bilaterally (all p< 0.02), with the non-improving patients having a decreased reward response compared to healthy controls and the improving patients. Repeated measure ANOVA showed a significant group*time interaction, most pronounced in left caudate (p=0.001), with the healthy controls and the improvers decreasing and the non-improvers increasing in reward anticipation activity after treatment.
Conclusion: The identified subgroup of patients improving in negative symptoms can be characterized by older age, more severe negative symptoms and a more pronounced improvement on total and general PANSS score. Further, they had a normal function of the reward system at baseline, while non-improving patients initially showed decreased striatal reward-activity. This finding together with the normalization of striatal reward disturbance following treatment in non-improving patients suggests that striatal reward disturbance might not be related to the negative symptom domain. The results are preliminary and analyses of specific negative symptom items and possible reward disturbances in prefrontal regions are planned.
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A POLYGENIC SCORE OF DRD2 CO-EXPRESSION PREDICTS BOLD ACTIVITY DURING WORKING MEMORY PERFORMANCE

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Background: Co-expressed genes are likely to be co-regulated and to cluster together in contributing to explain phenotypic variance. Genetic variants in the D2 dopamine receptor pathway are associated with schizophrenia and its intermediate phenotypes, like working memory (WM) cortical activity. However, it is not known whether DRD2 genetic variation is part of a common pathway characterizing risk for schizophrenia phenotypes. We hypothesized that novel genetic variants associated with transcription levels of genes in the D2 interactome would be associated with dorsolateral prefrontal (DLPFC) activity during WM performance.
Methods: Weighted gene co-expression network analysis identifies clusters of co-expressed genes (modules) based on transcriptome microarray data (Braincloud [1]). The sample included 199 subjects with postnatal age and RNA integrity estimate >7.0. We selected the module including the probe for the mRNA of the D2L isoform of the D2 dopamine receptor and computed its first principal component (module eigengene, ME). D2L receptors are mainly post-synaptic and are known to modulate WM physiology. We used ANOVA to investigate associations between SNPs within the module genes and the ME. We collapsed the effects of these SNPs into a polygenic score (PS) negatively correlated with the ME (R squared=0.4). A sample of 125 participants performed the 2-back WM task during fMRI and we associated the PS of each participant with DLPFC activity during 2-back.
Results: The module included 85 genes and was enriched for genes involved in DNA packaging (DAVID, corrected p=.009). The ME explained 33% of the module variance and was associated with eight SNPs surviving FDR correction for multiple comparisons at a threshold suitable for polygenic traits (corrected p<.25 [2]). DLPFC activity during WM negatively correlated with the PS (whole-brain cluster level Bonferroni corrected p<.05; PS explained 23% of the variance).
Conclusion: Shared variance among co-expressed genes was associated with genetic variants which also modulate a well-known intermediate phenotype of schizophrenia. Results are consistent with the established role of D2L in the DLPFC further suggesting that DRD2 is part of a common pathway. The robust fMRI statistics suggest that investigating ensembles of genes is relevant to understand the relationship between specific molecular pathways and specific brain/behavioral traits.
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COMPARATIVE HERITABILITY OF BRAIN STRUCTURE AND FUNCTION IN SCHIZOPHRENIA

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Background: The heritability of the brain's structure and function in schizophrenia remains elusive.
Methods: Total brain, grey and white matter and hippocampal volumes were established from structural MR images from twin pairs varying in their zygosity and concordance for schizophrenia. Brain function was indexed using a verbal fluency functional probe.
Results: Whole brain, grey and white matter volumes were significantly heritable, while the hippocampus was more environmentally sensitive. There was a significant phenotypic correlation between schizophrenia and reductions in all the brain volumes except for left hippocampus. For whole brain and grey matter and the right hippocampal volumes the aetiological links with schizophrenia were principally due to shared family environment. Patients and their unaffected relatives developed greater activation in the left inferior frontal gyrus, and greater deactivation in the left hippocampal and middle temporal gyri bilaterally. When the analysis was restricted to the unaffected relatives and healthy controls, a similar pattern was evident, with the unaffected relatives showing greater inferior frontal and left superior temporal activation, and greater right medial and lateral temporal deactivation. Genetic modelling indicated a phenotypic correlation between schizophrenia and increased activity in the inferior frontal gyrus and reduced activity in the left middle temporal gyrus and left hippocampus.
Conclusion: Whole brain, grey and right hippocampal volume reductions and altered frontal, medial and lateral temporal activation are linked to schizophrenia. The volume changes principally through correlated familial risk, which is probably linked to the shared familial environment, Altered medial and lateral temporal activity may be more intimately linked to the genetic risk for schizophrenia. The degree of influence of aetiological factors varies between brain structures and their function, leading to the possibility of a neuroanatomically specific aetiological imprint.
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