Original Paper

Dopamine D2 receptor stimulation modulates the balance between ignoring and updating according to baseline working memory ability

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Abstract

Background: Working memory (WM) deficits in neuropsychiatric disorders have often been attributed to altered dopaminergic signalling. Specifically, D_2 receptor stimulation is thought to affect the ease with which items can be gated into and out of WM. In addition, this effect has been hypothesised to vary according to baseline WM ability, a putative index of dopamine synthesis levels. Moreover, whether D_2 stimulation affects WM vicariously through modulating relatively WM-free cognitive control processes has not been explored.

Aims: We examined the effect of administering a dopamine agonist on the ability to ignore or update information in WM.

Method: A single dose of cabergoline (1 mg) was administered to healthy older adult humans in a within-subject, double-blind, placebo-controlled study. In addition, we obtained measures of baseline WM ability and relatively WM-free cognitive control (overcoming response conflict).

Results: Consistent with predictions, baseline WM ability significantly modulated the effect that drug administration had on the proficiency of ignoring and updating. High-WM individuals were relatively better at ignoring compared to updating after drug administration. Whereas the opposite occurred in low-WM individuals. Although the ability to overcome response conflict was not affected by cabergoline, a negative relationship between the effect the drug had on response conflict performance and ignoring was observed. Thus, both response conflict and ignoring are coupled to dopaminergic stimulation levels.

Conclusions: Cumulatively, these results provide evidence that dopamine affects subcomponents of cognitive control in a diverse, antagonistic fashion and that the direction of these effects is dependent upon baseline WM.

Keywords

Cognitive control, dopamine, individual differences, working memory

Introduction

A reduced ability to control thoughts and appropriately gate sensory information is a common feature of several neuropsychiatric disorders associated with disruption to fronto-striatal circuits (Arnsten, 2006; Dalley et al., 2011; Jahanshahi et al., 2015). Alterations in dopaminergic signalling are widely believed to be causally responsible for some of these deficits (Abi-Dargham et al., 2002; Buckholtz et al., 2010; Volkow et al., 2012). However, the neurocognitive mechanisms through which dopamine affects the gating of information in humans is not fully understood.

Stimulation of the D_2 dopamine receptor has been hypothesised to control information flow into and out of working memory (WM) through its expression in fronto-striatal circuits, allowing cortically bound representations to be either promoted or prohibited (Cools and D'Esposito, 2011; Frank and O'Reilly, 2006). These effects have also been argued to vary according to individual differences in baseline WM ability (Broadway et al., 2018), an effect putatively explained by the positive relationship between WM performance and striatal dopamine synthesis (Cools et al., 2008). There is now mounting evidence for a role of D_2 receptor stimulation in filtering out – or ignoring – irrelevant information (Bloemendaal et al., 2015; Broadway et al., 2018; Fallon et al., 2017c; Mehta et al., 2004). However, there is very little evidence that such effects are accompanied by changes in the cognitive inverse of ignoring: allowing new information to displace current information – updating the contents of WM.

Replenishing dopamine levels in Parkinson's disease (PD) patients has been found to improve both ignoring and updating, pointing to a common dopaminergic effect on the two processes (Fallon et al., 2017a). Haloperidol, predominantly a D_2 receptor antagonist, did not specifically affect either ignoring or updating, but impaired all WM functions through increasing the number of attentional lapses (Fallon et al., 2019). In that study, baseline WM

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proficiency also did not significantly modulate the effect haloperidol had on ignoring verses updating. Thus, there is insufficient evidence that D_2 receptors play the role that some influential computational models (Durstewitz and Seamans, 2008; Frank and O'Reilly, 2006) ascribe to them. However, haloperidol may not be pharmacologically selective (Zhang and Bymaster, 1999), and may exert some of its mnemonic effects through antagonising the D_1 receptor (Rieckmann et al., 2011; Sawaguchi and Goldman-Rakic, 1991), preventing us from drawing firm inferences concerning the specific role of D_2 receptors. Indeed, the specific effect pharmacological manipulation of the D_2 receptor has on updating and filtering of information largely rests upon the findings of (Frank and O'Reilly, 2006), who found increased updating and distractibility of mental representations in low-WM span individuals.

Here, we seek to provide further scrutiny of the hypothesis that D_2 receptor stimulation differentially affects ignoring and updating by examining the effects that cabergoline, a relatively selective D_2 agonist, has on these processes in healthy older adults using the exact paradigm as in previous studies (Fallon et al., 2017a). Older individuals were chosen to evaluate this hypothesis because, like PD patients, they show similar albeit distinct - depletion of dopaminergic functioning (Kaasinen and Rinne, 2002; Karrer et al., 2017). This group might therefore be an important one to study in view of the potential to improve their cognition with dopaminergic drugs. In contrast to PD patients, however, the absence of progressive neuronal pathology in healthy older adults provides a clearer window onto the effect dopamine has on cognitive functioning.

This study sought to improve our understanding of the role of dopamine in human cognition by also assessing whether cabergoline simultaneously affects relatively WM-free cognitive control. Here, we focussed on a well-established measure of overcoming response conflict – the Simon task. This provides a validated assay of responding to response conflict, when participants have to make responses incompatible with the spatial layout of stimuli, for example, making a left response to a stimulus presented on the right. Reduced dopamine levels have been found to impair the ability to overcome response conflict, thereby exacerbating the Simon effect (Ramdani et al., 2015; van Wouwe et al., 2016). Indeed, haloperidol administration can increase the Simon effect (Fallon et al., 2019). Furthermore, the authors of this study found that dopamine might affect the gating of items into WM by the same cognitive mechanism that is deployed for cognitive control during response conflict. They found a positive association between the deleterious effects of haloperidol on overcoming response conflict and the ability to ignore or prevent irrelevant information from entering WM. However, it remains unclear whether the observed coupling between ignoring and overcoming response conflict was due to the specific pharmacological effects of haloperidol. In this investigation, we therefore also examine whether there might be such an association with cabergoline.

Methods

Participants

Thirty (18 male; 12 female) participants participated in this study. Four (three male, one female) participants were excluded from the analysis: two people did not complete all of the tasks on both sessions, one person reported not understanding the tasks and one showed aberrant performance on the ignore/update task (>3 SDs above mean). Included participants had mean age 68.7 years (60–78). None showed evidence of dementia as assessed on the screening Addenbrooke's Cognitive Examination-III (ACE; range 88–100; mean score: 97.5). In order to take part, volunteers had to have normal or corrected-to-normal vision, no history of cardiovascular disease, normal QT interval (assessed with EEG), no recent recreational drug use, allergies to any medication, pregnancy or breastfeeding, inherited blood conditions, or lactose hypersensitivity. All participants gave written informed consent and the study was approved by the University of Oxford's ethics committee.

Design

Participants were tested in two sessions in a within-subject, double-blind, placebo-controlled study. In one session participants took a 1 mg cabergoline tablet, whereas in the other session an indistinguishable placebo capsule was administered (order counterbalanced).

Tasks

The proficiency of ignoring and updating was assessed using a delayed reproduction task (Fallon et al., 2017a). The task assesses recall by requiring participants to reproduce the exact features of memoranda, specifically their orientation. In all conditions, they had to remember the orientation of a pair of arrows that were presented at different spatial locations and in different colours (Figure 1). Participants' recall was probed by presenting one of the coloured arrows at the centre of the screen and asking them to rotate the arrow until it matched their memory of the previously encountered orientation of that arrow. For example, when probed with a magenta arrow (Figure 1) they had to rotate the arrow until it matched the orientation in which they previously saw the magenta arrow. Participants confirmed that they had rotated the arrow to its final position by pressing the space bar. Feedback was presented on the screen, which allowed them to discern how accurate they were: after every trial they were shown the correct orientation of the probed arrow.

There were four experimental conditions (Figure 1). The ability to protect the contents of WM from distracting information was assessed by presenting irrelevant items during the interval between encoding and probe (ignore condition). To isolate the effect of inserting distracters there was also a maintain (T1) condition. In this condition participants had to maintain information for the same time period as in the ignore condition.

In the update condition, rather than having to ignore new information presented during the delay period, participants had to encode this information into memory and allow it to displace the previous memoranda. Thus, in this condition, WM representations had to be updated such that previously encoded items now became irrelevant. Finally, in the maintain (T2) condition, there were no irrelevant items. Here, the maintenance period was matched to that for the relevant (middle) items in the update condition (so this is the temporal control for the update condition).

Note that maintain (T1) and maintain (T2) conditions have different durations because the period over which information to-be-remembered has to be retained is shorter in the update than in the ignore condition (2000 milliseconds vs. 6000 milliseconds).

The four conditions – ignore, update and each of their temporal controls – appeared in a randomised order.

Participants were not explicitly cued to ignore or update items into memory. They were simply instructed to remember only the last pair of arrows presented with the letter 'T'at screen centre (Figure 1). This acted as a cue to instruct them that they should remember only the arrows displayed on that screen. The task was administered on average ~3 h and 45 min after capsule administration (~3 h 42 min cabergoline session, ~3 h 52 in placebo session). For each session, the task contained 128 trials (32 trials each for ignore, update, maintain (T1) and maintain (T2) conditions).

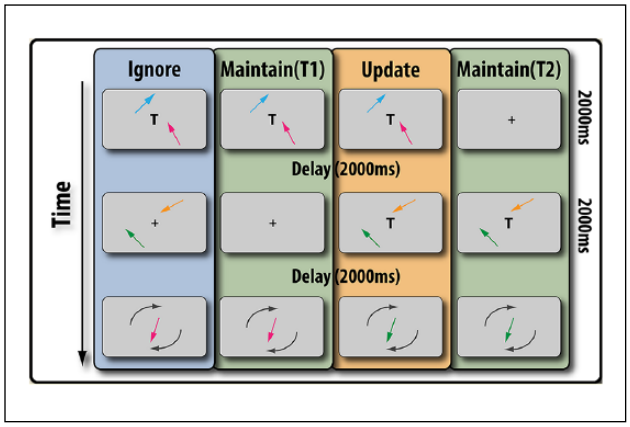

Figure 1. Ignore/update WM task.
In all four conditions, WM recall error was measured by presenting a pair of coloured arrows. After a variable delay, participants were probed to reproduce the orientation of one of these items. The probe arrow's colour indicated which item had to be recalled, for example, a blue probe arrow indicated that the orientation of the previously seen blue arrow needed to be reproduced. Participants had to reproduce the orientation by rotating the initial orientation of the probe arrow clockwise or counter-clockwise. In the ignore condition (left most panel), participants had to maintain their memory for the first pair of arrows encountered and ignore the second pair of arrows. In the update condition (3rd panel from left), participants again had to encode the initially presented pair of arrows but now, when presented with the second pair of arrows, they had to update these items into WM, and remove the previously encountered items from memory. The ignore and update conditions both had their own temporal controls to account for the differences in the retention period between the ignore and update conditions (maintain T1 and maintain T2). Across all conditions, participants were told that they had to remember only the last pair of arrows that were presented with the letter 'T' shown at screen centre.

Baseline working memory task. We used the same baseline WM task as in our previous study (Fallon et al., 2019). Briefly, participants had to remember the orientation of a single, centrally presented arrow (Figure 2A). Then, after a variable delay period (1000 ms or 2000 ms), they had to rotate the arrow clockwise or anti-clockwise until it matched the orientation of the arrow they had previously seen. The task contained 96 trials (48 trials for each delay duration). Participants completed the task on both the cabergoline and placebo sessions. Mean angular error was averaged across both sessions and delays. Note, participants completed the task directly after taking the capsule (on average 9 min after drug intake), thus making it unlikely that any drug effects would appear. Indeed, there were no significant effects in performance between the cabergoline and placebo sessions ($t(25) = 0.94$, $p = 0.35$, $d = 0.18$).

Response conflict (Simon) task. The version of the Simon task used here was also as used previously (Fallon et al. (2019) provides a full description). Briefly, participants had to indicate the direction of an arrow presented on the left or right of the screen (Figure 2B). A congruent trial occurred when the direction of the arrow matched its spatial location (e.g. a left-pointing arrow on the left side of the screen), whereas an incongruent trial occurred when there was a mismatch between the arrow direction and its presented location (e.g. a left-pointing arrow on the right side of the screen). Participants completed a single block of 50 congruent and 50 incongruent trials (intermixed). The task was administered ~4 h 40 min after capsule administration (~4 h 37 min cabergoline session, ~4 h 43 min placebo session).

Analysis

Mean angular error, calculated as the absolute angular difference between orientation of the target item and the response orientation

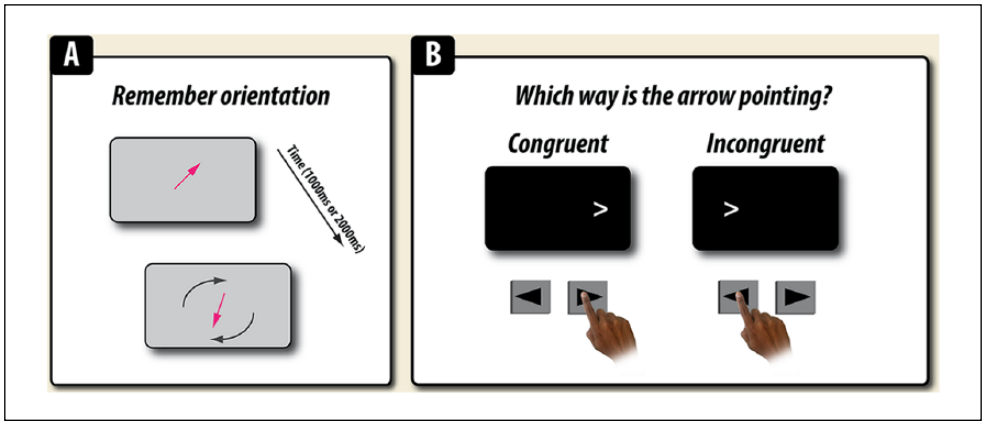

Figure 2. Baseline working memory and Simon tasks.
(A) In the baseline working memory task, the orientation of a single arrow had to be maintained and reproduced after either 1000 ms or 2000 ms delay. (B) In the response conflict (Simon) task, participants had to indicate the direction (left or right) of the arrow on the screen. Congruent trials occurred when the arrow appeared on the same side of the screen in which it was pointing. In contrast, incongruent trials were when the arrow pointed in a different direction to the side on which it was presented.

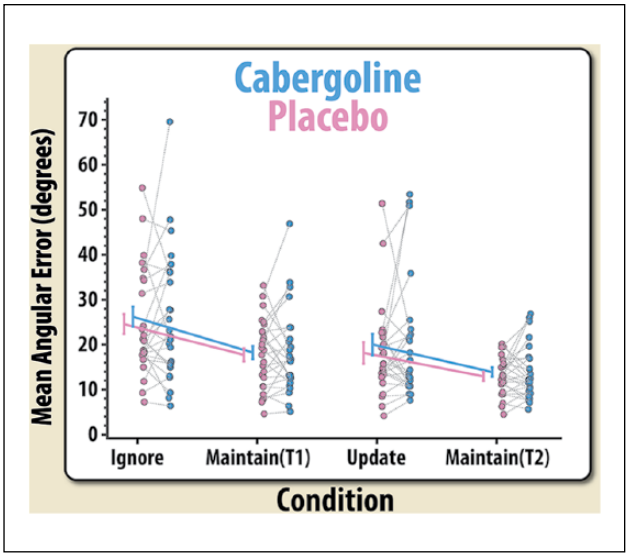

Figure 3. Absolute mean angular error.
Recall performance (absolute mean angular error from the response to the target orientation) for each condition in each of the drug sessions. Error bars (centred on the mean for each condition) reflect the standard error of the difference between the cabergoline and placebo conditions.

(angle to which the probed item was rotated) was our main metric of performance across both the ignore/update tasks, their maintain temporal controls and the baseline measure of WM. Data were analysed in JASP (JASP Team, 2018). The criterion for statistical significance was set at the conventional level ($\alpha = 0.05$) and appropriate estimates of effects size are also provided (e.g. Cohen's d (*d*) for parametric pairwise comparisons, rank biserial correlation (*rb*) for non-parametric contrast and omega squared (η^2) for ANOVAs). For the Simon task, the effect of drug on accuracy (arcsine transformed) and reaction time data for congruent and incongruent trials were analysed using a repeated measures ANOVA. Drug and congruence were entered as within-subject variables. For analysing recall on the ignore/update task, and the participants' maintain temporal controls, repeated measures ANCOVA with within-subject factors drug (placebo, cabergoline), retention period (2 s vs. 6 s delay) and presence of irrelevant information (maintain vs. ignore/update trials) was used. When examining the effect of baseline WM ability, we (as in Fallon et al., 2019) entered the mean absolute angular error as a mean-centred covariate. Similarly, to assess the association between the effect the drug had on response conflict and its effects on WM, we also entered our metric of drug effect on response conflict (accuracy on incongruent trials for placebo minus accuracy on incongruent trials for cabergoline) as a mean-centred covariate.

Results

Ignore/update task performance

The effect of cabergoline on performance in the ignore/update task was examined in a repeated measures ANCOVA with drug (placebo, cabergoline), delay (long, short) and presence of irrelevant information (present (ignore/update) vs. maintain only) and within-subject factors and baseline WM (standardised) as a between-subject covariate (see Table S1 for full results).

Recall was significantly impaired by the introduction of irrelevant information, i.e. when participants had to ignore or update WM contents compared to just maintain ($F(1,24) = 25.02$, MSE = 89.07, $p = 4.13 \times 10^{-5}$, $\eta^2_p = 0.51$) and for longer retention periods ($F(1,24) = 25.50$, MSE = 60.11, $p = 3.6 \times 10^{-5}$, $\eta^2_p = 0.52$). There was no significant interaction between retention period and presence of irrelevant information ($F(1,24) = 1.07$, MSE = 37.04, $p = 0.31$, $\eta^2_p = 0.01$). Thus, ignoring did not have a significantly different effect on recall compared to updating after taking temporal differences into account. With regard to drug effects, there was no significant main effect of drug or interaction between drug and response to irrelevant information or between drug and retention period (Fs < 1; Figure 3). Non-parametric analysis, and an analysis of precision, corroborated these analyses (see Supplementary Materials).

Baseline WM performance modulates performance on ignore/update task

Within the same analysis, baseline WM performance had a significant effect on overall performance on four conditions (ignore, maintain (T1), update and maintain (T2) of the ignore/update task ($F(1,24) = 11.50$, MSE = 330, $p = 0.002$, $\eta^2_p = 0.324$). Better baseline WM was positively associated with better overall recall. A significant four-way interaction was found between drug, presence of irrelevant information, retention period and baseline WM ability ($F(1,24) = 5.69$, MSE = 23.56, $p = 0.025$, $\eta^2_p = 0.192$).

In order to understand this interaction we can examine the correlation between baseline WM and a metric representing the drug's effect on ignoring vs. updating (calculated by computing the difference in the beneficial effect of the drug on ignoring [maintain (T1) minus ignore cabergoline] minus [maintain (T1) minus ignore placebo]) vs. updating ([maintain (T2) minus update cabergoline] minus [maintain (T2) minus update placebo]). Under this metric, positive scores indicate the drug impairs updating at the expense of ignoring and negative scores the converse (cabergoline impairs ignoring at the expense of updating).

This analysis revealed a significant negative relationship between baseline WM ability and the effect the drug had on improving performance on the ignore vs. update conditions (correlation analysis: $r(26) = -0.438$, $p = 0.025$; Figure 4). Thus, the worse a participant's baseline WM performance, the more the drug impaired ignoring at the expense of updating. Breaking this relationship down, the worse a participants' baseline memory the more the drug tended to impair ignoring ($r(26) = -0.28$, $p = 0.16$), but improve updating ($r(26) = 0.239$, $p = 0.24$). Though in neither case was this relationship statistically significant.

Simon task

For the response conflict task, there were – as anticipated – main effects of congruence on accuracy (arcsine transformed; $F(1,25) = 21.89$, MSE = 0.054, $p = 1.01 \times 10^{-5}$, $\eta^2_p = 0.543$) and reaction time ($F(1,25) = 36.25$, $p = 2.73 \times 10^{-6}$, $\eta^2_p = 0.592$). There was no significant main effect of drug on accuracy ($F < 1$) or significant interaction between drug and congruence ($F(1,25) = 2.58$, MSE = 0.024, $p = 0.12$, $\eta^2_p = 0.094$). A non-parametric pairwise comparison (Wilcoxon) between accuracy on incongruent trials for

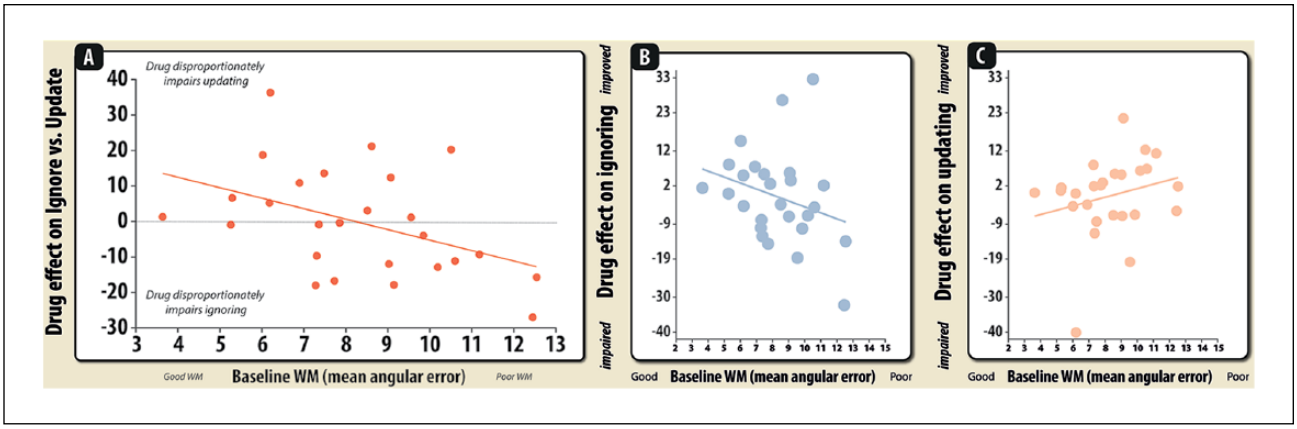

Figure 4. Relationship between baseline WM and drug effects.
Baseline WM ability (mean angular error averaged over both sessions) is associated with the differential effect the drug had on ignore vs. update performance. Individuals with better WM (lower error) were disproportionately impaired on updating compared to ignoring after cabergoline administration. The drug effect is calculated by computing the difference in the beneficial effect of drug on ignoring ([maintain (T1) minus ignore cabergoline] minus [maintain (T1) minus ignore placebo]) vs. updating ([maintain (T2) minus update cabergoline] minus [maintain (T2) minus update placebo]). Relationship between baseline WM ability (mean angular error) and the drug effect on ignoring (B) and updating (C). Drug effects on ignoring were calculated as the difference in recall (mean angular error in degrees) between ignoring and maintain (T1) trials in the drug session minus those in the placebo session. Correspondingly, drug effects on updating were calculated as the difference in recall (mean angular error in degrees) between updating trials and maintain (T2) trials in the drug session minus those in the placebo session.

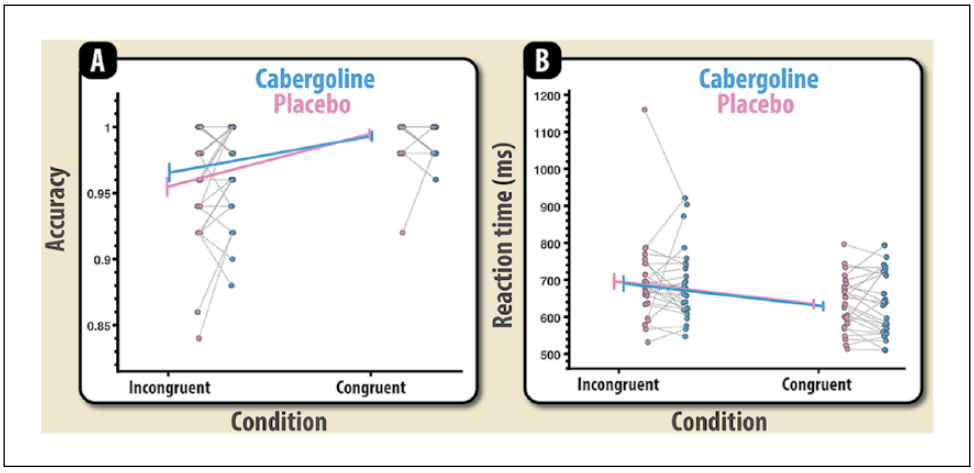

Figure 5. Cabergoline and response conflict task.
Effect of cabergoline on accuracy (A) and reaction time (B) for congruent and incongruent trials on the response conflict task. Error bars (centred on the mean for each condition) reflect the standard error of the difference between the cabergoline and placebo conditions.

the placebo and cabergoline session also found no significant drug effect ($W = 90$, $p = 0.240$, $rb = 0.487$). Similarly, for reaction time, there was no significant main effect of the drug or interaction between the drug and congruence (Fs < 1; Figure 5). There was no significant effect of drug on reaction time in the incongruent trials ($W = 201$, $p = 0.53$, $rb = 0.145$)

As in our previous study (Fallon et al., 2019), we next related the effect the drug had on overcoming response conflict (accuracy on incongruent trials in the placebo session minus drug session) to performance on the ignore and update task (see Table S2 for full results). There was a significant four-way interaction between drug, retention period, presence of irrelevant information and drug effect on response conflict ($F(1,24) = 6.75$, MSE $= 22.75$, $p = 0.016$, $\eta^2_p = 0.22$). To discern the direction of this relationship, we can relate our covariate – in this case drug effect on overcoming response conflict – with a single variable representing the differential effect the drug had on ignoring vs. updating (computed exactly as above).

The deleterious effects of drug on response conflict were found to be negatively associated with the differential effect of drug on ignoring vs. updating ($r(26) = –0.468$, $p =0.016$). Again, as above, we can examine whether simpler relationships exist between the covariate and the separate effects of drug on ignoring ([maintain (T1) minus ignore drug] minus [maintain (T1) minus ignore placebo]) and updating ([maintain(T2) minus update drug] minus [maintain (T2) minus update placebo]). Here, the relationship could be decomposed into there being an inverse relationship between the effects of the drug on response conflict and the drug's effect on ignoring ($r(26) = –0.391$, $p = 0.048$; Figure 6A), but no relationship between the drug's effect on updating ($r(26) = 0.151$,

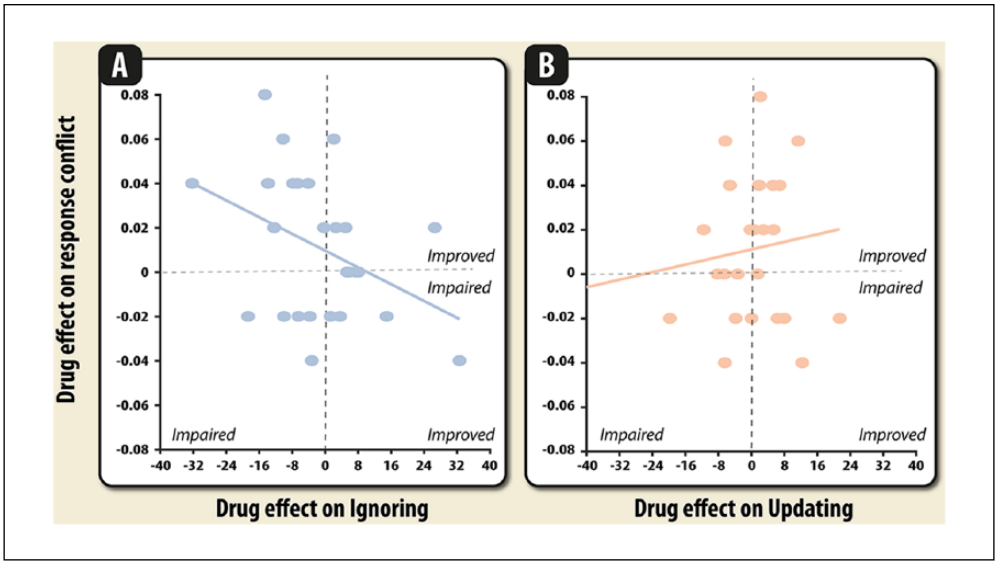

Figure 6. Relationship between drug effects on response conflict and working memory.
Relationship between the drug effect on response conflict (accuracy on incongruent trials in the placebo session minus drug session) and the drug effect on ignoring (A) and updating (B). Drug effects on ignoring were calculated as the difference in recall (mean angular error in degrees) between ignoring and maintain (T1) trials in the drug session minus those in the placebo session (as in Figure 4). Correspondingly, drug effects on updating were calculated as the difference in recall (mean angular error in degrees) between updating trials and maintain (T2) trials in the drug session minus those in the placebo session.

$p = 0.461$; Figure 6B). Thus, the more the drug impaired response conflict, the more the drug improved the ability to ignore irrelevant information.

Discussion

Dopamine, particularly through its action on the D_2 receptor, is often proposed to be integral to gating the contents of WM (Bloemendaal et al., 2015; Dodds et al., 2009; Kimberg et al., 1997; Li et al., 2013; Luciana et al., 1992; Mehta et al., 2004; Ott and Nieder, 2017), but the neurocognitive mechanisms behind this relationship have remained elusive. This study, performed on older people, has provided support for the notion that D_2 receptor stimulation affects WM through altering the balance between the proficiency of ignoring and updating – gating information into or out of WM.

Crucially, the direction of this effect varied according to individuals' baseline WM ability. Administration of cabergoline to individuals with poor baseline WM recall had a greater detrimental effect on their ability to ignore, compared to update, information (Figure 4). In contrast, the effect was reversed (greater difficulty with updating compared to ignoring) in individuals with better baseline WM recall. These findings are congruent with previous studies. For example, Frank and O'Reilly (2006) found that low-WM individuals showed improved accuracy on ignoring irrelevant items after cabergoline administration. Thus, this study has provided further evidence that cabergoline can enhance the robustness of mental representations in high-WM individuals, but, conversely, make representations less stable (promoting flexibility) in low-WM individuals.

Cabergoline exerted these effects without affecting the overall ability to overcome response conflict. However, consistent with previous results (Fallon et al., 2019), a coupling between the effect of D_2 drug administration on response conflict and ignoring was uncovered. Here, there was a negative relationship between these two: the more drug impaired conflict processing the more ignoring proficiency was improved (Figure 6). Thus, there was evidence of a relationship between gating information out of WM and an independent measure of cognitive control. Therefore, dopamine appears to have simultaneous effects on ignoring and response conflict.

Baseline WM ability modulates direction of cabergoline's effect on stability vs. flexibility

In contrast to models arguing that dopamine affects all forms of short-term recall (Sawaguchi and Goldman-Rakic, 1991), and the results from administering D_2 antagonists (Fallon et al., 2019), cabergoline did not influence overall WM recall (Figure 3). Rather, D_2 stimulation moderated the balance between ignoring and updating, and in divergent ways according to baseline WM performance. Cabergoline disproportionately impaired updating but improved ignoring in high baseline WM individuals, but exerted the opposite effects in low baseline WM individuals (Figure 4).

There has been growing prominence in the literature accorded to the concept that the balance between D_1 and D_2 receptors modulates the ease with which sensory information can be ignored or updated into WM (Bloemendaal et al., 2015; Broadway et al., 2018; Cohen et al., 2002; Fallon et al., 2017c; Frank and O'Reilly, 2006). These studies have been spurred on by hypotheses generated from biological-based computational models of how dopamine modulates neuronal functioning. Changing the balance of D_1 to D_2 activity is thought to change the energy barrier in the prefrontal cortex separating different mental states, with intermediate levels of D_1 stimulation supporting robust mental representations and high D_2 states allowing information to be flexibly handled (Durstewitz and Seamans, 2008).

Alternatively, or in addition, the computational problem of resolving the dynamics between stability and flexibility may also be executed at the level of the striatum. The prefrontal-basal ganglia WM model (PBWM; O'Reilly and Frank, 2006) argues that there is a division of labour in fronto-striatal circuits, with the D_1 dominated 'go' (or direct) pathway allowing for memory to be updated, whereas the D_2 dominated 'nogo' (indirect) pathway allows information to be filtered. Both of these models (Durstewitz and Seamans, 2008; Frank and O'Reilly, 2006) predict that the effect of administering cabergoline on the balance between D_1 and D_2 stimulation, and hence ignoring and updating, should vary according to tonic dopamine levels. However, prior to this study, there has been little evidence to support this claim. This is partly due to the inherent difficulty in testing this prediction in humans.

Although it is difficult to measure tonic dopamine levels in the human brain, it may be possible to use baseline WM performance as a proxy indicator. This contention is based upon work that reported a positive association between WM span (recall accuracy) and the level of striatal dopamine synthesis capacity (Cools et al., 2008). This provides a mechanistic basis for a much larger corpus of work showing that an individual's WM performance modulates the cognitive and neural effects of dopamine-altering drugs (Kimberg and D'Esposito, 2003; Kimberg et al., 1997; van der Schaaf et al., 2013). Thus, the present study's finding that the direction of cabergoline's effect on ignoring vs. updating proficiency varied with baseline WM performance accords well with the above models' (Durstewitz and Seamans, 2008; Frank and O'Reilly, 2006) predictions, i.e. that baseline dopamine levels affect the balance between putatively D_1- and D_2-mediated cognitive functions.

However, recently, individuals with high baseline WM recall (and thus putatively high striatal dopamine levels) were found to show impaired performance on ignoring compared to pure maintenance after administration of 1.5 mg cabergoline (Broadway et al., 2018). This is the opposite to what was presently observed. Here, superior baseline WM ability was associated with impaired updating compared to ignoring ability after 1 mg cabergoline administration. It should be noted, however, that a combination of factors make it difficult to compare these studies directly and likely explain such discrepancies. First, the higher dose used by Broadway and colleagues (2018) compared to the present (1.5 mg vs. 1 mg) could lead to different pre- vs. post-synaptic effects in our investigation (Meller et al., 1987). Second, the previous study assessed younger adults, whereas older adults were tested here. Age has been shown to affect dopaminergic parameters and response to dopaminergic drugs (Bäckman et al., 2006; Chowdhury et al., 2013; Guitart-Masip et al., 2016). Thus, the response to dopaminergic drugs may be qualitatively different in older compared to younger adults.

Third, though both studies putatively assessed distracter resistance, the psychological and neural computations actually recruited in these studies may be very different. The previous study required participants to selectively filter information within an array of memoranda (Broadway et al., 2018), which may be very different from selectively gating items that appear at different times (present study). Indeed, these two functions have been found to be dissociable and produce differential activation of fronto-striatal circuits (McNab and Klingberg, 2008; McNab et al., 2015; Murty et al., 2011). Finally, the two investigations used very different measures of baseline WM performance. Previous studies have used span-like measures to examine individual differences in WM (Fallon et al., 2017c; Kimberg and D'Esposito, 2003; Kimberg et al., 1997). These measures have the advantage of having been previously associated with striatal dopamine synthesis levels. However, their relationship to the tasks in WM may be more general and undefined. Here, we chose to address individual (baseline) WM ability in a manner fully congruent with the way in which gating in and out of WM was assessed, i.e. by measuring the precision of recall. Thus, the results presented here directly implicate baseline efficacy of WM recall in moderating whether a dopamine agonist will impair ignoring vs. updating. Moreover, a distinguishing feature of our baseline WM measure is that it does not simply tap short-term memory. Recall in this paradigm – as in other delayed reproduction tasks – involves an active retrieval process in which the arrow is rotated until, presumably, it matches some internal mnemonic template. Interference from this process is predicted by recent computational models of recall (Manohar et al., 2019), and experimental evidence has indicated it can affect the quality of recall (Tabi et al., 2019).

It should also be acknowledged that baseline WM ability could modulate the response to drugs independent of whatever effects it may have on baseline dopamine synthesis levels. For example, WM ability may index some general aspect of physiology that makes people respond to a greater extent to pharmacological manipulations.

Dopamine has common, but antagonistic, effects on ignoring and overcoming response conflict

WM is not the only cognitive control function affected by dopamine (Aarts et al., 2011; Eagle et al., 2008; Nieoullon, 2002). Several other forms of executive performance, such as reversal learning, inhibition, response selection, and set-shifting have been shown to be moderated by substances that act on the D_2 receptor (Dalley et al., 2007; Eagle et al., 2011; Logemann et al., 2017; Mehta et al., 2004; van Holstein et al., 2011; van der Schaaf et al., 2014). This raises the possibility that dopamine exerts its effects on WM tasks through affecting the control of memories vicariously through affecting general executive, or cognitive control, functions.

Recently, a positive association was reported between the negative effects of haloperidol (a D_2 antagonist) on the abilities to overcome response conflict and to ignore irrelevant items (Fallon et al., 2019). The greater the negative effects of haloperidol on overcoming response conflict the greater the negative effect of the drug on distracter resistance (ignoring). The relationship was also found to be cognitively specific, i.e. there was no such relationship between the drug's effect on response conflict and updating. The results were interpreted as reflecting the fact that dopamine may have common effects on the two functions, i.e. that distracter resistance and response conflict are impaired by same neurocognitive mechanism. The results of the present study support and extend these findings. Here, administering a D2 agonist, led to the relationship being reversed: the more cabergoline improved ignoring performance, the more it increased the Simon effect (impaired response conflict resolution). Several hypotheses present themselves in order to account for this reversal.

Previously, the positive association between the detrimental effect of haloperidol on response conflict and ignoring was explained in terms of creating a common deficit in suppressing relevant information across tasks, i.e. that haloperidol impaired the ability to suppress inappropriate mental representations irrespective of mnemonic requirements. The present data suggest that, at least in context of dopaminergic agonists, additional factors may also be at work. One possibility is that the negative association between the two factors in the present study could arise through similar mechanisms as observed in a previous study on the effects of cabergoline (Fallon et al., 2017c). Thus, the negative association between response conflict and ignoring could reflect the antagonistic effects cabergoline is having on the balance between the go and nogo pathways.

Cabergoline, through stimulating the inhibitory post-synaptic D_2 receptors present on the nogo pathway, could lead to a preponderance of activity in the go pathway. Under these pharmacological effects, it could be speculated that there would be a heightened, preferential response to the cue in the Simon task (boosting the processing of relevant information). In other words, the arrow cue is given direct, immediate access to the cortical representations that enable response generation. As a consequence of this exaggerated go signalling, poorer performance in ignoring could occur due to items, irrespective of their relevance, erroneously being allowed to enter WM.

Though this explanation is speculatively applied in the present case, such a dissociation has previously been reported. Methylphenidate, which boosts synaptic dopamine (and noradrenaline) levels, produced a similar dissociation, boosting the identification of targets, but impairing distracter resistance (ter Huurne et al., 2015). Methylphenidate's attention-boosting effects have also been found to directly relate to its capacity to modulate dopamine release and exert differential effects according to baseline functioning (del Campo et al., 2013). However, as in the earlier discussion concerning baseline WM and ignoring and updating, the same caveats also apply. There is a need to conduct further studies, in the same cohort of participants, possibly also incorporating combined administration of agonist and antagonist (van der Schaaf et al., 2014).

The effect of age

As mentioned, a potentially important factor in influencing the present results is that the present study was conducted in healthy older (+50 years of age) adults. Older adults were chosen to complement the findings from prior work in PD (Fallon et al., 2017a), given that examining the effects of cabergoline in this group allows us to see the effects of dopamine on WM in the healthy, but age-matched brain. It has also provided a useful window onto the effect that a dopaminergic augmentation has on a brain that has likely experienced depletion of many indices of dopaminergic functioning (Kaasinen and Rinne, 2002). Depletions in these variables have been regularly argued to be responsible for the characteristic cognitive decline observed in normal ageing (Bäckman et al., 2006). Accordingly, it could be tempting to pursue dopamine-altering compounds as potential cognitive enhancers in this group. The present work suggests that there may be minimal benefit, however, in augmenting the level of dopaminergic, at least D_2, stimulation, even in low-WM individuals. This is because, similar to methylphenidate (Fallon et al., 2017b) dopamine appears to act as a double-edged sword: improving one cognitive function (ignoring) at the expense of another (updating). Researchers interested in improving cognition in older adults may want to explore other pharmacological compounds or interventions.

Conclusion

Cumulatively, these results illustrate the importance of accounting for individual differences when assessing the effect of dopaminergic drugs, the necessity of decomposing WM into its constituent subcomponents to uncover these relationships, and acknowledging that dopamine has common, potentially antagonistic effects, on different cognitive control measures.

Authors' note

Sean James Fallon is now affiliated with National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol.

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Supplemental material

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