Progress in Neuropsychopharmacology & Biological Psychiatry 79 (2017) 112–119

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

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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ARTICLE INFO

Keywords:
Antipsychotic
Prefrontal
Neuroimaging
Psychotic disorders

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 Gulledge, 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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http://dx.doi.org/10.1016/j.pnpbp.2017.05.022
Received 1 March 2017; Received in revised form 28 April 2017; Accepted 26 May 2017
Available online 27 May 2017
0278-5846/

Combined with effects on serotonin receptors (predominantly post-synaptic 5-HT2a 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 (Andreasen 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 ratio's. In healthy subjects this task has shown to activate the ventromedial and dorsolateral prefrontal cortex (VMPFC and DLFPC), 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