Effects of aripiprazole and haloperidol on neural activation during the n-back in healthy individuals: A functional MRI study

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ABSTRACT

Objective: Antipsychotic drugs target neurotransmitter systems that play key roles in working memory. Therefore, they may be expected to modulate this cognitive function via their actions at receptors for these neurotransmitters. However, the precise effects of antipsychotic drugs on working memory function remain unclear. Most studies have been carried out in clinical populations, making it difficult to disentangle pharmacological effects from pathology-related brain activation. In this study, we aim to investigate the effects of two antipsychotic compounds on brain activation during working memory in healthy individuals. This would allow elucidation of the effects of current antipsychotic treatments on brain function, independently of either previous antipsychotic use or disease-related pathology.

Methods: We carried out a fully counterbalanced, randomised within-subject, double-blinded and placebo-controlled, cross-over study of the effects of two antipsychotic drugs on working memory function in 17 healthy individuals, using the n-back task. Participants completed the functional MRI task on three separate occasions (in randomised order): following placebo, haloperidol, and aripiprazole. For each condition, working memory ability was investigated, and maps of neural activation were entered into a random effects general linear regression model to investigate main working memory function and linear load. Voxel-wise and region of interest analyses were conducted to attain regions of altered brain activation for each intervention.

Results: Aripiprazole did not lead to any changes in neural activation compared with placebo. However, reaction time to a correct response was significantly increased following aripiprazole compared to both placebo ($p = 0.046$) and haloperidol ($p = 0.02$). In contrast, compared to placebo, haloperidol dampened activation in parietal (BA 7/40; left: FWE-corr. $p = 0.005$; FWE-corr. right: $p = 0.007$) and frontal (including prefrontal; BA 9/44/46; left: FWE-corr. $p = 0.009$; right: FWE-corr. $p = 0.014$) cortices and the left putamen (FWE-corr. $p = 0.004$). Compared with aripiprazole, haloperidol dampened activation in parietal cortex (BA7/40; left: FWE-corr. $p = 0.034$; right: FWE-corr. $p = 0.045$) and the left putamen (FWE-corr. $p = 0.015$). Haloperidol had no effect on working memory performance compared with placebo.

Conclusion: Cognitive functions are known to be impaired in schizophrenia and as such are an important target of treatments. Elucidating the mechanisms by which antipsychotic medications alter brain activation underlying cognition is essential to advance pharmacological treatment of this disorder. Studies in healthy individuals can help elucidate some of these mechanisms, whilst limiting the confounding effect of the underlying disease-related pathology. Our study provides evidence for immediate and differential effects of single-dose haloperidol and aripiprazole on brain activation during working memory in healthy individuals. We propose that these differences likely reflect their different receptor affinity profiles, although the precise mechanisms underlying these differences remain unclear.

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1. Introduction

Working memory is the process of temporarily holding in mind and manipulating multiple pieces of information for use in complex cognitive processes, such as learning and reasoning. Performance on this cognitive process is associated with activity of dopaminergic and serotoninergic systems (Williams and Goldman-Rakic, 1993; Jakab and Goldman-Rakic, 1998). Indeed, a poorer working memory performance has been associated with alterations of synaptic dopaminergic transmission in the dorsolateral prefrontal cortex (dlPFC) in individuals with schizophrenia (Abi-Dargham et al., 2002). Since these neurotransmitter systems are known primary targets of antipsychotic drugs, the pharmacological treatment of choice for schizophrenia, it is important to establish if and how these drugs affect working memory performance.

First generation antipsychotics (FGAs, such as haloperidol) are highly selective dopamine D2 receptors antagonists, with lower affinity for other receptors, such as serotonin (5-HT) receptors (Meltzer et al., 1989). Conversely, second generation antipsychotics (SGAs, such as risperidone) show a much broader profile, with affinity for both D2 and 5HT receptors. Among newer antipsychotics, aripiprazole is a partial D2 receptor agonist, in contrast to all other antipsychotics, which are full antagonists (blockers) of dopamine receptors. Aripiprazole is also a partial agonist of 5-HT$_{1A}$ receptors (Jordan et al., 2002), and similarly to haloperidol, has lower affinity for the 5-HT$_{2A}$ than for the D2 receptor. This different pharmacological profile has caused some to term aripiprazole a *third generation* antipsychotic (Keltner and Johnson, 2002).

Mounting evidence supports the assertion that antipsychotic drugs affect both brain structure and function, including working memory-related neural activation (Dazzan et al., 2005; Navari and Dazzan, 2009; Handley et al., 2013; Goozée et al., 2014). Furthermore, there may be different alterations depending on whether a FGA or SGA are administered. SGA administration appears to be related to increased activation in fronto-temporal areas, PFC, and posterior parietal cortex (Honey et al., 1999; Meisenzahl et al., 2006; Wolf et al., 2007; Ettinger et al., 2011). In contrast, decreased activation in the lateral PFC (at higher cognitive loads) has been reported for patients treated with an FGA compared to healthy controls (Ettinger et al., 2011). Only one study has failed to show a change in activation when patients were switched from FGA to SGA treatment for two weeks (Schlagenhauf et al., 2008). However, in this sample, the cross-sectional comparisons between healthy individuals and patients on olanzapine treatment showed lower BOLD response in the dlPFC of the patients, which was not evident when patients were initially treated with haloperidol. These studies suggest that different antipsychotic medications likely have differential effects on working memory-related brain activity, although further research is required to elucidate the mechanisms underlying these changes.

Studying the effects of antipsychotic administration on neural activation during working memory performance in individuals without psychosis provides an opportunity to investigate their effects independently from any underlying pathophysiological process and from symptom changes that may occur following treatment. However, to our knowledge only two studies have investigated antipsychotic effects on working memory function in healthy individuals, and each used only a single antipsychotic drug. One study explored activation following a single dose of the dopamine D2 receptor antagonist sulpiride (400 mg) in 20 healthy participants (Dodds et al., 2009). Here, neural activation following sulpiride did not differ compared with placebo nor did it correlate with performance. The only study conducted with aripiprazole, used positron emission tomography (PET) in 15 healthy males (Kim et al., 2013). This study found that aripiprazole significantly reduced frontal metabolism and the reduction was associated with longer reaction times during a working memory task.

It therefore remains unclear whether the effects of antipsychotics on working memory function result from an interaction with the pathophysiology of schizophrenia, and whether these effects may differ between D2 antagonists or partial agonists.

The current study is the first to explore the differential effects of a single dose of two different antipsychotic compounds on working memory, and their related neural activation, in healthy individuals using a double-blinded, placebo-controlled, cross-over design. We investigated working memory function after administration of haloperidol (a D2 antagonist) and aripiprazole (a D2 partial agonist) to the same healthy individuals. We further explored whether changes induced by either antipsychotic in any region of the working memory network were driven by antipsychotic-induced changes in the putamen, using a post-hoc psychophysical interaction (PPI) connectivity analysis. The putamen seed region was chosen as a known site of antipsychotic action, in particular for compounds with high affinity for D2 receptors, due to the high density of such receptors in this region. In addition to imaging parameters, reaction times and error rates were measured during the task as an assessment of working memory performance.

We predicted that a) both haloperidol and aripiprazole would reduce activation, particularly in regions of the PFC, when compared with placebo; but b) the reduction would be greater for haloperidol.

2. Materials and methods

2.1. Participants

Seventeen healthy, right-handed, English-speaking, Caucasian males, aged 18 to 33 (mean 23.0 years, SD 4.81) with mean IQ of 118.65 (SD 6.39), meeting safety and eligibility criteria for fMRI were recruited. All were non-smoking university students with no recent or current drug use (illicit or prescribed), no history of personal or familial psychiatric diagnosis, and no previous exposure to psychotropic medication.

This study was approved by the local Human Research Ethics Committee, and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants following full explanation of experimental procedures.

2.2. Procedures

2.2.1. Antipsychotic administration

Subjects received a single dose of haloperidol (3 mg), aripiprazole (10 mg), and placebo, administered in identical capsules across three visits. A fully counterbalanced, randomised within-subject, double blinded crossover design was used, ensuring that neither participant nor researcher knew which intervention was administered at each visit. A minimum of 14 days drug washout was ensured between visits, and no alcohol or medications were used for 24 h or caffeine for 6 h prior to scanning.

Three hours after drug administration, clinical side effects were measured using the Barnes Akathisia Scale (Barnes, 1989), the Simpson–Angus Scale (Simpson and Angus, 1970), and the Abnormal Involuntary Movement Scale (Guy, 1976). There were no significant differences across interventions in extra-pyramidal side effects ($F_{(1,16)} = 0.136$, n.s), tardive dyskinesia (no participants reported any symptoms), akathisia (no participants reported any symptoms), or systolic ($F_{(1,8)} = 0.378$, n.s.) and diastolic ($F_{(1,8)} = 0.202$, n.s.) blood pressure.

2.2.2. Working memory task

Participants completed a visual working memory task (n-back) as part of a battery of cognitive tests. The time of task presentation was counterbalanced to occur between 3.4 min and 5.0 h post-intervention. Task duration was 6.42 min, with numbers presented visually every 2 s. Joystick movement indicated when a number was presented that had been displayed 1 (1-back) or 2 (2-back) turns previously (according to instructions at the beginning of each block). 1- and 2-back conditions were presented 3 times, interleaved by a total of 6

control condition blocks, in which participants moved the joystick in response to the letter X (0-back). Fourteen letters, including up to three target stimuli, were presented in every block of 28 s. Working memory performance was measured by recording reaction time to correct response (RTC) and errors during the task.

2.2.3. BOLD acquisition

Neural correlates of the task were acquired using echo planar images (EPI) depicting blood oxygen level dependent (BOLD) contrast, in a General Electric Signa HDX 1.5 Tesla scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry. Twenty-nine ascending, interleaved axial slices (3 mm thick, 0.3 mm inter-slice gap) were acquired parallel to the intercommissural (AC-PC) plane during each session, with a repetition and echo time of 2 and 40 s, respectively. A high spatial resolution EPI image was also acquired for co-registration and normalisation of BOLD images.

2.2.4. Data analysis

2.2.4.1. Behavioural analysis. Behavioural data were analysed with the Statistical Package for Social Sciences, Version 15.0 (SPSS Inc.). Due to the greater number of control relative to 1- and 2-back blocks, proportion correct score (PC; number correct / total target trials) were analysed using Wilcoxon signed ranked test and chi-square to allow task difficulty to be investigated. Reaction times to correct (RTC) for all drugs and cognitive loads were analysed using a repeated measures 2-way ANOVA for main effects. Where significant main effects were found, two-way ANOVAs were used to compare each drug pair.

2.2.4.2. BOLD image analysis. All image analysis procedures were carried out using the Statistical Parametric Mapping suite (SPM, version 5-1782) developed by the Functional Imaging Laboratory, University College London (www.fil.ion.ucl.ac.uk/spm).

All images were first reoriented to the AC-PC line (using http://imaging.mrc-cbu.cam.ac.uk/imaging/FindingCommissures for guidance) before realignment. Within-subject registration was conducted using a two-pass, 6-parameter rigid body spatial transformation, in which images were first realigned to each other, then to the mean time series image and movement parameters extracted. The best quality high resolution EPI scan (selected from one of three sessions) for each participant was warped (normalised) to the standard EPI template in SPM5 (conforms to the ICBM NIH p-20 project) (Evans et al., 1993) to generate normalisation parameters to provide the optimal match between the standard template space, the high resolution image for each participant, and subsequently the EPI time series. Finally, images were smoothed with a 10 mm Gaussian kernel filter.

First level analysis of subject-specific fMRI data identified activation patterns for each subject representing main working memory (MWM), i.e. 1-back and 2-back compared with 0-back. Subsequently, maps containing activation exclusive to MWM function were entered into a random effects general linear regression model to explore group effects. Linear load was analysed by identifying activation patterns for each subject due to increasing task load from 0 to 2. Subsequently, maps containing activation exclusive to linear load were entered into a random effects general linear regression model to explore group effects. We investigated neural correlates of the functional task and task × intervention effects using a series of *T* tests.

Initially, a voxel-wise search was conducted at $p < 0.005$ (uncorrected for multiple comparisons) to identify regions of altered brain activation for each intervention. For regions identified, supra-threshold cluster-level statistics were accepted at $p < 0.05$, corrected for multiple comparisons across the whole brain.

Following this initial brain-wide search, a region of interest (ROI) approach was implemented by conducting small volume corrections of independent, a priori defined regions. These were anatomically defined, using the anatomical automatic labelling (AAL) toolbox extension

in SPM5 (Tzourio-Mazoyer et al., 2002). These corrections were applied to each contrast bilaterally and voxel-level statistics were accepted at $p < 0.05$, corrected for family-wise error (FWE). Selection of the a priori regions for small volume correction was based on regions known to be affected by haloperidol and aripiprazole (Lui et al., 2010; Handley et al., 2013), in addition to previously reported task-related regional activation identified in the literature (Owen et al., 2005). Therefore, regions of interest explored included inferior parietal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, putamen, and frontal pole. The putamen was also used as a region of interest due to the known effects of antipsychotic drugs at these locations.

All MNI co-ordinates were labelled using a combination of the Talairach and Tornaux atlas (Talairach and Tournoux, 1988), the fslview MNI structural atlas (Mazziotta et al., 2001), and the Brodmann template (Brodmann.nii) within MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron/main.html).

2.2.4.3. Post-hoc PPI analysis. A post-hoc psychophysical interaction (PPI) analysis was implemented in SPM-5 to assess whether modulation of activity in the putamen by haloperidol was driving altered activity elsewhere in the working memory network. PPI analyses investigate whether a given source or seed region is correlated with activity in other brain regions, as a function of a task-specific factor. The bilateral putamen was used as a seed region, to assess the effect of this region on activity in the rest of the brain over the task.

3. Results

3.1. Behavioural data of working memory task performance

Working memory task performance data are shown in Table 1.

There was no effect of drug intervention on the proportion of correct scores (PC; number correct / total target trials) at any cognitive load. There was an effect of load on PC for placebo only (χ^2 (2, $n = 19$) = 15.0, $p = 0.001$), with PC decreasing as cognitive load increased. There was no significant effect of cognitive load on PC for aripiprazole or haloperidol.

When we explored reaction times to correct response (RTC), we found that there was no main effect of cognitive load on RTC and no drug × load interaction. However, there was a main effect of drug on RTC ($F_{(2,28)}$ = 5.63, $p = 0.009$), suggesting an effect of antipsychotic drug on task performance. There was no significant main effect of drug or cognitive load, and no drug × load interaction, when haloperidol and placebo were compared.

When aripiprazole was compared with placebo, there was a significant main effect of drug on RTC in the aripiprazole condition ($F_{(1,16)}$ = 4.68, $p = 0.046$), such that RTC was longer following aripiprazole than placebo. There was no main effect of cognitive load on RTC and no drug × load interaction.

When the two antipsychotic medications were compared directly, there was a significant main effect of drug on RTC ($F_{(1,14)}$ = 6.67, $p = 0.02$), such that RTC was longer following aripiprazole than haloperidol. There was no main effect of load and no drug × load interaction.

In summary, aripiprazole did not affect accuracy but did lead to increased reaction times to correct response (RTC) compared to placebo and haloperidol. Haloperidol affected neither the accuracy nor the RTC of participants performing the n-back.

3.2. Effect of main working memory (MWM) on neural activation

Regions activated in the main working memory contrast are reported in Table 2.

In the placebo condition, large clusters of activation were observed in bilateral medial and inferior parietal cortex and left premotor cortex. Smaller regions of activation were observed in right ventrolateral PFC and the frontal pole.

Table 1
Working memory task performance; RTC = reaction time to correct response; PC = proportion of correct scores.

	Placebo mean (SD)			Haloperidol mean (SD)			Aripiprazole mean (SD)		
	0-back	1-back	2-back	0-back	1-back	2-back	0-back	1-back	2-back
PC	0.997 (0.014)	0.961 (0.083)	0.897 (0.138)	0.9967 (0.015)	0.957 (0.096)	0.920 (0.139)	0.958 (0.090)	0.855 (0.188)	0.869 (0.243)
RTC	515.0 (73.9)	546.9 (72.5)	602.0 (136.8)	505.4 (55.9)	546.4 (101.7)	574.5 (111.0)	586.2 (77.9)	617.3 (146.9)	619.8 (142.2)

Similarly, aripiprazole activated fronto-parietal regions overlapping with the regions reported above, and including bilateral inferior parietal cortex, right lateral premotor cortex, and bilateral dorsolateral PFC. There was also a small cluster of activation in the left dorsal cingulate. Haloperidol activated the bilateral posterior parietal cortex, bilateral premotor cortex, and dorsolateral PFC. Like aripiprazole, there was also activation in the left dorsal cingulate.

In summary, main working memory (MWM; i.e. regions activated by the n-back task in each drug condition) activated an extensive fronto-parietal network across all conditions (placebo, haloperidol, aripiprazole) (see Table 2). All clusters had an uncorrected threshold of $p < 0.005$, with an extent of at least 10 voxels. This network overlaps with what reported in working memory studies elsewhere in the literature (Owen et al., 2005).

3.2.1. Differential effects of antipsychotic medication on MWM

Brain activation during working memory performance was compared across each drug condition and small volume corrections were applied to identify regions of differential activation (Table 3).

Table 2
Main working memory activation: regions activated by the n-back task in each drug condition. Linear load working memory activation: regions activated by an increase in cognitive load in each drug condition. Coordinates refer to peak activation. All P values presented are corrected for multiple comparisons.

Brain region	Intervention	Cluster size	x	y	z	t	P value
Main working memory							
Medial and inferior parietal cortex							
Left	Placebo	3143	−28		46	8.93	<0.000
	Aripiprazole	2337	−28		44	8.08	<0.000
	Haloperidol	1236	−16		54	6.76	<0.000
Right	Placebo	3612	30		38	8.85	<0.000
	Aripiprazole	2744	30		40	7.82	<0.000
	Haloperidol	1356	24		52	6.65	<0.000
Premotor cortex							
Left	Placebo	5572	2	12	52	7.57	<0.000
	Haloperidol	359	−24	−2	56	6.28	0.001
Right	Aripiprazole	528	24	2	58	6.89	<0.000
	Haloperidol	520	28	2	68	6.60	<0.000
Right ventrolateral prefrontal cortex	Placebo	121	42	18	6	5.75	<0.000
Frontal pole	Placebo	78	−42	52	4	4.82	<0.000
Left dorsal cingulate							
	Aripiprazole	289	−2	10	54	6.21	0.001
	Haloperidol	324	−2	10	54	6.54	0.000
Dorsolateral prefrontal cortex							
Left	Aripiprazole	1867	−44	2	32	7.43	<0.000
	Haloperidol	151	−46	2	26	5.87	0.002
		54	−42	0	36	5.08	0.021
Right	Aripiprazole	532	42	34	26	6.57	<0.000
		180	40	8	32	5.48	<0.000
	Haloperidol	147	44	34	28	5.62	0.004
Linear load							
Medial and inferior parietal cortex							
Left	Placebo	9622	−28	−60	46	10.16	<0.000
	Haloperidol	2171	−14	−72	56	7.77	<0.000
	Aripiprazole	2520	−30	−58	44	7.86	<0.000
Right	Haloperidol	2520	28	−60	40	7.67	<0.000
	Aripiprazole	2601	32	−52	40	7.43	<0.000
Premotor cortex (lateral/medial)							
Left	Placebo	8619	−24	−2	56	8.85	<0.000
	Haloperidol	2127	−24	−2	56	7.10	<0.000
Right	Aripiprazole	370	26	2	56	5.83	0.002
Ventrolateral prefrontal cortex							
Right	Placebo	278	36	22	2	5.70	0.003
Frontal pole							
Left	Placebo	52	−40	54	4	5.21	0.013
Right	Haloperidol	14	36	54	24	5.00	0.024
Dorsolateral prefrontal cortex							
Left	Haloperidol	404	−46	24	32	6.75	<0.000
Right	Aripiprazole	469	−44	2	36	6.26	0.001
	Haloperidol	2466	−40	22	26	7.97	<0.000
	Aripiprazole	432	44	32	28	5.66	0.003
		131	44	32	28	5.32	0.009
		37	40	10	32	4.92	0.029

Table 3
Activation in regions of interest (defined a priori) following small volume corrections. Main working memory activation: differences in regions activated by the n-back task in different drug conditions. Linear load: differences in regions activated by increased cognitive load in different drug conditions, main effects and differential effects of antipsychotic medications. Coordinates refer to peak activation. All *P* values presented are corrected for multiple comparisons.

Brain region	Cluster size	*x*	*y*	*z*	*t*	*P* value
Main working memory						
Haloperidol < placebo						
Inferior parietal cortex						
Left	546	−58	−52	28	3.80	0.005
Right	1886	58	−54	38	3.65	0.007
Ventrolateral prefrontal cortex						
Left	341	−44	16	22	3.53	0.009
Right	50	40	18	8	3.35	0.014
Left thalamus/putamen	514	−4	−24	14	3.60	0.004
Haloperidol < aripiprazole						
Left putamen	56	−28	8	14	3.03	0.015
Inferior parietal cortex						
Left	31	−60	−52	28	2.96	0.034
Right	15	42	−64	36	2.83	0.045
Linear load						
Haloperidol < placebo						
Inferior parietal cortex						
Left	252	−12	−80	38	3.32	0.014
Right	1106	20	−56	36	3.51	0.009
Ventrolateral prefrontal cortex						
Left	38	−56	8	14	3.09	0.023
Right	44	38	18	4	3.06	0.025
Right dorsolateral prefrontal cortex	50	36	44	36	3.15	0.021
Haloperidol < aripiprazole						
Putamen						
Left	137	−26	6	16	3.31	0.007
Right	24	24	2	14	2.81	0.023
Right inferior parietal cortex	21	36	−32	28	2.98	0.030

Compared with placebo, haloperidol induced lower activation in bilateral inferior parietal cortex, bilateral ventrolateral PFC, and left thalamus/putamen. Compared to aripiprazole, haloperidol also induced lower activation in left thalamus/putamen and bilateral inferior parietal cortex (Fig. 1.). There were no regions of increased activation in the haloperidol condition compared to aripiprazole.

In summary, when we compared activation following aripiprazole with activation following placebo, we found no significant differences (increases or decreases) in activation in any brain region. However, haloperidol had an effect on neural activation during working memory performance compared to both placebo and aripiprazole.

3.3. Effects of linear load on neural activation

Table 2 shows regions of activation for the main effect of linear load (i.e. regions activated by an increase in cognitive load in each drug condition).

Linear load activation in the placebo condition was seen in left medial and inferior parietal cortex, left premotor cortex, right ventrolateral PFC, and right frontal pole.

Linear load in both drug conditions activated similar regions. Under aripiprazole, there was activation under increased cognitive load in bilateral medial/inferior parietal cortex and right premotor cortex. A large cluster of activation was seen in bilateral dorsolateral PFC. Similarly, under haloperidol, linear load activation was seen in left inferior parietal cortex, extending into left premotor. Further activation was seen in right inferior parietal cortex, and dorsolateral PFC. There was also a small cluster of activation in the right frontal pole.

In summary, similar regions implicated elsewhere in the literature during increased cognitive load were activated across all conditions in our study.

3.3.1. Differential effects of antipsychotic medication on linear load
Differential effects of antipsychotic medications are reported in Table 3.

Following the administration of haloperidol, there was lower activation than following placebo in bilateral inferior parietal cortex, bilateral ventrolateral PFC, and right dorsolateral PFC. Lower activation following haloperidol than after aripiprazole was seen in bilateral putamen, and right inferior parietal cortex. There were no regions of increased activation in the haloperidol condition.
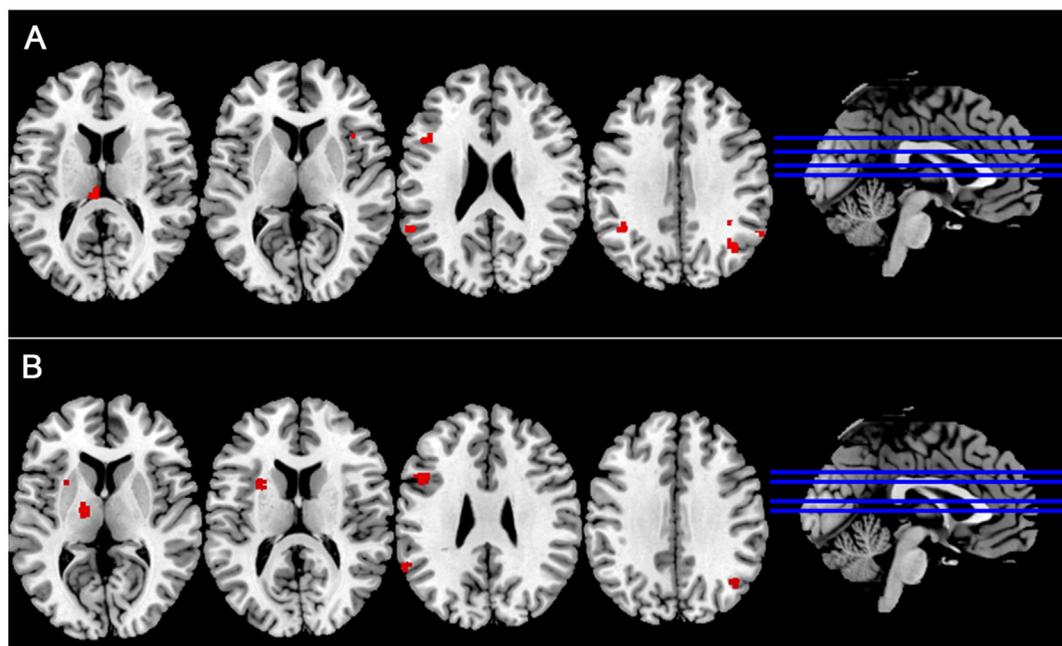

Fig. 1. Brain activation map showing differential effects of antipsychotic medications on main working memory function. Small volume corrections revealed significant differences for: (A) Haloperidol versus placebo—haloperidol leads to decreases in activation in bilateral inferior parietal cortex, bilateral vlPFC, and left thalamus/putamen; (B) haloperidol versus aripiprazole—haloperidol leads to decreases in activation in bilateral inferior parietal cortex and left putamen.

In summary, comparisons of effects of antipsychotics on linear load activation showed that this was affected by haloperidol but not aripiprazole. There were in fact no significant differences in linear load activation between aripiprazole and placebo in any brain region.

3.4. Post-hoc PPI analysis

We conducted a post-hoc PPI analysis to assess the dampening effect of haloperidol, compared to aripiprazole, in the bilateral putamen on other regions in the working memory network. The PPI analysis investigated whether this alteration was driving the changes seen elsewhere in the brain following haloperidol during the task.

However, the PPI analysis using the bilateral putamen as a seed region revealed no significant correlations with any other brain regions. This suggests that the altered activation in the putamen was medication specific and was not modulating activation elsewhere in the brain during working memory performance.

4. Discussion

This is the first study to investigate the effects of a D2 partial agonist like aripiprazole on brain activation during working memory, and to compare its effects to those of haloperidol and placebo in the same healthy individuals. Our results show that while haloperidol reduces activation in parietal and frontal cortex and in the putamen compared to placebo during a working memory task, the activation induced by aripiprazole does not differ from that of placebo. Furthermore, aripiprazole leads to increased reaction time to correct response (RTC) during working memory performance, whilst haloperidol has no effect on behavioural measures. These differences are likely to result from the differing pharmacological profiles of these two drugs: while haloperidol is a selective dopamine D2 antagonist, aripiprazole is a D2 partial agonist and affects a broader range of targets, including the serotonergic system.

We report here, for the first time, that aripiprazole does not alter brain activation during a working memory task. Whilst a previous study of single dose (mean 12.4 mg) aripiprazole administered in 15 healthy controls reported decreased frontal metabolism measured using PET (Kim et al., 2013), no other studies have investigated the effects of this antipsychotic on brain function during working memory in healthy individuals. Some studies in patients with schizophrenia report little change in neural activation following administration of other SGAs (Snitz et al., 2005; Schlagenhauf et al., 2008). However, others have found an association between SGAs and increased activation during a working memory tasks (Honey et al., 1999; Meisenzahl et al., 2006; Wolf et al., 2007; Ettinger et al., 2011). One explanation for these inconsistencies, particularly for the differences between aripiprazole and other SGAs, is that aripiprazole differs from other SGAs in its mechanism of action, and this is likely to result in differences in its neurophysiological effects. Whilst most SGAs have a broad receptor affinity profile, with affinity for both D2 and 5-HT receptors, aripiprazole is a partial, D2 receptor agonist, with much lower affinity for 5-HT$_{2A}$ than for the D2 receptor. Still, like other SGAs, aripiprazole is also a partial agonist of 5-HT$_{1A}$ receptors (Jordan et al., 2002). Considering these differences, it would be expected that aripiprazole exerts effects different from those of other SGAs.

The dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortices (vlPFC), and the posterior parietal cortex, form part of a larger network contributing to working memory performance, although the precise contribution of each region remains unclear (Liggins, 2009). The PFC likely plays a central role in the organisation and guidance of complex behaviours, collectively known as executive function, and disrupted PFC function, particularly in the dorsolateral region, has been associated with cognitive deficits in antipsychotic-naïve patients with schizophrenia (Macdonald et al., 2005). These results suggest that deficits exist independently of, and prior to, any alterations induced by antipsychotics. Nevertheless, working memory dysfunction is modulated by antipsychotic medications, possibly via action at dopamine D1 receptors and serotonin 5-HT$_{2A}$ receptors in the dlPFC (Williams et al., 2002). Our findings show that haloperidol (but not aripiprazole) decreases activation in both dlPFC and vlPFC activation, in the main working memory comparison and in the context of increased cognitive load. We also saw a differential effect of the two antipsychotics in the posterior parietal cortex, where again haloperidol, but not aripiprazole, dampened working memory-related activation, compared with placebo. These findings are consistent with evidence from patient studies that switching from an atypical to a typical antipsychotic is associated with increased activation in both the posterior parietal cortex and the PFC (Honey et al., 1999; Ettinger et al., 2011).

The effects seen in these regions after haloperidol administration may be explained by the modulatory effects this antipsychotic has on the dopamine system. Dopamine D2 receptors are not as abundant in the PFC as they are in the striatum. However, antagonism of haloperidol on striatal D2 dopamine receptors may well modulate activity of dopaminergic projections (via the ventral tegmental area) to the PFC, thus altering its function indirectly (Simpson et al., 2010). These projections have been shown to be important for working memory performance in patients, where abnormal striatal dopaminergic function is linked to altered PFC activation and worse task performance (Meyer-Lindenberg et al., 2002). Chronic D2 antagonism, such as that induced by antipsychotics, may lead to downregulation of D1 receptors in the PFC (Liggins, 2009). Whilst dopaminergic signalling in the posterior parietal cortex is less well-characterised than that in the PFC, there are known reciprocal connections between these two regions, which may convey visuospatial information during working memory performance (Goldman-Rakic, 1995). Therefore, it is possible that parietal changes are secondary to dopaminergic alterations in the PFC (Honey et al., 1999). Our results also show that haloperidol, but not aripiprazole, alters activation in the putamen. This is unsurprising given its specific antagonistic action on striatal D2 receptors. It is possible that the PFC alterations are a downstream effect of striatal dopaminergic changes. To explore whether the changes induced by haloperidol in the putamen, a region of the dorsal striatum, were driving changes elsewhere in the working memory network we conducted a PPI analysis. This analysis showed that the changes in PFC and posterior parietal cortex were not driven by the putamen alterations. Therefore, it is possible that the effects of haloperidol on the PFC occur directly via dopamine receptors found in this region. This mechanism finds support in animal models that have shown cognitive dysfunction following regional dopamine depletion of the PFC, which is reversed by administration of a dopamine agonist (Brozoski et al., 1979).

We also found differential effects of the two antipsychotics on behavioural performance. Whilst neither antipsychotic affected accuracy (proportion correct) at any cognitive load, there was an effect on reaction time to correct response (RTC). Aripiprazole was associated with a longer RTC to correct answers compared to both haloperidol and placebo. Elsewhere, aripiprazole has been associated with increased RTCs in healthy individuals (Kim et al., 2013), but with improved performance (measured by RTC or accuracy) in patients with schizophrenia (Schlagenhauf et al., 2008; Suzuki et al., 2011). It is possible that the effect of aripiprazole on working memory performance follows a U-shaped pattern, dependent on baseline functioning (Vijayraghavan et al., 2007). In particular, optimal working memory performance may rely on optimal PFC function, with suboptimal lower *or* higher activation in this region leading to worse performance. Therefore, the lack of working memory deficit at baseline in our healthy controls should be taken into account.

Whilst our results could point to an adverse effect of aripiprazole on working memory performance, caution must be taken when extrapolating data from healthy controls to clinical samples. Patients with schizophrenia have dysfunctional dopamine signalling, which may respond differently to antipsychotic treatment. Therefore, whilst we saw no

changes in brain function following aripiprazole in healthy controls, this may not hold for patients, in whom the baseline brain state may differ. As previously mentioned, there may be an inverted-U shape relationship between performance and brain dopaminergic function, such that the baseline upon which an antipsychotic acts determines the effect of treatment on performance (Vijayraghavan et al., 2007). Additionally, our findings relate to a single dose of an antipsychotic, whilst patients receive long-term treatment. Finally, some characteristics of our sample (such as the high level of homogeneity and the higher mean IQ) will differ greatly from the usual characteristics of patients with schizophrenia, thus limiting the generalizability of our results. It is therefore important that studies in healthy controls are complemented by clinical studies to elucidate the potential clinical effectiveness of different antipsychotic medications in improving cognition.

Nonetheless, the use of healthy controls is one of the strengths of our study, as it allows the effects of medication to be investigated independently from any underlying disease pathophysiology. A further strength of this study is its within-subjects design, counterbalanced for intervention, which allows a powerful, repeated measures analysis. This ensures that the same individuals received all three treatments, something that would not be practical to implement in a psychiatric sample. As such, any changes in working memory function are more likely due to the antipsychotic administered rather than to between-group differences.

In conclusion, our study indicates that there are immediate and differential effects of a single dose of haloperidol and aripiprazole on working memory function and neural activation in frontal and parietal cortices, and the putamen of healthy individuals. Furthermore, while aripiprazole leads to increased reaction time to correct response (RTC) during the working memory task, haloperidol does not affect performance during this task. Cognitive deficits are considered a prominent clinical feature of schizophrenia, linked to important outcomes including independent living (Harvey et al., 1998), work skills (Bowie et al., 2006), and social functioning (Addington and Addington, 2000). The neurotransmitter systems implicated in working memory and other cognitive functions are targeted and modulated by antipsychotic medications (Ellis and Nathan, 2001; Abi-Dargham et al., 2002). A better understanding of the effects of antipsychotics on these systems is essential to improving the pharmacological treatment of schizophrenia, particularly in the treatment of cognitive symptoms.

Contributors

RH and PD contributed to all aspects of the study and manuscript preparation. TM and HT collected data and contributed to the first draft. RG and SR undertook statistical analysis and prepared the manuscript. All authors contributed to and have approved the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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