20	.012
Duration	11	8.8	2-37	-	-	-	-
H&Y	2.1	0.7	2-3	-	-	-	-
UPDRS off	31.5	11.3	6-47	-	-	-	-
UPDRS on	17.2	6.9	5-31	-	-	-	-
LEDD (mg)	732.3	658.9	105-3010	-	-	-	-

Note. Age = Age (years), Education = years in education, MMSE = Mini Mental State Exam, BDI = Beck Depression Inventory H&Y = Hoehn & Yahr, UPDRS = Unified Parkinson's disease Rating Scale, LEDD = Levodopa Equivalent Dose, Duration = Disease Duration (months), *p* = statistical significance of between-groups t test.

We ran a mixed ANOVA with medication status (on vs off), rate (faster vs slower), and measure (CS1 vs CS2) as the within-subjects factors, and group (patients vs healthy controls) as the between-subjects factors. There was a significant four-way interaction between medication status, rate, measure, and group; $F(1,44) = 5.08$, $p = .029$, $\eta_p^2 = .10$. We then examined this interaction by completing two separate three-way ANOVAs on CS1 and CS2 scores independently.

Count Score 1

A mixed ANOVA with medication status (on vs off) and rate (faster vs slower) as the within-subjects factors, and group (patient vs control) as the between-subjects factor was conducted on CS1. Descriptive statistics are presented in Table 2.

There was no significant main effect of medication; $F(1,22) = .78$, $p = .38$, $\eta_p^2 = .02$, suggesting that medication status did not affect CS1. However, there was a significant main effect of group; $F(1,44) = 10.97$, $p = .002$, $\eta_p^2 = .20$, suggesting that patients scored more highly on CS1 overall. The main effect of rate was also significant; $F(1,44) = 68.11$, $p = <.001$, $\eta_p^2 = .61$, suggesting that CS1 was higher at the faster than the slower rate of RNG (Figure 1). There were no significant interaction effects.

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Table 2

Mean and Standard deviations for CS1 scores for patients on- and of- medication and healthy controls

	On-medication				Off-medication			
	Patient		Healthy Control*		Patient		Healthy control	
Rate	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Faster rate	70.83	40.36	46.91	23.65	62.74	24.73	45.69	25.42
Slower rate	37.26	16.56	25.17	11.97	39.39	14.25	23.48	12.38

Note. M = Mean, SD = Standard deviation, * = Unmedicated healthy control

Count Score 2

The same analysis was repeated on CS2. Descriptive statistics are presented in Table 3. There was no significant main effect of medication; F (1,44) = 3.64, p = .06, η_p^2 = .08, rate; F (1,44) = .31, p = .58, η_p^2= .01, or group; F (1,44) = .36, p = .55, η_p^2= .01. However, there was a significant interaction effect between rate and medication; F (1,44) = 5.06, p = .03, η_p^2 = .10 (Figure 1).

To explore this interaction further, two post-hoc bootstrapped within-subjects t-tests were performed on CS2 at each rate with medication as the independent variable. Owing to the fact that healthy controls did not take dopaminergic medication during this study, this analysis was conducted on patient scores only. Medication had no effect on CS2 at the faster rate; t (22) = -.24, p = .82, 95% CI [-8.23, 6.52]. However, medication did have a significant effect on CS2 at the slower rate; t (22) = -2.19, p = .09, 95% CI [-29.22, -2.96]. Inspection of descriptive statistics (Table 3) show that CS2 was increased in the on-state.

Table 3

Mean and Standard deviations for CS2 scores for patients on- and of- medication and healthy controls

	On-medication				**Off-medication**			
	Patient		**Healthy Control***		**Patient**		**Healthy control**	
Rate	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Faster rate	40.65	18.31	39.83	12.63	39.78	14.62	38.83	12.72
Slower rate	50.61	36.44	40.17	21.11	35.56	12.87	37.91	10.37

Note. M = Mean, SD = Standard deviation, * Unmedicated healthy control

To ascertain whether or not the on-medication improvement in CS2 scores represented a clinically significant change, the Minimally Clinically Important Difference (MCID) score was calculated. This is the pooled baseline standard deviation, multiplied by 0.2. A change between baseline and treatment greater than the MCID, is considered to represent a clinically meaningful change (Jaeschke, Singer, & Guyatt, 1989; Lemieux, Beaton, Hogg-Johnson, Bordeleau, & Goodwin, 2007). The MCID was originally developed for self-report outcome measures, but has since been applied in neuropsychological testing (Phillips et al., 2015).

Based on the calculated pooled baseline standard deviation of 12.88, a MCID of 2.58 was obtained. The difference between CS2 at the slowest rate off-medication and on-medication is 15.05, which is greater than the MCID. This suggests that the increase in on-medication CS2 scores represents a clinically important difference.

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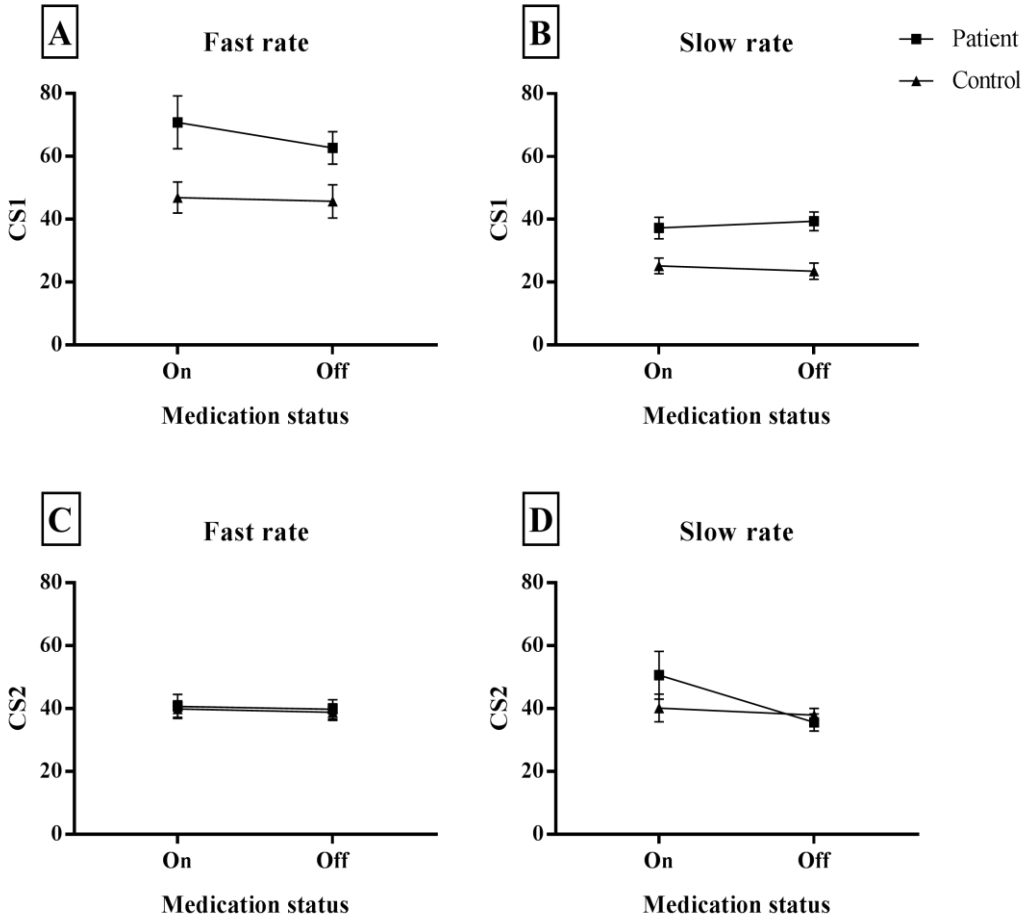

Figure 1. The effect of medication on CS1 scores at the fast (A) and slow (B) rate of RNG, and the effect of medication on CS2 scores at the fast (C) and slow (D) rate of RNG. Error bars represent the standard error of the mean.

RNG performance was not influenced by the patient's ability to keep up with the pacing stimulus

A possible confound is that the potential effect of dopaminergic medication on patients' psychomotor speed might have somehow influenced their ability to keep up with the pacing stimulus. To exclude this possibility, a 2x2 repeated measures ANOVA with medication status (on vs off) and rate (faster vs slower) was conducted on the total time taken to produce 100 numbers (patient data only). As expected, there was a significant main effect of rate; $F(1,22) = 304.5$, $p = <.001$, because it took longer for patients to produce 100 numbers at the slower rate. The main effect of medication was not significant; $F(1,22), = 0.34$, $p = .58$, and the interaction effect was not significant; $F(1,22) = 1.09$, $p = .31$. Therefore, dopaminergic medication did not influence how quickly patients were able to verbally produce numbers during RNG at either the slower or faster rates.

Exploratory correlational analysis with clinical and demographic variables

To explore any potential relationships between paced RNG performance and patient clinical/demographic variables, a series of bootstrapped Pearson's correlations were performed between CS1 and CS2 scores at each rate and medication status, and age, BDI, MMSE, disease duration, UPDRS change (calculated from UPDRS off-medication – UPDRS on-medication to assess the effect of medication on PD symptom severity), and H&Y scores (patient scores only).

MMSE scores positively correlated with CS2 off-medication at the slower rate of RNG ($r = .75$, $p = .08$, 95% CI [0.04, 1.00], suggesting that when medication had been stopped, patients with better general cognitive function made more attempts to execute controlled counting strategies under the lowest cognitive load. However, there was no relationship

between MMSE scores and any of the other paced RNG indices in other medication or cognitive load conditions.

Age, depressive symptomology, disease duration, Levodopa Equivalent Dose, time off-medication, UPDRS change, and H&Y scores did not correlate significantly with any measures of paced RNG performance on or off-medication.

Discussion

The main aim of this study was to examine the effect of dopaminergic medication administered to patients with PD on paced RNG performance (CS1 and CS2 scores). The absence of main effects of medication on CS1 and CS2 suggests that medication does not influence paced RNG performance overall. However, the significant interaction between medication and rate on CS2, suggests that dopaminergic medication increases patients' ability to engage in more controlled RNG strategies, only at the slower rate when the cognitive load is lowest. Given that dopamine agonists are the main pharmacological treatment for PD, but have also been associated with impulse control disorders in PD, our findings offer a potentially meaningful contribution to the existing literature. First, they suggest that automatic responding, as indexed by CS1, is not directly influenced by dopaminergic medication. Second, the results suggest that dopaminergic medication can promote the recruitment of controlled processing strategies (CS2), only when there is sufficient time to engage in more effortful behaviour.

The conclusion that dopaminergic medication might be beneficial for certain forms of impulsivity is supported by on-medication improvements observed during other tasks tapping inhibitory control such as in the Simon Task (van Wouwe et al., 2016) and in a moving dots task (Huang et al., 2015). It is also consistent with the proposed role of dopamine in cognitive control (Ott & Nieder, 2019) and in managing the brain and body's energy resources (Chakravarthy, Balasubramani, Mandali, Jahanshahi, & Moustafa, 2018).

The main effect of group on CS1, indicates that patients produced less random sequences of numbers during RNG than healthy controls. This suggests that the ability to suppress automatic responding during RNG is impaired in PD, irrespective of medication status. It is also consistent with previously observed PD-associated inhibitory control impairments relative to healthy controls during RNG (Brown et al., 1998; Dirnberger et al., 2005; Obeso et al., 2011).

The observed effect of rate on CS1 (greater recruitment of automatic counting strategies at the faster rate), suggests that the execution of automatic counting tendencies during RNG is load-dependent. We have previously demonstrated the load-dependent nature of RNG in PD patients, who showed a bias towards CS1, while healthy controls showed a bias towards CS2 (Brown et al., 1998) - the addition of a secondary task (manual tracking) reversed the bias in healthy controls and exacerbated the bias in patients (Brown et al, 1998). We have also demonstrated load-dependent paced-RNG performance in patients on- versus off- deep brain stimulation of the subthalamic nucleus (Williams et al., 2015). This load-dependence reflects the limited-capacity nature of the executive processes underlying RNG performance, which appears to render patients susceptible to influence from PD neuropathology and treatment. It may also have real-world implications for patients' decision-making under conditions that would introduce competition for cognitive control resources; for example, patients with PD may be more vulnerable when making decisions during times of increased stress or when decisions need to made quickly.

In order to test if RNG performance was related to clinical factors, we conducted an exploratory correlational analysis of RNG indices against the clinical measures used in this study. MMSE scores positively correlated with CS2 off-medication at the slower rate of RNG, suggesting that when medication had been stopped, patients with better general cognitive function made more attempts to execute controlled counting strategies under the lowest

cognitive load. While the inflated risk of Type 1 error associated with multiple comparisons means this finding should be interpreted with caution, this would be consistent with the theory that RNG performance is related to cognitive control. No other RNG indices correlated with any other clinical variables measured in this study, but it is possible that RNG performance is related to other clinical factors which were not assessed. A future avenue for research might be to investigate this possibility directly.

While our findings suggest that dopaminergic medication might improve certain forms of inhibitory control under specific conditions, deleterious effects of dopaminergic medication on other measures of inhibitory control in patients with PD have also been observed (Djamshidian et al., 2013; Huang et al., 2015; Wylie et al., 2012). Why might dopaminergic medication improve inhibitory control in PD during some neuropsychological tasks but exacerbate it on others? This discrepancy may relate to the fact that there are different forms of inhibitory control and impulsivity (Evenden, 1999), likely sub-served by distinct but overlapping neural substrates. In their review of impulsivity, compulsivity, and top-down control, Dalley, Everitt, and Robbins (2011) argue that impulsivity may be caused by 'chemical imbalance' in cortical areas as well as the striatum, which are adversely affected by loss of dopaminergic innervation in PD (Dalley et al., 2011; Surmeier, Graves, & Shen, 2014). They propose two distinct networks of neural circuitry for 'waiting impulsivity' and 'stopping impulsivity', involving distinct cortical regions and the ventral or dorsal striatum respectively. There are, therefore likely to be parallel anatomically and functionally segregated cortical-basal ganglia loops (Alexander, Delong, & Strick, 1986), supporting dissociable forms of impulsivity and inhibitory control which are topographically distributed across the striatum.

The effect of dopaminergic medication on inhibitory control in PD may also be influenced by disease duration. Nigrostriatal denervation in PD begins in posterior-dorsal striatal regions and advances to anterior-ventral regions with progression of the illness. The most severe loss

of dopaminergic neurotransmission is in posterior-dorsal regions of the striatum (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). Therefore, it is possible that the forms of inhibitory control represented in the posterior-dorsal regions of the striatum are 'treated' by dopaminergic therapy (leading to decreased impulsivity), while the types of impulsivity which are represented in anterior-ventral striatal regions which are less dopamine-depleted in early PD are 'over-dosed' by dopamine (leading to increased impulsivity). This would be the case until the later stages of the disease when these latter striatal regions also become dopamine depleted (Gotham, Brown, & Marsden, 1988). As such, disease duration and/or disease stage is potentially an important factor to consider when interpreting studies of dopaminergic medication on cognitive function and inhibitory control in PD. In support of this, a recent meta-analysis of medication effects on response inhibition in PD has found that medication had beneficial effects in patients with shorter disease duration (Manza, Amandola, Tatineni, Li, & Leung, 2017). Indeed, the patients in this study were at a relatively early stage of disease (Mean Hoehn & Yahr stage = 2.1), and although disease duration did not correlate with RNG performance in this sample, future research could aim to examine the effect of dopaminergic medication on RNG at later stages.

The type of inhibitory control assessed by RNG does not map neatly onto any of the previously defined forms of impulsivity (risky behaviours, motor inhibition, reflection impulsivity, delayed gratification). However, there may be some shared neural substrates, including cortico-striatal circuitry. Several approaches including imaging in healthy controls and PD patients (Dirnberger et al., 2005; Jahanshahi et al., 2000; Thobois et al., 2007), transcranial magnetic stimulation (Jahanshahi et al., 1998) recording of local field potentials from the subthalamic nucleus (Anzak et al., 2013), and a subthalamic deep brain stimulation on-off methodology (Williams et al., 2015), has previously provided evidence for the involvement of brain regions including the ldlPFC, globus pallidus, as well as the subthalamic

nucleus and its cortical connections in RNG. In addition, we have previously proposed that fronto-striato-subthalamic-pallidal circuits mediate controlled and automatic/habitual inhibition as well as action (Jahanshahi, Obeso, Rothwell, & Obeso, 2015). These circuits, particularly the motor circuit which is dysfunctional in PD, are also engaged during RNG performance (Dirnberger et al., 2005).

Limitations

The inclusion of healthy control data was to allow for comparison against 'normal' performance and to control for the effects of repeated assessment. The aim was not to assess the effect of dopaminergic medication on cognitive control in healthy individuals.

Caution should be exercised when interpreting the results of the MCID analysis on CS2 scores at the slowest rate of RNG. While this analysis suggested that medication resulted in a clinically meaningful improvement in patients' attempts to execute more controlled processing strategies during RNG, there is no universally accepted way of establishing whether or not a change represents a clinically and statistically significant change, and this is an issue in itself that requires further clarification (Page, 2014). Therefore, these findings should be considered preliminary, and warrant further exploration.

Conclusions

The aim of this study was to investigate the effect of dopaminergic medication for PD on RNG performance. Our results indicate that dopaminergic therapy does not influence the recruitment of automatic, habitual counting strategies during RNG, but does increase the recruitment of more controlled counting strategies under conditions of low cognitive load. This could mean that dopamine therapy may ameliorate some PD-associated deficits in inhibitory control by allowing patients to engage in more controlled processing, but only when there is sufficient time to do so.

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