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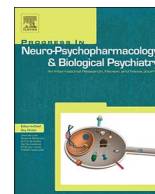
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Effects of aripiprazole versus risperidone on brain activation during planning and social-emotional evaluation in schizophrenia: A single-blind randomized exploratory study

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ABSTRACT

Impaired function of prefrontal brain networks may be the source of both negative symptoms and neurocognitive problems in psychotic disorders. Whereas most antipsychotics may decrease prefrontal activation, the partial dopamine D2-receptor agonist aripiprazole is hypothesized to improve prefrontal function. This study investigated whether patients with a psychotic disorder would show stronger activation of prefrontal areas and associated regions after treatment with aripiprazole compared to risperidone treatment.

In this exploratory pharmacological neuroimaging study, 24 patients were randomly assigned to either aripiprazole or risperidone. At baseline and after nine weeks treatment they underwent an interview and MRI session. Here we report on brain activation (measured with arterial spin labeling) during performance of two tasks, the Tower of London and the Wall of Faces.

Aripiprazole treatment decreased activation of the middle frontal, superior frontal and occipital gyrus (ToL) and medial temporal and inferior frontal gyrus, putamen and cuneus (WoF), while activation increased after risperidone. Activation increased in the ventral anterior cingulate and posterior insula (ToL), and superior frontal, superior temporal and precentral gyrus (WoF) after aripiprazole treatment and decreased after risperidone. Both treatment groups had increased ventral insula activation (ToL) and middle temporal gyrus (WoF), and decreased occipital cortex, precuneus and caudate head activation (ToL) activation.

In conclusion, patients treated with aripiprazole may need less frontal resources for planning performance and may show increased frontotemporal and frontostriatal reactivity to emotional stimuli. More research is needed to corroborate and extend these preliminary findings.

1. Introduction

Cognitive impairment is common in severe forms of psychotic disorders, such as schizophrenia (Barch and Ceaser, 2012). Indeed, performance deficits have been established on a wide range of neurocognitive tasks (Fatouros-Bergman et al., 2014). Impaired function of a fronto-striatal-parietal network has been implicated as a source of both negative symptoms and neurocognitive problems (Konstantakopoulos et al., 2011).

Dopamine and serotonin play a major role in the brain networks that are altered in schizophrenia and other psychotic disorders (Puig and Gullede, 2011; Dauvermann et al., 2014). According to the dopamine hypothesis, there is a twofold abnormality or imbalance. On the

one hand, there is a hyperdopaminergic state in the mesolimbic pathways, including the striatum. On the other hand, there is a hypodopaminergic state in the mesocortical pathways, which include the prefrontal cortex (Howes and Kapur, 2009). Whereas striatal hyperactivation has been related to positive symptoms, negative symptoms and cognitive problems have been related to impaired function of the prefrontal cortex (Brown and Thompson, 2010).

Antipsychotic drugs have been shown to be effective in the treatment of positive symptoms, but may have negligible or at best only very modest effects on negative or cognitive symptoms (Abi-Dargham, 2014). This may be caused by postsynaptic dopamine-2 receptor blockade of most antipsychotics in the prefrontal cortex that may already be in a hypodopaminergic state (Dauvermann et al., 2014).

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Combined with effects on serotonin receptors (predominantly post-synaptic 5-HT_{2a} antagonists), partial agonists of the dopamine D₂ receptor have shown to counterbalance the hypo- and hyperdopaminergic conditions respectively (Bortolozzi et al., 2007). The first commercially available drug of this type is aripiprazole. This antipsychotic improves both negative symptoms and cognitive dysfunction, although the effects may not be strong compared to similar effects of other antipsychotics (Fleischhacker, 2005). Moreover, animal studies have confirmed that aripiprazole acts as an agonist in frontal areas (Bortolozzi et al., 2007; Jordan et al., 2004).

It has been shown that specific antipsychotics have different effects on brain activation as measured by neuroimaging (Liemburg et al., 2012; Dazzan, 2014). We hypothesize that because of the partial antagonism of aripiprazole, the hypodopaminergic conditions of the mesocortical system will be balanced and activity of the frontal cortex will increase after treatment (Howes and Kapur, 2009). This would be in contrast to antipsychotics, like risperidone, that are thought to reduce a hyperdopaminergic state by blocking the postsynaptic D₂ receptors. Risperidone also shows major antagonistic affinity for serotonergic and adrenergic systems. One study in schizophrenia patients has shown increased prefrontal activation after aripiprazole treatment during a working memory task (Schlagenhauf et al., 2010). However, this study did not compare the effects to a strong dopamine antagonist and follow-up time was only three weeks. A behavioral study of effects of aripiprazole on alcohol consumption suggested a beneficial effect on cognitive control (Voronin et al., 2008), which is likely to be mediated by frontal cortex involvement. The current study aims to compare the effect of the partial dopamine agonist aripiprazole to the strong dopamine antagonist risperidone on task related brain activation.

We choose to study the effects using two different tasks that activate the prefrontal cortex. The Tower of London (ToL) task is a suitable task to investigate planning related brain activation in frontal-striatal-parietal brain circuits (Shallice, 1982). An early PET study using the ToL has shown decreased medial prefrontal activation in schizophrenia that was related to the severity of negative symptoms (Andreassen et al., 1992). A more recent fMRI study in schizophrenia patients also showed evidence for prefrontal dysfunction compared to healthy individuals (Rasser et al., 2005).

The second task is a socio-emotional processing task, the Wall of Faces (WoF) task, which measures the response to social-emotional ambiguity (Simmons et al., 2006). Subjects are asked to determine the dominant emotion or gender (control condition) in a group of faces in ambiguous or unambiguous ratios. In healthy subjects this task has shown to activate the ventromedial and dorsolateral prefrontal cortex (VMPFC and DLPFC), the ventral and dorsal anterior cingulate (ACC), and posterior parietal cortex (PPC) (Simmons et al., 2006; Dlabac et al., submitted). We have shown that patients have altered activation in the insula, ACC, prefrontal and precentral brain regions compared to controls, and hypoactivation of prefrontal (including vACC and VMPFC), parietal, temporal, striatal, precentral and occipital areas in relation to negative symptoms (Dlabac et al., submitted).

To summarize, in this study we investigated the effect of aripiprazole compared to risperidone treatment on brain activation in frontal-striatal-thalamic brain regions involved in planning and socio-emotional processing. We hypothesized that patients with a psychotic disorder will show larger increases in prefrontal activation after treatment with aripiprazole compared to patients treated with risperidone.

2. Methods

2.1. Subjects

This single-blind, parallel, randomized controlled trial (January 2008–August 2015), in which aripiprazole was compared to risperidone on brain function, was preregistered (EUDRA-CT: 2007-002748-79; NL17987.042.07) and executed in accordance to the declaration of

Helsinki after approval by the local ethical committee of the University Medical Center of Groningen (METC 2007.139). Baseline results of brain activation during both tasks (irrespective of medication) have been reported previously (Liemburg et al., 2014; Dlabac et al., submitted); the current report concerns the treatment effects, involving pre- and post fMRI measurements. Participating subjects gave oral and written consent after the procedure had been fully explained. Patients in this trial (n = 24) were recruited by clinicians from mental health care centers in the northern part of the Netherlands (Groningen), and randomly assigned (12 vs. 12) to treatment with either aripiprazole or risperidone in blocks of eight subjects. Randomization was performed by sealed envelopes created by the first author that were opened by an independent researcher not involved in the study and unfamiliar with the study content. Power analysis before starting the current trial was based on the study of Honey et al. (1999), who reported a study on activation of the frontal cortex and compared risperidone with a typical antipsychotic. Given the effect size of $t = 2.6$ ($\alpha = 0.01$) with an N of 10 in each group and a p-value of 0.007, we included N = 12 in each group to have a power of > 0.80. Moreover, from a clinical point of view, a previous study from our group has failed to find an effect of negative symptoms, but did find an effect on Subjective Wellbeing (n = 16, mean = 134.4, SD = 12.8 for aripiprazole; n = 17, mean = 118.6, SD = 18.6 for risperidone; $t = 2.8$, $p = 0.008$) (Liemburg et al., 2011), which resulted in a power of 0.78. Assuming that with subclinical effects the sample size could be reduced by a factor 2, > 10 subjects would be sufficient per group. Data of the current and former study are available upon request at the corresponding author.

Patients could be medication naïve at baseline, or use an oral antipsychotic other than the treatment drugs. Dosage could flexibly be adjusted by the clinician, but was preferably 7.5–15 mg for aripiprazole and 2–5 mg for risperidone. Clinicians were given a maximum of three weeks for switching to or starting the study medication, followed by six weeks of monotherapy with the target antipsychotic. Measurements took place a baseline and after nine weeks of treatment. If patients wished to stop their treatment but were willing to complete the study, the second measurement was conducted earlier but at minimum after six weeks.

Diagnosis was based on the Schedules for Clinical Assessment (SCAN 2.1) diagnostic interview (Giel and Nienhuis, 1996). All patients met DSM-IV criteria for a diagnosis of schizophrenia or a related non-affective psychotic disorder. A comorbid depression or history substance abuse (> 6 months before) was allowed. Patients had to abstain from drugs and alcohol 24 h before testing. Further exclusion criteria included age < 18 or > 60 years, MRI incompatible objects (e.g. medical pumps, prostheses, piercings, red tattoos), (suspected) pregnancy, claustrophobia, history of neurological abnormalities (e.g. epilepsy), history of severe head injury, brain infarction, and inability to provide informed consent.

2.2. Symptoms and demographics

Severity of symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Depression was measured with the Montgomery Asberg Depression Rating Scale (MADRS) (Williams and Kobak, 2008). Experienced (side) effects of the antipsychotics were measured by using the Subjective Response to Antipsychotics (SRA) (Wolters et al., 2006) and the Subjective Wellbeing under Neuroleptics (SWN) (Naber et al., 2001). Interviewers were by trained and certified as well as blinded to the allocated medication and to the rationale of the study.

Demographical data (age, gender, handedness) were also recorded. Since part of the subjects was young and had not finished education, the highest education level that a subject finished or expected to finish was recorded according to Verhage (range: 1. elementary school to 8. university) (Verhage, 1984). Type and dose of antipsychotic were also recorded pre-treatment and after treatment, and doses were converted

to haloperidol equivalents (Andreasen et al., 2010).

2.3. Imaging procedures

The tasks analyzed in this paper were part of an MRI protocol that also included an anatomy scan, a spectroscopy scan and a resting state scan. Tasks were presented using E-prime 1.2, which logged timing of the task and responses of the subjects. Subjects responded by button presses on an MR-compatible button box using the index and middle finger of their right hand.

We implemented the Tower of London based on a previous study (Lazeron et al., 2000). In the planning condition, two configurations were shown of three colored beads (blue, red, green) placed on three rods that could accommodate 1, 2 or 3 beads. Subjects had to indicate the minimum number of moves of beads needed to get from the upper configuration to the lower, based on two answers presented below. Only on top bead could be moved at a time. In the control condition subjects had to count the number of blue and red beads (Lazeron et al., 2000; van den Heuvel et al., 2003). Both conditions were alternated in block design (60 s, each five times repeated) interspersed with 30 s resting blocks with a fixation cross. Trials were self-paced and interspersed with a 250 ms fixation cross. Prior to scanning, the task was practiced on a laptop. After explanation, subjects were asked whether the instructions were clear. Five trials for the planning condition and 2 for the control condition were presented and oral feedback was given when subjects gave an incorrect answer or appeared unconfident. Hereafter, the subjects practiced two planning blocks and one control block without feedback.

The Wall of Faces task was based on a version in a previous study (Simmons et al., 2006). For each trial, an array of 32 affective faces (i.e. angry or happy) was presented to a subject. Participants were asked to identify the predominant emotion (affective trials, experimental condition) or the predominant gender (gender trials, control condition). The ratio of angry to happy faces and male to female faces could be equal (ambiguous, 16:16) or unequal (unambiguous, 26:6). In each trial, the array of faces was presented for the duration of 3 s with an additional 1.5 s response time. During face presentation and response time, the options “Angry - Happy” or “Female - Male” were displayed on the screen. Blocks of 8 trials (48 s) started with an instruction (“emotion” or “gender”) and were interleaved with a rest condition (24 s). Emotion and gender blocks alternated.

2.4. Image acquisition

MRI scans were acquired using a Philips Achieva 3 Tesla MRI scanner (Best, The Netherlands) with an 8-channel SENSE head coil. Subjects were placed in the scanner as comfortable as possible. Foam pads fixating the head restricted movement and earplugs and headphones reduced noise from the scanner. The task was presented on a screen visible via a mirror on top of the head coil.

During the tasks a pseudo-continuous arterial spin labeling (PCASL) sequence was acquired, because ASL is more stable in comparing measurements far apart in time, it enables quantification of baseline activity instead of only relative changes, has a lower inter-subject variability, and better functional localization (Liu and Wong, 2005; Wang et al., 2008). Control and labeling scans (TR = 4 s) were alternated. Labeling time was 1650 ms, delay time 1525 ms and acquisition time was 825 ms. Further parameters: flip angle 90°, 14 slices, FOV (ap, fh, rl) = 224 × 98 × 224 mm, voxel size 1.75 × 1.75 × 7 mm. The planes were oriented AC-PC and tilted 10–20° backwards to exclude air-related artifacts from the sinuses. When the whole brain could not be covered, coverage of the temporal lobes was assured by omitting part of the sensorimotor cortex.

2.5. Data analysis

To test for baseline differences, age, education and haloperidol equivalents were compared using a Mann Whitney *U* test because of non-normality, and gender, handedness and type of antipsychotic using a Chi-square test for independence.

The Positive, Negative and General pathology scale of the PANSS and MADRS total score were compared between both treatment groups using a repeated measures ANOVA with group as a between-subjects factor and measurement (pre vs. post) as a within-subjects factor. Results were corrected for multiple comparisons with a False Discovery Rate (FDR) correction. SRA and SWN scores are presented in the results for reference, but not compared between groups due to power problems.

ToL task performance was measured as reaction times (in seconds) and accuracy (% correct). A distinction was made between easy trials (1–2 moves/balls) and difficult trials (3–5 moves/balls). WoF task performance was measured by comparing reaction times (in seconds), and accuracy of the unambiguous trials (% correct). As there were no correct responses in the ambiguous trials, the response percentage of male faces for the gender trials and angry faces for the affective trials were measured. Missing entries were not included in the analysis. Performance was compared between both treatment groups using repeated measures ANOVA with group as a between-subjects factor and measurement as a within-subjects factor and results were FDR corrected.

Imaging data were analyzed using in-home scripts based on Statistical Parametric Mapping (SPM8; FIL Wellcome Department of Imaging Neuroscience, London, UK) routines and functions, running on Matlab R2009a (7.8.0.347). For detailed description of the analysis steps, see Supplementary Methods S1. In short, images were motion corrected, nuisance factors (motion, gray and white matter) were filtered from the data and images were subtracted to obtain perfusion images. After smoothing (FWHM = 8 mm), first level analyses were performed. Data were intensity normalized and spatially normalized and whole-brain analyses were performed using Statistical non-Parametric Mapping (SnPM) (Nichols and Holmes, 2002).

3. Results

A CONSORT flow diagram of the study indicating the numbers and reasons of exclusion can be found in Supplementary Fig. S1. Group did not differ significantly in age, gender, education, handedness and antipsychotic use (see Table 1). The high incidence of psychosis NOS was caused by patients not meeting the time criteria for a diagnosis of schizophrenia, as most of them were recently diagnosed with a first episode psychosis. One subject in the risperidone group had to be excluded due to artifacts in the ASL images during the ToL, and two during the WoF. One subject was scanned after six weeks and one after eight weeks because of side effects of risperidone and insufficient clinical effect of aripiprazole respectively. Findings from the SRA and SWN are reported in Supplementary Table S1.

Repeated measures ANOVA showed that there was a significant improvement of positive symptoms in both groups ($p < 0.0005$) and of general pathology ($p = 0.002$), and a trend for an improvement of MADRS depression ($p = 0.048$; not surviving FDR correction) (Supplementary Fig. S2). There was no significant effect of treatment group nor an interaction. There was no significant effect of either treatment on task performance in both tasks, or a difference between groups (see Supplementary Fig. S3).

In the planning > baseline contrasts of the ToL, significant activation in the cuneus, bilateral Middle Occipital Gyri (MiOG), right Inferior Temporal Gyrus (ITG), left Middle Frontal Gyrus (MiFG) and right Superior Parietal Lobule (SPL) was observed across patient groups at baseline. In the planning > count balls the precuneus, cuneus, left cingulate gyrus and right MiFG were activated. Increased task difficulty

Table 1
Demographic and clinical characteristics of both treatment groups.

	Aripiprazole		Risperidone		p-Value
	Mean/%	SD/N	Mean/%	SD/N	
Age (SD)	27.6	10.3	27.8	10.1	0.93
Gender (% male)	92%	11	83%	10	0.54
Education (SD) ¹	5.6	1.0	5.3	1.4	0.83
Handedness (% right)	83%	10	92%	11	0.54
Diagnosis (%)					0.68
Schizophrenia	33%	4	58%	7	
Schizophreniform disorder	8%	1	8%	1	
Schizoaffective disorder	8%	1	0%	0	
Delusional disorder	8%	1	8%	1	
Psychosis NOS	42%	5	25%	3	
Antipsychotic pre-study (%)					0.50
None	50%	6	50%	6	
Olanzapine	50%	6	33%	4	
Quetiapine	0%	0	8%	1	
Zuclopenthixol	0%	0	8%	1	
haloperidol equivalents pre-study (SD) ^a	3.3 mg	1.1	3.9 mg	4.7	0.43
dose aripiprazole/risperidone (SD)	7.7 mg	2.3	2.3 mg	1.0	–
haloperidol equivalents study (SD)	2.5 mg	1.1	3.6 mg	1.7	0.060

^a Only patients taking antipsychotics.

¹ Based on the system of Verhage (1984).

did not result in significant brain activation. Cluster information is shown in Supplementary Table S2 and Supplementary Fig. S4.

The analysis on the interaction between treatment and group showed that after treatment, patients treated with aripiprazole had a significant decrease in activation of the left MiFG and MiOG in the planning > count contrast, while patients treated with risperidone had an increased and similar activation respectively. Moreover, in the parametric modulation contrast aripiprazole treated patients showed a decrease in activation in the right middle and bilateral superior frontal gyrus (MiFG and SFG), while there was an increase in the risperidone group. In contrast, patients treated with aripiprazole showed increased activation in the posterior insula and ventral anterior cingulate gyrus after treatment, and risperidone treated patients a decrease. There was no effect in the planning > baseline contrast. See for significant clusters and graphs with condition specific median beta-values Fig. 1 (see also Supplementary Table S3).

In both groups, there was a significant decrease in activation in the bilateral cuneus in the planning > baseline contrast. In the planning > count contrast patients had decreased activation in the superior occipital gyri, precuneus and caudate head. For the parametric modulation contrast, there was an increased activation after treatment in the left anterior insula (Fig. 2; Supplementary Table S4).

The WoF did not reveal any activation when investigating all pre-treatment scans with a one-sampled *t*-test. In the ambiguous emotion > gender contrast, risperidone treated patients showed stronger activation of the right middle temporal gyrus (MiTG) and cuneus, and the left IFG and putamen after treatment, while activation in these areas decreased in the aripiprazole treated patients. However, the group analysis showed that after aripiprazole treatment activation increased in the right SFG and superior temporal gyrus (STG), and the left precentral gyrus in the emotion ambiguous > unambiguous contrast, contrasted by a decrease in the risperidone group (Fig. 3; Supplementary Table S5). In both groups, the MTG had increased activation after treatment during the emotion ambiguous > emotion unambiguous contrast (Fig. 4; Supplementary Table S6).

4. Discussion

This is the first exploratory study, to our knowledge, to investigate

the possible neural effects of aripiprazole compared to risperidone treatment in patients with a psychotic disorder during a planning task (Tower of London; ToL) and socio-emotional task (Wall of Faces; WoF). We observed potential different effects of the two distinct antipsychotics. Aripiprazole treatment decreased activation of the middle frontal, superior frontal and occipital gyrus (ToL; planning) and medial temporal and inferior frontal gyrus, putamen and cuneus (WoF; emotion), whereas activation increased after risperidone. In contrast, activation increased in the ventral anterior cingulate and posterior insula (ToL), and superior frontal, superior temporal and precentral gyrus (WoF) after aripiprazole treatment but decreased in those regions after risperidone. Both treatment groups had increased ventral insula activation (ToL), and decreased occipital cortex, precuneus and caudate head activation (ToL) and middle temporal gyrus (WoF) activation after treatment. Both groups also showed a significant improvement of positive symptoms, general pathology and depressive symptoms, but no change in negative symptoms.

When integrating the findings, treatment with aripiprazole appears to decrease lateral prefrontal and temporal activation during planning, mainly related to task difficulty, while activation increases during socio-emotional processing. Risperidone shows opposite results. Previous (longitudinal) patient treatment studies did not report significant prefrontal changes after aripiprazole treatment (Schlagenhauf et al., 2010; Sarpal et al., 2015; Ikuta et al., 2014; Schirmbeck et al., 2015). Moreover, single dose studies in healthy subjects show decreased prefrontal activation after aripiprazole treatment (Kim et al., 2013; Kim et al., 2008; Handley et al., 2013), but also preserved prefrontal and parietal brain activation (Goozee et al., 2015) or non-significantly increased frontal and temporal activation (Bolstad et al., 2015). In part of these studies, haloperidol decreased brain activation in these regions (Handley et al., 2013; Goozee et al., 2015; Bolstad et al., 2015). Concerning differences between patients and controls, long-term antipsychotic treatment in schizophrenia patients with putatively lower prefrontal dopamine levels than healthy subjects (Howes and Kapur, 2009) may result in a different prefrontal reaction than in healthy subjects after single-dose exposure (Vernaleken et al., 2006).

Importantly, complex patterns of decreases and increases in prefrontal activation may be caused by an interaction between task-complexity and resulting brain activation. The response of the prefrontal cortex to increased task load is thought to follow an inverted U-curve associated with dopamine transmission, with optimal performance at intermediate dopamine receptor stimulation (Mattay et al., 2003). In patients with schizophrenia this curve is shifted leftwards (Egan et al., 2001). Therefore, they may show increased activity to compensate performance problems, while activation and task performance drop if the maximum capacity is exceeded (Di Pietro and Seamans, 2008; Glahn et al., 2005). Similar patterns may be found in the temporal lobes, as abnormalities in both brain regions may result in similar symptoms (John, 2009). Thus, aripiprazole treatment may have resulted in decreased prefrontal effort with spared performance during planning and increased prefrontal responsivity during emotional stimuli, while risperidone may have opposite effects.

During socio-emotional processing, patients treated with aripiprazole showed increased activation of the superior temporal gyrus, which has been implicated in emotion processing and recognition (Simmons et al., 2006), and the precentral gyrus, for which increased activation to emotional stimuli has been reported after social cognitive training (Hooker et al., 2012).

We also observed increased ventral ACC and posterior insula activation after aripiprazole treatment during planning, contrasted to a decrease in the risperidone group. The posterior insula is a multimodal convergence zone for sensory information that processes exteroceptive and interoceptive information (Chang et al., 2013). The ACC has been implicated in emotional self-control, focused problem solving, error recognition, and adaptive response to changing conditions (Allman et al., 2001). Other studies have also found increased ACC activation

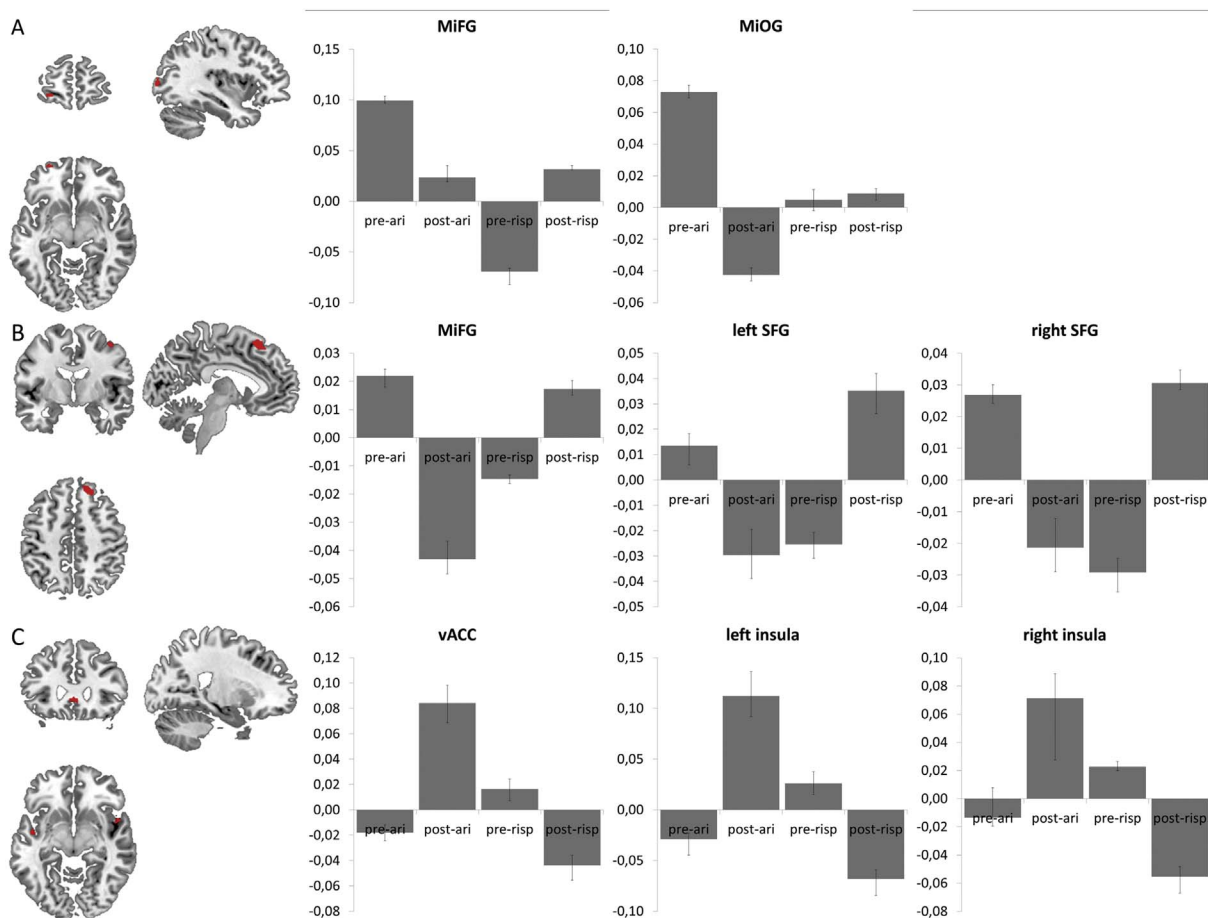


Fig. 1. Interaction during ToL between treatment and group with the interaction effect on the left and graphs depicting the mean beta-value per group on the right ($p < 0.001$, $k > 20$, pseudo- $T > 3$); A. Planning > count beads, B. Parametric modulation, C. Parametric modulation other direction (MiFG = middle frontal gyrus, MiOG = middle occipital gyrus, SFG = superior frontal gyrus, vACC = ventral ACC).

after treatment, although never specifically for aripiprazole (Schlagenhauf et al., 2010; Sarpal et al., 2015; Ikuta et al., 2014). Combining data from this study and a previous study (Liemburg et al., 2011) to increase power, patients treated with aripiprazole reported better scores on the Emotion regulation and better self-control subscales on the Subjective Wellbeing on Neuroleptics (Naber et al., 2001). Based on these findings, we speculate that this improved emotional awareness and self-control in patients treated with aripiprazole may be related to improved ACC and insula activation.

Besides differences, we also found several similar effects for both antipsychotics, as both treatment groups had an increase in ventral insula activation, and a decrease in activation of the occipital cortex,

precuneus and caudate head. Ikuta et al., 2014 observed reduced basal ganglia activation in both aripiprazole and risperidone treated patients, while Handley et al., 2013 showed increased striatal and insular cerebral blood flow after treatment with either haloperidol and aripiprazole in healthy subjects (Ikuta et al., 2014; Handley et al., 2013). It has been shown that striatal dopamine binding affects prefrontal metabolism (Kim et al., 2008). The insula has shown reduced perfusion and decreased lateral frontal coupling in healthy subjects after treatment with a dopamine receptor antagonist (Fernandez-Seara et al., 2011). Furthermore, Sarpal et al., 2015 observed increased connectivity from striatal regions to ACC, DLPFC, ACC, hippocampus and insula after treatment with aripiprazole and risperidone (Sarpal et al., 2015).

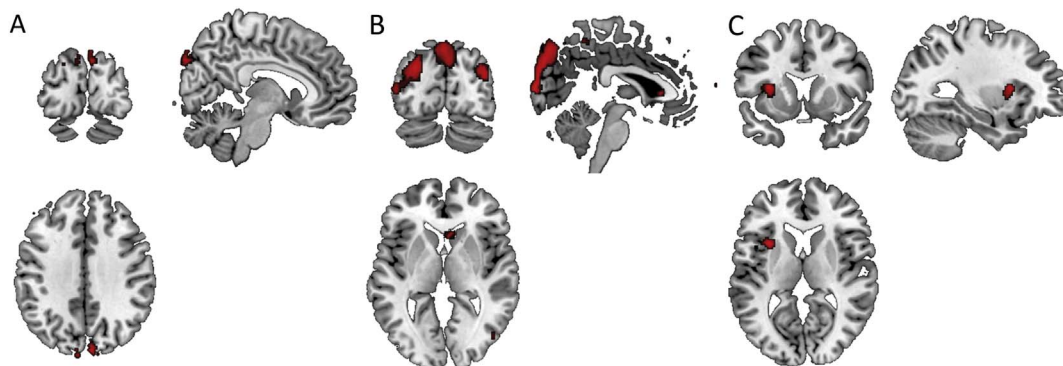


Fig. 2. Main effect of treatment during ToL ($p < 0.001$, $k > 20$, pseudo- $T > 3$); A. Planning > fixation pre- > posttreatment, B. Planning > count pre- > posttreatment, C. Planning > count, post- > pretreatment.

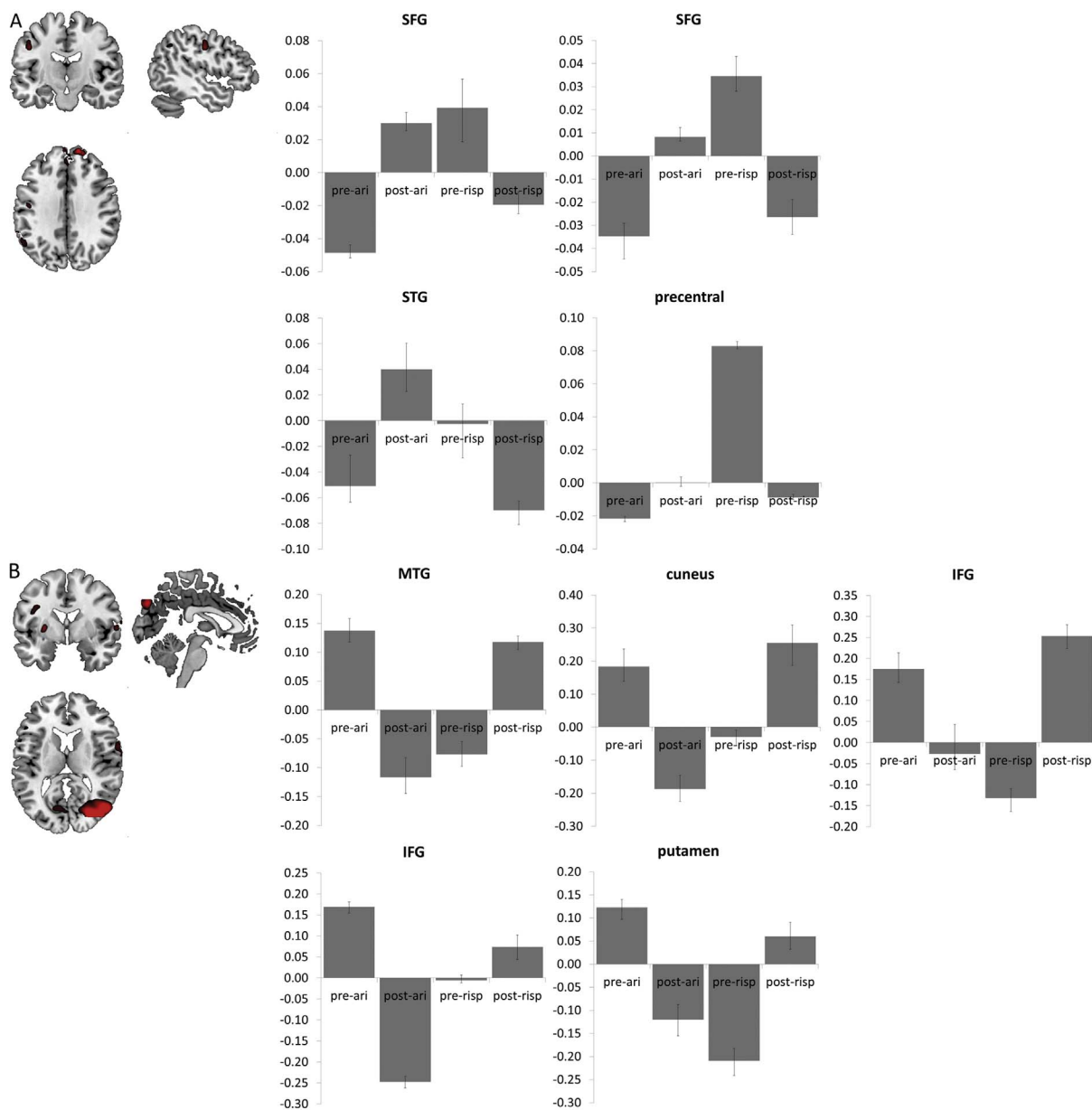


Fig. 3. Interaction during WoF between treatment and group with the interaction effect on the left and graphs depicting the mean beta-value per group on the right ($p < 0.001$, $k > 20$, pseudo- $T > 3$); A. Emotion ambiguous > emotion unambiguous, B. Emotion ambiguous > gender ambiguous (SFG = superior frontal gyrus, STG = superior temporal gyrus, precentral = precentral gyrus, MTG = middle temporal gyrus, IFG = inferior frontal gyrus).

Although speculative, these results could indicate that both aripiprazole and risperidone affected striatal dopamine binding in our study, but have a different prefrontal effect due to their receptor properties.

Both groups had a decrease in visual area activation after treatment that may be more pronounced in aripiprazole, and the latter group also had reduced putamen activation. Previous studies have also shown altered activation in posterior visual and parietal brain regions after treatment with both aripiprazole and strong dopamine receptor antagonists (Ikuta et al., 2014; Handley et al., 2013). Patients also have a lower activation in occipital regions compared to healthy subjects during ToL performance (Rasser et al., 2005). It has been suggested that from onset of psychosis, the earliest deficits may be found in parietal brain regions involved in visuo-spatial and associative thinking (Cannon et al., 2002). Moreover, there are known reciprocal connections between prefrontal and parietal brain regions, which may convey visuospatial information during working memory performance (Goldman-Rakic, 1995). As most subjects were recently diagnosed and

were medication free or only using antipsychotics for few weeks at the first scan, altered posterior activation in our study may be a secondary effect of dopaminergic alterations in the PFC (Honey et al., 1999).

Some limitations of this study should be mentioned. First, the sample size should preferably be larger and our correction method tolerated the risk for type-I errors to a certain extent. However, most pharmacological MRI studies till now have limited sample sizes, due to the challenging study design. Moreover, it has recently been suggested that stringent correction for multiple comparison may also lead to inflated false negative rates that may undermine reproducibility (Lohmann et al., 2017). Finally, a paper not specific for neuroimaging has stated that stringent testing for multiple comparisons is not obligated in exploratory studies, but is in confirmatory (Bender and Lange, 2001). Our findings certainly need confirmation, preferably in larger or combined samples. On a different note, whereas we hypothesized that aripiprazole would lead to a better improvement in negative symptoms than risperidone, patients in both groups did not improve on negative

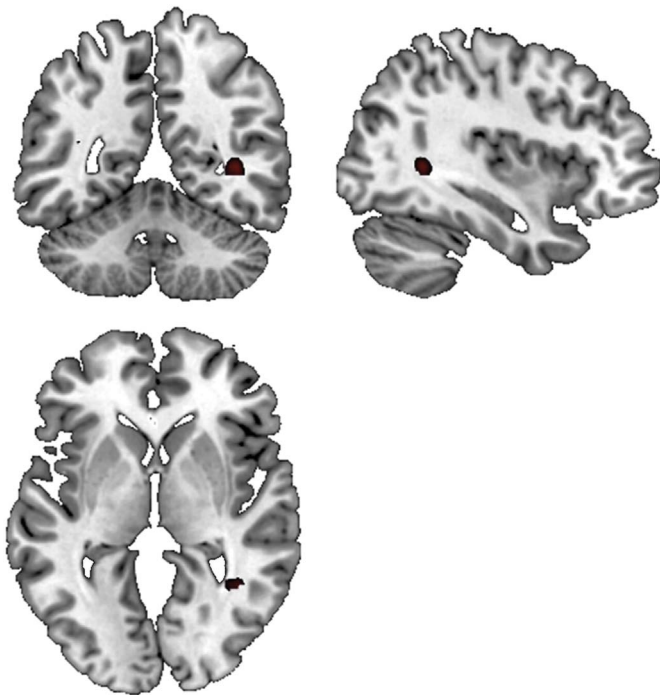


Fig. 4. Main effect of treatment during WoF ($p < 0.001$, $k > 20$, pseudo- $T > 3$); emotion ambiguous > emotion unambiguous post- > pretreatment.

symptoms but only on positive symptoms. However, aripiprazole treated patients reported a better subjective emotional wellbeing than risperidone treated patients (Supplementary Table 1; (Liemburg et al., 2011)). Effects of previous medication may also have an influence on the current findings, although two thirds of the subjects were medication free, and most other subjects only used antipsychotics for a few weeks before entering the study. Serum level measurements of antipsychotics may have helped to investigate both treatment adherence and dosage effects of treatment. Another limitation was the lack of activation in the baseline condition of the WoF task. That is, no significant activation difference was found for the emotion ambiguous vs. gender ambiguous and emotion ambiguous vs. emotion unambiguous in our patient sample, at baseline. This may be due to the fact that the different conditions are very similar in terms of visual input (array of faces on a screen) and cognitive processes. However, a previous studies from our group has shown however that, in healthy participants, ambiguous > unambiguous emotion resulted in significant differences in brain activation in the left middle occipital gyrus, the left DLPFC, the left lingual gyrus and the right middle occipital gyrus (Dlabac et al., submitted). Ambiguous emotion > gender showed higher brain activation in the left precentral gyrus in that study. Antipsychotic treatment may have normalized WoF related brain activation, which could not be shown post-treatment due to the small sample size. Finally, we did not separately investigate a possible learning effect of being scanned twice, which has been shown before (Ikuta et al., 2014). However, this should not be a problematic issue, as we did not observe improvement in performance of patients.

In conclusion, differential effects of risperidone and aripiprazole may be explained by their specific effects on the dopamine and serotonin system, but await further confirmation. During planning, prefrontal capacity of aripiprazole treated patients appeared to improve, while posterior brain regions show a similar response to both antipsychotics. During social-emotional processing, patients treated with aripiprazole may have a stronger brain response to emotional stimuli, in contrast to risperidone. Studies in larger samples are needed to further investigate putatively differential effects of atypical antipsychotics on cognitive and emotional processing.

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Contributors

E.J.L., HK and AA designed the study and wrote the protocol. E.J.L. wrote the first draft of the manuscript. FdV was involved in subject recruitment and helped writing the manuscript. All authors contributed to and have approved the final manuscript.

Ethical statement

This single-blind, parallel, randomized controlled trial (January 2008–August 2015), in which aripiprazole was compared to risperidone on brain function, was preregistered (EUDRA-CT: 2007-002748-79; NL17987.042.07) and executed in accordance to the declaration of Helsinki after approval by the local ethical committee of the University Medical Center of Groningen (METC 2007.139). Participating subjects gave oral and written consent after the procedure had been fully explained.

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