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Transdiagnostic signatures of functional brain responses during reward processing in the extended moods-psychosis spectrum

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The development of valid and feasible dimensional models of diagnostic classification on psychopathology engaged the psychiatric research community for the last decades. One influential research framework, the Research Domain Criteria initiative, characterizes mental functioning along basic domains. One domain implicated in a broad range of psychiatric conditions is the Positive Valence System which summarizes responses to positive motivational stimuli and subsumes different sub processes, such as reward responsiveness, reward anticipation, reward learning and reward valuation. Specifically, alterations in reward anticipation, centrally involving the ventral striatum, are a well-established observation in a range of psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder and autism spectrum disorder. This thesis investigated reward anticipation across mental disorders and focused on the relationship between transdiagnostic, categorical and dimensional approaches to psychiatric nosology. Specifically, the comparison of reward network alterations between distinct disorder groups was supplemented by investigating dimensional brain-behavior relationships, system-level circuit abnormalities and a novel potential endophenotype for psychosis.

Both presented studies consistently observed categorical group differences in ventral striatal activation during reward anticipation between healthy controls and patients with severe mental disorders, most prominently on the psychosis end of the extended moods-psychosis spectrum. This provides further evidence to the transdiagnostic relevance of this phenotype. In order to investigate whether shared or distinct psychological processes lead to the observed alterations, we applied a data-driven, explorative approach in study 1 and showed that neurocognitive behavioral measures covering aspects of affective, cognitive and social functioning were dimensionally and transdiagnostically related to markers of altered reward network processing. These results suggest that distinct brain-behavior relationships exist across nosological boundaries which point to shared underlying neural mechanisms and challenge more disorder-specific mechanistic theories of ventral striatal dysfunction.

Extending on these more explorative findings, study 2 used a more hypothesis-driven approach and proposed a new endophenotype for schizophrenia. In line with preclinical models of psychosis the activation of the reward system induced an overall reduction of functional connectivity between the ventral striatum and the hippocampus in psychotic but not mood disorders, that 1) was reduced in first-grade relatives with psychotic but not mood disorders, 2) related to polygenic risk scores for schizophrenia in a subset of healthy subjects, and 3) was associated with behavioral dimensions of positive and cognitive but not negative symptoms. This study provides evidence that ventral striatal-hippocampus coupling during reward processing is an endophenotype for psychotic disorders and relates to dimensional, clinically meaningful behavioral domains across the psychiatric spectrum.

Interestingly, both studies showed associations between blunted reward network functioning and indicators of cognitive performance measures (i.e., general cognitive functioning and memory performance) highlighting the role of cognitive abilities for transdiagnostic reward network alterations. In line with neurocognitive models of mental disorders this might suggest that cognitive control constitutes a domain- and disorder-unspecific pathophysiological mechanism in psychiatric conditions that might help to explain domain-specific transdiagnostic alterations, such as blunted reward network functioning.

Future studies are warranted to further build on our findings. First, large-scale, pre-registered, multi-site and multi-diagnosis research can reduce the inconsistencies between smaller-sized studies. Second, studies should further improve imaging protocols and ensure high data quality and comparability of patient and control data. Third, investigators should incorporate dimensional, behavioral measures using a comprehensive and ideally consistent neuropsychological test battery that also allows a

hierarchization of basic functioning domains with a specific focus on cognitive functioning. Overall, I believe that the presented results add to current disorder-specific mechanistic theories of ventral striatum dysfunction, can inform the development of pharmacological and therapeutic interventions and show the value of combining the strengths of traditional and modern attempts to classify mental disorders.