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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