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Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naïve first-episode psychosis patients

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ABSTRACT

Atypical antipsychotic medications generally maintain or increase gray matter amount and functioning. First-episode psychosis patients have lower gray matter volume in the middle frontal gyrus, as well as worse performance on spatial working memory tasks compared to controls. This study investigated the effects of short-term four- and eight-week atypical treatment on middle frontal thickness and spatial working memory in first-episode psychosis patients. Nineteen drug-naïve first-episode psychosis patients treated with risperidone or quetiapine and 26 controls completed structural magnetic resonance imaging, a spatial working memory task, and clinical assessment at three intervals (baseline, four weeks, and eight weeks; all patients and 23 controls completed all three assessments). Caudal and rostral middle frontal thicknesses were measured using the automated program Freesurfer. Positive, negative, and general symptoms of the Positive and Negative Syndrome Scale (PANSS) decreased significantly in patients, with most of the change occurring in the first four weeks of treatment. Patients demonstrated an increase in rostral middle frontal thickness over eight weeks of treatment compared to controls. There was a medium effect size relationship between reduction in negative symptoms at four and eight weeks, and a change in rostral middle frontal thickness over eight weeks. No changes were found in spatial working memory ability. Short-term atypical treatment with risperidone or quetiapine can increase prefrontal cortical thickness in psychosis. These findings are notable given the role of the rostral middle frontal region in cognition and the relationship between better cognitive functioning and better functional outcome in psychosis.

1. Introduction

The middle frontal gyrus is of particular interest in schizophrenia given its role in goal-directed behavior (MacDonald et al., 2000; De Pisapia et al., 2007). Drug-naïve first-episode psychosis (FEP) patients demonstrate lower middle frontal gray matter (Gur et al., 2000) and abnormalities in middle frontal brain activity (MacDonald et al., 2005; Snitz et al., 2005). These abnormalities are present early in the disorder (Fusar-Poli et al., 2010, 2011) and tend to be progressive (Pol and Kahn, 2008; Cobia et al., 2012), suggesting that early effective treatment is crucial. Some of the available atypical antipsychotic medications have been shown to maintain or increase gray matter amount and brain activity even within a short time frame of three weeks (Deng et al., 2009). The goal of this investigation was to determine whether short-term atypical treatment could increase middle frontal thickness and improve spatial working memory in drug-naïve FEP patients compared to controls.

A number of studies, using patients treated with typical antipsychotic medications for comparison, have demonstrated that atypical antipsychotic medication may maintain or increase gray matter volumes in youth with psychosis; however the clinical and/or functional significance of these potential changes are unclear. Dazzan et al. (2005) demonstrated that drug-naïve FEP patients treated for a mean length of eight weeks with mainly olanzapine, but also risperidone, quetiapine, sertindole, and amisulpride, maintained cortical gray matter in frontal, temporal, and occipital areas as opposed to patients on the typical antipsychotics chlorpromazine, sulpiride, haloperidol, thioridazine, droperidol, trifluoperazine, and zuclopenthixol. Consistent with this finding, a study comparing the typical haloperidol to the atypical olanzapine, found that FEP patients treated with haloperidol, but not olanzapine, lost frontal gray matter at weeks 12 and 24 (Lieberman et al., 2005). Furthermore, changes in gray matter in schizophrenia

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patients have been documented in as little as three weeks of treatment with amisulpride, olanzapine, risperidone, quetiapine, trifluoperazine, flupenthixol, or haloperidone. Specifically, with the majority of these patients receiving an atypical medication, cortical gray matter volume was increased in the superior and inferior prefrontal and inferior parietal regions and decreased in the medial prefrontal region (Deng et al., 2009).

As different regions of the brain demonstrate different responses to antipsychotic medication (Navari and Dazzan, 2009), this study specifically evaluated the middle frontal region, given its role in pathophysiology of psychotic disorders. Distinct components of the middle frontal region, the rostral and caudal areas, have been investigated (Kikinis et al., 2010). The rostral area encompasses parts of Brodmann area 46, which is considered part of the dorsolateral prefrontal cortex, whereas the caudal area is considered part of the premotor region (Desikan et al., 2006; Kikinis et al., 2010). Brodmann area 46 is consistently associated with working memory in schizophrenia (Casey et al., 1998; Wager and Smith, 2003). Working memory ability has been reliably demonstrated to be impaired in psychosis and associated with hypo- or hyper-activity in Brodmann area 46 (Manoach, 2003; Brahmbhatt et al., 2006). Given the role of the rostral middle frontal region in goal-directed behavior, it is an important target for intervention in psychosis.

In addition to investigating brain structure, studies have set out to determine whether the atypical antipsychotics can improve cognitive functioning. In this regard, studies have found spatial working memory improves after four weeks of risperidone treatment in drug-free treatment resistant schizophrenia (McGurk et al., 2004) and after eight weeks of risperidone or olanzapine treatment in schizophrenia or schizoaffective disorder (Harvey et al., 2003). However, this is not a wholly consistent finding, as six weeks of risperidone or olanzapine and risperidone treatment has been shown to reduce spatial working memory performance in drug-naïve FEP patients (Reilly et al., 2006, 2007).

In summary, to better understand the effects of short-term naturalistic treatment with atypical antipsychotics, risperidone or quetiapine, on the brains of drug-naïve patients in the early phases of their illness, we had three main objectives: (1) to determine whether middle frontal thickness and spatial working memory performance is lower in drug-naive FEP patients compared to controls at baseline, (2) to determine whether four or eight weeks of atypical medication treatment can increase middle frontal thickness and spatial working memory performance in FEP patients, and (3) whether there is a differential effect of atypical antipsychotic treatment on the rostral versus caudal area of the middle frontal region. We hypothesized that patients would have thinner middle frontal regions compared to controls at baseline, and that eight weeks of risperidone or quetiapine treatment would increase middle frontal thickness. Last, we hypothesized that the rostral middle frontal region would benefit more from atypical antipsychotic medication than the caudal middle frontal region.

2. Materials and methods

2.1. Participants

The sample consisted of 19 FEP patients (drug-naïve prior to study) and 26 healthy controls (see Table 1). Participants completed three assessments: baseline, four weeks, and eight weeks. All patients and 23 controls finished all three assessments. Twenty-six controls finished the baseline assessment, 25 controls completed the four week assessment, and 23 controls finished the eight week assessment. DSM-IV-TR diagnoses for patients were: schizophrenia (N = 6), schizoaffective disorder (N = 5), schizophreniform disorder (N = 5), psychosis not otherwise specified (NOS; N = 2), and major depressive disorder with psychotic features (N = 1). Of the 19 patients, 16 patients were on risperidone and three patients were on quetiapine at the start of the study, and 15 patients were on risperidone, three patients were on quetiapine, and one patient was on both risperidone and quetiapine at the mid-point of the study (see Table 2 for dosages). Thirteen patients began the medication on the same day as the baseline scan. The mean difference between medication start date and baseline scan was approximately three days (mean = 2.58; SD = 6.75). Percentage of patients taking different types of psychiatric medications is reported in Table 2. Ten patients were on no other prescribed psychiatric medications for the duration of the study.

FEP patients were recruited through the Vancouver Coastal Health Authority Community Mental Health Services Program and the Fraser Health Authority Early Psychosis and Intervention Program in British Columbia, Canada. Controls were recruited from the community via poster advertisements. Recruitment criteria for all participants included: normal or corrected vision, minimum estimated intelligence quotient (IQ) of 80, aged 14 to 45, no history of CNS infections, no history of head injury leading to loss of consciousness for more than five minutes, and no diagnosis of drug abuse or drug dependence for the previous six months. After complete description of the study protocol was approved by the University of British Columbia's Ethics Review Board, all participants provided written consent.

2.2. Clinical assessment

All participants had DSM-IV diagnoses confirmed by a psychiatrist (LCK) at baseline. Clinical information was gathered from self-report, clinical interview, and interview with family members where possible. Psychiatric symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) at baseline, four weeks, and eight weeks (Kay et al., 1987). Intelligence (IQ) was estimated using the Kaufmann Brief

Table 1
Participant characteristics.

	First-episode psychosis	Controls	Statistic
Sample size	19	26[a]	–
Age: range	18.9 (3.6): 14.3–26.3	20.9 (2.1): 17.7–25.3	$F(1, 43) = 5.70$, $p = 0.02$
% Males	57.9	65.4	$X^2(1) = 0.26$, $p = 0.61$
Estimated IQ	102.1 (10.5)	109.0 (8.5)	$F(1, 43) = 6.06$, $p = 0.02$
Education (years)	11.4 (2.7)	14.3 (1.8)	$F(1, 43) = 18.78$, $p < 0.001$
Mother's education (years)	12.8 (1.9)	13.5 (3.99)	$F(1, 42) = 0.51$, $p = 0.48$
Any alcohol use within month before recruitment	47%	85%	$X^2(1) = 7.11$, $p = 0.008$
Any marijuana use within month before recruitment	21%	19%	$X^2(1) = 0.02$, $p = 0.88$
Any tobacco use within month before recruitment	11%	8%	$X^2(1) = 0.02$, $p = 0.88$
Any other drug use within month before recruitment	21%	20%	$X^2(1) = 0.11$, $p = 0.74$

Mean and standard deviation or percentage of participants.
[a] 26 controls finished baseline assessment, 25 controls completed four week assessment, 23 controls finished the eight week assessment, and 23 controls finished all three assessments.