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Effects of environmental risks and polygenic loading for schizophrenia on cortical thickness

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ABSTRACT

There are established differences in cortical thickness (CT) in schizophrenia (SCZ) and bipolar (BD) patients when compared to healthy controls (HC). However, it is unknown to what extent environmental or genetic risk factors impact on CT in these populations. We have investigated the effect of Environmental Risk Scores (ERS) and Polygenic Risk Scores for SCZ (PGRS-SCZ) on CT.

Structural MRI scans were acquired at 3T for patients with SCZ or BD (n = 57) and controls (n = 41). Cortical reconstructions were generated in FreeSurfer (v5.3). The ERS was created by determining exposure to cannabis use, childhood adverse events, migration, urbanicity and obstetric complications. The PGRS-SCZ were generated, for a subset of the sample (Patients = 43, HC = 32), based on the latest PGC GWAS findings. ANCOVAs were used to test the hypotheses that ERS and PGRS-SCZ relate to CT globally, and in frontal and temporal lobes.

An increase in ERS was negatively associated with CT within temporal lobe for patients. A higher PGRS-SCZ was also related to global cortical thinning for patients. ERS effects remained significant when including PGRS-SCZ as a fixed effect. No relationship which survived FDR correction was found for ERS and PGRS-SCZ in controls.

Environmental risk for SCZ was related to localised cortical thinning in patients with SCZ and BD, while increased PGRS-SCZ was associated with global cortical thinning. Genetic and environmental risk factors for SCZ appear therefore to have differential effects. This provides a mechanistic means by which different risk factors may contribute to the development of SCZ and BD.

1. Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are psychiatric disorders characterised by overlapping symptomatology (Hilty et al., 2006; Bois et al., 2015) and multifactorial aetiologies (Hilty et al., 2006; Jablensky, 1997). Both are highly heritable (around 80%) due to a large number of relatively common genes of small effect (McGuffin et al., 2003; Matheson et al., 2011). Both have been proposed to be consistent with a neurodevelopmental model (Weinberger, 1987; Rapoport et al., 2012) which posits that SCZ and related disorders are influenced by both genetic and environmental factors impacting on the brain, at different developmental stages (Rapoport et al., 2012). Significant widespread cortical thinning is consistently found when comparing SCZ and BD patients to healthy controls (HC) (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010; Nesvåg et al., 2012; Knöchel et al., 2016). It is unclear however whether these differences are related to genetic and/or environmental risk factors previously associated with SCZ. Elucidating these components would help to further understand the underlying aetiologies of these disorders.

Decreases in grey matter volumes have been found before disease onset (McIntosh et al., 2011) and thinner cortices have been noted in SCZ patients when compared to HC in all lobes (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010). However, the most consistent findings have suggested that cortical thinning is most prominent in frontal and temporal regions (Kuperberg et al., 2003; Goldman et al., 2009; Rimol et al., 2010; van Haren et al., 2011; Sprooten et al., 2013),

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where it continues to decline after disease onset (Cobia et al., 2012). Despite reports of disease specific cortical alterations associated with BD, e.g. in orbitofrontal regions (Knöchel et al., 2016), many studies have also highlighted cortical thinning findings which overlap with the aforementioned SCZ deficits (Rimol et al., 2010; Hanford et al., 2016; Knöchel et al., 2016). Hence, frontal and temporal lobes are regions of interest for investigation of factors that could impact cortical deficits within SCZ and BD.

Both SCZ and BD have been associated with several environmental risk factors (van Os et al., 2010; Lawrie et al., 2011; Marangoni et al., 2016). Cannabis use, childhood adversity and obstetric complications (OC) have the strongest epidemiological evidence for an association with an increased risk of SCZ and BD, (Krabbendam and van Os, 2005; van Os et al., 2010; Rapoport et al., 2012; Matheson et al., 2013; Radhakrishnan et al., 2014; Stepniak et al., 2014; Marangoni et al., 2016). Urbanicity and migration are also strongly linked to SCZ (Krabbendam and van Os, 2005; van Os et al., 2010; Rapoport et al., 2012; Stepniak et al., 2014); however, as environmental risk factors for BD the evidence is less conclusive. Nevertheless, both migration and urbanicity have been linked to an increased incidence of BD (Pedersen and Mortensen, 2006; Cantor-Graae and Pedersen, 2013).

Although the evidence is limited, some of these factors have also been linked to deficits in cortical volume and thickness. Cannabis use has been associated with reduced global and frontal lobe volumes (Welch et al., 2011), cortical thinning in general (Habets et al., 2011), and, more specifically, in dorso-lateral prefrontal cortex (DLPFC) and anterior cingulate cortex (Rais et al., 2010). Childhood adversity/trauma has been associated with cortical thinning globally (Habets et al., 2011) and in the limbic system (Souza-Queiroz et al., 2016), as well as decreased subcortical structure volumes (Hoy et al., 2012; Barker et al., 2016a). So far, OC have not been significantly related to cortical thinning (Haukvik et al., 2009; Smith et al., 2015) but birth complications have been previously linked to reduced hippocampal and cortical volume (Cannon et al., 2002; van Erp et al., 2002) and may, alone or in accumulation with other risk factors, be linked to deficits in cortical thickness (CT). Migration and urbanicity are yet to be investigated in relation to CT but urbanicity has been linked with decreased grey matter volume in DLPFC within a healthy sample (Haddad et al., 2015).

Our knowledge of how these environmental risk factors impact upon CT in SCZ and BD is therefore inconclusive. Given a lack of knowledge about how these factors confer risk, it is desirable to determine if an accumulation of these risk factors has additional effects; some are likely to occur and impact development at different stages of life (Dean and Murray, 2005; Stepniak et al., 2014) and several of these factors can be experienced by any individual. Prima facie, it seems likely that a higher number of insults may result in greater biological effects. One aim of the current study is therefore to determine the impact of environmental risk factors, in accumulation, on CT.

Genome Wide Association Studies (GWAS) have advanced our understanding of the genetic underpinnings of SCZ and BD. Recently, Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) identified 108 genetic loci associated with SCZ, as well as several other markers that failed to reach genome-wide significance, suggesting a polygenic foundation to SCZ, with many genetic variants of individually small effect contributing to the overall phenotypic variation (International Schizophrenia Consortium, 2009). Strong evidence also exists for a polygenic basis for BD, with a strong overlap in the genetic variants associated with SCZ and BD (International Schizophrenia Consortium, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ripke et al., 2013). Using the summary data from the SWG-PGC GWAS (including alleles associated with the risk of SCZ as well as their effect sizes) as the training dataset, PGRS-SCZ can be created in an independent sample. Risk variants in the independent sample which are common to the training dataset are identified, these are then weighted by the effect sizes reported in the SWG-PGC GWAS and summed across individual genotypes in the independent sample (International Schizophrenia Consortium, 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Euesden et al., 2015). Higher positive scores indicate a greater polygenic risk for SCZ disorder.

Several studies have investigated the effect of these PGRS for SCZ (PGRS-SCZ) on clinical and cognitive phenotypes (McIntosh et al., 2013; Stepniak et al., 2014; Whalley et al., 2016). Thus far, structural neuroimaging phenotypes have been assessed with regard to the first SWG-PGC GWAS data, which identified 7 associated loci (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011), with inconsistent results (Terwisscha van Scheltinga et al., 2013; Papiol et al., 2014), making further investigation warranted.

Despite the fact that risk variants have been identified for BD separately (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011), there is still a substantial amount of shared variation between these psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ripke et al., 2013). Furthermore, PGRS-SCZ have been previously used for analysis within a combined BD and SCZ patient group (Ruderfer et al., 2014). Therefore, as the intention of the current study is to determine whether risks common to the development of both BD and SCZ are linked to CT, and the SCZ GWAS is more highly powered than the BD GWAS (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), we have used the PGRS-SCZ. A second aim of the current study is to determine if a relationship exists between PGRS-SCZ, created using the most recent PGC SCZ data, and CT.

Within the current study, global, frontal and temporal regions of CT were analysed to determine their relationship with PGRS-SCZ and environmental risk associated with SCZ. We hypothesised that both PGRS-SCZ and an accumulation of environmental risk factors would be inversely associated with cortical thinning in these regions, for both the patients and controls separately and when assessing differences between patients and controls. Due to the aforementioned overlap between structural findings, environmental, and genetic risk factors, and in order to increase power within the sample, SCZ and BD patient data were combined into one patient groups for analyses.

2. Methods

2.1. Participants

Detailed participant information has been reported previously (Whalley et al., 2015). Briefly, participants were recruited as part of the Scottish Family Mental Health Study, approved by the Multicentre Research Ethics Committee for Scotland (09/MRE00/81). Detailed clinical and MRI data were obtained for HC ($n = 41$) and patients with a DSM-IV diagnosis of SCZ ($n = 38$) or BD ($n = 20$) aged between 18 and 67 years. Clinical diagnoses were established using the structural interview for the DSM-IV (SCID; (First et al., 2002) conducted by one of two trained psychiatrists. For analyses purposes, SCZ and BD participants were combined into one patient group. Table 1 shows demographic information for both groups.

2.2. Imaging procedures

MR imaging was performed at Edinburgh's Clinical Research Imaging Centre (CRIC) (http://www.cric.ed.ac.uk/) on a Siemens Verio 3T MRI system (Siemens Medical Systems, Erlangen). Structural brain images were acquired using a T1-weighted magnetization prepared rapid acquisition gradient sequence parallel to the AC-PC line (repetition time 2300 ms, echo time 2.98 ms, inversion time 900 ms, flip angle 9°) resulting in 160 contiguous 1 mm slices of 256×256 voxels.

Brain scans were anonymised at the time of acquisition and a set protocol was adhered to for pre-processing of scans, regardless of

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