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A network perspective: The mediation of cognition by anatomical brain connectivity

Autor: Andrea Victoria King
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktormutter: Prof. Dr. M. Wessa

Objectives

Major challenges in research on the relationship between anatomical connectivity and cognition include a possible structure-function specificity and contributions to both impaired and preserved cognitive functions in neurodegenerative diseases. Therefore, this thesis investigated whether associations between properties of white matter tracts and a measure of response inhibition are specific to an a priori-defined network of fronto-basal ganglia connections and whether they are specific to response inhibition per se. In patients with memory deficits at a probable Alzheimer's disease prodrome, it was investigated how properties of anatomical connections contribute to impaired and preserved aspects of feedback-guided learning, which probes interactions between brain circuits mediating emotion and memory.

Methods

To determine a structure-function specificity for a network mediating response inhibition, connections between prefrontal, medial frontal and striatal regions as well as the corticospinal tract, that served as control pathway, were delineated using Diffusion Tensor Imaging (DTI) and probabilistic fiber tractography in a sample of 93 healthy adults. Correlations between several microstructural fiber characteristics and measures of stop-signal response inhibition, attention and processing speed were calculated in a tract-of-interest approach as well as in a whole-brain approach. To investigate contributions of tract characteristics to aspects of feedback learning in prodromal Alzheimer's disease, a network of connections between prefrontal, medial temporal and subcortical structures was delineated in 24 patients with amnestic mild cognitive impairment (aMCI) and 20 healthy controls in a similar approach. Correlations between local microstructure and measures of learning by positive feedback and learning by negative feedback were performed again in a tract-of-interest approach.

Results

Significant domain-specific associations between response inhibition and DTI metrics of fractional anisotropy (FA) and radial diffusivity (RD) were found in fibers connecting primarily right-hemispheric structures of STN region, preSMA/SMA, striatum and IFGoper in the tract-of-interest approach. In the whole-brain analysis, additional significant clusters were identified in the corpus callosum, optic radiation, inferior fronto-occipital tract and white matter of the precentral gyrus. However, a step-wise multiple regression analysis yielded FA in tracts connecting preSMA/SMA to the STN region and striatum, respectively, and RD in fibers connecting IFGoper to the STN region as best predictors of response inhibition performance (42% explained variance). In patients with aMCI, impaired learning from positive feedback and preserved learning from negative outcomes was found on a behavioral level. Among the pathways mediatng feedback learning, decreased FA and increased RD of fibers connecting the left-hemispheric amygdala to both hippocampus and entorhinal cortex was observed in aMCI patients. Interindividual variability of DTI metrics in these tracts was also associated with learning from positive outcomes. Microstructure of right-hemispheric tracts between amygdala and entorhinal cortex was related to learning from negative feedback, and was not compromised in aMCI patients.

Conclusions

On the one hand, the findings point to a specific contribution of white matter pathways connecting distinct basal ganglia structures with both medial frontal and ventrolateral prefrontal regions to

response inhibition. On the other hand, the results provide new insight into how variability in microstructure of anatomical connections contribute to both impaired and preserved aspects of learning behaviors in the early Alzheimer's disease process. The findings might have practical implications for diagnostic accuracy, allowing earlier detection of Alzheimer's disease even at the preclinical stage, and yield starting points for research on therapeutical interventions that make use of compensation strategies. Beyond the clinical sphere, the results might encourage future studies to elaborate brain networks for distinct aspects of cognition by combining structural and functional imaging methods.