Cognitive performance is associated with gray matter decline in first-episode psychosis

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ABSTRACT

Progressive loss of gray matter has been demonstrated over the early course of schizophrenia. Identification of an association between cognition and gray matter may lead to development of early interventions directed at preserving gray matter volume and cognitive ability. The present study evaluated the association between gray matter using voxel-based morphometry (VBM) and cognitive testing in a sample of 16 patients with first-episode psychosis. A simple regression was applied to investigate the association between gray matter at baseline and 80 months and cognitive tests at baseline. Performance on the Wisconsin Card Sorting Task (WCST) at baseline was positively associated with gray matter volume in several brain regions. There was an association between decreased gray matter at baseline in the nucleus accumbens and Trails B errors. Performing worse on Trails B and making more WCST perseverative errors at baseline was associated with gray matter decline over 80 months in the right globus pallidus, left inferior parietal lobe, Brodmann's area (BA) 40, and left superior parietal lobule and BA 7 respectively. All significant findings were cluster corrected. The results support a relationship between aspects of cognitive impairment and gray matter abnormalities in first-episode psychosis.

1. Introduction

Gray matter decline in early schizophrenia has been interpreted as supportive of a neurodegenerative model of the disorder, and can be seen even prior to the onset of overt psychotic symptoms. Gray matter abnormalities have been demonstrated in numerous neural networks. In a meta-analysis of thirty-one articles comparing gray matter volumes in patients with schizophrenia relative to healthy controls, decreased gray matter volumes were found in the bilateral insular cortex, anterior cingulate cortex (ACC), left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus, while increased gray matter was observed in striatal regions (Glahn et al., 2008). Gray matter volume reductions in prefrontal, temporal, and cingulate cortices are evident at illness onset, prior to initiation of antipsychotic treatment (Dazzan et al., 2012; Fusar-Poli et al., 2012; Leung et al., 2011). Applying aggregation of several Voxel-Based Morphometry (VBM) studies across 23 sites in Europe and North America, the largest discrepancies in gray matter concentration relative to healthy controls were found in networks including the superior temporal gyrus, inferior frontal gyrus, and insula (Gupta et al., 2014). Another large meta-

analysis examined brain volumes in antipsychotic-naïve patients and patients taking antipsychotic medications and found that the antipsychotic-naïve group demonstrated similar gray matter volume deficits, but to a lesser extent, and that increased losses are associated with longer duration of illness (Haijma et al., 2013). It has been observed that after initial decline, deficits tend to remain relatively constant with progression to chronic illness.

The pathogenesis underlying gray matter decline is poorly understood, although gray matter deficits have been implicated in cognitive impairment. In keeping with potential neurodegeneration, elevated glutamatergic metabolites, which are thought to be neurotoxic, at initial diagnosis of psychosis have been associated with cognitive impairments both at initial presentation, and at one-year follow-up (Dempster et al., 2015). It is plausible that glutamatergic metabolite excess demonstrated in early stages of the illness may play a role in gray matter decline, and furthermore, that an interplay between both processes may be responsible for the cognitive deficits characteristically seen in early schizophrenia. Given the significant functional sequelae of cognitive impairment in schizophrenia, as well as the paucity of current evidence-based treatments for neurocognitive deficits, further charac-

terization of brain-based associations of these deficits is important and may greatly improve current treatment protocols for schizophrenia. Volumetric abnormalities are present even prior to illness onset (Koutsouleris et al., 2010), and appear to be implicated in cognition even at this early stage of disease progression. The Iowa Longitudinal study was able to describe the degree of structural brain change overtime in a sample of first-episode psychosis patients, about half of which were antipsychotic naïve initially. This study found progressive gray matter changes in multiple brain regions in patients with first-episode psychosis relative to age-matched controls, most prominently in the frontal lobe and thalamus. Additionally, more striking changes were observed only in a subset of patients, suggesting that some patients experience more pronounced neurodegeneration following initial presentation than others (Andreasen et al., 2011). Premorbid intelligence is one factor that has recently been demonstrated to be implicated in the variable degree of gray matter change in early psychosis (Czepielewski et al., 2016) and patients that are impaired on neuropsychological tests have been found to have decreased total brain volume and gray matter deficits in the left precentral gyrus, medial parieto-occipital sulcus, bilateral middle occipital gyrus corresponding to Brodmann's area 19, left superior temporal gyrus, left anterior insula/inferior frontal gyrus, thalamus, amygdala, hippocampus/parahippocampal gyrus, and cerebellum (Woodward and Heckers, 2015). This suggests that any intervention to prevent/delay significant cognitive decline may be best initiated prior to the development of overt psychotic symptoms, and should be directed in nature to particular subgroups of individuals.

Several studies have demonstrated a relationship between gray matter volumes in patients with early schizophrenia, and both cognitive deficits. Gray matter volume in the prefrontal and temporo-parietal cortices, and most specifically, in inferior regions of the dorsolateral prefrontal cortex in patients with first-episode psychosis were found to be correlated with neuropsychological test performance (Minatogawa-Chang et al., 2009). In another study, patients with schizophrenia with lower WCST scores had reduced gray matter volume in the dorsolateral prefrontal cortex bilaterally, as well as in the ACC (Rüsch et al., 2007). In a sample of drug-naïve patients with first-episode schizophrenia compared to healthy controls, poorer working memory, verbal learning, and visual learning were associated with smaller hippocampal gray matter volume and impaired executive functioning was associated with smaller left orbital inferior frontal gray matter volume (Guo et al., 2014). A longer duration of untreated psychosis has been associated with significant gray matter reductions in orbital-frontal and parietal regions as well as significant reductions in overall whole brain gray matter (Malla et al., 2011), suggestive of particularly sensitive periods in terms of neural disease progression, supporting the importance of characterizing the association of gray matter change and cognition early in disease progression.

While many studies have investigated associations of gray matter volume and cognition at a single time point, there has been a paucity of studies investigating associations of gray matter change over the early course of schizophrenia with cognitive outcomes. Given significant individual variability in brain volume, investigating change in volumes over the early course of schizophrenia may be more sensitive to subtle changes in gray matter and their relationship to cognitive deficits. One study investigated 59 first-episode patients dichotomized into a deficit and non-deficit group in terms of cognitive impairment. While there were no brain volume differences between the groups at any single time points, patients clustered into a neurocognitive deficit group showed greater reductions in total gray matter volume and parietal tissue volume over 3-year follow-up (Aeysa-Arriola et al., 2013). Dichotomization of patients in this manner may not be in keeping with clinical presentation of cognitive impairment, which may be more accurately conceptualized on a continuum.

The present study investigated the association of gray matter volume over the early course following initial diagnosis of psychosis and several tests of cognition in a sample of initially drug naïve patients. Patients with a greater burden of cognitive impairment at initial presentation of illness may represent a group prone to further neurodegeneration, and may warrant different/additional support and/or monitoring. To our knowledge, this is the first study to investigate associations of cognitive impairment, as well as volumetric changes, longitudinally, in a sample of initially drug-naïve patients. We hypothesized that cognitive impairment at baseline would be associated with gray matter volume deficits at baseline. Reflecting ongoing neurodegeneration, we also hypothesized that gray matter volume changes over the course of 80 months, particularly in fronto-temporal and parietal regions, would be associated with impaired cognition at baseline.

2. Methods

2.1. Participants

Sixteen initially never-treated patients presenting with first-episode non-affective psychosis in London, Ontario volunteered for the study. Study protocol was fully explained, and written informed consent was obtained according to the guidelines of the Review Board for Health Sciences Research Involving Human Subjects at Western University. Participants were recruited from the PEPP (Prevention and Early Intervention Program for Psychosis) in London, Ontario. Participant demographic information is summarized in Table 1. Diagnoses were established using the SCID (Structured Clinical Interview for DSM-IV) (First et al., 2002) by a psychiatrist (P.C.W.). Two participants were diagnosed with schizoaffective disorder and fourteen with schizophrenia.

None of the patients had a history of head injury or of a drug or alcohol use disorder in the year prior to the scan, or of a serious medical illness (according to SCID and anatomical MRI). All patients reported no substance use on the day of the scan. The majority of the patients had completed grade 11 to grade 13 in terms of education (10 fell into that category). 2 had obtained less than a grade 10 education, 2 had completed 1–3 years of college or university, and 2 had completed over 3 years of college or university.

2.2. Scanning

The intention was to have each individual complete baseline Magnetic Resonance Spectroscopy (MRS) scanning and neuropsychological testing prior to starting antipsychotic treatment but for ethical and practical reasons, this was not always possible. At baseline scanning, 3 patients had started an antipsychotic medication; 2 were taking olanzapine (1 at 5 mg daily, 1 at 10 mg daily) and 1 was taking risperidone 3 mg QHS. At 80-month scanning 13 were taking antipsychotic medications (1 haloperidol at 1.5 mg; 3 risperidone at 5, 1, and 3 mg daily; 2 quetiapine at 50 and 600 mg daily; 2 clozapine at 200 and 450 mg daily; 4 olanzapine at 17.5, 20, 30, and 30 mg daily; and 1 person was taking clopixol depot 90 mg IM every 2 weeks).

Gray matter volumes were measured with VBM (Ashburner and

Table 1
Participant demographic data.

Variable	Minimum	Maximum	Mean	S.D.
Gender	Male = 13;	Female = 3		
Handedness	Right = 14;	Left = 2		
Age	17	44	24.08	7.21
DUP	4	384	103.51	104.01
DUI	25.71	645.14	289.54	178.98
SAPS Baseline	0	63	30.46	16.04
SANS Baseline	24	68	42.92	10.70

DUP = duration untreated psychosis in weeks. DUI = duration untreated illness in weeks. S.D. = standard deviation.