Risk variant for schizophrenia in the neurogranin gene impacts on hippocampus activation during contextual fear conditioning Open

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Dysfunction of the hippocampus constitutes a core finding in schizophrenia. In the current study, we observed diminished hippocampal activations during the acquisition of contextual fear in healthy carriers of the genome-wide supported risk variant for schizophrenia, rs12807809 in neurogranin.

Key features of schizophrenia, a highly heritable (60–80%), severe and common mental disorder, are declarative memory and contextual processing deficits.¹ Considerable research associated those impairments with structural and functional abnormalities in the hippocampus.² A recent genome-wide association study identified a relationship between schizophrenia and the single nucleotide polymorphism rs12807809 in the neurogranin gene.³ Neurogranin is abundantly expressed in the hippocampus, a key region of contextual learning and discrimination, where it is involved in the formation of spatial memory and long-term potentiation in the CA1 region via the postsynaptic control of calmodulin availability during synaptic plasticity induction.⁴ Earlier research trying to explore the effect of rs12807809 on brain functioning focused on tasks primarily mediated by the prefrontal cortex and did not detect any influence of neurogranin on cognition in schizophrenia.⁵

Contextual fear conditioning is highly hippocampus dependent⁶ and heritable (35–45%)⁷ and constitutes a paradigm that is well suited to examine the impact of rs12807809 on cognitive and contextual processing. During contextual fear conditioning, an originally neutral context is presented several times together with an unconditioned threat stimulus and subsequently becomes a conditioned context, which elicits conditioned anxiety responses.⁸ Impairments of contextual processing, for example, the interpretation of ambiguous stimuli based on the current spatial or temporal context or the inappropriate influence of distant contextual stimuli on performance, have been reported for schizophrenia (for a review, see Hemsley¹) and represent a vulnerability factor for the development of the disorder.⁹

Hence, we employed an imaging genetics approach in healthy volunteers to investigate the influence of rs12807809 on the hippocampus during a contextual fear conditioning paradigm using structural as well as

functional magnetic resonance imaging (fMRI). The investigation of healthy participants permitted the investigation of a possible differential impact of the variant on hippocampal function unconfounded by variables typically present in patients (for example, medication or epistasis with other risk variants). To assess conditioning performance, we additionally quantified skin conductance responses as well as self-report measures. Furthermore, neuropsychological variables and hippocampal volumes were determined (see Supplementary Material for details).

A total of 112 healthy volunteers of Caucasian descent (mean age (s.d.): 22.2 (4.1), 39 female), who previously underwent our conditioning paradigm were genotyped for rs12807809. Three of the study participants were CC homozygotes, 33 CT heterozygotes and 76 TT homozygotes (in Hardy–Weinberg

Figure 1 Decreased hippocampal activation during acquisition of contextual fear in carriers of the rs12807809 risk allele (TT, $N=76$) compared with rs12807809 homozygotes (TC/CC, $N=36$). (a) Contrast ($CS+ > CS-$; $x = -24$, $y = -37$, $z = -2$, $k = 37$; $t = 3.54$, $P < 0.05$) is family-wise error corrected (FWE) for the region of interest (ROI). Note that colors indicate t -scores. (b) Weighted-mean scores ($CS+ > CS-$) in the ROI separate for left (red) and right (green) hippocampus during late acquisition.

equilibrium: $P=1.00$). Given the small number of CC individuals we pooled subjects carrying at least one C allele and compared them with TT homozygotes ($N=76$). Both groups were comparable with respect to demographic variables and memory performance (see Supplementary Information).

Functional scans were acquired with an 1.5 Tesla scanner (Siemens, Erlangen, Germany) using an echoplanar imaging sequence and analyzed with SPM8. We used the General Linear Model to investigate genotype effects on the neural response to context conditioning. T1-weighted structural scans were conducted to manually assess hippocampal volumes with BRAINS2 (see Supplementary Information for details).

The skin conductance responses and self-reports in both groups showed that subjects learned successfully to differentiate dangerous from safe contexts (see Supplementary Information). On the structural level, no differences in the hippocampal volumes were found. However, homozygous T-allele carriers showed significantly decreased activations in the left hippocampus during acquisition (see Figure 1), indicating impaired hippocampal activity during contextual learning.

Schizophrenia is a complex disorder and many factors contribute to the development of the fully-fledged phenotype, ranging from behavioral to neural characteristics. In our current sample of healthy subjects we could not find any differences on a behavioral level, however, the observed decreased hippocampal activation during contextual learning might represent a vulnerability factor for the development of schizophrenia. This corroborates previous findings from conditioning studies with 30–50% of schizophrenic patients showing no learning at all. Additionally, neuroimaging studies found decreased hippocampal activity during memory tasks in schizophrenics.¹⁰ As independent replication of our results is necessary, conclusions must remain preliminary. However, investigating the impact of neurogranin on neural correlates of contextual processing in patients suffering from schizophrenia might further enhance our understanding of the disorder.

Conflict of interest

The authors declare no conflict of interest.

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Identification of tag haplotypes for 5HTTLPR for different genome-wide SNP platforms

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The length polymorphism repeat (5HTTLPR) in the promoter region of the serotonin transporter gene (SLC6A4, also known as 5HTT) is extensively studied in the context of psychiatric phenotypes, particularly in major depressive disorder. However, investigation of this polymorphism in the context of the current generation of large-scale genome-wide association studies is precluded, as the genotyping technology is limited to single-nucleotide polymorphisms (SNPs). Using genome-wide and 5HTTLPR genotype data from a total of 2823 unrelated individuals, we show that no single SNP is in high linkage disequilibrium (LD) with 5HTTLPR but some