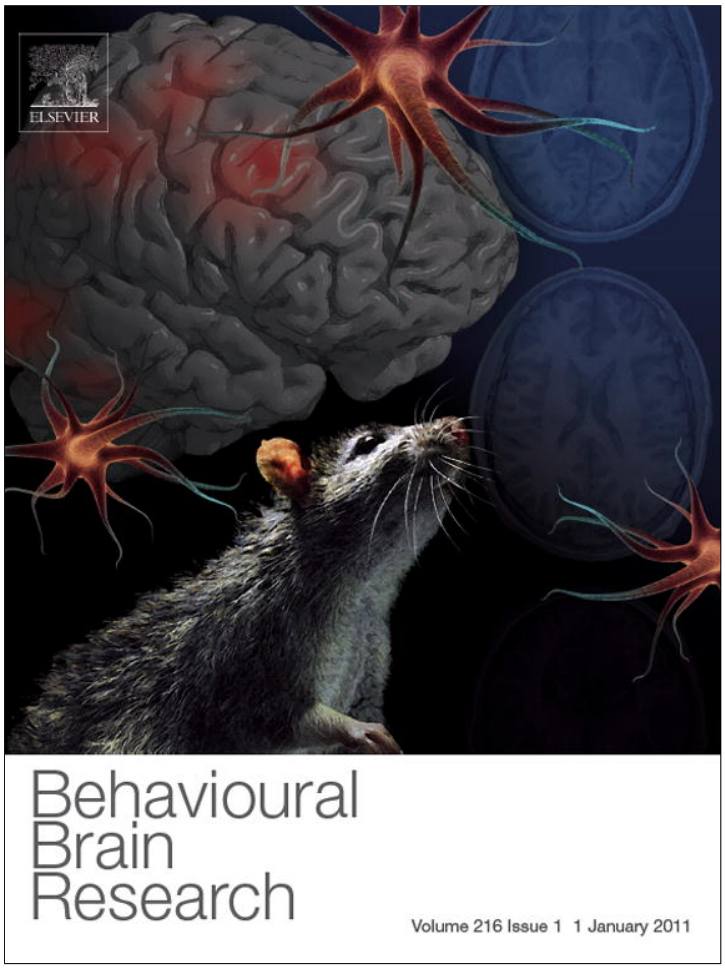

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Research report

Dopaminergic modulation of the updating of stimulus–response episodes in Parkinson's disease

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ABSTRACT

Increasing evidence suggests that the control of retrieval of episodic feature bindings is modulated by the striatal dopaminergic pathway. The present study investigated whether this may reflect a contribution from the ventral or the dorsal part of the striatum. Along the lines of the overdose hypothesis in Parkinson's disease (PD), functions known to rely on the dorsal striatum are enhanced with dopaminergic medication, while operations relying on the ventral circuitry are impaired. We found that partial mismatches between present and previous stimulus–response relations are, compared to control participants, abnormally low OFF DA medication and normalized ON DA medication. The results suggest that the dorsal striatum, but not (or not so much) the ventral striatum, is driving the flexible control of retrieval of stimulus–response episodes.

1. Introduction

The primate cortex represents the features of perceptual events as well as actions associated with these events in distinct, but tightly connected, brain regions [1,2]. The temporal binding of neural codes associated with perceptual features and actions offers a mechanism for integrating distinct features into more meaningful and complex events [3]. Studies of repetition effects offer some of the most compelling empirical evidence for the existence of mechanisms that bind features into more complex events. For instance, participants respond faster to letters presented in a previous display than to novel letters (a standard priming or repetition effect), and reactions are even faster if the repeated letter also appears in the same location as in the previous display [4]. This suggests that processing a letter appearing in a particular location induces a binding between the codes that represent the letter's shape and location (an "object file" in the terms of Kahneman and colleagues), so that repeating this exact conjunction of features enhances the efficiency of processing the stimulus event. Binding as an essential mechanism for constructing perceptual events is also illustrated by repetition effects that impede performance. When a subsequent event consists of only a partial repetition of features from the previous display, conflict results from the mismatch between the previously bound features and the current novel combination of features. In this situation, the automatic retrieval of bound features from the initial display must be reconfigured and updated to accommodate the novel binding of features in the present display, a process that slows response times and increases the potential for decision errors [5–7].

Repetition effects attributable to feature binding have been observed within and across various sensory/perceptual modalities as well as for perceptual and action features [8–11]. Regarding the latter, performance speed and accuracy are compromised if a stimulus feature repeats while the response changes, or if the response repeats while the stimulus feature changes, than if both stimulus and response repeat or if both alternate [11]. This suggests that the binding and integration of features spans codes representing perceived events, such as stimuli, and produced events, such as performed actions [12]. The present study focused on stimulus–response binding mechanisms that integrate stimulus and response features into complex events and on how the after-effects of stimulus–response binding affect performance.

Of particular relevance for the present study, there is evidence suggesting that the retrieval of stimulus–response bindings

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is mediated by dopaminergic pathways. Very recently we are able to demonstrate that genetic markers of striatal dopamine level, dopamine transporter gene (DAT1) gene, predict individual differences in the efficiency of updating stimulus-response episodes [13]. The performance of 9-repeat carriers of the DAT1 gene was more hampered by partial mismatches between present and previous stimulus–response relations compared to the performance of 10/10 homozygotes.

2. Purpose of study

The finding that the efficiency of updating stimulus–response bindings is predicted by genes related to striatal dopamine suggests that the striatum plays an important role in the control of the retrieval of such bindings. At the same time, however, it leaves open which particular subcomponent of the striatum is responsible. The present study aimed at distinguishing, even though in an indirect way, between two possible candidates: the ventral (i.e. nucleus accumbens, ventral putamen and caudate) and the dorsal striatum (i.e. the dorsolateral putamen and the dorsal parts of the caudate nucleus).

As noted by Cools [15], human functional imaging studies and studies on rodents suggest distinct roles for the dorsal striatum and the ventral striatum in stimulus–response and stimulus–outcome associations, respectively. The dorsolateral striatum has been related with the learning and adaptation of stimulus–response (S–R) 'habits' [16–18,45]. Accordingly, the dorsal striatum seems to be the prime candidate for establishing stimulus–response episodes. Indeed, one might consider the binding between feature codes a first step toward integrating them into a more durable memory trace, which would suggest that the short-term binding and the creation of longer-term associations may be handled by the same neural structures.

The rationale of the present study was that investigating Parkinson's disease (PD) patients may help to clarify the role of dopamine on the retrieval of stimulus–response binding mechanisms and offer support, albeit indirectly, for the potential role of dorsal vs. ventral striatal involvement in binding processes. PD is a neurodegenerative process originating in the midbrain, in particular in those dopaminergic neurons of the substantia nigra that project into the dorsolateral striatum (mostly the putamen; [19]). Only later, with the progression of the disease, these effects extend into the ventral striatum [20]. The primary treatment of PD aims to increase DA availability and activity, including, most prominently, medications functioning as a DA precursor (typically levo-dopa) or as a DA agonist [21]. However, regions of the striatum are presumed to be affected by the disease differentially; hence DA medication may produce contrasting effects on the functions associated with ventral and dorsal striatum. Although DA pharmacotherapy successfully improves motor deficits in PD, its effects on cognitive processes are more controversial. In a critical review of the literature, Cools [15] formulated the overdose hypothesis in PD suggesting that cognitive functions that rely on the heavily DA-depleted dorsolateral and motor loops, such as task-switching, improve with DA pharmacotherapy, whereas other aspects of cognition that depend on ventral striatum and remain relatively spared in early PD, such as reversal and extinction learning, are overdosed by dopamine therapy and negatively impacted as a result ([22]; for a recent review, see Ref. [23]).

Studying PD patients ON and OFF medication, and comparing their performance to a control group, provides a potentially useful tool for separating the involvement of dorsal and ventral striatum in stimulus–response binding mechanisms. Based on the overdose hypothesis, if PD patients OFF medication show partial-repetition costs comparable to healthy control participants but enhanced costs ON dopaminergic medication, this would suggest that stimulus–response updating is mediated by the ventral striatum and/or other brain regions receiving dopamine from the ventral tegmental area. If instead, according to the ameliorative effects of the dorsal striatum as a result of dopamine replacement therapy, the partial-repetition costs are abnormally low OFF medication and normalized ON medication, the opposite conclusion would be suggested: that stimulus–response updating is mediated by the dorsal striatum.

Table 1
Demographic characteristics, MMSE (mini mental state examination), UPDRS (unified Parkinson's disease rating scale) scores, LEDD (total levodopa daily dosage) and medication use (Mirapex, Stalevo, Requip) of PD patients.

Sample ($N = 11$)	Mean	Standard deviation
Age (yrs)	68.1	±6.9
Gender (male/female)	8/3	
Years of education	17.0	±2.5
MMSE	28.7	±0.3
UPDRS	19.9	±10.5
Years since disease onset	10.4	±7.1
LEDD	727.4 mg	±398.5

3. Methods

3.1. Participants

Eleven PD patients treated with anti-parkinsonian medication (L-DOPA and DA agonist) served as participants in the PD group, see Table 1 for the demographic characteristics. Patients with a mini-mental state examination (MMSE [24]) score lower than 25, history of major psychiatric disorders, psychoactive medication, alcoholism, stroke, neurosurgical operation or any other condition known to impair mental status other than PD were excluded. Fourteen healthy participants (9 males, 5 females), with a mean age of 71.1 years (SD = 3.0), and with a mean score of 29.0 (SD = 1.1, range 27–30) in the MMSE, served as control group. All subjects participated voluntarily and gave their written informed consent prior to participation, as part of procedures that complied fully with relevant laws and with standards of ethical conduct in human research as regulated by the University of Virginia human investigation committee (Table 2).

3.2. Task and apparatus

3.2.1. Questionnaires

The MMSE [24] assessed the global cognitive state of each patient to verify the absence of dementia.

3.2.2. Experimental paradigm

Stimulus–response binding after-effects were assessed by means of Hommel's [11] event-file task, which we adapted from Colzato et al. [25]. The task was implemented on a personal computer with a 17-in. digital display monitor. The computer screen, placed at a distance of ~90 cm, was positioned so that stimuli appeared at eye level. Stimuli consisted of colored pictures against a dark background. Responses to stimuli were right or left thumb button presses registered by comfortable handheld grips.

The task measured binding-related effects by detecting partial-repetition costs related to combinations of stimulus features (shape and color in our case) and combinations of stimulus features and the response. To manipulate the repetition vs. alternation of stimulus features and responses, each trial involved a response to the presentation of a prime stimulus (S1 → R1) followed by a response to presentation of a probe stimulus (S2 → R2), see Fig. 1. Prime and probe stimuli consisted of yellow or green colored images of a banana or of an apple. All four combinations of fruit and color where used in the task. Each trial began with the presentation of an arrowhead (stimulus duration = 1500 ms) that pointed to the left or to the right. The direction of the arrow indicated the direction of the response (left arrow = left hand; right arrow = right hand) that was to be made upon the onset of the prime stimulus (S1). After a 1000 ms interstimulus period, the prime stimulus appeared for 1000 ms, and participants made a response to this stimulus based solely on the direction of the preceding arrow. Thus, the correct R1 was signaled by the arrow in advance of S1. This was done so that S1 and R1 could be varied independently and intentionally to create orthogonal repetitions and alternations of stimulus shape, color, and response. After a response to the prime, the probe stimulus (S2) appeared. The response to the probe was selected on the basis of a pre-determined decision rule that mapped one fruit (apple or banana) to a left hand response and the alternative fruit to a right hand response. Although the color of the fruit was varied throughout the task, color was not a defining or relevant feature of the task or response goal (see Ref. [26]). Stimulus color could

Table 2
Means of mean reaction times and errors for responses to stimulus 2 (RT_{R2} in ms) as a function of DA medication (ON vs. OFF vs. control), the relationship between the responses (R1 and R2), and the relationship between the stimuli features (S1 and S2) for shape and color. Standard errors in parentheses. The rightmost column gives the partial repetition costs (see footnote 1), which differed significantly in response-shape between the two groups in RTs.

Medication		Response repeated		Response alternated		Partial repetition costs
		Shape repeated	Shape alternated	Shape repeated	Shape alternated	
RTs (ms)	ON	741 (59)	813 (66)	828 (63)	745 (52)	77.5* (9.0)
	OFF	759 (69)	786 (70)	820 (82)	769 (74)	39* (4.5)
	Control	731 (52)	827 (59)	780 (56)	750 (46)	63 (8.5)
Errors (%)	ON	8.0 (3.9)	16.2 (4.5)	14.8 (4.6)	6.0 (2.9)	8.5 (1.1)
	OFF	8.0 (3.3)	15.9 (4.6)	18.5 (4.3)	4.8 (1.8)	10.8 (1.9)
	Control	5.0 (3.1)	4.1 (2.6)	6.3 (3.5)	4.6 (2.1)	0.4 (0.4)

Medication		Response repeated		Response alternated		Partial repetition costs
		Color repeated	Color alternated	Color repeated	Color alternated	
RTs (ms)	ON	764 (61)	790 (64)	791 (55)	781 (58)	18 (0.0)
	OFF	765 (67)	780 (72)	798 (78)	791 (77)	11 (3.0)
	Control	759 (54)	799 (57)	771 (49)	759 (51)	26 (1.0)
Errors (%)	ON	13.1 (4.8)	11.1 (3.4)	10.2 (3.4)	10.5 (3.9)	−1.1 (−1.9)
	OFF	12.2 (4.4)	11.6 (3.7)	12.5 (2.9)	10.8 (3.0)	0.5 (−0.4)
	Control	3.8 (2.3)	5.3 (3.3)	8.0 (3.8)	2.9 (1.7)	3.3 (1.5)

* Significant group difference; $p < 0.05$.

repeat or alternate independently of stimulus shape and responses, thus creating a $2 \times 2 \times 2$-factorial design. Of particular relevance for the present study were repetitions and alternations of stimulus shape (the task-relevant stimulus feature) and response. Binding (of S1 and R1 features) and binding retrieval (induced by S2/R2 processing) would be indicated by a data pattern in which performance is better if both stimulus shape and response are repeated, or if both alternate, than if stimulus shape is repeated while the response is not, or vice versa.

The experiment was composed of a practice block with 10 practice trials, which were not further analyzed, and an experimental block with 196 experimental trials. The order of the trials was randomized, and all eight conditions appeared equally often. Half of the participants responded to the apple and the banana by pressing on the left and right key press, respectively, while the other half received the opposite mapping. The participants were asked to respond as quickly and accurately as possible.

3.2.3. Procedure and design

Parkinson participants completed two identical versions of the task ON their anti-parkinsonian treatments (L-DOPA, DA agonist) and OFF medication on different days, while control participants completed only one version of the task. The order of testing ON and OFF medication was counterbalanced across patients. Prior to completing the task, each participant signed the consent form and completed the MMSE. Testing OFF medication took place after a 12 h withdrawal period after which L-DOPA blood plasma concentrations are reduced to zero [27,28].

3.3. Statistical analysis

First, in Parkinson patients the effect of medication on the updating of stimulus–response episodes was assessed by means of $2 \times 2 \times 2$-ANOVAs with medication (ON vs. OFF) and with the repetition vs. alternation of response (R1 → R2), stimulus shape and color (S1 → S2) as within-participant factors. Second, the same ANOVAs (but without medication as factor) was run in the control group. Third, in order to compare the performance of Parkinson patients and control participants we run the ANOVAs with group (ON vs. control and OFF vs. control) as between-participant factor. We adopted a significance level of $p < .05$ for all statistical tests.

4. Results

After excluding trials with missing (>2000 ms) or anticipatory responses (<200 ms), mean reaction times (RTs) and proportions of errors (PEs) for R2 were analyzed. Table 1 provides an overview of the ANOVA outcomes for RTs and PEs obtained for R2.

4.1. ON vs. OFF

Replicating earlier findings [7,11], RTs revealed significant interactions between response and shape, the two task-relevant features, $F(1,10) = 8.76$, $p < 0.05$—repeating one but not the other feature slowed down responding, see Fig. 2. The error rates followed the same pattern: response interacted with shape, $F(1,10) = 9.13$, $p < 0.05$, indicating more accurate performance if both features were repeated or both alternated, as compared to conditions where one feature but not the other was repeated.

As predicted, the RT binding-type interaction between shape and response repetition was modulated by a three-way interaction involving medication, $F(1,10) = 6.65$, $p < 0.05$. Separate ANOVAs for ON and OFF DA medication, confirmed that the 77.5-ms partial-repetition costs observed ON DA medication was highly significant,

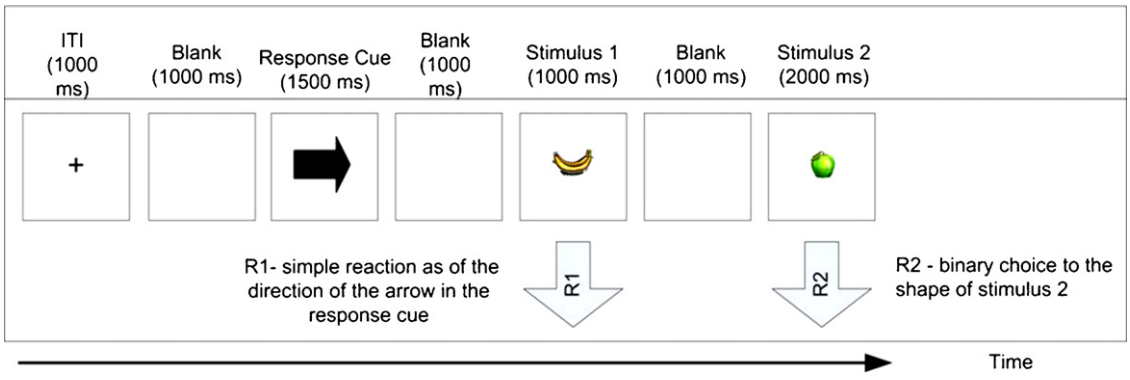

Fig. 1. Sequence of events in the event file task. A visual response cue signaled a left or right response (R1) that was to be delayed until presentation of the first stimulus S1 (S1 was used as a detection signal for R1). The second stimulus S2 appeared 1000 ms after S1. S2 signaled R2, a speeded left or right response according to the shape.

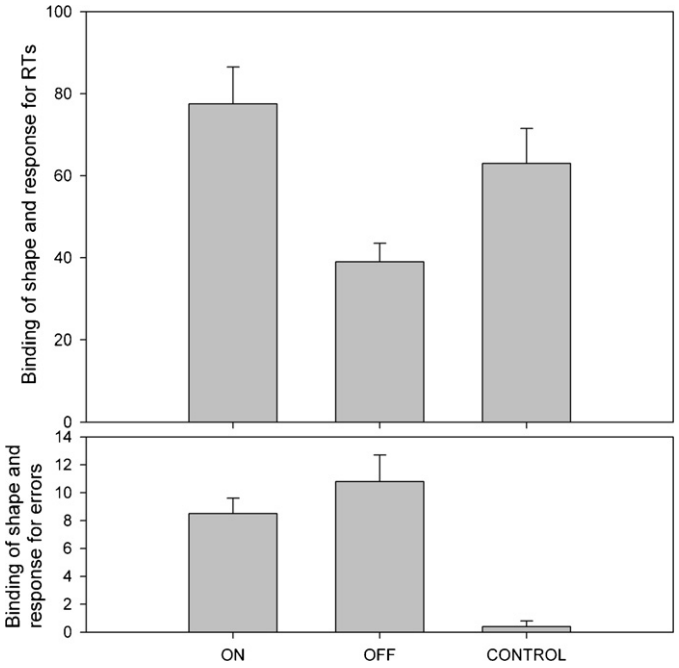

Fig. 2. Effects indicating stimulus–response binding in reaction times and error rates (on R2), for DA medication ON vs. OFF and control group. Vertical capped lines atop bars indicate standard error of the mean.

$F(1,10) = 10.99$, $p < 0.01$, while the 39 ms effect OFF medication fell below the significance criterion, $F(1,10) = 4.44$, $p = 0.06$, see Table 1 and Fig. 2. No further significant interactions were found involving medication, in both RTs and error rates.

4.2. Control group

We obtained significant two-way interactions between shape and response, $F(1,13) = 20.57$, $p < .001$, and between color and response, $F(1,13) = 15.46$, $p < .01$. Repeating or alternating shape or color and the response produced better performance than repeating one but not the other. No further significant interactions were found, in both RTs and error rates.

4.3. OFF vs. control

As expected from the hypothesized ameliorative effects of the dorsal striatum as a result of dopamine replacement therapy, the shape and response interaction was modulated by group, $F(1,23) = 6.75$, $p < 0.05$. Fig. 2 suggests that the shape-by-response interaction was strongly reliable for the control group, $F(1,13) = 18.60$, $p < 0.001$, indicating that patients OFF DA medication showed a decrement in the impact of the task-relevant visuomotor binding on behavior. Further, Parkinson patients OFF medication performed more errors than the control group, $F(1,13) = 19.40$, $p < 0.001$.

4.4. ON vs. control

No significant interactions were found involving group in RTs. Specifically, the RT binding-type interaction between shape and response repetition was not involved in a three-way interaction involving group, $F < 1$, suggesting that after-effects of shape-response did not differ between control participants and Parkinson patients ON medication. Moreover, Parkinson patients ON medication performed more errors than the control group, $F(1,13) = 14.78$, $p < 0.001$.

5. Conclusions

Our findings show that the after-effects of stimulus–response feature integration are modulated by dopaminergic medication in PD patients. This fits with previous suggestions that the control of retrieval of stimulus–response episodes is predicted by genetic predispositions related to striatal dopamine [13]. More specifically, the pattern of our findings are more consistent with predictions based on the hypothesized ameliorative effects of the dorsal striatum as a result of dopamine replacement therapy as opposed to predictions based on the hypothesized overdosing of the ventral striatum.

We observed that partial mismatches between present and previous stimulus–response relations are, compared to control participants, abnormally low OFF DA medication and normalized ON DA medication[1].

Along the lines of the hypothesized ameliorative effects of the dorsal striatum, we take our findings to suggest that DA in the dorsal striatum, but not (or not so much) in the ventral striatum, is driving the flexible control of the retrieval of stimulus–response episodes. These results are consistent with functions ascribed to the dorsal striatum as responsible for the control of habitual actions [29] and in representing action-outcome contingencies, which subserve adaptable goal-directed behavior across learning and memory [44].

Moreover, consistent with the idea that stimulus–response updating is mediated by the dorsal striatum is also the fact that partial-repetition costs observed OFF medication fell below the significance criterion albeit this effect is consistently observed in healthy older adults [43]. Converging evidence comes from a functional MRI study by Ref. [36]. PD patients, relative to healthy controls, showed reduced interference OFF medication and enhanced, but normalized, interference ON medication. This finding is in line with the notion that the dorsal striatum mediates interference related to assimilating new stimulus response' associations on selection across trials while the ventral striatum moderates learning stimulus–outcome associations.

Our results are also consistent with a previous study addressing negative priming in PD patients ON medication [30]. PD patients and controls responded to the location of shape stimuli, but color was included as an irrelevant feature. PD patients experienced larger negative priming costs when responding to either the location or the shape, but not to the color, that was associated with a distractor from the previous trial. This outcome fits well with the notion that the effects are directed toward the processing of task relevant features.

Furthermore, it is reasonable to assume that L-DOPA administration to PD patients not only "overdoses" the ventral striatum but also other non-depleted areas related to the cortical striatal loop in which the dorsal striatum is embedded, such as the motor cortex. Rascol et al. [37] suggested that L-DOPA may induce increased activation in the cortical motor cortex, a key area involved in the retrieval of stimulus–response episodes. Indeed, Kühn et al. [5] found that repeating a particular stimulus or response feature reactivates the neural representation (in the parahippocampal place area, the fusiform face area and/or motor cortex) of the stimulus or response feature that accompanied the repeated feature in the previous trial.

[1] We hesitate to interpret the fact that the partial-repetition costs did not pass the significance criterion OFF medication. Note that the effect size was still substantial and lays the neighborhood of effect sizes in age-matched healthy participants [43], suggesting that the failure to reach significance merely reflects the small sample size. Accordingly, we consider partial-repetition costs OFF medication significantly smaller than ON medication, but not necessarily zero.

In sum the present findings suggest that the dorsal striatum plays an important role in regulating the degree to which irrelevant information impacts the control of ongoing behavior.

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