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Volumetric, relaxometric and diffusometric correlates of psychotic experiences in a non-clinical sample of young adults

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ABSTRACT

Background: Grey matter (GM) abnormalities are robust features of schizophrenia and of people at ultra high-risk for psychosis. However the extent to which neuroanatomical alterations are evident in non-clinical subjects with isolated psychotic experiences is less clear.
Methods: Individuals (mean age 20 years) with (n = 123) or without (n = 125) psychotic experiences (PEs) were identified from a population-based cohort. All underwent T1-weighted structural, diffusion and quantitative T1 relaxometry MRI, to characterise GM macrostructure, microstructure and myelination respectively. Differences in quantitative GM structure were assessed using voxel-based morphometry (VBM). Binary and ordinal models of PEs were tested. Correlations between socioeconomic and other risk factors for psychosis with cortical GM measures were also computed.
Results: GM volume in the left supra-marginal gyrus was reduced in individuals with PEs relative to those with no PEs. The greater the severity of PEs, the greater the reduction in T1 relaxation rate (R1) across left temporoparietal and right pre-frontal cortices. In these regions, R1 was positively correlated with maternal education and inversely correlated with general psychopathology.
Conclusions: PEs in non-clinical subjects were associated with regional reductions in grey-matter volume reduction and T1 relaxation rate. The alterations in T1 relaxation rate were also linked to the level of general psychopathology. Follow up of these subjects should clarify whether these alterations predict the later development of an ultra high-risk state or a psychotic disorder.
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1. Introduction

Grey matter (GM) abnormalities have been identified in several structures in schizophrenia patients (Ellison-Wright et al., 2008; Haijma et al., 2013; Honea et al., 2005; Velakoulis et al., 2006; Vita et al., 2006; Wright et al., 2000). The most heavily implicated are the prefrontal, parietal, temporal, anterior cingulate cortices, and hippocampus (Kanaan et al., 2005). GM volume is reduced in chronic versus first episode schizophrenia patients (Meisenzahl et al., 2008) and falls progressively with age(Vita et al., 2012).

In order to delineate structural brain differences that might predispose to psychosis, it is important to examine them without confounding effects of medication or chronic illness. Studies that examine first-episode or drug naive patients overcome such issues to some extent. A number of studies have also focused on high-risk groups: individuals presenting with the At-Risk Mental State (ARMS) or those deemed to be at ultra-high-risk (UHR) for psychosis (Fusar-Poli et al., 2013; Simon et al., 2011). Studies of GM alterations in this group have found macroscopic changes in the cerebral cortex (Borgwardt et al., 2007; Mechelli et al., 2011). A meta-analysis of VBM studies (Fusar-Poli et al., 2011) showed that at-risk groups tend to show reductions in GM volume in many of the regions implicated in schizophrenia, although the changes are generally less severe (Ziermans et al., 2009, 2012). Other meta-analyses (Borgwardt et al., 2011; Fusar-Poli et al., 2011) also found that reduced GM volume in prefrontal, cingulate, temporo-parietal, insular and cerebellar regions were significant

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predictors of transition to full-blown psychosis. More recent, larger and better controlled studies show defined GM structural changes associated with both risk of (Cropley et al., 2016) and transition to psychosis (Cannon et al., 2014; Mechelli et al., 2011; Pantelis et al., 2003; Ziermans et al., 2009). Of particular interest is the North American Prodrome Longitudinal Study which showed that young adults who later transition to psychosis have reduced frontal grey matter compared to those who do not transition (Cannon et al., 2015). Another large cohort, The Philadelphia Neurodevelopmental Cohort, of young adults with psychotic experiences showed reduced grey matter volume in medial temporal regions (Satterthwaite et al., 2016).

While numerous studies have examined GM morphometry in schizophrenia and at-risk groups, other imaging modalities that can provide insights into cortical microstructure have seldom been explored. MRI methods commonly used to quantify myelination and microstructure in white-matter may be used as putative measure of cyto- and myeloarchitecture in cortex (Weiskopf et al., 2015). For example, T1 relaxometry (Homer and Beevers, 1985) is sensitive to myelin content in health and disease and can be used to derive high-resolution cortical myelin maps in vivo (Dinse et al., 2015; Lutti et al., 2013). To our knowledge, no studies have investigated in vivo cortical myelination using MRI in schizophrenia or in at risk-groups. Diffusion tensor imaging (DTI) (Basser et al., 1994), has been applied to investigate changes in cortical microstructure in a number of clinical groups (Kang et al., 2012; Muñoz Maniega et al., 2004; Oreja-Guevara et al., 2005; Rovaris et al., 2006; Vite et al., 2008), Most commonly, mean diffusivity (MD) is used as an inverse measure of cellular density. One recent study (Park et al., 2014) examined diffusivity of frontal and temporal cortices and found it to be higher in schizophrenia patients. To our knowledge, there are no published MRI studies of cortical diffusivity in non-familial at-risk groups.

There are several risk-factors associated with the development of psychosis. These include obstetric factors (Abel et al., 2010; Dalman et al., 2001; Foerster et al., 1991; Lewis, 2002; Rifkin et al., 1994) socio-economic disadvantage (Byrne et al., 2004; Gallagher et al., 2013; O'Donoghue et al., 2015; Werner et al., 2007), premorbid IQ (David et al., 1997; Woodberry et al., 2008; Zammit et al., 2004), childhood trauma and life stress (Gallagher et al., 2013; Kraan et al., 2015; Morgan and Fisher, 2007; Norman and Malla, 1993) and substance abuse (Kelly, 2000; Koskinen et al., 2009; Moore et al., 2007). The pathogenic processes underlying these factors are unknown and multiple mechanisms are possible. Some may operate through the cyto- and myeloarchitecture of the cerebral cortex.

This study utilises a large epidemiological birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013; Golding et al., 2001) cohort, which has rich biological, clinical and psychosocial data to examine the association between GM structure and PEs. Neuroimaging of this cohort has previously shown significant alterations white matter circuitry (Drakesmith et al., 2015, 2016). We tested the hypothesis that abnormalities in GM volume and myeloarchitecture are associated with PEs even in the absence of a clinically identified disorder. This approach has a number of advantages. In particular, it allows the examination of PEs without selection biases and confounding factors such as secondary effects of illness including pharmacological treatment. Furthermore, the cohort has accrued unbiased longitudinal data on a number of developmental and socio-economic variables that can constitute risk factors for psychosis, affording us an opportunity to identify any relationships between them and GM abnormalities that may also be linked to PEs.

2. Methods and materials

2.1. Subjects

Subjects were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013; Golding et al., 2001) cohort. The original sample consisted of pregnant women whose expected delivery dates were between April 1991 and December 1992 resulting in the birth of 15,458 foetuses (see Supplementary material, Section 1 for full description of cohort). 4320 subjects from the cohort were assessed for psychotic experiences (PEs) using the Psychotic-like Symptoms (PLIKS) semi-structured interview (Horwood et al., 2008; Zammit et al., 2008), conducted at 17/18 years of age by trained psychologists. Those who were found to have one or more psychotic experience were invited to undergo scanning. The presence of PEs was judged according to clinical criteria of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) and excluded experiences occurring due to waking, falling asleep, fever or drug consumption. PEs were further categorised as 'suspected' ($n = 44$), 'definite', ($n = 47$) and 'clinical disorder' (PEs plus functional deterioration and/or help-seeking; $n = 32$) (Zammit et al., 2013). 126 subjects with PEs were recruited and an equal number of randomly-selected controls, who had completed the same assessments but who were rated as not having had PEs experiences were also scanned. At the time of scanning all subjects were approximately 20 years old (see Table 1 for details).

Informed consent was obtained prior to scanning. Ethical approval was granted by the Cardiff University School of Psychology Ethics Committee and the ALSPAC Ethics and Law Committee. Of the subjects initially scanned, 3 PE subjects and 1 control were unable to complete the full MRI acquisition. While all participants completed the T1-weighted structural scan, the sample sizes for the relaxometry and diffusion MRI scans of the two groups were $n = 123$ and $n = 125$, respectively.

2.2. Risk factors

A number of candidate variables hypothesized to contribute to psychosis risk were obtained from the ALSPAC variable catalogue (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). These included age and gender plus 12 other risk-factors: (1) IQ at age 8 estimated from the WISC (Wechsler Intelligence Scale for Children (WISC-III^{UK})) (Golombok and Rust, 1992); (2) current general psychopathology at age 17/18 measured using the computerised Clinical Interview Schedule (revised: CIS-R) (Lewis et al., 1992); (3) parental social class (OPCS, 1991); (4) maternal education; (5) birth weight; (6) resuscitation at birth; (7) stressful life events at age 15/16 measured on the Development and Wellbeing Assessment (DAWBA) questionnaire (Goodman et al., 2000); (8) handedness; (9) tobacco use; (10) alcohol consumed; (11) cannabis consumption (all substance use data gathered at age 17/18); (12) month of birth.

Any missing data points for each subject were estimated using regression imputation (S. F. Buck, 1960) across the entire cohort. Descriptive and inferential statistics of all selected risk factors are detailed in Table 1.

3. Imaging

3.1. Structural MRI acquisition

All MRI data were acquired at Cardiff University Brain Imaging Research Centre, UK on a 3 T General Electric HDx MRI system (GE Medical Systems, Milwaukee, WI) using an eight-channel receive-only head RF coil. T1-weighted structural images were acquired with a 3D fast spoiled gradient echo (FSPGR) sequence (TR = 7.8 ms, TE = 3.0 ms, flip angle 20°, voxel size = 1 mm^3 isomorphic).

3.2. Relaxometry MRI acquisition and pre-processing

Relaxometry images were acquired using driven equilibrium single pulse observation of T1 with high-speed incorporation of RF field inhomogeneities (DESPOT1-HIFI) (Deoni, 2007). A series of spoiled gradient echo (SPGR) images was acquired with 8 flip angles plus an additional

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