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From genetic variants to biological pathways in neuropsychiatric traits

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This thesis contains a collection of genetic studies that address different neuropsychiatric traits and use different analytic approaches. The main objective of all studies was to identify genetic variants, genes or biological pathways for neuropsychiatric traits. The different chapters of my thesis illustrate the rapid advances made in the research field of neuropsychiatric genetics. In this final chapter, I summarize the findings of my research, followed by a general discussion of several topics that were central in my thesis and future directions in this research field.

1. Summary

The first part of this thesis describes two different methods to identify genetic variants, genes and biological pathways for Attention-Deficit/Hyperactivity Disorder (ADHD). In **chapter 2**, we investigated ADHD symptom scores in a large meta-analysis of genome-wide association studies (GWAS) in population-based pediatric cohorts. Analyzing these cohorts allowed us to study ADHD related behaviors in a much larger sample than the available samples containing ADHD diagnosed individuals. It has been suggested that a diagnosis of ADHD can be regarded as the extreme end of a continuous distribution of inattentive and hyperactive behaviors. Indeed, we showed that ADHD symptom scores and an ADHD diagnosis have strong genetic overlap ($r_g = 0.96$), suggesting that the same genetic factors underlie both phenotypes. Our GWAS of 17,666 children did not result in genome-wide significant loci, but we did detect three gene-wide significant genes, of which one is involved in neuronal development. Combining data from population-based and clinical cohorts to increase sample size and improve statistical power for GWAS will be a next step to identifying genetic variants for ADHD.

In **chapter 3**, we applied a different approach to test the hypothesis that synaptic function is involved in ADHD etiology. We performed a functional gene-set analysis to test whether synaptic processes are associated with ADHD. Gene-set analysis tests the joint effect

of multiple genetic variants in groups of functionally related genes, in order to increase statistical power compared to conventional GWAS. Nevertheless, we did not identify specific synaptic function categories for ADHD. Given the sample size of the study and the gene sets based on the biological knowledge at that time, our results do not support a large effect of common genetic variants in synaptic genes on ADHD. Larger sample sizes will be required to study a possible role of synaptic genes with smaller effects on ADHD.

We continued with investigating additional psychiatric disorders, with a focus on the genetic overlap between different disorders, which I describe in chapter 4. Because mounting evidence shows genetic overlap between multiple psychiatric disorders, we aimed to identify biological pathways that can explain this shared risk. By applying gene-set analysis combining data on five psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder (ASD), and ADHD), we found postsynaptic, neuron projection and brain-expressed sets of genes. Interestingly, not only the adult-onset disorders showed overlap in their associations with these sets, the childhood-onset disorders contributed to part of the gene-set associations as well. This suggests that specific biological functions play a role in the etiology of several psychiatric disorders across the life span.

The previous three studies utilized data of common genetic variants to investigate the etiology of neuropsychiatric disorders. However, rare genetic variants have been suggested to play an additional role. In chapter 5 we investigated the contribution of rare coding variants to the genetic architecture of alcohol consumption and tobacco use using data from the ExomeChip from eight research groups. We were not able to identify genome-wide significant rare variants in single-variant and gene-based tests for alcohol consumption and number of cigarettes per day despite large sample sizes of 12,466 and 7,432 individuals, respectively. Our results imply that rare variants in the exome with large effects do not contribute to variance in the two substance use traits.

In the final study of this thesis described in chapter 6 we performed a GWAS on a large sample of 113,006 individuals. The GWAS and gene-based analysis revealed several novel loci and genes for insomnia complaints, with *MEIS1* showing the strongest association. *MEIS1* has been related to restless legs syndrome (RLS) before and we showed a likely pleiotropic effect of *MEIS1* on both conditions. Sex-specific analyses suggested sex-specific as well as shared genetic factors across males and females. Furthermore, we showed substantial positive genetic overlap with internalizing and metabolic traits and a negative overlap with subjective well-being and educational attainment. These findings provide novel insight into the genetic architecture of insomnia complaints.