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Investigation of white matter abnormalities in first episode psychosis patients with persistent negative symptoms

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ABSTRACT

Aberrant white matter structures in fronto-temporal regions have previously been identified in patients with schizophrenia. However, scant research has focused on white matter integrity in patients presenting with a first episode of psychosis (FEP) with persistent negative symptoms (PNS). This study aimed to explore microstructure in the neurocircuitry proposed to be involved in PNS, by using a region-of-interest approach. Secondly, the relationship between individual negative symptoms and white matter were explored. Fractional anisotropy (FA) was measured in the fornix and three other tracts bilaterally including the uncinate fasciculus, superior longitudinal fasciculus and the cingulum bundle. Twelve patients with PNS were compared to a non-PNS group (52) and a healthy control group (51). Results showed that the PNS group had significantly lower FA values in the fornix when compared to healthy controls and that the non-PNS group had significantly lower FA values in the right uncinate fasciculus compared to healthy controls. Significant correlations were observed between SANS global score for anhedonia-asociality and lower FA values in the right cingulum bundle. Our results suggest that fronto-temporal white matter might be more closely related to PNS and that this relationship may possibly be mediated by greater anhedonia in PNS patients.

1. Introduction

The negative symptomatology of psychotic disorders is of considerable interest to researchers and clinicians due to their contribution to/correlation with poor functional outcome (Ho et al., 1998, Wood et al., 2006, Jordan et al., 2014), role in lower remission rates (Bodnar et al., 2008) and neurocognitive deficits such as verbal memory (Bilder et al., 2000, Heydebrand et al., 2004, Hovington et al., 2013). While some individuals with psychosis and negative symptoms might experience an improvement over time, a substantial percentage in first episode psychosis FEP (about 27%) (Hovington et al., 2012) will have negative symptoms that are largely resistant to treatment, or persisting negative symptoms (PNS). PNS are specifically characterized as primary or secondary negative symptoms (Malla et al., 2004, Buchanan, 2007) present for a minimum of 6 consecutive months (during periods of clinical stability) and with the minimal presence of positive, depressive and extrapyramidal symptoms (Buchanan, 2007, Hovington et al., 2012). Identifying a clinically homogenous subgroup of patients in early psychosis may help better delineate the etiology of negative symptoms.

It has been postulated that there are fronto-temporal deficits associated the pathophysiology of negative symptoms (Baare et al., 1999, Anderson et al., 2002, Szeszko et al., 2008, Rowland et al., 2009, Benoit et al., 2012, Hovington and Lepage, 2012). Accordingly, it is likely that white matter tracts connecting these fronto-temporal regions are also involved in manifestation of negative symptoms. It is also possible that the white matter connecting the above-mentioned gray matter structures is involved in the pathogenesis of negative symptoms. While white matter abnormalities have been reported in FEP (Chua et al., 2007, Price et al., 2010), albeit findings have been mixed (Peters et al., 2008). It is plausible that decreases in white matter may be specific to

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patients with greater negative symptoms severity (Sanfilipo et al., 2000, Wible et al., 2001).

Diffusion tensor imaging (DTI) allows for the in vivo study of white matter microstructure and integrity (Basser et al., 1994). There are various approaches to analyzing DTI data including region of interest (ROI), voxel-based and tract-oriented methods. Studies applying these types of analysis have provided evidence for fronto-temporal abnormalities in FEP (Price et al., 2008, Rowland et al., 2009) and fronto-temporo-limbic impairments (Ardekani et al., 2003, Koutsouleris et al., 2008). With regards to white matter integrity, fractional anisotropy (FA) (characterizes the degree of anisotropic diffusion) has been assessed in FEP patients as well as patients with deficit syndrome (DS). In patients with recent onset schizophrenia, lower FA values were reported in the uncinate fasciculus (UF), superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (Szeszko et al., 2008) when compared to healthy controls. Furthermore, lower FA values in the UF (bilaterally) correlated with negative symptom severity, specifically alogia and affective flattening (Szeszko et al., 2008). Similarly, in DS, findings have suggested a reduction in FA values in the SLF (Rowland et al., 2009) and the left UF (Kitis et al., 2012, Voineskos et al., 2013). Finally, other groups have also shown that negative symptom severity is associated with decreased FA in the inferior fronto-occipital fasciculus (Lee et al., 2013) and in the right fornix (Kunimatsu et al., 2012). Hence, the above-mentioned findings have led to various disconnectivity models for negative symptoms including fronto-temporal and fronto-temporo-limbic models.

Although there has been a large support for the disconnectivity model of psychosis, many questions remain in terms of the relationship between white mater microstructure and negative symptoms. Furthermore, PNS are often assessed cross-sectionally rather than at multiple time points to thoroughly measure their persistence over time. Thus, the primary objective of this longitudinal study was to explore microstructure in the neurocircuitry of first episode psychosis proposed to be involved in persistent negative symptoms by using a region of interest (ROI) approach. Due to previous studies highlighting the role of fronto-temporo-limbic connections in negative symptoms, we hypothesized that white matter related to these three areas might have lower FA values. Our second objective was to explore the relationship between individual negative symptom domains and our selected white matter tracts. Due to the exploratory nature with regard to this specific objective, no hypothesis was made.

2. Methods

2.1. Subjects

Participants were part of a longitudinal naturalistic outcome study of FEP treated in a specialized early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. Individuals aged 18 to 35 years from the local catchment area presenting affective or non-affective psychosis and who had not taken antipsychotic medication for more than one month and whose IQ was higher than 70 were admitted to the program as either in- or out-patients (for details see (Malla et al., 2003). Diagnosis of schizophrenia or related spectrum disorders was established using clinical evaluation by experienced psychiatrists and corroborated by an interview using the Structured Clinical Interview for DSM-IV (SCID-IV) First et al. (1998). The Douglas Institute Human Ethics Review Board approved research protocols and all patients who chose to participate in the study gave their written informed consent. Healthy controls were recruited through advertisements in local newspapers and were included only if they had no current or previous history of (a) any Axis I disorders, (b) any neurological diseases, (c) head trauma causing loss of consciousness, and (d) a first-degree family member with schizophrenia or related schizophrenia-spectrum psychosis. Current IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-III) (Wechsler, 1997).

2.2. Clinical assessment

Education level (number of school years completed), parental socio-economic status (SES) as per the Hollingshead two-factor index (Miller, 1991), Social and Occupational Functioning Assessment Scale (SOFAS), The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) and handedness (Oldfield, 1971) were acquired. As part of the longitudinal study, the following clinical variables were assessed at an initial assessment as well as at months 1,2,3,6,9 and 12 following the first evaluation. Negative and positive symptoms were quantified using the SANS (Andreasen, 1984) and the SAPS (Andreasen, 1983), respectively. The domain of attention in the SANS scale was not included in our analyses because previous factor analytical studies have shown that it loads on both negative and disorganization dimensions (Peralta and Cuesta, 1999, Malla et al., 2002). Evaluators at PEPP established an ICC of 0.74 on the SAPS and 0.71 on the SANS; all evaluator′s participated in inter-rater and intra-rater reliability sessions at least once a year to avoid evaluator drift. Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and extrapyramidal symptoms with the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). If prescribed, type and dose of anticholinergic medications taken were recorded. The type and dosage of antipsychotics taken were also recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003).

2.3. Identifying persistent negative symptoms

Clinical data from months 3,6,9, and 12 were analyzed to identify patients with PNS. PNS was defined as having a minimum score of three on one or more global items of the SANS (Malla et al., 2004; Hovington et al., 2012). These negative symptoms were required to be present after the initial stabilization of positive symptoms (month 3) and to be maintained for 6 consecutive months (months 6, 9 and 12) (Buchanan, 2007; Hovington et al., 2012). Based on previous findings, subjects with global ratings on “affective flattening” or “alogia” entirely based as a result of items “inappropriate affect” or “poverty of content of speech”, respectively were excluded as having negative symptoms (Malla et al., 2004). After the completion of the 12-month assessment, FEP patients were segregated into two groups (PNS and non-PNS).

Patients in the PNS group had primary negative symptoms in the absence of any positive (global rating of mild (2) or less, as measured by the SAPS), depressive (a total score of 4 or less on the CDSS) (Addington et al., 1993) or extrapyramidal symptoms (low to mild levels). Further, FEP patients who were administered their initial neuropsychological assessment later than nine months after entry into our program were also excluded given that since this was deemed too late given our PNS criteria.

2.4. Scanning procedures

Scans were acquired at the Montreal Neurological Institute (MNI) on a 1.5 T Siemens Sonata whole body MRI system. Structural T1 volumes were acquired for each participant using a three-dimensional (3D) gradient echo pulse sequence with sagittal volume excitation (repetition time=22 ms, echo time=9.2 ms, flip