Neural Mechanisms of a Genome-Wide Supported Psychosis Variant

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For over a century, disturbed interactions between brain areas have been proposed to underlie schizophrenia (*1*). Extensive work in patients (*1*, *2*) has demonstrated abnormal coupling between structures implicated in schizophrenia, dorsolateral prefrontal cortex (DLPFC) and hippocampal formation (HF), but the relevance for heritable risk was unclear. Through genome-wide association study and followup, a single nucleotide polymorphism (SNP) in *ZNF804A*, rs1344706, was recently found to be associated (*3*) with psychosis, affording an opportunity to establish neurogenetic risk mechanisms.

In 115 healthy genotyped German participants, we used functional magnetic resonance imaging (fMRI) and a well-validated executive cognition probe, the n-back task, related to heritable schizophrenia risk, DLPFC and HF activity, and candidate gene variation (*4*) [see (*5*) for task details and table S1 for sample description]. We studied task-related regional activation of DLPFC and HF and coupling between these structures. For this, we used "functional connectivity" (*2*), an established method that measures correlation between fMRI time series: two regions are functionally connected if their activities are significantly correlated. Although the robustness of this measure has not been formally established [but see (*6*)] and it is not directly indicative of structural or causal connections, functional connectivity has been used successfully to delineate the functional anatomy in health and schizophrenia (*2*) and the impact of genetic variation (*4*). Because rs1344706 has also been implicated in bipolar disorder (*3*), we also used an emotional face-matching task that shows altered activation and connectivity of amygdala linked to neuroticism and genetic risk for mood disorder (*4*). Cognitive probes were used as strong activators of neural systems to investigate genotype effects (a reverse genetics approach) (*4*). Rs1344706 effects on activation and connectivity were mapped across the brain by using the general linear model; because this entails multiple tests, we followed procedures shown to exert strong control of type I error in imaging genetics (*7*).

Regional brain activation was not significantly related to genotype [see (*5*) for result details], but connectivity of the most activated DLPFC locale was strongly altered (Fig. 1, A to C): In risk-allele carriers, connectivity both within DLPFC (same side) and to contralateral DLPFC was reduced. Conversely, the HF was uncoupled from DLPFC in non–risk-allele homozygotes but showed dose-dependent increased connectivity in risk-allele carriers. Lastly, the risk allele predicted extensive increases of connectivity from amygdala (Fig. 1D and table S2), including to hippocampus, orbitofrontal cortex, and medial prefrontal cortex. Rs1344706 genotype had no impact on performance [reaction time and percentage of correct answers (table S1)], and we did not find correlations between behavior and connectivity (*5*) (table S3), indicating that genetic variation is more penetrant on the neurobiological (imaging) phenotype level, as expected for intermediate phenotypes (*4*).

Because rs1344706 was associated with schizophrenia at a genome-wide level (*3*) and we used procedures that strongly control type I error (*7*), our findings establish dysconnectivity as a core neurogenetic mechanism, where reduced DLPFC connectivity could contribute to disturbed executive function (*1*) and increased coupling with HF to deficient interactions between prefrontal and limbic structures (*2*). Because amygdala connectivity is not implicated in genetic risk for schizophrenia (*6*), the observed effects on limbic connectivity might relate to bipolar disorder, where increased connectivity of amygdala has been observed and could contribute to emotional instability. More generally, our findings show that rs1344706, or genetic variant(s) in linkage disequilibrium (i.e., variants that are nonrandomly related), is functional in human brain. The molecular changes leading up to altered neural systems function remain to be elucidated. We speculate that, because genetic variation in dopaminergic and glutamatergic neurotransmission affects DLPFC or HF connectivity (*4*), examination of ZNF804A in those neurotransmitter cascades is warranted, as is its role in white matter development and plasticity. Lastly, our findings validate the intermediate phenotype strategy in psychiatry by showing that mechanisms underlying genetic findings supported by genome-wide association are highly penetrant in brain, agree with the pathophysiology of overt disease, and mirror candidate gene effects (*4*). Confirming a century-old conjecture by combining genetics with imaging, we find that altered connectivity emerges as part of the core neurogenetic architecture of schizophrenia and possibly bipolar disorder, identifying novel potential therapeutic targets.

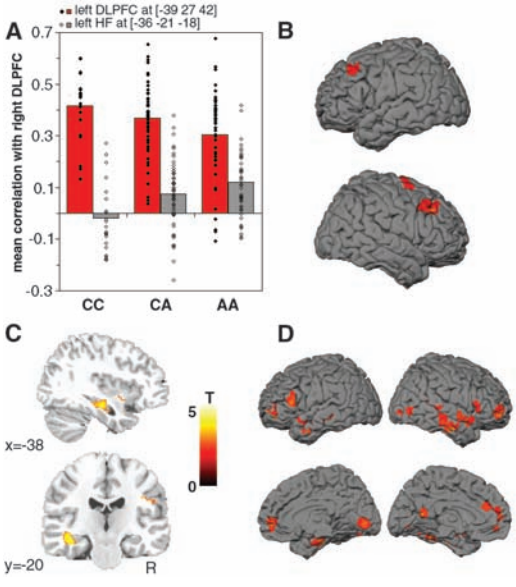

Fig. 1. (**A** to **C**) Altered functional coupling of the right DLPFC in rs1344706 risk-allele carriers. (A) Correlation coefficients (columns represent mean of Fisher *z*-transformed coefficients) reflecting connectivity with right DLPFC by genotype: connectivity with left DLPFC [at (–39 27 42)] shown as red columns and solid diamonds, connectivity with left HF [at (–36 –21 –18)] as gray columns and open diamonds. (B) Frontal brain regions where genotype predicts reduced connectivity with right DLPFC. (C) Brain regions in temporal lobe where genotype predicts increased correlation with right DLPFC. Thresholded for display at $P < 0.005$ within a cluster of more than 20 contiguous voxels. (**D**) Increased functional coupling of right amygdala in rs1344706 risk-allele carriers. Voxels significant at $P < 0.05$, false discovery rate corrected for multiple testing, are displayed.

References and Notes

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Supporting Online Material

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References

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