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LETTERS TO THE EDITOR

Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults

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Individuals who experience child abuse are at increased risk for developing posttraumatic stress disorder (PTSD) as a direct result of the abuse and upon exposure to subsequent trauma.[1] A recent examination[1] of PTSD symptoms in adults found evidence for a significant G × E interaction involving a quantitative measure of child abuse exposure and four single-nucleotide polymorphisms (SNPs) of *FKBP5* including two SNPs for which an association of the same alleles with peritraumatic dissociative symptoms in medically ill children had been reported.[2] A study[3] of gene expression in the peripheral blood of trauma-exposed individuals found that *FKBP5* is one of many genes whose upregulation immediately posttrauma is associated with risk for emergent PTSD at 4 months. Investigations[4–6] using maternal care and separation in rodent models of child abuse have observed altered expression of genes encoding proteins involved in the stress response and, in work[6] focusing on the glucocorticoid receptor (GR), have elegantly demonstrated that epigenetic mechanisms underlie these changes. Given *FKBP5*'s role in the regulation of GR sensitivity, the G × E interaction associated with PTSD risk is likely a consequence of differential response to posttrauma alterations in gene expression resulting from one or more polymorphisms. Because animal[4,5,7] and human[3] studies have also found posttrauma changes in the expression of genes encoding $GABA_A$ (γ-aminobutyric acid) receptor subunits that affect ligand affinity at the benzodiazepine binding site, we examined whether risk for PTSD is associated with similar G × E interactions involving *GABRA2* polymorphisms and childhood trauma exposure.

Interview data from twin and sibling participants ($N = 2594$) in a recently completed family study of adult twins (only one twin from any monozygotic pair was included) with or without a history of childhood trauma were analyzed. These individuals completed a semi-structured diagnostic telephone interview modified from the SSAGA-II[8] that assessed Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) PTSD and which included a separate detailed assessment of child abuse modified from the Christchurch Trauma Inventory.[9] MPlus[10] was used to create five first-order factors for which factor loadings were allowed to vary by gender, each representing a severe childhood stressor assessed in detail (that is, sexual abuse; physical abuse by mother, by father or by other adult household member; emotional and physical partner maltreatment by a parent) from which a single second-order childhood trauma factor was created. The prevalence of PTSD in the sample was 11.5%. In logistic regression analyses that corrected for the inclusion of multiple individuals from families, significant PTSD risk was found to be associated with childhood trauma factor score (CTFS): odds ratio 8.76 (95% confidence interval 6.53–11.75).

GABRA2 genotypic data (⩽4 SNPs in any single participant) were available on a subset of 259 individuals (46 of whom met criteria for lifetime PTSD) who were also participants in a linkage study of nicotine use and dependence.[11] SNPs were selected based on prior reports of association with alcohol[12]

Table 1 Risk for PTSD associated with interaction terms involving childhood trauma factor score and GABRA2 SNP genotype ORs and 95% CIs are shown (controlling for main effects of CTFS and genotype)

SNP and risk-associated allele	*Regression with 1 term for number of risk assoc alleles*	*Regression with separate variables coded for 1 or 2 copies of risk-associated allele*	
	CTFS × number of alleles	*CTFS × 1 copy*	*CTFS × 2 copies*
rs279836 T ($N = 238$)	2.33 (1.08–5.01)*	1.10 (0.26–4.71)	6.99 (1.22–40.21)*
rs279826 A ($N = 247$)	2.25 (1.02–4.97)*	1.42 (0.30–6.73)	5.83 (1.06–32.16)*
rs279858 A ($N = 241$)	2.34 (0.98–5.60)^	1.15 (0.28–4.63)	6.91 (0.89–53.63)^
rs279871 A ($N = 209$)	3.59 (1.47–8.74)*	1.93 (0.48–7.72)	21.14 (2.26–198.14)*

Abbreviations: CTFS, childhood trauma factor score; SNP, single-nucleotide polymorphism.
*$P < 0.05$; ^$P < 0.10$.

and nicotine dependence.[13] In preparation for analyses focusing on G × E interactions, logistic regression analyses were performed to evaluate main effects of SNP genotype coded either as number of risk-associated alleles or as separate variables for the presence of one and two alleles. No significant main effects were found for SNP genotype coded in either form, including when CTFS was added to these models. The results of logistic regression analyses that included G × E interactions involving CTFS and SNP genotype while controlling for main effects of CTFS and SNP genotype are displayed in Table 1. Findings across SNPs provide consistent support for G × E interactions involving CTFS and SNP genotype (those for rs279858 fell just below significance) coded as number of risk-associated alleles. When separate variables were coded for the presence of one or two risk-associated alleles, significant G × E interactions are only found for homozygous individuals. Further analyses controlling for DSM-IV nicotine and alcohol dependence diagnoses produced remarkably similar findings (Supplementary Table 1). To ensure that our results are specific to PTSD rather than major depressive disorder (MDD) with which PTSD has considerable comorbidity, we performed similar series of analyses focusing on MDD and found no evidence for significant G × E interactions (results not shown).

The strength of our findings and their consistency with prior investigations are extremely encouraging. However, our results must be considered preliminary until they are replicated. Animal and human studies suggest that individuals who experience childhood trauma are likely to undergo epigenetic modifications that alter expression of $GABA_A$ receptor subunits affecting ligand affinity at the benzodiazepine receptor binding site.[3–7] The G × E interactions that we observed may have resulted from one or more *GABRA2* polymorphisms (the four SNPs are known to be in linkage disequilibrium with r^2 values 0.86–0.97) that contributed to PTSD development in those experiencing childhood trauma exposure, perhaps by accentuating the postevent anxiogenic response[4,5] and facilitating traumatic memory formation.[14] Limitations that must be considered when interpreting our results include the limited number of individuals for whom both phenotypic data and DNAs (hence SNP genotype results) are available. Although their selection through participation in a linkage study of nicotine dependence may have introduced some bias, findings were unchanged in analyses controlling for nicotine dependence. The degree to which our results will be generalizable to samples not enriched for childhood trauma exposure is unclear. Similarly, as a minority of PTSD in our sample arose from traumatic events whose onset occurred after age 17 (28.3%), we do not have adequate power to determine whether our findings reflect risk for incident PTSD with subsequent trauma or primarily for emergent PTSD with childhood trauma. Additional research will be necessary to address these issues and to determine the polymorphism(s) underlying our findings. Our results suggest polymorphisms of genes for which posttrauma expression changes have been observed may provide fertile ground for future genetic studies of PTSD.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Elevated serum levels of the glial marker protein S100B are not specific for schizophrenia or mood disorders

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Recently, it was suggested that the glial protein S100B is involved in the pathogenesis of both, schizophrenia

and mood disorders. Our meta-analysis demonstrates that serum S100B is higher in major depressive disorder than bipolar I disorder, although S100B might not differentiate between schizophrenia and mood disorders.

S100B is a calcium-binding protein that may act as growth and/or differentiation factor for neurons and astrocytes.[1,2] It is located in and can be actively released from glial cells, namely oligodendro- and astroglia in the human brain.[3] Accordingly, one might consider S100B as a glial marker protein. Recently, it has been discussed that S100B plays a role in the pathogenesis of mood disorders and schizophrenia.[1,2,4,5] S100B is a susceptibility gene for bipolar disorder with psychosis, schizophrenia and cognitive dysfunction.[6–8] Various studies have shown that S100B is altered in serum and cerebrospinal fluid in mood disorders and schizophrenia.[1,2,4,5] It is related to clinical symptoms, that is the severity of depression, negative symptoms in schizophrenia, and influenced by serotonergic and antipsychotic drugs.[9] To validate the specificity of serum S100B we synthesize and compare here the results from a systematic and quantitative meta-analysis for schizophrenia and mood disorders (for details such as inclusion/exclusion criteria see references Schroeter[4], Schroeter[5]). We updated the meta-analysis to June 2008 by adding another study on schizophrenia.[10]

The meta-analysis included 19 studies involving 420 patients with schizophrenia, 173 patients with mood disorders and 577 control subjects. To adjust for systematic measurement effects we calculated the effect size of each study (d) according to Cohen[4,5] as the difference of the means of the patient (m_p) and control group (m_c) divided by the standard deviation of the control group (SD_c). This measure represents normalized elevations of S100B in the patient groups. Figure 1 illustrates the results. As there are no significant differences between depressive/manic episodes and remitted mood disorder *per se* ($P > 0.05$; two-tailed unpaired Student's *t*-test; results generally adjusted for inequalities of variance as tested by Levene's test, if necessary),[5] we consider here bipolar and major depressive disorder. Serum S100B reaches high effect sizes in schizophrenia (2.02 ± 1.78), major depressive disorder (3.0 ± 1.03) and bipolar I disorder (1.4 ± 0.44; mean ± s.d.; $T = 4.25$, 5.82, 6.4; degrees of freedom, d.f. = 13, 3, 3; $P = 0.001$, 0.01, 0.008; two-tailed one-sample Student's *t*-test against 0). Effect size was higher in major depressive disorder than bipolar I disorder ($T = 2.84$, d.f. = 6, $P = 0.029$), without significant differences in comparison with schizophrenia ($T = -1.03$, 0.68; d.f. = 16, 16; $P = 0.317$, 0.509; two-tailed unpaired Student's *t*-test). The effect remained significant if we included only studies investigating drug-free patients with schizophrenia (1.94 ± 1.33; $N = 7$; $T = 3.86$; d.f. = 6; $P = 0.008$; two-tailed one-sample Student's *t*-test against 0). For mania in bipolar I disorder and depression in major depressive disorder only two studies with drug-free patients were available, each reporting high effect sizes (1.62, 3.3). Our results support the hypothesis that S100B is involved in the pathogenesis of both, schizophrenia and mood disorders. Though S100B might not differentiate between schizophrenia and mood disorders, it dissociates mood disorders, namely major depressive and bipolar I disorder.

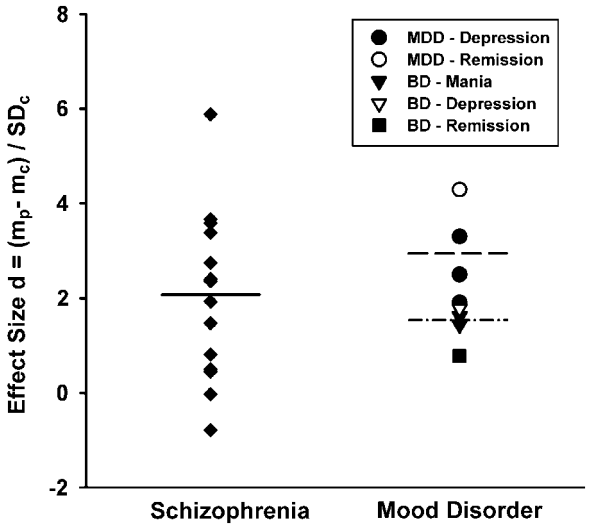

Figure 1 Effect sizes of S100B serum concentration in schizophrenia, and mood disorders for the single studies as identified by the systematic meta-analysis. BD, bipolar I disorder; MDD, major depressive disorder. Median is shown for schizophrenia (solid), major depressive disorder (dashed) and bipolar I disorder (dashed and dotted line).

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The relationship of anterior thalamic radiation integrity to psychosis risk associated neuregulin-1 variants

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Patients with schizophrenia, bipolar disorder and their unaffected relatives show white matter density and integrity reductions in the anterior limb of the internal capsule (ALIC).[1,2] These deficits have been recently localized to the anterior thalamic radiation (ATR) using tractography.[3] Neuregulin-1 (*NRG1*) is a gene associated with risk for schizophrenia[4] and bipolar disorder[5] as well as with white matter density and integrity in the medial prefrontal cortex[6] and the ALIC.[7] In this study, tractography reveals that these NRG1 effects can also be localized to the ATR.

The genotypes of two NRG1 single nucleotide polymorphisms (SNPs), SNP8NRG243177 and SNP8NRG221533, were determined from the DNA of 34 healthy control subjects using PCR (TaqMan, AssayByDesign). The number of subjects in each genotype group did not significantly deviate from the Hardy–Weinberg equilibrium for either SNP (TT = 6, CT = 12, CC = 16; TT = 17, CT = 13, CC = 4; Pearson's χ^2-tests: $P = 0.19$; $P = 0.54$). As expected, the SNPs were in linkage disequilibrium (Pearson's χ^2-test = 41.16, $P < 0.00001$, $D' = 0.9$). The genotype groups did not significantly differ with respect to sex, age, IQ (NART), alcohol consumption or education level. No subjects had a history of harmful substance misuse. The study was approved by the local ethics committee and all participants gave written informed consent.

Whole-brain diffusion-tensor imaging (DTI) data were acquired on a 1.5 T MRI scanner using a single-shot pulsed gradient spin-echo echo-planar imaging sequence with diffusion gradients ($b = 1000\,s\,mm^{-2}$) applied in 51 non-collinear directions. Forty-eight 2.8 mm contiguous axial slices were acquired with a field of view of 220 × 220 mm (TR = 17 s, TE = 93.4 ms and matrix = 96 × 96, zero-filled to 128 × 128).

The imaging data were pre-processed using the FSL toolbox (FMRIB, Oxford, UK). Left and right ATR were automatically segmented in each subject using neighbourhood tractography[8] as previously implemented.[3] The resulting tracts were checked by eye, blind to genotype group, and those that were truncated, branched or deviated from the expected anatomical structure were discarded. A mean fractional anisotropy (FA) value, weighted according to the likelihood of connection between the voxel and the seed point, was calculated for the left and the right ATR in each subject. (See Supplementary Material for a more detailed description of the acquisition methods and tractography analyses.)

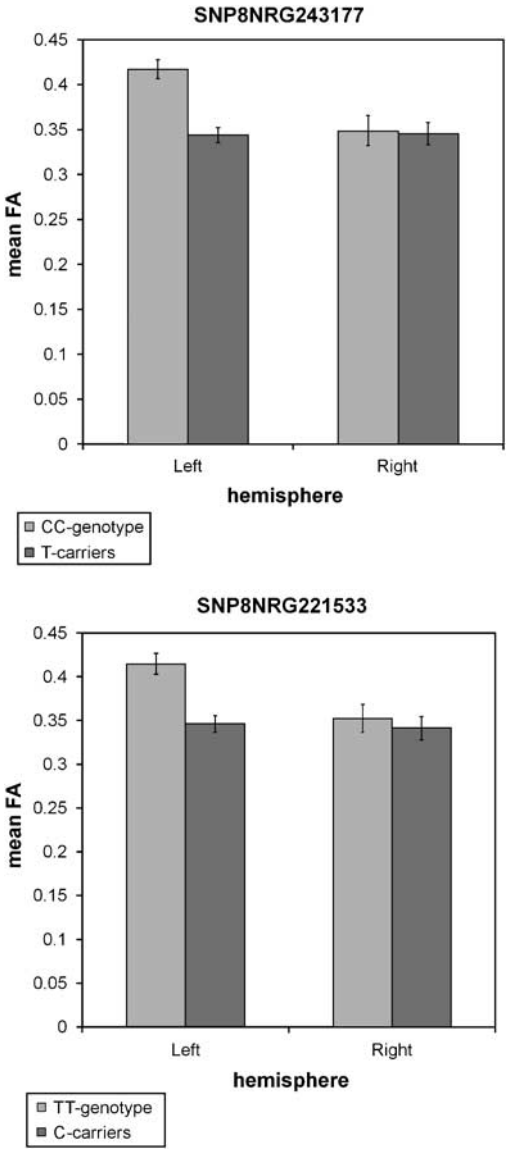

Figure 1 Effects of SNP8NRG243177 and SNP8NRG221533 genotypes on mean FA of left and right anterior thalamic radiation (ATR). The differences were significant for the left ATR only. SNP8NRG243177: $t = 5.52$ ($P < 0.001$); SNP8NRG221533: $t = 4.69$ ($P < 0.001$).

A total of 28 people provided usable tractography data for subsequent statistical analyses. The CT and TT groups were merged together in a T-carrier group to improve statistical power. The mean FA values of left and right ATR of each subject were analysed with SPSS (version 14; SPSS Inc.). Results were similar for both SNPs. Mixed model repeated-measures analyses with hemisphere as within-subject factor and FA value as dependent variable revealed that there were significant hemisphere × genotype interactions for both SNPs ($F = 14.138$, $P = 0.02$; $F = 7.18$, $P = 0.015$). Subsequent *t*-tests for each hemisphere separately (for both SNPs) resulted in a significant genotype effect for the left hemisphere only (Figure 1).

Here, in the first DTI tractography investigation of NRG1 and white matter integrity, we show that both the two risk-associated variants of NRG1, the 'T' allele at SNP8NRG243177 and 'C' allele at SNP8NRG221533, are associated with reduced white matter integrity in the left ATR. As the SNPs are in strong linkage disequilibrium, it is possible that both are indexing the same genetic effect. Although previous voxel-wise FA analyses have localized the effects of these SNPs to seemingly different anatomical regions,[6,7] the present data demonstrate that these effects may be common to a specific tract, the ATR.

It has been previously established that NRG1-erbB expression is important in axonal migration and myelination.[9] The ATR connects the dorsomedial and anterior thalamic nuclei with the prefrontal cortex. If psychosis-risk-related variants of NRG1 disrupt this connection, as we show here, this provides a possible explanation of the abnormal prefrontal function and connectivity often reported in psychosis, and a potential mechanistic link between variation in *NRG1* genotype and risk for psychotic disorders.

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