

Dorsal striatum does not mediate feedback-based, stimulus-response learning: An event-related fMRI study in patients with Parkinson's disease tested on and off dopaminergic therapy



Nole M. Hiebert^{a,b}, Adrian M. Owen^{a,b,c}, Hooman Ganjavi^d, Daniel Mendonça^e,
Mary E. Jenkins^e, Ken N. Seergobin^{a,e}, Penny A. MacDonald^{a,b,c,e,*}

^a Brain and Mind Institute, University of Western Ontario, London, Ontario, N6A 5B7 Canada

^b Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, N6A 5C1, Canada

^c Department of Psychology, University of Western Ontario, London, Ontario, N6A 5C2, Canada

^d Department of Psychiatry, University of Western Ontario, London, Ontario, N6C 0A7, Canada

^e Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, N6A 5A5, Canada

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ABSTRACT

Learning associations between stimuli and responses is essential to everyday life. Dorsal striatum (DS) has long been implicated in stimulus-response learning, though recent results challenge this contention. We have proposed that discrepant findings arise because stimulus-response learning methodology generally confounds learning and response selection processes. In 19 patients with Parkinson's disease (PD) and 18 age-matched controls, we found that dopaminergic therapy *decreased* the efficiency of stimulus-response learning, with corresponding *attenuation* of ventral striatum (VS) activation. In contrast, exogenous dopamine *improved* response selection accuracy related to *enhanced* DS BOLD signal. Contrasts *between* PD patients and controls fully support these within-subject patterns. These double dissociations in terms of behaviour and neural activity related to VS and DS in PD and in response to dopaminergic therapy, strongly refute the view that DS mediates stimulus-response learning through feedback. Our findings integrate with a growing literature favouring a role for DS in decision making rather than learning, and unite two literature that have been evolving independently.

1. Introduction

Learning to associate responses to specific stimuli seamlessly and without intent is essential for adaptive behaviour and is the basis for how organisms interact with and thrive in their environments (Thorndike, 1898). Stimulus-response learning can be probed using many different paradigms. In humans, the most traditional tasks involve associating abstract images with a manual response such as a key-press or button-press response in the presence of feedback (Boettiger and D'Esposito, 2005; Brovelli et al., 2008; Seger et al., 2010; Hiebert et al., 2014; Vo et al., 2014; Hampshire et al., 2016). The use of abstract images or images containing attributes that are difficult to verbalize and categorize based on previous experience facilitates learning through implicit mechanisms referred to as procedural learning (Ashby, 1998) mediated in part by the striatum (Ashby, 1998; Toni and Passingham, 1999).

Additionally, the use of abstract images as opposed to recognizable objects such as fruit or tools creates more difficulty in learning the stimulus-response associations, allowing more observations before learning asymptotes, facilitating a greater exploration of learning processes.

The view that the dorsal striatum (DS)—consisting of the bulk of the caudate nucleus and putamen—is critical for stimulus-response learning, is well-entrenched (Thompson, 1963; Yin and Knowlton, 2006; Brovelli et al., 2011; Chiu et al., 2017). Despite the prevalence of this view, learning is often preserved in patients (Exner et al., 2002; MacDonald et al., 2013; Hiebert et al., 2014; Vo et al., 2014) and animals (Atallah et al., 2007) with DS dysfunction.

Potentially underlying the discrepancies in the stimulus-response learning literature, response selection decisions and learning are often intrinsically confounded (McDonald and Hong, 2004; Jessup and

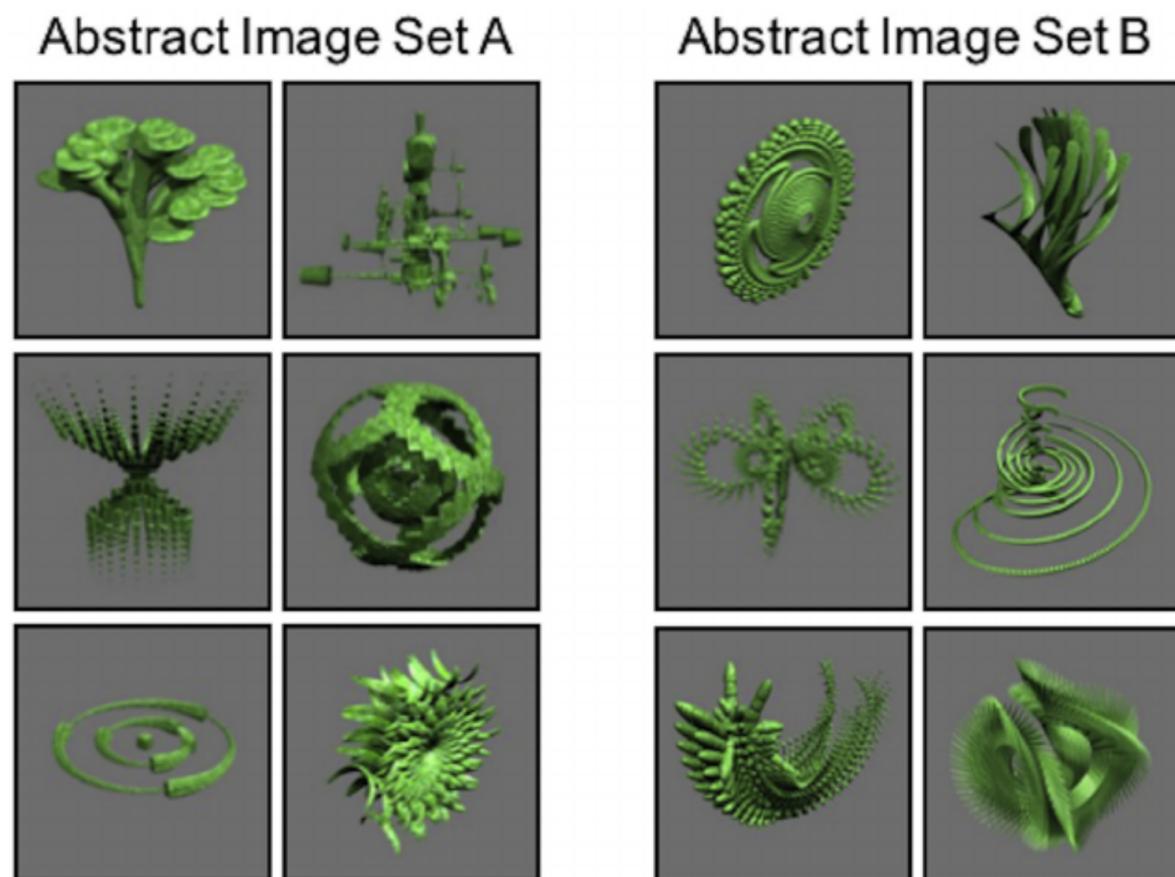
* Corresponding author. Brain and Mind Institute, Western Interdisciplinary Research Building, Room 5160, University of Western Ontario, London, Ontario, N6A 5B7, Canada.

E-mail address: penny.macdonald@lhsc.on.ca (P.A. MacDonald).

Table 1

Demographic, clinical, screening cognitive, and affective measures for PD patients and healthy controls.

Group	N	Age	Edu	Duration	l-dopa (mg)	DA (n)	UPDRS OFF	UPDRS ON
PD	19	65.73 (1.80)	15.21 (0.69)	3.95 (0.60)	599.50 (46.37)	9	12.16 (1.32)	15.26 (1.48)
CTRL	18	65.06 (1.70)	15.00 (0.59)	→	→	→	→	→
Group	ANART	MOCA	BDI-II OFF	BDI-II ON	BAI OFF	BAI ON	Apathy OFF	Apathy ON
PD	124.80 (1.63)	27.05 (0.52)	8.31 (1.21)	7.94 (1.23)	7.57 (1.42)	6.47 (1.30)	10.05 (1.06)	10.68 (1.13)
CTRL	124.45 (1.51)	27.00 (0.28)	3.53 (0.56)	3.53 (0.70)	2.41 (0.58)	2.05 (0.55)	9.88 (0.79)	10.29 (0.95)

**Fig. 1.** Abstract images presented in Phase 1 and Phase 2.

Abstract Image Set A and Set B refer to the images presented either on Session 1 or on Session 2. Images were associated with a button pressed by the index, middle, or ring finger buttons.

O'Doherty, 2011). In stimulus-response learning experiments, trials generally proceed as follows: a) a stimulus is presented and participants perform a response, and b) feedback regarding response accuracy is provided. Feedback is the means through which stimulus-response associations are learned. Accuracy in selecting a learned response provides the learning measure. Performance depends upon both decision and learning processes. Failing either to acquire stimulus-response relations or to correctly select learned responses produces impaired performance. Further, in fMRI studies, a) deciding upon and enacting a response, and b) learning from feedback, are typically treated as a single event with all significantly activated brain regions ascribed a role in learning *per se* (Poldrack et al., 1999; Jessup and O'Doherty, 2011). Accordingly, some brain regions that might underlie response selection could erroneously be assigned a role in learning. The objective of the current study was to directly test this confound in patients with PD, using a stimulus-response learning paradigm previously shown to separate decisions and learning, producing differential patterns of activity in dorsal and ventral striatum (Hiebert et al., 2014).

Combining fMRI with behavioural manipulations in patients with PD tested both off and on dopaminergic therapy, provides a powerful approach for investigating striatum-mediated cognitive functions. In PD, the quintessential motor symptoms arise when dopamine-producing neurons in the substantia nigra pars compacta (SNc) degenerate to seriously restrict dopamine supply to the DS (Kish et al., 1988). In contrast, dopamine-producing neurons in the adjacent ventral tegmental area (VTA) are relatively spared in PD, especially in the early disease stages,

and putamen (Kish et al., 1988). Consequently, in unmedicated PD patients, DS functions and neural activity are depressed, whereas VS operations and activation levels are spared.

Dopaminergic therapy remedies DS dopamine depletion and improves function (Cools, 2006; MacDonald et al., 2011). Unfortunately, exogenous dopamine distributes non-selectively, increasing dopamine even to the relatively-replete VS. As a consequence, dopaminergic medications have been shown to attenuate neural activity and worsen functions performed by VTA-innervated brain regions, presumably due to *dopamine overdose* (Cools, 2006; Robertson et al., 2018). In this way, comparing the OFF and ON states, a *double dissociation* in terms of behaviour and neural activity is observed comparing DS and VS.

If DS mediates stimulus-response learning, it is predicted that a) DS activity will correlate with learning measures and with the moment when stimulus-response association learning occurs (i.e., the Feedback Event, when outcome information regarding response accuracy is provided) and b) learning efficiency and DS signal will improve with dopaminergic therapy in PD. These outcomes are predicted because the DS is significantly dopamine depleted and its functions are impaired at baseline in PD. DS functions and activity *improve* with dopamine replacement (MacDonald and Monchi, 2011).

In contrast, if DS mediates stimulus-response decision performance and VS mediates stimulus-response association learning, as we expect, a) DS activity will correlate with accuracy of decision performance and with the moment when response selection occurs (i.e., the Stimulus-Response Decision Event), and b) accuracy of stimulus-specific decisions and DS

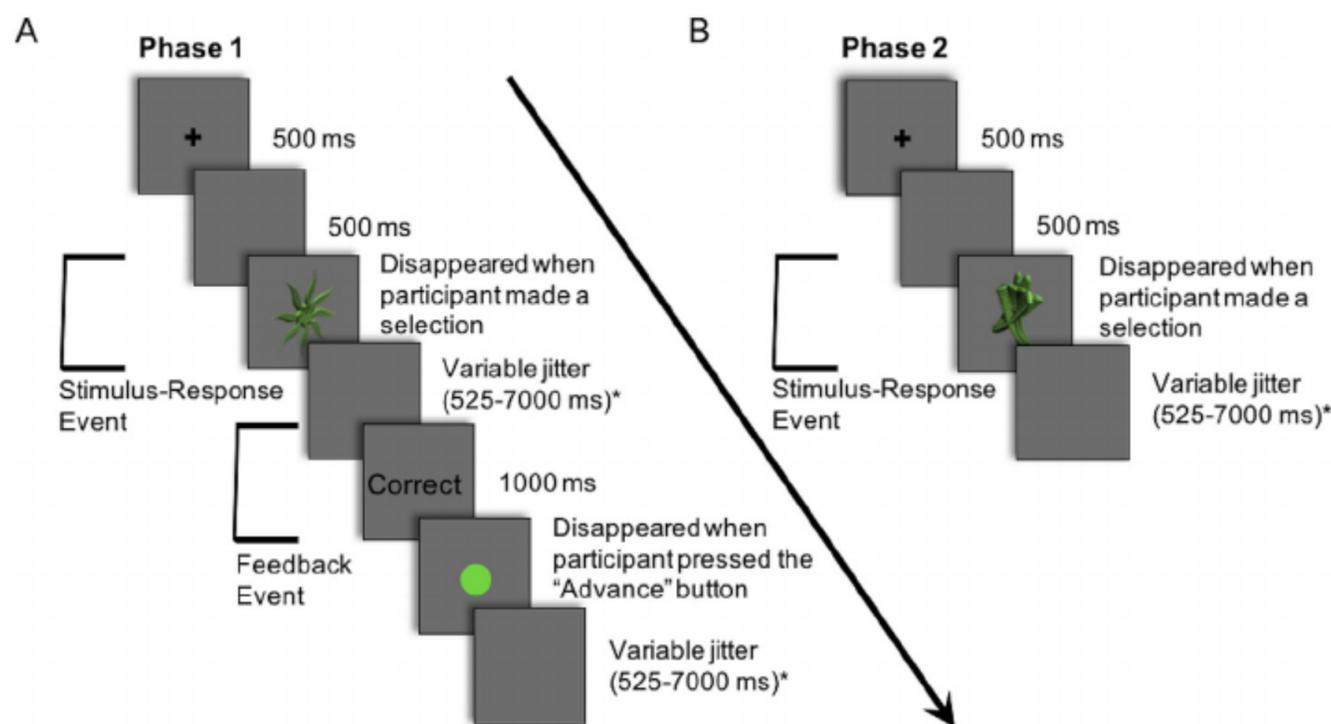


Fig. 2. Example of a single trial in Phase 1 and Phase 2.

A) Participants learned to associate six abstract images with one of three button-press responses in Phase 1. The following is an example of a trial: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented in the centre of the projection screen until a button-press response; (iv) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms) (v) feedback (i.e. 'Correct' or 'Incorrect'); appeared for 1000 ms; (vi) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms). B) Participants recalled the responses to the learned images in the absence of feedback in Phase 2. Trials in Phase 2 were identical to the Phase 1 except that feedback was omitted.

* The inter-stimulus and inter-trial intervals (ISI and ITI, respectively) were jittered between the response and feedback and between the offset of feedback and the beginning of the subsequent trial to create two fMRI events within each trial: a) the Stimulus-Response Decision Event and b) the Feedback Event for Phase 1. In Phase 2, the ITIs were jittered between the response and the subsequent trial, as the Feedback Event was omitted.

moment of learning during the Feedback Event, and b) efficiency of learning and VS signal will *decrease* with dopaminergic therapy in PD. These predictions are based on the knowledge that DS functions and activation improve with dopaminergic therapy in PD, whereas functions and activation of VTA-innervated brain areas are attenuated by exogenous dopamine in PD, which overdoses these relatively dopamine-replete regions.

2. Materials and methods

2.1. Participants

Twenty-three participants with PD and 19 age- and education-matched healthy controls participated in this experiment. All participants with PD were previously diagnosed by a licenced neurologist, had no co-existing diagnosis of dementia or another neurological or psychiatric disease, and met the core assessment for surgical interventional therapy and the UK Brain Bank criteria for the diagnosis of idiopathic PD (Hughes et al., 1992). All PD and no control participants were treated with dopaminergic therapy. Age- and education-matched controls were within five years of age (average difference was 3.6 years) and five years of education (average difference was 2.4 years) to the matched PD patient. Participants with PD were recruited through the movement disorders database at the London Health Sciences Centre. Participants abusing alcohol, prescription or illicit drugs, or taking cognitive-enhancing medications including donepezil, galantamine, rivastigmine, memantine, or methylphenidate were excluded from participating. Three patients with PD were excluded because they obtained a Montreal Cognitive Assessment (MoCA) score of 24 or less, and a further one PD patient and one control participant failed to show any evidence of

in movement disorders (P.A.M.) to assess the presence and severity of motor symptoms for all patients both off and on dopaminergic medication. Control participants were also screened to rule out undiagnosed neurological illness. Mean group demographic, as well as cognitive and affective screening scores for all patients and controls in each experimental group were recorded (Table 1). UPDRS motor subscale scores off and on dopaminergic therapy, daily doses of dopamine replacement therapy in terms of L-dopa equivalents (LED), and mean duration of PD was also recorded (Table 1). Calculation of daily LED for each patient was based on the theoretical equivalence to L-dopa(mg) as follows: L-dopa dose(mg) 1 L-dopa controlled release(mg) 0.75 L-dopa(mg) 0.33 if on entacapone(mg) amantadine(mg) 0.5 bromocriptine(mg) 10 cabergoline(mg) 50 pergolide(mg) 10 0 pramipexole(mg) 67 rasagiline(mg) 100 ropinirole(mg) 16.67 selegiline(mg) 10 (Wullner et al., 2010).

All participants provided informed written consent to the protocol before beginning the experiment according to the Declaration of Helsinki. This study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

2.2. Experimental design

Participants with PD were randomly divided into two groups and all participated in two sessions on separate days. Different stimulus-response pairs were used in Sessions 1 and 2. Both Sessions 1 and 2 were separated into two phases. Phase 1, the learning phase, constituted the phase during which stimulus-response associations were learned through feedback. Phase 2, the performance phase, comprised the phase during which stimulus-specific responses learned in Phase 1 were performed without further feedback. Participants with PD randomly assigned to

learning in Phase 1 in either Session 1 or 2 (explained below) and were therefore excluded from all analyses. Nineteen patients with PD and 18 age- and education-matched healthy controls were therefore included in the final analyses.

The motor sub-scale of the Unified Parkinson's Disease Rating Scale (UPDRS) was scored by a licenced neurologist with sub-specialty training

Group 1 (OFF-ON) performed Session 1 off dopaminergic therapy and Session 2 on dopaminergic therapy. In contrast, PD patients randomized to Group 2 (ON-OFF) performed Session 1 in the ON dopaminergic therapy state and Session 2 in the OFF state. Although control participants did not take dopaminergic therapy in either session, their data were analyzed to correspond to the ON-OFF order of the PD patient to whom

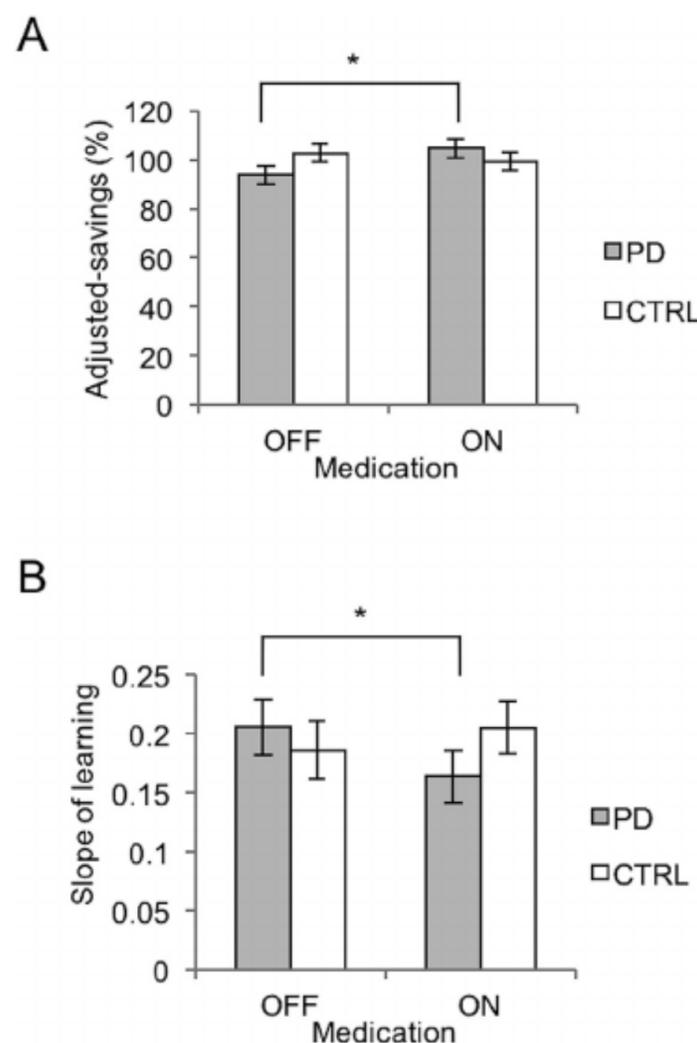


Fig. 3. Effect of PD and dopaminergic therapy on learning and response selection.

A) Effect of PD and dopaminergic therapy on adjusted-savings score. Adjusted-savings score served as a measurement of stimulus-specific response selection accuracy. Adjusted-savings score was measured using the following equation: percent accuracy in Block 1 of Phase 2 – percent accuracy in the last block of the Phase 1. Adjusted-savings score was significantly higher in PD patients tested ON compared to OFF medication. B) Effect of PD and dopaminergic therapy on slope of learning stimulus-response associations. Slope of learning served as a measurement of learning efficiency. To reiterate, slope was calculated using the block accuracy scores over the number of blocks in Phase 1 using the slope of the linear regression function (Microsoft Excel, 2011). Slope of learning was significantly slower in PD patients tested ON compared to OFF dopaminergic medication. All values are presented separately for PD patients tested OFF medication, PD patients tested ON medication, and control participants tested in the sessions designated as ON and OFF though control did not actually receive dopaminergic therapy. Error bars represent standard error of the mean. * $p < 0.05$.

they were matched. Matching was performed prior to data analysis at the time of data collection. This controlled for possible order, fatigue, and practice effects. Participants with PD took their dopamine medication as prescribed by their treating neurologist no more than 1.5 h before beginning their ON testing sessions, but abstained from taking *all* dopaminergic medication including dopamine precursors such as L-dopa, aromatic-L-amino-acid decarboxylase inhibitors such as carbidopa, and catechol-O-methyltransferase (COMT) inhibitors such as entacapone (Comtan) for a minimum of 12 to a maximum of 18 h, and dopamine agonists, such as pramipexole (Mirapex), ropinirole (Requip), or pergolide (Permax), as well as amantadine (Symmetrel), rasagiline (Azilect), and selegiline (Eldepryl or Deprenyl) for 16–20 h before beginning OFF

Table 2

Significant brain activations in contrasts of interest collapsed across Group (PD and control) and Medication (OFF and ON) reported in MNI space.

Contrast	Anatomical Area	Cluster Size	t	q^*	x, y, z
Phase 1: SR Events					
SR minus rest	Right dorsal caudate	75	5.76	0.001	12, 5, 5
	Right lingual gyrus	6928	12.33	0.001	6, 85, 7
	Left paracingulate gyrus	427	6.62	0.001	3, 20, 44
	Right middle frontal gyrus	285	6.55	0.001	48, 32, 32
SR minus FB	Right dorsal caudate	**	7.51	0.001	12, 5, 2
	Left occipital fusiform gyrus	3471	13.70	0.001	30, 76, 16
	Right postcentral gyrus	299	4.89	0.001	36, 31, 41
Phase 2: SR Events					
SR minus Rest	Right dorsal caudate	105	4.76	0.015	15, 1, 14
	Right lateral occipital cortex	3567	9.49	0.001	42, 73, 10
	Right precentral gyrus	1011	5.40	0.001	54, 11, 35
	Left precentral gyrus	1713	5.05	0.001	48, 5, 29
Phase 1: FB Events					
FB minus rest	Left postcentral gyrus	389	7.55	0.001	39, 28, 47
	Right postcentral gyrus	299	4.89	0.001	36, 31, 41
FB minus SR	No Suprathreshold activations				
FB Correct minus Incorrect	Right nucleus accumbens	150	4.87	0.007	18, 11, 7
	Left nucleus accumbens	123	4.49	0.016	18, 11, 1
FB Incorrect minus Correct	No suprathreshold activations				

Cluster size is reported in voxels. *Significance values are reported at $q < 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. **Cluster size unobtainable as peak coordinates are within a larger cluster.

N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

Feedback (i.e., 'Correct' or 'Incorrect') was provided after every response and in this way, participants learned to associate each of the abstract images with the appropriate button-press response through trial and error. Trials were organized into blocks. After each block, participants were provided with a percentage score, summarizing their learning performance. Participants completed a maximum of 12 blocks. Once participants scored greater than 75% on two successive blocks, Phase 1 ended. Our aim was to examine early learning. Further, we wanted to avoid accuracy reaching ceiling so that we could also investigate, as a separate measure, decision performance. If after 12 blocks the participant was not responding at an accuracy level greater than chance (~33%), his/her data were not included in the analysis for either the OFF or ON

testing sessions. All patients confirmed that they complied with these medication instructions. Ten PD patients and eight controls were in the OFF-ON group, whereas nine PD and ten controls were in the ON-OFF group.

In Phase 1, the learning phase of each session, participants learned to associate abstract images with one of three button-press responses. Images were computer-generated with *GroBoto* (Braid Art Labs, Colorado Springs, USA). In each trial, an abstract image appeared in the centre of a projection screen until the participant responded with a button-press.

Sessions. Before proceeding to Phase 1, participants received 20 practice trials with different images from those employed during the main experimental sessions to become familiar with the procedure. In Phase 2, the performance phase of each session, stimuli presented in Phase 1 were shown again. Participants were asked to provide the stimulus-specific button-press responses that they had learned in Phase 1. No feedback was provided to preclude new feedback-based learning during this phase that was aimed to test selection of accurate responses. Again, different sets of images were used in Session 1 and Session 2.

Table 3
Significant brain activations in omnibus contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	F	q*	x, y, z
Phase 1: SR Events					
Main Effect of Group (PD and control)	No suprathreshold activations				
Main Effect of Medication (ON and OFF)	No suprathreshold activations				
Group (PD and control) by Medication (ON and OFF) Interaction	Right dorsal caudate	55	9.04	0.010	12, 5, 5
	Right lingual gyrus	1616	32.92	0.001	6, 88, 7
	Left postcentral gyrus	629	20.06	0.001	45, 28, 41
	Left insular cortex	196	13.48	0.001	30, 23, 4
	Right precuneous cortex	34	12.66	0.001	9, 64, 47
	Right insular cortex	170	12.51	0.001	30, 23, 1
	Right superior temporal gyrus	91	12.10	0.001	57, 4, 13
	Right lateral occipital cortex	448	11.88	0.001	39, 58, 41
	Right middle frontal gyrus	113	10.78	0.002	45, 35, 29
	Left paracingulate gyrus	181	10.20	0.003	3, 20, 44
	Left cingulate gyrus	148	9.29	0.008	3, 46, 32
	Left angular gyrus	77	9.00	0.010	51, 55, 20
	Right angular gyrus	152	8.89	0.011	54, 49, 17
	Left frontal pole	147	8.29	0.022	3, 59, 17
Phase 1: FB Events					
Main Effect of Group (PD and control)	No suprathreshold activations				
Main Effect of Medication (ON and OFF)	No suprathreshold activations				
Group (PD and control) by Medication (ON and OFF) Interaction	Right nucleus accumbens	115	6.85	0.050	12, 5, 7
	Left postcentral gyrus	6385	19.12	0.001	39, 28, 47
	Right superior temporal gyrus	157	9.63	0.003	57, 4, 13
	Left inferior frontal gyrus	385	7.29	0.019	48, 14, 20
	Right cerebellum	126	7.59	0.025	18, 52, 22
	Left middle frontal gyrus	145	6.93	0.047	33, 26, 32

Cluster size is reported in voxels. *Significance values are reported at $q = 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast.

N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

Both Phases 1 and 2 of Sessions 1 and 2 were performed while fMRI measures were simultaneously recorded. Twelve abstract images were used in the experiment, six during each session of testing (Fig. 1). There were 24 trials per block in Phase 1 of each session, with each abstract image occurring four times in random order per block. Two images were assigned to each the second, third, and fourth button on the button box per session and participants pressed these buttons with their index, middle, and ring fingers, respectively. A button-press response was required to advance from the feedback phase to the next trial. In this way, in each trial, motor responses were included in both Stimulus-Response Decision and Feedback Events (Fig. 2A).

Trials in the Learning Phases proceeded as follows: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented until a button-press response was performed (i.e., the Stimulus-Response Decision Event); (iv) a blank screen appeared for a variable amount of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms) (v) feedback (i.e., “Correct” or “Incorrect”); appeared for 1000 ms followed by a green circle that appeared in the centre of the projection screen signifying to the participant to press the first button with his/her thumb to advance to the next trial (i.e., the Feedback Event); (vi) a blank screen appeared for a variable amount of time sampled from an exponential distribution (mean: 2500 ms; mini-

2.3. Statistical analysis

2.3.1. Behavioural

Executing stimulus-specific response selections in Phase 2 depended on how well these associations were learned during Phase 1 in each session. We hypothesized that PD and medication would affect learning. We therefore implemented measures to better isolate decision performance. First, we aimed to equate the degree to which stimulus-response associations were acquired across participants and sessions by imposing a learning criterion in Phase 1. That is, once participants reached a learning criterion of 75% correct on two consecutive blocks or once they completed 12 blocks, Phase 1 ended. Second, we used an adjusted-savings score to evaluate accuracy of stimulus-specific response selections during Phase 2. This score was calculated as follows for each session:

Table 4
Bayes’ factors for contrasts of interest in Phases 1 and 2.

Contrasts	Left DS	Right DS	Left VS	Right VS
PD patients collapsed across Medication session				
i) Stimulus-Response Decision Events in	1.768	8.705	0.561	3.124

mum: 525 ms; maximum: 7000 ms).

A distractor task lasting approximately 15 min (data not shown) was employed between the Phases 1 and 2 in both Sessions 1 and 2. This was to prevent rehearsal of stimulus-response associations as well as to make stimulus-response decisions more challenging. In Phase 2 of each session, participants performed three blocks of 24 trials, in which the same six images studied during Phase 1 were presented in random order, four times per block. Participants provided the button-press response that they had learned for each image during Phase 1. No feedback regarding accuracy was provided in Phase 2 of each session, precluding further feedback-based learning. Parameters for each trial in Phase 2 were otherwise identical to those in Phase 1 with the exception that the Feedback Event was omitted. Fig. 2A and B presents example trials in Phases 1 and 2.

Phase 1				
ii) Stimulus-Response Decision Events in Phase 2	4.911	2.396	1.222	0.363
iii) Correct minus Incorrect Feedback Events minus Rest in Phase 1	0.905	0.963	8.666	7.022
Control participants collapsed across Medication session				
i) Stimulus-Response Decision Events in Phase 1	1.505	3.691	0.827	1.003
ii) Stimulus-Response Decision Events in Phase 2	2.684	6.870	0.625	0.625
iii) Correct minus Incorrect Feedback Events minus Rest in Phase 1	0.129	0.117	4.843	7.042

Bayes' factors (BF_{10}) are presented for each of the four anatomical ROIs for contrasts of interest. Bayes' factors less than three indicate that the results strongly support the null hypothesis, that activation is not greater than zero.

Table 5

Significant brain activations in contrasts of interest for patients with PD OFF versus ON dopaminergic medication reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> *	<i>q</i> <i>svc</i>	<i>x, y, z</i>
Phase 1: SR Events						
OFF minus ON SR events	No suprathreshold activations					
ON minus OFF SR events	Right dorsal putamen	44	3.30	0.001	0.022	21, 2, 14
Phase 2: SR Events						
OFF minus ON SR events	No suprathreshold activations					
ON minus OFF SR events	Left dorsal caudate	43	3.68	0.001	0.024	12, 11, 14
	Right dorsal caudate	61	3.45	0.001	0.037	6, 2, 20
Phase 1: FB Events						
OFF minus ON FB events	Left ventral putamen	14	3.41	0.001	0.004	21, 5, 1
ON minus OFF FB events	No suprathreshold activations					
OFF minus ON Correct minus Incorrect FB events	Left ventral putamen	178	3.15	0.001	0.035	21, 20, 1
ON minus OFF Correct minus Incorrect FB events	No suprathreshold activations					

Cluster size is reported in voxels. *p* values are reported at a significance level of at $p = 0.001$ uncorrected at the voxel level. Small volume correction (SVC) was applied to striatal activations using the two DS two VS ROIs taken from Hiebert NM, A Vo et al. (2014). SVC data are presented at a threshold of $q_{SVC} = 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. **Cluster size unobtainable as peak coordinates are within a larger cluster.

N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

$$\frac{\%}{\%} = \frac{1}{1} \quad \frac{2}{1}$$

By weighting response-selection performance relative to previous learning performance in Phase 1, we corrected for learning differences between participants and across sessions. This score permitted evaluation of stimulus-specific response selection performance independent of medication effects on stimulus-response learning.

Efficiency of encoding stimulus-response associations across the Phase 1 of each session was estimated by the rate of change of correct responses across the session. The slope of change was measured by summing the scores obtained at the end of each block over the total number of blocks required to reach the pre-set learning criterion (i.e., standard slope of the linear regression function, Microsoft Excel, 2011), as follows:

$$\frac{-}{-2}$$

where *b* is the slope, and *x* and *y* are the sample means of the number of blocks and block scores, respectively.

For each of our dependent measures, adjusted-savings score and slope, 2 × 2 mixed ANOVAs with Group (PD versus control) and Medication (ON versus OFF) as the between-subject, and within-subject variables, respectively were carried out. Simple effects will be investigated in the case of significant interactions. Simple effects tests will include:

Within-subject

PD OFF versus PD ON

control OFF versus control ON

Between-subject

OFF PD versus control

ON PD versus control

2.3.2. Imaging acquisition

During data collection of this experiment, the MRI scanner at Robarts Research Institute at the University of Western Ontario was upgraded. fMRI data were collected either in a 3 T S Magnetom Trio (before upgrade) or Magnetom Prisma (after upgrade) with Total Imaging Matrix. Nine PD patients and seven control participants were scanned on the Magnetom Trio. The scanning parameters for each scanner before and after the upgrade were identical. We obtained a scout image for positioning the participant and T₁ for anatomical localization. Number of runs of T₂*-weighted functional acquisitions varied depending on the participant's rate of learning but ranged from a minimum of one to a maximum of four runs. Each run was of variable length and therefore consisted of a variable number of blocks of 24 trials. A distractor task lasting approximately 15 min was administered between Phases 1 and 2 in both sessions. All participants performed Phase 2 as the final fMRI run. All runs lasted on average 8 min with one whole brain image consisting of 43, 2.5 mm-thick slices taken every 2.5s. The field of view was oriented along the anterior and posterior commissure with a matrix of 88 × 88 pixels, an isotropic voxel size of 2.5 × 2.5 × 2.5 mm³. The echo time was 30 ms and the flip angle was 90°.

Table 6

Significant brain activations in contrasts of interest for healthy controls in the OFF versus ON groups.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> *	<i>q</i> <i>svc</i>	<i>x, y, z</i>
Phase 1: SR Events						
OFF minus ON SR events	No suprathreshold activations					
ON minus OFF SR events	No suprathreshold activations					
Phase 2: SR Events						
OFF minus ON SR events	No suprathreshold activations					
ON minus OFF SR events	No suprathreshold activations					
Phase 1: FB Events						
OFF minus ON FB events	No suprathreshold activations					
ON minus OFF FB events	No suprathreshold activations					
OFF minus ON Correct minus Incorrect FB events	No suprathreshold activations					
ON minus OFF Correct minus Incorrect FB events	No suprathreshold activations					

Cluster size is reported in voxels. *p* values are reported at a significance level of $p = 0.001$ uncorrected for multiple comparisons. *p* values are reported at the voxel level. Small volume correction (SVC) was applied to striatal activations using the two DS two VS ROIs taken from Hiebert NM, A Vo et al. (2014). SVC data are presented at a threshold of $q_{svc} = 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast.

**Cluster size unobtainable as peak coordinates are within a larger cluster.

N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

Table 7

Significant brain activations in contrasts of interest for patients with PD versus control participants OFF and ON dopaminergic medication reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> *	<i>q</i> <i>svc</i>	<i>x, y, z</i>
Phase 1: SR Events						
PD OFF minus control OFF	No suprathreshold activations					
control OFF minus PD OFF	Left dorsal caudate	10	3.21	0.001	0.027	6, 5, 5
PD ON minus control ON	No suprathreshold activations					
control ON minus PD ON	No suprathreshold activations					
Phase 2: SR Events						
PD OFF minus control OFF	No suprathreshold activations					
control OFF minus PD OFF	No suprathreshold activations					
PD ON minus control ON	Left dorsal caudate	8	3.75	0.001	0.020	12, 11, 17
control ON minus PD ON	No suprathreshold activations					
Phase 1: FB Events						
PD OFF minus control OFF	No suprathreshold activations					
control OFF minus PD OFF	Left ventral caudate	29	3.66	0.001	0.045	18, 23, 1
PD ON minus control ON	No suprathreshold activations					
control ON minus PD ON	No suprathreshold activations					

Cluster size is reported in voxels. *p* values are reported at a significance level of $p = 0.001$ uncorrected at the voxel level. Small volume correction (SVC) was applied to striatal activations using the two DS two VS ROIs taken from Hiebert NM, A Hiebert et al. (2014). SVC data are presented at a threshold of $q_{svc} = 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast.

N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

2.3.3. fMRI data analysis

Statistical Parametric Mapping Version 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used in conjunction with Matrix Laboratory (MATLAB; MathWorks, Inc., Natick, Massachusetts, United States) to complete fMRI analysis. Images were slice-time corrected, reoriented for participant motion, spatially normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8 mm full-width half-maximum Gaussian kernel, and high-pass filtered (0.0056 Hz). Realignment parameters used to correct for head movement were extracted and plotted for each participant and for each scanning run. A peak movement score was calculated by averaging the largest amplitude movement across each scanning run. An independent sample *t*-test was run on peak movement score between PD and control participants, and a paired *t*-test was conducted on PD patients on and off medication to ensure there was no effect of disease or medication status on head movement.

Individual participant data were modeled using fixed effects analysis using SPM8. Regressors were formed using onsets and durations of psychological events of interest, particularly Stimulus-Response Decision, Feedback, and post-feedback Rest Events, with the canonical hemodynamic response function. The inter-stimulus interval between Stimulus-Response Decision and Feedback Events was not explicitly modelled to minimize over fitting the data. If the randomly generated inter-trial interval (ITI) between the Feedback Event and the Stimulus-Response Decision Event for the next trial was between 525 and 2000 ms, the

multiplied by the three event types (i.e., Stimulus-Response Decision, Feedback, and Rest). A similar GLM was created to for Phase 2 in each session to investigate regional BOLD responses for Stimulus-Response Decision and Rest Events, with regressors corresponding to each of the three blocks completed in each of the sessions, multiplied by the two event types (i.e., Stimulus-Response Decision and Rest). Contrasts were made at the individual level for each session comparing Stimulus-Response Decision, Feedback, and Rest Events for Phase 1, and Stimulus-Response Decision and Rest Events for Phase 2. Correct and incorrect trials were examined separately. At the group level, two GLMs were created, one for Phase 1 and the other for Phase 2. The Phase 1 GLM consisted of separate regressors for correct and incorrect Stimulus-Response Decision minus Rest, and Feedback minus Rest Events for both PD and control participants, off and on medication, yielding 16 regressors. Age and Order were also added as covariates. Similarly, the Phase 2 model contained 8 regressors, separated into correct and incorrect Stimulus-Response Decision minus Rest Events for both PD and control participants, off and on medication.

First, group-level contrasts examined events collapsed across Group (PD and control) and Medication (OFF and ON) to confirm that we replicated the results from Hiebert et al. (2014). The contrasts of interest for Phases 1 and 2 were as follows: (i) Stimulus-Response Decision Events minus Rest in Phase 1, (ii) Stimulus-Response Decision minus Feedback Events in Phase 1, (iii) Stimulus-Response Decision Events minus Rest in Phase 2, (iv) Feedback Events minus Rest in Phase 1, (v) Feedback Events

final 500 ms of this interval was modeled to form the Rest Event. If the ITI was between 2000 and 4000 ms, the final 1000 ms comprised the Rest Event for that trial. Finally, for ITIs that were greater than 4000 ms, the final 2000 ms were included as the Rest measure. The aims were to a) separate the Stimulus-Response Decision, Feedback, and Rest Events as much as possible, and b) create Rest events with variable durations to match the Stimulus-Response Decision and Feedback Events. Stimulus-Response Decision Events were defined as the time from the onset of the abstract image until the participant made a button-press response. The Feedback Event was defined as the time from the onset of feedback ("Correct" or "Incorrect") until and including the button-press response that participants made when the green circle appeared on the projection screen, signalling their readiness to proceed to the next trial. This ended the Feedback Event. In this way, a motor response occurred during the Stimulus-Response Decision and Feedback Events.

A single General Linear Model (GLM) was created for Phase 1 in each session to investigate regional BOLD responses for Stimulus-Response Decision, Feedback, and Rest Events. Number of predictor functions corresponded to the number of blocks completed by each participant

minus Stimulus-Response Decision Events in Phase 1, (vi) correct versus incorrect Feedback Events in Phase 1. Peaks in these contrasts are reported at a significance level of $q = 0.05$ corrected for multiple comparisons using false discovery rate (FDR) at the voxel level, unless otherwise noted.

We then performed a set of 2 × 2 mixed ANOVAs with Group (PD versus control) and Medication (ON versus OFF) as the between-subject, and within-subject variables, respectively on activity in Stimulus-Response Decision and Feedback events separately in Phase 1. The following contrasts were examined: (i) Main Effect Group (PD versus control) for Stimulus-Response Decision Events, (ii) Main Effect of Medication (ON versus OFF) for Stimulus-Response Decision Events, (iii) Group (PD versus control) × Medication (ON versus OFF) Interaction for Stimulus-Response Decision Events, (iv) Main Effect Group (PD versus control) for Feedback Events, (v) Main Effect of Medication (ON versus OFF) for Feedback Events, and (vi) Group (PD versus control) × Medication (ON versus OFF) Interaction for Feedback Events. Significant Group × Medication interactions were investigated to justify further exploration of simple effects.

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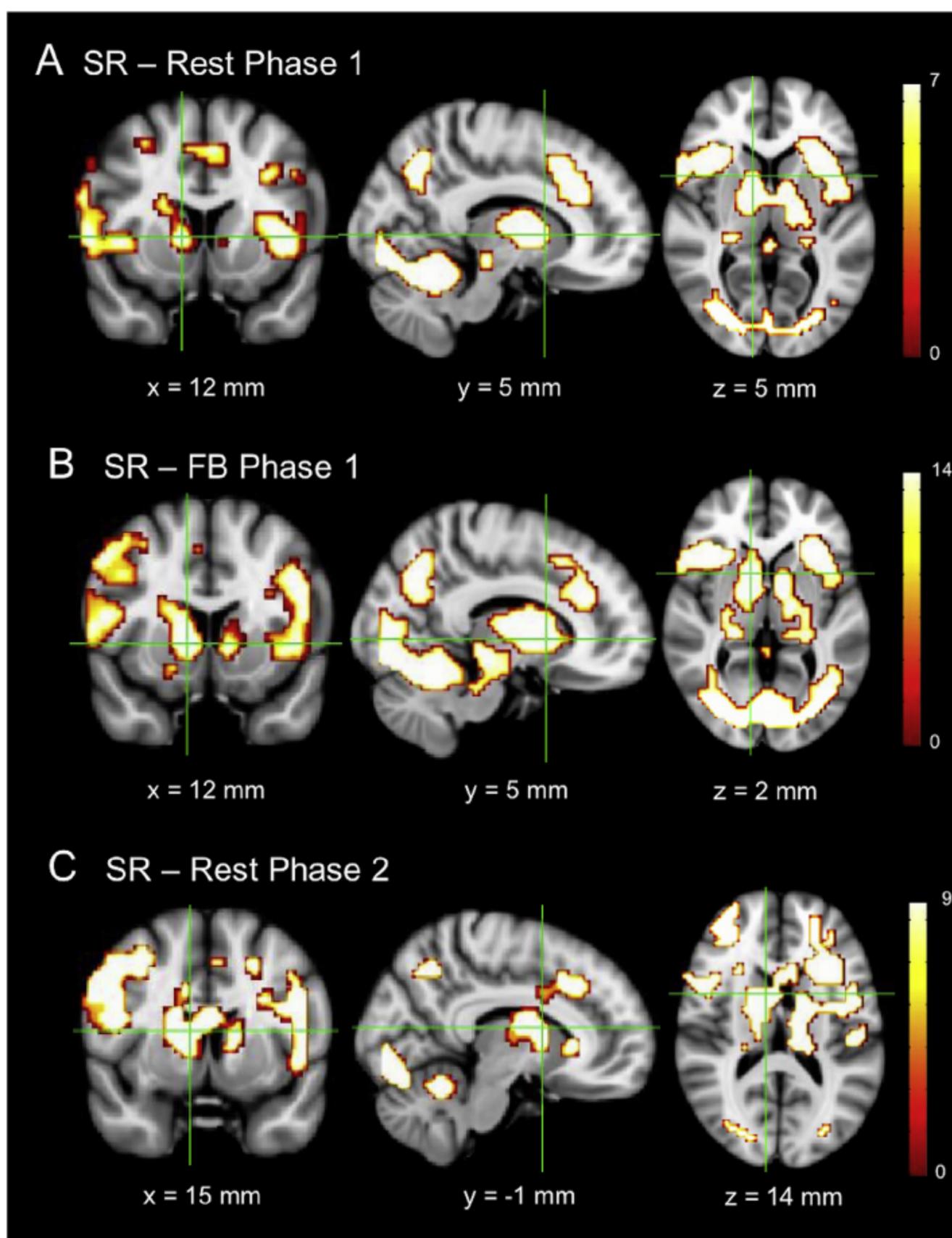
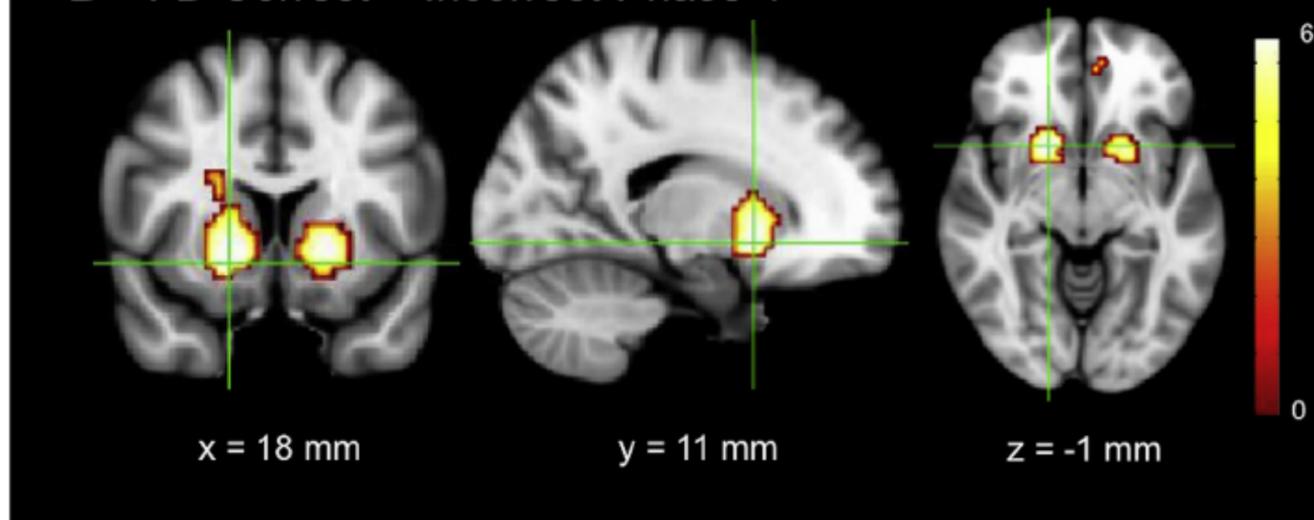


Fig. 4. Significant activations in contrasts collapsing across Group (PD and control) and medication status (OFF and ON).

Activation t -statistic maps are presented at a threshold of $p = 0.001$ uncorrected for multiple comparisons, as well as centred on the striatal activation for visualization purposes. A) BOLD signal for Stimulus-Response Decision Events minus Rest across all blocks in Phase 1. The cross-hairs are centred on the significant activity that arose in the right dorsal caudate (*peak coordinates*: 12, 5, 5; $t = 5.76$, $q = 0.001$). B) BOLD signal for Stimulus-Response Decision minus Feedback Events across all blocks in Phase 1. The cross-hairs are centred on the significant cluster that arose in the right dorsal caudate (*peak coordinates*: 12, 5, 2; $t = 7.51$, $q = 0.001$). C) BOLD signal for Stimulus-Response Decision minus Rest Events across all blocks in Phase 2. The cross-hairs are centred on the significant activity that arose in the left dorsal caudate (*peak coordinates*: 15, 1, 14; $t = 4.76$, $q = 0.015$). D) BOLD signal for correct minus incorrect Feedback Events across all blocks in the Phase 1. The cross-hairs are centred on the significant activation that arose in the right nucleus accumbens (*peak coordinates*: 18, 11, 7; $t = 4.87$, $q = 0.007$). A significant cluster was also present in the left nucleus accumbens (*peak coordinates*: 18, 11, 1; $t = 4.49$, $q = 0.016$). N.B. SR – Stimulus-Response Decision Events and FB – Feedback Events in the figure.

D FB Correct – Incorrect Phase 1



We next conducted Bayesian analysis, because critical conclusions regarding DS's role in stimulus-response learning depend on accepting null effects. Specifically, refuting the entrenched view that DS mediates stimulus-response learning is accomplished by showing that a) DS

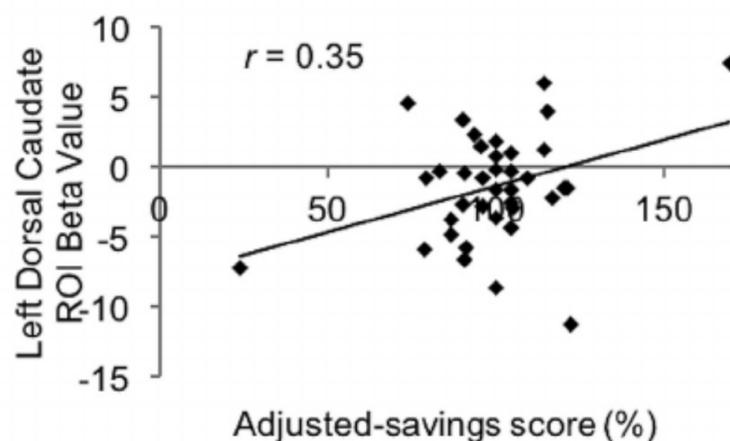
activation *does not* arise during the Feedback Event when stimulus-response associations are learned. There is a justified bias against publishing negative findings, in that with frequentist approaches, the probabilities of Type II (i.e., falsely failing to reject the null hypothesis) and

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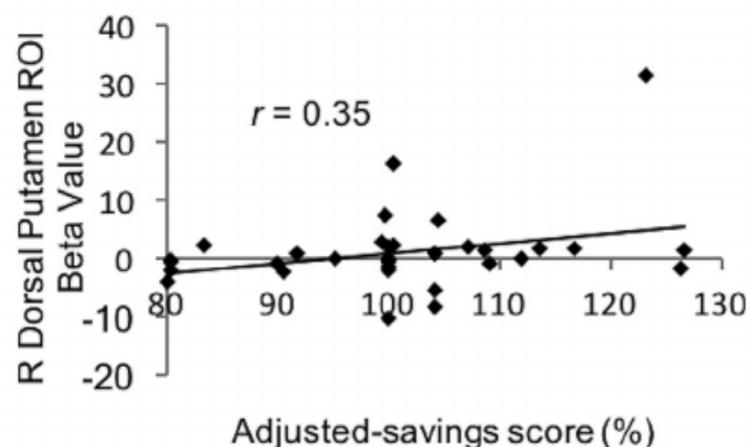
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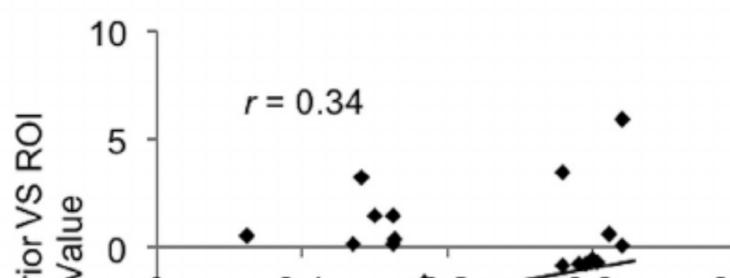
A PD Patients



B Healthy Controls



C PD Patients



significant effects was investigated by conducting Bayesian analyses on the strength of DS and VS activity during Stimulus-Response Decision and Feedback events, respectively. Bayes' factor one-sample *t*-tests were conducted separately for PD patients and control participants, using average beta values extracted from left and right anatomical DS and VS ROIs during Feedback and Stimulus-Response Decision Events in the following contrasts: (i) Stimulus-Response Decision Events across Phase 1 collapsed across Medication session (OFF and ON), (ii) Stimulus-Response Decision Events across Phase 2 collapsed across Medication session (OFF and ON), and (iii) Correct minus Incorrect Feedback events across Phase 1 collapsed across Medication session (OFF and ON).

ROIs were created using the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), and WFU PickAtlas (Maldjian et al., 2003) in conjunction with MarsBaR (Brett et al., 2002). The left and right DS ROI included left and right dorsal caudate nucleus and left and right dorsal putamen at a level of $z = 2$ mm in MNI space. The left and right VS ROIs were similarly created and included the left and right ventral caudate nucleus and putamen at a level of $z = 2$ mm in MNI space, as well as the nucleus accumbens. DS and VS are not distinct anatomical structures, which creates difficulty when attempting to separate them in an fMRI context. In a review, Postuma and Dagher (2006) define VS as $z = 2$, which we employed. Here, DS refers to portions of the caudate nucleus and putamen at a level of $z = 2$ mm in MNI space. VS was defined as the nucleus accumbens, caudate, and putamen at a level of $z = 2$ mm in MNI space.

Using the Bayes' factor of three as the cut-off, previously indicated to be the Bayesian corollary of $p = 0.05$ in frequentist hypothesis testing (Dienes, 2014), we tested whether the extracted beta values were indeed zero. If the Bayes' factor of the average beta value is less than three, it strongly supports the null hypothesis, that the activation level is not greater than zero.

Next, we investigated brain-behaviour correlations to confirm that behavioural performance was related to DS versus VS activity patterns. We tested whether BOLD signal in striatal regions correlated with behavioural indices of response selection decisions and learning respectively. Specifically, we tested whether activity in two DS versus two VS ROIs taken from Hiebert et al. (2014), correlated with the adjusted-savings score (i.e., our measure of response-selection decisions), and with learning slope (i.e., our measure of learning efficiency). Cor-

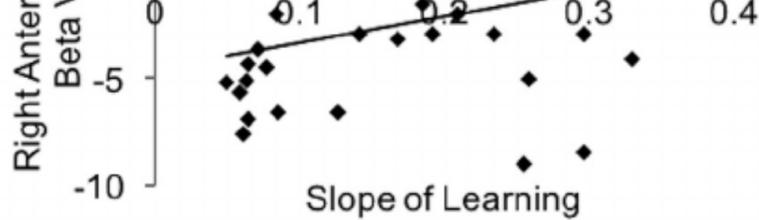


Fig. 5. Brain-behaviour correlations between BOLD signal in ROIs and measures of learning and stimulus-specific response selection.

A) Beta values extracted from the left dorsal caudate ROI in the Stimulus-Response Decision Events minus Rest contrast correlated positively and significantly with adjusted-savings in patients with PD on and off medication. B) Beta values extracted from the right dorsal putamen ROI significantly correlated with adjusted savings in healthy controls. C) Beta values extracted from the right anterior VS ROI in the Feedback Events minus Rest contrast, correlated positively and significantly with slope of learning in patients with PD on and off medication.

Type I errors (i.e., falsely rejecting the null hypothesis) are asymmetric. Type I errors are set at a clear maximum, usually less than 0.05, whereas Type II errors vary across studies in terms of magnitude and determinants not pre-determined by the experimenter (Dienes, 2014). Bayesian analysis allows directly contrasting the probability of the null and the alternative hypotheses in a symmetrical way, putting these hypotheses on an equal footing, and directly comparing the relative fit of the two models (Dienes, 2014). Bayesian analyses were therefore performed to investigate the strength of null effects that arose. Additionally, the strength of

relations were performed separately for PD and healthy control groups in the event that learning and response selection performance differed across groups collapsed across medication session. The two right and left DS and two right and left VS ROIs from Hiebert et al. (2014) were employed for the correlation analysis in the present study using the MarsBar Toolbox in SPM8 (Brett et al., 2002). DS ROIs were centered on the dorsal head of the caudate nucleus ($x = 18, y = 24, z = 6$), and dorsal putamen ($x = 29, y = 9, z = 6$). For VS, $x = 10, y = 8, z = 4$, and $x = 12, y = 18, z = 6$, centering on the nucleus accumbens and ventral caudate nucleus respectively were used. Spherical ROIs centred on the aforementioned coordinates were created with a radius of 6 mm. All cortical regions were defined using the Harvard-Oxford Cortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). All x, y, z coordinates are reported in MNI space. Beta values in our ROIs were extracted from four contrasts of interest: (i) Stimulus-Response Decision Events across Phase 2 for patients with PD across Sessions 1 and 2 (i.e., off and on dopaminergic medication), (ii) Feedback Events across Phase 1 for patients with PD across Sessions 1 and 2 (i.e., off and on medication), (iii) Stimulus-Response Decision Events across Phase 2 for healthy controls across Sessions 1 and 2, and (iv) Feedback Events across Phase 1 for healthy controls across Sessions 1 and 2. These average beta values for each ROI were correlated with behavioural measures of stimulus-specific response selection (i.e., the adjusted savings scores) and learning (i.e., slope values) for each group separately. Outlier analysis was performed for each significant correlation independently, using the interquartile

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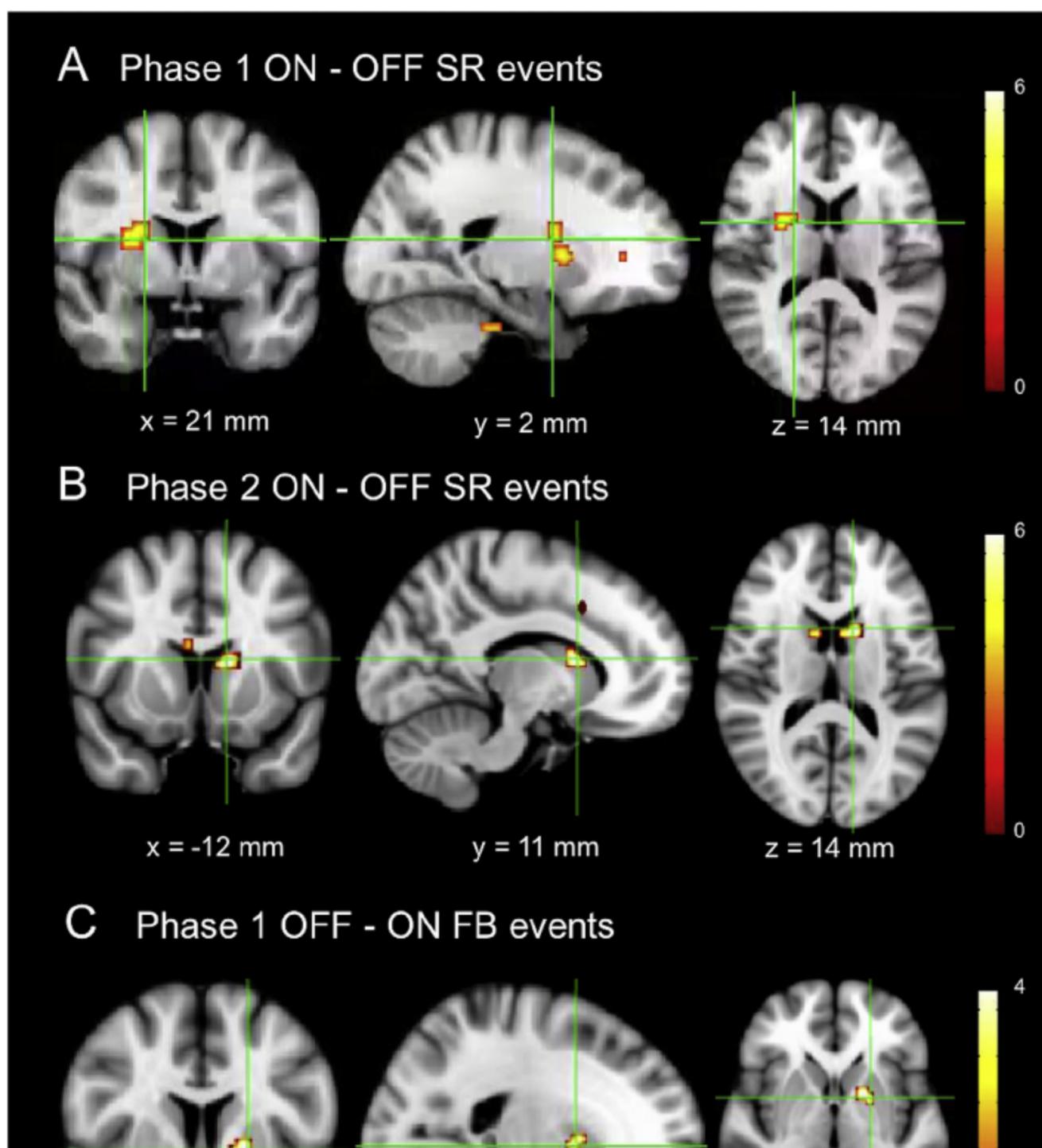
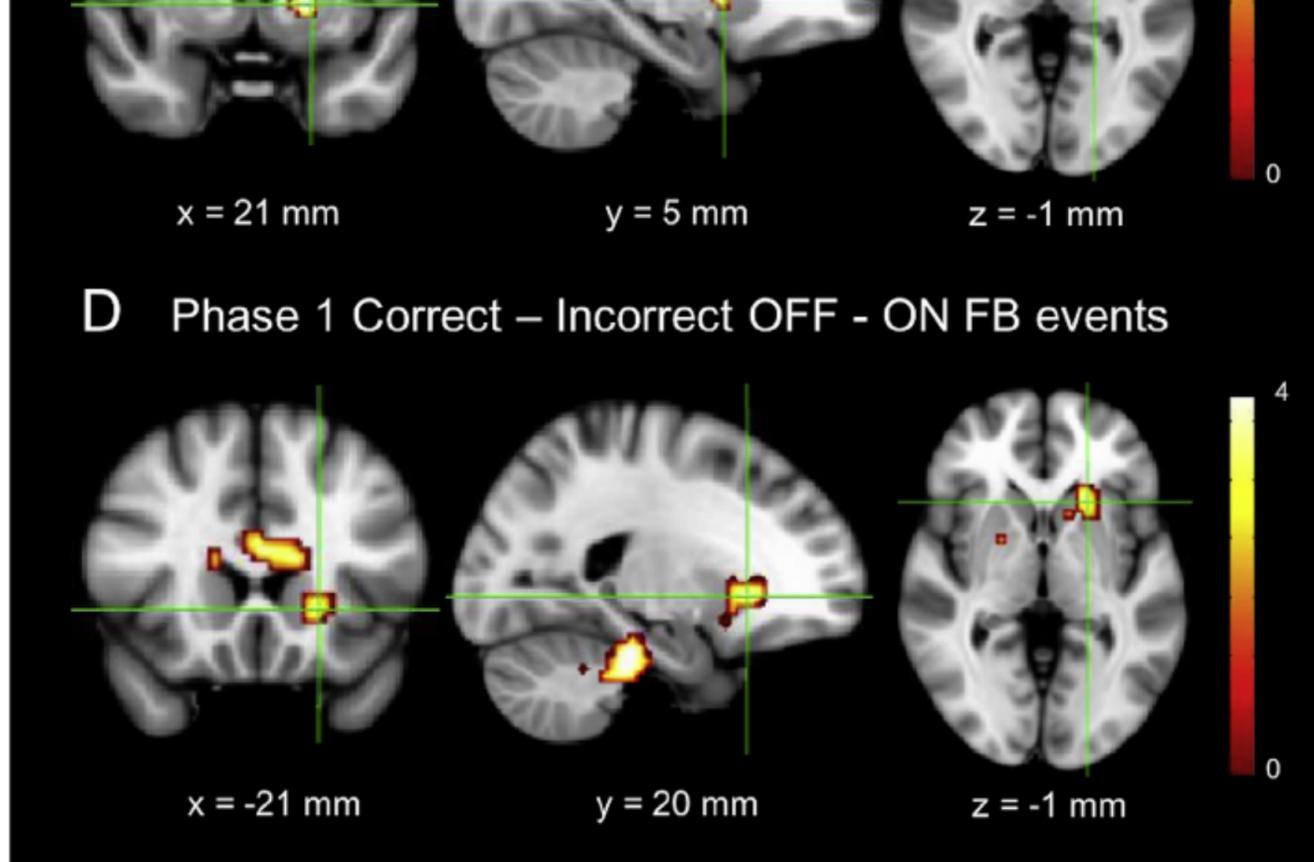


Fig. 6. Significant activations in contrasts examining only PD patients ON and OFF dopaminergic medication.

Activation t -statistic maps are presented at a threshold of $p = 0.001$ uncorrected for multiple comparisons and centred on the striatal activation. A) BOLD signal for ON minus OFF Stimulus-Response Decision Events across all blocks in Phase 1. The cross-hairs are centred on the significant cluster that arose in the right dorsal putamen (*peak coordinates*: 21, 2, 14; $t = 3.30, p = 0.001, q_{svc} = 0.022$). B) BOLD signal for ON minus OFF Stimulus-Response Decision Events across all blocks in Phase 2. The cross-hairs are centred on the significant activity that arose in the right dorsal caudate (*peak coordinates*: 12, 11, 14; $t = 3.68, p = 0.001, q_{svc} = 0.024$). Significant activity also occurred in the left dorsal caudate (*peak coordinates*: 6, 2, 20; $t = 3.45, p = 0.001, q_{svc} = 0.037$). C) BOLD signal for OFF minus ON Feedback Events across all blocks in the Phase 1. The cross-hairs are centred on the significant cluster in the left ventral putamen (*peak coordinates*: 21, 5, 1; $t = 3.41, p = 0.001, q_{svc} = 0.004$). D) BOLD signal for OFF minus ON correct minus incorrect Feedback Events across all blocks in Phase 1. The cross-hairs are centred on the cluster of activation in the left ventral putamen (*peak coordinates*: 21, 20, 1; $t = 3.15, p = 0.001, q_{svc} = 0.035$).

N.B. SR – Stimulus-Response Decision Events and FB – Feedback Events in the figure.



method. Briefly, data points located 1.5 interquartile range below the first quartile, and 1.5 interquartile range above the third quartile were removed, and the correlation was recalculated with the remaining data points.

Subsequently, events of interest were examined for PD and healthy controls separately comparing OFF and ON Medication sessions directly. These within-subject contrasts of interest for Phases 1 and 2 were as follows: (i) PD OFF versus ON Stimulus-Response Decision Events in

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Phase 1, (ii) PD OFF versus ON Stimulus-Response Decision Events in Phase 2, (iii) PD OFF versus ON medication for Feedback Events in Phase 1, (iv) PD OFF correct minus incorrect Feedback Events versus ON correct minus incorrect Feedback Events, (v) control OFF versus ON Stimulus-Response Decision Events in Phase 1, (vi) control OFF versus ON Stimulus-Response Decision Events in Phase 2, (vii) control OFF versus ON medication for Feedback Events in Phase 1, and (viii) control OFF correct minus incorrect Feedback Events versus ON correct minus incorrect Feedback Events. For OFF-ON contrasts in PD patients and controls, peaks within the striatum were considered predicted and are reported at a significance level of $p = 0.001$, uncorrected for multiple comparisons. To increase confidence in these uncorrected results, small volume correction (SVC) was applied to striatal activations using the two DS and two VS ROIs taken from Hiebert et al. (2014). SVC data are presented at a threshold of $q = 0.05$ FDR corrected at the voxel level and appear alongside whole-brain results in Tables 5–7. Peaks outside of the striatum are reported at a threshold of $q = 0.05$ FDR corrected at the voxel level. Striatal regions were again defined using the Harvard-Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom).

Next, to clarify our within-subject contrasts that explored the effects of dopaminergic therapy on DS and VS function in PD patients, we contrasted Group (PD versus control) in each of the Medication states separately. The contrasts of interest for Phases 1 and 2 were as follows: (i) Stimulus-Response Decision Events minus Rest in Phase 1, (ii) Stimulus-Response Decision minus Feedback Events in Phase 1, (iii) Stimulus-Response Decision Events minus Rest in Phase 2, (iv) Feedback Events minus Rest in Phase 1, (v) Feedback Events minus Stimulus-Response Decision Events in Phase 1, (vi) correct versus incorrect Feedback Events in Phase 1. For OFF-ON contrasts in PD patients and controls, peaks within the striatum were considered predicted and are reported both at a significance level of $p = 0.001$, uncorrected for multiple comparisons at the whole-brain level and corrected for multiple comparisons

Group ($F = 1$) or Medication ($F_{1,32} = 1.327$, $MSE = 235.00$, $p = 0.258$). The Group Medication interaction trended toward significance, $F_{1,32} = 4.007$, $MSE = 235.00$, $p = 0.054$, and was further investigated using pairwise comparisons. This revealed a significantly improved adjusted-savings score for participants with PD tested ON compared to OFF dopaminergic medication ($t = 2.24$, $p = 0.038$; Fig. 3A) as would be predicted if DS mediates decisions or response selections. There were no significant differences between OFF and ON sessions for control participants ($t = 0.70$, $p = 0.494$). Recall that control participants did not actually receive dopaminergic therapy but their data were analyzed to correspond to the ON-OFF order of the PD patient to whom they were matched. Additionally, there were no significant differences between PD and control groups for either the OFF ($t = 1.26$, $p = 0.104$) or ON ($t = 0.50$, $p = 0.308$) contrast.

3.1.3. Stimulus-response association learning measure

Efficiency of stimulus-response association learning was estimated using the slope of accuracy change over the total number of blocks required to reach the learning criterion in Phase 1 (i.e., 75% accuracy on two consecutive blocks). Slope was calculated using the linear regression function in Microsoft Excel (2011). A 2 × 2 mixed ANOVA on the slopes of learning obtained during Phase 1 was conducted with Group (PD versus control) as the between-subject factor and Medication Session (OFF versus ON) as the within-subject variable. There were no main effects of Group ($F = 1$) or Medication ($F = 1$). However, the Group Medication interaction was significant, $F_{1,35} = 4.46$, $MSE = 0.004$, $p = 0.042$. Investigated further using pairwise comparisons, we found significantly slower learning ON relative to OFF medication for PD patients ($t = 2.17$, $p = 0.044$; Fig. 3B) but no medication difference for control participants ($t = 0.92$, $p = 0.368$), replicating what we found previously in patients with PD (Hiebert et al., 2014; Vo et al., 2014) and supporting the dopamine overdose hypothesis. Additionally, there were no significant slope differences between PD and control

3. Results

3.1. Behavioural data

Demographic, affective, and clinical data are presented in Table 1 and behavioural data for Phases 1 and 2 are presented in Fig. 3.

3.1.1. Demographic, affective, and clinical data

There were no significant demographic differences between PD and control participants (Table 1). Participants with PD scored significantly higher on both Beck Depression Inventory II and Beck Anxiety Inventory compared to controls regardless of medication status as is expected based on previous research. No differences were found in terms of depressive or anxiety symptoms between participants with PD measured off or on their dopaminergic medication. UPDRS scores were significantly higher in participants with PD measured off relative to on dopaminergic medication ($t = 6.00, p = 0.0001$), signifying greater PD signs when patients were in the unmedicated state. There were no significant differences in peak head movement between PD patients and healthy controls ($t = 0.08, p = 0.94$) or between PD patients on and off medication ($t = 0.76, p = 0.46$).

3.1.2. Response selection decision behavioural measure

Accuracy of selecting previously-learned stimulus-specific responses was measured using an adjusted-savings score. The score obtained in Block 1 of Phase 2 was weighted relative to the final accuracy obtained during the last block of Phase 1 for each session. A 2×2 mixed ANOVA of the adjusted-savings scores was conducted with Group (PD versus control) as between-subject factor and Medication Session (OFF versus ON) as the within-subject variable. There were no significant main effects of

$q = 0.016$; Fig. 4D), and right nucleus accumbens (*peak coordinates*: 18, 11, -7; $t = 4.87, q = 0.007$; Fig. 4D), in the correct minus incorrect feedback contrast, however. No significant striatal region was active in the reverse (i.e., incorrect minus correct) contrast.

3.2.2. Group (PD vs. control) \times medication (OFF vs. ON) analysis

2×2 mixed ANOVAs with Group (PD versus control) and Medication (ON versus OFF) as the between-subject, and within-subject variables, respectively, were conducted on activity in Stimulus-Response Decision and Feedback events separately in Phase 1.

3.2.2.1. Phase 1 Stimulus-response decision events. The main effects of Group and Medication did not reach significance within or outside the striatum. However, a significant Group (PD and control) \times Medication (ON and OFF) interaction effect occurred for Stimulus-Response Decision Events revealing above-threshold right dorsal caudate activation (*peak coordinates*: 12, 5, 5; $F = 9.04, q = 0.010$).

3.2.2.2. Phase 1 feedback events. The main effects of Group and Medication did not reach significance for the Feedback Events. Again, however, the Group (PD and control) \times Medication (ON and OFF) interaction was significant examining feedback events revealing activation in the right nucleus accumbens (*peak coordinates*: 12, 5, -7; $F = 6.85, q = 0.050$). These interactions justify exploration of the simple effects below. Striatal and extra-striatal brain regions that were significantly activated during these contrasts are presented in Table 3.

3.3. Bayesian analysis

3.2. FMRI data

Significant activations in contrasts of interest are presented in Tables 2–7 and Figs. 4 and 6. Contrasts collapsing across Group and Medication Session are reported at a significance level of $q = 0.05$ FDR corrected at the voxel level. Contrasts examining patients with PD versus healthy controls, as well as exploring each group separately for OFF-ON effects are reported at a significance level of $p = 0.001$ for predicted striatal regions, uncorrected for multiple comparisons and corrected for multiple comparisons using SVC.

3.2.1. Groups and medication sessions collapsed

3.2.1.1. Stimulus-response decision events. Significant activity in the right dorsal caudate occurred during the Stimulus-Response Decision relative to Rest in Phase 1 (*peak coordinates*: 12, 5, 5; $t = 5.76, q = 0.001$; Fig. 4A). Significant right dorsal caudate activity also occurred in the Stimulus-Response Decision minus Feedback contrast in Phase 1 (*peak coordinates*: 12, 5, 2; $t = 7.51, q = 0.001$; Fig. 4B). When Stimulus-Response Decision Events were compared to Rest in Phase 2, significant activity in the left dorsal caudate (*peak coordinates*: 15, -1, 14; $t = 4.76, q = 0.015$; Fig. 4C) occurred. DS was preferentially recruited during the Stimulus-Response Decision Event, in both Phases 1 and 2, replicating our previous findings (Hiebert et al., 2014).

3.2.1.2. Feedback learning events. Correct and incorrect Feedback Events combined relative to Rest or relative to Stimulus-Response Decision Events revealed no significant striatal activations. Significant VS but not DS activity occurred in the left (*peak coordinates*: 18, 11, -1; $t = 4.49,$

were previously employed in Hiebert et al. (2014)—the study in which the current cognitive paradigm was first explored with fMRI in healthy young controls. BOLD signal in these ROIs was correlated with our behavioural measures of stimulus-response decision accuracy and feedback-based learning efficiency. The adjusted-savings score served as our measure of decision accuracy, and the slope of change in correctly associating stimuli and responses was used our measure of stimulus-response association learning.

3.4.1. Striatum and response-selection decisions

Beta values from each of the ROIs were correlated with adjusted-savings scores in OFF and ON sessions for PD patients and healthy controls separately. For PD patients, beta values extracted during Stimulus-Response Decision Events in Phase 2 from the left dorsal caudate ROI positively correlated with adjusted savings scores ($r = 0.35, t = 2.19, p = 0.035$; Fig. 5A). Using the interquartile method, outliers were removed and the correlation was recalculated. Without the outliers, the correlation was no longer significant ($r = 0.32, t = 1.88, p = 0.071$). For control participants, beta values extracted from the right dorsal putamen ROI significantly correlated with adjusted savings ($r = 0.35, t = 2.18, p = 0.042$; Fig. 5B). The presence of outliers was investigated using the interquartile method and none were found. Neither of the VS ROIs correlated with adjusted-savings scores in either the PD or the healthy control group.

3.4.2. Striatum and learning from feedback

Beta values from each of the VS and DS ROIs were correlated with slope of learning in the OFF and ON sessions combined for PD patients and healthy controls separately. A significant positive correlation arose

Beta values extracted from the two right and left anatomical DS and VS ROIs from key contrasts of interest involving Stimulus-Response Decision and Feedback Events (Table 4). Bayes' factor one-sample t -tests were conducted on beta values for each of the four ROIs extracted from each contrast of interest. In this analysis, a Bayes' factor of less than three is considered to significantly support the null hypothesis (Dienes, 2014).

3.3.1. Phase 1 Stimulus-response decision events

Contrasting Stimulus-Response Decision minus Rest events for Phase 1 in PD patients, collapsed across Medication session revealed a Bayes' factor greater than three in the Right DS in both PD patients and control participants, separately (Right DS: $BF_{10} = 8.705$; Right DS: $BF_{10} = 3.691$, respectively). Bayes' factor for Right VS was also greater than three in PD patients only ($BF_{10} = 3.124$).

3.3.2. Phase 2 Stimulus-response decision events

Contrasting Stimulus-Response Decision minus Rest events for Phase 2, collapsed across Medication session, revealed Bayes' factors greater than three in Left DS for PD patients ($BF_{10} = 4.911$), and Right DS for control participants ($BF_{10} = 6.870$).

3.3.3. Phase 1 correct minus incorrect feedback events

In the correct minus incorrect Feedback Events, collapsed across Medication session, PD patient's Bayes' factors for DS ROIs were far below three, indicating that beta values in these regions were not significantly above zero (Left DS: $BF_{10} = 0.905$; Right DS $BF_{10} = 0.963$). In contrast, Bayes' factors for VS ROIs were above three indicating that VS is preferentially activated during these events with beta values significantly above zero (Left VS: $BF_{10} = 8.666$; Right VS: $BF_{10} = 7.022$). A similar pattern arose in control participants (Left DS: $BF_{10} = 0.129$; Right DS $BF_{10} = 0.117$; Left DS: $BF_{10} = 4.843$; Right DS $BF_{10} = 7.042$).

3.4. Brain-behaviour correlations: PD and controls separately

Two right and left VS and two right and left DS ROIs utilized here

3.5.5. Feedback learning correct minus incorrect events OFF minus ON

Significantly greater activity occurred in the right ventral putamen, extending into the nucleus accumbens and ventral caudate (*peak coordinates*: 18, 11, 4; $t = 3.15$, $p = 0.001$, $q_{SVC} = 0.035$) when PD patients were tested off relative to on dopaminergic therapy. Again, this suggests that dopaminergic therapy attenuates VS activity, consistent with the dopamine overdose hypothesis.

3.5.6. Feedback learning correct minus incorrect events ON minus OFF

No significant striatal activity occurred in this contrast.

3.6. Healthy control: ON vs. OFF sessions

There was no preferential activity in the striatum in any contrasts comparing OFF and ON sessions in healthy controls (Table 6). This is as expected given that healthy control participants did not actually receive dopaminergic therapy in any condition and their data were simply analyzed to correspond to the OFF-ON state of the PD patient to whom they were matched.

3.7. PD versus controls

Contrasts comparing activity between PD and control groups are presented in Table 7.

3.7.1. OFF Stimulus-response decision events

between slope and beta value in the right ventral caudate ROI ($r = 0.34$, $t = 2.17$, $p = 0.037$; Fig. 5C) for PD patients only. No outliers were found in this correlation using the interquartile method. No other ROIs correlated significantly with slope. *Of greatest significance given our aim of directly testing the notion that DS mediates stimulus-response learning, levels of activation in our DS ROIs did not correlate with the slope of stimulus-response learning in either the PD or control groups.*

3.5. PD patients: OFF vs. ON sessions

Data comparing patients with PD ON and OFF medication are presented in Table 5 and Fig. 6.

3.5.1. Stimulus-response decision events OFF minus ON

There was no preferential activity in the striatum in this contrast for Phase 1 or 2 data.

3.5.2. Stimulus-response decision events PD ON minus OFF

Significant right dorsal putamen (*peak coordinates*: 21, 2, 14; $t = 3.30$, $p = 0.001$, $q_{SVC} = 0.022$) activity arose in the ON relative to OFF Session for Stimulus-Response Decision Events in Phase 1 (Fig. 6A). Significant left (*peak coordinates*: 12, 11, 14; $t = 3.68$, $p = 0.001$, $q_{SVC} = 0.024$) and right dorsal caudate (*peak coordinates*: 6, 2, 20; $t = 3.45$, $p = 0.001$, $q_{SVC} = 0.037$) activity occurred in the ON relative to OFF Session for the Stimulus-Response Decision contrast in Phase 2 (Fig. 6B). Overall, these results reveal a task-specific, dopaminergic therapy-related DS BOLD signal enhancement for decision enactment.

3.5.3. Feedback learning events OFF minus ON

When Feedback Events were investigated in the OFF minus ON contrast, significantly greater activity occurred in the left ventral putamen (*peak coordinates*: 21, 5, 1; $t = 3.41$, $p = 0.001$, $q_{SVC} = 0.004$; Fig. 6C), suggesting that medication dampened VS activity.

3.5.4. Feedback learning events ON minus OFF

No significant activity occurred in this contrast.

given our aim of critically testing DS's role in stimulus-response learning though, intensity of activation in DS ROIs did not correlate with our behavioural measure of learning efficiency in either the PD or control group. These results implicate DS in stimulus-specific response decisions entirely replicating our main finding in Hiebert et al. (2014), in which we used this paradigm in healthy young controls.

In contrast, in Phase 1 only, VS was preferentially activated during correct relative to incorrect Feedback Events. The Feedback Event in each trial is the moment during which learning stimulus-response relations occurs through deterministic outcome information. Further, we found that beta values in a VS ROI (i.e., right ventral caudate in the PD group) correlated significantly with learning slope, our measure of learning efficiency but not with adjusted-savings score our measure of decision accuracy. These findings support a role for VS in stimulus-response association learning also replicating our results with healthy young controls in Hiebert et al., (2014).

In agreement with our frequentist behavioural and fMRI analyses presented above, using Bayesian analyses we found that in both PD patients and healthy controls investigated separately, activation in DS ROIs correlated significantly with Stimulus-Response Decision Events in both Phases 1 and 2 of the experiment. In contrast and of critical importance given the main aim of our study, with Bayesian analysis, we confirmed that activation in DS ROIs was not significantly associated with stimulus-response association learning during Feedback events (i.e., the null hypothesis was supported). VS ROI beta values were significant during the Feedback event using Bayesian analyses concordant with our other in-

Contrasting PD minus control revealed no significant striatal activity in Phases 1 or 2. However, in the control minus PD contrast, controls exhibited significantly greater activation in the right dorsal caudate nucleus (*peak coordinates*: 6, 5, 5; $t = 3.21, p = 0.001, q_{SVC} = 0.027$) than PD patients who were in the OFF state in Phase 1. No significant activity arose in Phase 2 comparing control and PD participants.

3.7.2. ON Stimulus-response decision events

When PD patients were corrected with exogenous dopaminergic therapy in the ON Session, no significant striatal activity arose in the PD minus control or control minus PD contrasts. In Phase 2, in fact, significantly greater activation arose in the left (*peak coordinates*: 12, 11, 17; $t = 3.75, p = 0.001, q_{SVC} = 0.020$) and for PD patients relative to healthy age-matched controls. Recall that age-matched controls did not actually receive dopaminergic therapy and rather their data were simply analyzed to correspond to the dopaminergic state of the PD patient to whom they were matched. No significant striatal activity occurred in the reverse contrast (i.e., control minus PD).

3.7.3. OFF feedback events

No significant striatal activity arose for OFF sessions in the PD minus control contrast. A significant cluster arose in the left ventral caudate (*peak coordinates*: 18, 23, 1; $t = 3.66, p = 0.001, q_{SVC} = 0.045$) in the control minus PD contrast.

3.7.4. ON feedback events

Contrasting PD minus control or control minus PD revealed no significant striatal activity.

4. Discussion

In both Phases 1 and 2 across Sessions 1 and 2, we found that DS activity correlated preferentially with Stimulus-Response Decision Events and *not* with Feedback Events. It is notable that feedback-based learning was precluded by the omission of feedback in Phase 2. DS activation persisted in Phase 2 nonetheless, further casting doubt on DS's role in feedback-based learning. We also found that beta values in the left dorsal putamen in healthy controls in Phase 2 correlated with the accuracy of stimulus-specific response selections (i.e., adjusted savings score), intended as our behavioural measure of decision making. *Most significant,*

investigations in suggesting that the VS mediates stimulus-response association learning through feedback.

Strongly supporting these distinct cognitive roles for DS and VS, PD patients evidenced impaired response-selection performance, using the adjusted-savings score, off medication, which was normalized to control-level performance by dopaminergic therapy. It should be noted that we cannot clearly disentangle whether dopaminergic therapy improved recall of the stimulus-response associations or selection among responses with weakened associations to stimuli following delay and distraction. Both are critical components for accurate decision phase performance and indeed decision making. Conversely, efficiency of learning stimulus-response associations, assessed by our slope of learning measure, was equivalent for PD patients and healthy controls, off dopaminergic medication. However, the slope of learning was worsened by dopaminergic medication in our PD group. Recall that in PD, DS is dopamine depleted and its functions are impaired in the OFF state. DS functions are remediated by dopaminergic therapy. In contrast, VTA-innervated brain areas such as VS are relatively dopamine replete and their functions are normal at baseline. Their functions are actually worsened due to dopamine overdose in the ON state (Cools, 2006). Entirely confirming our interpretation of the behavioural patterns, DS signal associated with the Stimulus-Response Decision Event was enhanced by dopaminergic medications in PD patients using within-subject contrasts. In contrast, Feedback Event-related VS signal was depressed by exogenous dopamine therapy (i.e., dopamine overdose effect).

In contrast to our findings in PD, for healthy controls who did not actually receive dopaminergic therapy but whose data were analyzed to correspond to the ON-OFF order of the PD patients to whom they were matched, there were no response-selection accuracy or learning efficiency differences, or differential patterns of fMRI activity comparing the ON versus OFF sessions, as expected. These findings in controls suggest that differences observed for PD patients were not the result of order, practice, or stimulus effects across the OFF and ON sessions.

Bolstering our within-subject patterns in PD, between-group comparisons revealed that DS activation in PD patients was reduced relative to DS activation in healthy age-matched controls in the OFF state during Stimulus-Response Decision Events. DS activation between PD and healthy controls was equivalent, however, in the ON Sessions, once PD patients were medicated with dopaminergic therapy. Further, VS, but not DS, activation was decreased for PD patients relative to healthy controls

in the ON Session in the exact region (i.e., left ventral putamen) where dopaminergic therapy attenuated VS activation in the PD OFF-ON contrast, consistent with the dopamine overdose hypothesis.

4.1. Cognitive functions mediated by striatum

The striatum mediates cognitive functions (Atallah et al., 2007; MacDonald et al., 2014) in addition to its better-known role in motor control. We independently assessed response-selection decisions and stimulus-response learning, using behavioural measures and distinct fMRI events. We aimed to disentangle neural substrates specifically mediating these different cognitive processes. DS activation correlated with stimulus-response decisions whereas VS signal arose preferentially during delivery of feedback through which stimulus-response associations were learned. This entirely replicates our results in healthy, young individuals (Hiebert et al., 2014). Beyond correlational evidence, however, in PD patients, we found clear double dissociations in DS- and VS-mediated behaviour and preferential neural activity contrasting the OFF and ON dopaminergic therapy states. PD patients demonstrated *enhanced* stimulus-specific response-selection accuracy and DS activity during Stimulus-Response Decision Events, compared to *attenuated* stimulus-response association learning and VS activation during Feedback Events, on relative to off dopaminergic therapy. This pattern of

correlated with efficiency of learning assessed with slope measure. Further, learning efficiency and VS activation were reduced for PD patients on relative to off dopaminergic therapy, suggesting that VS, a VTA-innervated structure, was overdosed by exogenous dopamine. This result fits with the larger literature implicating VS in forms of implicit learning (Tricomi et al., 2009; Sommer and Pollmann, 2016; Vo et al., 2016; Pascucci et al., 2017; Vo et al., 2018), such as reward (Camara et al., 2010), stimulus-stimulus (MacDonald et al., 2011), sequence (Ghilardi et al., 2007), motor sequence (Feigin et al., 2003), and category learning (Shohamy et al., 2006).

4.2. Interpretation of extra-striatal activations

In contrasts where DS activation emerged, cortical regions previously implicated in decision making and categorization judgments were also revealed. These included occipital regions of the fusiform gyrus that have been implicated in decision making, specifically in motor planning and execution (Tosoni et al., 2016), as well as the lateral occipital cortex implicated in object recognition (Vernon et al., 2016). Object recognition performed by the ventral visual stream, is a required step toward enacting stimulus-specific response selections. The right middle frontal gyrus has been shown to implement and reprogramme action plans (Stock et al., 2016). Many of the brain regions that were significantly

results provides strong support for the concept that DS mediates response-selection decisions and not learning – the latter being mediated by VS rather.

Our results are completely at odds with the large literature attributing feedback-based learning to DS (Yin and Knowlton, 2006; Balleine et al., 2009; Hart et al., 2013). A potential explanation for the long-standing association of DS with stimulus-response association learning, despite increasing numbers of contradictory results (Reiss et al., 2005; Atallah et al., 2007; Grahn et al., 2008; Ohira et al., 2010; Robertson et al., 2015), relates to the common confounding of learning and decision-making processes (McDonald and Hong, 2004; Jessup and O'Doherty, 2011; Yang et al., 2017). In behavioural studies, learning is generally measured by the accuracy of stimulus-specific response selections that are provided as evidence that learning has occurred. Poor performance therefore could be the result of failing either to learn stimulus-response associations or to correctly select responses based on these learned associations. In fMRI studies, a) enacting a response when presented with a stimulus, and b) learning from feedback, are typically treated as a single event with all significantly-activated brain regions ascribed a role in learning *per se* (Poldrack et al., 1999; Jessup and O'Doherty, 2011; Dobryakova and Tricomi, 2013). By separately assessing response-selection decisions and learning, our approach aimed to resolve the discrepancy between studies that involve DS in feedback-based learning (O'Doherty et al., 2004; Boettiger and D'Esposito, 2005) versus those in PD patients (Swainson et al., 2000; Vo et al., 2014), and participants with DS lesions (Exner et al., 2002; Ell et al., 2006) that dispute the notion that DS mediates stimulus-response learning.

Our findings integrate with a growing literature favouring a role for DS in decision making rather than learning *per se*. In neuroimaging studies, DS activity consistently remains significantly increased above baseline *after* sequences (Reiss et al., 2005), categorization rules (Helie et al., 2010; Seger et al., 2010), stimulus-reward (Daw and Doya, 2006; Seger et al., 2010), and response-reward associations (Ohira et al., 2010) are well learned. Additionally, DS frequently correlates with response selections, particularly when an element of deliberation is required (Hiebert et al., 2017), even in contexts devoid of new learning (Grahn et al., 2008), such as in the Stroop task (Ali et al., 2010), and in making numeric magnitude judgments (MacDonald et al., 2011). This activation profile is inconsistent with a brain region mediating learning *per se* and is more in line with one that underlies decisions.

Our results, in contrast suggest that VS mediates learning stimulus-response associations. Replicating our previous findings (Hiebert et al., 2014), VS signal occurred specifically during the Feedback Event and

activated along with DS during response-selection events are reciprocally connected with the dorsal caudate nucleus, the body specifically, such as the precentral, postcentral, inferior, and fusiform gyri (Robertson et al., 2018; Tziortzi et al., 2014). These results highlight the fact that, whereas the DS does not function in isolation, it plays a key, central role in performing response-related decisions.

4.3. Effect of dopaminergic therapy on cognition in PD

The notion that abnormalities in dopamine across different brain regions cause cognitive as well as motor symptoms in PD has long been considered (Brown and Marsden, 1984; Gotham et al., 1988). Cognitive functions mediated by SNc-innervated brain regions such as the DS are expected to be improved by dopaminergic therapy, whereas the opposite pattern is expected for VTA-supplied brain regions such as VS in PD. This is due to different rates and degrees of degeneration of dopamine-producing neurons in SNc and VTA in PD. This theoretical framework successfully explains complex behavioural patterns in PD (Cools, 2006; Vaillancourt et al., 2013). This framework is prevalent and effectively accounts for behavioural patterns across a large number of PD studies (Cools, 2006; Dirnberger and Jahanshahi, 2013; Vaillancourt et al., 2013). Studies that fully support these concepts in a single experiment are lacking, however. Here, we provide direct support for this framework for understanding cognitive patterns in PD. We show *for the first time* that dopaminergic therapy *simultaneously* a) improved DS-mediated response selection and boosted DS signal and b) impaired VS-mediated stimulus-response learning and attenuated VS activity. Though a small number of previous investigations provide evidence of improved DS function and increased DS activity (Aarts et al., 2014) or impaired functions mediated by VTA-innervation brain regions and corresponding reduced signal (Cools et al., 2007; Van Eimeren et al., 2009; Kwak et al., 2012; Aarts et al., 2014), none have provided evidence of *these simultaneous and opposite effects* within the same participants, though a number of studies aimed to do so (Argyelan et al., 2008; Van Eimeren et al., 2009; Shiner et al., 2012; Aarts et al., 2014).

5. Conclusions

Our findings dispute the prevalent notion that DS mediates stimulus-response learning. We showed that DS mediates response selections whereas VS underlies feedback-based learning in PD patients and healthy age-matched controls. This study provides strong support for the view that DS has been erroneously ascribed a role in feedback-based, stimulus-

response learning due to methodology that confounds learning and response-selection processes. Our findings integrate with a growing literature favouring a role for DS in decision performance rather than learning *per se*.

Values are presented as group means and standard error of the mean (SEM) in braces. Screening cognitive and affective measures were completed on medication unless otherwise stated. Dopaminergic therapy was not administered to control (CTRL) participants at any time during the experiment. Their data are presented here in the ON-OFF order corresponding to their matched PD patient. Edu – Years of education; Duration – Number of years since PD diagnosis; L-dopa (mg) - L-dopa equivalent dose in mg; DA – number of PD patients on dopamine agonists; UPDRS OFF – Unified Parkinson's disease rating scale motor score off medication; UPDRS ON – Unified Parkinson's disease rating scale motor score on medication; ANART – National Adult Reading Test IQ Estimation; MOCA – Montreal Cognitive Assessment total score out of 30; BDI-II OFF – Beck Depression Inventory II score measured when patients with PD were off medication and for CTRL participants during the off session of their corresponding PD patient; BDI-II ON – Beck Depression

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Inventory II score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient; BAI OFF – Beck Anxiety Inventory score measured when patients with PD were off medication and for CTRL participants during the OFF Session of their corresponding PD patient; BAI ON – Beck Anxiety Inventory score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient; Apathy OFF – Starkstein Apathy Scale score measured when patients with PD were off medication and for CTRL participants during the OFF Session of their corresponding PD patient; Apathy ON – Starkstein Apathy Scale score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient.

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