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RESEARCH PAPER

Examining dorsal striatum in cognitive effort using Parkinson's disease and fMRI

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Abstract

Objective: Understanding cognition mediated by the striatum can clarify cognitive deficits in Parkinson's disease (PD). Previously, we claimed that dorsal striatum (DS) mediates cognitive flexibility. To refute the possibility that variation in cognitive effort confounded our observations, we reexamined our data to dissociate cognitive flexibility from effort. PD provides a model for exploring DS-mediated functions. In PD, dopamine-producing cells supplying DS are significantly degenerated. DS-mediated functions are impaired off and improved on dopamine replacement medication. Functional magnetic resonance imaging (fMRI) can confirm striatum-mediated functions. **Methods**: Twenty-two PD patients, off-on dopaminergic medication, and 22 healthy age-matched controls performed a number selection task. Numerical distance between number pairs varied systematically. Selecting between two numbers that are closer versus distant in magnitude is more effortful: the symbolic distance effect. However, selecting between closer versus distant number pairs is equivalent in the need to alter attention or response strategies (i.e., cognitive flexibility). In Experiment 2, 28 healthy participants performed the same task with simultaneous measurement of brain activity with fMRI. **Results**: The symbolic distance effect was equivalent for PD versus control participants and across medication sessions. Furthermore, symbolic distance did not correlate with DS activation using fMRI. In this dataset, we showed previously that integrating conflicting influences on decision making is (1) impaired in PD and improved by dopaminergic therapy and (2) associated with preferential DS activation using fMRI. **Interpretation**: These findings support the notion that DS mediates cognitive flexibility specifically, not merely cognitive effort, accounting for some cognitive deficits in PD and informing treatment.

Introduction

Impaired decision making is a complication of neurological illnesses, including Parkinson's disease (PD), with significant adverse consequences to the individual and society at large. These complex processes implicate a host of brain structures, including the striatum. The striatum is the input region of the basal ganglia, a collection of functionally linked subcortical nuclei, and previous investigations suggest that individual segments of the striatum mediate different elements of cognition. Despite their contiguity at a gross level of inspection, ventral and dorsal portions of striatum are characterized by subtle cytoarchitectural differences, and distinct, cortical, limbic, and

dopaminergic afferents,[1–3] as well as vascular supplies.[4] The ventral striatum (VS) comprises the nucleus accumbens and most ventral portions of the caudate and putamen. In contrast, the dorsal striatum (DS) includes the bulk of the caudate nucleus and the putamen. By partitioning cognitive functions attributed to VS and DS, two cohesive sets of cognitive operations are beginning to emerge.

In a recent study, we investigated the role of DS in decision making.[5] PD provides a robust model for investigating DS functions, as degeneration of the substantia nigra (SN) leads to impairment of DS-mediated motor and cognitive functions. Impairments are remedied by treatment with dopamine replacement medications such as L-3,4-dihydroxyphenylalanine (L-DOPA) or dopamine receptor agonists.[6,7] All participants in our original study performed a simple number selection task during which they repeatedly chose the larger or smaller number in a pair depending on a simultaneously occurring cue. A complete trial consisted of two consecutive selection events. In one condition, a number was repeated across the two events of the trial but it was of opposite relative magnitude (i.e., smaller or larger number in the pair) from one selection event to the next. In this incongruent condition, healthy participants are slower and more error prone in responding on the second selection event relative to a control condition in which no numbers are repeated.[8,9] Response interference arises due to integration of conflicting influences on selection. Off medication, PD patients showed less response interference than controls in the incongruent condition. When patients were tested on dopamine therapy, interference scores normalized. This pattern of impairment off medication and improvement on dopaminergic therapy in PD is the signature of a DS-mediated function. Further supporting our interpretation that DS mediates flexibly integrating competing influences on decision making in the incongruent condition, in a separate experiment with healthy young adults, DS activation was significantly greater for the incongruent relative to the control condition using functional magnetic resonance imaging (fMRI). We interpreted these results as evidence that DS mediates cognitive flexibility.

DS: cognitive flexibility or cognitive effort?

Although our results[5] add to a growing body of literature suggesting that DS underlies cognitive flexibility,[10–13] an important confound exists. Situations that require high cognitive flexibility are more effortful than conditions to which they are typically compared. The concept of cognitive effort has variably been defined as the proportion of limited-capacity central processing engaged,[14] the number of elementary processes enacted,[15] or the duration over which cognitive resources are expended.[16] In fact, it has also been suggested that DS mediates cognitive effort, indexing task difficulty, complexity, or attentional demand.[17–20]

The aim of the current study was to dissociate cognitive effort from cognitive flexibility. Returning to the data from our previous study, where we concluded that DS underlies reconciliation of conflicting influences on decision making,[5] we examined the effect of the distance between number pairs to test whether DS mediates cognitive effort generally or cognitive flexibility specifically. Longer response times (RTs) and more numerous errors arise in choosing between alternatives that are closer (e.g., ONE vs. TWO) versus more distant (e.g., ONE vs. FOUR) to one another along the number continuum.[21] This symbolic distance effect has been explained by greater overlap for closer pairs (1) in representational features[22] and/or (2) with respect to variance distributions surrounding their true locations along a representational continuum.[23,24] Although selecting between closer relative to more distant pairs of items is more effortful, indicated by increased latencies and error rates, these selections do not require greater cognitive flexibility. That is, between numerically closer and distant pairs, there is no greater need to shift attentional or response strategies, to suppress more habitual responses, or to reconcile conflicting influences on performance.

In Experiment 1, we directly tested whether DS mediates cognitive effort generally as opposed to cognitive flexibility specifically, contrasting the effect of PD and dopaminergic medication on the symbolic distance effect. In Experiment 2, we reanalyzed fMRI data for symbolic distance in healthy young adults performing the number selection task.

Experiment 1: Contrasting Symbolic Distance Effect in Patients With PD On and Off Dopamine Replacement Therapy

Method

Participants

Twenty-two PD patients without a co-existing diagnosis of dementia or cognitive impairment were included in the study. All patients met (1) the core assessment program for surgical interventional therapy criteria for the diagnosis of idiopathic PD[25] and (2) the U.K. brain bank criteria for the diagnosis of PD.[26] Twenty-two age- and education-matched healthy control participants were also included in the study. Patients and controls abusing alcohol, prescription or street drugs, or taking medications such as Donepezil, Rivastigmine, Galantamine, or Memantine were excluded from participation. Furthermore, if

patients described a change in function related to cognitive symptoms, performed below 100 on the Adult National Reading Test (ANART), or could not successfully draw a clock or copy a cube, they were excluded from the study. Two PD patients and one control participant were excluded owing to excessively high error rates. This study was approved by the Ethics Review Board of the Sudbury Regional Hospital and all patients provided informed consent according to the Declaration of Helsinki.[27]

Severity of disease was assessed for all patients, both off and on dopaminergic medication, using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) by a movement disorders neurologist (P. A. M.). All control participants had normal screening neurological examinations, save for three participants, two of whom were noted to have mild essential tremor, which did not hamper daily function, and one whose examination revealed diffuse hyper-reflexia relating to a previous cervical spine decompression surgery. Subsequent MRI of the brain was normal for this control participant. All patients and no controls were treated with dopaminergic medications. Mean group demographic information, screening cognitive measures, UPDRS scores off and on medication, and daily doses of dopamine replacement therapy in L-DOPA equivalents are presented in Table 1. There were no significant differences between PD patients and controls in demographic details.

Apparatus

The experiment was conducted on a 12.1″ widescreen laptop (Lenovo X201, Beijing, China) running at a resolution of 1280 × 800 on the Windows 7 operating system. The screen was angled for optimal viewing at a distance of ~50 cm. Responses were spoken into a standard desktop microphone.

Experimental design and procedure

All patients performed a number selection task off and on dopamine replacement therapy, during which they repeatedly chose either the smaller or larger number in a pair depending on a simultaneously presented cue. The OFF-ON orders were counterbalanced across participants. During ON testing sessions, PD patients took their dopamine replacement medication as prescribed. During OFF testing sessions, PD patients abstained from dopamine replacement therapy for a minimum of 12 and a maximum of 18 h prior to testing. Age- and education-matched control participants performed the selection task on two consecutive days. Data from control participants were analyzed to parallel the OFF-ON order of the patient to whom they were matched. At no time, however, did they receive dopaminergic medications.

During both OFF and ON testing sessions, participants performed 576 number selections, which were organized into 288 number selection couples, as explained below. Participants received 10 practice trials. All number selections proceeded as follows: (1) four crosses in the center of a computer screen for 500 msec, (2) a blank screen for 500 msec, (3) two number words one above the other, surrounded by a large or small box, (4) the participant spoke his/her response into a microphone, stopping the timer, (5) stimuli disappeared, and (6) a blank screen

Table 1. Experiment 1: demographics and clinical information, as well as screening cognitive and affective measures for PD patients and controls.

Group	*N*	Age	Education	Years disease	L-DOPA (mg)	DA (*n*)	UPDRS ON	UPDRS OFF
PD	22	63.18 (2.00)	13.82 (0.87)	5.16 (1.27)	480 (65.31)	6	17.22 (1.60)	22.36 (1.89)
CT	22	62.27 (1.63)	12.86 (0.65)	–	–	–	–	–

Group	ANART IQ	BDI-II ON	BDI-II OFF	Apathy	F-words	Recall	Clock	Cube
PD	120.34 (1.81)	7.55 (1.22)	9.15 (1.63)	10.68 (1.33)	10.86 (1.83)	6.27 (0.60)	3 (0)	1 (0)
CT	121.69 (1.49)	2.77 (0.77)	3.16 (0.86)	9.64 (1.06)	14.31 (1.21)	7.45 (0.68)	3 (0)	1 (0)

Values are presented as group means (SEM). Screening cognitive and affective measures were completed by patients on medication unless indicated otherwise. Control participants did NOT receive dopaminergic therapy during any session of the experiment. Their data are presented here to correspond to the OFF-ON order of the PD patient to whom they were matched. Education, years of education; Years disease, years since diagnosis of PD; L-DOPA, daily L-DOPA equivalent dose in mg; DA, number of patients taking dopamine agonists; UPDRS ON, Unified Parkinson's Disease Rating Scale motor score on medication; UPDRS OFF, Unified Parkinson's Disease Rating Scale motor score off medication; ANART IQ, National Adult Reading Test (Nelson and Willison, 1991) IQ estimation; BDI-II ON, Beck Depression Inventory II score measured for PD patients while they were treated with their usual dopamine replacement therapy and for control participants during the session that corresponded to the ON session of the PD patient to whom they were matched; BDI-II OFF, Beck Depression Inventory II score measured for PD patients while they abstained from their usual dopamine replacement therapy and for control participants during the session that corresponded to the OFF session of the PD patient to whom they were matched; Apathy, Apathy Evaluation Scale score; F-words, number of words beginning with the letter F generated in 1 min; Clock, score on clock drawing component of Montreal Cognitive Assessment (MOCA); Cube, score on cube copying component of MOCA.

appeared for 500 msec while the experimenter coded the accuracy of the response. On half of the number selections, the box was small, with thin lines, indicating that the participant should read aloud the smaller number in the pair. On the other half, the box was large, with thick lines, cueing the participant to read aloud the larger number in the pair. Participants were asked to respond as quickly, yet as accurately as possible. RTs were calculated as the time of the spoken response minus the onset of the number pair in milliseconds (msec). All sessions were recorded and reviewed to ensure coding accuracy.

The numbers ONE through EIGHT were presented repeatedly, in pairs, throughout the experiment. Although from the participants' perspective the task comprised recurring, independent, randomly ordered number pairings, trials were actually organized into prime-probe couples. On 67% of the trials, a number repeated across the prime and the probe and was either matched (congruent) or mismatched (incongruent) in terms of its relative magnitude (i.e., smaller or larger number in the pair) across these events. In the remaining 33% of the trials, no numbers repeated. In MacDonald et al.,[5] performance (i.e., latency and error rates) on only the probe events were analyzed to investigate the effect of stimulus magnitude association matches versus mismatches across consecutive events. Here, we examined latency and error rates for prime events only, comparing pairs with one (e.g., TWO vs. THREE), two (e.g., TWO vs. FOUR), or three (e.g., TWO vs. FIVE) distances along the number continuum. In the prime events, there was no systematic relation between the numbers appearing on the probe events of one trial and the prime events of the subsequent trial. Furthermore, the selection criterion (i.e., large or small) did not change from the probe event of one trial to the prime event on the subsequent trial. In this way, only numerical distance was systematically manipulated on the prime events. The position of the target (i.e., top or bottom) varied randomly on each prime and probe event. Figure 1 presents trial event sequences and three consecutive trials, comprising both prime and probe events, for each of the numerical distances between the pairs on the prime.

Results

Figure 2 presents the mean RTs and error rates by symbolic distance for PD and control participants, in OFF and ON medication sessions. RTs for correctly performed prime selections and error rates on prime events were analyzed using $2 \times 2 \times 3$ mixed analyses of variance (ANOVA) with group (PD vs. control) as the between subject factor, and medication session (OFF vs. ON) and numerical distance (one vs. two vs. three) as within-subject variables. The main effect of Symbolic distance was significant, with the longest RTs arising for the symbolically closest number pairs (i.e., one step) and the shortest RTs occurring for the most distant number pairs (i.e., three step), F (2, 84) = 40.01, Mean Squared error (*MSe*) = 1917.09, $P < 0.001$. The main effects of Group and Medication session, and the Group × Medication ($F < 1$), Group × Symbolic distance ($F < 1$), Group × Medication session × Symbolic distance, F (2, 84) = 2.14, *MSe* = 2310.35, $P > 0.120$, interactions were nonsignificant. Similarly, for errors, Symbolic distance was significant, with higher error rates occurring for the smallest numerical distance pairs, F (2, 84) = 10.99, *MSe* = 0.001, $P < 0.001$. No other main effects or interactions in terms of error rates were significant.

Experiment 2: Symbolic Distance Effect Using Functional MRI

Method

Participants

Twenty-eight healthy, young adults participated in Experiment 2. Participants had a mean age of 21.62 *(1.19)* and a mean of 15.05 (*0.82*) years of education. This study was approved by the Joint Ethics Committee of the *Regroupement Neuroimagerie Québec* and all participants gave informed consent according to the Declaration of Helsinki.[27] The behavioral and fMRI data from 13 participants were presented in MacDonald et al.[5] We collected data from an additional fifteen healthy young adults for this study with the aim of increasing statistical power.

Experimental design and procedures

Participants performed four to five blocks of 72 number selection trials in the fMRI scanner after receiving 10 practice trials. Trials proceeded as described in Experiment 1 except that (1) the intertrial interval was jittered randomly from 600 to 1200 msec and (2) number pairs remained on the screen until the experimenter scored the accuracy of participants' spoken responses. The experimental session was recorded and all responses were reviewed for scoring accuracy. Accurate RTs were determined using Audacity audio file processing software. RTs were calculated as the onset of a spoken response minus the onset of the number pair in msec. Numerical distance (i.e., one-, two-, vs. three-step symbolic distances) varied systematically on prime events.

MRI acquisition

Scanning was done in the 3T Siemens Trio Magnetom MRI with the Total Imaging Matrix technology scanner at

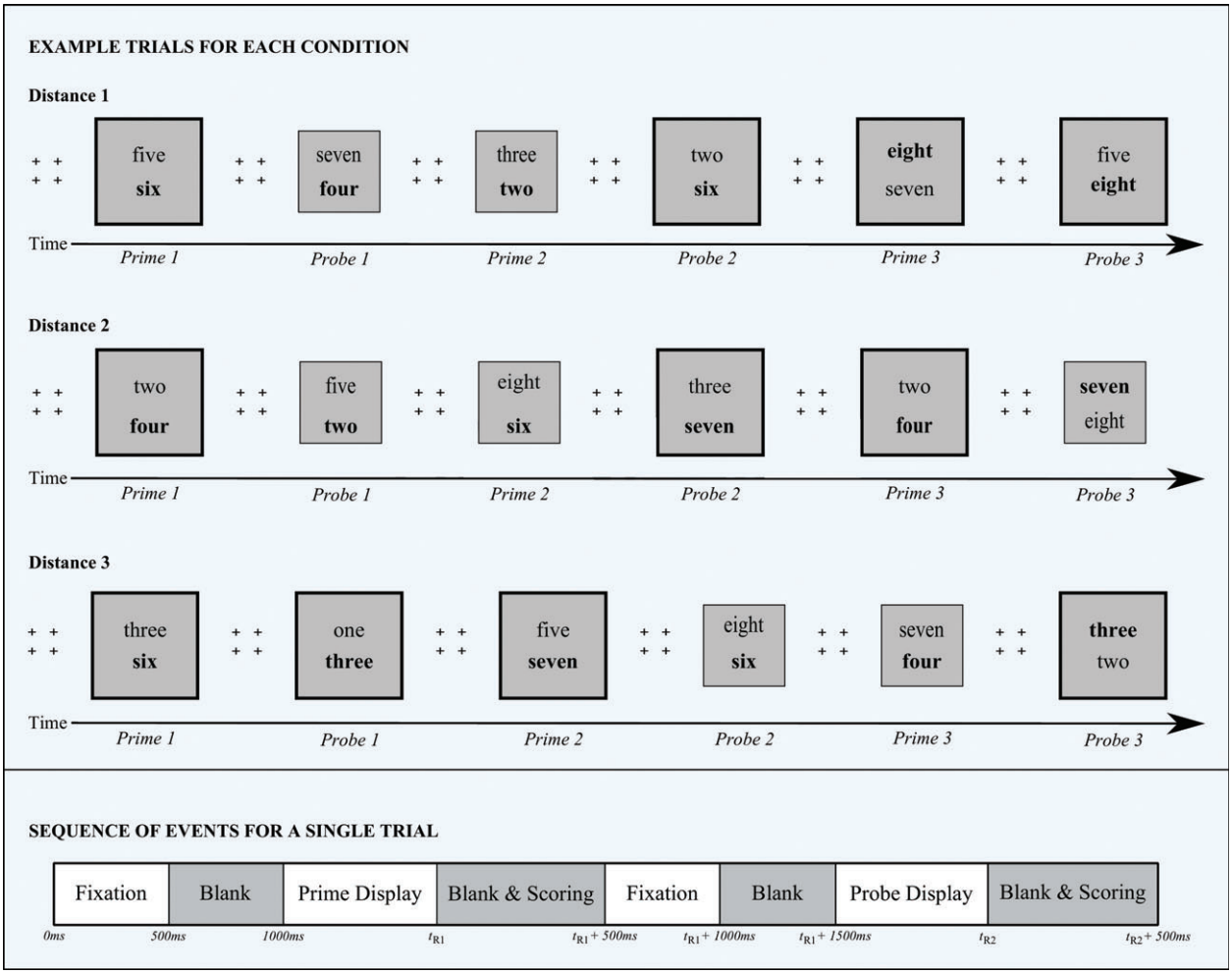


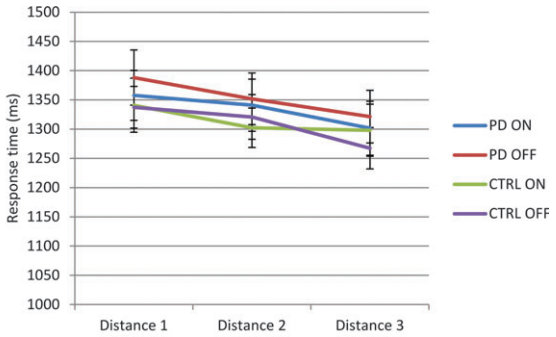
Figure 1. Three consecutive trials, each consisting of a prime and probe event, for symbolic distances of 1 (top), 2 (middle), and 3 (bottom) between number pairs on the prime event are presented. Four "plus" signs were presented to orient the participant's attention to the center of the computer screen, prior to each event. A large box with thick lines signaled that the larger number in the pair was the target. A small box with thin lines indicated that the smaller number in the pair was the target. Participants were instructed to read aloud the target number, for each event, as quickly yet as accurately as possible. For illustrative purposes in the figure only, the target is presented in bold, whereas the distracter appears in regular font. Notice that the selection criterion (i.e., larger or smaller number) did not change from the probe event on one trial and the prime event on the subsequent trial. Furthermore, note that there was no systematic relation between the numbers presented on the probe event on one trial and the numbers appearing in the subsequent prime event. Below the example trials, we present a timeline showing the sequence and durations of events for a single trial. Each trial began with a fixation stimulus (i.e. four plus signs) for 500 msec, followed by a blank screen for 500 msec. A pair of numbers was presented one above the other, within a large or a small box, constituting the prime event. The stimuli remained on the screen until the participant gave a response into a microphone, ending the timer. A blank screen was presented for 500 msec during which the experimenter scored the participant's response. A fixation stimulus and a blank screen were presented again, each for 500 msec, prior to the probe event, which consisted of two numbers one above the other within a large or a small box. The probe display ended when the participant gave a response into a microphone. A blank screen occurred during which the experimenter scored performance on the probe event.

the Functional Neuroimaging Unit of the CRIUGM. Scout for positioning the participant was followed by anatomical localization with T1. Four to five runs of T2*-weighted functional acquisitions followed, lasting 8.5 min each and consisting of 204 frames (1 per 2.5 sec). Each frame contained 36 slices along the anterior commissure/posterior commissure with 64 × 64 pixel matrix, an isotropic voxel size of 3.4 × 3.4 × 3.4 mm^3. The FA was 90° and the TE 30 msec.

MRI data analysis

Data analysis using fmristat analysis (Worsley et al.[28] as per Monchi et al.[13]) was performed. Frames 1–2 in each

A



B

		Distance 1	Distance 2	Distance 3
PD	ON	0.160	0.141	0.150
	OFF	0.158	0.137	0.141
CTRL	ON	0.146	0.120	0.147
	OFF	0.145	0.131	0.140

Figure 2. (A) Experiment 1: mean response times for selections on prime events as a function of the symbolic distance (1, 2, or 3) between number pairs, for PD patients and healthy controls in both experimental sessions. The blue line designates performance of PD patients on medication whereas the red line presents their performance off dopaminergic medication. Although control participants did not receive dopaminergic therapy during either experimental session, their data are presented to correspond to the OFF (mauve line) versus ON (green line) session of the PD patient to whom they were matched. Error bars represent SEM. (B) Experiment 1: mean error rates (SEM) for selections on prime events as a function of the symbolic distance (1, 2, or 3) between number pairs, for PD patients and healthy controls in both experimental sessions.

run were discarded. Remaining images were realigned to Frame 3 for motion correction and smoothed using a 6 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. Analysis was based on a linear model with correlated errors. The design matrix was convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. The correlation structure was modeled as an autoregressive process with autocorrelation parameter estimated from the least squares residuals, at each voxel. The autocorrelation parameter was first regularized by spatial smoothing and used to "whiten" the data and design matrix. The linear model was reestimated using least squares on the whitened data to produce estimates of effects and their standard errors. Effect files and anatomical images were then spatially normalized by nonlinear transformation into the standard proportional stereotaxic space of Talairach and Tournoux[29] using the algorithm of Collins et al.[30] and the ICBM152 atlas as an approximation. Runs, sessions, and participants were combined using a mixed effects linear model. Random effects analysis was performed by estimating the ratio of the random effects variance to the fixed-effects variance, regularizing this ratio by spatial smoothing with a Gaussian filter. The amount of smoothing was chosen to achieve 100 effective degrees of freedom.[31] Statistical maps were thresholded at $P < 0.05$ correcting for multiple comparisons using the minimum between a Bonferroni correction and random field theory in the single-group analysis. This corresponds to t-statistics equal to or above 4.7 or a cluster size larger than 550 mm^3 – only those peaks are reported here. Correctly performed magnitude judgements on prime events for number pairs with numerical distances of one, two, and three were analyzed for a linear trend. Durations of events, calculated from the onset of the number pair to the spoken response, were explicitly included in the design matrix.

Results

Behavioral data

Table 2 presents the mean RTs and error rates for prime events as a function of numerical distance. RTs for correctly performed trials and error rates were submitted to a one-way ANOVA with distance between prime number pairs (one vs. two vs. three) as the within-subject variable. The Symbolic distance effect was significant, owing to longer RTs and higher error rates for closer relative to more distant pairs, $F\ (1,\ 27) = 5.10$, $MSe = 2421.94$, $P < 0.050$, and $F\ (1,\ 27) = 4.78$, $MSe = 0.001$, $P < 0.025$.

fMRI data

Bold signal correlated with numerical distance was not significant in any region of the basal ganglia. Neural regions significantly associated with symbolic distance are presented in Table 3. Activity in bilateral occipital, fusiform, supplementary motor area, as well as cerebellum increased with closer symbolic distances. Activity in right inferior temporal gyrus, orbitofrontal, posterior parietal, and cingulate cortices and in left dorsal medial frontal and premotor cortices also correlated significantly with the symbolic distance manipulation, revealing greater activation for closest and least activation for farthest numerical distances between pairs. Lowering the criterion for significance, even at $P < 0.01$ uncorrected for multiple comparisons, no regions in basal ganglia correlated significantly with symbolic distance. When this was lowered further, there

Table 2. Experiment 2: mean response times (SEM) and error rates (SEM) for selections on prime events as a function of the symbolic distance (1, 2, or 3) between number pairs.

	RTs	Errors
Distance 1	1130 (50.39)	0.054 (0.010)
Distance 2	1088 (52.46)	0.046 (0.009)
Distance 3	1100 (54.31)	0.032 (0.008)

Table 3. Experiment 2: brain regions in which BOLD response significantly correlated with symbolic distance.

Anatomical area	*x*	*y*	*z*	*t*-stat	Cluster size
L occipital region	−42	−88	−6	6.01	26,176
L fusiform area	−44	−70	−16	5.78	26,176
L cerebellum	−54	−60	−32	4.58	26,176
L cerebellum	−18	−66	−18	4.02	26,176
R occipital region	18	−42	−82	6.03	20,144
R inferior temporal gyrus	40	−68	−20	5.34	20,144
R cerebellum	28	−62	−36	4.55	20,144
R fusiform area	54	−56	−14	4.55	20,144
R cerebellum	34	−46	−28	4.33	20,144
L supplementary motor area	−6	12	58	5.40	17,984
R cingulate cortex	10	20	46	4.47	17,984
R supplementary motor area	4	20	58	4.26	17,984
L dorsomedial frontal cortex	−2	52	44	4.15	17,984
L premotor cortical areas	−40	4	58	5.25	7392
	−26	−4	58	4.25	7392
	−64	0	32	4.44	7392
Vermis	2	−82	−36	5.3	2032
R medial orbitofrontal cortex	20	50	−10	4.48	1864
R posterior parietal cortex	34	−84	24	4.57	608

was a trend in the right caudate nucleus (8, 22 8, $t = 2.22$ $P = 0.05$, uncorrected for multiple comparisons).

Discussion

This study employed a simple number selection task to investigate the symbolic distance effect (1) in PD patients off and on dopaminergic medication relative to healthy age-matched controls and (2) with fMRI. In Experiment 1, we found that the symbolic distance effect was equivalent for PD patients and controls and was unaffected by dopaminergic medication status. In PD, DS is dopamine-depleted at baseline and functions are impaired. With dopamine replacement therapy, DS-mediated functions improve. Our findings are, therefore, inconsistent with the notion that the greater cognitive effort to distinguish closer relative to more distant number pairs (i.e., the symbolic distance effect) depends upon DS. In Experiment 2, using fMRI, we confirmed that the greater cognitive demand of choosing between numerically closer relative to distant pairs does not preferentially implicate DS.

DS in cognition

It has been suggested that DS' role is to promote cognitive flexibility, allowing updating of stimulus relevance and of stimulus–response mappings.[32] Conditions that are high in cognitive flexibility requirements also are typically more effortful and demand greater attention. The notion that DS mediates cognitive effort has also been proposed.[17–19] We addressed this possible confound and distinguished between these competing hypotheses using the symbolic distance effect. Selecting between numbers that are closer relative to more distant from one another along a continuum is more cognitively effortful but does not demand greater cognitive flexibility. Using PD as a model and fMRI, decisions that required more cognitive effort did not differentially rely on or implicate DS.

Using the same data reported here, we previously found that integrating discrepant stimulus magnitude associations across consecutive trials depended upon intact DS in PD patients and preferentially engaged DS in healthy young adults using fMRI.[5] These results are important in countering the possible arguments that this study lacked statistical power to find differences between PD patients in the OFF and ON states or that features of our imaging protocol somehow compromised our ability to detect significant and specific activations in DS. In fact, in our current Experiment 2, we further enhanced our power and potential to find preferential fMRI activation in DS by collecting data on an additional 15 participants for a total of 28 participants. This is considerably more participants than are included in typical fMRI experiments. Consequently, we feel confident that this study was adequately powered to detect activation differences in DS as a function of symbolic distance if DS truly mediates the symbolic distance effect. Considering our previous results, together with the present null findings, we argue, as have others, that DS specifically promotes cognitive flexibility, which includes shifting attention, reconciling varied and discrepant influences on decision making, and updating stimulus–response mappings.[5,11–13,32] DS does not merely index cognitive effort.

Brain regions mediating the symbolic distance effect and cognitive effort

Our findings are largely consistent with the existing neuroimaging literature on the symbolic distance effect and with the broader hypothesis that discriminating between closer relative to more distant number pairs requires greater cognitive effort. Numerous studies have reported that middle frontal and posterior parietal brain regions are activated in comparing smaller versus larger number distances as we have found here.[23,24,33–36] Whereas parietal regions are thought to be involved in the semantic representation of numerical magnitude, frontal regions are believed to play a role in mediating mechanisms of cognitive control and maintenance of a goal necessary for response selection.[33] In this study, activity in the anterior cingulate cortex (ACC) also correlated with closer relative to more distant symbolic distances, mirroring findings from magnitude comparison tasks in both adults[33,34] and children.[37] More generally, the

ACC has been associated with increased attentional and working memory load, consistent with this region's putative involvement in effortful cognition.[38] We further discovered activation in the orbitofrontal cortex, which has been implicated in mediating the affective components of decision making.[39] Finally, we found increased activity with closer relative to more distant number pairs in occipitotemporal regions, including cuneus, lingual gyrus, and right inferior temporal lobe. These brain regions have previously been implicated in more difficult task conditions such as when similarity between objects increased in terms of numerical magnitude, luminance, or physical size and as RTs increased.[23]

In contrast to previous investigations,[23,24,35–37] however, we did not find significantly increased activity in inferior parietal sulcus (IPS) as a function of symbolic distance. Certain methodological differences between this study and the existing literature might explain this discrepancy (e.g., number words vs. Arabic digits, selection criterion switching). The difference most likely to account for this discrepancy relates to selection criterion switching. Unlike nearly all previous investigations of the symbolic distance effect that required participants to consistently identify the larger or smaller number on every trial, our experiment involved selection criterion switching. Participants were instructed to select either the larger or the smaller number according to a simultaneously presented cue. The criterion for selecting numbers therefore changed from trial-to-trial, seemingly at randomly to the participant. In our previous analysis of this data set, we found that bilateral IPS activation was greater for trials on which participants had to switch versus maintain the selection criterion across prime and probe events.[5] Activation of IPS for task switching has been noted by others as well.[40] On the prime events that were analyzed here for symbolic distance, no response criterion switch was required from the probe event on the previous trial. However, the events analyzed here all occurred in the context of frequent selection criterion switching. We expect that this potentially activated IPS throughout the experiment and masked any symbolic distance-specific activation. Supporting this explanation, the only study of symbolic distance reported herein that also failed to find IPS activation using whole-brain analysis employed a similarly dynamic selection task in which participants were told to judge whether a visually displayed number was smaller or larger than a reference number based on a criterion that changed throughout the experiment.[41]

Implications for cognition in PD

Increasingly, the DS is implicated in cognition. Studies in patients with DS lesions and in healthy participants using fMRI are consistent in implicating DS in processes that require cognitive flexibility, such as in overriding prepotent responses, diverting attention from more salient to less salient stimuli, in integrating conflicting information, and in mentally rotating images.[10,11,42,43] In PD, significant degeneration of the SN at the time of diagnosis leads to substantial dopamine deficiency in the DS specifically. This DS dopamine depletion produces the motor abnormalities that characterize the disease and arguably leads to at least some of the cognitive deficits that are now increasingly recognized even early in the illness.[44] Like the motor symptoms, cognitive abnormalities that are presumed to relate to DS dopamine deficiency have been shown to improve with dopaminergic medication.[6,7] Consistent with these notions, there is a substantial body of evidence, including our previous study,[5] that cognitive flexibility is impaired at baseline in PD and improved by dopaminergic medication.[6,7]

However, the cognitive profile and the etiology of cognitive deficits in PD are complex. Some cognitive functions are spared, especially early in the disease course. Here we show that PD patients are not impaired in making cognitively effortful decisions per se and that performance in selecting between symbolically close versus distant number pairs is not affected by dopaminergic medication. In a separate experiment using fMRI and healthy participants, we found that this symbolic distance effect is not mediated by DS, supporting hypotheses about DS' role in cognitive deficits in PD. There are few examples of cognitive functions that are spared and unaffected by dopaminergic therapy in PD, owing in part to a justified bias against publishing null effects. Null effects are open to a number of interpretations, particularly the possibility of a Type 2 error (i.e., failing to find a true difference due to lack of power or other methodological error). This study, therefore, presents a unique opportunity because the likelihood of a Type 2 error is considerably reduced given that the findings described in this manuscript arose from a reanalysis of a data set in which significant OFF-ON medication effects in PD patients and preferential DS activation were previously detected.

In PD, yet other cognitive functions are normal at baseline but are worsened by dopaminergic medication.[6,7] This detrimental effect of dopaminergic therapy on some cognitive functions has been attributed to dopamine overdose of brain regions that endogenously are relatively dopamine replete.[6,45] In PD, the dopamine-producing cells in the ventral tegmental area (VTA) are relatively spared compared to those in the SN.[46] The VTA innervates VS, prefrontal, and limbic cortices, and it is hypothesized that these brain regions are overdosed by dopaminergic medication levels targeted to remediate the deficit in DS. Learning is the cognitive function that is

normal at baseline and most frequently worsened by dopamine replacement.[11,45,47–52] This fits with the literature linking learning with VTA-innervated brain regions.[53] Indeed, combining tests of learning in PD patients off and on dopaminergic medication with fMRI has revealed medication-related decreases in VS,[54,55] ventromedial prefrontal cortex, posterior insula,[56] as well as orbitofrontal cortex.[55]

Conclusion

The cognitive profile in PD is complex and the causes of cognitive dysfunction are undoubtedly multifactorial. These likely include DS dopamine deficiency, cortical neuronal abnormalities and loss, deficits in other neurotransmitter systems (e.g., cholinergic and serotonergic), as well as overdose of VTA-innervated brain regions (e.g., VS, prefrontal, and limbic cortex) from dopaminergic medication levels titrated to redress the substantial DS dopamine deficiency. Enhanced understanding of the cognitive functions mediated by DS, VS, as well as limbic and prefrontal cortices, will therefore promote the unraveling of this complex cognitive profile. As knowledge of the substrates of cognition becomes more crystallized, this will guide the design of cognitive studies in PD and will shed light on appropriate therapeutic strategies given a wide range of symptoms and individual patient priorities.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique, C. Proofing and final production.

Alex MacDonald: 1A, 1B, 1C, 3A, 3B, 3C.
Ken Seergobin: 1A, 1B, 1C, 2A, 2B, 2C, 3B.
Ruzbeh Tamjeedi: 1C, 3B.
Adrian Owen: 2C, 3B.
Jean-Sebastien Provost: 2A, 2B, 2C.
Oury Monchi: 1B, 3B.
Hooman Ganjavi: 1B, 1C, 3B.
Penny MacDonald: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B, 3C.

Conflict of Interest

Alex MacDonald, Ken Seergobin, Ruzbeh Tamjeedi, Adrian Owen, Jean-Sebastien Provost, Oury Monchi, and Hooman Ganjavi have nothing to disclose.

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