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Impact of cross-disorder polygenic risk on frontal brain activation with specific effect of schizophrenia risk

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ABSTRACT

Evidence suggests that there is shared genetic aetiology across the major psychiatric disorders conferred by additive effects of many common variants. Measuring their joint effects on brain function may identify common neural risk mechanisms. We investigated the effects of a cross-disorder polygenic risk score (PGRS), based on additive effects of genetic susceptibility to the five major psychiatric disorders, on brain activation during performance of a language-based executive task. We examined this relationship in healthy individuals with (n = 82) and without (n = 57) a family history of bipolar disorder to determine whether this effect was additive or interactive dependent on the presence of family history. We demonstrate a significant interaction for polygenic loading × group in left lateral frontal cortex (BA9, BA6). Further examination indicated that this was driven by a significant positive correlation in those without a family history (i.e. healthy unrelated volunteers), with no significant relationships in the familial group. We then examined the effect of the individual diagnoses contributing to the PGRS to determine evidence of disorder-specificity. We found a significant association with the schizophrenia polygenic score only, with no other significant relationships. These findings indicate differences in left lateral frontal brain activation in association with increased cross-disorder PGRS in individuals without a family history of psychiatric illness. Lack of effects in the familial group may reflect epistatic effects, shared environmental influences or effects not captured by the PGRS. The specific relationship with loading for schizophrenia is notably consistent with frontal cortical inefficiency as a circumscribed phenotype of psychotic disorders.

1. Introduction

Current diagnostic criteria in psychiatry are based around symptom patterns and course of illness, however, no symptom is uniquely associated with an individual condition, and symptoms vary between people with the same diagnosis. Psychosis, mood instability, and cognitive impairments for example are observed across multiple diagnoses. There is also considerable overlap in genetic contributions, as well as commonalities in implicated brain networks, for example the prefrontal cortex and medial temporal lobes (Phillips et al., 2003; Shaw and Rabin, 2009; Dickstein et al., 2013; Hong Lee et al., 2013). There is an increasing uncertainty therefore over the degree to which current diagnostic criteria define biologically-valid distinct entities, or whether common mechanisms contribute to multiple conditions or cross-disorder phenotypes.

To address such issues, previous imaging studies have employed a dimensional approach, by examining the neurobiology of specific symptoms crossing diagnostic boundaries. These have included individuals with, or at increased risk of, schizophrenia with and without mood symptoms (Whalley et al., 2008; Simon et al., 2010; Tomasino et al., 2011; Barbour et al., 2012), and patients with mood disorder with and without psychotic features (Sommer et al., 2007; Khadka et al., 2013). Although literature is limited, evidence suggests alterations in medial temporal lobe and limbic structures in association with mood-related symptoms across disorders (Tomasino et al., 2011), and alterations in lateral prefrontal functioning in association with psychosis, also transdiagnostically (Anticevic et al., 2013).

Genetic imaging studies have also examined the impact of shared genetic risk on underlying neurobiology. Previous studies have investigated the effects on neurobiology of individual SNPs identified as potential risk markers for illness within and across diagnostic groups (Mechelli et al., 2008; Chakirova et al., 2011; Papagni et al., 2011; Prata et al., 2011; Whalley et al., 2012a,b). Current evidence however suggests that for psychiatric disorders a substantial proportion of the heritability is explained by a polygenic component. We previously used the polygenic approach to demonstrate increased activation of mood-related limbic regions in association with increased polygenic loading for bipolar disorder (Whalley et al., 2012a,b, 2013).

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One recent study has used genetic strategies to explore *shared* genetic architecture across the 5 major psychiatric disorders using Psychiatric Genomics Consortium data (Smoller et al., 2013). The authors identified shared genetic effects between Attention Deficit Hyperactivity Disorder (ADHD), Autism (Aut), Bipolar disorder (BD), Major Depressive Disorder (MDD) and Schizophrenia (SCZ), in 33,332 cases and 27,888 controls (Smoller et al., 2013), firstly by examining effects of shared GWAS hits for BD and SCZ, and then by generating cross-disorder polygenic risk scores (PGRSs) to examine a broader set of common variants. This cross-disorder PGRS is likely to account for an even greater proportion of overall risk than for single disorder PGRS and allows examination of processes involved in enhanced risk across diagnostic groups (Smoller et al., 2013).

In the current study we examine the neural effects of this broader set of common variants on brain activation in regions previously associated with the 5 major psychiatric disorders, namely the prefrontal cortex and medial temporal lobe structures (Phillips et al., 2003; Shaw and Rabin, 2009; Dickstein et al., 2013). We also sought to test whether there was an additive or interactive effect of family history on the effect of PGRS on neural activation by examining groups with and without a family history of mood disorder. The paradigm, a language-based executive function task, was chosen as it had previously been shown to differentiate psychiatric patients, and those at increased familial risk, from healthy controls in these regions (McIntosh et al., 2008a,b; Whalley et al., 2011). Moreover, it probes frontal neuropsychological deficits in executive function, verbal initiation and verbal fluency seen across a range of psychiatric disorders (Clark et al., 2000; Arts et al., 2008; Booth and Happe, 2010).

We were also interested in examining whether there was any evidence for disease-specific brain activation associations by deconstructing the components of the cross-disorder PGRS into diagnosis-specific subscores (Smoller et al., 2013). Based on neuroimaging evidence described, we hypothesised that there would be abnormal frontal activation in association with increased loading for schizophrenia, and increased activation of medial temporal regions in association with mood disorder.

2. Methods

2.1. Study population

Individuals at high genetic risk of bipolar disorder I (BDI), because of a close family history of the disorder, and control subjects with no family history were recruited as part of the Scottish Bipolar Family Study (Sprooten et al., 2011; Whalley et al., 2011). Caseloads of psychiatrists across Scotland were searched for individuals diagnosed with BDI. Diagnoses were confirmed with the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (First et al., 2002) or the symptom checklist of Operational Criteria (OPCRIT) (McGuffin et al., 1991). Subjects with BD were asked to identify a first or second-degree relative (between 16–25 years) not suffering from the disorder. These unaffected individuals were invited to participate in this study provided they had at least one first degree, or two second degree relatives with BDI. Controls with no personal history of BD or family history of a mood disorder in first-degree relatives were identified from the personal contacts of the bipolar high-risk subjects. Exclusion criteria for all groups included a personal history of major depression, mania or hypomania, psychosis, substance dependence, an IQ <70 or clinical diagnosis of learning disability, or any major neurological disorder or history of head injury that included loss of consciousness, and any contraindications to MRI. A total of 82 bipolar high-risk and 57 controls provided suitable fMRI data and genetic information. All participants provided written informed consent and the study was approved by the multi-centre research ethics committee for Scotland. All participants included in the current study were unrelated.

2.2. Genotyping and derivation of polygenic scores

Genomic DNA was extracted from venous blood. Genotyping was conducted at the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (www.wtcrf.ed.ac.uk) using the Illumina OmniExpress 730K SNP array. PGRS analyses were performed in PLINK (Purcell et al., 2007) using imputed genotype data. Imputation was performed in accordance with the 1000 Genomes Project Protocol SNPs with an imputation quality score of $r2 > 0.3$ retained for analysis. Methods for creating PGRS are described elsewhere (Purcell et al., 2009). Summary statistics from the PGC GWAS Cross Disorder group (33,332 cases and 27,888 controls) were used as the training set to create cross-disorder PGRS for our samples (Smoller et al., 2013). Our primary analyses concerned those SNPs from the PGC data that met a significance level of $p = .5$ or less as previously described (Purcell et al., 2009; Whalley et al., 2012a,b, 2013), further details in Supplementary material.

2.3. Clinical assessments

All participants were interviewed by one of the two experienced psychiatrists (AMM, JES) using the SCID (First et al., 2002) to confirm the absence of any lifetime axis I disorders. Current symptoms were rated using the Young Mania Rating Scale (YMRS) (Young et al., 1978), Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), and the positive and negative syndrome scale (PANSS) (Kay et al., 1987).

2.4. Experimental paradigm

Subjects performed the verbal initiation section of the Hayling Sentence Completion Test (HSCT) (Burgess and Shallice, 1997) in the scanner (Whalley et al., 2004). This is an extension of the verbal fluency task and considered a test of executive function. Briefly, subjects were shown sentences with the last word missing and asked to think of an appropriate word to complete the sentence and press a button when they had done so. The task has four levels of difficulty, according to the range of suitable completion words suggested by the sentence context. This allowed a standard subtraction analysis (sentence completion versus baseline) and a parametric analysis (examining increasing activation with increasing task difficulty). Sentences were presented in blocks of fixed difficulty. The order of the blocks was pseudo-random, and each block was repeated four times using different sentences. Immediately after scanning, subjects were given the same sequence of sentences on paper and requested to complete each sentence with the word they first thought of in the scanner. 'Word appropriateness' scores were determined from the word frequency list of sentence completion norms (Bloom and Fischler, 1980).

2.5. Image processing and analysis

Scanning procedure details are contained in Supplementary material. EPI and T1 images were reconstructed into nifti format (Mayo Foundation, Rochester, MN, USA) using DICOM convert functions in SPM5 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London) running in Matlab (The MathWorks, Natick, MA, USA). Images were preprocessed using standard protocols in SPM5. All EPI images were realigned to the mean volume in the series. Functional images were then normalised according to standard co-registration procedures using the individual's structural scan. Finally, all realigned and normalised images were smoothed with an $8 \times 8 \times 8$ mm full width half maximum (FWHM) Gaussian filter.

First-level analysis was performed using the general linear model. At the individual subject level the data was modelled with four conditions corresponding to the four difficulty levels each modelled by a boxcar convolved with a synthetic haemodynamic response function. Estimates