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The merit of details: Dissecting the categorical diagnoses of psychiatric disorders

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Psychiatric disorders are highly heritable, however, it is a disenchanted fact that only a few variants contributing to the genetic susceptibility of psychiatric disorders have yet been successfully identified. This might be due to the clinical heterogeneity of the disorders. In this thesis, clinical features were defined in order to subphenotype specific subgroups of individuals that are supposed to be internally more homogeneous for etiologically relevant genes than clinical populations meeting broad diagnostic criteria of psychiatric disorders. Additionally, it was explored whether biologically more homogenous subphenotypes can be identified by varying instruments and whether studying age-dependent effects of susceptibility variants is of help in order to clarify inconsistent association results.

In study 1, the aims were to characterize the clinical symptomatology most strongly influenced by the bipolar disorder (BP) susceptibility locus *NCAN* and to explore the behavioral phenotype of Ncan knock-out (Ncan-/-) mice. Principal component and genotype association analyses were used to derive main clinical factor dimensions from 69 lifetime symptoms, and to determine which of these factor dimensions drive the association with the *NCAN* risk allele in patients with BP (n=641) and the genetically related disorders major depression (n=597) and schizophrenia (SCZ) (n= 480). In Ncan deficient mice a range of behavioral traits were assessed, including paradigms corresponding to bipolar symptoms in humans. In the combined patient sample, the *NCAN* risk allele was significantly associated with the "Mania" factor dimension, in particular the subdimension "Overactivity". Comparable to humans the Ncan deficient mice were hyperactive, and showed more frequent risk-taking and repetitive behaviors, less depression-like conduct, impaired pre-pulse inhibition, amphetamine hypersensitivity, and increased saccharin preference. These aberrant behavioral responses were reversed by the administration of lithium.

In study 2, the aim was to identify associations with symptom dimensions derived by a factor analytic approach at a genome-wide level. A principal component analysis was performed for 48 clinical lifetime symptoms in 927 BP patients. A genome-wide significant association with the factor dimension "Negative Mood Delusions" (*delusions of poverty, delusions of guilt, nihilistic delusions*) with the G-allele of rs9875793 was observed (allelic $\chi 2$ model: $P_G = 4.65 \times 10^{-8}$, OR= 2.66). Case-control analyses demonstrated that the G-allele of rs9875793 was associated with a specific subphenotype of BP. The G-allele of rs9875793 was uniquely overrepresented in the subgroup of patients with "Negative Mood Delusions" symptoms in comparison to control subjects (P_G=0.0001, OR=1.92). This specific overrepresentation of the G-allele in patients with "Negative Mood Delusions" symptoms in comparison with control subjects was independently observed in an European American sample (P_{EA}=0.028, OR=1.27). In this study, the feasibility of factor dimensions in clinical practice was demonstrated, as further support for the initial findings was observed simply screening patients for particular symptoms.

In study 3, the aim was to replicate the previously reported associations of the *NRG3* variant rs6584400 with psychotic symptoms and attention performance, and to explore whether these findings might be extended to BP. In the study 358 patients with SCZ and 111 patients with BP were included. The association between the number of rs6584400 minor alleles and psychotic symptoms in SCZ was replicated. Additionally, in both SCZ and BP patients, minor allele carriers of rs6584400 outperformed homozygous major allele carriers in the TMT. These significant findings suggest that the *NRG3* variant rs6584400 is implicated in the genetic susceptibility to cognitive deficits in both SCZ and BP. Further, these results provide evidence that with differing instruments genetic associations with subphenoypes of psychiatric disorders can be successfully identified.

In study 4, the aim was to explore whether genetic variation modifies the vulnerability to aging processes of the human brain. In focus was the C allele of the *SCN1A* variant rs10930201, recently observed to be significantly associated with poor short-term memory performance at a genome-wide level of significance. The interacting effects of the *SCN1A* vulnerability allele rs10930201 and age were examined in terms of brain activity and brain morphology in sixty-two healthy volunteers aged between 21 and 82 years. In C allele carriers, activity in the right inferior frontal cortex and the posterior cingulate cortex increased with age. Moreover, exploratory analysis revealed regional effects of rs10930201 on brain morphology. The results underline that the assessment of age-dependent genetic effects is of great value.

In sum, the present studies provide evidence that genetic research may benefit from approaches reducing the heterogeneity of psychiatric phenomenons. The subphenotyping approach has proven to configure a feasible strategy to identify genetically more homogeneous subgroups across diagnostic boundaries, facilitating the identification of susceptibility genes. Further, it has been shown that genetic associations with specific subphenotypes are replicable and studying interacting effects of age and genes is a potential strategy to clarify inconsistent results and to identify new susceptibility variants for cognitive decline.