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Exploration of the biological mechanisms in neuropsychiatric disorders using multimodal imaging

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The present doctoral thesis focused on the multimodal imaging investigation of brain mechanisms in neuropsychiatric disorders, emphasizing on the research questions of whether and how neurochemistry is associated with brain anatomical structures and brain functions. The aim of the thesis is to provide a biochemical insight underlying the altered brain morphology and functions in the two disorders studied, which might ultimately offer evidence for novel therapeutic implications. There are two brain imaging projects included in this thesis.

In project I, the first aim was to explore the mechanism of partial volume recovery during the first two weeks of abstinence from alcohol at a whole-brain level. The hippocampus was then chosen as a seed region, to investigate the abstinence-induced neurochemical changes and whether the hyperglutamatergic state induced by alcohol withdrawal may affect GM volume recovery in the hippocampus. We found cortical thickness alteration corresponds to the partial cortical volumetric recovery. Moreover, alcohol differentially impacts on sulci and gyri of the neocortex. Sulci are more susceptive to excessive alcohol consumption and abstinence-induced recovery. Lower subcortical volume was found in alcohol dependent patients at withdrawal, and no subcortical volume regain was observed during the initial two weeks of abstinence. In support of a 'hyperglutamatergic state' induced by withdrawal, our rat model demonstrated elevated Glu/Gln ratios during acute withdrawal (12h and 60h after stopping alcohol intake) and a trend towards an increase in Glu levels at 12h compared to control rats. The main novel finding of this study was that in both species a negative association was found between Glu markers and GM volume in the hippocampus after alcohol withdrawal (but not during withdrawal), suggesting that this tissue damage is a consequence of withdrawal and results from withdrawal-induced hyperglutamatergic neurotoxicity.

In project II, the study emphasized the additional value of multimodal imaging analyses to unravel group differences between BPD patients and HCs which could not be detected by BOLD response and ACC GABA levels per se. The superior aim was to explore the interrelationship between GABA, neural correlates of interference inhibition, and impulsivity traits in BPD. We found task-related functional connectivity and the association of fMRI measures with MRS derived GABA levels are significantly different between the two groups. These analyses give support for a disconnection of the fronto-striatal network during interference inhibition in BPD patients that is related to elevated impulsivity ratings, specifically the UPPS sensation seeking score. Our hierarchical analyses also give first evidence for the hypothesis that the fronto-striatal network during inhibitory control serves to mediate the association between ACC GABA levels and impulsivity symptomatology in patients with BPD. In other words, GABAergic transmission in the ACC drives the inhibitory-related fronto-striatal brain network, whereas the disruption of fronto-striatal connectivity is of core relevance to the sensation seeking symptom in BPD patients.

Taken together, multimodal imaging fusion analysis of neurobiochemistry - structure/function relationship can offer opportunities to deepen our understanding of neurobiological mechanism of brain disorders.