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A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism

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ABSTRACT

Parkinson's disease (PD) patients exhibit cognitive deficits, including reinforcement learning, working memory (WM) and set shifting. Computational models of the basal ganglia–frontal system posit similar mechanisms for these deficits in terms of reduced dynamic range of striatal dopamine (DA) signals in both medicated and non-medicated states. Here, we report results from the first study that tests PD patients on and off dopaminergic medications in a modified version of the AX continuous performance (AX-CPT) working memory task, consisting of three performance phases and one phase requiring WM associations to be learned via reinforcement feedback. Patients generally showed impairments relative to controls. Medicated patients showed deficits specifically when having to ignore distracting stimuli during the delay. Our models suggest that this impairment is due to medication causing excessive WM updating by enhancing striatal "Go" signals that facilitate such updating, while concurrently suppressing "NoGo" signals. In contrast, patients off medication showed deficits consistent with an overall reduction in striatal DA and associated Go updating signals. Supporting this dichotomy, patients on and off medication both showed attentional shifting deficits, but for different reasons. Deficits in non-medicated patients were consistent with an inability to update the new attentional set, whereas those in medicated patients were evident when having to ignore distractors that had previously been task relevant. Finally, in the feedback-based WM phase, medicated patients were better than unmedicated patients, suggesting a key role of striatal DA in using feedback to update information into WM. These results lend further insight into the role of basal ganglia dopamine in WM and broadly support predictions from neurocomputational models.
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1. Introduction

Parkinson's disease (PD) is associated with marked depletion of dopamine (DA) in the basal ganglia (BG) (Kish, Shannak, & Hornykiewicz, 1988). In addition to their well known motor symptoms, PD patients show reliable cognitive impairment as assessed by multiple measures, including reinforcement learning, planning, set shifting, and working memory (WM) (Amos, 2000; Charbonneau, Riopelle, & Beninger, 1996; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Gabrieli, Singh, Stebbins, & Goetz, 1996; Hodgson, Dittrich, Henderson, & Kennard, 1999; Lees & Smith, 1983; Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, 2004; Owen, Doyon, Dagher, Sadikot, & Evans, 1998; Partiot et al., 1996; Taylor, Saint-Cyr, & Lang, 1986). For example, Gabrieli et al. (1996) found that PD patients had a significantly lower WM span than that of healthy subjects. Neuroimaging studies reveal that, across a range of tasks, WM impairment in PD patients is associated with decreased activity of the BG (Lewis, Dove et al., 2003; Owen et al., 1998; Postle, Jonides, Smith, Corkin, & Growdon, 1997). Furthermore, BG activity is often reported during WM tasks in healthy subjects (Chang, Crottaz-Herbette, & Menon, 2007; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Along the same vein, lesion (Battig, Rosvold, & Mishkin, 1960; Divac, Rosvold, & Szwarcbart, 1967) and neurophysiological (Hikosaka, Sakamoto, & Usui, 1989; Kawagoe, Takikawa, & Hikosaka, 1998; Ljungberg, Apicella, & Schultz, 1992) studies with nonhuman primates also support a role for the BG in WM. Collins, Wilkinson, Everitt, Robbins, and Roberts (2000) found that Parkinsonian monkeys with depleted striatal DA were significantly impaired in comparison to controls in performing a spatial delayed-response (WM) task. Cognitive deficits in Parkinson's patients have been linked with depleted striatal DA levels, with intact frontal DA levels in early stages of the disease (Sawamoto et al., 2008). In this paper we provide preliminary evidence for a mechanistic explanation

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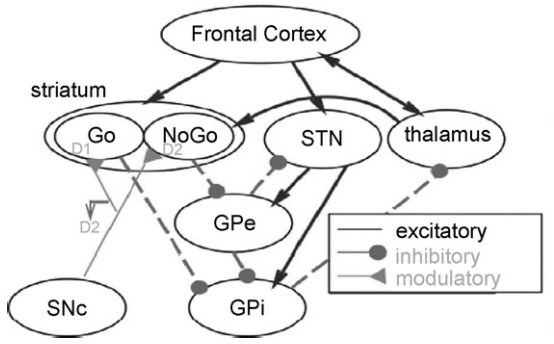

Fig. 1. A BG/DA-PFC model of WM performance, showing the direct ("Go") and indirect ("NoGo") pathways of the basal ganglia. The Go cells disinhibit the thalamus via the internal segment of globus pallidus (GPi), thereby facilitating the execution of an action represented in cortex. Actions range from selecting motor programs in premotor frontal regions, to updating WM representations in prefrontal regions. The NoGo cells have an opposing effect by increasing inhibition of the thalamus, suppressing actions from getting executed (or information from being updated). Dopamine from the substantia nigra pars compacta (SNc) projects to the dorsal striatum, causing excitation of Go cells via D1 receptors and inhibition of NoGo via D2 receptors. GPe = external segment of globus pallidus; STN = subthalamic nucleus.

for these effects, one that invokes a similar mechanism leading to dysfunction in both executive function/WM and those supporting more implicit reinforcement learning processes, as formalized in computational models of the basal ganglia–frontal cortical system (Moustafa & Maida, 2007; O'Reilly & Frank, 2006).

Systems level computational models tie together different experimental data in an attempt to provide an account for how different brain areas/neurotransmitters interact in behavioral performance, and provide a plausible mechanistic explanation for cognitive deficits in PD. In short, systems level models attempt to bridge the gap between brain and behavior (Kandel & Squire, 2000). Our modeling framework provides an account for how the BG, thalamus, and frontal cortex, along with DA and other neurotransmitters, interact in WM (Fig. 1). According to the models, the BG modulate both motor and cognitive actions, which are encoded in the motor and prefrontal cortices (Frank, Loughry, & O'Reilly, 2001; Houk, 2005; Houk et al., 2007; Moustafa & Maida, 2007; O'Reilly & Frank, 2006). In the motor domain, the models assume that BG output to the premotor cortex is responsible for action selection (Berns & Sejnowski, 1995; Djurfeldt, Ekeberg, & Graybiel, 2001; Grafton, 2004; Gurney, Prescott, & Redgrave, 2001; Khamassi et al., 2004; Suri, Bargas, & Arbib, 2001). Similarly, in the cognitive domain, the BG serve as a gate to modulate when and when not to update information into prefrontal cortex (Frank et al., 2001; Middleton & Strick, 2000; Middleton & Strick, 2002; O'Reilly & Frank, 2006), to be maintained in an active state, forming the basis of WM (Goldman-Rakic, 1995). In relation to this theory, Siessmeier et al. (2006) found that administering DA agents to healthy subjects led to a correlation between DA uptake in the striatum and DLPFC BOLD activity, possibly suggesting that the BG might drive activity in the PFC. Moreover, a recent neuroimaging study showed that the degree of BG activity was predictive of whether or not irrelevant information was unnecessarily stored in WM, and was predictive of WM capacity (McNab & Klingberg, 2008), directly supporting the idea that the BG provide a gate on WM updating.

Moreover, the role of DA is functionally similar across multiple BG subregions, and is therefore thought to play a similar role in modulating distinct behaviors that depend on BG circuits, including motor function, reward-based learning and performance, and higher level cognitive function (Fig. 1) (Delgado, 2007; Delgado, Miller, Inati, & Phelps, 2005; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Doya, 2000; Schultz, Dayan, & Montague, 1997; Shohamy et al., 2004; Suri & Schultz, 1998).

In particular, the models simulate the functions of "Go" and "NoGo" pathways in the BG in modulating the selection of an action in cortex. The Go cells in the BG direct pathway disinhibit the thalamus via the internal segment of globus pallidus (GPi), thereby facilitating the execution of motor cortical actions, or the updating of information into the prefrontal WM system. Conversely, the NoGo cells have an opposing effect by increasing inhibition of the thalamus, suppressing actions from getting executed, or preventing information from being updated into WM. An increase in striatal DA leads to an enhancement in the signal-to-noise ratio of Go activity via D1 receptors, while inhibiting NoGo activity via D2 receptors (Gerfen, 2000; Hernandez-Lopez et al., 2000). Thus, increase in DA levels (above tonic level firing) leads to an increase in Go firing and decrease in NoGo firing, while decrease in DA levels signals in DA firing (below tonic levels) have the opposite effect. Similarly in the cognitive domain, Go and NoGo signals can facilitate and suppress the updating of information into prefrontal WM representations (O'Reilly & Frank, 2006).

Also, our models simulate how changes in phasic DA levels in the striatum modify synaptic plasticity in the corticostriatal pathway (Reynolds, Hyland, & Wickens, 2001; Wickens, Begg, & Arbuthnott, 1996). The change in activation state as a result of this DA modulation can then drive learning appropriately, driving Go and NoGo learning to facilitate adaptive behaviors and suppress maladaptive ones (Frank, 2005). Thus even in non-reinforcement learning tasks, as participants update task-relevant information into WM which helps them perform well in the task, phasic DA signals drive Go learning to be more likely to update the same information in the future, and NoGo learning to be more likely to ignore the same task-irrelevant information (O'Reilly & Frank, 2006). Preliminary evidence for these effects being relevant for WM comes from empirical studies in ADHD patients (Frank, Santamaria, O'Reilly, & Willcutt, 2007) and in normal healthy subjects taking dopamine agents (Frank & O'Reilly, 2006) who also performed the AX-CPT described below. In short, our modeling framework suggests that the PFC is key for active maintenance of information in WM, whereas the BG is key for modulating when and when not to update information into WM, a function that becomes further ingrained across time.

Although DA medications ameliorate motor function, they can either enhance or impair cognitive function in both human PD patients and Parkinsonian animals (Cools, Altamirano, & D'Esposito, 2006; Cools, Barker, Sahakian, & Robbins, 2001a; Frank, Seeberger, & O'Reilly, 2004; Gotham, Brown, & Marsden, 1988; Lewis, Cools, et al., 2003; Swainson et al., 2000). For WM tasks in particular, DA medications might either enhance (Cooper et al., 1992; Costa et al., 2003; Lange et al., 1992; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Marini, Ramat, Ginestroni, & Paganini, 2003; Owen, Sahakian, Semple, Polkey, & Robbins, 1995) or impair (Poewe, Berger, Benke, & Schelosky, 1991) performance in PD patients. Our models suggest that DA medications, by increasing both tonic and phasic DA levels, enhance BG Go signals while impairing NoGo signals (Frank, 2005). In the attentional shifting domain, this implies that enhanced updating of a stimulus due to extensive training and/or an increase in striatal DA levels makes it difficult to subsequently ignore this information (prevent it from being updated) when shifting occurs. Thus, due to increased striatal tonic and phasic DA, medications can lead to enhancement or impairment depending on the task, whereas DA reduction in non-medicated PD leads to impaired Go performance and intact NoGo performance (Frank, 2005; see also Cools, 2006). Evidence for this dissociation comes from studies showing that patients on medication showed relatively better Go than NoGo probabilistic reinforcement learn-

Table 1
Demographic subject characteristics

Group	*n*	*n* Filt	Sex ratio (m:f)	Age	Years education	NAART (#correct)	YR DX	HY
Senior	14	14	10:4	65 (1.99)	15.56 (0.78)	39 (3.33)	N/A	N/A
PD	19	17	11:6	68.35 (1.42)	18.15 (0.87)*	44.52 (1.93)	6.88 (1.0)	2.41 (0.51)

Data represent mean (standard error). (*) Significantly different from healthy control subjects at the 0.05 level. We filtered out data for two patients who could not perform better than chance (50%) on the easiest AX and BY pairs in the simple WM phase; these patients likely did not understand overall task instructions and the remainder of their results are therefore uninterpretable. Similarly, when distractors were introduced in later phases, the same criterion was used to filter out two patients who may have become confused by the presence of distractors. NAART = North American Adult Reading Test; m = male; f = female; HY = Hohn and Yahr; YR DX = number of years with PD. NAART score is number of items correct rather than the conversion to IQ (which is only very approximate, and is a linear function of raw score); *n* filt is the final sample size and is used in data presented in Section 2.2.

ing, whereas non-medicated patients showed the opposite pattern (Frank et al., 2004). Similarly, in adult ADHD participants, stimulant medications increase Go learning but not NoGo learning, and this difference correlated with medication-improvements in working memory tasks in the face of distraction (Frank, Santamaria, et al., 2007). However, this framework has not yet been directly applied to empirically study higher level cognitive deficits in PD.

1.1. Goal of the study

We tested PD patients off and on their DA medications in several variants of the AX-CPT. The different variants, as described below, enable us to test specific predictions regarding when DA medications should enhance, and when they should impair, working memory function in PD. In brief, the central predictions of our framework described above are that (i) working memory demands require not only maintenance of information across a delay, but also knowing when and when not to update information into WM (Braver & Cohen, 2000; Frank et al., 2001; Moustafa & Maida, 2007; O'Reilly & Frank, 2006); (ii) "Go" signals in the basal ganglia, enhanced by DA medications, support updating of prefrontal WM; (iii) "NoGo" signals in the basal ganglia, abolished by DA medications, prevent updating of distracting information (Frank, 2005); and (iv) phasic changes in DA during task performance lead to Go and NoGo learning to enhance likelihood of updating task-relevant information across trials, while suppressing the likelihood of updating irrelevant information (O'Reilly & Frank, 2006). We therefore include different variants of the AX-CPT to test these distinct aspects of working memory in PD.

Importantly, the different variants also allow us to compare performance across disease and medication states in conditions that differ only by the critical aspect of interest, thereby minimizing any potential confounds that might arise with using altogether different tasks.

This approach enables us to make more specific predictions for when performance should be enhanced or impaired by DA medications. For example, the generally accepted wisdom is that medications enhance WM function because they elevate dorsal striatal DA levels, which are normally depleted in PD, and which interact with dorsolateral prefrontal areas in WM (Cools, 2006; Cools et al., 2001a). However, our framework suggests that even in dorsal striatum, tonic DA stimulation by medications may not always be beneficial for WM. Similarly, several recent studies report that PD patients show deficits in attentional set-shifting regardless of medication status (Lewis et al., 2005; Slabosz et al., 2006). This finding has been interpreted as evidence that attentional shifting deficits in PD are not dopaminergic. In contrast, our framework suggests that PD patients both on and off medication may have shifting deficits, but for different reasons, as described below.

2. Methods

2.1. Subjects

We tested 14 healthy controls and 19 Parkinson's patients both off and on medications (see Table 1). Parkinson's patients were recruited from the University of Arizona Movement Disorders Center. The majority of patients were taking a cocktail of dopaminergic precursors (levodopa-containing medications) and agonists: Six patients were on DA agonists only and two patients on DA precursors only. Control subjects were either spouses of patients, who tend to be fairly well matched demographically, or recruited from local Tucson senior centers. Subjects performed the task twice, once at a session, with at least one week in between the sessions. Some subjects could not return for a second session, and that surmounted to 2 patients that did not perform the task off medication, 3 patients that did not perform the task on medication, and 5 controls who did not return for a second (non-medicated) session. The order of on or off medication testing was randomized: 14 patients did the off medication session first and 14 patients did the on medications first. Patients in the off medication condition withheld taking their regular dose of all DA-related medications for a mean of 18 h prior to the experiment.

2.2. Task

The AX-CPT is a WM task in which subjects are presented with sequential letter stimuli (A, B, X, Y; printed in red), and are instructed to press one of two keys to each letter presentation (Fig. 2a) (Barch et al., 1997, 2001; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Servan-Schreiber, Cohen, & Steingard, 1996). In the simple WM phase, subjects were to press a key on the right side of the keyboard ("m") when A is followed by X (AX "target" trials) and to press a left key ("z") otherwise (AY, BX, and BY trials).

Subjects were given the following instructions: "In this task you will see the letters A, X, B, Y appear on the screen one at a time. Try to keep track of the letters.

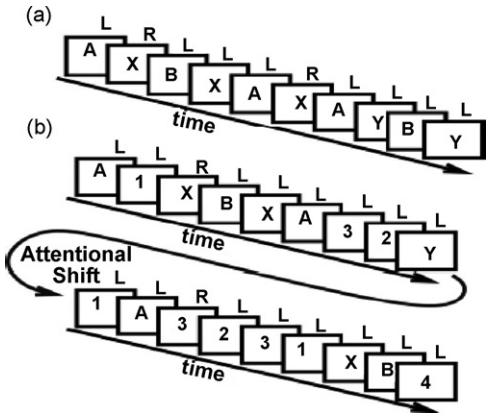

Fig. 2. The AX continuous performance task (AX-CPT). (a) Simple WM phase (standard version). Stimuli are presented one at a time in a sequence. The participant responds by pressing the right key (R) to the target sequence; otherwise, a left key (L) is pressed. Delay between each stimulus is 1 s. The AX target sequence occurs on 70% of trials, building up a prepotent expectation for target responses. (b) Distractor phase. The task is the same as in the standard version, but anywhere from zero to two distractors are presented sequentially during a 3-s delay period. Participants are instructed to respond to distractors with a left button push but are told to ignore these for the purpose of target detection. In the subsequent attentional shift phase, the target sequence consists of previously distracting number stimuli (1, 3), and the letter stimuli are now distractors.

You are looking for the sequence of an "A" followed by an "X". Every time you see a letter, press the "z" button, EXCEPT when you see an "A" and then an "X", press the "m" button! Press "ENTER" to see some examples".

Subjects then saw some examples correct and incorrect responses in different trial types. The task requires the subjects to remember which cue (A or B) was presented before which probe (X or Y) so they can respond correctly—hence it is a WM task. In the "expectancy" version employed here, AX target trials occur in 70% of the trials (Cohen et al., 1999). This procedure builds up a prepotent expectation for target sequences, and allows one to test different predictions regarding false positives to AY and BX trials (Braver & Cohen, 2000; Frank & O'Reilly, 2006; Servan-Schreiber et al., 1996). If participants successfully maintain contextual information (e.g., A) in working memory, then they should perform well at detecting the AX target sequence but will likely make more false positive errors on the AY sequence (due to prepotent anticipation of an X). Context maintenance should improve performance on the BX case, because one can use the B to know not to respond to the X as a target. The BY sequence serves as a control condition, and an index for generalized (non-WM) deficits, because neither the B nor the Y are associated with the target.

We also modified the standard task to include distractors, an attentional shifting phase, and finally, a feedback-based version of the task (Frank & O'Reilly, 2006). In the Distractor phase, 0, 1 or 2 distractors (white numbers) were presented sequentially during the delay interval (3000 ms). The instructions here were as in the previous phase but in addition subjects were told "OK, now it gets a little harder. The trick is that you will also see some white numbers in between the red letters". In the attentional shifting phase, previously distracting stimuli became task relevant (the target sequence was 1–3, and non-targets were 1–4, 2–3, 2–4), whereas previously task-relevant letters A, X, B, Y became distractors (see Fig. 2). The instructions here were as follows "Next, you have to pay attention and respond to the white numbers (1, 2, 3, 4) but IGNORE the red letters (A, X, B, Y). Instead of A–X, the "target" is now the sequence 1–3. Press "m" for the 1–3 sequence, and "z" for all other numbers".

Finally, subjects were tested on a feedback-based version similar to the original task (simple WM phase) except that (i) different letter stimuli (H, K, Z, P) were used; and (ii) subjects had to discover the target sequence by trial and error (i.e., correct or incorrect feedback). No distractors were present and the proportion of AX to AY, BX and BY trials was equal (25% each; using 70% targets would make it too easy to determine the target sequence). Participants were instructed to press the left button for each cue and the right button when they think they have seen the target sequence (initially by guessing). After each probe stimulus, feedback informed the participant whether they were correct or incorrect. The instructions here were "OK, in this last session you will have to figure out the target sequence by trial and error! At the end of each trial, you will get feedback to see if you were Correct or Incorrect – You will use this feedback to figure out the right sequence. You will see the letters P, Z, K, H. Press "z" for every letter, except when you think you've seen the target sequence, press "m". At first you will have to guess. You will figure out what the target sequence is as you get Correct/Incorrect feedback to your button presses".

Given the well studied role of striatal DA in reinforcement learning, this phase allows us to explicitly test whether striatal DA signals can be used to reinforce updating of WM representations in the context of a WM task, as suggested by our models (Moustafa & Maida, 2007; O'Reilly & Frank, 2006). Further, this version may correspond better to working memory tasks used in nonhuman primate experiments (e.g., delayed-response tasks (Diekamp, Kalt, & Gunturkun, 2002; Goldman-Rakic, 1995; Schultz, Apicella, & Ljungberg, 1993), in which animals must learn which working memory representations to reinforce via reward or lack thereof).

2.3. Data analysis

Two primary statistics have been used to assess WM function in this task.

2.3.1. WM context index

Because the AX sequence occurs with high (70%) probability, subjects can simply learn a prepotent response to stimulus X, so does not necessarily provide an index of WM performance *per se*. One solution to this problem is to focus instead on the BX (where increased WM facilitates performance) and AY cases (where increased maintenance can actually worsen performance, as described above). Specifically, we compute a working memory context index by subtracting AY percent accuracy from that of BX (Frank & O'Reilly, 2006; Frank, Santamaria, et al., 2007). A positive working memory context index indicates greater influence of working memory on choice behavior, whereas a negative context index indicates that choices are being dictated by incoming stimuli and are not influenced by working memory.

Note, however, that this logic assumes that participants "proactively" update information into prefrontal WM representations and maintain it throughout the delay period in anticipation of the probe. However, recent theoretical and empirical evidence suggests that in many cases, WM tasks involve encoding of the cue information, but not in a proactive manner. Instead, upon presentation of the probe, participants can "reactively" retrieve cue information from episodic memory (Braver, Gray, & Burgess, 2007). Moreover, Paxton, Barch, Racine, and Braver (2007) showed that older adults' performance and brain activity in AX-CPT is more consistent with this reactive WM strategy, as opposed to younger adults who use a proactive WM strategy. Critically, a reactive WM strategy would not be expected to produce AY false positives: if participants do not proactively maintain the A, they do not expect an X and can easily reject the Y as a non-target. Accordingly, the WM context index may not be appropriate for older adults, particularly for longer delays in which reactive strategies are more likely.

2.3.2. d′-Context

To address this complication, we also compute the more traditional d′ signal detection measure for assessing WM performance in this task, developed by Servan-Schreiber et al. (1996) and since employed in many studies to study WM in schizophrenia (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Cohen et al., 1999), and also employed by Braver et al. (2001) in older adults. The specific d′ measure computed compares AX hits to BX false alarms which is: $z(\text{AX}) - z(\text{1-BX})$, where z is the z-score. A small correction factor was applied in cases of a perfect hit rate (1.0) or false-alarm rate (0.0), to allow an unbiased estimation of d′ (Nuechterlein, 1991). This "d′-context" measure provides a more specific index of sensitivity to WM contextual information than standard d′ measures, as it directly assesses participants' discriminability between A or B context when they are presented with the same X probe (Braver et al., 2001; Cohen et al., 1999; Servan-Schreiber et al., 1996). Note also that d′-context does not include AY and so does not suffer from the complication of reactive vs. proactive strategies as does the WM context index. Finally, because it is a signal detection measure, d′-context controls for overall response biases, such as making more right than left responses.

2.3.3. Statistical analysis

For all analyses we used SAS v8.0 PROC MIXED to examine both between and within subject differences, using unstructured covariance matrices (which do not make any strong assumptions about the variance and correlation of the data, as do structured covariances). In all analyses, we controlled for session order and NAART by including them as covariates in all statistics done here to exclude any potential effects of IQ or practice effects across sessions (Frank & O'Reilly, 2006; Frank, Santamaria, et al., 2007). Where indicated, we tested for specific planned contrasts. In these contrasts, the number of degrees of freedom reflects the entire sample, and not just the participants involved in the particular contrast, because the mixed procedure analyzes both between and within effects, and controls for other variables of interest (e.g., session order) that apply across all participants. This procedure uses all of the data to provide a more stable estimate of the error term.

2.4. Predictions

Based on our models of BG/DA function in WM, we made the following hypotheses:

(1) *PD patients off medication* should have reduced BG/DA and therefore impaired Go signals to update WM, leading to deficits in AX-CPT. However, intact NoGo signals across trials should lead to a learned effect to ignore distractors. For example, Crofts et al. (2001) found that BG/DA depletion in monkeys led to *less* distractibility. The enhanced NoGo learning across trials should however make it particularly difficult to subsequently update these distractors into WM when they become relevant in the attentional shift. Furthermore, reduced phasic DA signals should be associated with particularly impaired ability to learn to reinforce WM representations in the feedback-based phase.
(2) *PD patients on medication* should have relatively elevated BG/DA and enhanced Go signals to update WM, leading to spared performance in the simple WM phase. However, because DA medications tonically elevate BG/DA, these can abolish BG NoGo signals, causing impaired ability to ignore distractors (Frank & O'Reilly, 2006). This deficit should be particularly evident when having to ignore distractors that were previously ingrained to be task relevant (due to prior Go learning), such as ignoring A, X, B, Y when they become distracting in the attentional shift phase. Finally, relative to non-medicated patients, normalized phasic DA signals should lead to enhanced ability to discover AX target sequences in the feedback-based phase.

3. Results and discussion

3.1. Simple WM phase

Because the simple WM phase involves just a short (1 s) delay between cue and probe, it is more likely to be associated with proactive WM (see Section 2.3.1), as measured by the WM context index (BX-AY). Critically, there was a significant effect of medication on this index across blocks, as the AX sequence becomes more prepotent ($F(1,30) = 13.4$, $p = 0.001$; Fig. 3b). Medication effects on the WM index were also significant in the second block by itself ($F(1,30) = 6.44$, $p = 0.01$). The d′-context also increased across blocks in medicated patients ($F(1,30) = 3.96$, $p = 0.045$), but not in non-medicated patients ($F(1,30) = 1.67$, $p = 0.21$). Further, in the second

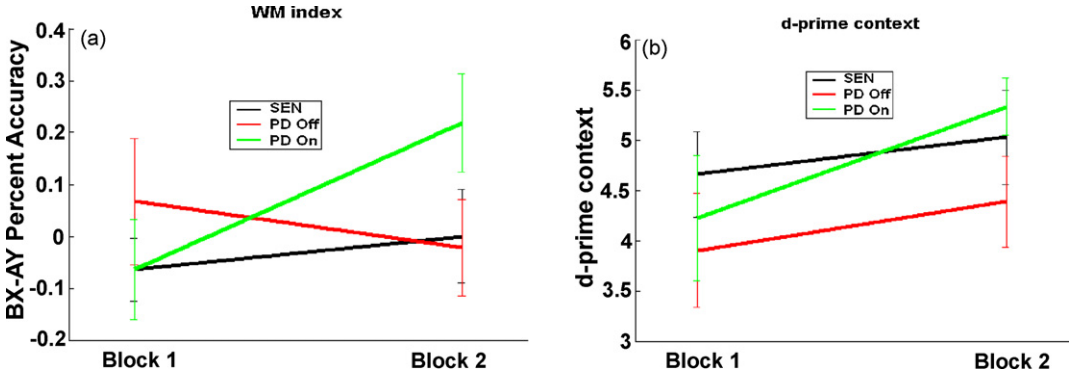

Fig. 3. Performance in the simple WM phase. (a) WM index measure. (b) d′-Context measure.

block, there was a trend for d′-context to be larger in medicated than in non-medicated patients ($F(1,30) = 2.98$, $p = 0.09$). There was no practice effect of learning across sessions on d′-context ($F(1,30) = 2.19$, $p = 0.18$) or WM index ($F(1,30) = 0.22$, $p = 0.65$).

These results were supported by analysis of individual trial types. For AY, performance increased across blocks in patients off medication, but decreased in patients on medication (interaction between medication status and block ($F(1,30) = 4.7$, $p = 0.032$) (see Table 2). The opposite numerical (but non-significant) trend was observed for BX trials, with patients on medication improving across blocks (medication × block interaction ($F(1,30) = 1.67$, $p = 0.18$). As predicted, medication and block interactions were not found with AX and BY trial types (all p's > 0.27). There was also no effect on practice effects across session on trial type (all p's > 0.2). Taken together, these data indicate that DA medications enhance WM updating, which is indexed by relatively better BX and worse AY performance.

3.2. Distractor phase

This phase is more demanding than the previous one since it includes the presentation of distractors and has a longer delay interval. Whereas DA medications enhanced WM in the simple phase (such that medicated patients showed higher WM index and d′-context than non-medicated patients and were unimpaired compared to controls), we hypothesized that these medications could cause inadvertent updating of distractors in this phase (Frank & O'Reilly, 2006).

Overall, patients' performance in this phase was impaired compared to control subjects. Unlike the previous phase, controls' d′-context was greater than that of both medicated ($F(1,28) = 9.96$, $p = 0.003$) and unmedicated ($F(1,28) = 6.13$, $p = 0.01$) patients (Fig. 4b). There was no medication effect in this phase ($F(1,28) = 0.73$, ns). In addition, there was no practice effect across sessions on d′-context ($F(1,28) = 0.8.$, $p = 0.19$). There were no medication effects or medication/block interactions with any trial type or with the WM index (all p's > 0.23). There were nonsignificant trends for controls to perform slightly better than off medication patients in AX trials ($F(1,28) = 2.54$, $p = 0.13$) and than on medication patients in AY trials ($F(1,28) = 2.91$, $p = 0.09$) (Table 3).

Table 2
Performance (accuracy rate) for each trial type in the simple WM phase, with standard error in parentheses

	SEN	PD off	PD on
AX			
B1	0.96 (0.01)	0.91 (0.03)	0.94 (0.01)
B2	0.97 (0.01)	0.97 (0.01)	0.97 (0.01)
AY			
B1	0.94 (0.03)	0.69 (0.1)	0.88 (0.06)
B2	0.88 (0.06)	0.84 (0.07)	0.74 (0.07)
BX			
B1	0.87 (0.04)	0.82 (0.08)	0.82 (0.08)
B2	0.88 (0.06)	0.78 (0.06)	0.96 (0.03)
BY			
B1	1.0	0.92 (0.01)	1.0
B2	0.98 (0.01)	0.95 (0.03)	0.98 (0.01)

B stands for block.

3.3. Attentional shifting phase

In this shifting phase, based on prior theoretical and empirical data (Frank & O'Reilly, 2006) we hypothesized that non-medicated patients would have difficulty updating previously irrelevant information. In contrast, shifting deficits in medicated patients should be seen when having to ignore previously relevant stimuli (see predictions above).

First, patients were overall impaired; d′-context was greater in controls than non-medicated patients ($F(1,28) = 3.97$, $p = 0.04$) and numerically but non-significantly better than medicated patients ($F(1,28) = 2.03$, $p = 0.17$) patients. See Table 4 for performance in all trial types. Consistent with existing literature (Lewis et al., 2005; Slabosz et al., 2006), we found that dopamine medications did not

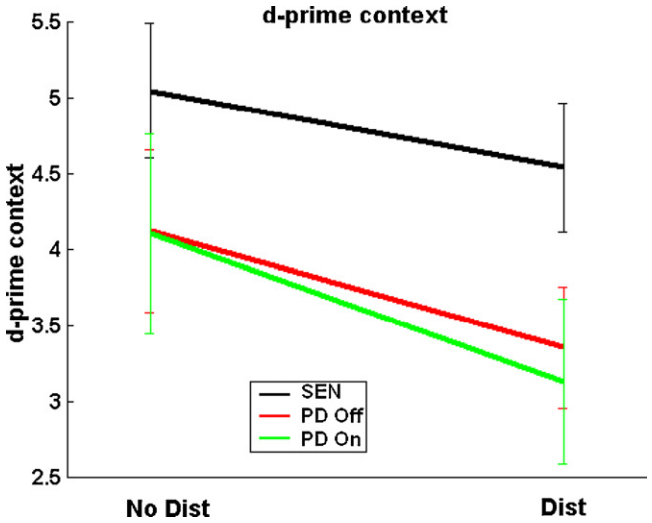

Fig. 4. Performance in the Distractor phase as measured by the d′-context measure. Dist/No Dist indicates trials that did/did not include the presentation of distractors during the delay.

Table 3
Performance (accuracy rate) for each trial type in the Distractor phase, with standard error in parentheses

	SEN	PD off	PD on
AX			
B1	0.96 (0.01)	0.87 (0.04)	0.89 (0.05)
B2	0.97 (0.01)	0.92 (0.03)	0.93 (0.01)
AY			
B1	0.93 (0.02)	0.90 (0.04)	0.90 (0.03)
B2	0.93 (0.02)	0.84 (0.04)	0.86 (0.04)
BX			
B1	0.82 (0.06)	0.83 (0.05)	0.73 (0.08)
B2	0.86 (0.06)	0.80 (0.07)	0.78 (0.08)
BY			
B1	0.98 (0.01)	1.0	0.96 (0.03)
B2	1.0	0.96 (0.02)	0.91 (0.04)

Table 4
Performance (accuracy rate) for each trial type in the attentional shifting phase, with standard errors in parentheses

	SEN	PD off	PD on
AX			
B1	0.95 (0.01)	0.87 (0.06)	0.86 (0.06)
B2	0.97 (0.01)	0.91 (0.03)	0.86 (0.08)
AY			
B1	0.97(0.02)	0.97(0.02)	0.64(0.09)
B2	0.98 (0.01)	0.83 (0.08)	0.80 (0.1)
BX			
B1	0.86 (0.06)	0.75 (0.09)	0.67 (0.1)
B2	0.80 (0.06)	0.79 (0.08)	0.71 (0.1)
BY			
B1	0.98 (0.01)	1.0	0.81 (0.1)
B2	1.0	1.0	0.86 (0.1)

Here for simplicity and consistency, AX refers to 1–3 trial types (AY = 1–4, BX = 2–3, BY = 2–4).

improve shifting performance. Moreover, there was a significant interaction between medication status and distractor presence on d′-context ($F(1,28) = 3.93$, $p = 0.05$), such that medicated patients' impairment was evident in the face of (previously task relevant) distractors, as predicted (see Figs. 5 and 6). In addition, there was no practice across sessions on d′-context ($p > 0.11$).

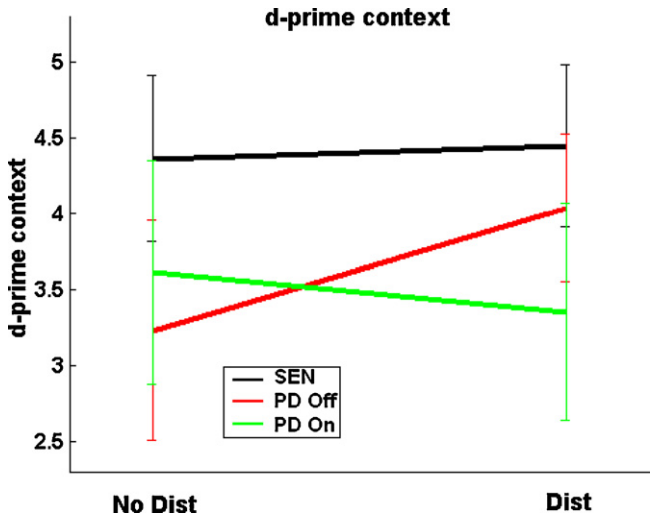

Fig. 5. Performance in the attentional shifting phase as measured by the d′-context. Dist/No Dist indicates trials that did/did not include the presentation of distractors during the delay. Also see Fig. 6b for within-subject medication effects on attentional shifting.

We also examined whether performance in medicated patients decreased across performance phases (simple to Distractor to Attentional-Shift), as the demands for ignoring distracting stimuli became increased. Indeed, the decrease in performance across phases was marginally significant in medicated patients (Fig. 6; $F(2, 30) = 3.1$, $p = 0.06$), but not in other groups (all p's > 0.6). This decreasing performance across phases in medicated PD was significant relative to controls ($F(2, 30) = 3.92$, $p = 0.05$). Finally, Fig. 6b shows the within-subject effect of medication on d′-context, showing that the only condition in which medicated patients showed worse performance was when they had to ignore previously task-relevant information in the shifting phase. These results are consistent with the hypothesis that in medicated patients, (i) larger phasic DA bursts to task-relevant stimuli during the Distractor phase potentiated Go signals to letter stimuli, and (ii) combined with medication-induced reduction of NoGo signals, these factors conspired to make it particularly difficult to ignore stimuli that had been previously reinforced.[1]

3.4. Interim summary

Overall, across all performance phases, the data are consistent with the notion that non-medicated patients show reduced updating (impaired Go, enhanced NoGo), and that medicated patients update excessively (enhanced Go, reduced NoGo). In the Distractor phase these effects cancel out (Fig. 6): medications enhance Go signals for updating for task-relevant information (which would enhance WM) but also suppress NoGo signals, causing inadvertent updating of distractors (which would impair WM). In the attentional shifting phase, the excessive updating is exaggerated in medicated patients since they now have to not only ignore distractors (task-irrelevant stimuli) but specifically those that used to be task relevant, and should therefore have been associated with prior Go learning across trials (and this learning is also expected to be enhanced due to increased phasic DA bursts). Finally, although medicated patients showed decreasing performance across phases as predicted by the specific demands in these successive phases, it is technically possible that these effects are related to decreased vigilance or fatigue across time. However, this possibility is unlikely, because as we describe next, medicated patients actually performed better than non-medicated patients, and equivalent to controls, in the feedback-based version of the task, which was the final phase administered.

3.5. Feedback-based phase

As described in Table 5, this phase is similar to the simple WM phase except that subjects learned to detect the target sequence (AX) as well as non-target sequences (BX, AY, BY) based on trial-and-error feedback. Notably, medicated patients were bet-

[1] One might assume that medication-induced potentiation of Go signals to distractors during the Distractor phase would actually make it *easier* to update these stimuli when they become relevant during the Shift. However, Although there is a *performance* effect during the Distractor phase such that Go processes are overall enhanced (due in part to reduction of NoGo processes), and leading to greater updating of distractors, critically Go signals to distractors are not associated with Go *learning*, which would be required to potentiate the updating of distractors in the subsequent phase. This is because the distractors are not task relevant and should therefore not be associated with phasic DA bursts needed for Go learning. Further, enhanced phasic Go learning signals to task-relevant stimuli in the Distractor phase should *impair* performance in the shifting phase, making it harder to ignore previously relevant stimuli, particularly if NoGo signals are also reduced.

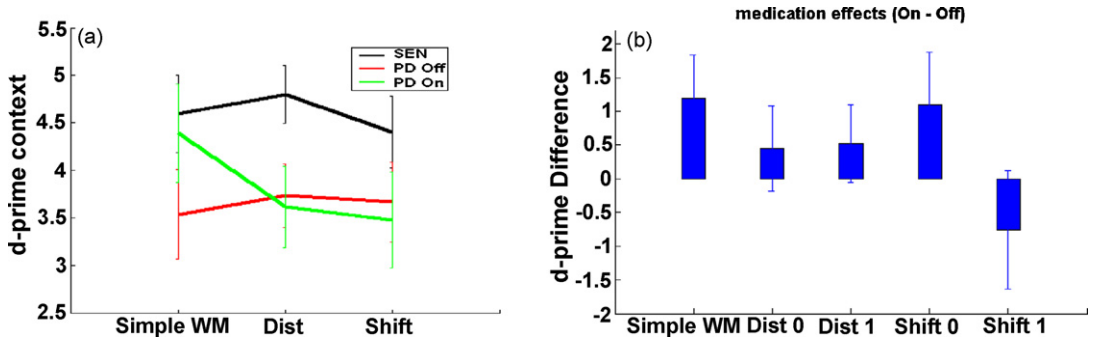

Fig. 6. (a) Performance in all groups across performance phases. (b) Within-subject effect of medication (on–off) showing the effect of distractors in patients' performance. Medicated patients' performance is worse than that of non-medicated patients in the attentional shifting phase only when previously task-relevant distractors are presented. Dist refers to the Distractor phase. Dist 1 (or 0) refers to trials in the Distractor phase that do (or do not) have distractors in the delay interval. Similarly, Shift 1 (or 0) refers to trials in the attentional shifting phase that do (or do not) have distractors in the delay interval.

Table 5
Performance (accuracy rate) for each trial type in the feedback-based phase, with standard error in parentheses

	SEN	PD off	PD on
AX			
B1	0.75 (0.09)	0.5 (0.12)	0.51 (0.12)
B2	0.75 (0.08)	0.38 (0.11)	0.66 (0.11)
AY			
B1	0.75 (0.08)	0.84 (0.09)	0.81 (0.1)
B2	0.81 (0.06)	0.75 (0.08)	0.76 (0.08)
BX			
B1	0.76 (0.08)	0.76 (0.06)	0.75 (0.07)
B2	0.77 (0.08)	0.61 (0.11)	0.70 (0.09)
BY			
B1	0.76 (0.08)	0.70 (0.07)	0.62 (0.13)
B2	0.77 (0.08)	0.68 (0.1)	0.73 (0.08)

Here for simplicity and consistency, AX refers to HK trial types (AY = HZ, BX = PK, BY = PZ).

ter than non-medicated patients at discriminating between target and non-target sequences, as revealed by a significant interaction between block and medication status on d′-context ($F(3, 27) = 3.34$, $p = 0.03$). In addition, non-medicated patients showed a decrement in d′-context across blocks which was significantly different from controls ($F(3,27) = 2.81$, $p = 0.05$), who did not differ from medicated patients ($F(3, 27) = 0.27$, $p = 0.82$) (Fig. 7). In addition, there was no practice effect across sessions on d′-context ($F(1,28) = 1.35$, $p = 0.26$).

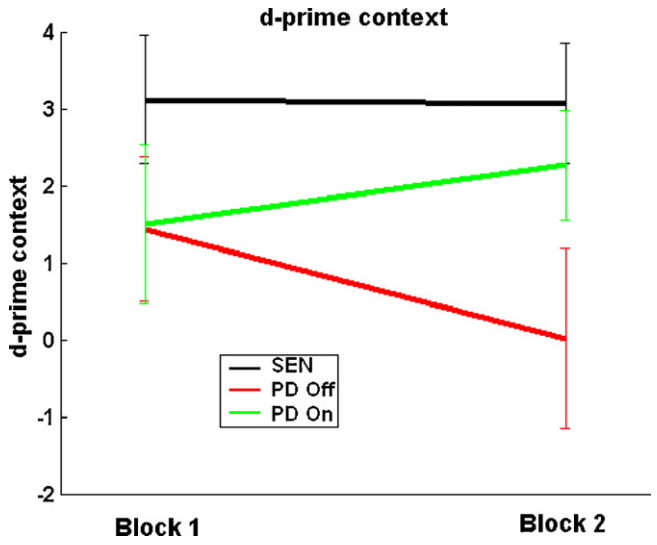

Fig. 7. Performance in the feedback-based phase as measured by d′-context.

Finally, although medicated patients' performance was numerically higher than that of non-medicated patients in all trial-types, a particularly demanding aspect of this phase is being able to use feedback to detect the target AX sequence (since all other non-targets simply require the same motor response to obtain positive feedback, and these occur on 75% of trials). In AX trials, the interaction between block and medication status was significant ($F(3,27) = 2.91$, $p = 0.05$), showing that non-medicated patients were less able to apply reinforcement to working memory representations.

4. General discussion

According to our models, low levels of available DA in PD made patients relatively impaired at Go-dependent WM updating and learning but allowed them to learn to ignore irrelevant information (NoGo learning; Frank, 2005; Frank & O'Reilly, 2006; O'Reilly & Frank, 2006). This was evident by a reduced WM context index and less AY false positives in the simple WM phase, impaired updating of the new task-relevant set in attentional shifting, and impaired performance to discover WM associations via reinforcement feedback. DA medication reversed these biases and enhanced Go performance while concurrently impairing NoGo performance, leading to deficits when distractors were present, particularly in the attentional shifting phase when to-be-ignored distractors were previously task relevant. Further, medicated patients' enhanced performance across blocks in both the simple and feedback-based WM phases is consistent with the notion that medication-induced elevations in striatal DA support both Go updating and reinforcement-based synaptic modification in the corticostriatal pathway.

The overall low performance in medicated patients in the Distractor phase relative to the simple WM phase could be because medications led to updating of distractors during the delay, which could have interfered with stored WM information. Unmedicated patients were impaired in both phases, supporting the notion that reduced DA led to reduced updating of WM regardless of whether distractors were present. This is in agreement with the model's prediction which makes sense of the constellation of results; nevertheless an alternative interpretation could be related to the increase in delay interval across task phases. Future studies will be needed to determine the contribution of delay vs. distractor presence in PD and medication-related deficits.

In the attentional shifting phase, medicated patients performance was actually worse than that of non-medicated patients

when distractors, which were previously task relevant, were presented during the delay. Further, the observation that non-medicated patients performed similar to controls in this case, and not in the previous phase, supports the notion that they had exhibited reduced Go learning to update these previously task-relevant stimuli, together with intact NoGo learning to ignore them during the shift. In contrast, non-medicated patients showed clear deficits relative to controls when there were no distractors, which is typically considered the "easy" condition, and is therefore a counterintuitive result. Nevertheless, this is perhaps expected if patients show overall Go learning deficits to update new stimuli, particularly those that had previously been ignored (intact NoGo learning).

The results from the feedback-based phase suggest that low DA in non-medicated patients prevented them from learning to use feedback signals to drive WM updating, supporting predictions from models of BG and PFC. These findings might provide evidence that DA medications improve WM updating, particularly in a context in which it has to be learned via trial and error, as in rat and monkey experiments.

4.1. Relation to other studies

As mentioned above, the overall idea that the BG modulate the updating of information into WM in consistent with results of a recent imaging study in which increased BG output was associated with enhanced filtering of irrelevant information in WM (McNab & Klingberg, 2008).

Our models suggest that BG and DA play a similar function across different motor and cognitive tasks, such as decision making and working memory (see also Houk, 2005). As suggested by the models, patients' performance and DA medication effects in the simple WM phase were analogous to PD patients' performance in a probabilistic selection task (Frank et al., 2004). In this task, subjects learned to select one of two stimuli, and based on feedback after each selection, subjects learned to either select (Go) a positive stimulus or not to select (NoGo) a negative stimulus. Like WM, this task relies on the integrity of the BG and striatal DA. Frank et al. found unmedicated patients to be better at NoGo learning than medicated patients, whereas DA medications reversed this bias. Furthermore, we recently found that healthy subjects with enhanced D2 genetic function are better NoGo learners than those with less efficient D2 function (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Those results support the notion that NoGo learning is dependent on D2 receptors prevalent in the BG (Brown, Bullock, & Grossberg, 2004; Frank, 2005; Frank et al., 2004; Gerfen, 2000), and which are upregulated and supersensitive in PD. We hypothesize that overall increased NoGo signals in the BG prevented non-medicated patients from updating information into WM, causing deficits across all performance phases.

Along the same lines, Cools et al. (2006) found that medicated, but not unmedicated, PD patients were impaired at probabilistic reversal learning (also see Tomer, Aharon-Peretz, & Tsitrinbaum, 2007 for similar results). According to our models, this is possibly due to impairment in NoGo learning since reversal learning requires suppressing a habitual response as well as selecting another response (Frank, 2005). This prediction was confirmed in a follow-up study in which medicated patients were impaired only at reversing due to unexpected negative, and not positive, feedback (Cools et al., 2006). Similarly, Jentsch, Olausson, De La Garza, and Taylor (2002) found that monkeys who were administered cocaine, a DA stimulant that has been shown to increase striatal DA levels (Inada et al., 1992), were impaired at reversal learning.

Filoteo, Maddox, Ing, and Song (2007) found that medicated PD patients were only impaired when attention and not WM processes are more emphasized, in the context of an explicit category learning task. That emphasizing WM enhances performance is generally consistent with data in the simple WM phase in which medicated PD patients showed enhanced performance. One limitation of this study is that Filoteo et al. did not study medication withdrawal effects on task performance, and so their results can be due to either PD or DA medications.

In a previous psychopharmacological study (Frank & O'Reilly, 2006), we found that healthy subjects, particularly those with low working memory span, who also performed the AX-CPT under cabergoline (D2 agonist) showed an enhanced Go bias to update working memory. In other words, cabergoline enhanced WM indices in the simple WM phase (with no distractors), but led to significant WM impairments in the Distractor phase, in which case updating of distractors can cause interference. It is worth noting that healthy participants' pattern of data under cabergoline was similar to that of medicated patients in the current study (who were also taking D2 agonists for their Parkinsonian symptoms). Accordingly, these results might suggest that negative effects of medication are due to D2 agonists.

In a previous study in which adults with ADHD performed the simple WM and Distractor phases of the AX-CPT, we found that stimulant medications to have differential effects than PD DA medications used here (Frank, Santamaria, et al., 2007). ADHD-related stimulant medications enhanced WM performance in the Distractor phase whereas DA agonists and precursors had no effect in the same phase in PD patients. These differences could be related to effects of these medications on striatal DA function. There is evidence that stimulant medications increase phasic DA (Frank, Santamaria, et al., 2007; Schiffer et al., 2006), and this effect may be relatively stronger than that on tonic DA levels.[2]

Stimulants have also been associated with selective enhancements of activity and plasticity in the "Go" pathway (Yano & Steiner, 2005). Together these effects are posited to enable updating of task-relevant information, without concomitant increases in distractibility. In contrast, as discussed throughout this paper and prior studies, DA agonists used to treat PD are likely to increase both tonic stimulation onto DA receptors as well as phasic release. The tonic stimulation would enhance the gating of stimuli across the board (whether or not they are task relevant). Accordingly, patients on DA agonists may be more likely to update relevant stimuli but may also be more distractible. Consistent with this, medicated PD patients were actually more distractible during the shifting phase, which required ignoring distractors that used to be task relevant (and therefore would have had stronger Go associations and be that much harder to ignore). Finally, another contributing factor could be that subjects with ADHD were required to respond with a button press to distractors, but PD patients were not (unpublished pilot data showed that instructing PD patients to respond to distractors made the task harder to perform).

4.2. Attentional shifting

The overall attentional shifting impairment found in non-medicated PD patients in the present study is in agreement with other studies in the context of more traditional set shifting tasks (Lewis et al., 2005; Monchi et al., 2004; Slabosz et al., 2006). With regard to the role of DA medication in set shifting and PD, mixed

[2] Stimulant medications block the DA transporter (DAT), which is involved in rapid clearance of striatal DA via reuptake during phasic release, when DA is most elevated (Cragg, Hille & Greenfield, 2002). In the tonic state, there are other mechanisms to eliminate DA from the synapse (e.g., COMT enzyme and MAO) even if the DAT is blocked. So DAT blockade by stimulants may allow phasic DA to be restored in ADHD (which is associated with an overabundance of DAT).

results have been reported. For example, Hayes, Davidson, Keele, and Rafal (1998) reported set shifting enhancement in medicated PD patients. However, multiple other studies reported set shifting deficits in both medicated and non-medicated PD patients (Cools, Barker, Sahakian, & Robbins, 2001b; Owen et al., 1993; Ravizza & Ciranni, 2002). Lewis et al. (2005) concluded that set shifting deficits in PD patients are not related to dopaminergic function but to some neurotransmitter, such as acetylcholine, which are found to be affected in PD as well. The reason for these different results could be due to differences in the nature of the tasks used. Specifically, our task involves presentation of a task-relevant stimulus, followed by a delay in which potential distractors are presented, before participants have to respond to a probe. In the attentional shifting phase, the category of task-relevant vs. distracting stimulus is reversed, but the task remains a working memory task. In contrast, other shifting tasks studied in PD and cited above involve presenting a task-relevant stimulus simultaneously with an irrelevant stimulus, such that one must attend to the relevant stimulus while simultaneously ignoring the irrelevant one, and is not subsequently distracted during a delay. As discussed below (see model limitations), these kinds of tasks may be more demanding on the perceptual filtering system, which is quite different than taxing the WM system (Lavie & De Fockert, 2005).

Furthermore, the shifting tasks used by Hayes et al. (1998) required shifting across different trials within one phase. Subjects were presented with a sequence of bi-dimensional stimuli and were cued to press one of two buttons depending on which dimension is relevant. A similar task design was used and also similar results were found in Cools et al. (2001b) study. On the other hand, in the AX-CPT, shifting occurred after an extended block of trials in which participants had to repeatedly pay attention to one dimension (red letters) while ignoring the other dimension (white numbers); this shifting after multiple trails is similar to the tasks used by Owen et al. (1993) (see below for further discussion). The impairment seen in medicated patients in the present study could be due to the fact that shifting in the AX-CPT is more demanding than that used by Hayes et al. (1998); it seems that shifting to attend to stimuli after ignoring them for an entire phase is more difficult than shifting across trials. Based on our models, shifting deficits in medicated patients may be due to an inability to ignore stimuli (i.e., NoGo impairment) after multiple enhanced Go signals to update these same stimuli, as captured by the shifting phase in the AX-CPT. Shohamy et al. (submitted for publication) found that medicated PD patients successfully shifted but in order to do so, they "opted out" of a reversal and shifted attention to new stimuli. Although this task did not include the presentation of distractors, these results support the idea that medications selectively impair NoGo learning to reverse previous associations, so that reversals could be successfully accomplished by focusing on Go learning to completely new stimuli (see section on model limitation for further discussion).

The type of medications (dopamine precursors and/or DA agonists) can also potentially explain the differences in results reported with the role of DA medications in set shifting performance. Medicated PD patients in Lewis et al. (2005) and Slabosz et al. (2006) studies were tested only on L-dopa. However, most PD patients in our study were both on L-dopa and D2 agonists, which could have further increased tonic D2 stimulation more than that of L-dopa alone. As mentioned above, a tonic increase in D2 stimulation should abolish NoGo signals and lower the threshold of WM updating, which in turn could have allowed distractors to be gated into WM.

Over the past years, Owen and colleagues have been studying the factors under which set shifting occur in PD. Set shifting deficits can be due to either perseveration or learned irrelevance, among other factors. Perseveration has to do with the inability to shift away from a previously relevant dimension while learned irrelevance have to do with inability to shift to a previously irrelevant dimension (Owen et al., 1993). Note that learned irrelevance can be understood as an instance of exaggerated NoGo learning, making it harder to attend to previously irrelevant stimuli. Owen et al. found that set shifting deficits in unmedicated PD patients are due to perseveration and learned irrelevance whereas medicated patients' set shifting deficits are due to learned irrelevance. The occurrence of perseverative errors in PD has been assumed to be due to cortical dementia (Amos, 2000), which is in agreement with frontal patients showing preservative errors in Owen et al. (1993) study, although Suri and Schultz {1999} argued that striatal DA levels could be responsible for perseverative errors.

Building on earlier work by Owen et al., Slabosz et al. (2006) studied under which factors learned irrelevance deficits occur in PD patients. They found that both medicated and unmedicated patients were more impaired on shifting from a fully irrelevant dimension than from a partially irrelevant (and reinforced) dimension. Lavie and De Fockert argued that set shifting performance can be controlled by either a perceptual or WM system (see above). The IDS/EDS shifting task used by Owen and colleagues could have possibly taxed the perceptual filtering system which is different from a WM filtering system like in the AX-CPT. To sum up, the series of experiments done by Owen and colleagues studied the different factors under which set shifting deficits occur. We however studied a simpler version of set shifting that occurs within the WM domain. That unmedicated patients in Owen et al. (1993) study were more impaired than medicated patients and that the opposite was the case in our study suggest that PD and DA medications might affect both perceptual and WM filtering mechanisms differently. These effects require further investigation within one group of PD patients under medication manipulation. Note also that Owen et al. (1993) study involved two groups of patients, those that were never-medicated and those that were medicated. Because it was not a within-subject design, it is likely that some medicated patients were more advanced in their disease progression, and may still have reduced striatal DA levels despite being medicated.

4.3. Feedback-based WM

The results of this study show that medicated patients were better than non-medicated patients in the feedback-based phase, including discovering working memory target sequence across trials, whereas non-medicated patients did not. Our interpretation of these effects is that they result from enhanced Go learning across trials to update relevant cues in working memory and to guide future responses. (Note that this same mechanism in part explains the impairment in ignoring previously task-relevant stimuli during the attentional shift).

We are not familiar with any other study that used feedback in the context of a WM task with PD patients. Unlike WM, the role of striatal DA in reinforcing motor actions/plans has received much attention in the literature (Costa, 2007; Frank, 2005; Graybiel, 2005; Reynolds et al., 2001). That prefrontal DA is important for learning to update cues into WM has been well motivated by Braver and Cohen (2000) model. Based on the BG anatomy (Middleton & Strick, 2000, 2002) and our models (Moustafa & Maida, 2007; O'Reilly & Frank, 2006), striatal DA is also important for feedback-based performance of WM tasks. This should not be surprising, for the following reasons. First, nonhuman animals are trained to perform WM tasks based on reinforcement delivery, known to increase striatal DA levels (Roitman, Stuber, Phillips, Wightman, & Carelli, 2004; Schultz et al., 1997; Wise, 2006). The same mechanism is not fully appreciated with humans yet, though some studies shows that feedback-based performance in humans recruits neural

mechanisms similar to those that subserve reinforcement learning and instrumental conditioning in nonhuman animals (Aron et al., 2004; Delgado, 2007; Delgado et al., 2005, 2000; Shohamy, Myers, Geghman, Sage, & Gluck, 2006; Shohamy et al., 2004). Second, a large body of experimental data suggests that the BG support WM processes (Battig et al., 1960; Chang et al., 2007; Diekamp et al., 2002; Divac et al., 1967; Hikosaka et al., 1989; Kawagoe et al., 1998; Levy, Friedman, Davachi, & Goldman-Rakic, 1997; Ljungberg et al., 1992; Monchi et al., 2001). Further, another line of research shows that striatal DA is important for reward-based learning (Schultz et al., 1997; Suri & Schultz, 1998; Waelti, Dickinson, & Schultz, 2001) and that phasic DA is important for synaptic modification in the corticostriatal pathway (Reynolds et al., 2001; Reynolds & Wickens, 2002; Wickens et al., 1996). It is not surprising then that striatal DA and the role of the BG in WM are related. Supporting this claim, Collins et al. (2000) found that damaging striatal DA interferes with learning a delayed-response task: Parkinsonian animals either took significantly more trials than controls to learn the task or could not learn it at all. Indeed, it is the goal of neurocomputational models to integrate data from these lines of research in order to provide a unified account for how striatal DA and BG interact in WM performance (Frank, 2005; Moustafa & Maida, 2007; O'Reilly & Frank, 2006).

The purpose of this phase was only to scratch the surface of the role of DA in feedback-based WM performance in PD. Future research should further investigate the effects of positive vs. negative feedback type (Ashby & O'Brien, 2007), distractors, and changes in reinforcement probabilities (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Frank et al., 2004; Hampton, Bossaerts, & O'Doherty, 2006) on WM. Our computational framework provides an account of how these factors influence feedback-based WM. These factors have received much attention in the domain of motor learning (Ashby & Ell, 2001; Daw et al., 2006; Frank et al., 2004; Hampton et al., 2006; Knowlton, Mangels, & Squire, 1996; O'Doherty, 2004) but hopefully future research will study their effects on WM as well.

4.4. Relation to other models of BG and PFC

Our models share with most existing models (Amos, 2000; Ashby, Ell, Valentin, & Casale, 2005; Berns & Sejnowski, 1995; Braver & Cohen, 2000; Dominey, 1995) the assumption that the PFC is key for active maintenance of information in WM as reported in many experimental studies (Barch et al., 1997; Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; Goldman-Rakic, 1995; Miller, Erickson, & Desimone, 1996; Sawaguchi & Iba, 2001). However, these models differ in which brain areas are incorporated and/or the functions assigned to those brain areas or neurotransmitters.: some models address the role of PFC (Cohen, Braver, & Brown, 2002) in WM while others (Amos, 2000) address BG and PFC interactions in WM.

For example, Amos (2000) proposed a neural model that integrates the role of BG and PFC in Wisconsin Card Sorting Task performance. In this model, DA subserves the modification of the signal-to-noise ratio, while no role is given for both striatal and prefrontal DA in synaptic modification. This model also did not simulate the role of the BG indirect pathway in performance. Our models, on the other hand, assume that striatal DA is important for both modifying the signal-to-noise ratio and also for synaptic modification (learning) in the corticostriatal pathway in agreement with existing physiological studies (Costa, 2007; Reynolds et al., 2001; Reynolds & Wickens, 2002; Wickens et al., 1996).

Further, Ashby et al. (2005) proposed a neurocomputational model of WM that also integrates the role of BG and PFC in WM. This model successfully simulates performance in WM span tasks. However, this model does not incorporate the BG indirect pathway, which we argue to be subserving NoGo performance (Frank, 2005). Similar to our models, Berns and Sejnowski (1995) hypothesize that the indirect pathway subserves NoGo performance. However, it is not clear in that model what the role of DA is for this function. Also like our models, Beiser and Houk (1998) model suggests that the BG modulates representations in the PFC. However, again this model does not incorporate the role of DA in learning and performance and does not incorporate the BG indirect pathway.

Other classes of WM models focus on the role of PFC in performance. For example, Braver and Cohen (2000) proposed a computational model that simulates performance in WM tasks, which assumes that mesocortical DA subserves the gating of information into WM (also see Constantinidis, Franowicz, & Goldman-Rakic, 2001; Durstewitz, Seamans, & Sejnowski, 2000). This is possibly the first model to assume that DA is simultaneously important for reward-based learning of WM tasks, and plays a direct role in gating. Unlike the Braver and Cohen's study, Cohen et al. (2002) focus on the theoretical function of PFC DA receptors in WM and cognitive control performance. They suggested that different D1 and D2 receptors within PFC itself subserve opposing functions, such that tonic DA acts to enhance WM maintenance via PFC D1 receptors, whereas phasic DA bursts enhanced WM updating via PFC D2 receptors. Cohen et al.'s theory, and the more biophysically detailed model of Durstewitz et al, on the role of PFC D1 receptors in WM maintenance is generally consistent with our models, although we did not directly simulate D1 receptor stimulation. Our models differ in the proposed mechanism for updating, which relies on BG function in our models. This assumption is based on physiological findings suggesting that BG modulation of thalamocortical activity is a more plausible mechanism for gating, due to (a) slow temporal dynamics of DA in PFC, which is not efficient for rapid WM updating, and (b) because the BG mechanism enables *selective* updating of some aspects of WM while continuing to maintain other information, as is required for many real-world WM tasks. In contrast, a direct DA-based gating mechanism may enforce all PFC representations to be gated simulataneously due to the global nature of the DA signal. However, the present findings do not differentiate between both models' predictions: although DA medications are well known to increase striatal DA levels in PD, most imaging studies are limited in the ability to detect potential DA increases that may also occur in PFC, and gating of information into WM can take place in either structure. Nevertheless, as discussed above, imaging data from McNab and Klingberg (2008), together with other converging evidence, strongly suggest that the BG control gate to update WM information into PFC, and shifting between different task-relevant stimuli (Cools et al., 2007).

4.5. Model limitations

Overall, though our models' predictions are generally in agreement with the present results, they do have limitations. These limitations are related to the performance of complex WM and attentional tasks that our models did not address.

First, it is reported that the neural mechanism underlying the performance of WM tasks is not only dependent on the basal ganglia and PFC circuits; it is increasingly apparent that the hippocampus is involved in WM processes (Braver et al., 2007; Paxton et al., 2007; Ranganath, Cohen, & Brozinsky, 2005; Rissman, Gazzaley, & D'Esposito, 2007). Some existing data suggest that the hippocampus is involved in more complex WM tasks. As alluded to above, Braver and colleagues argue that there are two brain mechanisms for WM: proactive and reactive. The former has to do actively maintaining information in WM and is suggested to be controlled by the PFC. The latter has to do with episodic retrieval of information from WM and is suggested to be controlled by the hippocampus

(Braver et al., 2007). Paxton et al. (2007) argued that subjects switch to the reactive WM system when WM tasks have longer delay intervals or when PFC is dysfunctional as in healthy aging (Paxton et al., 2007). Further, Rissman et al. (2007) argued that subjects switch to a hippocampal-based WM mechanism when WM load increases. The AX-CPT does not address WM load manipulations since it is always one stimulus that subjects are supposed to maintain in WM. Very few models address the role of the hippocampus in WM, but interactions between these different structures is a ripe area for future modeling.

It is also important to note that neither our model nor the AX-CPT directly address the interaction between WM capacity limitations and perceptual/attentional processes. In a series of studies, Lavie and colleagues have shown that increased perceptual load during encoding actually *reduces* distractibility effects, whereas increased working memory load increases distractibility (see Lavie & De Fockert, 2005 for review). Lavie's dual theory of attention addresses many aspects of attention that our models do not simulate, most notably in the domain of perceptual selection (Lavie, Hirst, de Fockert, & Viding, 2004). Nevertheless, our BG-PFC model is an instantiation of the cognitive control attention mechanism proposed by Lavie. Though Lavie et al. argue that the PFC is key for selective attention, our models extend this argument to suggest that a particular role for the BG in selectively updating some WM representations in PFC as a mechanism for selective attention. Notably, if the updating threshold is too low (due to an imbalance between Go and NoGo activity levels), then distractors presented during a delay will be more likely to be updated and will interfere with previously stored information, thereby reducing WM capacity (Frank & O'Reilly, 2006; O'Reilly & Frank, 2006). This aspect of the model nicely fits with the recent imaging results of McNab and Klingberg (2008) who showed a strong relationship between WM capacity and a higher BG updating threshold (i.e., more filtering of irrelevant information). Nevertheless, a recent study by Forster and Lavie (2007) showed that distractibility differences between subjects vanish if perceptual load is increased. Thus our model predicts that individual differences in WM capacity due to BG filtering might apply only under conditions of limited perceptual load, whereas other mechanisms (e.g., at the level of visual thalamus (Lavie & De Fockert, 2005)) may apply at the perceptual level.

It is also important to note that our models simulate attentional shifting in terms of knowing which of multiple stimuli to update into working memory and shifting to update new stimuli when appropriate. This demand contrasts with selective attentional tasks, such as the Wisconsin Card Selection and intra/extra-dimensional shifting tasks (Lewis et al., 2005; Taylor et al., 1986), in which attentional shifting occurs across different dimensions of the same stimuli. Our models currently do not simulate differential performance in the extra/intra-dimensional shifting (Lewis et al., 2005) or task switching tasks (Cools et al., 2001a) that were also found to rely on the BG and PFC. Nevertheless, there are other related models of these phenomena which rely on similar mechanisms (O'Reilly, Noelle, Braver, & Cohen, 2002; Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005), but which do not specifically flesh out the role of the BG.

5. Conclusion

To sum up, in agreement with existing literature, this study shows that PD patients have deficits in some aspects of WM and higher cognitive function, and suggest a key role for the BG in these processes. Importantly, the study also shows that DA medications might lead to enhancements or impairments depending on which phase of the task PD patients are performing, as evidenced by the use of a single task having distinct WM and attentional shifting segments, and broadly consistent with our neurocomputational models. Although there are other BG and other neurocomputational modes that simulate WM (Amos, 2000; Ashby et al., 2005; Berns & Sejnowski, 1995; Braver & Cohen, 2000; Dominey, 1995), some of which emphasize similar principles to our models (e.g., PFC is key for active maintenance of information), we are not aware of others that have made specific predictions for effects of PD and medications across a range of tasks (e.g., decision making and working memory).

To our knowledge, this is the first study to report WM enhancements and impairments associated with DA medications in PD patients, dependent on distractors, shifting, and learning. We are hopeful that the AX-CPT will provide further constraints for understanding cognitive function in PD as it has in the schizophrenia domain (Braver et al., 2001; Cohen et al., 1999; Servan-Schreiber et al., 1996).

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