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Fronto-striatal plasticity processes in humans: glutamatergic and genetic mechanisms

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This thesis investigated fronto-striatal plasticity processes in the human brain via a multilevel (genes, brain, behavior) and multimodal neuroimaging (functional- and structural magnetic resonance imaging, magnetic resonance spectroscopy) approach. Neuroplasticity—an intrinsic property of our nervous system—can act in fronto-striatal circuits, specifically in the 'motor-loop'. Within this circuitry, the striatum, as key structure, and glutamate, as important neurotransmitter, enable the acquisition and automatization of motor skills (e.g. playing an instrument). On a molecular level, brain-derived neurotrophic factor, a neurotrophin, is known to influence cellular plasticity processes, and a single-nucleotide polymorphism of the brain-derived neurotrophic factor gene (*BDNF* val^{66}met), has been related to impairments in hippocampal learning and plasticity in humans. However, research and respective findings on the influences of this genetic variant in motor skill learning within the fronto-striatal motor-circuitry remain fragmented.
135 healthy right-handed subjects (mean age = 26.96 +/- 9.05 years, 80 females, 54 Met allele carriers) participated in this study. They received training on a sequential visual isometric pinch task in the laboratory and motor skill learning was measured via increases on a speed-accuracy trade-off function (skill measure). Subsequently, magnetic resonance imaging was performed. For functional magnetic resonance imaging, an adapted version of the pinch-force task was used, consisting of the trained, a novel and two control conditions. Furthermore, structural magnetic resonance imaging and magnetic resonance (glutamate) spectroscopy was conducted. Genomic DNA was extracted from whole blood according to standard procedures. Data were analyzed using classical toolboxes for brain imaging data (SPM8, VBM8), for spectroscopy data (LCModel) as well as Matlab-routines and statistics programs for behavioral data and further analysis. To validate the structural neuroimaging results, data of an independent replication sample of 286 healthy right-handed subjects (mean age = 33.39 +/- 9.8 years; 154 females, 101 Met allele carriers) were analyzed.
The behavioral results indicated that skill measure constantly increased across the training period. Further analysis also revealed a significant difference in motor skill learning among carriers of the *BDNF* val^{66}met polymorphism (i.e., impairment in motor skill learning in Met allele carriers). On a structural level, the same individuals also tended to have significantly greater gray matter volume in the striatum, a finding that was replicated in the validation sample. Neurochemically, Met allele carriers did not have altered resting state striatal glutamate concentration or deviations from Val allele carriers in any other of the measured metabolites. Functional neuroimaging data demonstrated strong task-effects within a cortico-striatal motor network and plausible training-related brain activations. However, no functional alterations in (training-related) activity within the fronto-striatal motor network for carriers of the Met variant were observed.
The behavioral findings of this study complement previous findings on deficits of Met allele carriers of the *BDNF* val^{66}met polymorphism in long term motor skill learning and reinforce our understanding of the molecular basis of this functional variant. The observed structural effects were interpreted as a compensatory mechanism for hippocampal deficits and are discussed in light of the limitations of the present study. The non-significant genotype results on glutamate concentration and (training-related) brain function are also consistent with the prior literature. Furthermore, this pattern of results points to the distinct qualities of the three neuroimaging methods used in this study and highlights the uniqueness of this multilevel and multimodal neuroimaging approach to study fronto-striatal learning and plasticity processes in humans. The scientific and possible clinical implications of these findings were discussed.