ZNF804A genetic variation (rs1344706) affects brain grey but not white matter in schizophrenia and healthy subjects

I. Nenadic[1]*, R. Maitra[1], F. B. Basmanav[2], C. C. Schultz[1], C. Lorenz[1], C. Schachtzabel[1], S. Smesny[1], M. M. Nöthen[2,3], S. Cichon[3,4,5], J. R. Reichenbach[6], H. Sauer[1], R. G. M. Schlösser[1] and C. Gaser[1,7]

[1] *Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany*

[2] *Institute of Human Genetics, University of Bonn, Bonn, Germany*

[3] *Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany*

[4] *Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany*

[5] *Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland*

[6] *Medical Physics Group, Institute for Diagnostic and Interventional Radiology I (IDIR I), Jena University Hospital, Germany*

[7] *Department of Neurology, Jena University Hospital, Jena, Germany*

Background. Genetic variation in the gene encoding *ZNF804A*, a risk gene for schizophrenia, has been shown to affect brain functional endophenotypes of the disorder, while studies of white matter structure have been inconclusive.

Method. We analysed effects of *ZNF804A* single nucleotide polymorphism rs1344706 on grey and white matter using voxel-based morphometry (VBM) in high-resolution T1-weighted magnetic resonance imaging scans of 62 schizophrenia patients and 54 matched healthy controls.

Results. We found a significant ($p<0.05$, family-wise error corrected for multiple comparisons) interaction effect of diagnostic group x genotype for local grey matter in the left orbitofrontal and right and left lateral temporal cortices, where patients and controls showed diverging effects of genotype. Analysing the groups separately (at $p<0.001$, uncorrected), variation in rs1344706 showed effects on brain structure within the schizophrenia patients in several areas including the left and right inferior temporal, right supramarginal/superior temporal, right and left inferior frontal, left frontopolar, right and left dorsolateral/ventrolateral prefrontal cortices, and the right thalamus, as well as effects within the healthy controls in left lateral temporal, right anterior insula and left orbitofrontal cortical areas. We did not find effects of genotype of regional white matter in either of the two cohorts.

Conclusions. Our findings demonstrate effects of *ZNF804A* genetic variation on brain structure, with diverging regional effects in schizophrenia patients and healthy controls in frontal and temporal brain areas. These effects, however, might be dependent on the impact of other (genetic or non-genetic) disease factors.

Introduction

Schizophrenia has a substantial genetic basis, and a significant number of these genetic risk variants have recently been identified through genome-wide analyses (Sullivan *et al.* 2012). The mechanisms through which variation in risk genes, copy number variants, or rare mutations affect the developing brain and interact in its arising pathophysiology are still far from being clear. The *ZNF804A* gene (coding for zinc finger protein 804A) has been suggested to harbour common risk variants for schizophrenia (O'Donovan *et al.* 2008), which has been replicated in several studies across different ethnic groups (Li *et al.* 2012; Zhang *et al.* 2012; Schwab *et al.* 2013). The rs1344706 single nucleotide polymorphism (SNP) has been of particular interest, as it has been linked to brain structural, functional and cognitive variation (Donohoe *et al.* 2010). Two recent studies have shown an impact of *ZNF804A* rs1344706 genetic variation on cognitive function and brain activation patterns in tasks related to cognitive control (Thurin *et al.* 2013) and working memory for faces (Linden *et al.* 2013), respectively, as well as connectivity measures in healthy subjects (Paulus *et al.* 2013). As such functions are putative

* Address for correspondence: I. Nenadic, M.D., Department of Psychiatry and Psychotherapy, Jena University Hospital, Philosophenweg 3, 07743 Jena, Germany.

(Email: igor.nenadic@uni-jena.de)

endophenotypes for schizophrenia, the link to *ZNF804A* might provide an understanding on how the gene or gene products act on the biological substrates of psychosis, including schizophrenia and other psychiatric disorders (Donohoe *et al.* 2010; Hess & Glatt, 2014).

ZNF804A might, however, also affect brain development; hence, brain structural changes related to variation in one or more SNPs may thus reflect an enduring impact of the gene's function (Donohoe *et al.* 2010). A first volumetric study of *ZNF804A* (rs1344706) in healthy subjects showed larger total white matter volumes in risk-allele carriers along with reduced grey matter in the angular gyrus, parahippocampal gyrus, posterior cingulate and medial orbitofrontal gyrus (Lencz *et al.* 2010). A subsequent volumetric study in schizophrenia patients and healthy controls demonstrated an effect of the same marker on total and frontal white matter volume in schizophrenia patients (risk-allele carriers having larger volumes), but only total white matter volume in healthy controls (Wassink *et al.* 2012). A more detailed recent voxel-based morphometry (VBM) study also revealed effects on regional grey matter in schizophrenia patients and healthy controls (Donohoe *et al.* 2011), whereby homozygous risk-allele carriers for rs1344706 differed in regional grey matter of the dorsolateral prefrontal cortex, hippocampus and amygdala compared with heterozygotes and non-risk-allele homozygotes. This last study, in particular, also suggested that effects of this polymorphism might, in fact, diverge markedly between healthy controls and schizophrenia patients, i.e. that effects vary both regionally and in direction, such as findings of increased hippocampal grey matter in risk-allele homozygotes in the patient sample, but not within the control sample (Donohoe *et al.* 2011). Similarly, we found cortical thickness to show dissociated effects in patients and controls (Schultz *et al.* 2014), with risk-allele carriers within the patient group having thicker prefrontal and temporal cortices, while in the healthy control group risk-allele homozygotes had thinner cortices. Despite the existing evidence, the effects and regional distribution remain unclear, and as with many other imaging genetics findings in schizophrenia, there is a lack of replication.

In the present study, we aimed to extend the evidence for effects of rs1344706 and its risk allele (A) on brain structure in both healthy controls and schizophrenia subjects by using VBM to map regional brain structural differences on a voxel-by-voxel basis, with the particular emphasis to replicate and extend the previous findings on (*a*) the regional pattern of effects, and (*b*) the divergence of effects between schizophrenia patients and healthy controls.

Method

Subjects

We included 62 patients with a Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnosis of schizophrenia (44 male, 18 female; mean age 31.6 years, S.D.=11.5 years; all on stable antipsychotic medication) and 54 healthy controls from the community (29 male, 25 female; mean age 29.5 years, S.D.=9.9 years), who had no current or previous psychiatric treatment or diagnosis. All subjects provided written informed consent to a study protocol approved by the Jena Medical School Ethics Committee, in accordance with the Declaration of Helsinki. Groups did not differ in age (*t* test: $p=0.291$, two-tailed) or gender (χ^2 test: $p=0.055$). Groups differed in overall performance on the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest B), an estimate of pre-morbid intelligence quotient (IQ) [available for 58 schizophrenia patients and 37 controls; analysis of variance (ANOVA): $F=9.312$, $p=0.003$]. None of the subjects had any major medical or neurological condition. Part of this sample has been used in a recent analysis of *ZNF804A* effects on cortical thickness (Schultz *et al.* 2014), whereas for the present analysis, the sample has been expanded to allow analysis of a larger cohort with another methodological approach.

Genotyping using Sanger sequencing

Individual genotypes for the studied polymorphism were retrieved from sequence data generated by Sanger sequencing. Genomic DNA sequences covering rs1344706 and the flanking up- and downstream regions were retrieved from the UCSC Genome Browser based on the human genome build GRCh37/hg19 (http://genome.ucsc.edu/cgi-bin/hgGateway). Primer design was performed by keeping a minimum distance of about 150 base pairs (bp) up- and downstream from the target base. Primer sequences are obtainable from the authors upon request. Amplicons were generated under standard polymerase chain reaction (PCR) conditions. Resequencing was carried out with BigDye v3.1 (Applied Biosystems, USA) sequencing reagents employed according to the manufacturer's protocol. Data were generated on the Applied Biosystems 3130xl Genetic Analyzer, and SeqMan II (DNASTAR Inc., USA) software was used for data visualization. Electropherograms were evaluated independently by two raters.

Genotype distribution in schizophrenia patients was 23, 33 and six for AA, CA and CC, respectively, and 19, 28 and seven in healthy controls. Genotype distributions did not deviate significantly from Hardy–Weinberg equilibrium in patients and controls

($p_{patients}$=0.234, $p_{controls}$=0.504). The rs1344706 minor (C) allele frequency (MAF) observed in our samples (MAF=0.375) was very similar to the MAF observed in 1000 Genomes (MAF=0.393; http://www.1000genomes.org/). ANOVA with the factors diagnosis and genotype did not show effects of diagnosis (p=0.758), genotype (p=0.188) or their interaction (p=0.543) on the variable age. For pre-morbid IQ estimates (see above, available for 58 patients and 37 controls), there was also no effect of genotype (p=0.496), or diagnosis x genotype interaction (p=0.114), but only for factor diagnosis (as shown above).

Magnetic resonance imaging (MRI) and VBM

We obtained T1-weighted high-resolution MRI scans on a 1.5 T Siemens Magnetom Vision plus system (Siemens, Germany) using a three-dimensional Fast Low Angle SHot (FLASH) sequence (repetition time= 15 ms, echo time=5 ms, flip angle α=30°, 192 sagittal slices, field of view=256×256 mm, with voxel dimensions 1×1×1 mm^3). Images were visually inspected for artefacts and underwent automated quality control using an algorithm provided in the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm8/).

For post-processing and VBM analysis, we used the VBM8 toolbox, a freely available toolbox based on Statistical Parametric Mapping software SPM8 (Institute of Neurology, UK) and Matlab (Mathworks, USA). VBM8 is based on the general VBM approach proposed by Ashburner & Friston (2000, 2005), implementing the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm for non-linear normalization (Ashburner, 2007). Grey matter and white matter maps were extracted from MRI data for each subject and underwent non-linear normalization using DARTEL. We defined an internal grey matter threshold of 0.2 for both grey matter maps and white matter maps, thus choosing a more conservative value to limit edge effects. Smoothing was performed with a 12 mm full-width at half-maximum (FWHM) Gaussian kernel for grey matter maps and 20 mm FWHM for white matter maps. The Anatomical Automatic Labeling (AAL) toolbox was used for anatomical labelling (Tzourio-Mazoyer *et al.* 2002). In addition to regional analysis of grey and white matter, the VBM toolbox also estimates total brain grey matter and white matter volume by assigning the corresponding number of voxels to either tissue type multiplied by the voxel volumes, thus allowing analysis of effects of genotype on global parameters as well.

Statistical analysis

We first used multivariate ANOVA (with SPSS 20; IBM, USA) to test effects of genotype on total brain grey matter and total white matter volumes by defining the factors group (schizophrenia; controls) and genotype (AA; CA; CC) and the covariates age and gender (to remove variance related to these variables), and using Pillai's trace.

VBM statistics were carried out in SPM8 using a general linear model defining diagnostic group (schizophrenia; healthy control) and genotype (AA; CA; CC) while using age and gender as covariates (again, to remove their effect on variance) and applying a height threshold of p<0.001 (uncorrected) throughout all analyses. This choice of threshold was based on the existence of previous VBM analyses, as mentioned above, and thus allowed us to either replicate (or refute) previous findings in these mentioned areas, while whole-brain testing allowed us to expand analysis to other areas as well. Our main hypothesis of divergent effects of rs1344706 was tested with an interaction of group x genotype; furthermore, we also tested effects of genotype in schizophrenia patients and effects of genotype in healthy controls separately; we performed each of these three tests for both grey and white matter, respectively.

Results

Total brain grey matter and white matter

Overall multivariate ANOVA (for grey matter and white matter) revealed no significant effect of factor diagnosis ($F_{2,107}$=0.223, p=0.801) or genotype ($F_{4,216}$=1.831, p=0.124), but a significant diagnosis x genotype interaction ($F_{4,216}$=3.109, p=0.016). Tests of between-subject effects revealed significant group differences only for the interaction of diagnosis x genotype for total brain white matter ($F_{2,116}$=3.318, p=0.04), but not for grey matter ($F_{2,216}$=1.267, p=0.286) and neither for grey nor white matter for the diagnosis or genotype effects alone. Both age and gender had significant effects on total brain grey matter and white matter, respectively (both p<0.001).

VBM analysis of grey matter

In schizophrenia patients, there were several significant regional effects of genotype on grey matter (see Fig. 1), including the left temporal pole and anterior part of the inferior temporal gyrus, bilateral lateral temporal cortices, right superior temporal and supramarginal gyri, bilateral inferior prefrontal gyri, left medial cerebellum, left orbitofrontal cortex and posterior right thalamus.

In healthy controls, we found several significant regional effects of genotype (see Fig. 2), including the left middle temporal gyrus (lateral temporal cortex),
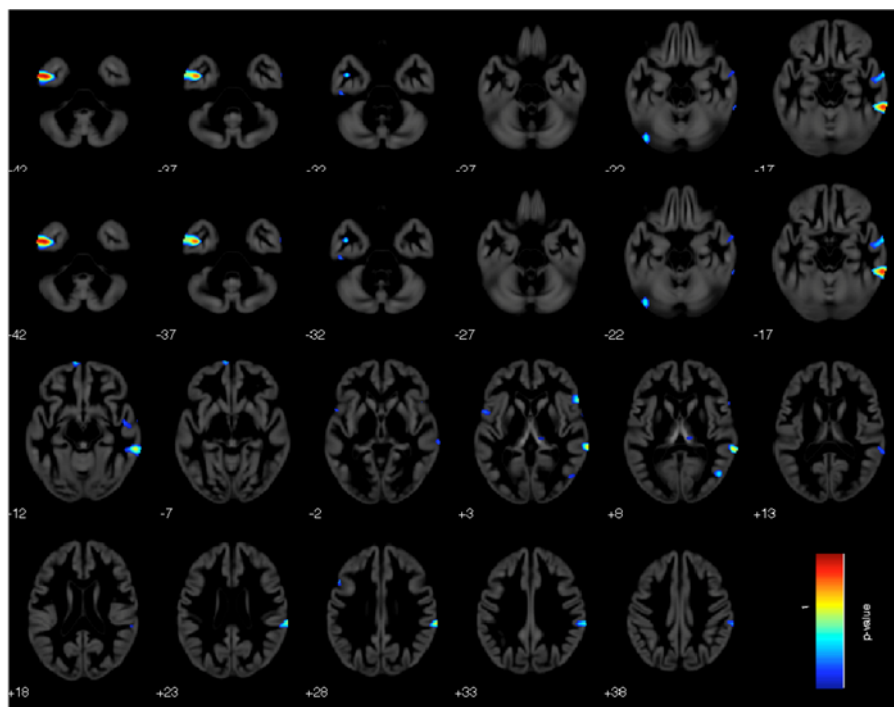
Fig. 1. Voxel-based morphometry analysis of effects of *ZNF804A* genotype (rs1344706) on grey matter in schizophrenia patients ($p<0.001$, uncorrected).
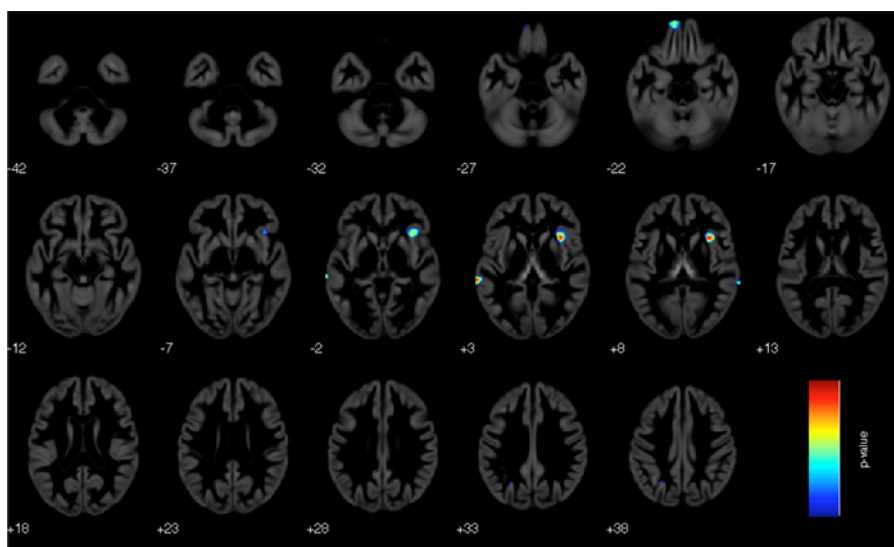

Fig. 2. Voxel-based morphometry analysis of effects of *ZNF804A* genotype (rs1344706) on grey matter in healthy controls ($p<0.001$, uncorrected).

right insular cortex, left orbitofrontal cortex and right superior temporal cortex.

The interaction analysis of diagnosis x genotype for regional grey matter also resulted in significant findings (see Fig. 3) in some of the above-mentioned clusters. Of note, parts of three of these clusters actually showed significance levels that also survived family-wise error (FWE) correction for multiple comparisons (as implemented in SPM, peak-level): one cluster in the left orbitofrontal cortex (coordinates −6, 62, −20; FWE-corrected $p=0.021$), right middle/superior temporal gyrus (69, −39, 6; FWE-corrected $p=0.029$) and left middle temporal gyrus (−68, −39, 3; FWE-corrected $p=0.034$) (see Table 1 and Fig. 4).
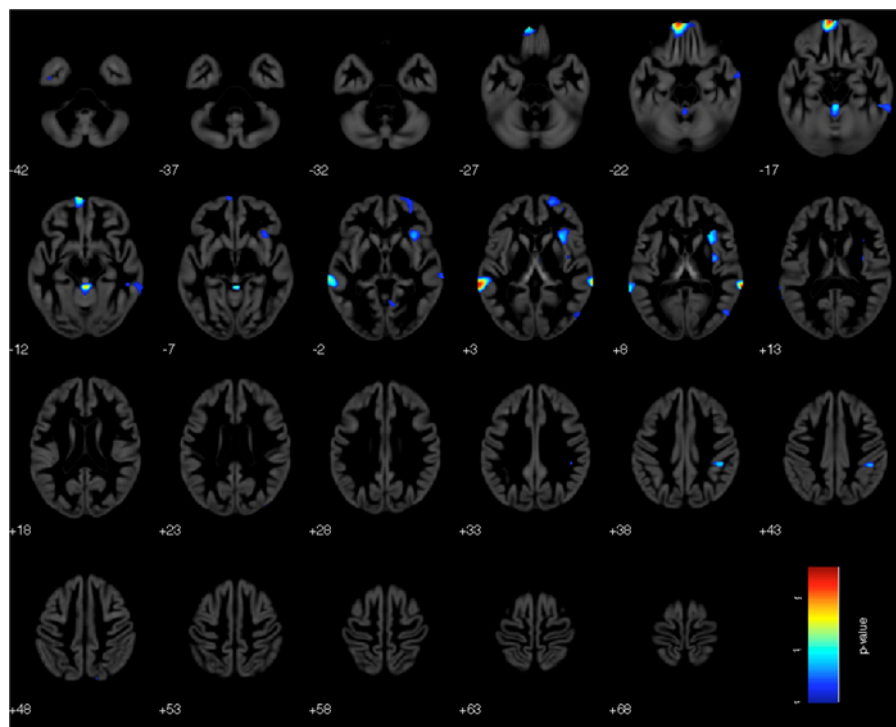
Fig. 3. Voxel-based morphometry analysis of interaction effects of *ZNF804A* genotype (rs1344706) x diagnostic group (schizophrenia; healthy controls) ($p<0.001$, uncorrected).

Results of group comparison of grey matter differences between patients and healthy controls are provided in online Supplementary Fig. S1.

In addition to the above results, we inspected the plots for profiles of genotype-related changes, i.e. to identify the subgroup contributing most to the effects. Assessing the distribution of grey matter values across the groups, a rather consistent pattern emerged. For the interaction analysis, the effect was caused by smaller grey matter values for AA homozygotes (compared with AC heterozygotes) in the healthy control group, whereas in the schizophrenia group grey matter values for AA homozygotes were higher compared with AC heterozygotes. The CC homozygotes often took an intermediary position. However, these subgroups were very small, thus making direct comparison more difficult. For the genotype effects within each group, we found that AA homozygotes in the schizophrenia group had higher grey matter values than the AC heterozygotes across all significant larger clusters. Within the healthy control group analysis, inspection of plots also confirmed smaller grey matter values for AA homozygotes (in significant clusters) in contrast to AC heterozygotes (except for the anterior insula cluster, where the two groups were similar, but CC homozygotes showed larger effects), thus confirming the overall pattern of an inverted (or diverging) effect of AA *versus* AC carrier status in schizophrenia patients *versus* controls.

VBM analysis of white matter

There were no significant effects of genotype on white matter in either schizophrenia patients or healthy controls, and no significant effects of a diagnosis x genotype interaction for white matter (all at the predefined threshold of $p<0.001$).

Discussion

As its main result, our study identified effects of *ZNF804A* on regional brain structure in the left orbitofrontal and left and right lateral temporal cortices with a significant diagnostic group x genotype interaction. In these regions, variation in rs1344706 led to diverging effects in patients and controls. Further major effects (at uncorrected levels of significance) were seen in multiple frontal, temporal and parietal cortical areas, where the gene's impact was different for the two diagnostic groups. While these findings add to the increasing identification of brain structural effects of this schizophrenia risk gene, they partially confirm a peculiar effect of this SNP. This effect is related to the markedly different impact of the SNP in patients and healthy subjects. Previous morphometry studies have already suggested such effects on grey matter density (Donohoe *et al.* 2011), as well as on cortical thickness in our own previous work (Schultz *et al.* 2014). There is also increasing evidence for *ZNF804A* effects

Table 1. *Anatomical overview of regions with significant effects (p<0.001, uncorrected) in voxel-based morphometry analysis of ZNF804A (rs1344706) genotype effects (only clusters with at least k=10 voxels listed) in schizophrenia patients, healthy controls, and interaction effects of diagnosis x genotype*

Anatomical region	MNI coordinates of maximum voxel: x, y, z	k, number of voxels
Genotype effects in schizophrenia patients ($p<0.001$)		
Left inferior temporal cortex	−50, −3, −45	1180
Right inferior (/middle) temporal cortex	64, −40, −17	664
Right supramarginal gyrus, superior temporal cortex	69, −37, 4	907
Right inferior frontal gyrus	58, 21, 3	252
Left cerebellum	−42, −78, −23	151
Left medial orbitofrontal cortex	−8, 66, −11	120
Right middle temporal gyrus	66, −1, −17	438
Right middle temporal/middle occipital cortex	48, −69, 7	181
Left lower cerebellum	−14, −81, −50	101
Left inferior frontal gyrus	−51, 15, 28	31
Left rolandic operculum/temporal pole	−56, 8, 0	120
Left inferior temporal cortex	−48, −25, −33	79
Right inferior temporal cortex	58, −1, −39	33
Right temporal pole/superior temporal gyrus	62, 3, 1	12
Right thalamus	12, −25, 6	70
Genotype effects in healthy controls ($p<0.001$)		
Left middle temporal gyrus	−68, −34, 1	181
Right insula	33, 15, 6	770
Left superior orbitofrontal cortex/gyrus rectus	−9, 57, −23	233
Right superior temporal gyrus	69, −39, 9	45
Left middle occipital cortex	−24, −60, 36	42
Interaction effects of diagnosis x genotype ($p<0.001$)		
Left gyrus rectus/orbitofrontal cortex	−6, 62, −10*	1291*
Right middle/superior temporal gyrus	69, −39, 6*	371*
Left middle temporal gyrus	−68, −39, 3*	834*
Vermis/left cerebellum	2, −40, −12	651
Right supramarginal gyrus	42, −37, 37	217
Right insula	32, 17, 7	950
Right inferior/middle temporal gyrus	52, −39, −15	364
Right insula	34, −7, 9	199
Right superior/middle frontal gyrus	20, 60, 3	535
Right middle temporal/occipital cortex	50, −72, 7	160
Right middle temporal gyrus	63, −4, −21	119
Right lingual gyrus	9, −61, −3	76
Left inferior temporal cortex	−42, −6, −42	20
Left middle occipital cortex	−38, −78, 3	11

MNI, Montreal Neurological Institute.

* Parts of these clusters are also significant at $p<0.05$, family-wise error corrected.

on brain function. Two recent electroencephalography (EEG) studies revealed an impact of rs1344706 on P300 amplitude/responses (Del Re *et al.* 2014; O'Donoghue *et al.* 2014).

Imaging genetics studies have generally aimed to evaluate the effect of particular risk genes (or risk scores) on brain structures. Often, however, it is unclear how gene expression or gene products might influence brain structure in later life. For *ZNF804A*,

there is growing evidence that effects start during early brain development. This has been shown in fetal brains, where rs1344706 variation had a strong impact on *ZNF804A* allelic expression during the second trimester of intra-uterine development, but not in adult brains (Hill & Bray, 2012). Expression in postmortem brains seems to differ between patients and healthy controls, but this observation is only incompletely understood (Okada *et al.* 2012;
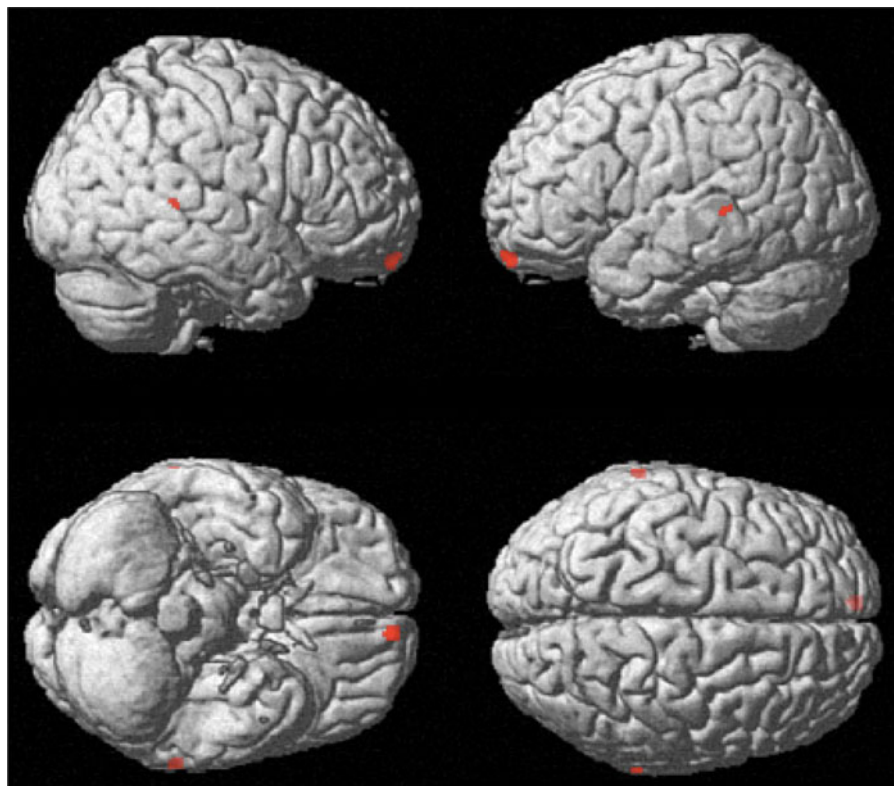
Fig. 4. Render view of voxel-based morphometry analysis of interaction effects of *ZNF804A* genotype (rs1344706) x diagnostic group (schizophrenia; healthy controls) ($p<0.05$, family-wise error correction for multiple comparisons).

Schultz *et al.* 2014), as is the regional pattern of physiological expression (Buonocore *et al.* 2010). Also, recent studies suggest an indirect action of *ZNF804A* by modulating the gene expression of other risk genes (Girgenti *et al.* 2012).

While in many instances genetic risk factors have demonstrated stronger impact of a particular risk gene in patients compared with controls, this might not be the case (at least not generally) for rs1344706. While the mentioned VBM study of Donohoe *et al.* (2011) reported preserved brain structure in patients, one volumetric study found larger regional white matter volumes in risk-allele carriers, together, however, with more severe psychotic symptoms (Wassink *et al.* 2012). In contrast, a large study of healthy subjects did not find statistically significant effects on brain structure (Cousijn *et al.* 2012). Given that volumetry, VBM and analysis of cortical thickness assess three different aspects of brain morphometry, our findings are most comparable with the studies of Donohoe *et al.* (2011) with respect to methods. In fact, these authors analysed schizophrenia and healthy control cohorts of roughly similar size to ours (using the older VBM5 toolbox). While their regional findings only partially overlap with ours (including anterior temporal pole and temporal cortical areas, although with somewhat different location), they also share

similarities. The authors reported that AA risk homozygotes showed opposite effects in patient *versus* control groups, with higher grey matter density for AA homozygotes in patients, but not controls. Similarly, effects of *ZNF804A* on cortical thickness have received support from two recent studies (Voineskos *et al.* 2011; Schultz *et al.* 2014), though there has been also one failure to replicate (Bergmann *et al.* 2013).

Functional studies, however, do suggest effects of *ZNF804A* genotypes in patients to exceed those seen in healthy controls (Rasetti *et al.* 2011). Given that there are also a number of studies demonstrating effects of rs1344706 in healthy subjects (Esslinger *et al.* 2009; Walter *et al.* 2011; Linden *et al.* 2013; Mohnke *et al.* 2014), further studies might elucidate (within the same cohort) the interaction of structural and functional effects.

Our study failed to identify any affects of *ZNF804A* on white matter density. Although VBM of white matter is inferior to diffusion tensor imaging (DTI) applications, which captures also quantitative measures of white matter damage (e.g. assessing fractional anisotropy), our results fit into the current literature on *ZNF804A* and white matter tracts. Previous DTI studies have mostly failed to confirm a clear impact of *ZNF804A* on white matter architecture or fractional anisotropy measures (Voineskos *et al.* 2011; Sprooten

et al. 2012; Wei *et al.* 2013). One previous white matter VBM study (of T1-weighted MRI) suggested an interaction of group and genotype (rs1344706) in left prefrontal white matter (Wei *et al.* 2012), but our study did not replicate this finding. In two more recent studies, one found lower fractional anisotropy in risk-allele carriers in several regions including the corpus callosum and left forceps minor (Ikuta *et al.* 2014), while a second study failed to show any significant impact of *ZNF804A* on white matter microstructure in a large healthy subject sample (O'Donoghue *et al.* 2014).

Conclusions

In conclusion, our study provides evidence for significant divergence of *ZNF804A* (rs1344706) effects on grey matter in prefrontal and temporal brain areas. Effects of prefrontal, temporal and parietal grey matter differ not only according to genotype, but the genotype-related effects are different between schizophrenia patients and controls. There was, however, no effect on white matter density. While our results confirm divergence of structural effects across different groups, further studies are needed to clarify the microstructural changes underlying these effects.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714001159.

Declaration of Interest

None.

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