The impact of the CACNA1C gene polymorphism on frontolimbic function in Bipolar Disorder

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Genome-wide association studies in bipolar disorder (BD)1 have implicated a single-nucleotide polymorphism (rs1006737, G-A) in the CACNA1C gene, which encodes for the alpha 1c (CAV1.2) subunit of the voltage-gated, L-type calcium channel. Neuroimaging studies of healthy individuals report that this risk allele modulates brain function within limbic (amygdala, anterior cingulate gyrus) and hippocampal regions during tasks of reward processing2,3 and episodic memory.4 Moreover, animal studies suggest that the CaV1.2 L-type calcium channels influence emotional behaviour through enhanced neurotransmission via the lateral amygdala pathway.5 On the basis of this evidence, we tested the hypotheses that the CACNA1C rs1006737 risk allele will modulate neural responses within predefined prefrontal and subcortical regions of interest during emotional face processing and that this effect would be amplified in BD patients.

A total of 116 individuals of white British descent comprising 41 euthymic patients with BD, 25 of their first-degree relatives without any Axis I disorder and 50 healthy controls, were genotyped for the CACNA1C rs1006737 polymorphism (Table 1, Supplementary Material). These comprised 54 G homozygotes (BD patients: N=17; relatives: N=9; controls: N=28), 47 AG heterozygotes (BD patients: N=19; relatives: N=10; controls: N=18) and 15 A homozygotes (BD patients: N=5; relatives: N=6; controls: N=4), in Hardy-Weinberg equilibrium ($P = 0.92$). Because of their small number AA individuals were considered together with AG heterozygotes within each diagnostic group (BD patients: N=24; relatives: N=16; controls: N=22) in further analyses. There was no effect of genotype or genotype by diagnosis interaction on demographic variables ($P > 0.15$). Carriers of the CACNA1C rs1006737 risk allele had higher depressive and manic symptom scores ($P = 0.01$) with this effect being more pronounced in patients ($P < 0.02$) (Table 1, Supplementary Material).

All participants completed a functional magnetic resonance imaging facial affect recognition task comparing fearful with neutral faces (Supplementary material), which had previously been used in imaging genetics.6 Anatomical and gradient-echo echoplanar imaging data were acquired during

the same session using a 1.5 T GE Neuro-optimized Signa Magnetic Resonance system (General Electric, Milwaukee, WI, USA). We examined the effect of genotype, group and their interaction on predefined prefrontal (lateral and medial prefrontal cortex and anterior cingulate cortex) and subcortical (amygdala, hippocampus) regions of interest known to be associated with fear facial affect processing6,7 or to be modulated by CACNA1C rs1006737.2,3,4 Full factorial analysis of variance with response time, age and symptom scores as covariates was implemented in SPM5 (http:/www.fil.ion.ucl.ac.uk/spm/software/spm5) (Supplementary material); statistical inferences were based on a threshold of $P < 0.05$ with family-wise error correction.

Independent of diagnostic group, the right amygdala (x=26 y = └2 z = └26 z-score = 4.60) showed greater activation during fear-face recognition relative to neutral faces in AA/AG compared with GG individuals (Figure 1). A significant effect of group was noted in the right ventrolateral prefrontal cortex (vlPFC; x=52 y=38 z = └10 z-score = 3.71). A significant genotype ┐ diagnosis interaction was also observed in the right vlPFC (x=54 y=36 z = └12 z-score = 3.64). The right vlPFC expressed reduced activation in individuals with the high-risk allele compared with those with the low-risk variant in BD patients, but not in their relatives or controls (Figure 1).

This report confirms previous findings that genetic variation in the CACNA1C gene modulates amygdala function during emotional processing.2 This effect is, however, diagnosis independent. Moreover, we provide the first formal evidence of a disease-specific influence of the CACNA1C genotype on brain function The present findings suggest that the CACNA1Crs1006737 polymorphism impacts on vlPFC activation during fear processing in BD carriers of the risk allele but not their unaffected relatives. The ventral PFC is thought to contribute to emotional regulation by modulating amygdala activation particularly in response to environmental threats.7

It is still unclear whether rs1006737 or another variant in linkage disequilibrium is causally linked to the risk of BD and to our findings. However, our results implicate CACNA1C in functional

changes within emotional systems that are consistent with increased amygdala reactivity and reduced prefrontal control.

Conflict of interest

The authors declare no conflict of interest.

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Figure 1 Statistical parametric map (SPM) showing the effect of CACNA1C rs1006737 polymorphism on amygdala function during fear-face processing in bipolar disorder (BD) patients, their unaffected relatives and controls (top), and genotype¬ diagnosis interaction in the ventrolateral prefrontal cortex (vlPFC) (bottom); SPM thresholded at $P < 0.05$, family-wise error corrected.