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ORIGINAL ARTICLE

Effects of *ZNF804A* on auditory P300 response in schizophrenia

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The common variant rs1344706 within the zinc-finger protein gene *ZNF804A* has been strongly implicated in schizophrenia (SZ) susceptibility by a series of recent genetic association studies. Although associated with a pattern of altered neural connectivity, evidence that increased risk is mediated by an effect on cognitive deficits associated with the disorder has been equivocal. This study investigated whether the same *ZNF804A* risk allele was associated with variation in the P300 auditory-evoked response, a cognitively relevant putative endophenotype for SZ. We compared P300 responses in carriers and noncarriers of the *ZNF804A* risk allele genotype groups in Irish patients and controls ($n = 97$). P300 response was observed to vary according to genotype in this sample, such that risk allele carriers showed relatively higher P300 response compared with noncarriers. This finding accords with behavioural data reported by our group and others. It is also consistent with the idea that *ZNF804A* may have an impact on cortical efficiency, reflected in the higher levels of activations required to achieve comparable behavioural accuracy on the task used.

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INTRODUCTION

A single-nucleotide polymorphism (SNP) rs1344706 located within zinc-finger binding protein 804A (*ZNF804A*) was the first genetic variant to achieve genome-wide significance for psychosis (odds ratio = 1.1; $P = 9.96 \times 10^{-11}$).[1] Association with schizophrenia (SZ) has been replicated in a series of additional studies since then,[2–6] and a meta-analysis by Williams *et al.*,[7] of 21 274 cases and 38 675 controls has confirmed this association with both SZ (odds ratio = 1.10; $P = 2.5 \times 10^{-11}$) and SZ and bipolar disorder combined (odds ratio = 1.11; $P = 4.1 \times 10^{-13}$). In addition to the common variants identified, evidence of excess copy number variants at the *ZNF804A* locus in psychiatric cases has also been reported,[8] although rare non-synonymous *ZNF804A* risk variants have yet to be identified.[9] Following *de novo* polymorphism discovery and detailed association analysis in the Williams *et al.*,[7] meta-analysis, rs1344706 remained the most strongly associated marker in the gene. Collectively, therefore, these data make the association between rs1344706 and SZ risk, one of the most compelling to date in the field.[10]

rs1344706 is located in intron 2 of *ZNF804A* that maps to chromosome 2q32.1. Consisting of four exons and transcribing a protein of 1210 amino acids, *ZNF804A* is brain expressed but is of unknown function. Proteins with this zinc-finger domain were originally identified as DNA-binding molecules with a role in transcription but have diverse interactions with many molecules including RNA and proteins. Bioinformatic analysis of the conserved mammalian sequence around rs1344706 suggests the presence of transcription factor-binding sites. The functional mechanism by which the risk allele contributes to aetiology is unclear. Williams *et al.*[7] examined genotype and lymphoblastoid expression data from the GeneVar database and identified that the rs1344706 risk allele was associated with higher protein expression. The risk allele has also been associated with a pattern of altered functional connectivity in several brain regions, including the dorsolateral pre-frontal cortex, the hippocampus and the amygdala in a sample of healthy participants.[11,12]

Neuropsychological, structural and functional imaging studies of the *ZNF804A* risk allele have yielded apparently conflicting results. In the largest neuropsychological study to date, we observed that patient (but not control) risk carriers showed a pattern of relatively intact cognitive performance in the areas of episodic and working memories, findings that exactly replicated in samples of German patients and controls.[13] In a follow-up structural imaging study based on an independent sample of Italian patients and controls, we observed the same pattern of results: patient risk carriers showed relatively intact hippocampal volumes.[14] As the intermediate phenotypes approach generally assumes that illness risk will be at least partly mediated by a deleterious effect on brain structure and function, these data are counterintuitive. Our interpretation of these findings was that *ZNF804A* may be particularly associated with an illness subtype in which cognitive and associated grey matter deficits are less prominent. Although a number of studies have since supported this view[15,16] others have not,[17,18] or they have suggested that *ZNF804A* may instead have a deleterious impact on aspects of social cognition.[19,20]

The present study investigated the effects of *ZNF804A* rs1344706 on performance during an EEG task designed to measure the P300 event-related potential. The P300, which is

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measured over midline scalp electrodes and is thought to index cortical processes relevant to memory and attention, has been widely used to investigate SZ genetic risk variants to date.[21–26] Based on our earlier neuropsychological and structural imaging studies of both memory function and the hippocampus, we hypothesised that the risk allele might again be associated with relatively intact ('better') performance compared with noncarriers.

MATERIALS AND METHODS

Informed consent was obtained from 150 Irish participants in total consisting of 60 patients and 90 controls. All patient participants were outpatients in a stable phase of their illness, contacted through their local service. Diagnosis was confirmed using the structured clinical interview schedule for the Diagnostic and Statistical Manual 4th edition (Structured Clinical assessment for the DSM[27]), case note review and collateral information (where available) by a trained psychiatrist or psychiatric nurse. All cases were assessed using a consensus diagnosis approach and independent diagnostic review by a psychiatrist (AC). All patients were aged 18–60 years and satisfied the criteria of being of Irish Decent (Irish parents and grandparents), with no history of head injury or loss of consciousness and no current cannabis abuse or history of drugs or alcohol abuse. In addition to demographic information and information about handedness[28] collected for both cases and healthy participants, symptom severity was also assessed in cases using the scales for the assessment of positive symptoms and scales for the assessment of negative symptoms.[29] All participants reported normal or corrected to normal vision and all were medicated use atypical antipsychotics.

Healthy participants, consisting largely of respondents to local media advertisements, were also aged between 18–60 years and satisfied the criteria of having (a) no history of psychosis (based on clinical interview); (b) no history of head injury or loss of consciousness; (c) Irish descent (Irish parents and grandparents); (d) no first degree relative with a diagnosis of psychosis (DSM-IV); and (e) no current cannabis abuse or history of drugs or alcohol abuse. Psychiatric history and family history was screened based on a semi-structured interview before EEG assessment. None of the controls were on psychotropic medication at the time of testing (Table 1).

The SNP rs1344706 was genotyped using a Taqman SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems, Carlsbad, CA, USA). The call rate for the Taqman genotyping was 100% and samples were in Hardy–Weinberg equilibrium ($P>0.05$). Along with these samples, a number of HapMap CEU DNA samples (www.hapmap.org) were genotyped for rs1344706 for quality control purposes and were all found to be concordant with available online HapMap data for this SNP. Insufficient DNA quantity or quality for genotyping purposes meant that 24 participants were not included in the analysis.

EEG stimuli and presentation

The P300 was evoked using a standard auditory oddball paradigm consisting of pseudorandomised binaural presentation of a train of frequent (non-target) tone pips of 1000 Hz interspersed with rare target stimuli (at 1500 Hz) presented binaurally through headphones. Interstimulus interval was 1560 ms, with a tone loudness of 80 dB sound pressure level. Eighty percent of the tones were standard 'non-targets' and 20% were 'targets'. Participants were instructed to listen to the tones while keeping their eyes open and fixated on a central cross and press a mouse key in response to the target tones only.

Electrophysiological data acquisition and analysis

Electrophysiological data were collected for 129 of the 150 participants using a 128-channel system. Patients' data, which was collected over a longer time period, were collected using either the same 128-channel system ($n=32$) or an earlier 72-channel system ($n=18$). In both systems, data was acquired by the ActiveTwo BioSemi electrode system (Biosemi BV, Amsterdam, The Netherlands) digitised at 512 Hz with an open passband from DC to 150 Hz. Only data from electrodes occupying the same site on the scalp in the 128-channel and the 72-channel caps were used in analysis. These electrode sites were determined by digitising the electrode locations from both 72 and 128 caps, and projecting these digitised montages onto an average head that consisted of 81 channels derived from the BESA 81-channel configuration (www.BESA.de).

For both electrode groups, horizontal and vertical electro-oculograms were also recorded. The Biosemi amplification system replaced the "ground" electrodes with two separate electrodes: common mode sense active electrode and driven right leg passive electrode (for more on the function of the common mode sense and driven right leg electrodes, see (www.biosemi.com/faq/cms&drl.htm). For the baseline correction, a baseline −100 ms to 0 for the P300 was used. For analysis and display purposes, data were subsequently filtered with a 0-phase-shift 40 Hz low-pass filter (48 dB/octave) after acquisition. No high-pass filter was used. Only sweeps related to correct responses to the target tones were included in the analysis for the P300 paradigm. Artefact correction was based on the surrogate model of artefact topography & artefact rejection.[30]

Event related potential analyses

All event related potential (ERP) analyses were performed using BESA Software Version 5.2 (BES, Grafling, Germany). Of 134 participants who completed the P300 paradigm, 13 data sets were removed due to excessive noise despite artefact correction. Together with genotyping dropouts, this resulted in 97 participants ultimately being included in this analysis. On average, 46.36 (s.d. 27.26) sweeps were available for patients and 62.01 (s.d. 23.47) for controls. Given the small number of minor allele homozygous carriers ($n=13$), a two-group comparisons was conducted, comparing homozygous 'AA' risk carriers with carriers of 1 or 2 copies of the risk 'C' allele. For controls, ~59.85 ± 23.41 sweeps per individual were averaged for the *ZNF804A* AC+CC genotype group and 67.03 ± 24.72 for the AA group with an epoch of −100 to 1000 ms. For cases, ~40.20 ± 25.38 sweeps per individual were averaged for the AC+CC group and 48.40 ± 27.28 for the AA group with an epoch of −100 to 1000 ms. A set of three scalp sites was chosen along the midline electrode chain (FCz, Cz and CPz) based on topographical analysis of the grand-average group data; this revealed a midline-parietal topography consistent with that

Table 1. Demographic tables as per genotype group for the P300 including age, gender, years of education, medication information and symptomatology

	Cases				*Healthy participants*			
	AA (n = *11*)	*AC* (n = *13*)	*CC* (n = *6*)	*Comparison* (P)	*AA* (n = *31*)	*AC* (n = *29*)	*CC* (n = *7*)	*Comparison* (P)
Age (years)	41 (13.7)	47.8 (11.2)	40.2 (9.7)	0.14	38.8 (11.1)	41.1 (13.3)	40.2 (9.7)	−0.69
Gender (no. of females)	5	6	0	0.09	13	18	3	−0.02
Education (no. of years)	13.5 (2.3)	12.2 (2.5)	13.3 (1.4)	−0.45	16.9 (1.3)	16.2 (2.3)	16.3 (1.7)	−0.14
PANSS positive	25.3 (3.5)	28.8 (4.5)	26.8 (7.2)	−0.16				
PANSS negative	19.1 (7.7)	19.6 (7.5)	26.0 (6.2)	−0.12				
SAPS	1.3 (0.7)	1.6 (0.7)	1.1 (1.3)	−0.4				
SANS	1.3 (0.8)	1.1 (0.9)	1.5 (1.7)	−0.40				
Chlorpromazine equivalents	753 (681)	571 (255)	296 (147)	−0.67				

Abbreviations: PANSS, positive and negative symptom scale; SAPS, scale for the assessment of positive symptoms; SANS, scales for the assessment of negative symptoms.

previously reported in the literature.[31] For statistical analysis (conducted in SPSS v.16, IBM Corp., New York, NY, USA), P300 measures were submitted to analysis of covariance with *ZNF804A* genotype (AA versus AC+CC) and diagnosis (case versus control) was entered as the between-subject factors, P300 response at each electrode site as within-subject factors, with age and gender entered as covariates. P300 amplitude was defined both as (1) the area under the curve and (2) the peak amplitude, and (versus the 0-uv baseline) in the interval 250–550 ms, spanning the P300 component.

RESULTS

No differences were observed between *ZNF804A* risk carrier versus non-risk carrier groups for age, gender or education (measured in years) in either patients or healthy controls (all $P>0.05$). For patients, no differences were observed between risk carriers and non-risk carriers in either positive symptom severity, negative symptom severity or years since diagnosis, consistent with our earlier report on the clinical effects of *ZNF804A* based on a sample of ~1000 cases.[32]

Auditory P300 ERP analyses

No significant behavioural differences in P300 task performance were observed between genotype groups (AA versus AC+CC) either for the total number of targets presented or the number of correct responses or the number of errors made (Table 2).

Contour maps of the P300 response stratified according to genotype groups for both cases and controls are presented in Figure 1, and line graphs of P300 response at each of the three representative electrodes in the midline, parieto-temporal region where response was maximal are presented in Figure 2. Both figures suggest a stronger P300 response in homozygous risk 'AA' carriers versus AC+CC carriers across both groups.

For electrode CPz, the position at which P300 response was observed to be maximal, a main effect of genotype was found both in area under the curve ($F(1,97)=7.55$; $P=0.007$) and peak amplitude measures ($F(1,97)=5.26$; $P=0.02$)). There was no interaction effect found at CPz between genotype and diagnoses groups. In case peak amplitude measures were influenced by latency variability,[33] we also ran the amplitude analysis based on mean amplitude; the significance of our results remained unchanged.

Inspection of Figures 1 and 2 further suggested that the difference in P300 response was strongest in healthy participants. Consequently, patient and healthy participants were also analysed separately; healthy control 'AA' risk carriers demonstrated significantly greater amplitudes than AC/CC carriers, again both for peak amplitude measures ($F(1,67)=5.11$; $P=0.02$) and area under the curve measures ($F(1,67)=8.23$; $P=0.006$). For cases, although the same pattern and direction of differences were observed, these were not statistically significant possibly because of the smaller number of cases available and the increased variability in response (peak amplitude ($F(1,30)=1.29$; $P=0.26$) and area under the curve measures ($F(1,30)=2.02$; $P=0.16$)).

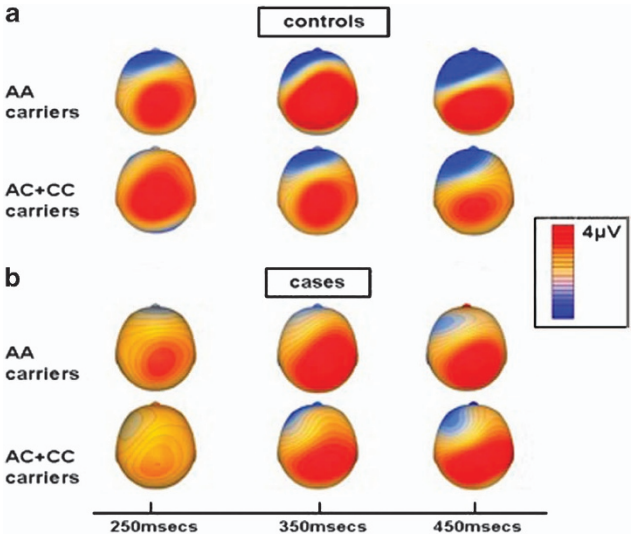

Figure 1. Contour maps of the P300 response stratified according to genotype groups (`A' risk the risk allele) for (**a**) controls and (**b**) cases. These topographic maps show the distribution of amplitude on the scalp for 250, 350 and 450 ms, the range of the P300 component.

DISCUSSION

A central tenet of the intermediate or endophenotype approach in SZ genetics research is that SZ risk is at least partly mediated by a deleterious effect on brain structure or function. Examples supporting this view include the proposed candidate genes *Dysbindin*, *COMT* and *NRG1*.[34–36] In the case of *ZNF804A*, however, an association with poorer cognition has been less clear. In the present study, we observed significant associations between *ZNF804A* genotype and variation in the P300 response. Specifically, risk allele carriers showed a relatively larger P300 response over midline scalp electrodes than noncarriers. This difference was observed as a main effect across the whole group, although *post hoc* analysis revealed the effect to be strongest in the healthy participant samples, a larger sample than was available for patients.

These findings are consistent with a number of other neuropsychological studies of *ZNF804A* published since then in which risk allele carriers outperform noncarriers,[15,16,37] though not all.[17,18] Earlier findings from our lab indicated that the *ZNF804A* risk allele was associated with relatively preserved cognitive functioning in patients.[13] In that earlier study, patients who were risk carriers showed smaller deficits in performance during both auditory and visual working memory and episodic memory tasks in large independent samples of Irish and German patients. The extent to which the P300 phenotype investigated here correlates with cognitive phenotype measures previously associated with *ZNF804A* is noteworthy. In a *post hoc* correlational analysis of 66 individuals for whom measures of both cognition and the P300 were available, a trend level positive correlation was observed in

Table 2. Mean rates times (plus s.d.) of correct and incorrect responses during the P300 paradigm

	Cases			*Controls*		
	AC/CC (n = 20)	*AA (n = 10)*	*Test*	*AC/CC (n = 36)*	*AA (n = 31)*	*Test*
Mean, no. of targets (s.d.)	41.8 (32.9)	56.8 (41.1)	t(0.33), NS	62.3 (34.2)	70.4 (33.4)	t(0.36), NS
Correct responses (s.d.)	99.1 (0.1)	111.5 (23.8)	t(0.22), NS	98.0 (30.3)	100.8 (31.5)	t(8.1), NS
Incorrect responses (s.d.)	0	0		0	0	

Abbreviation: NS, not significant.

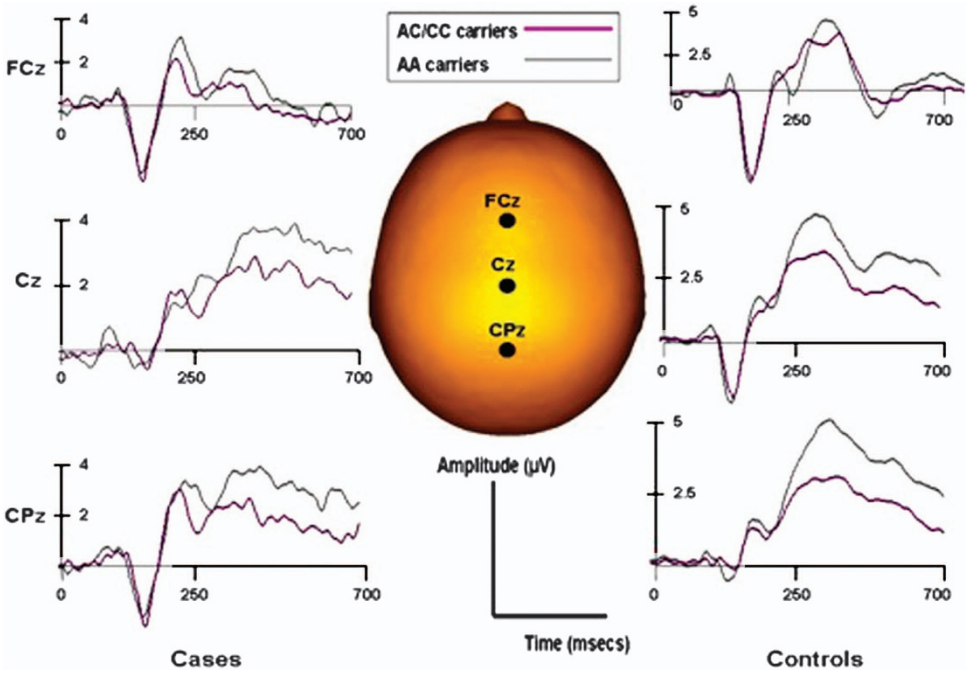

Figure 2. An overall illustration of P300 grand-average waveforms for Irish cases and controls across genotype groups (AC/CC carriers in purple; CC carriers in grey) as depicted through line graphs of P300 response at each of the three representative electrodes in the midline, parieto-temporal region where response was maximal, FCz, Cz and CPz. The effect was found to be maximal at the electrode site CPz.

working memory but not episodic memory. Although confirmation of this association in suitably powered samples is required, these data suggest that these *ZNF804A*-associated neuropsychological and EEG phenotypes are not independent and are likely to at least partly overlap phenotypically. Finally, the findings of the present P300 study is consistent with a second *ZNF804A* P300 study submitted to this journal (del Re *et al.,* manuscript submitted) based on a different oddball task. In that study, ~7% of variance in P300 response was explained by genotype. In our study, a similar amount of variance was explained: 5.7% of variance in CPz peak amplitude and 7.8% of CPz area under the curve (based on the eta-squared value for the analysis of covariance statistics undertaken).

We have previously argued that the *ZNF804A* rs1344706 risk allele may be related to a pattern of relatively preserved cognition. As an alternative to this 'preserved cognition' hypothesis, previous neuroimaging studies of other SZ risk variants have interpreted relatively increased cortical activity (in the absence or a corresponding improvement in task response behaviour) to indicate cortical inefficiency.[38–40] We had not interpreted our previous neuropsychological findings in this way because the effect was found only in patients and not controls. In this study, however, the finding of a main effect of risk carrier status on P300 response across the entire sample is more consistent with this possibility. Furthermore, increased activation in risk carriers is observed despite comparable performance at a behavioural level. On this basis, an interpretation of our findings as reflecting cortical compensatory activity to overcome *ZNF804A*-related inefficiency is also plausible in our view. One caveat to this interpretation is that while this effect was observed for the full sample, when patients and controls were considered separately, the effect remained significant for the controls only and not the patients. However, the direction of effect was the same across both samples, and the failure to achieve significance in patients may simply have reflected the smaller sample size available and the increased variability in response.

Finally, a series of reports by Esslinger *et al.*,[11,12] Walter *et al.*[19] and Hargreaves *et al.*[20] suggested that *ZNF804A* may have a deleterious effect on aspects of social cognition. There is some evidence that social cognition may be sub-served by a system of brain regions neuroanatomically distinct from those involved in 'traditional' neuropsychological processes.[41,42] If true, and social cognition is part of the mechanism by which *ZNF804A* mediates SZ risk, then the associations observed in the present study may reflect pleiotropic effects that are completely independent of the risk pathway. In considering this relationship, it is noteworthy that whereas the association with preserved cognitive performance has previously been reported in cases, and in this study as a main effect across patients and controls, the association with poorer social cognition to date has only been reported in healthy participants.

Methodological considerations

The healthy participants in this study were a subset of those who previously took part in our behavioural study and who were agreeable to return to participate in an EEG study. As previously discussed in that study, a bias towards above-average IQ healthy participants reflected the opportunistic sampling method used in recruiting through local advertising on a national volunteering website and university campus posters. It is unclear whether or how this above-average ability may have influenced the healthy participant data discussed here. The sample also included a wide age range of participants, although genotype-related differences did not appear to influence the significance of the results either when the data are inspected following stratification by age or when age is included/excluded in the analysis.

Although genotype effects were found in a total sample of 97 Irish participants, a relatively large sample for EEG research, the low frequency of the minor allele resulted in our opportunistically combining genotype groups to offset issues of small group size. Consequently, in this study, as in our earlier imaging study, we were only able to test a recessive model (comparing AA versus AC/CC carriers). Although this decision could be supported by the comparability of the 'AC' and 'CC' group, we were unable to assess any gene-dosage effects associated with this allele. Finally, the

task used in our study was designed to specifically elicit the P300 (P3b), and in so doing focused on one of the most specific, well-studied, large, easily isolated paradigms in cognitive neuroscience.[43] However, the P300 findings observed do not appear to be specific to this task as the accompanying study by del Re *et al.* (manuscript submitted) found the same effect using a different task design.

CONCLUSIONS

ZNF804A continues to be a strongly implicated common genetic variant for SZ. This study, building on previous neuropsychological evidence, suggests that *ZNF804A*'s risk carriers show higher levels of cortical activation during the P300 response in the absence of behavioural differences. We conclude that this variant, like other SZ risk variants, may be associated with increased cortical inefficiency that is reflected in the higher levels of activations required to achieve comparable behaviour.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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