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Dissertations-Kurzfassung

D_2 Antidopaminergic Modulation of Brain Structure, Brain Function and Behavior

Autor: Heike Tost
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. A. Meyer-Lindenberg

A wide range of human phenotypes are modulated by the impact of dopamine signaling on the frontal lobes. In line with this concept, several neuropsychiatric model disorders of dopamine dysfunction have been associated with abnormalities in these domains, in particular deficits in voluntary motor control, cognitive performance, and neuroimaging markers of prefrontal efficiency, and neuronal plasticity. However, the interpretation of existing empirical data on dopamine-related deficit symptoms in patient populations is often complicated by the presence of medication confounds, especially in schizophrenia. This multimodal pharmaco-neuroimaging study aimed to disentangle some of these confounding factors by examining the effects of a single dose of the dopamine D_2 antagonist haloperidol (5mg per 70kg) on motor behavior, cognitive performance, motor loop function, and brain structure in healthy human subjects. At the level of cognition, the work examined the predictive value of dual-state model of prefrontal function by Seamans and Durstewitz. In line with the prediction of the model, a receptor-dependent cognitive performance profile was observed; while those functions presumed to be D_2-sensitive proved to be significantly impaired (i.e., attentional set shifting), the presumed D1-sensitive or nondopaminergic domains remained largely unaffected (i.e., working memory). This outcome provides evidence for the ecological validity of the examined model, and supports the conclusion that different dopamine receptor subtypes in the brain modulate cognitive functions in a task-specific way. Furthermore, the findings suggest that some (but not all) of the prefrontal deficits in medicated schizophrenia patients might be induced by antipsychotic agents. At the level of brain function, this study examined the predictive validity of cortical-striatal-thalamic-cortical network model in the scenario of motor task performance under acute D_2 receptor blockade using fMRI – with mixed results. While the observed significant drug-induced decreases in functional response in the frontal cortex are well in line with the model's prediction, the evidenced functional decrease in the striatum contradicts the notion, that a metabolic increase, as previously evidenced in resting-state studies, is the only possible outcome of the drug-induced downregulation of the indirect basal ganglia pathway. In line with other accumulating evidence in the literature, the outcome of this study questions the utility of over-simplistic models of basal ganglia function. In addition, a pronounced drug-induced increase in functional lateralization was detected in higher order motor cortices; this finding strongly suggests that prior reports on lateralization abnormalities in medicated patient populations should be interpreted with caution, as they are likely impacted by drug-related confounds. At the level of brain structure, this is the first study to demonstrate rapid, reversible alterations in striatal gray matter volume and connectivity induced by a D_2 antagonist in healthy humans. The temporal profile of these changes reflected the pharmacokinetic profile of haloperidol and predicted, with high accuracy, the severity of drug-induced motor impairments. Here, the work demonstrates that the identified mechanism promotes the formation of acute extrapyramidal symptoms by impacting the structural and functional coupling properties of the cortical-striatal motor loop, and underscores the critical relevance of dopamine D_2 receptor signaling for short-term human plasticity.