The polygenic risk for bipolar disorder influences brain regional function relating to visual and default state processing of emotional information

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ABSTRACT

Genome-wise association studies have identified a number of common single-nucleotide polymorphisms (SNPs), each of small effect, associated with risk to bipolar disorder (BD). Several risk-conferring SNPs have been individually shown to influence regional brain activation thus linking genetic risk for BD to altered brain function. The current study examined whether the polygenic risk score method, which models the cumulative load of all known risk-conferring SNPs, may be useful in the identification of brain regions whose function may be related to the polygenic architecture of BD. We calculated the individual polygenic risk score for BD (PGR-BD) in forty-one patients with the disorder, twenty-five unaffected first-degree relatives and forty-six unrelated healthy controls using the most recent Psychiatric Genomics Consortium data. Functional magnetic resonance imaging was used to define task-related brain activation patterns in response to facial affect and working memory processing. We found significant effects of the PGR-BD score on task-related activation irrespective of diagnostic group. There was a negative association between the PGR-BD score and activation in the visual association cortex during facial affect processing. In contrast, the PGR-BD score was associated with failure to deactivate the ventromedial prefrontal region of the default mode network during working memory processing. These results are consistent with the threshold-liability model of BD, and demonstrate the usefulness of the PGR-BD score in identifying brain functional alternations associated with vulnerability to BD. Additionally, our findings suggest that the polygenic architecture of BD is not regionally confined but impacts on the task-dependent recruitment of multiple brain regions.

1. Introduction

Bipolar Disorder (BD) is a complex disorder characterized by mood dysregulation resulting in significant psychosocial impairment (van der Voort et al., 2015). Family, twin, adoption and genome-wide association (GWAS) studies have consistently shown a substantial genetic contribution to disease etiology (Smoller and Finn, 2003; Alsabban et al., 2011) with heritability estimates ranging from 0.6 to 0.8 (Smoller and Finn, 2003; Lichtenstein et al., 2009). It is widely acknowledged that the genetic architecture of the BD is polygenic and consistent with a threshold-liability model (Gottesman and Shields, 1967). Candidate gene and GWAS genetic studies have identified a number of single-nucleotide polymorphisms (SNPs) that are associated with increased risk for BD (International Schizophrenia Consortium et al., 2009;

Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Green et al., 2013). Individual risk-alleles for BD have been shown to influence brain structure and function in healthy individuals (Kempton et al., 2009; Bigos et al., 2010; Erk et al., 2010; Franke et al., 2010; Krug et al., 2010; Wessa et al., 2010; Heinrich et al., 2013; Paulus et al., 2014), patients with BD (Mechelli et al., 2008; Perrier et al., 2011; Chakirova et al., 2011; Prata et al., 2011; Soeiro-de-Souza et al., 2012; Dima et al., 2013; Tesli et al., 2013) and their unaffected relatives (Lelli-Chiesa et al., 2011; Jogia et al., 2011; Whalley et al., 2012; Erk et al., 2014; Delvecchio et al., 2015). Collectively, these studies have established that risk-variants for BD are linked to brain alterations considered relevant to the pathophysiology of the disorder. For example, meta-analyses of functional magnetic resonance imaging (fMRI) studies have consistently shown increased activation in the amygdala and decreased activation in the ventrolateral prefrontal cortex (vlPFC) across a number of cognitive tasks in patients with BD compared to healthy controls (Chen et al., 2011; Delvecchio et al., 2013). Similarly, GWAS-supported risk-alleles in the CACNA1C and ANK3 genes, have been independently

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associated with increased amygdalar activity in patients with BD (Dima et al., 2013; Jogia et al., 2011) and in the vlPFC (Jogia et al., 2011).

However, individual GWAS-supported genetic loci only account for a very small fraction of the risk of BD (Visscher et al., 2012). In response, the polygenic risk (PGR) score method has been developed to quantify the extent to which common risk-variants may collectively capture variation in susceptibility to disease (International Schizophrenia Consortium et al., 2009). The PGR score for BD (PGR-BD) is calculated in each individual by aggregating variation across GWAS loci nominally associated with BD into a quantitative score (International Schizophrenia Consortium et al., 2009; Dima and Breen, 2015), with the current PGR-BD explaining ~5% of the variance to BD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Two previous studies have used the polygenic risk score method to examine the cumulative impact of BD-related risk-conferring SNPs on task-related brain activation during an emotional processing (Tesli et al., 2015) and a word generation task (Whalley et al., 2012). During emotional processing, a positive association was found in patients with BD and in controls between PRG-BD score and brain activation in the right vlPFC. In the word generation task a positive association was also present between the PGR-BD score and amygdalar activation in unaffected relatives of patients and in controls. Neither study found an interaction between PGR-BD score and diagnostic group on the patterns of brain activation. This evidence collectively suggests that the influence of common risk-alleles on brain function may be more informative with regards to brain phenotypes related to vulnerability to BD rather than overt disease. The PGR method has a relatively higher explanatory power compared to single SNP examinations (Dima and Breen, 2015), and may be useful in identifying regions where the additive effect of common risk-alleles converges to confer vulnerability to BD.

Based on the above we examined the effect of a PGR-BD on brain fMRI data from patients with BD, unaffected relatives and unrelated healthy controls while performing a facial affect and a working memory processing task. Current models of BD emphasise increased neural response to affective stimuli coupled with reduced efficacy of the neural systems responsible for cognitive control (Phillips et al., 2003; Cerullo et al., 2009). We therefore chose the facial affect and working memory tasks as the former maps onto the ventral PFC-limbic pathway (Dima et al., 2011; Vuilleumier and Pourtois, 2007) implicated in the ability to process the emotional significance of stimuli and the later engages frontoparietal regions involved in cognitive control (Dima et al., 2014; Niendam et al., 2012; Owen et al., 2005). Additionally, previous studies have reported brain functional abnormalities in patients with BD while performing these tasks (Cerullo et al., 2009) thus demonstrating their relevance to BD. Using two different paradigms on the same study sample we aimed to test whether the polygenic load for BD has a localized effect to a region or a network of regions that are task dependent and may represent a common pathway linking genetic risk to BD-related brain abnormalities.

2. Material and methods

2.1. Participants

Euthymic patients with BD (n = 41), their unaffected first-degree relatives (n = 25) and demographically matched unrelated healthy individuals (n = 46) were selected from the VIBES study (Frangou, 2009) (Table 1). All participants were of white British ancestry. They were assessed using the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised (DSM-IV) for Axis I diagnoses (First et al., 2002a, 2002b). Patients that fulfilled the criteria for BD, type I according to the DSM-IV (APA, 1994) were included. The relatives were carefully selected from the VIBES sample based on the absence of any lifetime history of psychopathology. The sample included 17 BD patients-sibling pairs from 17 different families. Unrelated healthy individuals were selected based on the absence of

Table 1
Sample characteristics.

	Patients with bipolar disorder (n = 41)	Unrelated controls (n = 46)	Unaffected relatives (n = 25)
Age (years)	44.3 (11.9)	40.3 (13.2)	39.7 (13.7)
Sex (male/female)	20/21	25/21	13/12
IQ	117.9 (17.9)	112.6 (14.5)	115.8 (18.5)
Polygenic risk score[a]	0.37 (0.04)	0.32 (0.06)	0.35 (0.04)
HDRS total score[b]	4.8 (5.3)	0.1 (0.5)	0.14 (0.4)
YMRS total score[b]	1.4 (3.0)	0.2 (0.6)	0.0 (0.0)
BPRS total score[b]	27.5 (4.0)	24.3 (0.7)	24.1 (0.4)
Age of onset (years)	24.7 (8.0)	–	–
Duration of illness (years)	20.2 (10.5)	–	–
Depressive episodes (n)	5.7 (7.5)	–	–
Manic episodes (n)	5.6 (7.7)	–	–
Facial affect recognition accuracy (%)	90.3 (4.1)	93.1 (4.8)	90.1 (5.2)
Facial affect recognition response time (sec)[c]	1.4 (0.20)	1.10 (0.24)	1.09 (0.14)
2-back accuracy (%)	83 (11.6)	88 (15.6)	92.3 (12.5)
2-back response time (sec)	0.65 (0.19)	0.63 (0.31)	0.62 (0.35)

Continuous data are shown as mean (standard deviation); BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale); YMRS = Young Mania Rating Scale.
[a] Patients > Controls (p = 0.002).
[b] Patients > Relatives, Controls (p < 0.02).
[c] Patients > Relatives, Controls (p < 0.007).

family history and personal lifetime history of psychiatric disorders. In all participants, current IQ was assessed using the Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997) and psychopathology was rated using the Hamilton Depression Rating Scale (Hamilton, 1960) (HDRS), Young Mania Rating Scale (Young et al., 1978) (YMRS) and Brief Psychiatric Rating Scale (Lukoff et al., 1986) (BPRS). Psychopathology was assessed weekly in patients over a period of 1 month prior to testing and at each assessment they scored below 7 in the HDRS and YMRS. Patients were also required to have remained on the same type and dose of medication for a minimum of 6 months. The BPRS, HDRS and YMRS scores were highly correlated (all r > 0.73, p < 0.0001). To avoid collinearity we used the total BPRS score as a covariate in subsequent neuroimaging analyses because, unlike the two other scales, it is applicable to nonclinical populations.

2.2. DNA extraction and genotyping

We obtained DNA from the participants using buccal swabs and conventional procedures. All participants were genotyped on the Psych Chip (Illumina Infinium PsychArray-24). Data quality was controlled in PLINK v1.07 (Purcell et al., 2007) using the same parameters as described in Coleman et al. (2016). SNPs were excluded when missingness > 1%, minor allele frequency (MAF) < 0.01 or Hardy-Weinberg equilibrium (HWE) < 0.00001 and participants were excluded when missingness > 1%. Sex and relatedness checks were carried out, in addition to principal component analyses to confirm self-reported ethnicities (Patterson et al., 2006).

2.3. Polygenic risk scores

Genome-wide polygenic risk scores for BD (PGR-BD) were generated with the PRSice software (http://prsice.info/; Euesden et al., 2015) using the most recent Psychiatric Genomics Consortium (PGC) GWAS of BD from the cross disorder study (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The SNPs used were those selected by the analysts of those studies using P-value-informed clumping in PLINK with a cut-off of $r^2 = 0.25$ within a 200-kb window, and excluding the Major Histocompatibility Complex (MHC) region of the

genome because of its complex linkage disequilibrium structure. Of 108,834 clumped SNPs from the original analyses of BD, 108,217 existed in our data. For each participant, seven PGR-BD scores were generated using SNPs with p-values <0.001 (SNPs: 417), 0.05 (SNPs: 9715), 0.1 (SNPs: 16,691), 0.2 (SNPs: 28,450), 0.3 (SNPs: 38,207), 0.4 (SNPs: 46,753) and 0.5 (SNPs: 54,127).

2.4. Facial affect recognition paradigm

Three negative facial emotions (fear, anger and sadness) were examined in three event-related experiments presented in a random order during a single acquisition session. In each experiment, 10 different facial identities (www.paulekman.com) depicting 150% intensity of an affective or a neutral facial expression were presented in a pseudorandom order interspersed with a fixation cross. Each stimulus (affect and neutral faces; fixation cross) was displayed for 2 s and repeated 20 times. Participants were instructed to indicate whether the face was emotional or neutral. Response time and accuracy data were collected.

2.5. Working memory paradigm

The 2-back task was presented as an alternating block paradigm incorporating the active (2-back) and baseline (0-back) conditions. Participants were instructed to respond to target letters by button press. In the baseline condition, participants responded to the X letter. In the 2-back condition participants responded when the letter presented matched the one in the preceding 2 trials. Each stimulus was presented for 2 s. There were 18 epochs in all, each lasting 30 s. Response time and accuracy data were collected.

2.6. Image acquisition

Anatomical and functional imaging data were acquired during the same session using a General Electric Sigma 1.5 Tesla. A high-resolution T1-weighted structural image was acquired for each participant in the same session in the axial plane for co-registration (inversion recovery prepared, spoiled gradient-echo sequence; repetition time = 18 ms, echo time = 5.1 ms, flip angle = 20°, slice thickness = 1.5 mm, matrix size = 256 ∗ 192, field of view = 240 ∗ 180 mm, voxel dimensions = 0.9375 ∗ 0.9375 ∗ 1.5 mm).

For the facial affect recognition paradigm, 450 T2-weighted MR images reporting blood-oxygen-level dependent (BOLD) contrast were acquired (repetition time = 2000 ms, echo time = 40 ms, flip angle = 70°, slice thickness = 7 mm, matrix size = 64 ∗ 64, voxel dimensions = 3.75 ∗ 3.75 ∗ 7.7 mm). For the 2-back paradigm, a total of 180 T2-weighted MR volumes depicting BOLD contrast were acquired (repetition time = 3000 ms, echo time = 40 ms, flip angle = 90°, slice thickness = 3 mm, matrix size = 64 ∗ 64, voxel dimensions = 3.75 ∗ 3.75 ∗ 3.30 mm).

2.7. Functional neuroimaging data analysis

Data were analysed in SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/). Data from each paradigm were analysed separately. For both paradigms, fMRI images were realigned, normalized and smoothed using an 8-mm full-width-half maximum Gaussian kernel. For the facial affect recognition paradigm, each participant's fMRI data from the three event-related experiments (fear, anger or sadness) were concatenated and vectors of onset representing correct responses were convolved with a canonical hemodynamic response function. The means of the three sessions as well as the transition at the end of each session were also modelled and images for the affect > neutral faces contrast were produced for each participant. For the 2-back paradigm, the smoothed single-participant images were analysed using the linear convolution model, with vectors of onset representing the active (2-back) and baseline (0-back) condition. For each participant, images for the 2-back > baseline contrast were produced.

2.8. Effect of PGR-BD score on task-related activation

For each task separately, contrast images from each participant were entered into second-level analyses using one-sample t-tests to identify clusters of increased task-related activation at p < 0.05 with Family Wise Error (FWE) correction and cluster size (k) > 20. The BPRS total score and relatedness were added as covariates. Beta value from the supra-threshold clusters were then extracted using the eigenvariate function in SPM8 and entered into a multivariate model to examine the effect of PGR-BD and its interaction with group (BD patients, unaffected relatives, unrelated healthy controls) in SPSS22, with relatedness as a covariate.

2.9. Effect of PGR-BD score on group differences on task-related activation

The effect of group (patients, relatives controls) was examined separately for each paradigm (affect faces > neutral faces; 2-back > baseline) using a general lineal model in SMP8 with the BPRS total score as covariate. In each of these analyses, supra-threshold clusters signifying group differences were identified using FWE correction of p < 0.05, k > 20. Beta values were extracted from each supra-threshold cluster using the eigenvariate function in SPM8. To test whether the PGR-BD score explained additional variance in group differences, Pearson's correlation analyses were used to examine the relationship between mean signal change in the suprathreshold clusters and PGR-BD score in SPSS22, with relatedness as a covariate.

3. Results

3.1. Polygenic risk scores

We used one-way analysis of variance to compare patients, relatives, controls on PGR-BD scores derived using seven statistical thresholds (i.e., using SNPs with p-values < 0.001, 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5). Although the effect of group was significant at all thresholds, the highest difference (F = 5.94, p = 0.004) was found for the PGR-BD score using 16,691 SNPs with p < 0.1. This PGR-BD score was higher in patients than controls (p = 0.002) while in relatives it was numerically intermediated between that of patients (p = 0.06) and controls (p = 0.09) (Table 1). All subsequent analyses and results refer to this PGR-BD score. In the patient group, no significant correlations were found between PGR-BD and symptom severity (based on the total score of the HDRS, YMRS and BPRS), age of onset, duration of illness, and number of depressive and manic episodes (p > 0.27).

3.2. Behavioural task performance

Details of task performance are shown in Table 1. Patients' medication type and dose did not correlate with performance on either task (all p > 0.40). In the facial affect recognition paradigm, we found a main effect of group on response time (p = 0.004), with BD patients being slower than the other two groups (p < 0.007). However, the PGR-BD score showed a significant negative correlation with response time to affect compared to neutral faces when controlling for group (r = −0.31, p = 0.003). In the 2-back task, there was no effect of group and no significant correlations were found between PGR-BD score and task performance.

3.3. Effect of PGR-BD on task-related activation

3.3.1. Facial affect recognition

In all participants, activation in the affect > neutral faces contrast was found in the visual association and prefrontal cortical areas

(Supplemental Table 1; Fig. 1A). There was a main effect of PGR–BD score (F = 2.03, p = 0.04) but no group by PGR–BD interaction (F = 0.99, p = 0.46). The PGR–BD score influenced mean signal change in the visual cortex (peak MNI coordinates at: x = −32, y = −88, z = 2; p = 0.006) (Fig. 1B).

3.3.2. Working memory

In all participants, activation in 2-back > baseline contrast was found in the ventral and dorsal lateral prefrontal cortex and in the parietal cortex (Supplemental Table 1; Fig. 2A). There was a main effect of PGR–BD score (F = 2.83, p = 0.01) but no group by PGR–BD interaction (F = 1.13, p = 0.33). The PGR–BD score influenced mean signal change in medial prefrontal cortex (peak MNI coordinates at: x = 22, y = 48, z = −14; p = 0.004) (Fig. 2B).

3.4. Effect of PGR-BD on group differences on task-related activation

3.4.1. Facial affect recognition

In the contrast affect > neutral faces, an effect of group was noted in the anterior cingulate cortex (ACC) and right superior frontal gyrus, where BD patients showed, respectively, increased and decreased

activation compared to their relatives and unrelated healthy individuals (Supplemental Table 2). No significant correlation between the PGR–BD score and signal change in the suprathreshold clusters was identified (p > 0.05).

3.4.2. Working memory

No effect of group was noted in the 2-back > baseline contrast.

4. Discussion

The current study examined the cumulative impact of common risk-alleles for BD, expressed as a polygenic risk score (PGR-BD), on brain activation during facial affect and working memory processing in patients with BD, unaffected relatives and unrelated controls. As expected, the PGR-BD score was higher in BD patients. Relatives had intermediate values that were not statistically different from that of either patients or controls. In line with previous reports (Whalley et al., 2012; Tesli et al., 2015), there was a significant effect of PGR-BD on task-related BOLD signal change independent of group but no significant PGR-BD score by group interactions. The current findings therefore support the notion that the polygenic load method is more informative in terms of
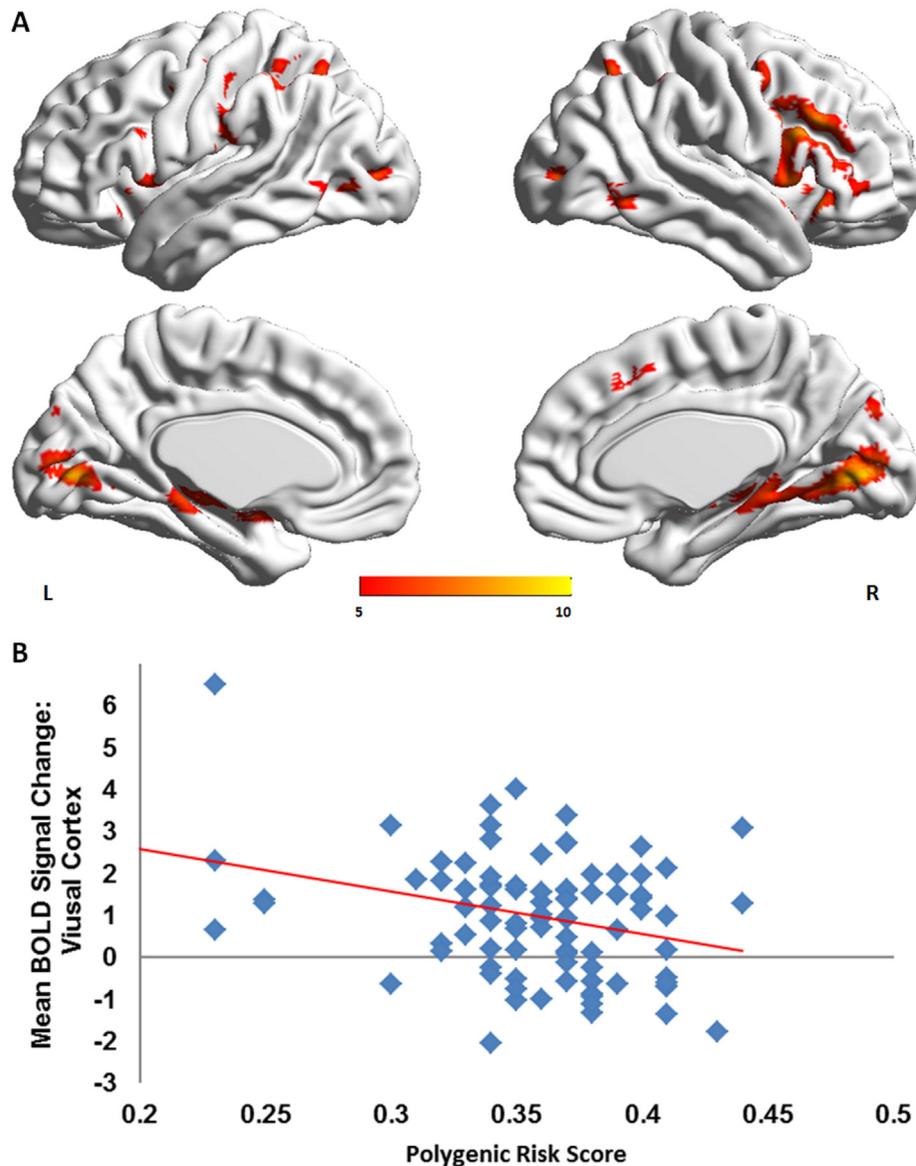
Fig. 1. A) Task related activation during the facial affect recognition task (at p < 0.05 Family Wise Error correction; peak MNI coordinates of suprathreshold clusters in Supplemental Table 1). B) Association between polygenic risk score for bipolar disorder and activation in the visual association cortex.
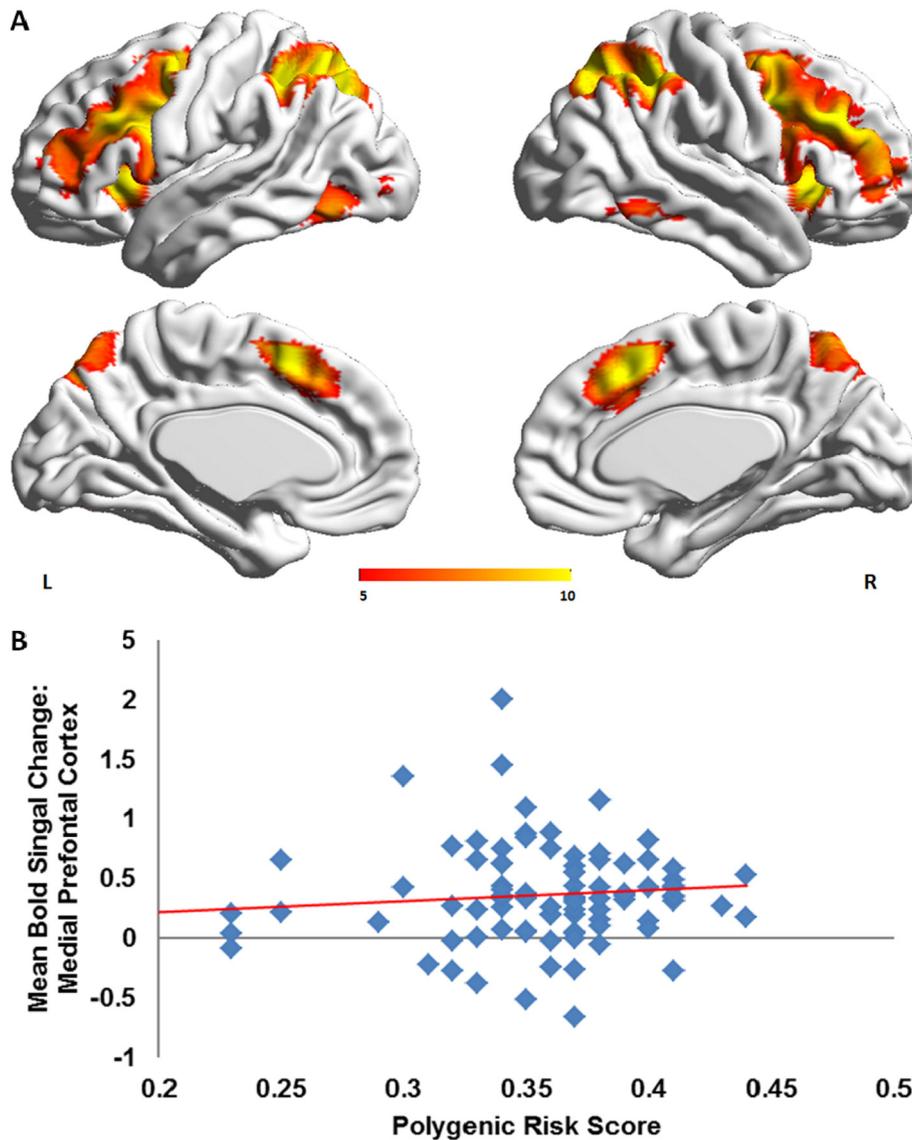
Fig. 2. A) Task related activation during the 2-back task (at p < 0.05 Family Wise Error correction; peak MNI coordinates of suprathreshold clusters in Supplemental Table 1. B) Association between polygenic risk score for bipolar disorder and activation in the ventromedial prefrontal cortex.

identifying patterns of neural activation that mediate vulnerability to BD rather than symptom expression. This is consistent with the liability-threshold model of BD since a significant number of risk-alleles are also present in healthy individuals that are unlikely to ever develop BD. Our results also suggest that the effect of polygenic load for BD is not localized to a single region or pathway, irrespective of task. Instead we found that the PGR-BD score influenced task-dependent brain activation.

During the facial affect recognition task, we found a negative association between the PGR-BD score and activation in the visual association cortex. This region is part of the ventral visual pathway, which together with the amygdala and ventral prefrontal regions, form the core facial affect processing network (Dima et al., 2011; Vuilleumier and Pourtois, 2007). Reduced visual cortical activation and connectivity during facial affect processing (Pavuluri et al., 2007; Dima et al., 2016) has been previously reported in patients with BD and have been consistently coupled with increased amygdalar and decreased vlPFC activation (Chen et al., 2011; Delvecchio et al., 2013). Studies of single SNPs on brain function during emotional processing have found risk-variants to be related to increased amygdalar activation (Jogia et al., 2011; Dima et al., 2013; Tesli et al., 2013). However, when considering thousands of risk-conferring alleles, as reflected in the PGR-BD score, we

found that their additive effect on the facial affect network involved primarily the recruitment of visual cortical regions. These findings add to the growing evidence of visual information processing abnormalities in patients with BD observed in visual backward masking (McClure, 1999), vernier acuity (Kéri et al., 2005), motion discrimination (Chen et al., 2006; O'Bryan et al., 2014), context modulation (Yang et al., 2013) and early visual evoked potentials (Yeap et al., 2009). It is suggested therefore that abnormalities in early sensory processing of affective visual stimuli may contribute to inadequate emotional regulation and predispose individuals to development of the BD.

In the 2-back task, we found a positive association between the PGR-BD score and activation in the ventromedial prefrontal cortex (vmPFC), a brain region integral to the Default Mode Network (DMN), whose activity represents emotional processing during the default state (Gusnard et al., 2001; Raichle et al., 2001). Typically, vmPFC activation is reduced during cognitively demanding task consistent with the fact that such tasks attenuate emotional processing (Gusnard et al., 2001). Failure to deactivate this region has been repeatedly reported in patients with BD both during acute episodes (Pomarol-Clotet et al., 2012; Fernández-Corcuera et al., 2013) and during remission (Pomarol-Clotet et al., 2015). Similar abnormalities in the deactivation of the vmPFC have also been reported in unaffected relatives of patients

(Thermenos et al., 2010; Alonso-Lana et al., 2016) and have been previously linked to risk-variants in the ANK3 gene (Delvecchio et al., 2015). Our findings further confirm that abnormalities in suppressing vmPFC activation are likely to represent a genetically mediated vulnerability trait for BD that is linked to greater polygenic load for the disorder.

The main limitation of the current study relates to the sample size which is relatively small for the purposes of genetic studies and could be a potential reason why we did not find any significant group by PGR-BD interaction. On the other hand, the main advantage of the polygenic risk score method is that it provides a quantitative measure of the polygenic load of each study participant without relying on their genetic distance from an affected proband. Moreover, the PGR-BD allows modelling the cumulative effect of multiple risk-variants for BD and is known to explain a greater proportion of phenotypic variance that single riks-alleles (International Schizophrenia Consortium et al., 2009; Dima and Breen, 2015).

In conclusion, we demonstrated that the polygenic risk architecture of BD influences the function of regions known to be involved in the sensory and default state processing of emotional information. Functional abnormalities in the visual cortex and ventromedial prefrontal regions of the DMN emerge as genetically influenced vulnerability traits of BD. The current results also indicate that the effect of genetic load for BD on brain function affects task-related recruitment of different brain regions. Future imaging genetics studies with large samples would be uniquely informative in mapping the spatial distribution of the genetic risk to BD on brain processes during various cognitive tasks and may lead to the discovery of biological pathways that may be crucial in mediating the link between genetic factors and alterations in brain networks in this disorder.

Acknowledgements

Appendix A. Supplementary results

Supplementary data to this article can be found online at http://dx.doi:10.1016/j.nicl.2016.10.022.

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