Networks of action control
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In isolation, no single node in the brain can achieve the goal of deliberately initiating or inhibiting a planned action. To understand how we implement action plans this dissertation focused on co-activation, and examined how different regions within our brain work together as a network. In the following sections I will summarize and interpret the obtained results, while arguing how the relay of information between the cortex and basal ganglia is key in the implementation of all controlled actions. Before concluding, I will discuss some limitations of our current approach, and outline possible future directions.

A hyperdirect-indirect route to stop all actions

In the last decade, a consistent body of literature had identified the rIFG, preSMA, and the basal ganglia as key nodes in the process of full response inhibition (for a review see Chambers et al., 2009; Aron, 2011). However, in humans a direct comparison of dominant models that could best explain the activity pattern within and among these regions was missing. In chapter two, we aimed to fill this gap by using an region of interest (ROI) approach in combination with the ancestral graphs method to test specific hypotheses about two well-defined fronto-basal ganglia pathways associated with the process of response inhibition. We identified the optimal model when the hyperdirect and the indirect pathway were combined in one model. The reliability of these findings was assessed in chapter four, where again the combined hyperdirect-indirect model was best predictive for the pattern of brain activation during both reactive and proactive stop trials. In addition, the overall model strengths of the hyperdirect-indirect model were found to be higher for successful stopping as compared to failed stopping. Based on these findings, we propose that both the hyperdirect and indirect pathways play a crucial role in the process of response inhibition and work together to implement control on trials where participants are required to fully stop a planned response. In addition, we propose that when the communication between the key areas in the hyperdirect-indirect route is more efficient, suppression of basal ganglia output with downstream inhibitory effects on the primary motor cortex (M1) is more likely to succeed.

The dynamics of top-down projections map onto the behavioral efficiency to stop

Another important observation in chapter two was made when we inspected the relationship between behavioral indices of response inhibition and top-down con-
connection strength of the hyperdirect-indirect model. On successful stop trials, the individual efficacy to fully stop a response (SSRT) was differentially predictive for the strength of effective connectivity from cortical areas (rIFG and preSMA) to the striatum. Participants who had higher connection strengths between the preSMA and the striatum needed more time to stop a response, whereas higher connection strengths between the rIFG and the striatum were related to shorter SSRT. This relationship was further supported by the strong negative relationship between the two cortex to striatum connections. On failed stop trials, we found that the amount of experienced interference as indexed by the Simon effect was predictive for effective connectivity in the hyperdirect-indirect model. Participants who experienced more interference also had a stronger connection between the preSMA and the striatum. From a theoretical perspective, the striatum is thought to weigh all incoming information to facilitate the selection and implementation of actions, while simultaneously suppressing competing alternatives. When planned responses need inhibition, stronger connection strengths from the preSMA might reflect an increased level of observed conflict (i.e., go is now changed in stop), while projections from the rIFG into the striatum help to update the relevance for an inhibitory act. On a broader perspective, the close relationship between performance control and the fronto-basal ganglia connections point toward a top-down mechanism that underlies inhibitory action control.

Proactive control: neural mechanisms and connectivity networks

Chapters three and four focused on the neural indices of proactive response inhibition. In chapter three, we examined proactive inhibitory control using a conditional stop paradigm. Participants were asked to stop planned responses when a beep followed (for example) a right button press signal (“critical” direction), but to keep on going when a beep followed a left press signal (“noncritical” direction). In chapter four, a probabilistic stop task (i.e., where cues indicate the likelihood of stop signal presentation) was used to examine strategic response adjustments when participant anticipate an increased chance of stop signal presentation. In both chapters, proactive inhibitory control was reflected in increased reaction times and accuracy levels during go trials when the need of potential stopping was higher (either indicated by a cue, or critical direction). The results of formal mathematical analysis of go trial responses further indicated that participants become more cautious when the probability of a stop signal presentation is increased. In chapter three, fMRI analysis of go trial data comparing “critical” with “noncritical” trials found increased activity in regions typically used for “reactive stopping” (i.e., rIFG, preSMA, STN, striatum). In addition, a greater degree of slowing on “critical” go trials was related to a higher level of activation within these regions. Chapter four supported these results, and further showed that when the likelihood of a stop-signal was increased, the hyperdirect-indirect model was proactively and fully recruited on go trials. These findings indicate that when the likelihood of stopping is increased, participants are motivated to prepare a
stop plan proactively even when the signal for response inhibition is omitted.

The strategic gain of proactive preparation

In *chapter two*, we suggested that top-down control of the basal ganglia mostly involves the communication of conflict (i.e., between new and already prepared action plans) and the need to actively update or change prepared action plans. But what if preparation reduces conflict, and so removes the need to actively change prepared plans. One possibility could be that the advance preparation of multiple action plans (i.e., a plan to go and stop) reduces the reliance of the basal ganglia on the prefrontal cortex to gate selected actions. Support for this hypothesis was found in *chapter four*, where we compared top-down connection strengths from the cortex into the basal ganglia during reactive and proactive stop trials. That is, when the likelihood of a stop trial presentation was small, actual stop trials were accompanied by stronger top-down projections from the rIFG and the preSMA into, respectively, the striatum and STN to accomplish successful response inhibition. These top-down projections were weaker when participants were expecting stop-signals, and had already prepared the hyperdirect-indirect network proactively. These findings suggested that top-down control is strongest in an unpredictable environment, where the prefrontal cortex plays an important (updating/conflict resolving) role in the implementation of new salient plans (i.e. change go to stop now). Importantly, these results further indicate that the advance preparation of action plans reduces the need for reactive top-down control of the basal ganglia, making the prefrontal cortex more available for other internally maintained goals.

A sensory informed route for perceptual action selection

In *chapter five*, we examined how the cortex and basal ganglia interact to select and initiate action plans. To define a desired motor output, we often integrate sensory information from our environment with abstract goals and response plans. Most theories of action selection have focused on the interplay between the goal-oriented prefrontal cortex (PFC) and the basal ganglia. In *chapter five*, we examined how information from sensory regions is integrated into this circuit to facilitate response selection. We further investigated the dynamics of information relay by manipulating the quality of sensory information used for action selection. That is, fMRI data was collected while participants performed a stop task, with faces as go stimuli containing low-, high-, or all spatial frequencies. Supporting theoretical frameworks, go trial fMRI activity was best represented when *both* the facilitating direct pathway, and the more deliberate and balancing indirect pathway (including the STN) originated from the striatum (Mink, 1996; Redgrave et al., 1999). Importantly, the optimal model contained effective connectivity projections from both the PFC and sensory regions into the basal ganglia. Originating from the PFC, the striatum received inputs from the DLPFC.
and the preSMA. Additionally, sensory regions within the ventral stream (related to face processing or scene content/saliency) projected into the basal ganglia, while the dorsal stream (related to the integration of sensory information) linked with both the basal ganglia and the prefrontal cortex. Given these results, we conclude that perceptual decision-making is based on the communication of both raw stimulus information (sensory to basal ganglia) and abstract response plans (prefrontal cortex to basal ganglia).

Cortico-basal ganglia dynamics of information relay

A second goal of chapter five was to examine how the ease of stimulus identification affects the strength of information relay between the cortex and basal ganglia. In behavior, prolonged reaction times and increased error rates confirmed that gender identification in faces becomes more difficult with the selective removal of spacial frequency information. Formal analysis of reaction time data indicated that when information accumulation progresses slowly, the required accuracy levels are lowered to afford timely action selection. Importantly, the ease of stimulus identification and related strategic adjustments were also reflected in the dynamics of information relay between the cortex and basal ganglia. When stimulus identification was difficult, the DLPFC and the fusiform face area increased their effort to convey both raw and processed stimulus information into the striatum. Concurrently, the influence of preSMA on the striatum, and lateral occipital projections into the STN were weakened to allow for lowered criteria for correct decisions. In the previous chapters, we observed that the communication between cortex and basal ganglia is key in the implementation of active response inhibition. Observations from chapter five extend these findings by highlighting the importance of cortico-basal ganglia dynamics in action selection. In our opinion, these results show that perceptually optimal decisions are framed in the basal ganglia through top-down adjustments from the prefrontal cortex, and bottom-up stimulus evaluations from the sensory cortex.

Perceptual uncertainty in Action Control

In chapter five, we established how the manipulation of spatial frequency information affects cortico-basal ganglia dynamics during action selection. However, while we observed more efficient inhibition times when spatial frequency information was removed, these effects were not significant when tested in the fMRI scanner. Recently, a study focusing on the effects of fMRI noise on performance, showed a significant reduction of behavioral effects when participants were tested while hearing MRI scanner noise (Hommel et al., 2011). In line with these findings, we observed (in chapter two) that in the stop-simon task, long inter-trial intervals chosen to gain an optimal BOLD estimation per trail (for connectivity analysis), together with the conduction of the experiment in the MRI scanner weakened the magnitude of the strong interference effect usually observed in this
task. Therefore, to better understand how perceptual uncertainty affects action control, *chapter six* focused exclusively on behavior. In a series of seven behavioral studies, we examined how different types of spatial frequency information affect the process of response inhibition and selection. Participants underwent a stop-signal task, a two choice speed/accuracy balance experiment, and a variant of both these tasks where prior information was given about the nature of stimuli. In all experiments, stimuli were either intact, or contained only high- or low-spatial frequencies. Overall, drift diffusion model analysis showed a decreased rate of information processing when spatial frequencies were removed, whereas the criterion for information accumulation was lowered. When spatial frequency information was intact, the cost of response inhibition increased (longer SSRT), while a correct response was produced faster (shorter reaction times) and with more certainty (decreased errors). Note that these results were consistent across three separate experiments conducted with the stop-signal task. When we manipulated the motivation to respond with a deadline (i.e., be fast or accurate), removal of spatial frequency information slowed response times only when instructions emphasized accuracy. However, the slowing of response times did not improve error rates, when compared to fast instruction trials. To conclude, our behavioral studies suggest that the removal of spatial frequency information differentially affects the speed of response initiation, inhibition, and the efficiency to balance fast or accurate responses. However, more research is needed to understand why results from within the scanner differ from results outside the scanner.

**Future research**

In this dissertation we complement neurophysiological, primate, and computational modeling work on the role of fronto-basal ganglia circuits during voluntary action control (Mink, 1996; Hikosaka & Isoda, 2010; Frank, 2006). However, two important issues require further research. First, we encourage future work to question both the validity and reliability of the reported findings. Although we report some replications, more work form different labs, and from other disciplines is essential to better interpret our current results. For example, to examine the validity of our connectivity results, future work could combine TMS with an fMRI-ancestral graphs study. Here, regions important for the reported networks could be disrupted to evaluate network validity. Second, we encourage future work to combine model-driven connectivity approaches across multiple imaging techniques. Although this dissertation sheds some light on the interplay between the cortex and basal ganglia in action control, we add very little when one considers aspects of timing. Because action control is often a rapid and efficient process, the combination of techniques such as EEG or MEG with deep brain stimulation (DBS) could greatly benefit our current beliefs about the interplay between cortex and basal ganglia.
Concluding remarks

In brief, the studies reported in this dissertation focus on the interplay between the cortex and the basal ganglia when responses are selected or need inhibition. Based on the studies conducted, the following conclusions can be drawn: 1) response inhibition recruits a fronto-basal ganglia circuit with both the deliberate indirect, and the fast response-braking hyperdirect pathway. 2) This inhibitory circuit is also recruited proactively (already during action preparation) when we anticipate a high chance of future stopping. 3) Perceptual decision-making recruits a cortico-basal ganglia circuit containing the facilitating direct and the more deliberate indirect pathway. 4) When response selection is based on perceptual information, the direct and indirect pathways originating from the striatum are informed by incoming information from the goal-oriented PFC and the information oriented sensory cortex. In conclusion, the model-driven connectivity approach used in this dissertation highlights the importance of cortico-basal ganglia routes in the formation of deliberate action plans.