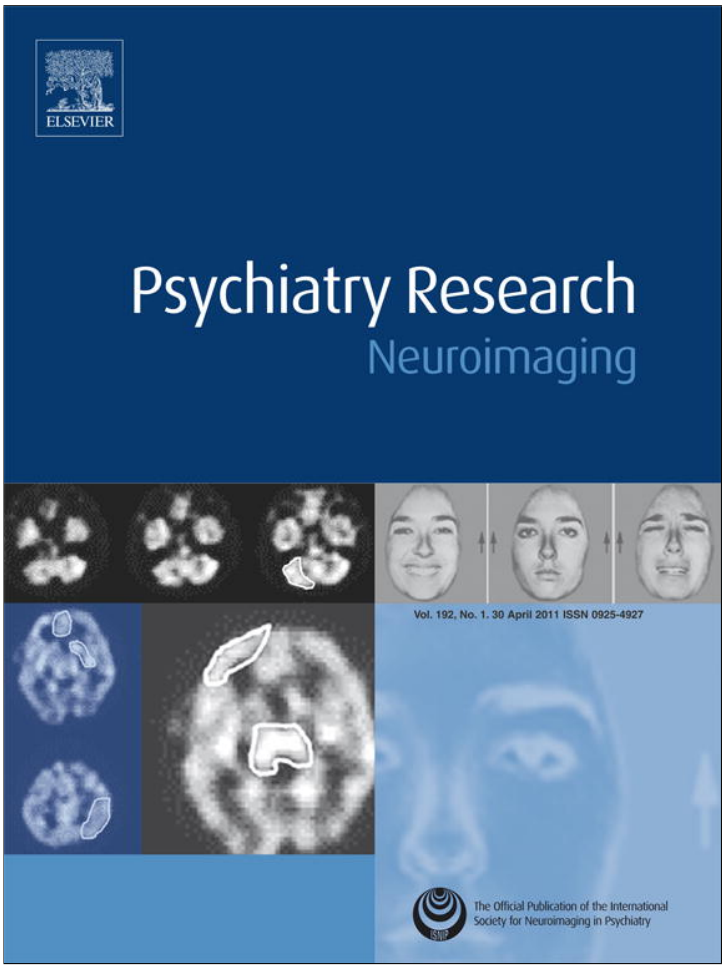

Psychiatry Research: Neuroimaging 192 (2011) 20–28

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

The effects of DISC1 risk variants on brain activation in controls, patients with bipolar disorder and patients with schizophrenia

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ARTICLE INFO

Article history:
Received 10 February 2010
Received in revised form 12 November 2010
Accepted 13 January 2011

Keywords:
DISC1
fMRI
The Hayling Sentence Completion Task
Bipolar disorder
Schizophrenia

ABSTRACT

Three risk variants (rs1538979, rs821577, and rs821633) in the Disrupted-in-Schizophrenia-1 (DISC1) gene have previously been associated with both schizophrenia and bipolar disorder in a recent collaborative analysis of European cohorts. In this study we examined the effects of these risk variants on brain activation during functional magnetic resonance imaging (fMRI) of the Hayling Sentence Completion Task (HSCT) in healthy volunteers ($n=33$), patients with schizophrenia ($n=20$) and patients with bipolar disorder ($n=36$). In the healthy controls the risk associated allele carriers of SNPs rs1538979 and rs821633 demonstrated decreased activation of the cuneus. Moreover, there was an effect of SNP rs1538979 in the pre/postcentral gyrus with decreased activation in healthy controls and increased activation in patients with schizophrenia. In the bipolar group there was decreased activation in the risk carriers of SNP rs821633 in the inferior parietal lobule and left cingulate cortex. Clusters in the precentral gyrus, left middle temporal gyrus and left cerebellum were found to be significant on examining the group × genotype interactions. These findings may provide a better understanding of the neural effects of DISC1 variants and on the pathophysiology of schizophrenia and bipolar disorder.

1. Introduction

Schizophrenia and bipolar disorder are highly heritable neuropsychiatric disorders. One candidate gene of interest, Disrupted-in-Schizophrenia-1 (DISC1), was first identified at the breakpoint of a balanced t(1;11) chromosomal translocation that segregated with schizophrenia, bipolar disorder and recurrent major depression in a large Scottish family (St Clair et al., 1990; Millar et al., 2000). Members of the family who carry the translocation showed deficits in P300 event-related potential (ERP) amplitude, even in the absence of a clinical diagnosis (Blackwood et al., 2001). This suggests that the variation in DISC1 may affect core brain processing. The DISC1 protein has been shown to be involved in multiple processes such as neurite extension as well as neuronal proliferation, migration and signaling through interaction with a number of proteins including nuclear distribution element-like (Ndel1, also known as NUDEL), fasciculation and elongation protein zeta-1 (FEZ1) and phosphodiesterase 4B (PDE4B) (Millar et al., 2005; Porteous et al., 2006). Recent evidence suggests its involvement in intracellular signaling through PDE4B, glycogen synthase kinase 3 beta (GSK3b) and microtubule-associated protein kinase (MAPK) pathways (Millar et al., 2005; Hashimoto et al., 2006; Mao et al., 2009; Ming and Song, 2009). DISC1 is widely expressed in the brain including the hippocampus, cerebellum, cerebral cortex, and hypothalamic and thalamic nuclei (reviewed in Chubb et al., 2008).

Linkage and association studies in multiple populations have found evidence for an association between several genetic variants in DISC1 and various mental illnesses; to date, these include schizophrenia, bipolar disorder, recurrent major depression and autistic spectrum disorders (Mackie et al., 2007; Chubb et al., 2008). However, establishing which variants across the European population show the strongest statistical evidence of association has not, until recently, been possible. A recent collaborative study of DISC1 sought to unify the multiple association studies by examining a set of haplotype-tagging SNPs and their possible association with bipolar disorder and

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doi:10.1016/j.pscychresns.2011.01.015

schizophrenia in four European cohorts (three from the UK and one from Finland) with prior linkage evidence (Hennah et al., 2008). This study identified three SNPs that singly or in combination increased the risk of developing schizophrenia or bipolar disorder (rs1538979, rs821577, and rs821633).

There is considerable evidence that these SNPs are associated both with the risk of clinical disorder and clinical traits. The previously defined risk allele of rs821577 has been associated with significantly higher scores on social anhedonia, and the risk allele of marker rs821633 has been strongly associated with lower scores on social anhedonia when analyzed conditionally on the absence of the risk alleles at rs1538979 and rs821577 (Tomppo et al., 2009). It was recently discovered that rs821577 was associated with increased anxiety and depression and higher levels of neuroticism, either independently or in combination with the risk allele for SNP rs821633 (Harris et al., 2010). In addition, a number of studies have explored the impact of variation in DISC1 on brain structure, IQ and cognition (Paunio et al., 2004; Burdick et al., 2005; Cannon et al., 2005). In contrast to this wealth of research, however, relatively few studies to date have explored the impact of DISC1 variants on brain function using functional magnetic resonance imaging (fMRI).

The majority of studies examined the effect of functional SNPs rs821616 (Ser704Cys), rs6675281 (Leu607Phe) and rs1411771 on brain function (Callicott et al., 2005; Di Giorgio et al., 2008; Prata et al., 2008; Szeszko et al., 2008; Nicodemus et al., 2010), but no study has yet investigated the brain activation effect of the SNPs identified in the four European cohorts. In the current research we examined the association of DISC1 rs1538979, rs821577 and rs821633 SNPs with brain activation level during the Hayling Sentence Completion Task (HSCT) in healthy participants and those with schizophrenia or bipolar disorder. We employed the verbal initiation section of the HSCT in the scanner (Burgess and Shallice, 1997; Whalley et al., 2004) as it invokes executive cognitive processes and engages a network of fronto-temporal cortical and sub-cortical regions that are known to be implicated in schizophrenia and bipolar disorder to differing extents (Curtis et al., 2001; Lawrie et al., 2002; Fu et al., 2006). We anticipated that 'risk-allele' carriers of the DISC1 rs1538979, rs821577 and rs821633 SNPs would demonstrate differential patterns of activation compared with the non-carriers and that this would vary across the groups. Such findings would suggest that the DISC1 rs1538979, rs821577 and rs821633 SNPs may contribute to increasing the risk of schizophrenia or bipolar affective disorder by modifying brain physiology.

2. Methods

2.1. Subjects

Functional MRI scans from 33 healthy controls, 20 patients with schizophrenia and 36 patients with bipolar I disorder were used to evaluate the association between the three risk variants of DISC1 (rs1538979, rs821577, and rs821633) and brain activation during the HSCT. Detailed information about the recruitment of these individuals has been provided previously (McIntosh et al., 2008). To be included in the study, patients with bipolar disorder and schizophrenia were required to have at least one first- or second-degree relative with the same diagnosis. The diagnostic status of the patients was established using the Operational Criteria Checklist (McGuffin et al., 1991) and confirmed with the Structured Clinical Interview for DSM-IV (SCID). Clinical symptoms were assessed using the Young Mania Rating Scale (Young et al., 1978), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All participants were matched on age, gender and IQ, the last being determined by the National Adult Reading Test (NART). If there were related subjects in the study, only one of the family members was chosen randomly and accepted into the further analysis, and the others were excluded, so all three groups (33 healthy controls, 20 patients with schizophrenia and 36 patients with bipolar I disorder) consisted of unrelated subjects. The demographic and clinical characteristics of study participants including medication are detailed in Table 1. Statistical analysis of demographic details was conducted using one-way analysis of variance (ANOVA) or chi-square tests, as appropriate, in SPSS for Windows (version 14.0, SPSS Inc., USA). Differences in demographic details (age, gender, handedness and NART IQ) were examined across all groups. Examinations of clinical measures (PANSS scores, HAM-D, Young Mania Rating Scale, duration of illness and medication) were conducted on patient groups only. All patients included in this study had been in stable pharmacological treatment for at least 8 weeks.

2.2. Genotyping

Genomic DNA was extracted from blood and the DISC1 SNPs rs1538979, rs821577 and rs821633 were genotyped using TaqMan® SNP genotyping assays on an ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems), at the Wellcome Trust Clinical Research

Table 1
Demographic and clinical characteristics.

Characteristics	Groups							
	Bipolar disorder participants ($N=36$)		Schizophrenia participants ($N=20$)		Healthy controls ($N=33$)			
	N	%	*N*	%	*N*	%	χ^2	*p*
Male	20	55.6	13	65.0	18	54.6	0.62	0.732
Right-handed	34	94.5	19	95.0	31	93.9	0.03	0.987
	Mean	SD	Mean	SD	Mean	SD	*F*|*t*	*p*
Age (years)	39.3	10.8	37.0	10.1	37.3	12.1	0.17	0.681
NART IQ	111.3	10.9	107.8	9.6	113.3	7.2	0.24	0.627
PANSS positive score	7.3	0.6	10.5	2.9	–	–	5.35	<0.001
PANSS negative score	8.7	3.7	10.5	3.9	–	–	1.74	0.09
PANSS general psychopathology score	18.1	4.6	22.1	6.4	–	–	2.46	0.020
Young Mania Rating Scale score	0.6	1.2	1.0	2.8	–	–	0.69	0.494
HAM-D	2.3	5.9	3.6	6.7	–	–	0.72	0.477
Duration of illness (years)	18.8	11.1	16.7	10.2	–	–	0.68	0.500
Treatment received								
	N	%	*N*	%	*N*	%	*F*	*p*
Lithium	20	54.1	0	0.0	–	–	17.28	<0.001
Antipsychotic	18	48.6	23	100.0	–	–	17.28	<0.001
Antidepressant	18	48.7	8	34.8	–	–	2.10	0.147

Facility Genetics Core, Western General Hospital, Edinburgh. Assay numbers were C_12001934, C_1433206 and C_1433126, respectively. Genotype groups were clustered on the basis of carrying at least one risk allele (dominant model). Risk alleles were defined as the alleles: T-allele at rs1538979, G-allele at rs821577, and C-allele at rs821633, based on the findings of Hennah et al. (2008). Within each diagnostic group for each SNP, two sub-groups were subsequently formed: 1. carriers of 'risk associated' allele (CT + TT for rs1538979, GT + GG for rs821577, CT + CC for rs821633), and 2. non-carriers (CC for rs1538979, TT for rs821577, and TT for rs821633).

2.3. Experimental paradigm

fMRI scans were obtained while participants performed the verbal initiation section of the HSCT in the scanner (Whalley et al., 2004). The experimental procedure consisted of presenting participants with a sentence with the last word missing. They were requested to silently think of a word to complete the sentence and press a button when they had done so. The task had four levels of difficulty according to the range of suitable completion words suggested by the sentence constraint: low, medium low, medium high and high (Bloom and Fischler, 1980). Low to high sentence constraint represents decreasing difficulty, the low constraint sentences potentially being completed in many ways (for example, 'His ability to work was…') and the high constraint sentences being limited to one possible answer only ('Bob proposed, but she turned him…'). The task also had a baseline visual condition. Pseudorandomized block design was used with a total number of 16 blocks and a total scanning time of 13.3 min. Each block lasted 40 s, consisting of eight sentences, and each block was repeated four times using different sentences. Each sentence was presented for a period of 3 s followed by a fixation cross for 2 s. The participants were asked to respond at any time by pressing a button until the next sentence appeared. The rest condition was of 40 s duration, appearing after every four blocks (therefore, there were only four rest conditions during the task) and consisted of viewing the screen with white circles on a black background. This design allowed a standard subtraction analysis (all levels of sentence completion difficulty versus baseline) and a parametric analysis examining increasing activation with increasing task constraint.

Immediately after the scanning, participants 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), which provides probabilities of possible responses. 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, and so on. Mean word appropriateness scores and reaction times were calculated for each constraint level in order to compare performance across genotype groups.

2.4. Scanning procedure

The scanning procedure and subsequent processing were described in a previous publication (McIntosh et al., 2008). Briefly, subjects were imaged at the Brain Imaging Research Centre for Scotland (Edinburgh, Scotland, UK) on a GE Signa LX 1.5 T scanner (General Electric Medical, Milwaukee, Wisconsin) equipped with 23 mT/m "echospeed" gradients, with a rise time of 200 μs. The functional imaging protocol consisted of axial gradient-echo planar images (EPI) (TR/TE = 4000/40 ms; matrix = 64 × 128; field of view = 220 × 440 mm) acquired continually during the experimental paradigm. Thirty-eight contiguous 5-mm slices were acquired within each TR period. Each EPI acquisition was run for 204 volumes, of which the first four volumes were discarded. Visual stimuli were presented using a screen (IFIS; MRI Devices, Waukesha, Wisc.) placed in the bore of the magnet.

2.5. Scan processing

The echo planar images were converted to ANALYZE format (Mayo Foundation, Rochester, Minn.). Scan and first level statistical analyses were performed using SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London) running in Matlab (MathWorks, Natick, Mass.). For each subject, echo planar image volumes were realigned to the mean volume in the series using rigid body transformations. None of the included subjects had significant motion artifacts. The images were then normalized to a study-specific echo planar image template generated from all individuals in the study using a linear affine transformation followed by nonlinear deformation, and resampled using sinc interpolation to cubic voxels of size 8 mm^3. Normalized images were spatially smoothed with a 6-mm full-width half-maximum Gaussian filter to minimize residual inter-subject differences and in order to meet assumptions for statistical analysis.

2.6. Statistics

At the individual subject level, the data were modeled with five conditions (the four difficulty levels and the rest condition), each modeled by a boxcar convolved with a synthetic hemodynamic response function (McIntosh et al., 2008). The estimates of the subjects' movement during the scan were also entered as "covariates of no interest". Before fitting the model, the subjects' data were filtered in time using a high-pass filter (400-second cutoff), and temporal auto-correlations were accounted for by imposing an AR (Kendell and Brockington, 1980) model. Contrasts were constructed to examine all four sentence completion conditions versus rest and areas of increasing activation with increasing task difficulty (the parametric contrast).

All second level statistical analyses were conducted in SPM8 due to the improved factorial modeling available in this version of the software. For each contrast of interest (sentence completion versus baseline and parametric effects), one contrast image per subject was entered into a second-level random effects analysis. The main effect of task, the main effects of diagnostic group, the effect of genotype within diagnostic groups and genotype × group interactions were examined using a full factorial ANOVA model in SPM8. Genotype and group were entered as two factors in the design matrix with two levels of genotype (risk-allele carriers and non-carriers) and three diagnostic groups (healthy controls, patients with schizophrenia and patients with bipolar affective disorder). Genotype by group interactions were examined between all three groups and with the patient groups combined. Statistical maps were thresholded at a level of $p<0.001$ (uncorrected) and regions were considered significant at a cluster level of $p<0.05$, corrected for multiple comparisons. All coordinates are quoted in Montreal Neurological Institute (MNI) convention (http://www.mni.mcgill.ca).

3. Results

Thirty-three healthy controls, twenty patients with schizophrenia and thirty-six patients with bipolar I disorder underwent fMRI scanning whilst performing the HSCT and were genotyped. There were no statistically significant differences between the three diagnostic groups in terms of age, gender, handedness or NART IQ. Patient groups differed on measures of PANSS positive and PANSS general scores ($p<0.001$, and $p=0.02$ respectively, see Table 1). In all groups each of the three SNPs was in Hardy–Weinberg Equilibrium.

For rs1538979 group numbers split according to risk:non-risk carriers were $n=6:27$ for controls, $n=7:13$ for patients with

schizophrenia, and $n=7{:}25$ for bipolar disorder respectively. For rs821577 group numbers split according to risk:non-risk carriers were $n=24{:}9$ for controls, $n=9{:}10$ for patients with schizophrenia, and $n=21{:}10$ for bipolar disorder. For rs821633 group numbers split according to risk:non-risk carriers were $n=18{:}16$ for controls, $n=9{:}11$ for patients with schizophrenia, and $n=20{:}16$ for bipolar disorder. Minor differences in group numbers between the SNPs reflect difficulties relating to undetermined alleles in some participants. There were no statistically significant differences for the any of the demographic measures or any of the clinical variables within each of the diagnostic groups between risk and non-risk carriers.

3.1. Performance

The three groups did not differ significantly between each other in their performances on the task for either word appropriateness scores ($F=0.613$, $p=0.544$) or reaction time measures ($F=0.559$, $p=0.574$) nor for any of the individual constraint levels: high ($F=0.493$, $p=0.613$), medium high ($F=0.534$, $p=0.588$), medium low ($F=1.237$, $p=0.297$) and low ($F=1.921$, $p=0.154$).

We also compared the performances of risk-allele carriers against non-carriers for rs1538979, rs821577, and rs821633 in each diagnostic group separately and found no statistically significant difference between the genotype sub-groups.

3.2. Main effect of task (see Supplementary Table 1)

We identified a distributed network of regions across all groups including the left and right middle temporal gyrus, right inferior temporal lobe, right superior frontal gyrus, left medial frontal gyrus, left precentral gyrus, right inferior occipital gyrus, left cuneus, right precuneus and left cerebellum that expressed increased activation for the sentence completion versus baseline contrast. The left middle frontal gyrus, left superior frontal gyrus, left and right inferior frontal gyrus, left insula and right cerebellum were more engaged during the parametric contrast.

3.3. Main effect of diagnostic groups (see Supplementary Table 2)

There was no effect of diagnostic groups found for the sentence completion versus baseline contrast with the selected standard threshold. Patients with bipolar disorder expressed greater activation in the left middle temporal gyrus (MNI coordinates: $x=-54$, $y=-58$, $z=10$; Z-score $=4.29$; $p<0.0001$ corrected for multiple comparisons) and in the right middle frontal gyrus (MNI coordinates: $x=40$, $y=42$, $z=-4$; Z-score $=4.54$; $p=0.012$ corrected for multiple comparisons) relatively to healthy controls for the parametric contrast. However, there was no statistical difference between healthy controls and patients with schizophrenia or between patients with schizophrenia and patients with bipolar disorder. As these subjects reflect the genotyped subset of a previous larger study on these participants (McIntosh et al., 2008), and the main focus of the article is the effect of genotype, these findings are provided as supplementary material.

3.4. Within-groups genotype effects (see Table 2)

In order to examine the effects of genotype, risk allele carriers and non-carriers were compared within each group of participants for each SNP separately. By this contrast we sought to determine whether the risk associated allele of each SNP would have an impact on brain physiology compared with the non-risk associated allele.

Within healthy controls, carriers of the risk allele of rs821633 demonstrated significantly reduced brain activation in the right cuneus compared with non-carriers (p corrected $=0.034$, $z=4.80$; $k_E=308$, MNI coordinates: $x=12$, $y=-96$, $z=8$) for the sentence completion versus baseline contrast. For the parametric contrast those carrying the risk allele of rs1538979 demonstrated reduced activation of the left postcentral gyrus (p corrected $=0.002$, $z=4.94$; $k_E=626$, MNI: $x=-56$, $y=-14$, $z=36$), the right postcentral gyrus (p corrected $=0.012$, $z=4.80$; $k_E=437$, MNI: $x=4$, $y=-46$, $z=68$) and the left cuneus (p corrected $=0.007$, $z=4.57$; $k_E=488$, MNI: $x=-32$, $y=-74$, $z=26$) when compared with non-carriers.

Within the schizophrenia group activation was significantly increased in those carrying the risk allele of rs1538979 compared to non-carriers in the left postcentral gyrus (p corrected $=0.001$, $z=4.39$; $k_E=775$, MNI coordinates: $x=-46$, $y=-22$, $z=46$) for the sentence completion versus baseline. This cluster expands into the left precentral gyrus.

Within the group of patients with bipolar disorder, carriers of the rs821633 risk allele showed significantly reduced activation in the right inferior parietal lobule (p corrected $=0.027$, $z=4.29$; $k_E=330$, MNI: $x=28$, $y=-60$, $z=34$) and in the left cingulate gyrus (p corrected $=0.045$, $z=4.01$; $k_E=285$, MNI: $x=-14$ $y=10$, $z=36$) compared with non-carriers for the sentence completion versus baseline contrast.

3.5. Interaction between genotype and diagnostic groups (see Table 3)

There were three regions of significant group × genotype interaction. The first region was the left cerebellum for the sentence completion versus baseline contrast for rs1538979 (p corrected $=0.012$, z $=4.14$; $k_E=457$, MNI: x $=-16$, y $=-76$, z $=-28$). Graphs indicated that this originated from increased activation in risk allele carriers relative to non-carriers in patients with schizophrenia, and the opposite in the control group (reduced activation in risk allele carriers versus non-carriers); see Fig. 1. The

Table 2
Effect of genotype within group.

SNP	Groups	Comparison	Cluster (voxel)	Z-score	p- value (FWE-corrected)	MNI coordinates (x, y, z)	Region (BA)
Sentence completion versus baseline							
rs1538979	Schizophrenia	$(CT+TT)^*>CC$	775	4.39	0.001	−46, −22, 46	Left postcentral gyrus (BA 2)
rs821633	Healthy controls	$(CC+CT)^*<TT$	308	4.80	0.034	12, −96, 8	Right cuneus (BA 17)
rs821633	Bipolar disorder	$(CC+CT)^*<TT$	330	4.29	0.027	28, −60, 34	Right inferior parietal lobule (BA 7)
rs821633	Bipolar disorder	$(CC+CT)^*<TT$	285	4.01	0.045	−14, 10, 36	Left cingulate gyrus (BA 24)
Parametric							
rs1538979	Healthy controls	$(CT+TT)^*<CC$	626	4.94	0.002	−56, −14, 36	Left postcentral gyrus (BA 3)
rs1538979	Healthy controls	$(CT+TT)^*<CC$	437	4.80	0.012	4, −46, 68	Right postcentral gyrus, right paracentral lobule (BA 5, 7)
rs1538979	Healthy controls	$(CT+TT)^*<CC$	488	4.57	0.007	−32, −74, 26	Left cuneus, left precuneus, left middle occipital gyrus (BA 18, 19, 31)

* denotes risk allele carrier group.

Table 3
Interactions between genotype and diagnostic groups.

SNP	Comparison	Cluster (voxel)	*Z*-score	*P*- value	MNI coordinates (*x*, *y*, *z*)	Affected area (BA)
Sentence completion versus baseline						
rs1538979	risk-allele carriers>non-carriers in controls<schizophrenia	457	4.14	0.012	−16, −76, −28	Left cerebellum
Parametric						
rs1538979	risk-allele carriers>non-carriers in controls<patients	489	4.56	0.007	−56, −16, 36	Left precentral gyrus (BA4)
rs1538979	risk-allele carriers>non-carriers in controls<patients	366	4.52	0.024	−32, −74, 26	Left middle temporal gyrus (BA 39)

other areas of the group×genotype interaction were the left precentral gyrus (p corrected = 0.007, z = 4.56; k_E = 489, MNI: x = −56, y = −16, z = 36) and the posterior part of the left middle temporal gyrus (p corrected = 0.024, z = 4.52; k_E = 366, MNI: x = −32, y = −74, z = 26) where there was the greater effect of risk allele carriers of rs1538979 relative to non-carriers in patient groups combined with opposite effects seen in the control group for the parametric contrast, see Fig. 2.

4. Discussion

In the current study we examined the effects of three DISC1 SNPs, rs1538979, rs821577 and rs821633, on brain function in three groups using fMRI and the Hayling Sentence Completion Task (Burgess and Shallice, 1997; Whalley et al., 2004; Whalley et al., 2006). All groups activated typical task associated regions for this paradigm (Whalley et al., 2004), indicating they were performing the task appropriately in the scanner. We report overall different patterns of activation relating to the three SNPs between the groups. In the healthy controls, the risk associated allele carriers of SNPs rs1538979 and rs821633 demonstrated relatively decreased activation of the cuneus across both contrasts; however, this pattern was not seen in either of the patient groups. Other findings in the healthy controls indicated an effect of SNP rs1538979 in the pre/postcentral gyrus, where there was relatively decreased activation in the risk allele carriers versus non-carriers. This particular SNP also demonstrated effects in the left postcentral gyrus in the schizophrenic group, but in the opposite direction (increased in risk carriers). When interactions were examined, there was found to be a significant effect of group (controls versus patient groups combined) in this postcental region. For rs821633 the bipolar patient group showed decreased activation in the risk carriers in the inferior parietal lobule and left cingulate cortex, not seen in either of the other groups. In addition, there were two other regions of significant interaction between genotype and diagnostic groups. The first interaction was between rs1538979 and patients (schizophrenia and bipolar groups combined) versus controls in the left middle temporal gyrus. The second interaction was between rs1538979 and patients with schizophrenia versus controls in the left cerebellum.

Previous studies have reported involvement of DISC1 in neuronal migration, dendritic organization, neurogenesis, and 3′-5′-cyclic adenosine monophosphate (cAMP) signaling (Miyoshi et al., 2003; Millar et al., 2005; Porteous et al., 2006) which associates with neurodevelopment and supports the idea of potential importance of the DISC1 SNPs in the pathophysiology of such illnesses as schizophrenia and bipolar disorder. There is also evidence suggesting that the DISC1 SNPs may have a role in multiple cognitive brain processes (Burdick et al., 2005; Callicott et al., 2005; Thomson et al., 2005; Ishizuka et al., 2006; Liu et al., 2006; Porteous et al., 2006). Previous genetic imaging studies have suggested that variations of the DISC1 gene are associated with structural and functional abnormalities of the prefrontal cortex (Cannon et al., 2005; Hashimoto et al., 2006; Prata et al., 2008; Szeszko et al., 2008; Takahashi et al., 2009), and hippocampus (Callicott et al., 2005; Di Giorgio et al., 2008). Notable differences between the current findings and studies above relate to the differences in the SNP selection. The current study focused on SNPs identified as those with the highest statistical association in the four European cohorts (Hennah et al., 2008) which have not been as widely investigated as the non-synonymous functional polymorphisms Ser704Cys and Leu607Phe. A number of studies on these two latter functional polymorphisms have, however, also indicated differences

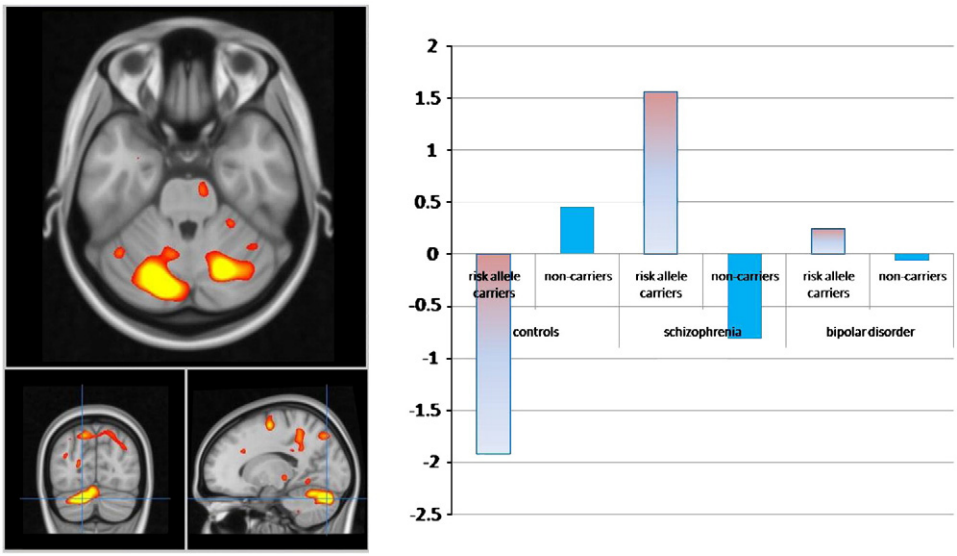

Fig. 1. Significant rs1538979×diagnostic group interaction for sentence completion versus baseline contrast in the left cerebellum. The image demonstrates greater activation in the left cerebellum in healthy controls for non-carriers>risk allele carriers with opposite effect in the schizophrenia group (risk allele carriers>non-carriers). Cluster significant at p<0.05 corrected cluster level for multiple comparisons across the whole brain. The graph demonstrates extracted values for SPM for the cluster of significance. All images are overlaid onto standard brain in MNI space using Mango software package (http://ric.uthscsa.edu/mango). Images are thresholded at T≥2.

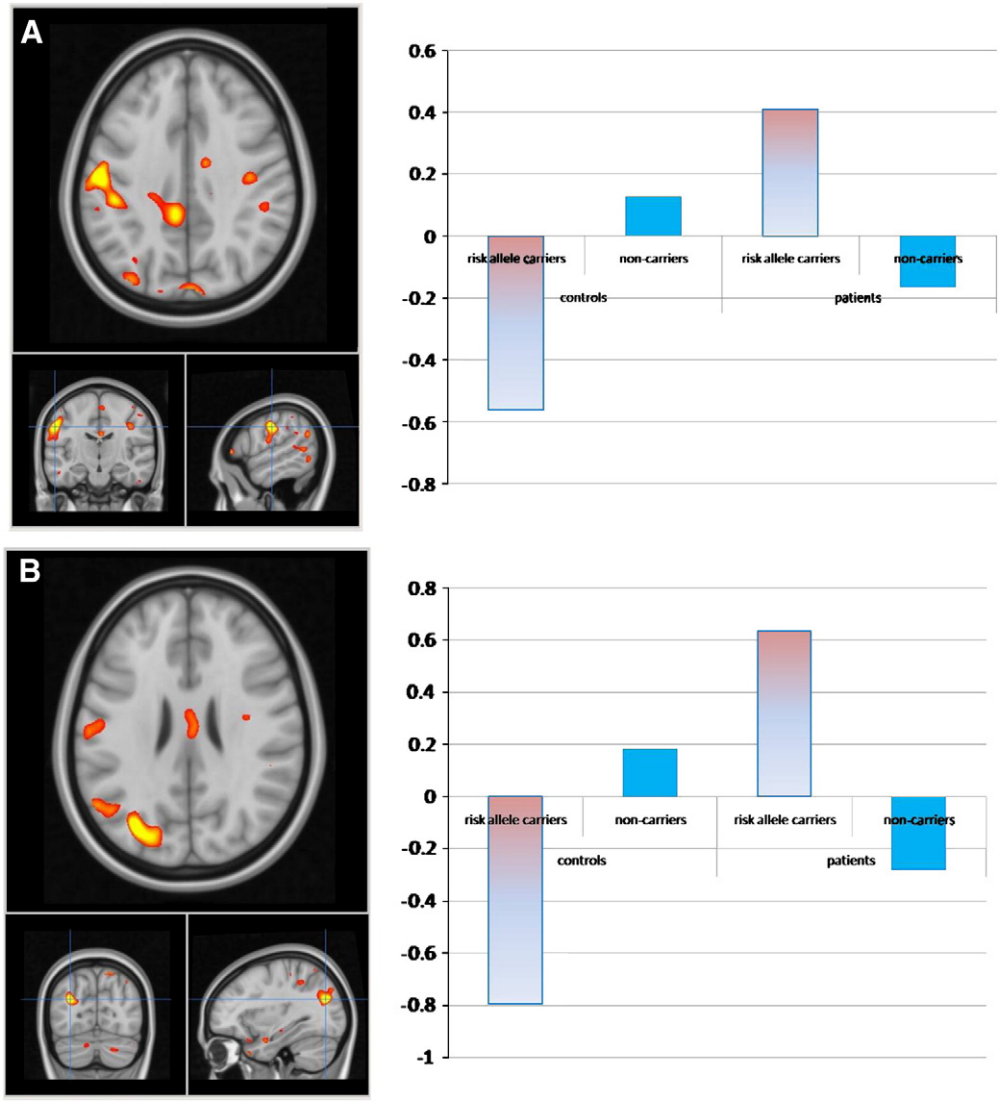

Fig. 2. Brain regions showing significant rs1538979 × diagnostic group interactions for the parametric contrast. These images demonstrate greater activation in A. the left precentral gyrus, and B. left middle temporal gyrus in healthy controls for non-carriers > risk allele carriers with opposite effect in patients with schizophrenia and in patients with bipolar disorder (risk allele carriers > non-carriers). Cluster significant at $p < 0.05$ corrected cluster level for multiple comparisons across the whole brain. The graphs demonstrate extracted values for SPM for the cluster of significance. All images are overlaid onto standard brain in MNI space using Mango software package (http://ric.uthscsa.edu/mango). Images are thresholded at $T \geq 3$.

involving the traditionally associated prefrontal and hippocampal regions, including the cingulate (Hashimoto et al., 2006; Szeszko et al., 2008) and parietal cortices (Takahashi et al., 2009). This suggests some similarity with the current findings and emerging evidence of a pathophysiological role of these regions in schizophrenia and bipolar disorder (Dankert et al., 2004; Kindermann et al., 2004; Maruff et al., 2005; Pavuluri et al., 2007).

The two anatomical regions showing an effect of the DISC1 genotype were the pre/postcentral gyrus (within the patient groups) and cuneus (within healthy controls). These former are known to contribute to somatosensory and motor functions and structurally have been reported to be affected in schizophrenia (Job et al., 2002; Zhou et al., 2007; Glahn et al., 2008; Borgwardt et al., 2010), as well as in bipolar disorder (Lyoo et al., 2004). Whilst psychotic symptoms are clearly linked to abnormalities of perception and willed action served by these regions, a clear link to the psychopathology of psychiatric disorder is so far unproven. An interaction with treatment rather than the underlying etiology of these disorders is also possible. The cuneus has been reported to be involved in visual perception in functional co-operation with the occipito-temporal cortex (Fink et al., 1996; Krasnow et al., 2003). Functional imaging studies of word-based tasks have indeed reported activation differences in these regions in schizophrenia (Ragland et al., 2008), as well as in bipolar disorder (Malhi et al., 2007). It is also considered as part of the default mode network, a common network of regions which demonstrate relatively more activation at baseline and attenuated activation during task condition over a range of cognitive tasks (Raichle et al., 2001; Raichle and Snyder, 2007). Abnormal default mode networks have indeed been reported in schizophrenia (Abbott et al., 2010). The presence of the genotype × diagnostic group interaction in the precentral gyrus suggests different effects of the DISC1 SNPs in this brain area in controls and patient groups.

Two more regions appeared as regions of a significant genotype × diagnostic group interaction: the left cerebellum and the left middle temporal gyrus. The left cerebellum demonstrated a significant interaction effect between the controls and schizophrenia group for SNP rs1538979. This is supported by the previous studies which reported that the left cerebellum as an area is known to be involved in language processing (Ackermann and Hertrich, 2000; Murdoch and Whelan, 2007) and in the formation of delusions (Whalley et al., 2007). The left middle temporal

gyrus appeared as a region of a significant genotype × diagnostic group interaction with patient groups combined for SNP rs1538979. The left middle temporal gyrus has been previously associated with delusions in patients with schizophrenia (Spencer et al., 2007). Job et al. (2002) identified gray matter decreases in brain regions including the left middle temporal gyrus in patients with schizophrenia. This area was also reported to be involved in the neural basis of psychotic symptoms (Whalley et al., 2007) as well as in emotional discrimination (Guitart-Masip et al., 2009).

Two regions in our study were associated with the effect of genotype in patients with bipolar disorder. Risk allele carriers of rs821633 were found to demonstrate reduced activation compared with non-carriers in the inferior parietal lobe and cingulate gyrus. The inferior parietal cortex is considered an important component of the frontal–limbic–temporal–parietal neural network (Torrey, 2007) and plays an essential part in sensory integration (Pearlson et al., 1996), with the concept of 'self' (Ruby and Decety, 2001; Kjaer et al., 2002; Uddin et al., 2005), executive function (Buchsbaum et al., 2005) and emotional dysregulation (Pavuluri et al., 2007; Zhao et al., 2007), and hence is relevant to bipolar disorders. Similarly, the cingulate cortex is of critical importance for the processing of emotions, mood regulation (Vogt, 2009), and executive function and is part of a limbic circuit closely connected with the prefrontal cortex, hippocampus, amygdala and insula. These areas are of established importance to the pathophysiology of bipolar disorder (Brooks et al., 2010). Previous structural and functional imaging studies have established a role for other DISC1 polymorphisms in these regions in healthy controls (Hashimoto et al., 2006; Szeszko et al., 2008). This evidence suggests that DISC1 mutations might affect brain structure and function even in healthy populations.

Our study is subject to some limitations. Firstly, the patient groups were medicated and it is possible that this may have affected the level of BOLD signal during scanning, or that the activation differences observed in these groups represent an interaction with medication. It is the case, however, that some of the activation differences occurred in a medication free control group and the patients selected for this study were clinically stable. Secondly, due to the number of participants in each of the genetic subgroups, we appreciate that the current study is somewhat underpowered regarding the examination of interaction effects. For this reason we also fully present within-group findings and all of the interactions reported here were significant at standard thresholds at the whole brain level. Whilst it is always desirable to conduct large studies, we considered the effects of genotype across these groups (Mechelli et al., 2008). Thirdly, rs1538979 was previously reported only as a risk factor in the presence of rs821633 (Hennah et al., 2008). Moreover, on its own, rs821633 appeared to be a protective variant which becomes a risk factor only in combination with either or both of rs1538979 and rs821577 (Hennah et al., 2008). All our participants possessed different combinations of these DISC1 SNPs. Unfortunately, we were not able to test SNP–SNP interactions as we did not have sufficiently large groups for this type of analysis.

In summary, it has previously been shown that three SNPs of DISC1: rs1538979, rs821577 and rs821633, are associated with the risk of schizophrenia, bipolar disorder or both disorders in a large collaborative re-analysis of association studies across Northern European populations. In the current study we demonstrate that these SNPs are associated with altered brain activation in the cuneus, postcentral gyrus, inferior parietal cortex and cingulate gyrus during the Hayling Sentence Completion Task. These areas have been previously associated with sensory integration, visual processing, emotional dysregulation and regulation of attention and implicated in both schizophrenia and bipolar disorder (Whalley et al., 2004; Buchsbaum et al., 2005; Pavuluri et al., 2007; Zhao et al., 2007; McIntosh et al., 2008). The genotype × diagnostic group interactions identified may indicate a disease-specific pattern of these SNPs in the pre/postcentral gyrus, cerebellum and middle temporal gyrus. A larger study may provide a more comprehensive understanding of how DISC1 rs1538979, rs821577 and rs821633 could be involved in the pathophysiology of psychiatric illness.

Supplementary materials related to this article can be found online at doi:10.1016/j.pscychresns.2011.01.015.

Financial disclosures

The authors have no biomedical financial interests or potential conflicts of interest.

Acknowledgements

Dr. Goultchira Chakirova was supported by the SINAPSE (Scottish Imaging Network — A Platform for Scientific Excellence) collaboration (www.sinapse.ac.uk) and by the Medical Research Council (http://www.mrc.ac.uk/index.htm). Dr. David Porteous is supported by the Chancellor's Award for Research from the HRH Duke of Edinburgh. Dr. Pippa A. Thomson is supported by an RCUK fellowship. Dr. William Hennah is a long term EMBO research fellow. Professor Stephen M. Lawrie is supported by a NARSAD Senior Scientist Award. Dr. Jeremy Hall is funded by a Scottish Senior Clinical Fellowship. Dr. Andrew M. McIntosh is supported by the Health Foundation UK through a Clinician Scientist Fellowship and by a NARSAD Independent Investigator Award. Dr. Heather C. Whalley is supported by a Royal Society Dorothy Hodgkin Fellowship. Financial support for the scans was provided by the Sackler Foundation.

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