

Impact of a microRNA *MIR137* Susceptibility Variant on Brain Function in People at High Genetic Risk of Schizophrenia or Bipolar Disorder

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A recent 'mega-analysis' combining genome-wide association study data from over 40 000 individuals identified novel genetic loci associated with schizophrenia (SCZ) at genome-wide significance level. The strongest finding was a locus within an intron of a putative primary transcript for microRNA *MIR137*. In the current study, we examine the impact of variation at this locus (rs1625579, G/T; where T is the common and presumed risk allele) on brain activation during a sentence completion task that differentiates individuals with SCZ, bipolar disorder (BD), and their relatives from controls. We examined three groups of individuals performing a sentence completion paradigm: (i) individuals at high genetic risk of SCZ ($n = 44$), (ii) individuals at high genetic risk of BD ($n = 90$), and (iii) healthy controls ($n = 81$) in order to test the hypothesis that genotype at rs1625579 would influence brain activation. Genotype groups were assigned as 'RISK–' for GT and GG individuals, and 'RISK+' for TT homozygotes. The main effect of genotype was significantly greater activation in the RISK– individuals in the posterior right medial frontal gyrus, BA 6. There was also a significant genotype*group interaction in the left amygdala and left pre/postcentral gyrus. This was due to differences between the controls (where individuals with the RISK– genotype showed greater activation than RISK+ subjects) and the SCZ high-risk group, where the opposite genotype effect was seen. These results suggest that the newly identified SCZ locus may influence brain activation in a manner that is partly dependent on the presence of existing genetic susceptibility for SCZ.

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INTRODUCTION

Schizophrenia (SCZ) and bipolar disorder (BD) share some genetic risk factors and abnormalities in brain structure and function (Craddock *et al*, 2005; Lichtenstein *et al*, 2009; Purcell *et al*, 2009), the latter are also evident to some degree in unaffected relatives (Whalley *et al*, 2005; Fusar-Poli *et al*, 2007). To understand the differential pathophysiologies of these conditions and potentially identify specific markers for vulnerability, it is important to identify genetic factors related to each disorder and any associated brain differences.

Recently, the largest genome-wide association study (GWAS) to date, which included over 40 000 individuals, identified one of the strongest novel genetic associations in SCZ (Ripke *et al*, 2011). This occurred on chromosome 1p21.3 at rs1625579, within an intron of a primary transcript for a microRNA (miRNA), *MIR137*. MicroRNAs are short, noncoding RNA molecules that bind to target sequences on mRNA transcripts and act as post-transcription regulators. They are critical in brain development and function, and are consequently important in neurodevelopmental disorders such as SCZ and BD (Perkins *et al*, 2007). Typically, individual miRNAs are involved in regulating the expression of multiple genes and therefore could explain the complex phenotypic expression associated with these conditions. Indeed, postmortem studies have indicated differential expression levels of several miRNAs in prefrontal regions in SCZ and BD vs healthy controls (Perkins *et al*, 2007; Forero *et al*, 2010; Kim *et al*, 2010; Beveridge *et al*, 2011). In terms of *MIR137* specifically, normal levels

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of expression are required for regulating the balance of neuronal proliferation and differentiation (Sun *et al*, 2011; Shi *et al*, 2010; Smrt *et al*, 2010; Szulwach *et al*, 2010). Although the expression pattern has yet to be fully established, it is enriched in neurons, particularly in the dentate gyrus, a region implicated in psychiatric disorders and known to undergo neurogenesis into adulthood (Sempere *et al*, 2004; Smrt *et al*, 2010). It is also notable that genes associated with SCZ, including *TCF4*, *CACNA1C*, and *c10orf26*, are also targets of *MIR137* (Ripke *et al*, 2011).

Studying the effect of *MIR137* on traits associated with SCZ and BD in unaffected individuals at increased genetic risk for the illnesses may help elucidate the pathological mechanisms of the polymorphism in the absence of psychotropic medication and other illness associated factors, which could confound the results. Examining two high genetic risk populations, one for SCZ and one for BD, also allows examination of whether *MIR137* has a specific effect in the SCZ high-risk sample, or whether it has a more general effect on other psychiatric disorders. We examined the effect of variation in *MIR137* (rs1625579) on brain activation in (i) those at high genetic risk of SCZ ($n=44$), (ii) those at high genetic risk of BD ($n=90$), and (iii) healthy controls ($n=81$), during performance of a sentence completion task. This task differentiates patients with SCZ, BD, and those at increased familial risk for both disorders, from healthy controls (Whalley *et al*, 2004, 2011; McIntosh *et al*, 2008b). It activates language-related regions involved in the pathophysiology of both disorders (Lawrie and Abukmeil, 1998; Shenton *et al*, 2001; Glahn *et al*, 2008; Minzenberg *et al*, 2009). Moreover, it probes neuropsychological deficits in executive function, verbal initiation, and verbal fluency commonly observed in patients (Gourovitch and Goldberg, 1996; Heinrichs and Zakzanis, 1998; Bokar and Goldberg, 2003; Arts *et al*, 2008).

Mounting evidence implicating prefrontal and medial temporal regions in both SCZ and BD, and expression of *MIR137* in medial temporal lobe regions, led us to focus on these regions of interest (the prefrontal cortex, amygdala, and hippocampus). We also report other brain regions that reached significance at the whole brain level (Phillips *et al*, 2003; Smrt *et al*, 2010; Szulwach *et al*, 2010). We examined whether there were differences in activation according to *MIR137* genotype across all groups, and whether there were diagnosis-specific differences in genotype between the groups. We hypothesized that there would be a greater influence of the genotype in the SCZ high-risk group, given the genetic association with phenotype in that group alone (Ripke *et al*, 2011).

MATERIALS AND METHODS

Study Population

The study examined healthy subjects with no personal or family history of a psychiatric disorder, a group at familial risk of BD, and a group at familial risk of SCZ. These are referred to as 'diagnostic' groups to avoid confusion with genotype categorization. No individuals met criteria for a psychiatric disorder and none had received psychotropic medication for a psychiatric disorder. The controls and bipolar high-risk group were recruited as part of the

Scottish Bipolar Family Study (Whalley *et al*, 2011). The SCZ high-risk group originated from the Edinburgh High-Risk Study (Hodges *et al*, 1999; Johnstone *et al*, 2000).

Individuals with a diagnosis of BDI or SCZ were identified across Scotland. Diagnosis of affected subjects was confirmed with the Operational Criteria symptom checklist (OPCRIT; McGuffin *et al*, 1991) using data from clinical case notes and the structured clinical interview for DSM-IV disorders (SCID; First *et al*, 2002). To address issues relating to the substantial overlap in inheritance between the conditions, we excluded unaffected family members where there was a relative with the alternative disorder in equal or closer proximity to the original proband. Unaffected relatives of these individuals between the ages 16–25 years with at least one first-degree or two second-degree relatives with BDI or SCZ were invited to participate in the study. Unaffected, unrelated control subjects were identified from the social networks of the bipolar high-risk subjects.

Only unrelated individuals were included in the current analysis. 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 81 controls, 90 unrelated bipolar high-risk, and 44 SCZ high-risk participants provided suitable fMRI data along with genetic information, see Table 1. Written informed consent was provided by all participants and studies were approved by the Multicentre Research Ethics Committee for Scotland.

Genotyping

Genomic DNA was extracted from venous blood. Genotyping was conducted by the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (<http://www.wtcrf.ed.ac.uk>) and used a standard TaqMan/PCR-based assay (TaqMan, AssayByDesign, Applied Biosystems, Foster City, California). Subjects were typed for the G/T alleles at SNPs rs1625579 (Ripke *et al*, 2011). As it is the common variant that is reported to be the risk allele (T), the groups were split into those carrying two copies of the risk allele (TT, referred to as 'RISK +'), and those carrying only one or no copies (GG or GT, referred to as 'RISK -'). Tests of Hardy-Weinberg equilibrium (HWE) were performed using the genetics package in 'R' (version 2.12.1, R Foundation for Statistical Computing).

Experimental Paradigm

Participants performed the Hayling sentence completion paradigm in the scanner (see Burgess and Shallice, 1997; Whalley *et al*, 2004). Subjects were shown sentences with the last word missing and asked to silently think of an appropriate word to complete the sentence and press a button. This was a blocked design with four levels of difficulty according to sentence context. Sentences were assigned difficulty levels based on the frequency of the most typically presented word in the list of norms (Bloom and Fischler, 1980). The baseline condition consisted of viewing a screen of white circles on a black background. Each block

Table 1 Demographics and Behavioral Measures for Groups Separated into *miR137* Subgroups

	Controls (n = 81)			Bipolar high risk (n = 90)			Schizophrenia high risk (n = 44)			Between group comparison (F/Z/ χ^2 , p)
	RISK– (n = 31)	RISK+ (n = 50)	Within group comparison (T/Z, p)	RISK– (n = 24)	RISK+ (n = 66)	Within group comparison (T/Z, p)	RISK– (n = 18)	RISK+ (n = 26)	Within group comparison (T/Z, p)	
<i>Demographics</i>										
Mean age (years; S.D.)	21.49 (2.23)	20.67 (2.42)	1.55, 0.13	21.69 (2.28)	20.79 (2.97)	1.35, 0.18	26.97 (3.08)	26.10 (3.49)	0.56, 0.40	67.72, < 0.001
Gender (M/F)	17:14	20:30	1.70, 0.19	13:11	32:34	0.23, 0.63	6:12	12:14	0.72, 0.40	0.86, 0.65
Handedness (R/Other)	27:4	49:1	3.93, 0.05	24:0	58:8	3.19, 0.02	16:2	19:7	1.86, 0.39	10.82, 0.09
Mean NART IQ	111.90 (7.52)	110.32 (8.04)	0.88, 0.38	111.04 (9.03)	108.30 (8.22)	1.36, 0.18	98.56 (8.51)	101.42 (9.69)	1.01, 0.32	24.19, < 0.001
<i>Behavioral measures</i>										
Mean reaction time (ms)	2471 (542)	2464 (631)	0.47, 0.96	2529 (640)	2529 (654)	0.01, 0.99	2568 (687)	2275 (726)	1.24, 0.22	0.48 0.62
Mean word appropriateness	3.11 (0.58)	2.98 (0.48)	0.98, 0.33	2.90 (0.59)	2.90 (0.58)	0.26, 0.98	3.25 (0.46)	3.09 (0.38)	1.23, 0.23	3.10, 0.047

RISK– group refers to homozygotes and GG homozygotes; RISK+ refers to TT homozygotes.

Age and IQ were entered as covariates into the imaging analysis, see text for further details.

Bold values indicate statistical significance.

lasted 40 s. The order of the blocks was pseudo-random. Each block was repeated four times using different sentences. This design allowed a standard subtraction analysis (sentence completion *vs* baseline) and the more tightly constrained parametric analysis (examining areas of increasing activation with increasing task difficulty).

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). A score of one was given to the most frequently produced word in the word frequency list, a score of two for the next most frequently produced word, etc.

Analysis of demographic data used two sample *t*-tests or ANOVAs and χ^2 tests for continuous and categorical data as appropriate. Between-group comparisons for the behavioral data including mean reaction time and word appropriateness were also conducted using two sample *t*-tests or ANOVAs. All analyses were conducted using SPSS for Windows (version 14.0, SPSS, USA).

Scanning Procedure

Imaging was carried out at the Brain Imaging Research Centre of Scotland on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, WI). For the bipolar family study, the functional imaging protocol consisted of axial gradient-echo planar images (EPIs; TR/TE = 2000/40 ms; matrix = 64×64 ; field of view (FOV) = $240 \times 240 \text{ mm}^2$) acquired continually during the experimental paradigm. Twenty-seven contiguous 5 mm slices were acquired within each TR. Each EPI acquisition was run for 404 volumes. The first four were discarded. Data for the SCZ high-risk family study was collected non-concurrently and hence there were unavoidable technical differences to the above (TR/TE = 4000/40 ms; matrix = 64×128 ; FOV = $220 \times 440 \text{ mm}^2$). Thirty-eight contiguous 5 mm slices was acquired within each TR and

each EPI acquisition was run for 204 volumes, of which the first four were discarded. The T1 sequence yielded 180 contiguous 1.2 mm coronal slices (matrix = 192×192 ; FOV = 24 cm; flip angle 8°).

Image Processing and Analysis

EPI and T1 images were reconstructed into nifti format (Mayo Foundation, Rochester, MN) in SPM5 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London) running in Matlab (The MathWorks, Natick, MA). Images were pre-processed using standard protocols available in SPM5. EPI images were realigned to the mean volume in the series. The functional images were then normalized according to standard co-registration procedures using each individual’s structural scan. All realigned and normalized images were smoothed with an $8 \times 8 \times 8 \text{ mm}^3$ full-width half-maximum Gaussian filter.

First level statistical analysis was performed using the general linear model approach. At the individual subject level, the data was modeled with four conditions corresponding to the four difficulty levels each modeled by a boxcar convolved with a synthetic hemodynamic response function. Estimates of the subject’s movement during the scan were entered as ‘covariates of no interest’. The participants data were filtered in the time domain using high pass filter (128 s cutoff) and serial correlations were accounted for by using the autoregressive (AR(1)) model. Contrasts were constructed to examine all four sentence completion conditions *vs* baseline, and areas of increasing activation with increasing task difficulty (parametric contrast).

Second Level Analysis

For each contrast of interest (sentence completion *vs* baseline and parametric effects), one contrast image per subject was entered into a second-level random effects

analysis. A full factorial ANOVA model was used to compare the three groups. *F* tests determining the main effect of genotype were examined, followed by tests of genotype*group interactions. Genotype and group were entered as two factors with two levels of genotype, (RISK– (GG and GT) and RISK+ (TT)) and three ‘diagnostic’ groups (healthy controls, individuals at high-risk of BD, and individuals at high-risk of SCZ). This analysis was conducted controlling for age and verbal intelligence as measured with the National Adult Reading Test (Nelson, 1982), as analysis of demographic data indicated differences between the three groups (see Table 1). Pairwise *t*-tests were conducted to determine the direction of any interaction effects. For all analyses, statistical maps were thresholded at a level of $p < 0.005$ (uncorrected) and regions were considered significant at a cluster level of $p < 0.05$, corrected for multiple comparisons across the whole brain. Based on prior hypothesis, small volume corrections were also applied for the prefrontal cortex, amygdala, and hippocampus created using the WFU PickAtlas (Tzourio-Mazoyer *et al*, 2002; Maldjian *et al*, 2003). All coordinates are quoted in Montreal Neurological Institute (MNI) convention (<http://www.mni.mcgill.ca>). Images are overlaid onto standard brain in MNI space using Mango software package (<http://ric.uthscsa.edu/mango>).

RESULTS

Demographic, Clinical, and Behavioral Measures

Of the 81 controls, 50 subjects were RISK+ and 31 subjects were RISK– (two GG homozygotes). Of the 90 bipolar high-risk subjects, 66 were RISK+ and 24 were RISK– (four GG homozygotes). Of the 44 SCZ high-risk subjects, 26 were RISK+ and 18 were RISK– (one GG homozygote). Allele frequencies did not differ from the HWE across all groups ($p = 0.99$), or within each of the diagnostic groups (controls $p = 0.50$, bipolar high risk $p = 0.21$, SCZ high risk $p = 0.66$).

Demographic details are presented in Table 1. Within each diagnostic group there were no significant differences in age, gender, handedness, or IQ between the genotype groups, with the exception of a trend for a difference in handedness within controls between the genotype groups. There were no significant differences between the diagnostic groups in terms of gender or handedness, however, there were differences in mean age and mean IQ. These were

entered as covariates into the statistical model used to assess the imaging data.

Statistical analyses of the behavioral data within the diagnostic groups revealed no significant differences in within-scanner reaction times or word appropriateness scores between the genotype groups. There were, however, differences in mean word appropriateness scores between the diagnostic groups. This is explored further in terms of brain activation below.

Task-Related Brain Activation Patterns

All subjects demonstrated the expected patterns of brain activation and behavioral responses, indicating subjects were performing the task appropriately in the scanner (Whalley *et al*, 2004, 2011; McIntosh *et al*, 2008a). Regions activated across the groups for the sentence completion *vs* baseline contrast included the left medial prefrontal regions, including supplementary motor area (BA 6), lateral prefrontal regions, left lateral temporal cortex, sub-cortical structures including the lentiform and thalamus extending to hippocampal regions, left lateral parietal cortex, occipital lobes bilaterally, and right cerebellum. For the parametric contrast, all groups demonstrated activation in similar areas including left lateral and medial prefrontal cortex, left lateral temporal cortex, and right cerebellum, for further details see Supplementary Figure 1.

Genotype-Dependent Differences in Brain Activation

Sentence completion *vs* baseline. For sentence completion *vs* baseline, there were no significant main effects of genotype across the groups. There were, however, significant genotype*group interactions in the left amygdala ($p < 0.01$, $K_E = 109$, $F = 10.25$, $x = -24$, $y = 6$, $z = -16$, restricted to region of interest as defined by the WFU PickAtlas tool; Tzourio-Mazoyer *et al*, 2002) and left pre/postcentral gyrus ($p = 0.03$, $K_E = 459$, $F = 9.97$, $x = -44$, $y = -10$, $z = 30$, corrected at the whole brain level; Table 2, Figure 1a). There were no significant differences in the other pre-specified regions of interest.

Further *t*-tests examining the direction of interaction revealed this was significantly different between the controls (in the direction of RISK– greater activation than RISK+) *vs* the SCZ high-risk group (RISK– less activation than RISK+) for both the amygdala ($p = 0.030$, restricted to regions of interest as above) and pre/postcentral gyrus

Table 2 Genotype*group Interactions and Main Effect of Genotype

Contrast	<i>p</i> value	Extent (voxels)	<i>F</i> value	Peak height (coordinates in mm)	Region
<i>Genotype*group interaction</i>					
Sentence completion <i>vs</i> baseline	0.007	112	10.57	–26 6 –16	Left amygdala ^a
Sentence completion <i>vs</i> baseline	0.029	459	9.97	–44 –10 30	Left pre/postcentral gyrus, BA4/ BA3
<i>Main effect of genotype (across groups)</i>					
Parametric contrast	<0.001	831	13.04	12 –14 62	Right posterior medial frontal gyrus, BA6

Abbreviation: BA, Brodmann area.

See results section for pairwise comparisons and direction of difference.

^aIndicates small volume correction.

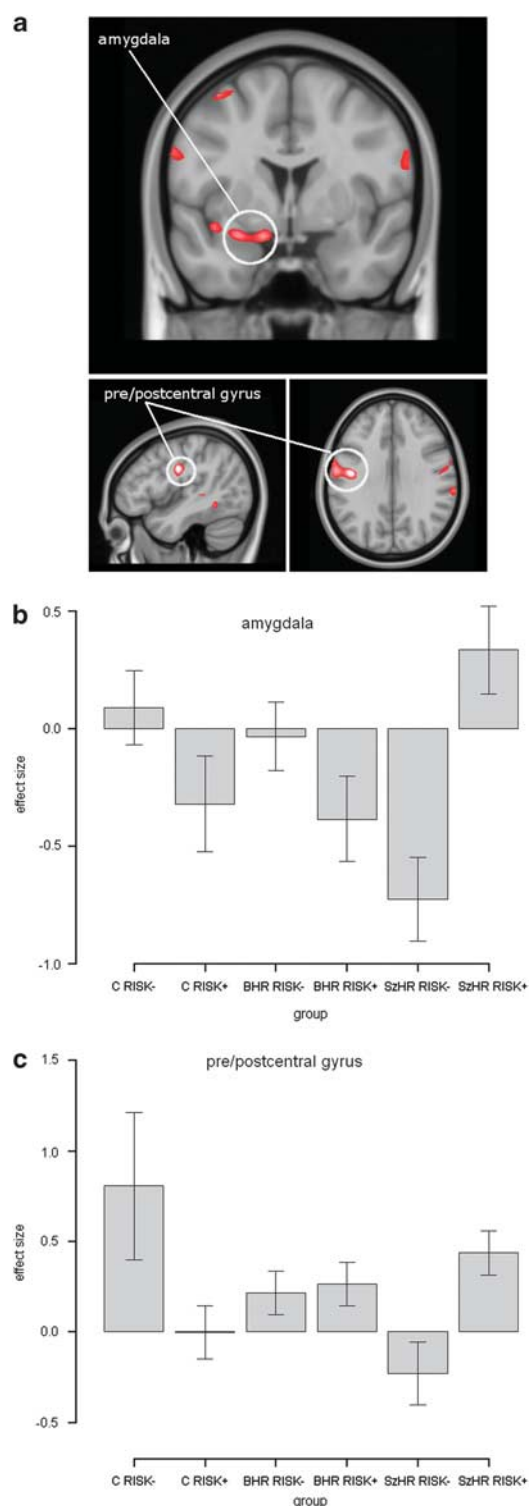


Figure 1 Genotype*group interaction for *MIR137*. (a) Depicts genotype by group interactions in left amygdala and left pre/postcentral gyrus for sentence completion vs baseline. Images are overlaid onto standard brain in MNI space using Mango software package (<http://ric.uthscsa.edu/mango>). Map represents F -statistic images thresholded equivalent to p uncorrected = 0.005, see Materials and Methods for further details. (b, c) Depicts graphs of extracted data for the clusters of significant interaction, see text for further details.

($p = 0.005$, corrected at the whole brain level). These regions did not demonstrate significant interactions for the controls and bipolar high-risk comparison, nor between the SCZ

high-risk and bipolar high-risk subjects. Graphs of the extracted data are presented in Figure 1b and c. For the amygdala, there was a general decreased activation across all groups for this contrast, with the exception of the SCZ high-risk RISK+ group.

There was no significant association between the extracted data from either of these clusters and behavioral measure of word appropriateness score, either within or across groups.

Parametric contrast. For the parametric contrast, there was a significant main effect of genotype across all groups in the right posterior medial frontal gyrus ($p < 0.01$, $K_E = 831$, $F = 13.04$, $x = 12$, $y = -14$, $z = 62$, corrected at the whole brain level), extending to superior frontal gyrus and to paracentral lobule, see Figure 2a and b. Further t -tests examining the direction of effect indicated this was in the direction of RISK- greater activation than RISK+ ($p < 0.001$). There were no significant genotype*group interactions for this contrast.

There were also no significant associations between the extracted data from this cluster and behavioral performance as determined by the word appropriateness scores, either within or across groups.

DISCUSSION

We have demonstrated a common effect of the *MIR137* genotype across controls and two groups of individuals at high risk of major mental illness on activation in the right posterior medial frontal gyrus. We have also shown significant differential effects of the *MIR137* genotype across groups in the left amygdala and left pre/postcentral gyrus. In regions where a significant interaction was found, differences occurred between controls and SCZ high-risk sample, not between the controls and bipolar high-risk group, nor between the familial groups themselves. These findings suggest, therefore, that there is a specific effect of *MIR137* on the SCZ high-risk sample, with additional general effects across the groups. This pattern is compatible with the GWAS mega-analysis, in which the association was primarily seen with the diagnosis of SCZ, rather than BD (Ripke *et al*, 2011). As previously described, the task was found to engage typical language-related regions and behavioral performance measures indicating that subjects were performing the task appropriately in the scanner (Whalley *et al*, 2004, 2011). Importantly, we were able to show that the above effects of genotype in the absence of the confounding disease and medication effects that compromise studies of patient populations. Also, there were no significant relationships between the main findings of interest and measures of behavioral performance on the task.

One of our main findings was an overall effect of the *MIR137* genotype across the diagnostic groups for the parametric contrast in the right posterior medial frontal gyrus, encompassing BA6 and supplementary motor areas, SMA and preSMA. This region demonstrated a reduced gradient of brain response to increasing task difficulty in those homozygous for the risk allele (RISK+) vs those heterozygous or homozygous for the 'protective' allele (RISK-), irrespective of diagnostic group (Figure 2b, and

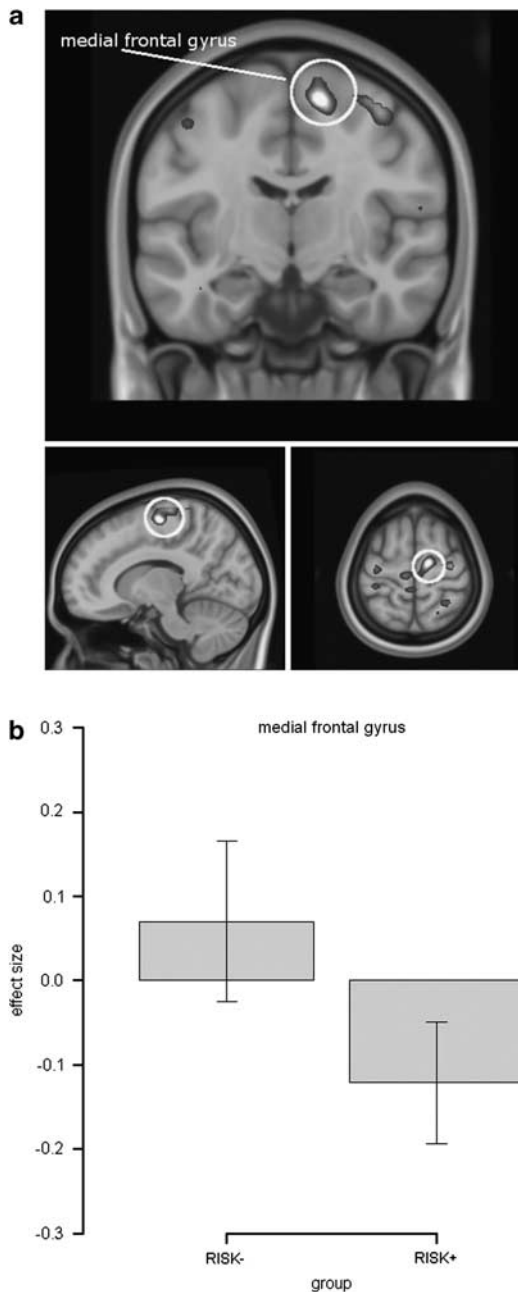


Figure 2 Main effect of *MIR137* genotype across groups. (a) Depicts effects of genotype across all three groups in the left posterior medial frontal gyrus for the parametric contrast. Images are overlaid onto standard brain in MNI space using Mango software package (<http://ric.uthscsa.edu/mango>). Map represents F-statistic images thresholded equivalent to p uncorrected = 0.005, see materials and methods for further details. (b) Depicts graphs of extracted data for the cluster of significant main effect of genotype, see text for further details. For groups additionally separated for 'diagnostic' grouping, see Supplementary Figure 2.

see Supplementary Figure 2). The parametric contrast examines levels of difficulty based on sentence constraint. This finding is therefore unlikely to be purely attributable to the simple motor response of button pressing. Indeed, this brain area is engaged in response to increasing task load (Whalley *et al*, 2004), and is activated in other executive and language-processing tasks (Rypma *et al*, 1999; Jansma *et al*,

2000; Bitan *et al*, 2007). This region has also been repeatedly shown to be abnormal in SCZ (McGuire *et al*, 1995; Honey *et al*, 2005; Exner *et al*, 2006). Although this region is in general implicated in the planning of motor actions, recent research indicates more diverse roles, eg, linking cognition to action (Nachev *et al*, 2008). It also forms part of the network of regions in the cognitive dysmetria model of SCZ where dysfunction, or disconnection, between cortico-thalamic–cerebellar regions are postulated to contribute to the abnormal coordination of mental processing underlying features of the disorder (Andreasen *et al*, 1998).

In addition to diagnostic independent effects, we also report significant genotype*group interactions in the amygdala and pre/postcentral gyrus. In particular, the amygdala has been repeatedly implicated in neurobiological models of SCZ (Phillips *et al*, 2003; Strakowski *et al*, 2005). In general, we found decreased activation of the amygdala during sentence completion *vs* rest, as we have reported previously (Whalley *et al*, 2011). The SCZ high-risk RISK+ group, however, failed to demonstrate this normal task-related deactivation. In SCZ, abnormally reduced responses of the amygdala to emotional *vs* neutral stimuli have previously been reported (Schneider *et al*, 1998; Phillips *et al*, 1999; Gur *et al*, 2002; Williams *et al*, 2004; Romaniuk *et al*, 2010), proposed to derive from an increased response to neutral stimuli (Schwartz *et al*, 2003; Holt *et al*, 2006; Surguladze *et al*, 2006; Hall *et al*, 2008; Romaniuk *et al*, 2010). Together with behavioral studies showing deficits in emotion recognition, it is suggested there is an overactivation and misinterpretation of ambiguous stimuli as being emotionally salient. This response is considered to contribute to clinical symptoms such as delusions, where neutral stimuli may be incorrectly perceived as threatening (Phillips *et al*, 2003). With regard to the current task, the paradigm is primarily an executive, non-emotional task. We speculate therefore that this finding may reflect an abnormal amygdala response in the SCZ high-risk RISK+ group to non-emotional stimuli. It should be considered, however, that since the common variant is reported to be the risk allele for *MIR137*, those individuals in the RISK- group also carry a copy of the risk allele. Another interpretation of the data, therefore, is that the comparison of the RISK-/+ group represents a comparison of those with/without the 'protective' allele. In this case, the interpretation would be that the presence of the 'protective' allele is associated with normal amygdala function, and that those in the SCZ high-risk RISK+ group without the protective allele do not demonstrate the expected deactivation during the task. It is notable that emotional processing bias and amygdala dysfunction has previously been reported in BD (Wessa and Linke 2009) and in their unaffected relatives (Whalley *et al*, 2011). In apparent contrast to these findings, we found no association between *MIR137* genotype and amygdala dysfunction in the bipolar high-risk sample. It is possible that the effect of *MIR137* risk genotype on brain activation in the bipolar high-risk sample is negligible against a background of presumed multiple genetic risk variants for BD and amygdala dysfunction.

The other cluster showing an interaction effect was in the pre/postcentral gyrus. The pattern of response in this region was different from that of the amygdala cluster above, reflecting that this is a task-activated region. The graph of

extracted values demonstrated greater activation in the control RISK− group *vs* the control RISK+ group, whereas the reverse was seen for the SCZ group (RISK− < RISK+). Indeed, the only group to demonstrate reduced activation during the task was the SCZ high-risk RISK− group. The pre/postcentral gyrus is primarily considered to be involved in somatosensory processing and motor functions, but its role has more recently been shown to also include higher cognitive tasks including executive functioning and linguistic processing (Whalley *et al*, 2004; Minzenberg *et al*, 2009). It is also reported to be affected in SCZ (Tanskanen *et al*, 2010; Job *et al*, 2002; Zhou *et al*, 2005; Glahn *et al*, 2008), and there are reports of associations of abnormalities in this region with clinical symptoms seen in the disorder (Kircher *et al*, 2001; Zhou *et al*, 2005; Nenadic *et al*, 2010; Jardri *et al*, 2011) together with neurological soft signs such as sensory integration deficits (Dazzan *et al*, 2004).

The importance of miRNAs have only relatively recently been realized. MicroRNAs are involved in many developmental processes spanning developmental timing, apoptosis, differentiation, and morphogenesis (Ambros 2004). As such, abnormalities seen in neurodevelopmental disorders could originate from disruption of post-translational processes under control by miRNAs (Sempere *et al*, 2004). The functional role and expression pattern of *MIR137* has yet to be fully determined. This variant was chosen because it was identified by one of the largest GWAS to date (Ripke *et al*, 2011). At present there is a rather limited literature. It is considered to be enriched in neurones, particularly, in the dentate gyrus and it is thought to have multiple functions during different stages of neurodevelopment (Shi *et al*, 2010; Smrt *et al*, 2010; Szulwach *et al*, 2010). Two recent molecular studies indicate *MIR137* is involved in multiple epigenetic mechanisms regulating the balance of neuronal proliferation and differentiation (Sun *et al*, 2011; Smrt *et al*, 2010; Szulwach *et al*, 2010). In one study, overexpression in the dentate gyrus resulted in inhibition of dendritic morphogenesis and maturation of neurones, whereas reduced expression had the opposite effect (Smrt *et al*, 2010). In another study, overexpression promoted proliferation of adult neural stem cells and reduced expression resulted in enhanced differentiation (Szulwach *et al*, 2010). Deficits in expression may therefore interfere with normal synaptic morphogenesis and signal transduction, thereby affecting aspects of cognitive function as seen in SCZ (Sempere *et al*, 2004). Effects have also been indicated out-with hippocampal regions, eg, reduced expression of *MIR137* in the frontal cortex has been reported in a small number of sporadic Alzheimer's Disease patients (Geekiyana and Chan 2011).

One limitation of the study was that the two high-risk samples were collected separately, with consequent unavoidable minor differences in the samples. The main demographic differences are controlled for using standard statistical approaches. The main methodological difference was that a TR of 4 was used for the SCZ high-risk study and a TR of 2 was used for the bipolar family study. It should be stressed, however, that both studies were conducted on the same scanner using the same paradigm design. Differences in TR are reported to primarily effect the number of data points collected and therefore efficiency of the experiment, with minimal impact on noise and smoothness of the data (Smith *et al*, 2007). For the current study with relatively

long blocks optimized for the longer TR, we considered the impact of the different TRs to be minimal, especially given quantitative analysis of activation maps suggesting the location and extent of activation was consistent across the studies (see Supplementary Figure 1). We have previously reported acceptable reproducibility both between and within scanning sites at the group and subject level, suggesting the viability of combining fMRI data sets (Gountouna *et al*, 2011; Suckling *et al*, 2012). We cannot completely exclude the possibility that these differences may impact on the current findings. However, such confounding effects are most likely to be evident at the between diagnostic-group level. Genotype effects and interactions between genotype and diagnostic group are less susceptible to the effects of differences in imaging prescription, as individuals of each genotype were scanned using both versions and the interaction effects were estimated using a model that took account of these differences. There was also a significant difference in one of the measures of behavioral performance, word appropriateness, between the diagnostic groups. Examining associations between these measures and the extracted data, however, revealed no significant relationships, indicating that these differences were not impacting on the main findings. It is also the case that although there were differences between diagnostic groups, there were no significant differences in either measures of performance between the genotype groups. Another limitation is that this is a relatively small sample size in terms of genetic studies, however, we would like to note that it is a relatively large sample size given other imaging studies, particularly, given the difficulties in recruiting and practicalities of scanning individuals at high familial risk of mental disorder. Finally, another issue is that some of the high-risk subjects have not yet passed the maximal risk period for development of the disorder. It is possible that some of these familial individuals may develop either of these disorders. Conversely, it is also true that the majority of individuals will remain well, therefore, markers for resilience will also be seen in the high-risk groups. Clinical follow-up of these individuals will clarify whether these differences are RISK− related or protective. Also, due to the diversity of functional imaging paradigms applied across the field and due to practicalities in recruiting such a large familial sample, we were not able to perform a replication analysis of these findings. The findings should therefore be viewed considering these limitations.

In summary, mounting evidence suggests that variation in *MIR137* could contribute to neural abnormalities seen in the major psychiatric disorders and potentially offers novel etiological pathways and therapeutic opportunities. As yet knowledge of these underlying pathways are only just beginning to be established, however, the current study indicates diagnosis independent and differential effects of *MIR137* genotype in regions previously implicated in these psychiatric disorders.

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DISCLOSURE

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REFERENCES

- Ambros V (2004). The functions of animal microRNAs. *Nature* 431: 350–355.
- Andreasen NC, Paradiso S, O'Leary DS (1998). 'Cognitive dysmetria' as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull* 24: 203–218.
- Arts B, Jabben J, Krabbendam L, van Os J (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med* 38: 771–785.
- Beveridge NJ, Gardiner E, Carroll AP, Tooney PA, Cairns MJ (2011). Schizophrenia is associated with an increase in cortical microRNA biogenesis. *Mol Psychiatry* 15: 1176–1189.
- Bitan T, Burman DD, Chou T, Lu D, Cone NE, Cao F et al (2007). The interaction between orthographic and phonological information in children: an fMRI Study. *Hum Brain Mapp* 28: 880–891.
- Bloom PA, Fischler I (1980). Completion norms for 329 sentence contexts. *Mem Cognit* 8: 631–642.
- Bokat CE, Goldberg TE (2003). Letter and category fluency in schizophrenic patients: a meta-analysis. *Schizophr Res* 64: 73–78.
- Burgess P, Shallice T (1997). *The Hayling and Brixton Tests*. Thames Valley Test Company Limited: Bury St Edmunds.
- Craddock N, O'Donovan MC, Owen MJ (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet* 42: 193–204.
- Dazzan P, Morgan KD, Orr KG, Hutchinson G, Chitnis X, Suckling J et al (2004). The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain* 127: 143–153.
- Exner C, Weniger G, Schmidt-Samoa C, Irle E (2006). Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. *Schizophr Res* 84: 386–396.
- First MB, Spitzer RL, Miriam G, Williams JBW (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. Biometrics Research, New York State Psychiatric Institute: New York.
- Forero DA, van der Ven K, Callaerts P, Del-Favero J (2010). miRNA genes and the brain: implications for psychiatric disorders. *Hum Mutat* 31: 1195–1204.
- Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E et al (2007). Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 31: 465–484.
- Geekiyana H, Chan C (2011). MicroRNA-137/181c regulates serine palmitoyltransferase and in turn amyloid beta, novel targets in sporadic Alzheimer's disease. *J Neurosci* 31: 14820–14830.
- Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL et al (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol Psychiatry* 64: 774–781.
- Gountouna VE, Job DE, McIntosh AM, Moorhead TW, Lymer GK, Whalley HC et al (2011). Functional magnetic resonance imaging (fMRI) reproducibility and variance components across visits and scanning sites with a finger tapping task. *Neuroimage* 49: 552–560.
- Gourovitch ML, Goldberg TE (1996). Cognitive deficits in schizophrenia: attention, executive functions, memory and language processing. In: Pantelis C, Nelson HE, Barnes TRE (eds). *Schizophrenia A Neuropsychological Perspective*. Wiley: Chichester, UK. pp 72–86.
- Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI et al (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry* 159: 1992–1999.
- Hall J, Whalley HC, McKirdy JW, Romaniuk L, McGonigle DJ, McIntosh AM et al (2008). Overactivation of fear systems to neutral faces in schizophrenia. *Biol Psychiatry* 64: 70–73.
- Heinrichs RW, Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12: 426–445.
- Hodges A, Byrne M, Grant E, Johnstone E (1999). People at risk of schizophrenia. Sample characteristics of the first 100 cases in the Edinburgh High-Risk Study [see comment]. *Br J Psychiatry* 174: 547–553.
- Holt DJ, Kunkel L, Weiss AP, Goff DC, Wright CI, Shin LM et al (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr Res* 82: 153–162.
- Honey GD, Pomarol-Clotet E, Corlett PR, Honey RA, McKenna PJ, Bullmore ET et al (2005). Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function. *Brain* 128: 2597–2611.
- Jansma JM, Ramsey NF, Coppola R, Kahn RS (2000). Specific vs nonspecific brain activity in a parametric N-back task. *Neuroimage* 12: 688–697.

- Jardri R, Pouchet A, Pins D, Thomas P (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry* **168**: 73–81.
- Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM (2002). Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. *Neuroimage* **17**: 880–889.
- Johnstone EC, Abukmeil SS, Byrne M, Clafferty R, Grant E, Hodges A *et al* (2000). Edinburgh high risk study—findings after four years: demographic, attainment and psychopathological issues. *Schizophr Res* **46**: 1–15.
- Kim AH, Reimers M, Maher B, Williamson V, McMichael O, McClay JL *et al* (2010). MicroRNA expression profiling in the prefrontal cortex of individuals affected with schizophrenia and bipolar disorders. *Schizophr Res* **124**: 183–191.
- Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK (2001). Neural correlates of formal thought disorder in schizophrenia: preliminary findings from a functional magnetic resonance imaging study. *Arch Gen Psychiatry* **58**: 769–774.
- Lawrie SM, Abukmeil SS (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies.[see comment]. *Br J Psychiatry* **172**: 110–120.
- Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF *et al* (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**: 234–239.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**: 1233–1239.
- McGuffin P, Farmer A, Harvey I (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Arch Gen Psychiatry* **48**: 764–770.
- McGuire PK, Silbersweig DA, Wright I, Murray RM, David AS, Frackowiak RS *et al* (1995). Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *Lancet* **346**: 596–600.
- McIntosh A, Whalley HC, McKirdy J, Hall J, Sussmann J, Shankar P *et al* (2008a). Differences in dorsal and ventral prefrontal function separate bipolar disorder from schizophrenia. *Schizophrenia Research* **98**: 40.
- McIntosh AM, Whalley HC, McKirdy J, Hall J, Sussmann JE, Shankar P *et al* (2008b). Prefrontal function and activation in bipolar disorder and schizophrenia. *Am J Psychiatry* **165**: 378–384.
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* **66**: 811–822.
- Nachev P, Kennard C, Husain M (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci* **9**: 856–869.
- Nelson H (1982). *The National Adult Reading Test Manual*. Windsor: NFER-Nelson.
- Nenadic I, Smesny S, Schlosser RG, Sauer H, Gaser C (2010). Auditory hallucinations and brain structure in schizophrenia: voxel-based morphometric study. *Br J Psychiatry* **196**: 412–413.
- Perkins DO, Jeffries CD, Jarskog LF, Thomson JM, Woods K, Newman MA *et al* (2007). microRNA expression in the prefrontal cortex of individuals with schizophrenia and schizoaffective disorder. *Genome Biol* **8**: R27.
- Phillips ML, Drevets WC, Rauch SL, Lane R (2003). Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol Psychiatry* **54**: 515–528.
- Phillips ML, Williams L, Senior C, Bullmore ET, Brammer MJ, Andrew C *et al* (1999). A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. *Psychiatry Res* **92**: 11–31.
- Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF *et al* (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**: 748–752.
- Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA *et al* (2011). Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* **43**: 969–976.
- Romaniuk L, Honey GD, King JR, Whalley HC, McIntosh AM, Levita L *et al* (2010). Midbrain activation during Pavlovian conditioning and delusional symptoms in schizophrenia. *Arch Gen Psychiatry* **67**: 1246–1254.
- Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JD (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage* **9**: 216–226.
- Schneider F, Weiss U, Kessler C, Salloum JB, Posse S, Grodd W *et al* (1998). Differential amygdala activation in schizophrenia during sadness. *Schizophr Res* **34**: 133–142.
- Schwartz CE, Wright CI, Shin LM, Kagan J, Whalen PJ, McMullin KG *et al* (2003). Differential amygdalar response to novel vs newly familiar neutral faces: a functional MRI probe developed for studying inhibited temperament. *Biol Psychiatry* **53**: 854–862.
- Sempere LF, Freemantle S, Pitha-Rowe I, Moss E, Dmitrovsky E, Ambros V (2004). Expression profiling of mammalian microRNAs uncovers a subset of brain-expressed microRNAs with possible roles in murine and human neuronal differentiation. *Genome Biol* **5**: R13.
- Shenton ME, Dickey CC, Frumin M, McCarley RW (2001). A review of MRI findings in schizophrenia. *Schizophr Res* **49**: 1–52.
- Shi Y, Zhao X, Hsieh J, Wichterle H, Impey S, Banerjee S *et al* (2010). MicroRNA regulation of neural stem cells and neurogenesis. *J Neurosci* **30**: 14931.
- Smith S, Jenkinson M, Beckmann C, Miller K, Woolrich M (2007). Meaningful design and contrast estimability in FMRI. *Neuroimage* **34**: 127–136.
- Smrt RD, Szulwach KE, Pfeiffer RL, Li X, Guo W, Pathania M *et al* (2010). MicroRNA miR-137 regulates neuronal maturation by targeting ubiquitin ligase mind bomb-1. *Stem Cells* **28**: 1060–1070.
- Strakowski SM, Delbello MP, Adler CM (2005). The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* **10**: 105–116.
- Suckling J, Barnes A, Job D, Brennan D, Lymer K, Dazzan P *et al* (2012). The neuro/PSYGRID calibration experiment: identifying sources of variance and bias in multicenter MRI studies. *Hum Brain Mapp* **33**: 373–386.
- Sun J, Ming GL, Song H (2011). Epigenetic regulation of neurogenesis in the adult mammalian brain. *Eur J Neurosci* **33**: 1087–1093.
- Surguladze S, Russell T, Kucharska-Pietura K, Travis MJ, Giampietro V, David AS *et al* (2006). A reversal of the normal pattern of parahippocampal response to neutral and fearful faces is associated with reality distortion in schizophrenia. *Biol Psychiatry* **60**: 423–431.
- Szulwach KE, Li X, Smrt RD, Li Y, Luo Y, Lin L *et al* (2010). Cross talk between microRNA and epigenetic regulation in adult neurogenesis. *J Cell Biol* **189**: 127–141.
- Tanskanen P, Ridler K, Murray GK, Haapea M, Veijola JM, Jaaskelainen E *et al* (2010). Morphometric brain abnormalities in schizophrenia in a population-based sample: relationship to duration of illness. *Schizophr Bull* **36**: 766–777.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N *et al* (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**: 273–289.

- Wessa M, Linke J (2009). Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int Rev Psychiatry* **21**: 357–367.
- Whalley HC, Simonotto E, Flett S, Marshall I, Ebmeier KP, Owens DG *et al* (2004). fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. [see comment]. *Brain* **127**: 478–490.
- Whalley HC, Sussmann JE, Chakirova G, Mukerjee P, Peel A, McKirdy J *et al* (2011). The neural basis of familial risk and temperamental variation in individuals at high risk of bipolar disorder. *Biol Psychiatry* **70**: 343–349.
- Whalley HC, Whyte MC, Johnstone EC, Lawrie SM (2005). Neural correlates of enhanced genetic risk for schizophrenia. *Neuroscientist* **11**: 238–249.
- Williams LM, Das P, Harris AW, Liddell BB, Brammer MJ, Olivieri G *et al* (2004). Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. *Am J Psychiatry* **161**: 480–489.
- Zhou SY, Suzuki M, Hagino H, Takahashi T, Kawasaki Y, Matsui M *et al* (2005). Volumetric analysis of sulci/gyri-defined *in vivo* frontal lobe regions in schizophrenia: precentral gyrus, cingulate gyrus, and prefrontal region. *Psychiatry Res* **139**: 127–139.

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