K'ING'S
College
LONDON

King's Research Portal

Link to publication record in King's Research Portal

EFFECTS OF ARIPIPRAZOLE AND HALOPERIDOL ON NEURAL ACTIVATION DURING A SIMPLE MOTOR TASK IN HEALTHY INDIVIDUALS: A FUNCTIONAL MRI STUDY

Rhianna Goozee[1°], Owen O'Daly[2°], Rowena Handley[3], Tiago Reis Marques[1], Heather Taylor[1], Grant McQueen[1], Kathryn Hubbard[1], Carmine Pariante[4,5], Valeria Mondelli[4,5], Antje A.T.S. Reinders[1*], Paola Dazzan[1,5*]

[1] Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK;

[2] Centre for Neuroimaging Sciences (CNS), King's College London, UK;

[3] now with Bristol-Myers Squibb

[4] Department of Psychological Medicine, Institute of Psychiatry, King's College London, UK;

[5] NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Kings College London, London, UK

° These authors made equal contribution (i.e. joint first authors)

* These authors are attributed as joint last authors.

Abstract

The dopaminergic system plays a key role in motor function and motor abnormalities have been shown to be a specific feature of psychosis. Due to their dopaminergic action, antipsychotic drugs may be expected to modulate motor function, but the precise effects of these drugs on motor function remain unclear. We carried out a within-subject, double-blind, randomized study of the effects of aripiprazole, haloperidol and placebo on motor function in 20 healthy men. For each condition, motor performance on an auditory-paced task was investigated. We entered maps of neural activation into a random effects general linear regression model to investigate motor function main effects. Whole-brain imaging revealed a significant treatment effect in a distributed network encompassing posterior orbitofrontal/anterior insula cortices, the inferior temporal, and postcentral gyri. Post-hoc comparison of treatments showed neural activation after aripiprazole did not differ significantly from placebo in either voxel-wise or region of interest analyses, with the results above driven primarily by haloperidol. We also observed a simple main effect of haloperidol compared with placebo, with increased task-related recruitment of posterior cingulate and precentral gyri. Furthermore, region of interest analyses revealed greater activation following haloperidol compared with placebo in the precentral and post-central gyri, and the putamen. These diverse modifications in cortical motor activation may relate to the different pharmacological profiles of haloperidol and aripiprazole, although the specific mechanisms underlying these differences remain unclear. Evaluating healthy individuals can allow investigation of the effects of different antipsychotics on cortical activation, independently of either disease-related pathology or previous treatment.

Corresponding author: Rhianna Goozee

1. Introduction

Antipsychotic medications, the pharmacological treatment of choice for schizophrenia, can alter motor function, leading to akathisia and extra-pyramidal motor side effects (EPS). However, the ability to induce motor side effects varies across different antipsychotics, although all of them target the dopaminergic system, which plays a fundamental role in regulating motor function. For example, haloperidol, a first generation antipsychotic (FGA), has been associated with EPS and alterations of motor neural activation in patients with schizophrenia, whilst second generation antipsychotics (SGA), such as olanzapine or quetiapine, are less likely to induce EPS. However, newer antipsychotics, such as aripiprazole (also termed a third generation antipsychotic), are also known to induce akathisia (inner restlessness, with outwardly observed rocking, fidgeting, and restlessness), although they have different effects on the dopaminergic system. To understand the effects of antipsychotics on motor function, it is therefore important to investigate what, if any, effect antipsychotic medications have on motor neural mechanisms without the confounding influence of disease pathophysiology.

This is particularly important because motor function deficits, particularly in processing speed and psychomotor activity, are well documented in schizophrenia and other psychotic disorders, even in antipsychotic-naïve individuals (Liddle, 1987; Dazzan et al., 2004; Dickinson et al., 2007; Morrens et al., 2007; Dazzan et al., 2008). Motor function is modulated by dopaminergic signalling, particularly within the nigrostriatal system. Alterations within this system likely underlie the motor dysfunction observed in these patients. It is therefore essential to clarify the specific effects of different antipsychotic medications on motor function and its associated brain activation, independently from any underlying pathophysiological process.

First generation antipsychotics (FGAs, such as haloperidol) have selective high affinity for, and antagonistic action at, dopamine D2 receptors, but lower affinity for other receptors, such as serotonin (5-HT) receptors (Meltzer et al., 1989). Conversely, second generation

3

Corresponding author: Rhianna Goozee

antipsychotics (SGAs, such as risperidone) have broader affinities, showing antagonism at both D2 and 5HT receptors. Aripiprazole has often been referred to as a third generation antipsychotic due to differences in its affinities for, and action at, dopamine and 5-HT receptors. Importantly, aripiprazole is a partial D2 receptor agonist, rather than a full antagonist (blocker) of dopamine receptors. Partial agonists have both agonist and antagonist actions, depending on the presence of competing full agonists. Therefore, when there are excessive amounts of an endogenous ligand (i.e., in this case dopamine) they act to reduce overstimulation of a receptor. In addition to partial D2 agonism, aripiprazole is a partial agonist of 5-HT$_{1A}$ receptors (Jordan et al., 2002). Similarly to haloperidol, but in contrast to other SGA, aripiprazole also has lower affinity for the 5-HT$_{2A}$ than for the D2 receptor.

The effects of antipsychotics on the brain have been investigated using behavioural and neuroimaging paradigms. Specifically, functional imaging paradigms have been used with simple activation tasks to investigate neural activation underlying motor function in both patients and healthy individuals. These tasks include finger-tapping, which reliably activates a motor loop of cortico-striatal-thalamo-cortical regions (Alexander et al., 1990).

a) Antipsychotic effects on motor performance and associated neural function in patients with schizophrenia

FGA and SGA may affect motor ability differently, given the differing modes of action of these different classes of medication. Behavioural studies have suggested that whilst FGA seem to have little effect on motor performance, SGA have been associated with improvement in motor ability in patients with schizophrenia (Woodward et al., 2005). Furthermore, switching from FGA to SGA may actually be associated with improved motor function (Ahn et al., 2009; Cuesta et al., 2009; Keefe et al., 2007; Cuesta et al., 2001), thus supporting arguments for superior benefit in cognitive function with SGA than FGA.

Studies investigating the effects of antipsychotics on motor activation in schizophrenia report mixed findings. Muller and colleagues (2002a, b) compared neural activation during a finger-

4

Corresponding author: Rhianna Goozee

tapping task in patients with schizophrenia (10 treated with haloperidol, 10 with olanzapine, 10 untreated) and healthy controls. Haloperidol treatment was associated with lower basal ganglia activation in patients than in healthy controls, whilst olanzapine was associated with lower motor cortex activation in patients than in healthy controls during the task (Muller et al., 2002a,b). However, decreased cortical activation has been reported in association with FGA but not SGA treatment elsewhere (Braus et al., 1999). It is possible that SGA treatment leads to normalisation of motor activation in patients. For example, a longitudinal study of functional connectivity reported that patients showed greater connectivity than healthy controls at baseline, but this normalised with three weeks olanzapine treatment, such that patients became more similar to healthy controls (Stephan et al., 2001). This was further supported by another study on the effects of olanzapine on motor activation in patients (Bertolino et al., 2004). Here, Bertolino and colleagues (2004) found that baseline hypoactivation in patients was altered, such that motor activation came to resemble that in healthy controls after eight weeks of olanzapine treatment.

b) Antipsychotic effects on motor performance and associated neural activation in healthy individuals

Interpretation of studies in patients is complicated by the presence of altered activation patterns that may be associated with disease pathophysiology. Therefore, studies have investigated the effect of antipsychotics on motor performance in healthy individuals, to evaluate their effects on motor function independently of underlying pathophysiology or symptom profiles. While most reported no effect of haloperidol on motor performance (Liem-Moolenaar et al., 2010; Wezenberg et al., 2007; Lynch et al., 1997; Honey et al., 2003), one did report psychomotor impairments following a single dose of either haloperidol or olanzapine, with impairments induced by haloperidol lasting longer (Beuzen et al., 1999). Impaired performance on motor tasks (including increased reaction times/impaired speed of response) has been more often seen in healthy controls following administration of olanzapine than after haloperidol (Beuzen et al., 1999; Wezenberg et al. ,2007; de Bruijn et al., 2006;

Corresponding author: Rhianna Goozee

Morrens et al., 2007). However, to date only one study investigated the effect of aripiprazole on motor performance in 20 healthy controls and did not find any effect (Liu et al. 2009), possibly because of its novel pharmacological profile.

To our knowledge, only one study has investigated neural activation during a motor task after haloperidol in healthy controls (Tost et al., 2006). This study found decreased activation in several regions, lateralised to the non-dominant hemisphere. These included anterior cingulate and parietal regions, such as supplementary motor area, primary somatomotor cortex, premotor cortex, and also putamen, thalamus and cerebellum. In contrast, no study has evaluated neural activation during motor function following aripiprazole, either in patients or healthy controls.

It therefore remains unclear whether and how different antipsychotics (D2 antagonists or partial agonists) affect simple motor function and its related neural activation. We explored for the first time the differential effects of a single dose of two different antipsychotics on motor function in healthy individuals using fMRI with a longitudinal, repeated measures design.

We investigated motor function using a joystick task after administration of haloperidol (a D2 antagonist) and aripiprazole (a D2 partial agonist) to the same healthy individuals. Based on previous studies, we predicted that haloperidol, but not aripiprazole, would reduce activation of cortical motor regions, including anterior cingulate, supplementary motor and premotor areas, and subcortical regions, including putamen and thalamus, compared with placebo.

Corresponding author: Rhianna Goozee

2. Materials and methods

2.1 Participants

Twenty healthy, right-handed, English speaking, Caucasian male university students, participated in this study. They were aged 18 to 33 years (mean 23.0 years, SD 4.5), with mean IQ of 118.3 (SD 6.1) measured using the National Adult Reading Test (NART) (Nelson 1982). Their body mass index was within the normal range (mean 23.6, SD 3.7) and all were non-smokers, with no recent or current drug use (illicit or prescribed). They had no previous exposure to psychotropic medications and did not have a personal or family history of psychiatric illness.

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 after the nature of the experimental procedures was explained to them.

2.2 Procedures

2.2.1 Antipsychotic administration

*S*ubjects received a single dose of haloperidol (3mg), aripiprazole (10mg), and placebo, administered in identical capsules across three visits, in a fully counterbalanced, randomized within-subject, double-blind crossover design. A minimum of 14 days' drug washout was ensured between visits, and no alcohol or medications were used for 24 hours, or caffeine for 6 hours, prior to scanning. Time of administration before scanning and dose of antipsychotic ensured comparable levels of striatal D2 receptor occupancy for the two compounds to within the 'window of therapeutic range' (65-80%) during the scan (Kapur et al. 2000). A 16 ml blood sample was collected immediately before MRI scanning to assess antipsychotic plasma levels. The mean plasma level of haloperidol was 1 µg/L (SD 0.6; range 0.5 – 2.5 µg/L), and of aripiprazole was 42 µg/L (SD 11; range 23 – 55 µg/L).

Corresponding author: Rhianna Goozee

Three hours after drug administration, clinical motor effects were measured using the Barnes Akathisia scale (Barnes, 1989), the Simpson-Angus scale (Simpson & Angus, 1970), and the Abnormal Involuntary Movement Scale (Guy, 1976). Both haloperidol and aripiprazole induced more extra-pyramidal side effects than placebo ($\chi^2 = 7.3$, $p < 0.05$). There were no significant differences across interventions in tardive dyskinesia ($\chi^2 = 2.0$, n.s.) or akathisia (no participants reported any symptoms). There were also no differences in systolic ($F(2,32) = 2.16$, n.s.) or diastolic ($F(2,32) = 0.15$, n.s.) blood pressure.

2.2.2 Motor task

Participants completed a battery of cognitive tests after administration of each intervention. They completed an auditory-paced motor task in which they were presented with a tone through headphones. During an experimental block, the word 'move' was visually presented indicating that participants should move a joystick with their right hand when they heard a tone. During a control block, the word 'rest' was presented indicating that no movement was required even if tones were heard. For each intervention, participants completed five control and five experimental blocks, each lasting 17.5 seconds. During experimental blocks, targets were presented every 1.5 – 3.5 seconds, jittered to prevent automated rhythmic responses and with a total of 7 targets per block. Jittered tones were presented during the control blocks, although no response was required. The whole task lasted 3 minutes and 15 seconds, with rest and experimental blocks separated by a 2 second interval.

2.2.3 BOLD acquisition

Echo planar images (EPI) depicting blood oxygen level dependent (BOLD) contrast were obtained in a General Electric Signa HDX 1.5 Tesla scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry. Thirty-eight ascending, interleaved axial slices (3mm thick, 0.3mm inter-slice gap) were acquired parallel to the intercommissural (AC-PC) plane during each session, with a repetition time of 2.5 seconds and an echo time of 40 seconds. BOLD

images provided neural correlates of the task. In addition, a high spatial resolution EPI image was also acquired for co-registration and normalisation of functional images.

2.2.4 Data analysis

2.2.4.1 Missing data

Not all participants were included in all analyses. The reasons for missing data included image acquisition fault (n=1) and side effects after either haloperidol or aripiprazole resulting in missing functional motor task data after taking the antipsychotic (haloperidol, n=1; aripiprazole, n=3). As a result, the analysis of differences (for each intervention) in performance and activation during the motor task was based on n = 18 subjects for haloperidol versus placebo, n = 15 for haloperidol versus aripiprazole, and n = 17 for aripiprazole versus placebo.

2.2.4.2 Behavioural analysis

Behavioural data were analysed in the Statistical Package for Social Sciences, Version 15.0 (SPSS Inc.). Number correct (NC) and reaction time to correct response (RTC) were recorded. Depending on whether data met the assumption of normality, T tests or chi-square tests were run to compare behavioural scores for haloperidol versus placebo, haloperidol versus aripiprazole, and aripiprazole versus placebo. Our results showed that neither antipsychotic intervention altered the behavioural performance on the task compared with placebo or one another, as measured by number correct (NC) or reaction time to correct (RTC) (Table 1). As such, we present only the data for neural activation in our results below.

[Table 1]

2.2.4.3 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

Corresponding author: Rhianna Goozee

College London (www.fil.ion.ucl.ac.uk/spm). Images were reoriented to the AC-PC line (using http://imaging.mrc-cbu.cam.ac.uk/imaging/FindingCommissures for guidance) prior to realignment. A 6-parameter rigid body spatial transformation was used for within-subject registration to realign images to each other and then to the mean time series image, and movement parameters were extracted. A good quality EPI image (selected visually from one of three sessions) was normalised using 16 nonlinear iterations and 7x9x7 basis functions to the standard EPI template in SPM5 (conforms to the ICBM NIH p-20 project; (Evans et al., 1993)). This generated normalisation parameters for optimal matching between the standard template space, the high resolution image, and subsequently the EPI time series. Finally, images were smoothed with a 10mm Gaussian kernel filter.

For the first level analysis, subject-specific fMRI data identified activation patterns for each subject representing areas activated by the simple motor task. These maps, containing activation exclusive to motor function, were entered into a random effects general linear regression model to explore group effects. These contrasts were taken forward to a random effects group-level model. Specifically, a repeated-measures ANOVA was implemented as a flexible factorial. In addition, we included three nuisance regressors encoding dosing order (i.e., dose 1, 2, and 3) in the model to control for potential order effects. Supra-threshold cluster-level statistics were then accepted at $p < 0.05$, corrected for multiple comparisons across the whole brain.

Whilst a voxel-wise approach allowed us to explore regions affected by the antipsychotic medications across the whole brain, we also used a region of interest approach to specifically investigate brain regions known to be associated with motor performance. Small volume corrections (SVC) were conducted using independent, a priori, anatomically defined regions, identified in the anatomical automatic labelling (AAL) toolbox extension of SPM5 (Tzourio-Mazoyer et al., 2002). We selected nine a priori regions, with our choice informed by a meta-analysis (Witt et al., 2008). These included precentral gyrus, postcentral gyrus, supplementary motor region, inferior parietal, inferior frontal (pars opercularis), putamen,

Corresponding author: Rhianna Goozee

caudate, thalamus, and cerebellum. SVC were applied to each contrast bilaterally, with voxel-level statistics accepted at $p < 0.05$ corrected for family-wise error (FWE). All MNI co-ordinates were labelled using a combination of the Talairach and Tornaux atlas (Talairach & 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).

Corresponding author: Rhianna Goozee

3. Results

3.1. Main motor effects on neural activation

The main motor effects (i.e. regions activated by the motor task experimental condition across each drug condition) activated an extensive brain network (Table 2; Figure 1).

The largest significant cluster of increased activation was centred in the right cerebellum ([x y z] = [22 -54 -28], F = 10.48, p < 0.001), with a smaller cluster centred in the left cerebellum ([x y z] = [-34 -62 -30], F = 5.75, p < 0.001).

Five further less extensive clusters of increased activation were seen during motor task performance. The first was centred in the left postcentral gyrus ([x y z] = [-34 -28 56], F = 7.70, p < 0.001), extending into the left supramarginal gyrus. There were two clusters centred in the left central operculum ([x y z] = [-44 -2 10], F = 6.28, p < 0.001 and [x y z] = [-58 -20 18], F = 5.30, p < 0.001), extending into the left thalamus and parietal operculum, respectively. There was a fourth cluster centred in the right inferior frontal operculum ([x y z] = [46 12 2], F = 5.48, p = 0.001). The final cluster was centred in the superior temporal gyrus ([x y z] = [64 -32 16], F = 5.02, p = 0.004). There was also a trend-level significance for a cluster centred in the right caudate ([x y z] = [26 -10 30], F = 5.20, p = 0.099).

[Table 2]

[Figure 1]

3.3 Treatment effects

3.3.1 Main effect of treatment

The repeated measures ANOVA revealed three clusters of activation where a significant main effect of treatment was observed (Table 3; Figure 2).

12

Corresponding author: Rhianna Goozee

The first significant cluster was centred in the posterior orbital gyrus (anterior insula) ([x y z] = [-32 16 -18], F = 20.11, p = 0.002). The second cluster was centred in the inferior temporal gyrus ([x y z] = [-48 -58 -16], F = 15.38, p = 0.027), and the final cluster was centred in the postcentral gyrus ([x y z] = [-28 -30 56], F = 13.73, p = 0.037).

[Figure 2]

Figure 3 shows the parameter estimates for each drug session for regions displaying a significant main effect of drug treatment.

[Figure 3]

3.3.2 Haloperidol versus placebo

Haloperidol led to increased activation in a number of regions compared with placebo, with five clusters of significant activation (see Table 2 for cluster coordinates and Figure 4 for activation patterns).

A first cluster was centred in the left anterior insula ([x y z] = [-32 -16 -18], Z = 6.24, p < 0.001), extending into the posterior orbital gyrus and the inferior orbital frontal gyrus. There were bilateral clusters centred in the inferior temporal gyrus, smaller on the right (L: [x y x] = [-48 -58 -16], F = 5.47, p = 0.002; R: [x y x] = [52 -42 -16], F = 4.50, p = 0.027). Further, there was a cluster in the left postcentral gyrus ([x y z] = [-28 -39 56], F = 5.21, p < 0.001), which extended into the bilateral precentral gyrus. The final cluster was centred in the left posterior cingulate gyrus ([x y z] = [-6 -48 16], F = 5.04, p = 0.023).

There were no regions of lower activation during the motor task following haloperidol administration when compared with placebo.

[Figure 4]

3.3.2 Haloperidol versus aripiprazole

13

Corresponding author: Rhianna Goozee

Haloperidol induced greater activation than aripiprazole in two significant clusters. Cluster coordinates are listed in Table 2 and the activation patterns are illustrated in Figure 4.

First, there was greater activation in the left posterior orbital gyrus ([x y z] = -36 24 -22], F = 4.63, p = 0.045), extending into the left anterior insula. The second cluster was centred in the right postcentral gyrus ([x y z] = [34 -30 68], F = 4.59, p < 0.001).

There were no regions of significantly lower activation during the motor task following haloperidol administration compared with aripiprazole.

3.3.3 Aripiprazole versus placebo

We found no differences in brain activation during the motor task when aripiprazole and placebo were compared directly.

Figure 5 shows the parameter estimates for each drug session for additional regions identified in exploratory and hypothesis-led directional contrasts between drug sessions.

[Figure 5]

3.4 Region of interest analyses

In the repeated-measures ANOVA, hypothesis-led analysis using small volume correction identified main effects of treatment in the a priori specified anatomical regions of interest at trend-level of significance. These were in the precentral gyrus ([x y z] = [-28 -30 56], T = 13.73, Z = 3.87, P = 0.069) and post-central gyrus ([x y z] = [-28 -30 46], T = 13.35, Z = 3.82, P = 0.089), although they likely reflect a common activation spanning both regions. The analysis also identified a significant main effect in the putamen ([x y z] = [24 4 -6], T = 10.74, Z = 3.44, p < 0.088).

Corresponding author: Rhianna Goozee

The post-hoc directional t-tests comparing treatments directly showed significantly greater task-related activation for haloperidol compared with placebo in the precentral gyrus ([x y z] = [-28 -30 56], T = 5.21, Z = 4.38, p < 0.001), the postcentral gyrus ([x y z] = [-26 -30 54], T = 5.15, Z = 4.34, p = 0.011), and the putamen ([x y z] = [24 4 -6], T = 4.61, Z = 3.99, p = 0.012). Furthermore, a trend-level effect was also observed in the supplementary motor area ([x y z] = [2 -20 72], T = 4.17, Z = 3.68, p=0.057). Interestingly, haloperidol was also associated with a significant reduction in task-related BOLD activity in the caudate nucleus ([x y z] = [8 18 10], T = 4.13, Z = 3.66, p = 0.036).

When assessing the degree to which haloperidol modulated task-related regional brain recruitment relative to aripiprazole, we found evidence for significantly greater levels of activity in the postcentral gyrus ([x y z] = [34 -30 68], T = 4.59, Z = 3.98, p = 0.042), and at trend level in the precentral gyrus ([x y z] = [36 -28 68], T = 4.34, Z = 3.81, p = 0.011) in the haloperidol sessions. However, following correction for multiple comparisons, only the difference between haloperidol and placebo in the precentral gyrus remained significant.

Corresponding author: Rhianna Goozee

4. Discussion

This is the first study to examine the effects of aripiprazole on brain activation during a simple motor task in healthy individuals. Our main finding is that motor activation following aripiprazole did not differ from placebo. In contrast, following haloperidol there was an extensive increase in activation in frontal, temporal and insular regions, as well as in regions of the primary motor cortex, compared with both placebo and aripiprazole. These different effects are likely to be explained by the different pharmacological profiles of these two antipsychotics. While haloperidol is a selective dopamine D2 antagonist, aripiprazole is a D2 partial agonist, acting on other receptors, including those of the serotoninergic system.

Performance of the paced motor task was associated with significantly elevated BOLD signal in a distributed network including the contralateral sensorimotor cortices (postcentral and parietal operculum), the SMA, the ipsilateral cerebellum and subcortically the dorsal caudate nucleus, the putamen and thalamus. As described earlier, these regions form the basis of the cortico-striato-thalamocortical loop identified by Alexander et al. (1990). Similar patterns of activation are also consistent both with the findings of recent ALE meta-analyses of finger-tapping tasks (Witt et al., 2008) and simple motor movements (Turesky et al. 2016), with these regions reflecting a core network underlying basic motor performance. Here, the SMA was linked to voluntary action and planning, while the basal ganglia and cerebellum are heavily implicated in both the initiation, control and timing of motor action and these aspects likely contribute to these two structures recruitment in this context. In both meta-analyses, task performance was also associated with increased activation of the inferior frontal operculum extending into the insula. This area has previously been implicated in externally paced motor performance, albeit visually cued (Witt et al., 2008). While perhaps not initially considered a motor area, the insula has extensive reciprocal connectivity with motor and sensory areas (Augustine 1996), and it is considered a motor association area linked to the upper body and hand (Chollet et al. 1991; Weiller et al. 1992). In patients with Parkinson's disease, performance of externally-cued joystick movement was similarly associated with recruitment

16

Corresponding author: Rhianna Goozee

of this network of brain regions. More importantly, impairment of dopamine signalling, due to the removal of L-dopa therapy, was associated with enhanced activation in the sensorimotor cortices, which accords with our findings (Maillet et al. 2012).

There appeared to be no effect of either treatment on performance of the task, although aripiprazole did increase reaction times at a trend level. The lack of a clear effect may have been due to ceiling effects, with high levels of performance in healthy individuals meaning that there was little variability in inter-individual performance. However, given that haloperidol did affect neural activation but not behavioural performance, it is possible that higher activation in this condition reflected the need for motor regions to work harder to achieve comparable performance. Nonetheless, the absence of a significant behavioural effect gives confidence that the differences in neuronal recruitment indexed by the observed changes in BOLD contrast following haloperidol administration are not simply central representations of performance deficits.

Examining our neuroimaging data, we report, for the first time, that aripiprazole does not alter brain activation during performance of a motor task. This is in contrast with other SGA, which have been reported to decrease activation of cortical motor regions in patient populations (Muller et al., 2002a,b). This might reflect differences between the mechanisms of action of aripiprazole and other SGAs, such as the D2 antagonism of many SGAs as opposed to the partial D2 agonism of aripiprazole. Furthermore, aripiprazole has a lower affinity for the 5-HT2A than the D2 receptor, and partial affinity for 5-HT1A receptors. This profile may also explain why aripiprazole has been found in clinical trials to have a low risk of inducing extrapyramidal motor side effects (Fleischhacker, 2005).

In contrast to aripiprazole, our hypothesis-led analyses revealed that haloperidol enhanced activation in several regions compared with both placebo and aripiprazole, including the putamen. Increased activation here may result from an autoreceptor response following D2 blockade. Previous work by our group has also shown greater perfusion in the putamen

Corresponding author: Rhianna Goozee

following challenge with haloperidol (Handley et al., 2013), which may reflect an increased need for energy supply. Conversely, caudate activation was lower following haloperidol than placebo, suggesting a smaller autoreceptor response (and similarly this region showed lower perfusion than the putamen). In addition, differences between the activation seen in these regions may reflect their involvement in motor function, which relies more on putamen activation, while the caudate underlies cognitive activities. Recent findings in rodents have also highlighted the complexity of the interaction between haloperidol and discrete neural populations in the striatum (Yael et al. 2013). Specifically, haloperidol reduces medium spiny neuron activity and increases the likelihood of oscillatory activity, while increasing the firing of tonically active neurons (TANs). Importantly, the impact of these effects seems dependent upon cortical input. Consequently, the observed differences may reflect various complex interacting factors.

Our exploratory whole-brain analyses identified a main effect of drug in a contralateral network of brain regions, including the posterior and lateral aspect of the orbitofrontal cortex, the inferior temporal, and postcentral gyri. Post-hoc directional tests confirmed that activation was enhanced in the temporal lobe following haloperidol compared with placebo, but that no such effect of aripiprazole was evident. Neither was a difference in temporal activation seen when the FGA and SGA study arms were compared. This finding is consistent with the greater dopaminergic modulation of FGAs than SGAs, and with the fact that the temporal lobe is densely populated with dopamine receptors and may be an extrastriatal site of action for antipsychotic medications (Tuppurainen et al., 2009). The temporal lobe is consistently implicated in the pathophysiology of schizophrenia, and evidence suggests this activation may reflect a response to the auditory stimulation that provided the pacing in this task (Jones et al., 2004).

A task-related enhancement of the OFC and postcentral gyrus was evident on haloperidol compared with both placebo and, importantly, aripiprazole, suggesting that these regions were not even moderately modulated by aripiprazole. The orbitofrontal cortex contributes to the

Corresponding author: Rhianna Goozee

limbic cortico-striato-thalamocortical circuit, which is linked to ventral striatal information processing (Alexander et al., 1990). Indeed, abnormalities of OFC have been related to the presence of both psychotic and cognitive symptoms in patients with schizophrenia (Waltz et al. 2007). Our finding of enhanced activation following haloperidol would be consistent with prior evidence that haloperidol, but not the SGA sertindole, increases metabolism in this area (Buchsbaum et al. 2009). This could be related to its therapeutic effects, as evidence from animal models suggests that antipsychotics reduce the impact of NMDA hypofunction and dopamine hyperfunction on OFC neurons, normalizing their function (Homayoun & Moghaddam 2008).

As mentioned previously, haloperidol is a full dopamine antagonist, whereas aripiprazole is a partial agonist, with accompanying serotoninergic action. Therefore, the differences in activation we observed may be related to the partial agonism at D2 receptors of aripiprazole, or its serotoninergic modulation. Dopamine is primarily implicated in motor function, but further modulation after aripiprazole may occur indirectly via its serotoninergic action (Meltzer 2004), which has also been shown to play a role in motor function (Hasbroucq et al., 1997; Jacobs & Fornalt, 1997). Compared with haloperidol, there was lower activation following aripiprazole in several brain regions. Drugs that increase serotonin neurotransmission increase contralateral cortical motor activation, and so in the present case, 5HT2A receptor antagonism following aripiprazole may have mediated the lower activation observed (Loubinoux et al., 2002). Furthermore, aripiprazole induced lower activation than haloperidol in regions of the prefrontal cortex (e.g. the inferior frontal gyrus), an area that is modulated by serotonin activity (Mann et al., 1996; Bowen et al., 1989). Nonetheless, aripiprazole did not alter activation in any of these areas when compared with placebo, suggesting that dopaminergic signalling is of primary importance in determining alterations from healthy activation following antipsychotic administration.

To our knowledge, no other study has explored the effects of aripiprazole on neural activation associated with motor function in healthy controls, making comparison difficult.

Corresponding author: Rhianna Goozee

Only one study explored the effect of haloperidol and, in contrast to us, found decreased activation in motor networks after this drug (Tost et al., 2006). This could be due to methodological differences, as our study benefited from a much larger sample and used a lower haloperidol dose than did Tost and colleagues. It is possible that in a smaller sample a pattern of increased activation could have not been detected. Also, participants in their study performed a more demanding task, using their non-dominant hand, with self-paced, repetitive finger to thumb coordination, and the direction regularly changed. This task, and the use of a greater dose of haloperidol, may mean that the dopamine antagonism elicited overrode any potential compensatory mechanism.

Our participants completed the task with their right (dominant) hand and the effects we saw appeared to be lateralised. Increased activation during motor function following haloperidol compared with placebo was seen mainly in the contralateral (left) hemisphere. A review of motor cortex lateralisation in healthy individuals has reported that motor tasks elicit activation primarily in contralateral motor areas, which is consistent with our results (Mattay and Weinberger, 1999). Furthermore, our results suggest that haloperidol does not interfere with normal lateralised motor activation patterns. This is contrary to proposals presented elsewhere that reduced lateralisation of cognitive or motor activation in patients with schizophrenia is due to medication effects (Mattay et al., 1997; Walter et al., 2003; Bertolino et al., 2004). Indeed, studies investigating the effects of antipsychotic treatments in patients have suggested there may be lateralised effects on motor activation. For example, in one study reduced contralateral activation in the primary motor cortex was seen in unmedicated patients (Bertolino et al., 2004). However, after 8 weeks of treatment, there was increased lateralisation such that patients did not differ from healthy controls (Bertolino et al., 2004).

Caution must also be taken when extrapolating data from healthy individuals to patient populations. In schizophrenia, dopamine signalling is disrupted, and the brain may respond differently to antipsychotic medications that modulate this neurotransmitter. Thus, while aripiprazole did not alter brain function in our healthy sample, this may not be true in

20

Corresponding author: Rhianna Goozee

patients, who are starting from a different baseline brain state. Furthermore, patients receive long-term, multiple doses of antipsychotic medications, whereas studies in healthy individuals commonly use a single dose. These limitations highlight the need to integrate studies in healthy populations with clinical studies (particularly in antipsychotic-naïve patients) to explore the potential effects of different antipsychotic medications on motor function, and its relationship with symptomatic improvement. In addition, we did not record information on actual responses made by participants, particularly any made to the tone during the rest condition. This may be relevant to the interpretation of the contrast between experimental and rest conditions. In fact, if participants are responding during the rest blocks, this may reduce the differences seen. However, any response during rest would be likely to make the two conditions more similar rather than introducing more difference.

Despite these limitations, investigating healthy controls is a major strength of our study. This approach allows the effects of antipsychotic drugs on brain function to be examined without the confounding influence of underlying disease pathophysiology. Comparing two different drugs and placebo within the same individuals, as we do in this within-subjects and counterbalanced design, gives greater confidence that changes in motor activation are due to the antipsychotic rather than between-group differences. Such a powerful, repeated measures analysis would not be easy to implement in patients with psychosis as changing medications in this way would have ethical implications.

Motor function deficits are widely reported in schizophrenia and may underlie a number of other cognitive deficits associated with the disorder (Salthouse, 1996). Furthermore, abnormalities in motor function are observed in patients with schizophrenia who have never taken antipsychotic medications (Pappa & Dazzan, 2009). Antipsychotics exert modulatory effects on cognitive functions, including simple motor function, and antipsychotic generation plays a role in determining these effects. This study provides evidence for differential effects of FGA and SGA administration on neural activation associated with simple motor function in a healthy population without the complication of disease-related pathophysiology. Motor

21

Corresponding author: Rhianna Goozee

deficits and other neurocognitive impairments have been associated with clinical and functional outcome in schizophrenia (Lepage et al., 2014). As such, they are a potentially suitable target for antipsychotic treatment, and a better understanding of the effects of antipsychotics on this domain is essential to improve the pharmacological management of schizophrenia.

Acknowledgements

Corresponding author: Rhianna Goozee

References

Ahn, Y.M. et al., 2009. Changes in neurocognitive function in patients with schizophrenia after starting or switching to amisulpride in comparison with the normal controls. *Journal of Clinical Psychopharmacology*, 29(2), pp.117–123.

Alexander, G., Crutcher, M. & M, D., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research*, 85, pp.119–146.

Augustine, J.R., 1996. Circuitry and fimctional aspects of the insular lobe in primates including humans. *Brain Research Reviews*, 22, pp.229–244.

Barnes, T., 1989. A rating scale for drug-induced akathisia. *The British Journal of Psychiatry*, 154, pp.672–676.

Beuzen, J. et al., 1999. A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. *Journal of Psychopharmacology*, 13(2), pp.152–158.

Bowen, D. et al., 1989. Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proceedings of the National Academy of Sciences of the United States of America*, 86(23), pp.9504–9508.

Braus, D. et al., 1999. Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. *Schizophrenia Research*, 39, pp.19–29.

de Bruijn, E.R.A. De et al., 2006. Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. *Brain Research*, 1105, pp.122–129.

Buchsbaum, M.S. et al., 2009. FDG-PET and MRI imaging of the effects of sertindole and haloperidol in the prefrontal lobe in schizophrenia. *Schizophrenia Research*, 114(1–3), pp.161–171. Available at: http://dx.doi.org/10.1016/j.schres.2009.07.015.

Chollet, F. et al., 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Annals of Neurology*, 29(1), pp.63–71.

Cuesta, M.J. et al., 2009. Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. *The British Journal of Psychiatry*, 194(5), pp.439–445.

Cuesta, M.J., Peralta, V. & Zarzuela, A., 2001. Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. *Schizophrenia Research*, 48(1), pp.17–28.

Dazzan, P. et al., 2008. Neurological abnormalities and cognitive ability in first-episode psychosis. *British Journal of Psychiatry*, 193, pp.197–202.

Dazzan, P. et al., 2004. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain*, 127(1), pp.143–153.

Dickinson, D., Ramsey, M. & Gold, J., 2007. A meta-analysis comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of general psychiatry*, 64(5), pp.532–542.

Evans, A.C. et al., 1993. 3D statistical neuroanatomical models from 305 MRI volumes. In *Nuclear Science Symposium and Medical Imaging Conference, 1993., 1993 IEEE Conference Record.* IEEE, pp. 1813–1817.

Fleischhacker, W.W., 2005. Aripiprazole. *Expert opinion on pharmacotherapy*, 6(12), pp.2091–2101.

Guy, W., 1976. *Abnormal involuntary movement scale (AIMS)*, Rockville, MD.

Handley, R. et al., 2013. Acute effects of single-dose aripiprazole and haloperidol on resting

Corresponding author: Rhianna Goozee

cerebral blood flow (rCBF) in the human brain. *Human brain mapping*, 34, pp.272–282.

Hasbroucq, T. et al., 1997. Serotonin and human information processing: fluvoxamine can improve reaction time performance. *Neuroscience Letters*, 229(3), pp.204–208.

Homayoun, H. & Moghaddam, B., 2008. Orbitofrontal cortex neurons as a common target for classic and glutamatergic antipsychotic drugs. *Proceedings of the National Academy of Sciences*, 105(46), pp.18041–18046.

Honey, G.D. et al., 2003. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. *Brain: a journal of neurology*, 126, pp.1767–81.

Jacobs, B.L. & Fornalt, C.A., 1997. Serotonin and motor activity. *Current Opinion in Neurobiology*, 7, pp.820–825.

Jones, H.M. et al., 2004. Cortical effects of quetiapine in first-episode schizophrenia: a preliminary functional magnetic resonance imaging study. *Biological psychiatry*, 56(12), pp.938–942.

Jordan, S. et al., 2002. The antipsychotic aripiprazole is a potent , partial agonist at the human 5-HT 1A receptor. *European Journal of Pharmacology*, 441, pp.137–140.

Kapur, S. et al., 2000. Relationship Between Dopamine D2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-Episode Schizophrenia. *American Journal of Psychiatry*, 157, pp.514–520.

Keefe, R. et al., 2007. Effects of Olanzapine, Quetiapine, and Risperidone on Neurocognitive Function in Early Psychosis: A Randomized, Double-Blind 52-Week Comparison. *American Journal of Psychiatry*, 164, pp.1061–1071.

Lepage, M., Bodnar, M. & Bowie, C.R., 2014. Neurocognition: Clinical and Functional Outcomes in Schizophrenia. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, 59(1), pp.5–12.

Liddle, P., 1987. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *British Journal of Psychiatry*, 151, pp.145–151.

Liem-Moolenaar, M. et al., 2010. Psychomotor and cognitive effects of a single oral dose of talnetant (SB223412) in healthy volunteers compared with placebo or haloperidol. *Journal of psychopharmacology*, 24(1), pp.73–82.

Liu, Y. et al., 2009. Subjective, cognitive/psychomotor, and physiological effects of aripiprazole in Chinese light and heavy smokers. *Drug and alcohol dependence*, 101(1–2), pp.42–52.

Loubinoux, I. et al., 2002. A single dose of the serotonin neurotransmission agonist paroxetine enhances motor output: double-blind, placebo-controlled, fMRI study in healthy subjects. *NeuroImage*, 15(1), pp.26–36.

Lynch, G. et al., 1997. The effects of haloperidol on visual search, eye movements and psychomotor performance. *Psychopharmacology*, 133(3), pp.233–239.

Maillet, A. et al., 2012. Levodopa Effects on Hand and Speech Movements in Patients with Parkinson's Disease : A fMRI Study. *PLoS ONE*, 7(10), p.e46541.

Mann, J.J. et al., 1996. Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers. *Journal of cerebral blood flow and metabolism*, 16(3), pp.418–26.

Mazziotta, J. et al., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical transactions of the Royal Society of London.Series B, Biological sciences*, 356(1412), pp.1293–1322.

Meltzer, H., Matsubara, S. & Lee, J., 1989. Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine. *The Journal of Pharmacology and Experimental Therapeutics*, 251(1), pp.238–246.

Corresponding author: Rhianna Goozee

Meltzer, H.Y., 2004. What's atypical about atypical antipsychotic drugs? *Current opinion in pharmacology*, 4(1), pp.53–57.

Morrens, M. et al., 2007. Psychomotor and memory effects of haloperidol, olanzapine, and paroxetine in healthy subjects after short-term administration. *Journal of clinical psychopharmacology*, 27(1), pp.15–21.

Nelson, H.E., 1982. *National Adult Reading Test*, Windsor, UK: NFER-Nelson.

Pappa, S. & Dazzan, P., 2009. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychological medicine*, 39(7), pp.1065–1076.

Salthouse, T., 1996. The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103(3), pp.403–428.

Simpson, G.M. & Angus, J.W.S., 1970. A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, 45(S212), pp.11–19.

Stephan, K. et al., 2001. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. *Psychological medicine*, 31, pp.1065–1078.

Talairach, J. & Tournoux, P., 1988. *Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: an approach to cerebral imaging* First., Thieme.

Tost, H. et al., 2006. D2 antidopaminergic modulation of frontal lobe function in healthy human subjects. *Biological Psychiatry*, 60(11), pp.1196–1205.

Tuppurainen, H. et al., 2009. Dopamine D2/3 receptor binding potential and occupancy in midbrain and temporal cortex by haloperidol, olanzapine and clozapine. *Japanese Society of Psychiatry and Neurology*, 63, pp.529–537.

Turesky, T.K., Turkeltaub, P.E. & Eden, G.F., 2016. An Activation Likelihood Estimation Meta-Analysis Study of Simple Motor Movements in Older and Young Adults. *Frontiers in Aging Neuroscience*, 8, p.238.

Tzourio-Mazoyer, N. et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), pp.273–289.

Waltz, J.A. et al., 2007. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biological Psychiatry*, 62(7), pp.756–764.

Weiller, C. et al., 1992. Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Annals of Neurology*, 31(5), pp.463–472.

Wezenberg, E. et al., 2007. The role of sedation tests in identifying sedative drug effects in healthy volunteers and their power to dissociate sedative-related impairments from memory dysfunctions. *Journal of Psychopharmacology*, 21(6), pp.579–587.

Witt, S.T., Laird, A.R. & Meyerand, M.E., 2008. Functional neuroimaging correlates of finger-tapping task variations: an ALE meta-analysis. *NeuroImage*, 42(1), pp.343–56.

Woodward, N.D. et al., 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *The International Journal of Neuropsychopharmacology*, 8(3), pp.457–472.

Yael, D. et al., 2013. Haloperidol-induced changes in neuronal activity in the striatum of the freely moving rat. *Frontiers in System Neuroscience*, 7, p.110.

Corresponding author: Rhianna Goozee

Tables and figure legends

Table 1: *Motor task performance under each intervention*

Table 2: *Neural correlates of significantly increased activation during the experimental condition of the motor task, and areas showing significant increases following haloperidol, compared with placebo and aripiprazole.*

Table 3: *Motor function region of interest analysis after haloperidol compared with placebo, and after haloperidol compared with aripiprazole.*

Figure 1:1 *Brain regions significantly activated during the performance of the motor task during the placebo session (pFWE < 0.05 on the basis of cluster extent).*

Figure 2: *Brain regions where a significant main effect of treatment was evident in the repeated measures ANOVA (pFWE < 0.05 on the basis of cluster extent).*

Figure 3: *Plots of parameter estimates for each drug session for regions displaying a significant main effect of drug treatment.*

Figure 4: *Brain regions where Haloperidol significantly increased task-related activation compared to the Placebo (red) and Aripiprazole (Yellow) sessions (P(FWE) <0.05 on the basis of cluster extent). Common areas shown in orange.*

Figure 5: *Plots of parameter estimates for each drug session for additional regions identified in exploratory and hypothesis-led directional contrasts between drug sessions.*