5.8 Summary and Conclusion

This thesis investigated the relevance of striatal GABA levels for action control processes. Neurocomputational models suggest that the striatal microcircuit constitutes an inhibitory network that performs response selection. The efficiency of this network increases with inhibitory strength and is dependent on unimpaired cell functioning. A novel combination of MRS, EEG, fMRI and behavioural data was applied to examine the relation of striatal GABA levels with action control and its electrophysiological correlates as well as activity in fronto-striatal networks. To investigate mechanism underlying superior performance, APTs were compared to age-matched controls. Higher striatal GABA levels were predictive for better task performance in all three action control core functions. This is the first direct demonstration of the importance of striatal GABA and MSN functioning for action control processes and corroborates neurocomputational models of the striatal microcircuit. The MRS signal primarily reflects extrasynaptic GABAergic tonic inhibition that plays an important role for the regulation of network excitability and information processing. Thus, it is plausible that higher GABA levels enhance action control by optimizing the regulation of network dynamics resulting in sharper signal selection, more reliable synchronizational processes, and flexibility between functional network states. The effect of GABA is mediated by enhanced attentional gating, increased reliability of neuronal synchronization processes, and higher BGN network activity. Especially mechanisms related to D1 functioning likely contributed to these results which points to a stronger tonic inhibition of D1 MSN. Superior performance in APTs stems from an increased effect of striatal GABA, likely mediated by potentiated receptor function or altered strength of connectivity in fronto-striatal circuits.

Modulation of GABAergic transmission seems to relate to cognitive performance through an inverted U-shaped function. This may be the result of positive effects mediated by extrasynaptic GABA$_A$Rs which have a higher sensitivity to many modulators, whereas negative effects due to overstimulation of synaptic GABA$_A$Rs only emerge at high doses (see figure 5). To gain insight into these processes future studies should selectively target synaptic and extrasynaptic GABAergic inhibition in the striatum and fronto-striatal circuits. Furthermore, implementing tonic inhibition, mechanisms of volume transmission and differential extrasynaptic receptor density on MSN into computational models may further elucidate the exact mechanism of striatal GABA and move modelling closer towards actual anatomy and physiology. Finally, understanding the role of GABA in fronto-striatal circuits together with
its dysfunction in related diseases will pave the way for emerging treatment targeted at this transmitter system.

References


