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Corticostriatal circuitry function and plasticity during working memory learning

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Corticostriatal brain circuitries play an essential role in basic and high-level functions of the human brain, such as motor control, goal-director behavior, cognition, as well as learning and memory. Growing evidence supports a “gating” function of basal ganglia, particularly the striatum, within the motor and cognitive domains. Study 1 of this thesis was conducted as a cross-sectional functional magnetic resonance imaging (fMRI) study in a sample of 74 healthy participants performing a Sternberg working memory (WM) task to investigate whether striatal activation during working memory varies across task phase (i.e., encoding and retrieval) and stimulus familiarity (novel vs. practiced items). Further connectivity analyses (using dynamic causal modeling) were applied to explore by which corticostriatal connectivity mechanism the task-phase specific involvement of the striatum is achieved (i.e., top-down or bottom-up control). Activation analyses demonstrated a highly significant engagement of the anterior striatum, particularly during the encoding of novel WM items. Dynamic causal modeling (DCM) of corticostriatal circuit connectivity identified a selective positive modulatory influence of novelty encoding on the connection from the dorsolateral prefrontal cortex (DLPFC) to the anterior striatum. These data extend prior research by further underscoring the relevance of the basal ganglia for human cognitive function and provide a mechanistic account of the DLPFC as a plausible top-down regulatory element of striatal function that may facilitate the “input-gating” of novel working memory materials. The brain derived neurotrophic factor (BDNF) promotes neural synaptic growth and has become the most widely studied neutrophin. Growing evidence demonstrates that a specific *BDNF* polymorphism, *Val66Met*, impacts memory performance and brain function, resulting in poor performance and abnormal brain activity or connectivity in risk-allele carriers (Met allele carrier). Study 2 of this thesis was conducted in a longitudinal approach, over a two-week learning period with regular fMRI acquisition and additional 14-week follow-up measurement. The aim was to characterize learning-induced changes in cognitive behavior and brain function and its modulation by effects of the *BDNF Val66Met* genotype. Therefore, a sample of 23 healthy subjects performing a modified Sternberg WM task was examined, and exponential decay modeling (i.e., learning curves) was applied using the parameters τ (learning speed*)* and α (learning gain*)* to examine learning-induced effects. Behavioral analyses demonstrated that *BDNF* risk allele carriers (Met allele carriers) showed significant WM deficits at the beginning and at the 14-week follow-up measurement (i.e., long after the training interval). Interestingly, Met allele carriers were able to compensate for the initially disadvantageous effect by repetitive training. The behavioral WM deficits could be directly linked to a delayed signal decay in the DLPFC and a lack in the increase in corticostriatal connectivity in Met allele carrier. Further, a faster and higher increase in functional connectivity resulted in a higher follow-up performance, indicating the importance of forming a connectivity “scaffold” for long-term consolidation, which seems to be limited in *BDNF* risk allele carriers. These results extend prior knowledge by demonstrating immediate and long-term WM learning deficits and impaired neural plasticity in *BDNF* risk allele carriers. Taken together, this thesis highlights the role of corticostriatal circuits for WM learning and may provide new insights into the relationship between regulated BDNF signaling on short-term and long-term plasticity.