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The impact of psychosis genome-wide associated ZNF804A variation on verbal fluency connectivity

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ABSTRACT

Schizophrenia (SCZ) and bipolar disorder (BD) have high heritability. Genome-wide association studies (GWAS) have identified *ZNF804A* as a significant risk gene for both illnesses. A validation of this finding at the brain systems-level is imperative as there is still little understanding of how it heightens risk. Based in part on our recent findings of an effect on widespread decreased white matter microstructural fractional anisotropy (putatively a proxy of its integrity), particularly strong in SCZ, we asked whether the risk allele has a detrimental effect on regional brain activation and functional connectivity during a type of cognitive processing which is, together with its neural correlates, impaired in BD and SCZ: verbal fluency. Functional MRI and genotype data was collected from 80 healthy volunteers, and 54 SCZ and 40 BD patients. A standard multifactorial analysis of variance using statistical parametric mapping and significance correction of FWE $p < 0.05$ was used. We found the GWAS risk allele A was associated with decreased positive functional coupling between the left precentral gyrus/inferior frontal gyrus (i.e. the most highly recruited area for the task) and: 1) the left inferior frontal gyrus, and 2) the left posterior cingulate gyrus, encompassing the precuneus; both as a main effect across controls and psychosis patients. Such association of the risk allele with reduced functional connectivity (with no area where the opposite main effect was detected), converges with findings in other tasks, our previous finding of its widespread impact on brain white matter microstructure, and with the dysconnectivity hypothesis of SCZ.

1. Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) have high heritability. Genome-wide association studies (GWAS) have robustly identified *ZNF804A* as a significant risk gene for both illnesses (Gurung and Prata, 2015), by virtue of it containing the rs1344706 polymorphism for which the adenine (A) allele was slightly more common in both patient groups. A validation of this finding at the brain systems-level is imperative as there is still little understanding of how it heightens risk. *ZNF804A* expresses the zinc-finger protein 804A with a domain typical of a transcription factor in the developing hippocampus, the cortex, and the adult cerebellum (Gurung and Prata, 2015). Consistent with a neurodevelopmental role, we recently found the risk allele (A) to be highly significantly associated with widespread decreased white matter microstructural fractional anisotropy (putatively a proxy of its integrity) across healthy subjects, as well as patients with SCZ and with BD - but particularly strongly in SCZ (Mallas et al., 2016). We now asked whether it would, consequently, have a detrimental effect (and possibly larger in SCZ patients) on regional brain activation and functional connectivity during a type of cognitive processing which is, together with its neural correlates, affected in BD and SCZ, and their healthy relatives (Curtis et al., 2001; Daban et al., 2006): verbal fluency (Prata et al., 2009). Such effect would be consistent with previous findings associating it with a decrease in functional connectivity during

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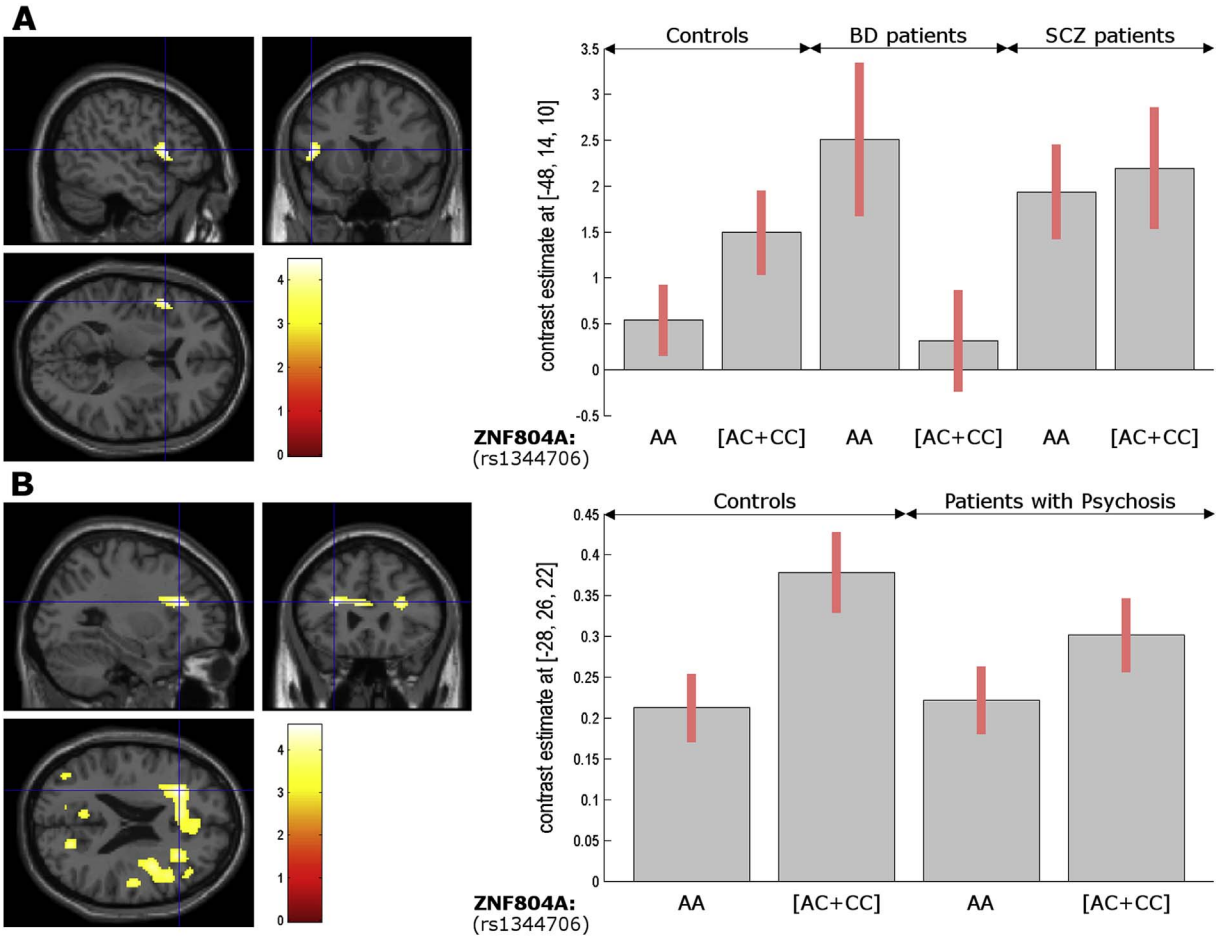

Fig. 1. – Part A: Genotype-by-diagnosis interaction in the left inferior frontal gyrus, pars triangularis/opercularis, where risk allele adenine (A) [vs. Cytosine (C) carriers] was associated with higher regional activation (Y-axis) in BD, but the reverse was seen in healthy volunteers (X-axis). **Part B:** Main effect of *ZNF804A* rs1344706 genotype on functional connectivity, whereby risk allele A homozygotes [vs. Cytosine (C) carriers] showed decreased connectivity between the left precentral gyrus/inferior frontal gyrus, pars opercularis (seed) and the left inferior frontal gyrus, pars triangularis/opercularis (Y-axis), across controls and patients with history of psychosis (i.e. the whole SCZ and 75% of the BD group; X-axis). Regions are represented when surviving $p < 0.001$ uncorrected (see Table 1). Parameter estimates are for verbal fluency > repetition in the left inferior frontal gyrus, pars triangularis/opercularis (Part A: −48 14 10, z-score = 4.39, voxel-wise FWE-corrected p-value = 0.03; Part B: −28 26 22, z-score = 4.42, voxel-wise FWE-corrected p-value = 0.02; between-subjects SEM bars are in red). Brain regions are labelled using an automatic-labelling atlas(*) and confirmatory visual inspection of a manual book atlas(**). *(*) Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage 15, 273–289.* https://doi.org/10.1006/nimg.2001.0978. *(**) K. Mai, J., Paxinos, G., Voss, T., 2008. Atlas of the Human Brain, 3rd Edition, 3rd ed. Academic Press, San Diego.* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

working memory (Esslinger et al., 2009; Rasetti, 2011). On behaviour, effects seem smaller or less detectable, with one study showing a weak-to-modestly linked allele (in terms of linkage disequilibrium) to be marginally associated with better category fluency, but not verbal fluency, in healthy males (Nicodemus et al., 2014); and the present risk allele with worse visuo-motor performance, but again not verbal fluency nor verbal learning (Lencz et al., 2010).

2. Material and methods

We genotyped (for *ZNF804A* rs1344706) and scanned, with functional MRI, 174 English native speakers [80 healthy volunteers without history of mental illness, 54 patients with SCZ and 40 with BD (75% of whom had a history of psychosis symptoms)], recruited from the SLAM NHS Trust and diagnosed according to DSM-IV (methodological detail and references are available in Supplement 1). This yielded 84 rs134470684 allele A homozygotes and 90 allele C carriers, and given the very low frequency of allele C in Caucasian population, we grouped the non-risk allele C homozygotes with the heterozygotes. The study was approved and reviewed by the National Health Service (NHS) South East London Research Ethics Committee, UK (Project "Genetics and Psychosis (GAP)" reference number 047/04) and was carried in accordance with the latest version of the Declaration of Helsinki. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. There were no demographic differences (at $p < 0.05$) between genotype or diagnostic groups, other than CPZ-equivalent medication and male:female being higher, and IQ lower, in patients with SCZ (see sample's demographics in Supplement 2). The verbal fluency task [where subjects are required to overtly generate a word starting with a visually-displayed letter; or overtly read the word "rest" (control or repetition condition)], image acquisition, pre-processing and analysis using SPM software was performed as described earlier (Prata et al., 2009). A multifactorial ANOVA was used to test for the main effect of genotype (A homozygotes vs. C carriers) and its interaction with diagnosis (controls vs. BD vs. SCZ; or all psychosis patients, i.e. 100% of SCZ group + 75% of BD group, vs. controls). These effects were tested on whole-brain regional activation and on functional connectivity, including connectivity that would depend on task trials (i.e. psychophysiological interaction; PPI). Main effect of task is reported for completeness, but not discussed, as it has already been described in a highly overlapping sample (Prata et al., 2009). Incorrect response trials were excluded to avoid confounding effects of task performance. For connectivity, we used, as seed, the 6-mm radius sphere where the main effect of task was the highest (i.e. left precentral