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Dopamine guides competition for cognitive control: Common effects of haloperidol on working memory and response conflict

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Abstract

Several lines of evidence suggest that dopamine modulates working memory (the ability to faithfully maintain and efficiently manipulate information over time) but its specific role has not been fully defined. Nor is it clear whether any effects of dopamine are specific to memory processes or whether they reflect more general cognitive mechanisms that extend beyond the working memory domain. Here, we examine the effect of haloperidol, principally a dopamine D₂ receptor antagonist, on the ability of humans to ignore distracting information or update working memory contents. We compare these effects to performance on an independent measure of cognitive control (response conflict) which has minimal memory requirements. Haloperidol did not selectively affect the ability to ignore or update, but instead reduced the overall quality of recall. In addition, it impaired the ability to overcome response conflict. The deleterious effect of haloperidol on response conflict was selectively associated with the negative effect of the drug on ignoring – but not updating – suggesting that dopamine affects protection of working memory contents and inhibition in response conflict through a common mechanism. These findings provide new insights into the role of dopamine D₂ receptors on human cognition. They suggest that D₂ receptor effects on protecting the memory contents from distraction might be related to a more general process that supports inhibitory control in contexts that do not require working memory.

Introduction

Working memory (WM) refers to our capacity to both store and manipulate our internal representations over short time periods. A variety of work from various modalities and across different model systems has suggested that adequate levels of dopaminergic stimulation are necessary to support visual WM (Brozoski, Brown, Rosvold, & Goldman, 1979; Clatworthy et al., 2009; Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008; Eckart, Fuentemilla, Bauch, & Bunzeck, 2014; Simioni, Dagher, & Fellows, 2017; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). However, a precise definition of the role of dopamine in WM has proved elusive. Here, we seek to address and evaluate several competing hypotheses about the role and specificity of dopamine in visual WM.

A prominent idea in the literature is that dopamine might have a specific role in distracter-resistance, protecting the contents of WM from irrelevant information (Bloemendaal et al., 2015; Broadway, Frank, & Cavanagh, 2018; Cools, Sheridan, Jacobs, & D'Esposito, 2007; Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004). However, few studies have investigated whether the effect of dopamine on distracter-resistance is off-set, or co-occurs, with changes in other aspects of WM, such as maintenance and updating. For example, recently, D₂ agonist administration was found to impair recall when distracters had to be ignored, but improved it in the absence of distracters (Fallon, Zokaei, Norbury, Manohar, & Husain, 2016). However, it is unclear whether changing D₂ stimulation levels should affect the way all classes of distracting or irrelevant information are dealt with.

Levels of D₂ stimulation have also been associated with changes in the cognitive inverse of distracter resistance – updating items in memory (Bäckman & Nyberg, 2013; Lövdén et al., 2017; Salami et al., 2018). Indeed, it has been suggested that ignoring and updating may be antagonistically coupled to one another and vary according to ratio of D₁ to D₂ dopamine receptor stimulation (Durstewitz & Seamans, 2008; Hazy, Frank, & O'Reilly, 2007; Rolls, Loh, Deco, & Winterer, 2008). Congruent with

this hypothesis, methylphenidate, a drug that increases catecholamine levels, improved ignoring but impaired updating in healthy young adults (Fallon, van der Schaaf, ter Huurne, & Cools, 2016). Thus, far from affecting all types of irrelevant information equally, the effect of changing the level of D₂ receptor stimulation might vary greatly according to the cognitive provenance of that information, i.e., whether it has to be prevented from entering WM (ignoring) or modified (updated).

Here, we investigate these hypotheses by examining the effect of 2.5mg Haloperidol on **visual** WM in a double-blind, placebo-controlled design. Crucially, unlike many previous studies in young healthy controls, we measured WM recall not in a binary fashion, but in a way where the quality of fidelity of mnemonic representations could be assessed, and the source of this error decomposed (Ma, Husain, & Bays, 2014). In order to characterise the effect of Haloperidol on the quality of recall, we used a task that allowed us to examine three separate factors: effect of varying the retention period, changes in the need to deal with irrelevant information and isolate the potentially separate effects on ignoring and updating, while adjusting for temporal differences in retention period (**Figure 1**). If the above models of dopaminergic modulation of cognitive control are correct, then haloperidol should exert differential effects on these three different components of WM. A recent study in patients with Parkinson's disease (PD), using the same paradigm as in the present study, found that withdrawing medication in PD patients impaired ignoring and updating performance but did not modulate the effect of retention period (Fallon et al, 2017). This suggests that dopamine affects both ignoring and updating. However, it is unclear whether this finding generalises to healthy adults and the pharmacological specificity (receptor mechanisms) remains unspecified.

Finally, we also address the role of two other modifying variables that may be important when assessing the role of haloperidol on WM: individual differences in WM and cognitive control processes that require minimal WM deployment. The effect of manipulating D₂ stimulation levels on WM varies according to individual differences in baseline WM function (Frank & O'Reilly, 2006; Gibbs &

D'Esposito, 2005; Kimberg & D'Esposito, 2003; Kimberg, D'esposito, & Farah, 1997; Wallace, Vytlačil, Nomura, Gibbs, & D'Esposito, 2011), which is often presumed to reflect baseline differences in dopamine synthesis (Cools et al., 2008). Thus, here, we also examined whether the effects of haloperidol on recall varied according to baseline WM functioning. However, in contrast to other studies that have used "span" tasks, baseline recall was measured in the same fashion in which it was to be assessed under drug: memory for orientations. This enables baseline WM to be assessed in a manner that is directly relatable to the task being modified by drug administration.

WM is not the only cognitive control process known to be affected by dopamine; reversal learning, inhibition, response selection, set-shifting have all found to be affected by changing the level of D₂ receptor stimulation (Logemann et al., 2017; Mehta et al., 2004; van Holstein et al., 2011, 2011). These findings raise the possibility that dopamine may affect WM vicariously through influencing general cognitive control mechanisms, i.e., processes that support WM, but do not necessarily involve the manipulation of mental representations. Response conflict – as exemplified in the Simon effect – is a paradigmatic example of a (relatively) WM-free cognitive control process. The Simon effect arises when making motor responses that are incompatible with the sensory layout of the stimuli, e.g., responding right to a stimulus presented on the left. The task can be regarded as WM-free because all the information needed to perform the task is present at the time of the response. Performance of the task has been found to be impaired in low dopamine states (Ramdani et al., 2015; van Wouwe et al., 2016a). However, the effect of D₂ antagonists remains unexplored.

Method

Participants

30 people (16 Male; 14 Female) participated in this study. Demographics are shown in **Table 1**. For the ignore/update WM task, the data from one person was excluded from the following analyses due to having pronounced difficulty remembering orientations on both sessions. Subsequent modelling (see below) revealed that this participant was responding to the target orientation on less than 60% of trials on both drug and placebo sessions. Their exclusion did not affect the significance of any of the results. One participant did not complete the Simon task (see below) on both sessions, thus their data was not included in the analysis.

	N	Mean	Std. Deviation
Age	30	25.0	4.23
Employment Status	30	23 Student, 7 Employed	-
Total Years Education	30	17.4	2.47
Ravens	30	8.0	2.1
ACE	30	96.1	3.0

Design

The study was a within-subject, double-blind, placebo-controlled design. There were two testing sessions. On one of these testing sessions participants took a placebo tablet and on the other they ingested a 2.5mg Haloperidol tablet (the two were indistinguishable). The order of these sessions was counterbalanced. Haloperidol is predominantly a dopamine D₂ receptor antagonist, having a far greater affinity for D₂ compared to D₁ receptors (Arnt & Skarsfeldt, 1998; Zhang & Byrmaster, 1999), and preferentially affects D₂ binding in the striatum after acute administration (Beninger, Baker, Florczyński, & Banasikowski, 2010). Human studies of the cognitive effects of haloperidol have tended

to use doses between 2 – 2.5 mg (Frank and O'Reilly, 2006). We opted to use 2.5mg in order to accentuate the modest effect of 2mg doses observed in a previous study (Frank & O'Reilly, 2006), while also avoid the sedative effects that may be observed at higher doses.

Tasks

Working memory Ignore and Update task

Figure 1 | Ignore/Update WM task.

Across all four conditions, WM recall error was measured by presenting a pair of coloured arrows (2000ms) and, after a variable delay, a coloured probe arrow (one of the encoded pair). The colour of the probe arrow indicated which item needed to be recalled, e.g., if the arrow was magenta then the orientation of the previously encoded magenta arrow needed to be reproduced. This could be done by rotating the arrow clock/counterclockwise until it matched the desired orientation. In the ignore condition (left most panel), participants had to retain their memory for the initially presented orientations whilst ignoring an irrelevant set of arrows presented during the delay period. In contrast, in the update condition (3rd panel from left), participants were presented with the same initial pair of arrows that had to be retained as the ignore condition, but this time the new set of arrows presented during the maintenance period had to be loaded into working memory, completely displacing memory for the previous pair of arrows. Given the temporal disparity in the retention period for ignore and update conditions, two conditions, where no irrelevant information was presented, served as temporal controls for the ignore (maintain T1) and update conditions (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.

Common to all experimental conditions was that the fidelity – or quality – of visual WM recall was assessed using a delayed adjustment task (Wilken & Ma, 2004). The version used here was exactly the same as in a previous study on patients with Parkinson’s disease (Fallon, Mattiesing, Muhammed, Manohar, & Husain, 2017). In all conditions, participants were presented for 2 seconds with two differently coloured arrows (randomly orientated), presented at different spatial locations equidistant from screen centre. At probe, they were shown only one arrow, which had the colour of one of the arrows-to-be-remembered but with a randomly offset orientation. Participants were required to rotate the probe arrow until it matched the probed target orientation.

For example, if a magenta arrow oriented at 45° was presented as one of the two arrows in the memory display, and a magenta arrow was subsequently displayed at probe, participants had to rotate the arrow to match their memory of the orientation of that arrow in the original memory display. After rotating the arrow to its desired orientation, participants had to press the space bar to confirm their response. Subsequently, they were given feedback about their performance – with the true orientation of the target simultaneously presented with their response.

The four experimental conditions varied according to whether irrelevant items were presented and the retention period for which items had to be maintained (Figure 1A). In the Ignore condition, irrelevant distracters were presented during the interval between encoding and probe. In the Update condition, participants were presented with new memoranda during the interval between initial memory display and probe. This time, however, they were required to allow the newly presented information to displace the previously presented items. Thus, in this condition WM representations had to be updated such that previously encoded items now became irrelevant. Given the temporal disparity in the retention periods between the ignore and update conditions (6000ms vs 2000ms), we also included two temporal control conditions. In the Maintain (T1) condition, participants simply had to maintain information for the same time period as in the ignore condition, but no distracters were presented

(enabling this condition to function as the temporal control to the Ignore condition). Finally, there was another Maintain (T2) condition, but this time the maintenance period was matched to that for the items in the update condition (so this is the temporal control for the Update condition).

The conditions were intermixed throughout the experiment. Rather than being explicitly told to ignore or update items, a single instruction served to enable the appropriate performance on all four conditions. Participants were told that they had to remember *only* the last pair of arrows that were presented with the letter “T” displayed at screen centre (**Figure 1A**). This acted as a cue to instruct them that they should only remember the arrows displayed on that screen.

Baseline working memory Task

This study aimed to assess whether baseline individual differences in **visual** WM influence the effect that haloperidol has on WM recall. Here, we measured recall again using a continuous response, delayed adjustment task. In this case, participants had to remember the orientation of just a single arrow presented at screen centre for either 1000ms or 2000ms, after which they were presented with a single arrow probe in the centre, but with a randomly offset orientation. Just as in the main experimental task, they had to rotate the arrow clockwise or anti-clockwise until it matched the orientation of the arrow they had previously seen. Participants completed 96 trials (48 trials for each delay duration) and completed the task twice: once on the haloperidol session and once on the placebo session. To obtain one metric of performance, we averaged mean angular error (see below) across both sessions and delays. Note that this task was performed prior to any likely effects of drug and there was no significant difference due to drug ($t(28) = .673, p = .53$).

Response conflict (Simon) task

On each trial, participants were first presented with a black dot at the center of the computer screen for 1 second. A left-pointing or right-pointing arrow then appeared and they were required to make quick and accurate responses on the keyboard, by pressing the key ('<' or '>') that matches the direction of the arrow stimulus (**Figure 1B**). Crucially, the arrow stimulus could appear on either the left or right side of the screen, giving rise to a congruent or incongruent trial. A congruent trial occurred when the direction of the arrow stimulus matched the spatial location it appeared at (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). The experiment comprised a single block of 50 congruent and 50 incongruent trials presented in a random order. No feedback on accuracy was given and there was no time limit imposed on responding, i.e. the arrow stimulus remained on screen until a response was recorded.

Figure 2 | Baseline working memory and Simon tasks

A) Baseline working memory task. Participants had to remember the orientation of a single arrow and reproduce this arrow after a variable (1000ms or 2000ms) delay. **B)** Response conflict (Simon) task. Participants had to respond indicating whether the arrow was pointing left or right. Trials could be congruent if the arrow was pointing in the same direction as the side of the screen on which it appeared. Alternatively, incongruent trials were when the arrow pointed in a different direction to the side on which it was presented.

Procedure

After providing informed consent, participants were administered the placebo/haloperidol capsules in a double-blind fashion. After this, they completed the baseline WM task (mean start time 11:26 minutes after capsule administration). Participants then completed a saccade control and motor control task (to be reported elsewhere). The Ignore/Update task was then performed (mean start time after tablet: 4 hrs13 mins). Following this, the response selection task was performed (mean start time after tablet: 5 hrs 23 mins).

Analysis

For the ignore/update (and baseline) WM task, the main measure of recall was mean angular error, calculated as the absolute angular difference between orientation of the target (angle at which the item was presented) and the response orientation (angle to which the probed item was rotated). Trials in which participants responded too fast (<400ms) or took too long (>10000ms) were excluded from analysis (<.04% of trials). Data were analysed in SPSS 22.0 (IBM Corp). Repeated measures ANOVA 2 x 2 x 2 was used to examine the effect of the within-subject factors **retention period** (2 vs. 6 second delay) and **presence of irrelevant information** (maintain vs. ignore/update trials) and drug (placebo, haloperidol).

It should be noted that there were differential effects of haloperidol on ignoring and updating to be observed, this would manifest as a significant interaction between retention interval (short and long) vs. presence of irrelevant information (maintain only or irrelevant information present) as a function of drug. Reaction times (time to select and confirm an orientation) were recorded, but were not of theoretical interest (though note, there was also no evidence that drug administration slowed responses; $F < 1$).

For the Simon Task, the effect of drug on accuracy and reaction time data for congruent and incongruent trials were analysed using a repeated measures ANOVA, with drug and congruence as within-subject variables.

Decomposing the sources of error on the WM task

Absolute mean angular error reflects the overall quality of recall, but is potentially a heterogeneous combination of different components. It is often tempting to conclude that reduced recall error reflects a greater fidelity of stored mental representations, but this is not necessarily the case. For example, in addition to the variability with which the probed item is remembered, some error will also result from guesses (chance-level responding). On a 360° response space, these errors will manifest as uniform errors across this space (Ma et al., 2014). Others have also argued that some of the error on these tasks also comes from responses to the encoded, but not probed items (P. M. Bays, Catalao, & Husain, 2009): in other words, when participants reported the orientation of an item that was encoded but not actually asked to be reported. Such errors are referred to as misbinding errors because the participant associated the wrong orientation with the colour of the probed bar.

We adopted two complementary approaches to obtain purer sources of understanding participants' error on the Ignore/Update task. Firstly, a chance-corrected precision level (reciprocal of circular SD – minus chance (uniform responding) across the space was calculated. Secondly, in order to more formally identify the source of participants' error during the WM task, a probabilistic model of response selection was applied to the data (P. M. Bays et al., 2009), using the following equation:

$$p(\hat{\theta}) = \alpha \phi_{\kappa}(\hat{\theta} - \theta) + \sum_{i=1}^m \beta_i \phi_{\kappa}(\hat{\theta} - \varphi_i) + \gamma \frac{1}{2\pi}$$

where $\hat{\theta}$ represents response orientation, $p(\hat{\theta})$ is the probability of the given response orientation, ϕ_κ is a von Mises probability density function that has a concentration κ and is centred on zero, m is the number of incorrect items in the display (in this case 1 or 3, indexed by i), θ is the probed target angle, φ_i are the angles of the incorrect items, and α, β_i, γ are proportions of each component of the response distribution, satisfying $\alpha + \sum \beta_i + \gamma = 1$. This model therefore has three free parameters, α, β, κ . The model was fit using freely available code (P. M. Bays et al., 2009). This allowed us to extract four parameters that relate to specific aspects of recall.

1. **kappa** (or κ) reflects the variability or recall. A higher kappa values indicates that there is less variability around the target orientation (similar to precision) and participants are more accurate.
2. **alpha** (α) Probability of responding to the target orientation. The higher this value, the greater the probability participants were responding to the target orientation.
3. **β (rates of misbinding)** is the probability of producing one of the incorrect (non-probed) orientations. The higher this value, the higher the probability that participants were responding to one of the incorrect items.
4. **The γ (guessing)** parameter reflects the probability that participants' responses were uniform across the entire response space. Intuitively, if participants had no memory for the presented orientations, then looking at the angular error between their responses and the target orientation should produce a 'flat' distribution across the entire response space ($-\pi$ to $+\pi$), i.e., there would be no 'bump' at the target orientation.

The same modelling approach we previously applied for the effect of drug in PD patients (Fallon et al., 2017) was applied to the data (the experiments were identical). Thus, the models were fit separately for each participant and each drug session. Furthermore, in order to have sufficient trials (>50) to obtain reliable parameter estimates for model fitting, we collapsed across trials that required

irrelevant information to be manipulated (ignore and update conditions) and the maintain only (maintain T1 and maintain T2). Note that the purpose of this analysis was to investigate why overall error differed between conditions, by examining sources of error. So, given that only main effects of drug administration were found, we restricted our analysis to examine differences between drug and placebo sessions irrespective of distractor conditions. Thus, for statistical analysis, parameter estimates were averaged across the irrelevant information and maintain only conditions for each subject.

Non-parametric analyses (Wilcoxon signed-rank) were then performed on the data from the drug and placebo sessions. Again, similar to previous study, we used the Akaike Information Criterion (AIC) to evaluate the above model. The model fit for the full model was better (AIC = 1492) compared to the full model without the guessing (γ) parameter (AIC = 2042) and without the misbinding (β) parameter (AIC = 1579).

Results

Haloperidol impairs overall WM recall

First, we examined the effect of haloperidol on recall in terms of absolute mean angular error between the target and the response. This analysis included drug (placebo, haloperidol), delay (short, long) and presence of irrelevant information, in other words ignoring/updating (absent, present). Consistent with the results of previous studies (Fallon, Mattiesing, Dolfen, Manohar, & Husain, 2018), there was a significant main effect of delay on recall ($F(1,28) = 58.10, p < .001$; **Figure 3**), such that error was reduced for short compared to long delays. Having to deal with irrelevant information, regardless of whether this was in the ignore or update condition, also significantly impaired recall ($F(1,29) = 36.82, p < .001$). This effect varied, however, according to whether irrelevant information had to be dealt with in update or ignore contexts ($F(1,28) = 39.89, p < .001$).

Recall error on ignore trials was significantly higher than its temporal control ($t(28) = 7.31, p < .001$), but there was no significant difference between updating and its temporal control ($t(28) = 1.08, p = .29$). Thus, overall the pattern of errors, as shown in previous studies, indicates that recall decreased with longer retention periods and that ignoring, but not updating, exerted a disproportionate decrease in recall.

Figure 3 | Effects of Haloperidol on recall

Mean absolute angular error of the response orientation from the target orientation for 29 participants. Error bars reflect the standard error of the mean.

With regards to the effects of drug, recall error on haloperidol was significantly higher than when on placebo ($F(1,28) = 5.17, p = .031$; **Figure 3**). Importantly, however, haloperidol's effect on recall did not significantly vary according to delay or the presence of irrelevant information ($F(1,29) = 1.73, p = .20$). None of the other effects were significant ($F_s < 1$). In order to guard against the effects of influential

observations, a complementary non-parametric test was conducted on overall recall performance on the drug and placebo conditions. Again, error was significantly higher after haloperidol compared to placebo ($Z = 2.19, p = .028$). In summary, haloperidol significantly impaired the quality of recall across all four conditions, with no condition-specific effects being observed.

Haloperidol increases the level of guessing

In order to uncover the underlying mechanisms behind the above difference in the quality of WM recall we adopted two strategies. Firstly, we calculated the chance-corrected precision for each of the tasks. Secondly, we fitted a probabilistic model of response selection to our data.

Performing the same ANOVA on chance-corrected precision as for the mean angular error revealed that precision was reduced for longer retention period ($F(1,28) = 25.10, p < .001$) and when irrelevant information was present ($F(1,28) = 12.43, p = .001$). The effect of irrelevant information also significantly varied according to whether it was presented in the ignore or update conditions ($F(1,28) = 6.46, p = .017$). However, there was no significant main effect of drug ($F(1,28) = 2.046, p = .164$) and no significant interactions with drug ($F < 1$). These results suggest that subtracting the effect of guesses on responding removes the effect of drug on WM. We formally followed this issue up by fitting a probabilistic model of response selection to the data.

Modelling: To uncover the source of impaired recall on haloperidol a probabilistic model of response selection was fitted to the data. Given that we only found a significant main effect of drug, we restrict ourselves to reporting the effects of drug, i.e. collapsing across condition (**Figure 3**).

Figure 4 | Effect of Haloperidol on modelling parameters.

Haloperidol specifically increased guessing responses without affecting kappa (concentration parameter), frequency of responses to the target (probed) orientation or misbinding. $N = 29$. Error bars reflect the standard error of the mean.

Kappa: The concentration parameter refers to the *distribution* of the responses made with respect to the presented memoranda. A higher kappa indicates a greater concentration of responses around the memoranda and so can be seen as indicative of good recall. Haloperidol did not significantly affect kappa values ($Z = .941, p = .347$).

Target response: The target parameter refers to the likelihood that the responses were centred on the target memoranda. There was no significant effect of haloperidol in influencing the proportion of target responses ($Z = 1.65, p = .098$).

Misbinding: This parameter refers to systematic errors in recall that occur when a participant responds to the non-target item, i.e., they have incorrectly bound the target's colour with a non-target orientation. Haloperidol did not significantly affect misbinding ($Z = .205$, $p = .838$). To confirm that haloperidol did not affect the levels of misbinding (attraction) to the orientation of non-target items we performed an additional model-free analysis on the absolute mean angular distance between the response orientation and the non-target orientation(s). This analysis revealed that there was no significant difference between the mean angular distance between responses and non-target orientations according to drug ($F < 1$).

Guesses: The guessing parameter – the likelihood that the response bears no relationship with any of the memoranda – was significantly increased when participants were taking haloperidol compared to when they were taking placebo ($Z = 2.02$, $p = .043$). Thus, taking the drug increased the likelihood of participants guessing during recall. Given that drug significantly affected guess rates, we performed a supplemental analysis to investigate the relationship between this parameter and our measure of baseline WM. There was no significant correlation between the effect negative haloperidol on guess rates and baseline (mean angular error) WM ($\rho = .20$, $p = .28$). Thus, the precise parameter responsible for generating the relationship between baseline WM and the effect drug had on WM could not be isolated.

In summary, the modelling suggests that the most prominent mechanism through which haloperidol impaired recall was through an increase in guessing. In contrast, there was no evidence that haloperidol affected the precision of mental representations or induced the component features of memoranda to be inappropriately conjoined together, i.e., no increase in misbinding.

Effect of haloperidol depends upon baseline working memory

To examine the modulatory role of baseline WM performance, we included this variable as a mean-centred covariate in our analysis of drug effects on mean angular error. As expected, higher performance on the baseline WM performance was significantly associated with overall better recall on all four conditions of the ignore/update task ($F(1,28) = 62.55, p < .001$). Moreover, baseline WM performance also significantly interacted with the effect of delay period on the WM task ($F(1, 28) = 15.81, p < .001$). This was due to a positive correlation between WM performance and retention period ($r(30) = .60, p < .001$), such that individuals with lower baseline WM performance experienced a greater cost to recall from having to retain information for longer periods of time.

Figure 5 | Relationship between baseline WM performance and effect of haloperidol. There was a significant positive association between baseline WM performance (averaged mean absolute angular error, assessed prior to drug/placebo administration) and the drug cost (Drug minus placebo mean angular error across all four conditions of the ignore/update task). The worse participants performed on the baseline WM task, the more impaired they were on haloperidol

In terms of drug effects, baseline WM performance significantly moderated the extent to which haloperidol impaired performance on all four conditions of the ignore/update task ($F(1,28) = 5.50$, $p = .031$), an effect due to there being a positive association between WM baseline error and the impairing (drug minus placebo) effects of haloperidol ($r(30) = .39$, $p = .031$). Thus, the poorer participants were at baseline WM, the more they were *impaired* after taking haloperidol (**Figure 6**). This effect was selective as baseline WM performance did not significantly interact with the effect of irrelevant information or retention period, or combination of variables (all p 's $> .29$). In summary, baseline WM performance appeared to predict the effect that drug administration had on overall recall, but this effect did not significantly vary according to condition.

Haloperidol impairs response selection during cognitive conflict

Figure 6 | Effect of haloperidol on the Simon task. Accuracy and reaction times on Simon task ($N = 28$). Error bars are SEMs.

Accuracy: As expected, participants had lower accuracy on incongruent compared to congruent trials ($F(1,27) = 24.96, p < .001$). Haloperidol impaired accuracy ($F(1,27) = 5.41, p = .028$). The effect of congruence on accuracy was significantly moderated by drug administration ($F(1,27) = 6.30, p = .018$). This was due to haloperidol significantly *impairing* accuracy for incongruent responses ($t(27) = 2.82, p = .009$), but not congruent responses ($t < 1$).

Reaction time (correct responses only): Participants were slower for incongruent compared to congruent trials ($F(1,27) = 74.13, p < .001$). There was no significant main effect of drug ($F(1,27) = 1.82, p = .18$) and no interaction between drug and congruence ($F < 1$).

Supplemental analyses examined whether the effect of drug on congruency varied according to the congruence of the previous trial. This was not the case either for accuracy or reaction times (three-way interaction between drug, congruence of the current trial and congruence of previous trial was not significant; $F_s < 1$).

Haloperidol's effect on response selection is related to ignoring

Figure 7 | Relationship between effect of haloperidol on ignoring and updating and response selection on Simon task

The effect of haloperidol on ignoring information on the WM task was strongly related to its effect on response selection on the Simon task (indexed by [Haloperidol incongruent] – [Placebo incongruent] accuracy). However, there was no such association for updating WM contents and response selection. ($N = 28$).

To examine the relationship between the effects of haloperidol on WM and response selection (Simon task), we included the effect drug had on response selection (accuracy on Haloperidol incongruent trials minus Placebo incongruent trials) as covariate in our analysis of recall on the ignore/update task. This revealed that there was significant four-way interaction between drug, delay period, presence of irrelevant information and the drug effect on response selection ($F(1,27) = 8.34, p = .008$). Breaking this interaction down into whether response selection affects ignoring (minus its temporal control) or updating (minus its temporal control), revealed that negative effects of drug on response selection and the negative effects of drug on ignoring were positively correlated with each other ($r(28) = .603, p = .001$), i.e., the more that drug impaired response selection in an individual, the more it impaired ignoring in that individual.

Further decomposing this result, there was a significant *negative* relationship between the drug-induced impairment in response selection and ignore (minus temporal control) performance during the haloperidol session ($r(28) = -.545, p = .003$). Whereas, the drug-induced impairment on response selection tended to be positively related on ignore trials performance during the placebo session ($r(28) = .358, p = .062$). Thus, individuals who were more impaired at response selection after taking haloperidol had better ignore performance on the placebo session, but worse performance on ignore in the haloperidol session. In contrast to the strong association between drug's effect on response selection and ignoring, there was no relationship between the drug's effect on response selection and its effect on updating ($r(28) = .097, p = .622$).

It should be noted, however, that there was no significant relationship between an individual's level of response selection (placebo congruent accuracy minus placebo incongruent accuracy) and placebo ignoring (minus temporal control) performance ($r(28) = .131, p = .50$). Therefore, it is not the case that – in the absence of drug – ignoring and response selection performance are coupled within an individual. Thus, haloperidol appears to have induced a significant association between response selection and ignoring. Cumulatively, this finding shows that there was an association between the drug's effect on response selection and its effects on ignoring. The greater the drug impaired response selection, the greater it impaired ignoring on our WM task.

Discussion

This study attempted to decompose the multifaceted ways in which blocking D₂ dopamine receptors can affect WM and served to disentangle some of its direct from indirect effects on mnemonic representations (**Figure 8**). Haloperidol significantly impaired overall quality of **visual** WM recall, irrespective of whether that information had to be ignored, updated or maintained for longer durations

(Figure 3). Application of a probabilistic model of response selection to the data revealed that this effect is likely to have occurred due to an increase in the number of guesses or random responses

(Figure 4). This perhaps indicates that the drug increases the likelihood of attentional lapses or off-task distractibility, i.e., not directly accentuating the impact of within-task presented distracters, but a more generalised form of distractibility or attentional impairment, possibly akin to that found in attention-deficit hyperactivity disorder, a condition with prominent dopaminergic basis (Volkow, Fowler, Wang, Ding, & Gatley, 2002).

The deleterious effects of haloperidol, however, were not uniform across participants. In fact, whether the drug improved or impaired participants' WM recall was found to be significantly associated with their baseline level of WM performance. The worse a participant's performance at baseline, the worse their recall after taking haloperidol **(Figure 5)**. Consistent with other findings on the role dopamine in WM-free cognitive control process (Cropley, Fujita, Innis, & Nathan, 2006; Nieoullon, 2002; van Schouwenburg, Aarts, & Cools, 2010), the ability to exert top-down control on the Simon task was impaired by drug administration, as haloperidol selectively impaired the ability to inhibit a prepotent response on incongruent trials **(Figure 6)**. Crucial for understanding the interconnected and overlapping neurocognitive architecture supporting WM and response conflict, common effects of haloperidol were found on these two functions **(Figure 7)**. The effect of drug on response conflict was related to the effect the drug had on a specific WM subcomponent (ignore irrelevant distracters). Thus, specific components of WM (ignoring) can be associated with changes in WM-free cognitive control processes that enable individuals to overcome response conflict.

Figure 8 | Overview of results.

Haloperidol was found to have detrimental effects on both WM recall (putatively due to increase attentional lapses or off-task distractibility) and on the ability to overcome response conflict (Simon effect). The negative effect of haloperidol on response conflict was found to be related to a specific sub-component of WM – the ability to ignore irrelevant information. It is suggested that this relationship reflects a common role of D_2 receptors in being able to appropriately select the information that is used to guide responding. A seemingly parallel strand of the findings was that the positive or negative effects of Haloperidol on WM recall appeared to be influenced by baseline-absence of drug – WM ability. High baseline WM participants had improved WM after haloperidol, whereas low baseline participants were impaired.

Decomposing the effects of Dopamine on WM

For decades, dopamine has been intimately associated with WM (Brozoski et al., 1979; Ott & Nieder, 2017; Puig & Miller, 2015; Vijayraghavan et al., 2007; Zahrt, Taylor, Mathew, & Arnsten, 1997). However, parsing the exact cognitive effects of D_2 stimulation has proved problematic. There are many possible reasons why recall can go awry (Ma et al., 2014), but the diverse ways in which WM can break down might have been obscured by the means with which memory has been probed. Traditional measures have usually required participants to make binary judgements (match or non-match) on

whether the presented sample stimuli matches the memoranda. Thus, memory for items is implicitly assumed to exist in an all-or-none format.

Newer methodologies have gauged the quality of mnemonic representations by asking participants to reproduce the exact features of a remembered item, e.g., orientation (Paul M. Bays & Husain, 2008). As well as providing enhanced sensitivity, these measures have allowed researchers to infer the structure of mental representations from the pattern of responding by applying computational models of memory (P. M. Bays et al., 2009). Here, by applying such a model, we were able to uncover that haloperidol appeared to impair WM through increasing the level of guess responses (**Figure 4**). Increases in guesses occur when the participant's response bears no relationship to any of the presented items. Thus, they occur when there is a complete lack of any mnemonic representations that should normally guide responding and suggest that these representations have either not formed or been quickly ablated. As such, they may likely result from an increase in off-task distractibility or attentional lapses that may either have occurred at encoding or maintenance (Adam & Vogel, 2017; Unsworth & Robison, 2016).

This conclusion accords well with previous studies that have provided indirect evidence for this claim by demonstrating that guess responses are increased in Parkinson's disease, a disorder associated with dopaminergic abnormalities (Fallon et al., 2017; Zokaei et al., 2014). Therefore, the main effect of haloperidol may have been to increase overall, task-independent distractibility, or forgetfulness, without specifically affecting distracter resistance. Moreover, this increase in forgetfulness after haloperidol was not associated with increased levels of misbinding, i.e., the drug did not increase the likelihood that participants would erroneously report the orientation of a non-probed item as the correct item. Again, this is consistent with previous work showing that administration of the D₂ agonist cabergoline (Fallon, Zokaei, et al., 2016) or Parkinson's disease (Fallon et al., 2017; Zokaei et al., 2014)

does not affect the level of misbinding. Thus, it is not the case that dopaminergic leads to an increase in irrelevant information displacing relevant information.

With regard to the mechanisms responsible for generating this increase in forgetfulness, although most research has focused on the processing of externally presented stimuli, there is a growing understanding on the role of self-generated, or off-task, thoughts in influencing the efficacy – either positively or negatively – of cognitive control (Smallwood and Schooler, 2015). Consistent with the concept that haloperidol can increase general distractibility independently of distracter resistance, the effects of externally presented distracting stimuli may be distinct from distraction induced by off-task, internal distraction (Smallwood & Schooler, 2015). Moreover, a physiological mechanism through which haloperidol may exert such an effect is via modulation of the default mode network (Raichle et al., 2001), which has been found to be engaged during off-task (mindwandering) and can be modulated by dopaminergic compounds (Cole et al., 2012, 2013). Indeed, administration of haloperidol can increase the connectivity between midbrain regions and components of the default mode network (Cole et al., 2012), suggesting a point of leverage between dopamine and off-task distractibility. Thus, the change in connectivity in these regions in response to haloperidol may be a candidate mechanism for the increased distractibility (as indexed by overall guessing) during WM.

The possibility that dopaminergic alterations can induce endogenously-driven distraction is also in agreement with the presumed role dopamine has in promoting ADHD symptomatology (del Campo, Chamberlain, Sahakian, & Robbins, 2011; Volkow et al., 2002) and with a specific role for D₂ receptor availability in influencing how these deficits respond to neurostimulants (del Campo et al., 2013).

Dopamine alters the effect irrelevant information has on cognitive control

Parsing the cognitive effects of the D₂ modulation is complex. A key question about its biological functions concerns whether it has an equal role controlling the influence of irrelevant information on the quality of mental representations and the output of those mental representations (actions). The aim of this study was to provide some clarity on this issue by examining the common effects dopamine had on controlling the influence of irrelevant information (ignore and updating) on mnemonic representations and responding, even when there was no need to maintain such representations (Simon Task).

Haloperidol (2.5mg) has recently been found to increase the Stop-Signal Reaction Time (SSRT), a measure of the time needed to inhibit an action (Logemann et al., 2017) and the availability of D₂ receptors in the dorsal striatum is negatively related to SSRT (SSRT), indicating that higher levels of D₂ receptors lead to better inhibitory functions (Ghahremani et al., 2012). Less evidence exists for the dopaminergic modulation of the Simon effect, yet manipulations that decrease dopamine have been found to decrease the Simon effect. For example, depleting the levels of dopamine precursors or withdrawing patients with Parkinson's disease from their medication lead to strengthen the Simon effect (Ramdani et al., 2015; van Wouwe et al., 2016b). Here, we illustrate the role of the D₂ receptors in resolving response conflict. Haloperidol impaired the accuracy on incongruent, but not congruent trial on the Simon task, without affecting response latencies (**Figure 6**). Thus, haloperidol only appeared to affect the accuracy of responding when there was a need to overcome irrelevant information (the spatial location of the cue). Therefore, blocking the actions D₂ receptors seems to impair the ability to exert top-down control and suppress prepotent responses that arise in conflict situations and select the appropriate mental representation to guide responding.

The effect of haloperidol on suppressing irrelevant mnemonic representations was more complicated and indirect. Haloperidol did not significantly affect the efficacy of dealing with irrelevant information, either retroactively in the case of updating or proactively in the case of ignoring. Thus, there is little

evidence to suggest that antagonism of D₂ receptors have the pervasive effect on gating the flow information into WM as is commonly assumed (Durstewitz & Seamans, 2008; Hazy et al., 2007). There was also no evidence for individual differences in baseline WM function modulating this effect. Despite a strong association between D₂ receptor modulation and the ability to filter out distracters (Bloemendaal et al., 2015; Cools et al., 2007; Frank & O'Reilly, 2006), the mechanisms behind this association have not been articulated and the role of WM-free cognitive control processes in influencing this function have not been quantified.

Here, the specific effect of haloperidol on ignoring was found to be associated with drug's effect on response inhibition (incongruent responses on the Simon task). On the incongruent trials in the Simon task there are minimal requirements on WM: all of the information that participants need to perform the task are presented on the screen. Thus, the generation of errors in these trials is unlikely to be mnemonic, but rather occurs due to a failure to select relevant (direction of cue) from the irrelevant (location of the cue). The association between ignoring and response inhibition suggests that D₂ receptors, and by extension specific circuits within the frontostriatal systems that are modified by the activity of this receptor, do not affect the impact of distracters on the quality of WM representations after distraction, but only affect a subcomponent – the need to inhibit or exert control over competing representations in order to guide responding. This suggests that antagonism of D₂ receptors can selectively affect the proficiency of ignoring by impairing the relatively WM-free ability to select the appropriate mental representation to guide responding (**Figure 8**).

It could be expected that if this mechanism was responsible for coupling ignoring and overcoming response conflict, then updating should be similarly affected, as irrelevant information is also presented. However, recently, using a similar WM task, we found that the irrelevant – initially presented – information in the update condition is almost entirely purged from WM, i.e., there is very little evidence to suggest that the to-be-removed information in the update condition lingers to corrupt

WM representations (Fallon et al, 2018). This suggests that the selection process at retrieval may be fundamentally different in the ignore and update conditions.

Importantly, there was no association between the proficiency of responding to incongruent trials and ignore trials at baseline (placebo). Thus, there was not a general relationship between incongruent responding and ignoring. Rather, such a relationship materialised only when haloperidol was administered. Cumulatively, therefore, this study has distilled the various ways that dopamine can affect the efficacy of ignoring and found that it is likely that dopamine affects ignoring through its common effects on response selection.

Individual differences predict the effect of haloperidol on WM

It has been well established that individual differences in brain chemistry can modulate the cognitive effects of pharmacological substances (Cools et al., 2009; Kasparbauer et al., 2015; Mattay et al., 2003; Spronk et al., 2016). Many studies have found that baseline performance on various WM tasks or measures can determine whether drugs have positive or negative affects (Kimberg & D'Esposito, 2003; Kimberg et al., 1997; van der Schaaf, Fallon, ter Huurne, Buitelaar, & Cools, 2013; van Holstein et al., 2011), an effect often attributed to the reported association between WM and dopamine levels (Cools et al., 2008). Several investigators have interpreted these individual differences within the framework that there is an inverted-U shape function linking the level of dopaminergic stimulation to cognitive performance (Williams & Goldman-Rakic, 1995). Under this conceptual framework, individuals with low baseline WM (dopamine levels) are likely to be improved by increased dopamine levels, whereas individuals with high baseline WM (dopamine) levels will be impaired by the same medication. This was not observed in our study.

Similar to Kimberg and D'esposito, 2003, drug administration appeared to exacerbate the differences that were present at baseline – poor performers got worse, whereas good performers got better after haloperidol (**Figure 5**). Moreover, task-specific effects of drug were not observed. These apparent inconsistencies may be due to the effects of D₂ receptor antagonism (where the effects may be pre- or post- synaptic for different individuals) or perhaps reflect a deeper non-linear relationship between the ratio of D₂ to D₁ receptor stimulation and behaviour that may be task or domain-specific. In any case, this finding underlies the importance of assessing baseline performance of participants prior to drug administration.

Alternative explanations

One hypothesis for some of the results in this manuscript is that haloperidol, via modifying dopamine levels, affected the willingness - or ability - of participants to perform effortful tasks. For example, one of the reasons why the drug impaired performance on incongruent trials, but not congruent trials, on the response selection task is that the former is more effortful than the latter. However, this hypothesis does not explain other aspects of the present results. Haloperidol was found to impair performance across all four conditions (ignore, update and two maintenance) of a working memory task, despite performance, and hence putative effort, being different across these four tasks. Other work, using the same experimental paradigm in patients tested on and off their dopaminergic medication, also found no evidence to suggest that dopamine affects tasks according to their putative effort level (Fallon et al, 2017). Thus, there is little evidence to suggest that the present results are due to the different effort levels required for each of the respective tasks.

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