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Altered DLPFC-hippocampus connectivity during working memory independent replication and disorder specificity of a putative genetic risk phenotype for schizophrenia

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Schizophrenia (SCZ) and bipolar disorder (BD) and to a lesser degree major depressive disorder (MDD) are highly heritable psychiatric disorders that cause great suffering to those afflicted by them as well as to their relatives and society in general. In recent years, considerable progress has been made with regards to identifying the genomic variants that are associated with these disorders, especially for SCZ, which has been at the forefront of psychiatric genetics. However, the biological mechanisms underlying these complex disorders are still poorly understood. This is due to the fact that the behavioral symptoms that characterize these disorders are highly emergent phenomena that result from a complex interplay of biological factors but are also responsive to environmental factors. To move closer to the genetic basis of these disorders, researchers have therefore focused much effort on the study of intermediate phenotypes. Intermediate phenotypes are heritable phenomena that are associated with the genetic predisposition for disease and manifest at an intermediate place in the pathological pathway from genes to behavior. A particularly promising intermediate phenotype for SCZ has been deficient working memory processing, whose neurophysiological correlates can be objectively and reliably measured with modern in vivo neuroimaging methods like functional magnetic resonance imaging (fMRI). A well-established method called functional connectivity aims to assess deficient working memory processing by measuring the correlation of brain activity between regions that are crucial for working memory performance. Prior research has shown, that patients with SCZ, their first-degree relatives as well as healthy carriers of a genomic variant associated with psychosis but even animal models of SCZ show an altered functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and the hippocampus.

This thesis could show, that first-degree relatives of patients with SCZ show altered DLPFC-hippocampus functional connectivity during working memory. This confirms evidence from a prior study and thereby strengthens the case for altered DLPFC-hippocampus connectivity as an intermediate phenotype for SCZ. The demonstration of this phenotype in unaffected first-grade relatives is particularly important since it suggests that altered DLPFC-hippocampus connectivity is not merely an epiphenomenon of the disorder. By providing a truly independent replication, following a rigorous, methodical approach, which accounts for a wide-range of potential confounds, this thesis provides an important contribution to a field which is vulnerable to false-positive findings.

The second part of this thesis expands current knowledge by testing for altered DLPFC-hippocampus connectivity in first-degree relatives of patients with BD and MDD, which have a strongly overlapping genetic basis. Since especially BD shares roughly 80% of the genetic basis with SCZ and shows similar clinical manifestations, most prominently in the form of psychosis, the outcome of no differences in BD and MDD relatives as compared to controls is somewhat surprising. However, this suggests, that altered working memory processing in the form of altered DLPFC-hippocampus functional connectivity is related to the genetic variance that is unique to SCZ making it a promising candidate for elucidating the pathological components specific to SCZ.