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Striatum in stimulus-response learning via feedback and in decision making.

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Striatum in stimulus–response learning via feedback and in decision making

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ABSTRACT

Cognitive deficits are recognized in Parkinson's disease. Understanding cognitive functions mediated by the striatum can clarify some of these impairments and inform treatment strategies. The dorsal striatum, a region impaired in Parkinson's disease, has been implicated in stimulus–response learning. However, most investigations combine acquisition of associations between stimuli, responses, or outcomes (i.e., learning) and expression of learning through response selection and decision enactment, confounding these separate processes. Using neuroimaging, we provide evidence that dorsal striatum does not mediate stimulus–response learning from feedback but rather underlies decision making once associations between stimuli and responses are learned.
In the experiment, 11 males and 5 females (mean age 22) learned to associate abstract images to specific button-press responses through feedback in Session 1. In Session 2, they were asked to provide responses learned in Session 1. Feedback was omitted, precluding further feedback-based learning in this session. Using functional magnetic resonance imaging, dorsal striatum activation in healthy young participants was observed at the time of response selection and not during feedback, when greatest learning presumably occurs. Moreover, dorsal striatum activity increased across the duration of Session 1, peaking after most associations were well learned, and was significant during Session 2 where no feedback was provided, and therefore no feedback-based learning occurred. Preferential ventral striatum activity occurred during feedback and was maximal early in Session 1.
Taken together, the results suggest that the ventral striatum underlies learning associations between stimuli and responses via feedback whereas the dorsal striatum mediates enacting decisions.

Introduction

Parkinson's disease (PD) is a common movement disorder, though cognitive impairments are now recognized. Movement symptoms associated with PD appear when degeneration of dopamine-producing cells of the substantia nigra (SN) is sufficient to seriously interrupt dopamine supply to the *dorsal* striatum (DS; Kish et al., 1988). In contrast, dopamine-producing cells in the ventral tegmental area (VTA) are relatively spared and dopamine supply to its efferent, the *ventral* striatum (VS), along with the limbic and frontal cortices, is better preserved (Haber and Fudge, 1997). The striatum is the input region for a collection of subcortical nuclei, known as the basal ganglia, that are generally implicated in movement regulation and increasingly in cognitive functions. VS includes the nucleus accumbens and ventral portions of the caudate nucleus and putamen, and is considered separately from DS – comprising the bulk of the caudate and putamen – because they have distinct dopaminergic inputs (Voorn et al., 2004; Wickens et al., 2007), vascular supplies (Feekes and Cassell, 2006), and functions (Cools, 2006; MacDonald and Monchi, 2011). As the pathophysiology predicts, dopamine replacement medications, such as L-3,4-dihydroxyphenylalanine (L-dopa) or dopamine receptor agonists, considerably improve DS-mediated symptoms, both motor and cognitive. However, in PD, these medications impair cognitive functions performed by VTA-innervated regions, such as VS, presumably a result of dopamine overdose of these relatively dopamine-replete regions (Cools, 2006). Accordingly, understanding cognitive functions mediated by these striatal sub-regions is an important aim. Along with motor symptoms, this knowledge could guide medication titration to address cognitive symptoms that are ranked highly as a cause of reduced quality of life in PD (Barone et al., 2009; Schrag et al., 2000).

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DS has been implicated in learning associations between stimuli and responses (See Ashby et al., 2007; Yin and Knowlton, 2006 for reviews), including in early goal-directed or feedback-guided learning (Balleine et al., 2009; Boettiger and D'Esposito, 2005; Brovelli et al., 2011; Brown and Stern, 2013; Foerde et al., 2013; Garrison et al., 2013; Hart et al., 2014; O'Doherty et al., 2004). This ability to learn associations among stimuli, responses, and outcomes of actions is essential for adaptive behavior. Despite considerable evidence suggesting that DS mediates learning, in some cases, learning is preserved in non-human animals (Atallah et al., 2007; McDonald and Hong, 2004; Ragozzino, 2007) and in patients (Ell et al., 2006; Exner et al., 2002; Shin et al., 2005) with DS lesions, casting doubt on this notion. Furthermore, learning is often *worsened* by dopaminergic therapy in PD, not expected if DS mediates learning stimulus–response associations (Cools et al., 2007; Feigin et al., 2003; Ghilardi et al., 2007; MacDonald et al., 2013a,b; Seo et al., 2010; Shohamy et al., 2006; Tremblay et al., 2010).

This discrepancy in the literature regarding DS' role in stimulus–response learning is potentially explained by increasing evidence that DS mediates decision making, coupled with a methodological feature of many learning studies. Decision making refers to the process of representing and assigning values and probabilities to different response options, then choosing and performing a response (Rangel et al., 2008; Ryterska et al., 2013). Investigations of learning frequently combine enacting decisions with learning per se (Jessup and O'Doherty, 2011; McDonald and White, 1993). For example, typical paradigms proceed as follows: a) a stimulus is presented and participants decide among a set of responses, b) feedback about accuracy of response is provided, through which stimulus–response associations are learned. In functional magnetic resonance imaging (fMRI) studies, a) selecting and enacting a response, and b) learning from feedback are treated as a single event, neural activity is merged, and all significantly-activated brain regions are ascribed a role in learning (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Jessup and O'Doherty, 2011; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008).

Our aim was to directly test the notion that DS underlies early learning of associations between stimuli and responses through feedback. In the experiment, participants learned to associate abstract images and specific button-press responses through feedback. Using fMRI, we investigated whether DS was differentially activated at the time of response selection versus during feedback-based learning.

Materials and methods

Participants

Sixteen healthy, young adults participated in this experiment (11 males and 5 females). Participants had a mean (SEM) age and education level of 22 (0.56) and 16.20 (0.31) years, respectively. Two participants were excluded from the analyses. One participant failed to reach a pre-set learning criterion as described further below and imaging data from the other participant did not sync correctly with the behavioral task. Participants abusing alcohol, prescription or street drugs, or taking cognitive-enhancing medications including Methylphenidate (Ritalin) were excluded from participating. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study. All participants provided informed written consent to the approved protocol before beginning the experiment, according to the Declaration of Helsinki (1991).

Procedures

All participants performed a task during which they learned to associate abstract images with one of three button-press responses in Session 1. Images were computer-generated with *GroBoto* (Braid Art Labs, Colorado Springs, USA). On each trial, an abstract image appeared in the center of a projection screen until the participant responded with a button-press. 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 in Session 1. Trials were organized into blocks. After each block, participants were provided with a percentage score, summarizing their learning performance. A minimum learning criterion of 74% on two successive blocks was required to complete Session 1. The performance criterion was selected for two reasons: 1) piloting data indicated that most participants could achieve 74% in a reasonable number of blocks, and 2) our aim was to investigate early learning. Before proceeding to Session 1, participants received 20 practice trials with different images from those employed during the main experimental sessions. In Session 2, recall of the correct button-press response for each of the abstract images presented during Session 1 was tested. No feedback was provided to preclude new feedback-based learning during this session.

Sessions 1 and 2 were performed in the MRI scanner. Twelve abstract images were used in the experiment (Fig. 1). There were 24 trials per block in Session 1, with each abstract image occurring twice in random order. Four images were assigned to each of the second, third, and fourth buttons on the button box 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, motor responses were included in both decision making and feedback phases.

Trials in Session 1 proceeded as follows: (i) a cross appeared in the center 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 (mean range: 564–4200 ms); (iv) a blank screen appeared for 1400–1800 ms; (v) feedback (i.e., "Correct" or "Incorrect") appeared for 1000–1500 ms, the screen went blank until the participant pressed the first button with his/her thumb to advance to the next trial (mean range: 1800–6000 ms); and (vi) a blank screen appeared for 400–800 ms.

Two distractor tasks (data not shown) were employed between Sessions 1 and 2 to prevent rehearsal of stimulus–response associations. In Session 2, participants performed three blocks of 24 trials, in which the same 12 images studied during Session 1 were presented in random order, twice per block. Participants provided the button-press response that they had learned for each image in Session 1. No feedback regarding accuracy was provided, precluding new feedback-based learning. Parameters for each trial in Session 2 were otherwise identical to those in Session 1. Figs. 2A and B present example trials in Sessions 1 and 2.

Behavioral data analysis

Efficiency of encoding stimulus–response associations across Session 1 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:

$$b = \frac{\sum (x-\overline{x})(y-\overline{y})}{\sum (x-\overline{x})^2}$$

where b is the slope, and x and y are the sample means of the number of blocks and block scores, respectively. Slopes were calculated in the same manner separately for the first and second halves of Session 1 to investigate differential rates in learning across the session. The percentage of accurate responses in the final block of Session 1 (i.e., the highest accuracy score achieved) measured learning efficacy. In Session 2, decision

Fig. 1. Abstract images shown in the experiments. The 12 images were presented in Sessions 1 and 2. Images were computer-generated with *GroBoto* (Braid Art Labs, Colorado Springs, USA).

making based on previously-learned associations was measured with an adjusted-savings score, calculated as follows: average accuracy in Session 2 ÷ accuracy in the last block of Session 1 × 100.

Imaging acquisition

FMRI data were collected in a 3 Tesla Siemens Magnetom Trio with Total Imaging Matrix MRI at Robarts Research Institute at the University of Western Ontario. 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 three runs. Each run consisted of three blocks of 24 trials. Distractor tasks were administered after Session 1. All participants performed Session 2 as the final run. All runs lasted on average 8 min with one whole brain image consisting of 43, 2.5 mm-thick slices taken every 2.5 s. The field of view was oriented along the anterior and posterior commissure with a matrix of 88 × 88 pixels, an isotropic voxel size of $2.5 \times 2.5 \times 2.5\ mm^3$. The echo time was 30 ms and the flip angle was 90°.

FMRI data analysis

Statistical Parametric Mapping version 5 (SPM5; 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. The first ten functional volumes (i.e., 25 s) were discarded, during which participants became familiar with the testing situation. Images were slice-

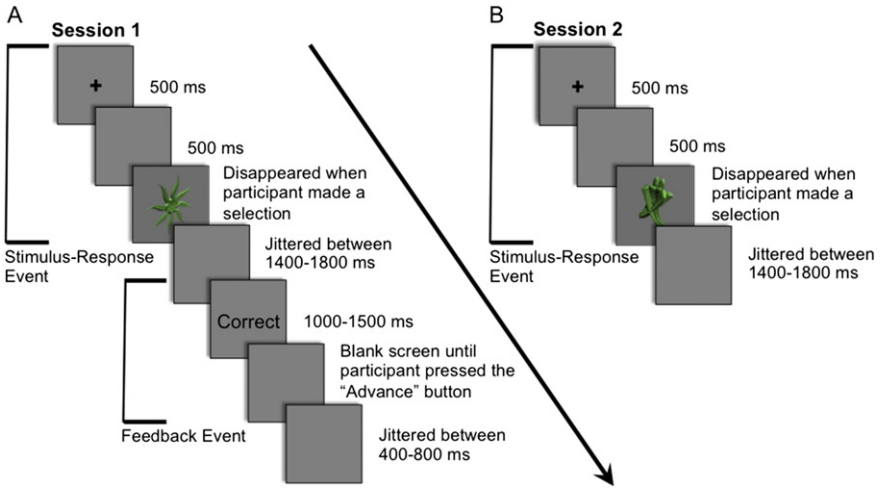

Fig. 2. Example of a single trial in Sessions 1 and 2 of the experiment. The experiment was completed in the MRI scanner with healthy participants. A. Session 1: Participants learned to associate 12 abstract images with a button-press response through feedback. The following is an example of a trial. Trials in Session 1 proceeded as follows: (i) a cross appeared in the center 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 (mean range: 564–4200 ms); (iv) a blank screen appeared for 1400–1800 ms; (v) feedback (i.e., "Correct" or "Incorrect") appeared for 1000–1500 ms, the screen went blank until the participant pressed the first button with his/her thumb to advance to the next trial (mean range: 1800–6000 ms); and (vi) a blank screen appeared for 400–800 ms. B. Session 2: During the test phase, stimulus-specific button-press responses for stimuli learned in Session 1 were performed in the absence of feedback. The parameters for each trial in Session 2 were otherwise identical to those in Session 1.

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).

Individual participant's data were modeled using fixed effects analyses in SPM5. Predictor functions were formed by convolving onsets and durations of psychological events of interest, namely stimulus–response and feedback events, with the canonical hemodynamic response function. The stimulus–response event was defined as the time from onset of the abstract image until the participant made a button-press response. The feedback event was defined as the time from onset of feedback, (i.e., "Correct" or "Incorrect") for 1000–1500 ms, until the button-press to advance to the next trial. In this way, a motor response was included in both stimulus–response and feedback events. General linear models (GLM) were created for both stimulus–response and feedback events for Session 1. The first GLM investigated regional blood oxygenation level dependent (BOLD) activity associated with the stimulus–response event relative to the rest of the trial elements in a block. Number of regressors corresponded to number of blocks to reach the pre-set learning criterion in Session 1. An analogous model was created for feedback events, which convolved onsets and durations of feedback in Session 1. Finally, a GLM investigated stimulus–response events relative to the rest in Session 2 for all trials in a block, with three regressors corresponding to the three blocks performed by all participants.

To investigate brain areas with activity that paralleled learning behavior, models examining activity early and late for both stimulus–response and feedback events in Session 1 were created. Because number of blocks to reach the pre-set learning criterion varied across participants, individualized contrasts were implemented. Session 1 was divided in half and blocks in the first half were considered early and blocks in the second half were considered late. Contrast images were collected and examined together at the group level in a *t*-test in SPM5 for both stimulus–response and feedback events separately. A secondary analysis separated correct and incorrect feedback events, modeling them separately.

Region of interest analysis

To test our predictions regarding the involvement of the striatum in stimulus–response learning and decision making, regions of interest (ROIs) were created using the MarsBaR toolbox for SPM5 (Brett et al., 2002). We selected separate ROIs for VS and DS. For VS, coordinates ($x = \pm 10, y = 8, z = -4$) were taken from Cools et al. (2002), centering around the nucleus accumbens and including portions of the posterior ventral caudate and putamen. Another ROI for VS was created to incorporate anterior portions of the VS. Coordinates for the anterior VS ROI ($x = \pm 12, y = 18, z = -6$) were taken from MacDonald et al. (2011). Brovelli et al. (2011) employed a stimulus–response learning paradigm with healthy participants using fMRI. Peaks of activity that were related to learning were reported in the bilateral head of the dorsal caudate nucleus, as well as in anterior and middle portions of the left dorsal putamen and anterior right putamen. The activation that centered on the left dorsal caudate head, and not the surrounding cortex, served as the center of our dorsal caudate ROI ($x = \pm 18, y = 24, z = 6$). The average coordinates in MNI space of the left and right dorsal anterior putamen activations served as the center of our dorsal putamen ROI ($x = \pm 29, y = 9, z = 6$). Spheres with a radius of 5 mm were centered on the ROIs discussed above. Peaks within the striatum were reported at a significance level of $p < 0.05$, corrected for multiple comparisons, using Bonferroni correction for the eight regions of interest in the analysis. Fig. 3 depicts each ROI in MNI space. Striatal areas were defined using the Harvard–Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). All *x*, *y*, *z* values are reported in MNI space.

Beta values were used to determine the level of activation present in VS and DS in each of the contrasts of interest described below. Further, average beta values for VS and DS are presented graphically in Fig. 5. For the figures, average beta values for VS in each of the contrasts of interest were obtained by averaging beta values of the bilateral anterior and posterior VS ROIs. For the figures, average beta values for DS were similarly calculated by combining beta values of the bilateral dorsal caudate and putamen ROIs.

There were eleven contrasts of interest involving Session 1 and Session 2: (i) stimulus–response events versus the rest in Session 1, (ii) feedback events versus the rest in Session 1, (iii) stimulus–response versus feedback events in Session 1, (iv) early stimulus–response events versus the rest in Session 1, (v) late stimulus–response events versus the rest in Session 1, (vi) early feedback events versus the rest in Session 1, (vii) late feedback events versus the rest in Session 1, (viii) early stimulus–response versus feedback events in Session 1, (ix) late stimulus–response versus feedback events in Session 1, (x) correct versus incorrect feedback in Session 1, and (xi) stimulus–response events versus the rest in Session 2.

Results

Behavioral data

Behavioral data for Sessions 1 and 2 are presented in Table 1. Efficiency of learning stimulus–response associations was estimated by the slope of accuracy scores achieved for each block over the total number of blocks required to reach the pre-set learning criterion using the standard slope of the linear regression function in Microsoft Excel (2011). Learning slopes were significantly greater than zero ($t = 10.32, p < 0.001$); evidence that participants successfully learned stimulus–response associations through feedback across Session 1. Participants on average required five blocks to complete Session 1. We expected that greater learning would occur early relative to late in the session. To test this assumption, Session 1 was divided into early and late, to investigate changes in the rate of learning. Indeed, the slope of learning was significantly steeper early relative to late in the session ($t = 4.00, p = 0.002$; Fig. 4).

The percentage of correct responses in the final block in Session 1 was not statistically different from accuracy in the initial block of Session 2 ($t = 1.79, p = 0.097$, with numerically greater accuracy in Session 1 than Session 2), confirming that no new learning occurred in Session 2 where feedback was not provided. In Session 2, an adjusted-savings score was obtained to measure retention of associations learned in Session 1 (Table 1). On average, in Session 2, participants had a mean (SEM) percentage accuracy of 91.8% (0.01).

FMRI data

Significant activations in ROIs are reported at a significance level of $p < 0.05$, corrected for multiple comparisons (Table 2). Analyses of beta values for contrasts of interest are presented in Fig. 5.

Session 1

Enacting stimulus–response decisions and receiving feedback: overall. Activation in the left dorsal caudate during stimulus–response events relative to rest trended toward significance ($t = 2.57, p = 0.089$). During this period, stimuli are presented and a specific response is selected and enacted. For the stimulus–response minus feedback contrast, no significant striatal activation occurred.

Significant activation occurred in the right posterior VS ($t = 3.48$, $p < 0.05$) in the feedback event relative to rest. During the feedback phase, the response outcome is revealed and participants *learn* whether or not a stimulus is associated with a specific response. DS activity was not detected during the feedback phase, even using a liberal criterion of

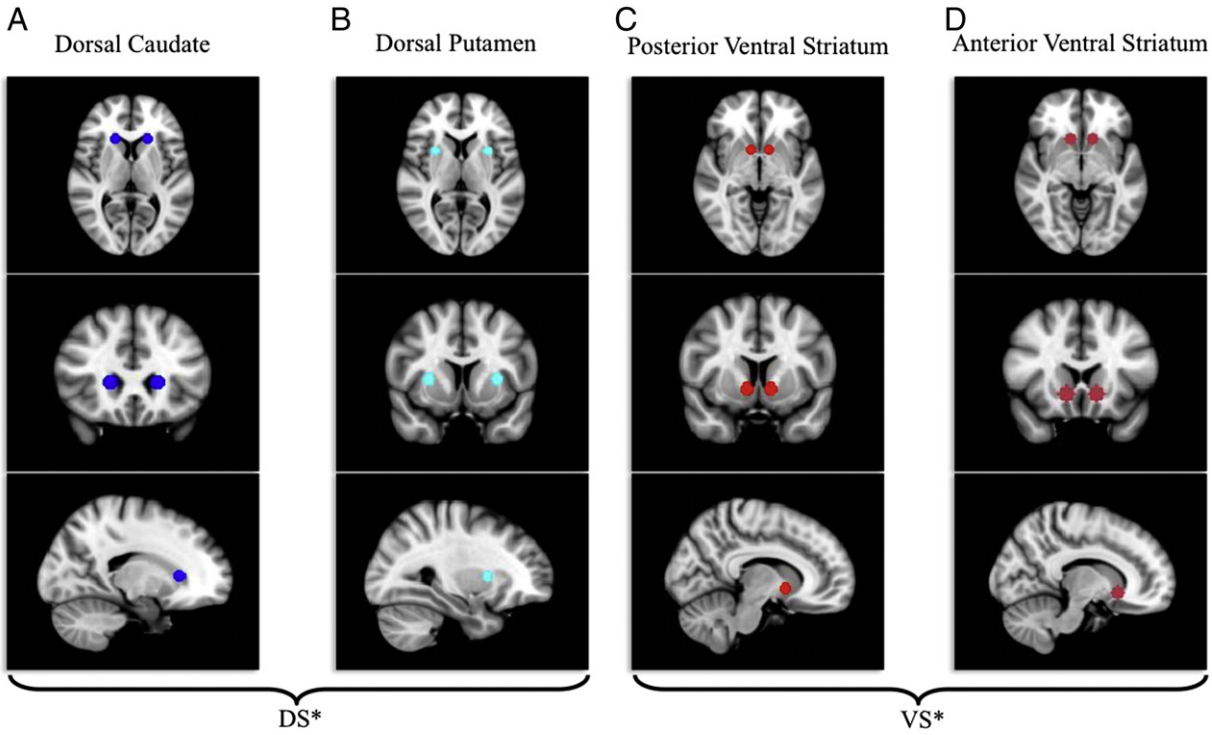

Fig. 3. Regions of interest used in the analysis. Regions of interest (ROIs) used in the fMRI analysis. A. Spherical ROI for dorsal caudate (±18, 24, 6) with a radius of 5 mm. B. Spherical ROI for the dorsal putamen (±29, 9, 6) with a radius of 5 mm. Coordinates for the dorsal caudate and dorsal putamen ROI were taken from Brovelli et al. (2011). C. Spherical ROI for posterior VS (±10, 8, −4) with a radius of 5 mm. Coordinates were taken from Cools et al. (2002). D. Spherical ROI for anterior VS (±12, 18, −6) with a radius of 5 mm. Coordinates were taken from MacDonald et al. (2011). *When average BOLD signal was examined using beta values, beta values from the left and right dorsal caudate and dorsal putamen were combined to obtain a mean signal change for DS. A mean signal change for VS was similarly obtained by combining the left and right posterior VS and anterior VS.

$p < 0.05$, uncorrected for multiple comparisons. Significant activation occurred in the left and right posterior VS ($t = 3.02$, $p < 0.05$, and $t = 3.35$, $p < 0.05$, respectively) in the feedback minus stimulus–response contrast.

Enacting stimulus–response decisions and receiving feedback: early. From our behavioral analyses, learning to associate stimuli to specific button-press responses was maximal early and slowed late in Session 1. We predicted that brain regions implicated in learning would be most active early in Session 1. When stimulus–response events were examined during the early part of Session 1 alone, no striatum activity was associated significantly with stimulus–response events relative to the rest or relative to feedback events. Even when we used a liberal threshold of $p < 0.05$ uncorrected for multiple comparisons, no striatum activity was associated with stimulus–response events in the early part of the experiment.

For feedback events relative to rest early in Session 1, significant activation occurred in the right posterior VS ($t = 3.19$, $p < 0.05$) and trended toward significance in the right anterior VS ($t = 2.53$, $p = 0.07$). Significant activation occurred in the left posterior VS ($t = 3.36$, $p < 0.05$), right anterior VS ($t = 3.81$, $p < 0.05$) and right posterior VS ($t = 4.03$, $p < 0.05$) for the contrast of feedback minus stimulus–response events early in Session 1.

Table 1
Behavioral results

Session 1		Session 2	
Learning slope	Final block score (%)	First block score (%)	Adjusted-savings (%)
0.143 (0.014)	92.86 (5.70)	89.00 (1.66)	99.25 (1.81)

All values reported are means (SEM). Learning slope was measured by the standard slope of the linear regression function in Microsoft Excel (2011) using the scores obtained at the end of each block over the total number of blocks required to reach the pre-set learning criterion. Adjusted-savings (%) in Session 2 was calculated by the following equation: (average score in Session 2 ÷ score in the last block of Session 1 × 100).

Enacting stimulus–response decisions and receiving feedback: late. Considering trials late in Session 1 only, significant activation in the right dorsal putamen ($t = 3.19$, $p < 0.05$) occurred for the stimulus–response minus rest contrast as well as the stimulus–response minus feedback contrast ($t = 2.95$, $p < 0.05$).

For the reverse contrast (i.e., feedback minus stimulus–response events) significant activation occurred in the left anterior VS ($t = 2.12$, $p < 0.05$), left and right posterior VS ($t = 3.37$, $p < 0.05$ and $t = 3.81$,

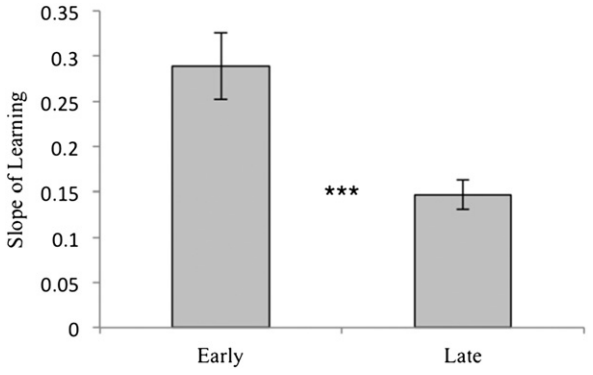

Fig. 4. Average learning slopes early and late in Session 1 Average learning slopes were calculated for early and late halves of Session 1. Error bars represent SEM. Participants' scores obtained after each block in Session 1 were first divided into early and late halves, and slopes were calculated for each phase using the standard slope of the linear regression function in Microsoft Excel (2011). Asterisks indicate a statistically significant difference between the early and late slopes (***$p < 0.01$).

Table 2
Significant ROI activations in the contrasts of interest

Anatomical area	*t* value	$p_{corrected}$
SR events minus rest in Session 1		
Left dorsal caudate	2.57	0.089*
FB events minus rest in Session 1		
Right posterior VS	3.48	0.016
FB events minus rest early in Session 1		
Right anterior VS	2.53	0.070*
Right posterior VS	3.19	0.021
FB events minus rest late in Session 1		
Right posterior VS	2.54	0.068*
SR events minus rest late in Session 1		
Right dorsal putamen	3.19	0.015
FB minus SR events in Session 1		
Left posterior VS	3.02	0.022
Right posterior VS	3.35	0.0099
FB minus SR events early in Session 1		
Left posterior VS	3.36	0.0097
Right anterior VS	3.81	0.0031
Right posterior VS	4.03	0.0018
FB minus SR events late in Session 1		
Left anterior VS	2.12	0.022
Left posterior VS	3.37	0.0012
Right anterior VS	1.66	0.055*
Right posterior VS	3.81	0.00039
SR minus FB events late in Session 1		
Right dorsal putamen	2.95	0.026
FB correct versus incorrect trials in Session 1		
Correct minus Incorrect		
Left anterior VS	2.59	0.061*
Left posterior VS	3.86	0.0027
Right anterior VS	2.72	0.045
Right posterior VS	4.33	0.00079
SR events minus rest in Session 2		
Left dorsal caudate	3.18	0.012
Right dorsal caudate	3.18	0.012

Coordinates of each ROI are as follows: dorsal caudate ($x = \pm 18, y = 24, z = 6$), dorsal putamen ($x = \pm 29, y = 9, z = 6$), posterior VS ($x = \pm 10, y = 8, z = -4$) and Anterior VS ($x = \pm 12, y = 18, z = -6$). Striatal regions that trended toward significance are reported with an asterisk (*).

$p < 0.05$, respectively) and trended toward significance in the right anterior VS ($t = 1.66$, $p = 0.055$).

Correct vs. incorrect feedback. Brain regions that mediate learning should be sensitive to the outcomes associated with actions (i.e., feedback). Significant bilateral posterior VS activation (left posterior VS: $t = 3.86$, $p < 0.05$; right posterior VS: $t = 4.33$, $p < 0.05$) and right anterior VS ($t = 2.72$, $p < 0.05$) arose for correct minus incorrect feedback. For incorrect minus correct feedback, there were no significant striatal activations. Therefore, overall, there were no significant peaks in DS for correct minus incorrect or for incorrect minus correct feedback.

Session 2

Enacting stimulus–response decisions in the absence of feedback. Brain regions that mediate feedback-based learning should not be significantly active once stimulus–response decisions are well learned and when no feedback is provided. Significant bilateral dorsal caudate activation arose in the stimulus–response events minus rest contrast (left dorsal caudate: $t = 3.18$, $p < 0.05$; right dorsal caudate: $t = 3.18$, $p < 0.05$) in Session 2.

Discussion

Using a relatively standard paradigm (Boettiger and D'Esposito, 2005), we tested a prevalent view that DS mediates aspects of feedback-based stimulus–response learning (see Ashby et al., 2007; Garrison et al., 2013; Hart et al., 2014; O'Doherty et al., 2004; Yin and Knowlton, 2006 for reviews). In the experiment, participants learned to associate abstract images and specific button-press responses through feedback in Session 1. On each trial, participants provided a response to a stimulus and then received feedback regarding the accuracy of the response. In this way, we conceptualized these phases as decision making and learning in each trial and modeled them separately to examine regional brain activity that correlated with these distinct processes. In Session 2, participants performed the associations learned in Session 1 but in the absence of feedback. Using fMRI, the pattern of DS

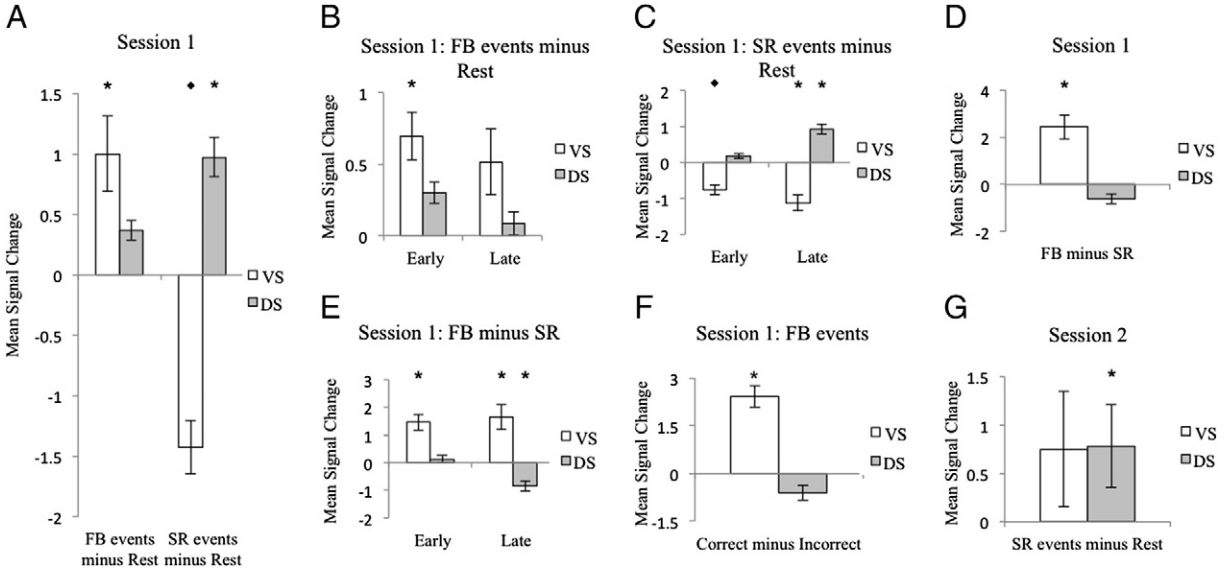

Fig. 5. Mean beta values for VS and DS for contrasts of interest Mean beta values for VS were determined by combining beta values in the left and right posterior and anterior VS. Mean beta values for DS were similarly determined by combining beta values in the left and right dorsal caudate and putamen. Mean beta values for DS and VS are presented for each contrast of interest. Error bars represent SEM. A. Mean beta values for SR events minus rest and FB events minus rest in Session 1. B. Mean beta values for FB events minus rest early and late in Session 1. C. Mean beta values for SR events minus rest early and late in Session 1. D. Mean beta values for FB minus SR events in Session 1. E. Mean beta values for FB minus SR early and late in Session 1. F. Mean beta values for correct minus incorrect FB events. G. Mean beta values for SR events minus rest in Session 2. Asterisks indicate a statistically significant difference in each condition from zero (*$p < 0.05$, ♦$p < 0.1$).

activity was inconsistent with what would be expected of a brain region mediating learning. DS was preferentially activated at the time of response selection rather than during learning via feedback and did not appear to track the progression of learning. DS activation also arose in Session 2 where response selection occurred without feedback, and therefore in the absence of new feedback-based learning.

DS in feedback-based learning or decision making?

We modeled stimulus–response and feedback events independently to examine brain regions associated with performing decisions versus early learning of stimulus–response associations based on feedback, respectively. The notion that the stimulus–response and feedback events represent separate processes—decision making in the former and learning in the latter—has been suggested by others as well (Foerde and Shohamy, 2011; Rangel et al., 2008; Ryterska et al., 2013). This design differs from many learning studies that combine decision making (i.e., stimulus–response events) and learning from outcomes (i.e., feedback events) into a single event, assigning all brain regions whose activity correlates with these merged processes a role in learning (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008, but see Aron et al., 2004; Daniel and Pollmann, 2010; Haruno and Kawato, 2006; Helie et al., 2010; Rodriguez, 2009; Waldschmidt and Ashby, 2011 for investigations that separated stimulus–response and feedback events). Significant DS activation arose in the stimulus–response or decision making event of our trials and not in the feedback or learning phase. To eliminate the possibility that DS activity arose for stimulus–response events simply because a motor response occurred during this phase, a specific button-press response was also required in the feedback event of our experiment.

There was no significant DS activation in the early part of Session 1 when learning was maximal according to our behavioral data. In contrast, significant DS activation arose only late in Session 1, *after* stimulus–response associations were well learned. This pattern is opposite to what is expected for brain regions that mediate learning. Brain regions underlying learning are also expected to be sensitive to feedback valence. There were no significant peaks in DS for contrasts of correct versus incorrect feedback. Finally, significant DS activation arose during Session 2 where no feedback was given and therefore no feedback-based learning could occur. Collectively, these results are inconsistent with the contention that DS mediates early stimulus–response learning based on feedback in our experimental paradigm and instead suggest a more primary role in decision making.

We conceive that initially responses are selected arbitrarily and later are based on biases between stimuli and specific responses that evolve through feedback. We consider the phase during which a response is selected and enacted to be more reflective of decision making processes though the mere act of performing a specific response to a particular stimulus can also contribute to establishing stimulus–response (re) mapping. Receiving outcome information is arguably a more critical step in the process of learning associations in stimulus–response paradigms such as the one that we have implemented, however (Worthy et al., 2013).

We used multiple strategies for uncovering brain regions that support learning versus decision making. The patterns of DS activation consistently were those expected for a brain region associated with decision making and not feedback-based learning. Our results are therefore at odds with the notion that DS mediates learning associations between stimuli and responses via feedback (Ashby et al., 2007; Foerde et al., 2013; Garrison et al., 2013; Yin and Knowlton, 2006). So how can our findings be reconciled with the literature supporting this claim? Again, many fMRI investigations of learning confound decision making and learning by combining neural activity associated with both response-selection and feedback events (Delgado et al., 2005; Dobryakova and Tricomi, 2013; Jessup and O'Doherty, 2011; Nomura et al., 2007; Poldrack et al., 1999; Ruge and Wolfensteller, 2010; Xue et al., 2008). The conclusion that DS activation in these studies reflects a role in learning could be a misinterpretation. For example, Delgado et al. (2005) examined learning to associate cards with concepts of 'high' versus 'low' via feedback. As is typical, they considered response selection (i.e., high vs. low decisions) and feedback portions of each trial as a single event. Compared to baseline, they found significant peaks in the dorsal caudate nucleus and VS, concluding that both mediate learning. Combining decision making and feedback events caused ambiguity. Consequently, concluding that preferential DS activation was related to the response selection operation, whereas VS activity reflected learning through feedback is an alternative explanation for these data that is equally plausible, and in line with our findings.

The finding that DS activation was maximal late in the learning session when behavioral change and learning are actually diminishing has been reported by others. Despite the disconnect with behavioral indices of learning, and focusing on the fact that experience appears to modulate DS activity, this result is offered as support for its role in learning nonetheless (Boettiger and D'Esposito, 2005; Seger et al., 2010; Toni and Passingham, 1999). The frequent finding that DS activity remains significantly increased above baseline after sequences (Reiss et al., 2005), categorization rules (Helie et al., 2010; Seger et al., 2010), or stimulus–reward (Daw and Doya, 2006; Seger et al., 2010), and response–reward (Delgado et al., 2005; Ohira et al., 2010) associations have been acquired should challenge the notion that DS underlies learning, yet has not instigated such a revision. The alternative interpretation that DS mediates response selection, which predictably improves once stimulus–response associations are learned, accounts for both the pattern of brain–behavior relations and the observation that DS activity changes with exposure to learning events. Using single-cell recording in a go/no-go reversal learning paradigm in rats, Takahashi et al. (2007) found increased DS activity for rewarded odor cues only *after* behavioral learning criteria were achieved. These findings, like ours, support the view that DS mediates decision making, not learning *per se*. Indeed, there is a growing literature that implicates DS in performing decisions (Atallah et al., 2007; Grahn et al., 2008; Jessup and O'Doherty, 2011; MacDonald et al., 2014; McDonald and Hong, 2004; Postle and D'Esposito, 1999; Smittenaar et al., 2012) and consequently the results presented here unite two literatures that have advocated disparate functions for DS.

DS in habit formation or decision making?

Regions of DS have also been theorized to support later forms of learning that do not depend upon feedback, such as habit formation (Ashby et al., 2010; Balleine et al., 2009; Ruge and Wolfensteller, 2013; Tricomi et al., 2009). Habit formation refers to strengthening of stimulus–response associations that become independent of outcomes and even resistant to feedback (Tricomi et al., 2009). The notion is that early stages involve goal-directed learning that implicate VS and dorsomedial striatum/caudate. This early learning is transferred to dorsolateral striatum/putamen, which is instrumental in strengthening associations (i.e., later habit formation; Tricomi et al., 2009).

Although we have shown that early, goal-directed, feedback-based learning is not associated with DS activation, even in our dorsomedial/caudate ROI, our results do not entirely rule out the possibility that DS activation observed late in Session 1, and only at the time of response enactment, reflected a role in habit formation. However, this possibility is lessened by the fact that we focused on early phases of learning in this experiment, having set our learning criterion to 74% accuracy on two consecutive blocks. This was specifically to avoid over-learning in the current experiment.

Others have failed to support the notion that habit formation depends upon DS (de Wit et al., 2011). Further, a recent meta-analysis of 35 fMRI studies of reinforcement learning through feedback – the

majority of which combined neural activity for response selection/decision and feedback phases – found both VS and DS to be equally associated with performing *feedback-based* learning. This meta-analysis casts doubt on the theory that VS mediates feedback-based learning and DS underlies later habit formation (Garrison et al., 2013), unless the contention is that both forms of learning co-occur.

Evidence supporting our view that DS mediates decision making rather than learning per se is provided by Atallah et al. (2007). They investigated the role of DS in learning versus selecting responses that relied on learned associations. In a Y-maze task using odor cues, they observed impairment in rats' ability to consistently select a rewarded versus unrewarded arm for animals receiving infusions of inhibitory gamma-amino butyric acid (GABA) agonist to DS compared to a saline solution during the learning phase of the experiment. At first blush, this seemed to suggest that animals receiving inhibitory infusions to DS were learning associations between odor cues and rewards more poorly. When both groups were later tested once the infusions were stopped, however, both experimental and control groups performed the selection task similarly. This demonstrated that associations were learned equally well for both experimental and control (i.e. saline-infused) groups during Session 1. Rather, inhibition of DS impaired the animal's ability to use learned associations to perform selections reliably. To complement this interesting finding, in another experiment, they found that GABA infusions to DS at test phase resulted in impaired selection performance compared to saline infusions to DS, although both groups had previously shown identical learning of these odor–reward associations during the training phase. Taken together, these results challenge the direct involvement of DS in learning and instead suggest a more specific role in performance, as we claim here. The fact that DS inhibition did not impair early feedback-based learning disputes contentions that portions of DS are critical for goal-directed, early, learning through feedback (Balleine et al., 2009; Boettiger and D'Esposito, 2005; Brovelli et al., 2011; Brown and Stern, 2013; Foerde et al., 2013; Garrison et al., 2013; Hart et al., 2014). That DS integrity was essential for adequate stimulus–response performance even early in the training phase is also at odds with the notion that DS mediates later-stage habit formation specifically.

VS in stimulus–response learning

Our results implicate VS in learning stimulus–response associations. VS activation occurred during the feedback event, peaked early, and decreased across Session 1. VS was sensitive to valence of feedback, exhibiting greater activity for correct than incorrect outcomes. Together, these results are highly consistent in suggesting that VS mediates early stimulus–response learning via feedback. Traditionally, VS has been implicated as a key region in reward learning and processing (Camara et al., 2010; Cools et al., 2002; Delgado, 2007; Delgado et al., 2000; Knutson and Cooper, 2005; O'Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010). However, studies have recently been published that implicate VS in learning situations that are devoid of reward and punishment, for example in stimulus–stimulus association learning (MacDonald et al., 2011), sequence learning (Ghilardi et al., 2007; Seo et al., 2010), motor sequence learning (Feigin et al., 2003), and category learning (Shohamy et al., 2006). That VS could mediate stimulus–response association learning is highly in line with many of these learning situations and has been suggested by others as well (Abler et al., 2006; Daniel and Pollmann, 2010; O'Doherty, 2004; O'Doherty et al., 2003).

Conclusion

In our experiment, we demonstrated that (i) DS does not mediate early feedback-based stimulus–response learning but is implicated in performing response decisions, and (ii) VS underlies stimulus–response association learning. Our findings challenge the claim that DS mediates stimulus–response learning via feedback (Balleine et al., 2009; Boettiger and D'Esposito, 2005; Brovelli et al., 2011; Brown and Stern, 2013; Foerde et al., 2013; Garrison et al., 2013; Hart et al., 2014), and recast it as a brain region mediating decision making, integrating with a growing literature supporting this view (Atallah et al., 2007; Grahn et al., 2008; Jessup and O'Doherty, 2011; MacDonald et al., 2014; McDonald and Hong, 2004; Postle and D'Esposito, 1999; Smittenaar et al., 2012).

Implications for cognition in Parkinson's disease

Cognitive dysfunction is an undisputed symptom of PD that leads to significant impairment in quality of life (Barone et al., 2009; Schrag et al., 2000). The etiology of cognitive impairments in PD is complex but it is now clear that at least a subset of these symptoms arises from dysfunction of the striatum itself (Ray and Strafella, 2012). In PD, DS-mediated functions are compromised at baseline and improved by dopamine replacement therapy. Conversely, VS functions are relatively spared off medication and worsened by dopaminergic therapy, most notably at early stages of the disease (Cools, 2006; MacDonald and Monchi, 2011). Understanding VS- and DS-mediated cognitive functions therefore informs cognitive symptoms in PD and has implications for treatment. Currently, dopaminergic therapy is titrated to relieve DS-mediated motor symptoms, without taking into account the potential overdose of VTA-innervated regions. Ultimately, this greater understanding will prompt clinicians to formulate medication strategies that include both motor and cognitive symptoms, as well as individual patient priorities.

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