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Effects of *MIR137* on fronto-amygdala functional connectivity

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ABSTRACT

Background: *MIR137* is implicated in brain development and encodes a microRNA that regulates neuronal maturation and adult neurogenesis. Recently, a common genetic variant within *MIR137* showed genome wide evidence of association with schizophrenia, and with altered amygdala activation in those at genetic risk for schizophrenia. Following this evidence, we investigated the effects of *MIR137* genotype on neuronal activity during face processing.

Methods: By grouping 81 healthy participants as carrier or non-carriers of the *MIR137* rs1625579 risk allele associated with schizophrenia, we investigated *MIR137*'s effects on altered cortical response during an fMRI face processing task and altered functional connectivity using the amygdala as a seed region.

Results: Homozygous carriers of the risk allele were observed to show relatively increased functional connectivity between the right amygdala and frontal regions that play a key role in emotion processing and regulation (e.g. the cingulate and prefrontal cortex).

Conclusions: Our findings provide the first evidence that the rs1625579 variant affects fronto-amygdala functional connectivity, providing further evidence that *MIR137* may contribute to forms of psychosis in which affective symptoms are more prominent.

Introduction

MIR137 is one of a group of genes that encode microRNAs (miRNA)—small non-coding RNA molecules modulating gene expression. *MIR137* is highly expressed in the brain, particularly in medial temporal regions, and plays an important role in neurogenesis and dendritic morphogenesis (Smrt et al., 2010). In a meta-analysis of genome-wide association studies (Ripke et al., 2011) (GWAS), a common single nucleotide polymorphism (SNP), rs1625579, within the *MIR137* gene showed the strongest genome-wide evidence for schizophrenia. The mechanisms by which the rs1625579 variant increases schizophrenia risk are unknown; however, in animal studies, altered expression of other miRNAs has been reported in key components of the brain's emotional network(s). For example, changes in miRNA expression in the amygdala and medial prefrontal cortex—in response to acute stress and maternal deprivation, suggest a role for this class of molecule in emotion regulation (O'Connor et al., 2011). In support of this hypothesis, we recently reported an association between this variant and mood congruent psychotic symptoms in a large sample of patients with psychosis, despite relatively subtle effects observed on cognition (Cummings et al., 2012). This implies that *MIR137* may be associated with forms of psychosis in which affective symptoms are more prominent.

Emotion processing deficits have been proposed as a core clinical feature of schizophrenia (Aleman et al., 2005) and may be related to genetic risk (Gur et al., 2007). Variation in amygdala activation, a brain region that plays an important role in assigning emotional value to stimuli and in forming emotional memories, has recently been associated with *MIR137* (Whalley et al., 2012). In this study a genotype-by-group interaction on activation in the amygdala during the Hayling sentence completion task was observed. This task is typically associated with a deactivation of the amygdala (Whalley et al., 2011); however, among participants with high genetic risk for schizophrenia, homozygous risk allele carriers showed comparatively less deactivation in the amygdala compared to homozygous and heterozygous non-risk carriers. The authors suggest that this finding may reflect a misattribution of emotional salience in the high-risk homozygous risk group to the stimuli presented in the task, which were considered to be non-emotional. However, effects of *MIR137* genotype on brain function during a task designed to measure emotion processing have yet to be reported. Face processing tasks may be particularly useful for examining genetic effects on emotion processing, as evidence suggests that impairments in processing emotional information from facial stimuli may be related to the genetic architecture of schizophrenia (Gur et al., 2007).

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MIR137 has been shown to play a role in the shaping of dendrites, raising the possibility that this gene may affect functional connectivity in the brain, which has been proposed as a possible etiological mechanism in the pathogenesis of schizophrenia (Friston, 1998; Stephan et al., 2009). Altered dendritic morphology has been suggested as a factor contributing to the aberrant functional connectivity observed in schizophrenia (Meyer-Lindenberg et al., 2005) as it may affect synaptic plasticity between groups of neurons (Stephan et al., 2009). A recent study by Lett et al. (2013) reports that schizophrenia patients homozygous for the rs1625579 risk allele have relatively reduced fractional anisotropy, an index of structural brain connectivity, throughout the brain compared to non-risk carriers. While the exact relationship between white matter integrity and functional connectivity is not fully understood, congruent results between the two modalities have been reported (Damoiseaux and Greicius, 2009), suggesting that global effects of rs1625579 on white matter integrity may also have effects on functional connectivity.

The purpose of the present study was to investigate the impact of the rs1625579 variant within *MIR137* on brain activity during emotion processing in a sample of healthy individuals. We employed a widely-used face processing task that includes both angry and neutral facial stimuli (Grosbras and Paus, 2006; Schneider et al., 2011; Tahmasebi et al., 2012; Thyreau et al., 2012). We considered both brain activation and functional connectivity of the amygdala using an established seed-based correlation approach (Erk et al., 2010; Esslinger et al., 2009; Paulus et al., 2013) with the aim of delineating the role of rs1625579 genotype on the neurobiological underpinnings of emotion processing. In doing so we sought to test the hypothesis that the *MIR137* risk allele is associated with significant differences in amygdala activity and functional connectivity during emotion processing. Testing this hypothesis is important because of the evidence both that emotional processing is aberrant in schizophrenia and that dysconnectivity is a significant feature of the disorder. Showing that *MIR137* is related to both is important for understanding (1) the genetic basis of schizophrenia and (2) the genetic architecture of emotion processing.

Material and methods

Participants

In total, 98 healthy volunteers participated in the study. Inclusion criteria required that participants be right-handed, aged 18 to 65, have no history of co-morbid psychiatric disorder, no history of substance abuse in the preceding six months, no prior head injury with loss of consciousness and no history of seizures. Participants were recruited using local media advertisements. In addition to satisfying the above criteria participants were screened for family history of schizophrenia. Volunteers were of Irish ancestry (i.e. had Irish maternal *and* paternal grandparents) and all provided written informed consent in accordance with local ethics committee guidelines.

MRI

Participants were imaged using a Philips Intera Achieva 3T MR system. Functional imaging consisted of whole-brain BOLD EPI in which 40, 2.4 mm slices were acquired with a 1 mm slice gap and the following imaging parameters: TR = 2200 ms; TE = 30 ms; FOV = 220 × 220 mm; and flip angle = 75°. The duration of functional scanning was 160 TRs. Structural imaging consisted of a T1-weighted image (180 slices; duration 6 min) using a TFE gradient echo pulse sequence, with a slice thickness of 0.9 mm and 230 × 230 FOV.

Face processing task

During fMRI, subjects performed face processing task designed by Grosbras and Paus (2006) and adapted for the IMAGEN study (Schneider et al., 2011; Schumann et al., 2010; Tahmasebi et al., 2012; Thyreau et al., 2012) (http://www.imagen-europe.com/). In this task, subjects were asked to passively watch a series of 2–5 second black-and-white video clips of faces showing neutral or angry facial expressions, or moving circles (i.e. control condition). Videos were presented in 18 second blocks, with 4–7 video clips presented per block. In the course of the task 5 neutral face blocks were presented and 5 angry face blocks were presented; every second block was a control block of which there were 9, resulting in 19 blocks in total. All subjects performed the same task, i.e. the total number of exposures to each condition was the same between subjects. After scanning, subjects completed a brief task where they were shown pictures of faces and asked to determine whether these matched faces seen during the task. Of the 5 pictures presented in this follow-up task, subjects who answered correctly for 4 or 5 pictures were included in further fMRI analysis. 8 subjects were excluded due to poor performance (<4 correct answers) or missing data for this follow-up task.

Genotyping

Genetics analysis was carried out using DNA obtained from saliva samples that were collected using Oragene DNA self-collection kits (DNA Genotek). The rs1625579 SNP was genotyped on a TaqMan® SNP genotyping assay on a 7900HT sequence detection system (Applied Biosystems). The call rate for TaqMan genotyping was >95% and the samples were observed to be in Hardy–Weinberg Equilibrium.

Data processing and analysis

After realignment of raw EPI data (fMRI section), graphical plots of estimated time series of translations and rotations were carefully inspected for excessive motion in each subject, defined as >3 mm translation and/or >3° rotation in any direction. Overall, 1 subject exhibited rotation >3° and was excluded from further fMRI analysis. 8 additional subjects were excluded due to bad quality MRI data and/or significant artefacts. Of the 81 remaining subjects, there were 1 'GG' homozygote, 25 'GT' heterozygotes and 55 'TT' homozygotes. Due to the relative infrequency of 'GG' homozygotes, we compared subjects carrying 0 or 1 copy of the risk allele ('GG'/'GT'; N = 26) with homozygous risk 'T' allele carriers ('TT'; N = 55). The allele frequencies observed in our sample were as expected (the risk 'T' allele was reported as the common allele in Ripke et al. (2011)) and we used the same grouping strategy as was used in other imaging genetics investigations of this SNP (Lett et al., 2013; Whalley et al., 2012).

fMRI

Image processing and statistical analyses were conducted using Statistical Parametric Mapping (SPM 8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on MATLAB R2011b (v7.13; http://www.mathworks.co.uk/). Functional images were realigned to the mean functional image, spatially normalised into a standard stereotactic space (Montreal Neurological Institute (MNI) template) with a voxel size of 3 mm × 3 mm × 3 mm and were subsequently smoothed with a 10 mm FWHM (full width at half maximum) isotropic Gaussian filter (i.e. a kernel width 2–3 times greater than the original voxel size).

Statistical analysis was performed using a standard general linear model (GLM) in SPM 8 (Friston et al., 1994). For each condition, a boxcar function representing stimulus presentation was created and convolved with a haemodynamic response function (HRF) to model neural responses at each voxel. The first-level GLM included these convolved condition regressors, plus 6 regressors modelling head movement. Condition effects at each voxel were then calculated using a t-contrast, producing a statistical parametric map of the following contrasts for

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each subject (the same contrasts used in previous studies using this task, e.g. Schneider et al., 2011):

1.) All faces (angry and neutral) versus control to model face-specific activation
2.) Angry faces versus neutral faces to model emotion-specific activation.

Individual SPMs were then entered into a second-level random effects model to determine task effects at the group level (one-sample t-test across the sample and independent t-test between genotype groups). For the comparison of genotype groups, a region of interest (ROI) analysis of the amygdala was also employed, using a bilateral amygdala mask constructed using the automated anatomical labelling atlas within the Wake Forest University Pickatlas (Maldjian et al., 2003, 2004; Tzourio-Mazoyer et al., 2002). Due to the previously reported effects of gender on amygdala function (Kilpatrick et al., 2006), and the trend for significant differences in the distribution of the sexes between the two genotype groups (see Subject demographics section), gender was added to the analyses of genotype effects as a covariate.

Functional connectivity analysis

Functional connectivity was assessed using a seed based correlation approach, similar to that used by Esslinger et al. (2009), Erk et al. (2010), and Paulus et al. (2013), to examine the effects of GWAS psychosis risk variants on functional connectivity. Amygdala masks were obtained as described above (fMRI section). Both right and left amygdalae were used as seed regions in two separate connectivity analyses. Time series from the amygdala were extracted using first eigenvariates from all voxels within the amygdala mask (Esslinger et al., 2009). This time series was temporally filtered using a high-pass filter of 128 s to remove low-frequency signals and task-related variance was removed by applying an effects-of-interest F-contrast of the six movement parameters (Esslinger et al., 2009; Paulus et al., 2013). Noise was excluded from this seed by selecting voxels active for the faces versus control contrast at a threshold of $p < 0.5$ (Esslinger et al., 2009); this threshold was not used for statistical inference. We chose the faces versus control contrast as there was no significant effect of the angry versus neutral faces contrast on amygdala activity across our group, similar to previous studies using this task (Schneider et al., 2011). One subject did not show right or left amygdala activation at this threshold; this subject was excluded from further connectivity analysis.

To account for noise, first eigenvariates from all voxels within masks of white matter (WM) and cerebrospinal fluid (CSF) were extracted, and entered, together with task and movement regressors, into a new fixed-effects GLM with the amygdala time-series as the regressor of interest. Task-related variance was also removed from WM/CSF time series by applying an effects-of-interest F-contrast of the six movement parameters. The WM and CSF masks were kindly provided by Esslinger, C. and Paulus, F. (personal correspondence). These masks have previously been used in imaging genetics studies examining the effects of GWAS psychosis risk variants on functional connectivity (Esslinger et al., 2009; Paulus et al., 2013). Individual connectivity maps produced by the analysis were then compared between genotype groups using an independent t-test in SPM 8. Gender was also added to second-level functional connectivity analyses as a covariate. For all analyses, statistical parametric maps were initially 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 across the whole brain using the family-wise error rate (FWE). MNI coordinates of results were converted to Talairach space using BrainMap GingerALE 2.1 (Eickhoff et al., 2009; Turkeltaub et al., 2012) and anatomic localisation of these coordinates was performed using Talairach Client 2.4.3 (Lancaster et al., 1997, 2000).

Results

Subject demographics

Independent t-tests were performed to compare age and years of education between genotype groups; a Pearson's chi-squared test was performed to compare gender frequencies between genotype groups. There were no significant differences between genotype groups for age or years of education ($p > 0.05$) with a trend for significant differences in the distribution of the sexes ($p = 0.07$; see Table 1).

Functional activation

Across our sample, the faces versus baseline contrast was associated with significant neural activation in clusters incorporating key regions involved in face processing including the middle temporal gyrus and amygdala, consistent with previous studies using this task (Grosbras and Paus, 2006; Schneider et al., 2011) ($t_{(81)} = 23.44$, $p < .05$, corrected; see Table 2 and Fig. 1). Several of these brain regions, including the bilateral amygdala, also survived correction for multiple comparisons at a voxel-level FWE-corrected threshold (see Supplemental Table 1). The angry versus neutral faces contrast was associated with significant neural activation in a cluster incorporating the left cingulate gyrus/BA 32 ($t_{(81)} = 4.67$, $p < .05$, corrected; see and Table 2 and Fig. 1). These activations did not differ between genotype groups for either the faces versus control or angry versus neutral face contrasts. In addition, ROI analysis within the bilateral amygdala did not reveal significant differences between genotype groups for the faces versus control or angry versus neutral face contrasts, both at a threshold of $p < 0.05$ FWE-corrected at the cluster level, and at an exploratory threshold of $p < 0.05$ uncorrected.

Functional connectivity

'T' homozygotes showed significantly increased functional connectivity between the right amygdala and two clusters incorporating (1) the right cingulate gyrus/BA 31 and left BA 24; and (2) the right inferior frontal gyrus/BA 47 ($t_{(80)} = 5.17$, $p < .05$, corrected; see Table 3 and Fig. 2). There were no significant left amygdala connectivity differences between genotype groups. As an additional data quality check, in each individual the average parameter estimates of all voxels were calculated for each cluster that showed a significant connectivity difference between genotype groups. Next, average parameter estimates were checked in SPSS (19.0.0) for the presence of outliers. No outliers were identified.

Discussion

This study investigated the functional effects of the genome-wide associated schizophrenia risk variant rs1625579 within *MIR137* on neural activation in healthy participants. A functional connectivity analysis of this data revealed an effect of genotype on amygdala functional connectivity. Compared to subjects carrying one or no copies of the

Table 1
Subject demographics.

	Mean age (s.d.[a])	Mean years of education (s.d.)	Gender (M:F)
GG/GT (N = 26)	28.50 (9.52)	17.88 (3.65)	10:16
TT (N = 55)	27.95 (8.04)	17.39 (3.12)	33:22
Statistic[b]	t = 0.273	t = 0.629	$\chi^2 = 3.289$
p value	0.786	0.531	0.070

[a] s.d. = standard deviation.
[b] The statistical tests used are listed in the Subject demographics section.

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Table 2
Clusters, including individual peaks, showing significantly increased functional activation during face (angry and neutral) versus control, and angry versus neutral face conditions, corrected for multiple comparisons at the cluster-level.

Cluster	Extent (voxels)	p value[a]	Condition	Cluster peaks	t-Value	Z-value	Peak coordinates (MNI)
1[b]	5318	<0.001	Faces	Right middle temporal gyrus/BA 22	23.44	>8	54 −40 7
				Right middle frontal gyrus/BA 46	18.39	>8	48 23 22
				Right cerebellum	17.21	>8	42 −49 −20
2[c]	2431	<0.001	Faces	Left cerebellum	15.39	>8	−15 −76 −35
				Left fusiform gyrus/BA 37	14.47	>8	−42 −49 −20
				Left middle temporal gyrus/BA 21	14.32	>8	−60 −49 10
3	1288	<0.001	Faces	Left inferior frontal gyrus/BA 9	11.41	>8	−39 11 25
				Left inferior frontal gyrus/BA 47	8.93	7.42	−39 32 −2
				Left middle frontal gyrus/BA 6	8.16	6.94	−42 2 49
4	409	<0.001	Faces	Right superior frontal gyrus/BA 6	10.69	>8	6 14 58
				Right superior frontal gyrus/BA 8	5.03	4.68	9 44 43
5	676	<0.001	Angry	Left anterior cingulate/BA 32	4.67	4.37	−12 29 19
				Left cingulate/BA 32	4.51	4.25	−9 26 28
				Left cingulate/BA 32	4.46	4.20	−9 23 37

[a] p values are FWE-corrected for multiple comparisons at the cluster level; Faces = All faces (angry and neutral) versus control condition; Angry = Angry versus neutral faces condition.
[b] The significant right amygdala activation reported in the main text is contained within this cluster.
[c] The significant left amygdala activation reported in the main text is contained within this cluster.

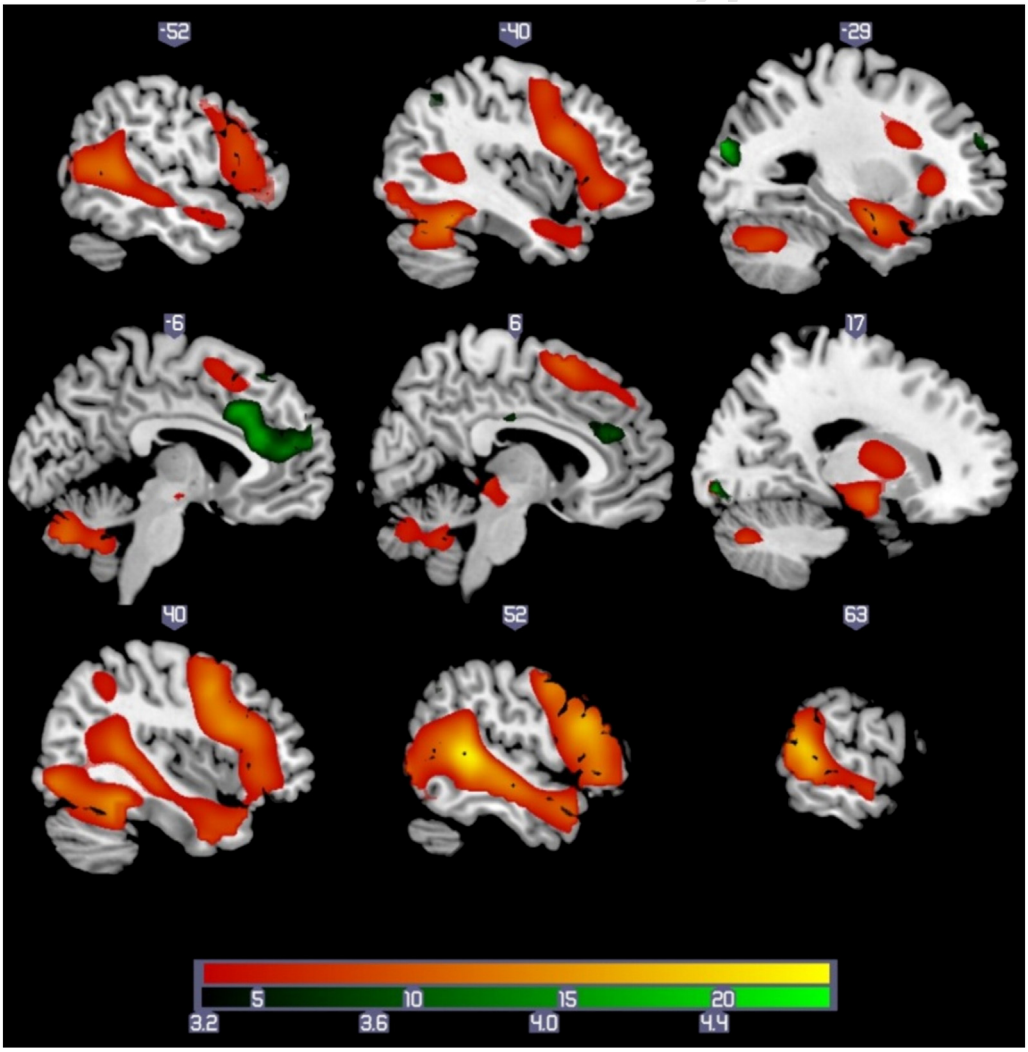

Fig. 1. Functional activation associated with face processing task. Red-yellow: Brain regions showing increased activation during the face (angry and neutral) versus control condition (N = 81; one-sample t-test; significance is set at $p < 0.001$ uncorrected without a cluster threshold for display purposes; d.f. = 80). Green: Brain regions showing increased activation during the angry versus neutral face condition (N = 81; one-sample t-test; significance is set at $p < 0.001$ uncorrected without a cluster threshold for display purposes; d.f. = 80). Colour bars represent t-values. Each 2D sagittal slice is labelled with an x-coordinate (MNI space). Clusters are rendered on the 'ch256' brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of figure (e.g. changing the size/resolution) performed using MS Paint and Paint.NET v3.5.10.

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Table 3
Clusters showing significantly increased functional connectivity with the right amygdala in rs1625579 'TT' homozygotes compared to 'GG'/'GT' carriers.

Cluster	Extent (voxels)	p value[a]	Cluster peaks	t-Value	Z-value	Peak coordinates (MNI)
1	651	<0.001	Right cingulate gyrus/BA 31	5.17	4.78	12 −43 37
			Left cingulate gyrus/BA 24	4.56	4.28	−12 −1 49
			Left cingulate gyrus/BA 31	4.28	4.04	0 −28 37
2	95	0.036	Right inferior frontal gyrus/BA 47	4.60	4.31	39 20 −11

[a] p values are FWE-corrected for multiple comparisons at the cluster level.

risk allele ('GG'/'GT' carriers), homozygous risk allele ('T') carriers showed increased functional connectivity between the right amygdala and frontal regions involved in emotion processing and regulation, including the cingulate and prefrontal cortex.

Emotion processing in the brain can be conceptualised as being mediated by two distinct, yet interconnected pathways/systems (Phillips et al., 2003). The ventral system, which includes the amygdala and insula, is thought to be responsible for attaching emotional significance to stimuli and producing an affective state; the dorsal system, which includes the lateral prefrontal cortex and supragenual/posterior cingulate, is thought to play a role in emotion regulation, the ability to alter one's reaction to an emotional stimulus (Ochsner and Gross, 2005). This is achieved in part through an inhibitory effect on neuronal firing in the amygdala (Stein et al., 2007). Since altered functional connectivity has been proposed as a key etiological factor in the pathogenesis of schizophrenia (Friston, 1998), altered connectivity between the regions that comprise these systems may contribute to emotional deficits, a key clinical feature of the disorder. For example, altered fronto-amygdala functional connectivity has been observed in schizophrenia patients relative to healthy controls during emotion perception (Das et al., 2007) and in psychosis prone subjects during emotional reappraisal (Modinos et al., 2010).

Although our original aim was to examine differences in amygdala activation in response to emotional faces, the face processing task used in the present study was not associated with increased amygdala activation while viewing angry faces compared to viewing neutral faces. As such, the amygdala activity observed in our sample may represent face processing, rather than emotion processing per se. However, the lack of a significant amygdala response to the angry faces compared to the neutral faces may also reflect participants' emotional responses to both types of facial stimulus. Healthy subjects have responded similarly to both emotional and neutral faces (Lee et al., 2008) and reported neutral faces as emotional stimuli (Ille et al., 2011) during other face processing tasks. Participants may interpret neutral faces as emotional stimuli due, for example, to their structural properties (e.g. high or low eyebrows (Adams et al., 2012)) or presentation context (e.g. depending on the types of faces/stimuli preceding the neutral faces in the task) (Wieser and Brosch, 2012).

The present finding of increased connectivity between the amygdala and key regions involved in emotion regulation may reflect an increased regulatory response in the risk group while processing the facial stimuli. However, this conclusion is speculative due to the fact that we observed an altered pattern of connectivity over an experimental period that also included non-facial stimuli. As such, we cannot rule out the possibility that this effect is stationary and face processing independent. Future studies could use psychophysiological interaction (PPI) analysis to examine gene effects on functional connectivity related to specific experimental conditions (e.g. face processing) (Friston et al., 1997). Our study, based on a sample size which was in the average range for the type of analyses conducted, may not be sufficiently powered for PPI due to the low statistical power associated with this technique, which results in high incidence of false negatives (O'Reilly et al., 2012).

Although we observed a significant increase in amygdala connectivity in risk allele homozygotes, we observed no risk allele effects on amygdala activation in the present study, despite highly significant bilateral activation in this region across our sample in response to facial stimuli. This is in contrast to Whalley et al., who reported increased amygdala activation in *MIR137* risk allele homozygotes during a

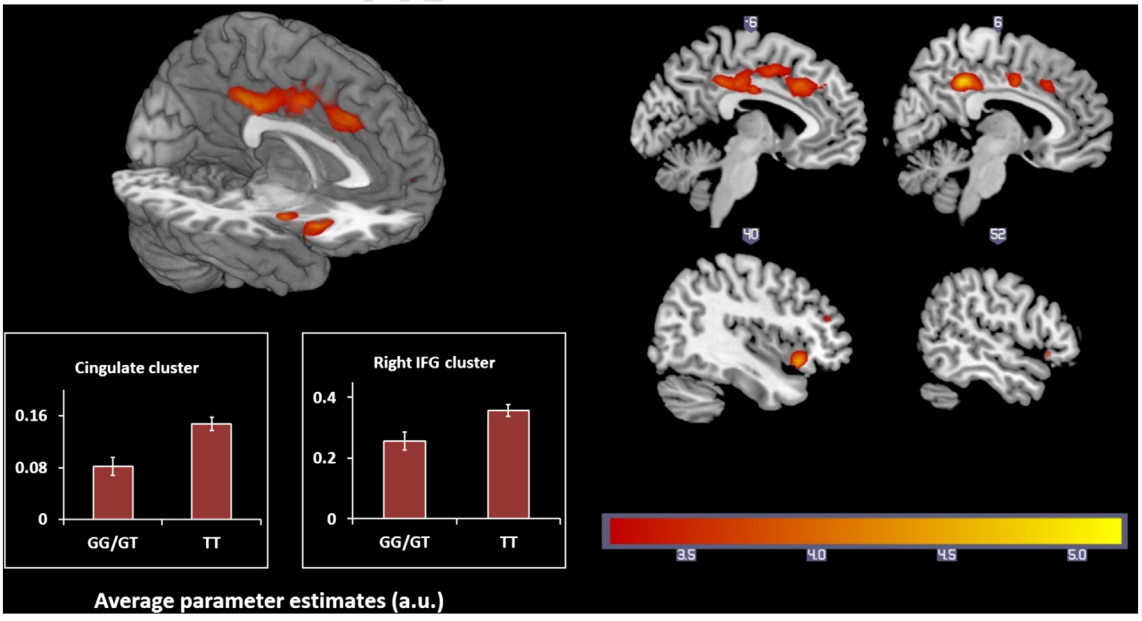

Fig. 2. Effects of *MIR137* variation on fronto-amygdala functional connectivity. Red-yellow: Brain regions showing relatively increased connectivity with the right amygdala in risk 'T' homozygotes relative to 'G' carriers (N = 80; independent t-test between genotype groups; significance is set at $p < 0.001$ uncorrected without a cluster threshold for display purposes; d.f. = 77). Colour bars represent t-values. Each 2D sagittal slice is labelled with an x-coordinate (MNI space). Clusters are rendered on the 'ch256' brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Bar graphs were constructed as described in the Functional connectivity section; a.u. = arbitrary units. Additional editing of figure (e.g. changing the size/resolution) performed using MS Paint and Paint.NET v3.5.10.

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sentence completion task in first degree relatives of patients with schizophrenia but not in relatives of patients with bipolar disorder and subjects at low genetic risk. Besides the different paradigms, this is an important difference between our study which consisted of healthy controls without a family history of schizophrenia and overall lower genetic risk of the disorder compared to the sample examined in Whalley et al. It has previously been suggested that functional connectivity may represent a more sensitive intermediate phenotype in identifying neural circuits affected by schizophrenia risk variants compared to measures of neural activation (Meyer-Lindenberg, 2009). As such, while we were unable to detect differences in cortical activation in our healthy control sample, the use of functional connectivity may have enabled us to already detect rs1625579 specific effects on amygdala function in individuals with a comparably lower genetic risk for the disorder. Potential interactions with other environmental and genetic risk factors in first degree relatives of patients with schizophrenia might then further impact these effects on the level of neural system connectivity and contribute to the finding of altered amygdala activation.

While patients with schizophrenia show consistent differences in amygdala function (Aleman and Kahn, 2005; Shayegan and Stahl, 2005), the degree to which the genetic basis of these differences is schizophrenia specific, or relate to psychosis more broadly is unknown (Rasetti et al., 2009). While *MIR137* was associated with schizophrenia but not bipolar disorder in the Ripke et al. (2011) study, whether the effects of *MIR137* on amygdala connectivity observed in the present study of healthy participants are only relevant to schizophrenia risk is uncertain. miRNAs are suggested to represent novel therapeutic targets for emotion-related disorders such as anxiety and depression (O'Connor et al., 2011). miRNA levels are altered in these disorders, and both antidepressants and mood stabilisers alter miRNA levels in the brain. It is interesting to speculate about whether the present finding that *MIR137* variation may affect emotional networks in a manner that has relevance for other psychiatric disorders also.

The impact of rs1625579 on measures of brain function and connectivity is likely to interact with, and be influenced by, other variants that confer risk for schizophrenia. For example, several genome-wide associated psychosis risk genes, including *ZNF804A*, *CACNA1C*, *TCF4* and *CSMD1*, are targets of *MIR137*. *ZNF804A* was the first variant to show an effect on functional connectivity, and also showed increased amygdala-related connectivity with other cortical regions. As such, an important direction for future imaging genetics studies will be to examine the possible additive or epistatic effects of variants in these genes on functional connectivity of neural circuits during face processing (Nicodemus et al., 2010). Finally, functional connectivity between the amygdala and cingulate is also sensitive to environmental stress, such as urban upbringing (Lederbogen et al., 2011). Whether and how the functional connectivity effects of *MIR137* observed are mediated by environmental experience will be an important question for future imaging genetics studies.

Conclusions

In conclusion, our study reports for the first time the effects of a genome-wide associated schizophrenia risk variant, rs1625579, within *MIR137*, on functional connectivity between the amygdala and (1) the cingulate and (2) the prefrontal cortex, brain regions that play an important role in emotion processing and regulation. This is the first study to demonstrate effects of *MIR137* on functional connectivity, and provides further evidence that the rs1625579 variant may contribute to forms of psychosis in which affective symptoms are more prominent, building on previous findings that the variant is associated with mood congruent psychotic symptoms. Further research on this variant may uncover novel molecular pathways associated with illness risk, which may inform future treatment strategies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.12.019.

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Conflict of interest

All authors have declared that there are no conflicts of interest in relation to the subject of this study.

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