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Increased gyrification in schizophrenia and non affective first episode of psychosis

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ABSTRACT

Background: Prefrontal cortex gyrification has been suggested to be altered in patients with schizophrenia and first episode psychosis. Therefore, it may represent a possible trait marker for these illnesses and an indirect evidence of a disrupted underlying connectivity. The aim of this study was to add further evidence to the existing literature on the role of prefrontal gyrification in psychosis by carrying out a study on a sizeable sample of chronic patients with schizophrenia and non-affective first-episode psychosis (FEP-NA) patients.
Methods: Seventy-two patients with schizophrenia, 51 FEP-NA patients (12 who later develop schizophrenia) and 95 healthy controls (HC) underwent magnetic resonance imaging (MRI). Cortical folding was quantified using the automated gyrification index (GI). GI values were compared among groups and related to clinical variables.
Results: Both FEP-NA and patients with schizophrenia showed a higher mean prefrontal GI compared to HC (all $p < 0.05$). Interestingly, no differences have been observed between the two patients groups as well as between FEP-NA patients who did and did not develop schizophrenia.
Conclusions: Our results suggest the presence of a shared aberrant prefrontal GI in subjects with both schizophrenia and first-episode psychosis. These findings support the hypothesis that altered GI represents a neurodevelopmental trait marker for psychosis, which may be involved in the associated neurocognitive deficits.

1. Introduction

Several studies consistently support the evidence that brain disconnectivity plays a key role in the pathophysiology of schizophrenia (Friston and Frith, 1995; Friston, 2002; Schmitt et al., 2011; White and Hilgetag, 2011), with particular regards to prefrontal cortex (PFC) (Rubinov and Bullmore, 2013; Zhou et al., 2015; Wheeler and Voineskos, 2014). In particular, the tension exerted by the viscoelastic nerve fibers is thought to influence cortical folding (Van Essen, 1997), with literature documenting that alterations in connectivity may lead to an altered cortical folding (Rakic, 1988; Konrad and Winterer, 2008; White et al., 2010).

In general, cortical folding has been considered an early neurodevelopmental process, which occur prior to birth and continuing into childhood (White et al., 2010; Garel et al., 2001). Importantly, this process is responsible for the correct development of convolution patterns and cortical organization through its association with myelination, synaptogenesis and pruning (Casey et al., 2005; White et al., 2010).

In this context, the investigation of cortical folding in schizophrenia might be of paramount importance, especially due to the neurodevelopmental origins of this disabling psychiatric illness (Owen et al., 2011). Indeed, it has been proposed that abnormal gyrification,

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which provides an index of degree and pattern of folding of brain cortex and an indirect sign of altered connectivity, represents a brain marker for schizophrenia (White and Gottesman, 2012). In this regard, the Gyrification Index (GI), which measures the ratio of the exposed cortical surface to the cerebral hull (Moorhead et al., 2006; Zilles et al., 1989), is among the most reliable methods used to quantify surface morphology.

In this perspective, it has been shown that the PFC is a core structure consistently found to be associated with schizophrenia, as reported by several functional (Zhou et al., 2015) and structural (Levitt et al., 2010; Castellani et al., 2012) neuroimaging studies. Indeed, the PFC has been found to be associated with selective deficits in specific cognitive domains, including working memory, executive functions and attention, abilities often found to be impaired in schizophrenia (Arnsten, 2011; Pratt et al., 2008; Nenadic et al., 2012; Brambilla et al., 2013a, 2013b). Additionally, in schizophrenia, PFC alterations have been also reported to be associated with positive and negative symptoms (Der-Avakian and Markou, 2012; Goghari et al., 2010; Nenadic et al., 2012; Delvecchio et al., 2017a). Therefore, the investigation of abnormal GI in this structure represents a window for deepen our knowledge on whether PFC deficits occur earlier during brain development. Nonetheless, the evidence reporting the role of prefrontal cortical folding in schizophrenia have led to contrasting results (White and Hilgetag, 2011). Indeed, although PFC hypergyria has been reported in patients suffering from schizophrenia (Falkai et al., 2007; Vogeley et al., 2001; Nenadic et al., 2015), other authors have, in contrast, reported hypogyria (Bonnici et al., 2007; Cachia et al., 2007; Kulynych et al., 1997; Mancini-Marie et al., 2015; McIntosh et al., 2009; Nesvag et al., 2014; Palaniyappan et al., 2011; Palaniyappan and Liddle, 2012; Tepest et al., 2013) or no abnormalities (Highley et al., 2003). Similarly, the same mixed picture have been reported in first-episode patients with schizophrenia (Narr et al., 2004; Janssen et al., 2014; Wiegand et al., 2005), while only one study has investigated cortical gyrification in non-affective first-episode psychosis (FEP-NA) (Palaniyappan et al., 2013), showing hypogyria in the PFC.

Therefore, our study aimed at better clarifying the role of abnormal prefrontal gyrification in psychosis by carrying out a study on a sizeable sample of patients with FEP-NA and with chronic patients with schizophrenia. Based on previous evidence, we hypothesized that patients with schizophrenia would show abnormally folded PFC compared to healthy controls (HC), although the direction of this disruption is still not well elucidated. Moreover, by extending the analyses to FEP-NA patients we are in the position to explore, and to further clarify, whether altered PFC gyrification can be considered an early distinctive marker for psychosis and, in turn, an indirect sign of a altered underlying connectivity.

2. Methods

2.1. Participants

The sample included 51 FEP-NA, 72 patients with schizophrenia, and 95 HC. All subjects gave signed informed consent. Patients with FEP-NA were recruited within the PICOS project, which has been extensively previously described by our group (Lasalvia et al., 2012). In order to be eligible for the PICOS project only psychopathological criteria were used and the over-inclusive screening methodology of the WHO ten-country study (Screening Schedule for Psychosis; Jablensky et al., 1992) was adopted. For FEP-NA patients, the inclusion criteria were: (1) presence of (a) at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre or grossly inappropriate behavior, or (b) at least two of the following symptoms: loss of interest, initiative and drive, social withdrawal, episodic severe excitement, purposeless destructiveness, overwhelming fear, marked self-neglect; (2) first lifetime contact with any mental health service located in PICOS area during the study period resulting from symptoms listed in (1). The exclusion criteria for FEP-NA patients were: (1) prior treatment with an antipsychotics for >3 months; (2) mental disorders due to a general medical condition; (3) moderate to severe mental retardation. The formal best-estimate diagnosis was made six months after the recruitment. Among the FEP-NA patients, 12 had later develop schizophrenia and met the following diagnoses: Paranoid schizophrenia (n = 10) and Undifferentiated schizophrenia (n = 2). The remaining 39 FEP-NA patients who did not develop schizophrenia were diagnosed with: Acute transitory psychosis (n = 13), Non-organic, non-specific psychosis (n = 11), Persistent delusional psychotic syndrome (n = 7), Schizoaffective syndrome (n = 6), Acute delusional syndrome (n = 1), Acute psychosis with schizophrenic symptoms (n = 1). Patients with schizophrenia eligible for the study were selected by means of the South-Verona Psychiatric Care Register (PCR) (Tansella and Burti, 2003), a community-based mental health register, as previously reported in our publications (Delvecchio et al., 2017a, 2017b; Brambilla et al., 2013a, 2013b). They had chronic illness. Specifically, the majority of them had residual schizophrenia and were clinically stable (N = 43) whereas the others were either in the acute phase or in remission after an acute episode.

For both patients with schizophrenia and FEP-NA patients, a formal ICD-10 diagnosis was assessed by using the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1992). Two psychiatrists independently reviewed the relevant information and formulated the ICD-10 diagnosis. In the cases the consensus was not reached, the opinion of a third psychiatrist was solicited to clarify diagnostic problems. A non-parametric Mann-Withney *U* test was performed for comparing GI values, Intra Cranial Volumes (ICVs) and age of FEP-NA who did (N = 12) and did not (N = 39) develop schizophrenia. The results showed that the merging of the two sub-groups in a unique group of FEP-NA was possible. Specifically, no differences emerged in GI and ICV ($p > 0.1$). Instead there was a significant age difference (mean age ± SD for FEP-NA who did and did not develop schizophrenia was 30.52 ± 8.75 and 40.22 ± 11.82 respectively). The potential effect of age on the variable of interest (i.e. GI) was, in any case, factored out in the following analyses as it was entered as covariate. The clinical symptomatology of all patients was evaluated using the 24 item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Moreover, alcohol or substance abuse was assessed with two specific item sections (sections 11 and 12) of the SCAN. All patients with schizophrenia and FEP-NA patients with other Axis I disorders, alcohol or substance abuse, history of traumatic head injury with loss of consciousness, epilepsy or other neurological or medical diseases, including hypertension and diabetes, were excluded from the study. Patients' medication was recorded and chlorpromazine equivalent dosages were calculated.

HC were recruited through word of mouth and advertisements in the geographically defined catchment area of South Verona. They had no history of head injury or psychiatric Axis I disorder, determined using a brief modified version of the Structured Clinical Interview for DSM-IV- Non patient version, no history of psychiatric disorder among first-degree relatives, no history of alcohol or substance misuse and no current major medical illness. The demographic and clinical details are presented in Table 1.

2.2. Magnetic resonance imaging (MRI) protocol

Magnetic resonance scans were acquired with a 1.5 T Siemens Magneton Symphony Maestro Class scanner, Syngo MR, 2002B (Siemens, Erlagen, Germany). A standard head coil was used for radio-frequency transmission and reception of the magnetic resonance signal; restraining foam pads were used to minimize head motion. First, T1-weighted images were obtained to verify each participant's head position and the image quality, with acquisition parameters repetition time (TR) 450 ms, time to echo (TE) 14 ms, flip angle 90°, field of view (FOV) 230 × 512 mm^2, 18 slices, slice thickness 5 mm, matrix size 384 × 512, number of excitations (NEX) 2. Proton density and T2-

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