Networks of action control
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At the core of this dissertation lies the question of how different regions in our brain collaborate (as a network, or system) to initiate or withdraw controlled actions. But what is action control? To give an example, I repeatedly had to control and suppress the urge to go outside and enjoy a drink with friends on a sunny terrace, in order to pursue the more deliberate goal of finishing my dissertation. On some days, this goal was easily reached when the rain outside was uninviting and the motivation to nail this thesis flooded my thoughts. Unfortunately, on other days, I failed dramatically as the sun outside repeatedly hit my retina and incoming text invitations drained my motivation to stay inside and keep writing. Fortunately, even on the days that I satisfied the urge to go outside and enjoy the sun, I could still be cautious and restrain my behavior by leaving early or drinking less. When doing so, I was strategically adapting my behavior for a fresh writing marathon the next day. Additionally, when the dissertation was progressing slowly, I was sometimes compelled to help suppress my automatic urges proactively by closing the curtains, or turning off my phone. This example illustrates how behavior unfolds in the adaptation or suppression of automatic responses to pursue more deliberate and goal-oriented action plans (i.e., write and finish dissertation).

Paradigms of Action Control

Many experimental paradigms have been designed to study goal-oriented behavior while we prepare or suppress planned actions. In experimental psychology, these include paradigms that tap into the ability to reactivity suppress a planned motor response, to prepare an inhibitory plan in advance (proactively), or to respond strategically to internal or external demands.

Perhaps the most popular framework to study response inhibition has been the stop-signal task (Figure 1.1A), where incidental stop-signals designate that a planned response has to be withdrawn (Logan & Cowan, 1984; Logan & Burkell, 1986; Band, Van Der Molen, & Logan, 2003; Aron & Poldrack, 2006; Wildenberg et al., 2006; Verbruggen & Logan, 2009a; Leotti & Wager, 2010). Performance in the stop-signal task is often interpreted through the horse-race model, which asserts that initiation and inhibition processes are independent and compete for the first finishing time (Logan & Cowan, 1984; Logan, 1994; Band et al., 2003). That is, a planned response is inhibited, if the inhibition process finishes before the initiation process. However, if the initiation process finishes first, the planned response escapes inhibition and a response is produced. As we go back to the example above, response inhibition entails the on-time suppression of the upcom-
ing urge to go outside and drink wine. The time needed to successfully inhibit a planned response is referred to as the stop signal reaction time (SSRT) and can be estimated from the proportion correct stop trials (i.e., successful inhibition) and the distribution of correct reaction times (RT) (Logan, 1994; Band et al., 2003; Verbruggen & Logan, 2008).

The deliberate act of response inhibition can also be prepared in advance when stop-signals occur more frequently (Verbruggen & Logan, 2009b; Zandbelt & Vink, 2010; Ramautar, Slagter, Kok, & Ridderinkhof, 2006), or when environmental cues indicate an increased need for potential stopping (Chikazoe et al., 2009; Swann et al., 2009; Braver, 2012). In general, proactive control involves a preparatory step before automatic response tendencies are triggered. In our example, this would mean the advance closing of the curtains to prevent the sun from triggering my urge to go outside. Proactive response inhibition entails the advance preparation to stop planned movements even when stop-signals are omitted. Experimentally, proactive response inhibition can be studied by varying the probability of stop trial presentation in a cued or blocked design (Figure 1.1B). For example, in the cued version, participants are informed about the probability of stop signal occurrence at the onset of each trial (i.e., low or high). On go trials, the increased likelihood of stop signal presentation often results in prolonged reaction times and improved accuracy levels. Note that participants receive no signal to inhibit or stop planned responses during these trials. The increase in reaction times, when the cue indicates a high probability for potential stopping, is interpreted as the behavioral manifestation of proactive response inhibition. Additionally, the observation that response times are adjusted to match the increasing likelihood of stop-trial presentation suggests that the proactive preparation of action plans is adapted to the level of information that is available.

The concept of action control has not only been studied with paradigms that focus on the process of response inhibition. In fact, studying how motivational or environmental changes affect response selection is essential to fully grasp how we control our actions (Ridderinkhof, Cohen, & Forstmann, 2011; Cisek & Kalaska, 2010). In our example, both environmental influences (i.e., sun or rain outside) and motivational aspects (i.e., hang out with friends to drink wine or the more you write the sooner you finish) had a significant influence on my eventual decision to inhibit or release my urges. Perceptual decision-making is one field that focuses on the influence of motivation and sensory information in action selection. The process of perceptual decision-making entails the voluntary selection of a motor response from a set of alternatives, based on information gathered from the sensory system (Figure 1.1C) (Schall, 2001; Heekeren, Marrett, Bandettini, & Ungerleider, 2004; Palmer, Huk, & Shadlen, 2005; Gold & Shadlen, 2007; Cisek & Kalaska, 2010). Using detailed cognitive process models that describe most stages of decision making, this field has progressed our understanding of how motivation and sensory information from the environment each influence response selection (Smith & Ratcliff, 2004; Bogacz, 2007; Purcell et al., 2010; Ratcliff & Smith, 2010). That is, changes in motivation (i.e., be fast or accurate)
have been repeatedly related to adjustments in response cautiousness or strategy (Forstmann, Dutilh, et al., 2008; Forstmann et al., 2010), while changes in the external sensory environment were related to the ease of information gathering or accumulation (Heekeren et al., 2004; Huk & Shadlen, 2005; Drugowitsch, Moreno-Bote, Churchland, Shadlen, & Pouget, 2012).

As described above, researchers have been able to draw detailed conclusions about latent psychological processes by analyzing the entire RT distribution using cognitive process models. In this dissertation, I will use cognitive process models such as linear ballistic accumulator (LBA) model (Brown & Heathcote, 2008), or a hierarchical version of the drift diffusion model (DDM) (Ratcliff & McKoon, 2008; Wiecki, Sofler, & Frank, 2012), to understand how latent processes that underlie action control are affected by motivational or environmental changes. For example, when instructions motivate fast or accurate responses, cues motivate an increased need for proactive inhibitory control, or sensory information used for decision-making is more difficult to process.

Neural Mechanisms of Action Control

Experimental psychology has successfully generated cognitive paradigms that capture the efficiency of action control, which enables the goal-oriented initiation or suppression of responses. For example, these tasks help to quantify the ability to inhibit automatic responses in the normal population as well as in common psychological disorders, ranging from loss of control exhibited by drug abusers, to the impulsivity of children with ADHD (Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Wildenberg et al., 2006; Ravenzwaaij, Dutilh, & Wagemakers, 2012). Importantly, the use of these paradigms has also enabled neuroscientists to ask how action control is implemented within the brain.

Capturing the full realm of action control, the prefrontal cortex (PFC) is thought to direct the initiation and inhibition of planned responses in close synchrony with the response-gating basal ganglia. Focusing on the PFC, a large body of research has consistently demonstrated that suppressing an already initiated manual response depends critically on the right inferior frontal gyrus (rIFG) and the presupplementary motor area (preSMA) (Aron & Poldrack, 2006; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Mostofsky & Simmonds, 2008; Nachev, Kennard, & Husain, 2008; Chambers, Garavan, & Bellgrove, 2009; Buch, Mars, Boorman, & Rushworth, 2010; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Verbruggen, Aron, Stevens, & Chambers, 2010; Aron, 2011). Although the precise role of these regions is not fully understood, the rIFG is thought to update the planned go response by sending an inhibitory signal towards the basal ganglia, while the preSMA detects conflict (i.e., stop instead of go) and prepares the basal ganglia for signals from the rIFG. During response selection, the preSMA is often associated with the evaluation of response strategies (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Isoda & Hikosaka, 2007; Forstmann, Dutilh, et al., 2008; Forstmann et al., 2010; Hikosaka & Isoda, 2010; Alexander & Brown, 2011;
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Cavanagh et al., 2011), while the dorsolateral prefrontal cortex (DLPFC) integrates sensory information from the environment to reach a decision (Heekeren et al., 2004; Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006; Philiastides, Auksztulewicz, Heekeren, & Blankenburg, 2011; Sajda, Philiastides, Heekeren, & Ratcliff, 2011). Both during response initiation and inhibition the PFC is thought to communicate abstract action plans (i.e., go or stop) towards the basal ganglia that are described as gating the release or inhibition of selected action plans. In more detail, the subthalamic nucleus (STN) is described to fully “brake” or “slow” the planned motor output (Isoda & Hikosaka, 2008; Cavanagh et al., 2011; Swann et al., 2011), while the striatum evaluates and weighs all action intentions (Mink, 1996; Frank, 2011).

Theoretical Networks of Action Control

Supported by the studies above, classical work has suggested that a fronto-basal ganglia network is key in the initiation or inhibition of planned responses (Alexander, DeLong, & Strick, 1986; Mink, 1996; Redgrave, Prescott, & Gurney, 1999; Nambu, Tokuno, & Takada, 2002; Frank, 2006; Nambu, 2009). Mechanistically, this framework contains three separate pathways from the cortex into the basal ganglia. Most projections terminate in the striatum, from where two (out of the three) pathways depart. A “direct” pathway projects into the thalamus via the globus pallidus interna (GPI) to facilitate the selected action, while an “indirect” pathway via the globus pallidus externa (GPe) and STN allows the integration of additional information by adaptively slowing the motor output (Frank, 2006; Cavanagh et al., 2011). A third, “hyperdirect” pathway involves direct projections from the cortex into the response braking STN, and inhibits the thalamus output to the primary motor cortex (M1) by exciting the GPI.

The described cortico-basal ganglia pathways each play a special part in the selection and suppression of action plans. Perhaps the most intuitive way of looking at these pathways is by imagining the network as a traffic light system (Figure 1.2). Here, red represents the full fast brake on all responses via the “hyperdirect” pathway, orange is the more deliberate weighing of options to go or stop via the “indirect” pathway, while green represents the full press on the gas pedal to initiate a selected response via the “direct” pathway.

This dissertation aims to specify how PFC and basal ganglia regions collaborate as a network to either prevent me from going outside, slow my intention to drink wine, or release my urge to enjoy the sunny terrace. Therefore, I will systematically examine the relative contribution of each pathway across various experiments emphasizing response selection, inhibition, or both. To specify the role of these pathways within the brain, I will use a recently developed, model driven, connectivity method for the analysis of functional magnetic resonance imaging (fMRI) data (Waldorp, Christoffels, & Ven, 2011). Furthermore, by exploring how motivational and environmental adaptations (known to affect behav-
ior) modulate these described networks, I hope to contribute to our understanding of the dynamic brain that enables the flexibility of voluntary action control.

Outline

The research examined in this dissertation can be divided roughly into two parts. In the first part (*chapters 2-4*), we examine brain mechanisms and networks that
enable reactive or proactive response inhibition. In the second part (chapters 5-6), we focus on networks that enable perceptual response selection, and variables that modulate processes of action control.

In chapter two, we propose that response inhibition might be mediated via a fast hyperdirect pathway connecting the right inferior frontal gyrus (rIFG) and the pre-supplementary motor area (preSMA) with the subthalamic nucleus (STN) or, alternatively, via the indirect pathway between the caudate and globus pallidus externa (GPe). To test the relative contribution of these two pathways to inhibitory action control, we applied an innovative quantification method for effective brain connectivity termed Ancestral Graphs (Waldorp et al., 2011).

In chapter three, we focus on the neural indices of proactive response inhibition. We model this experimentally by measuring the degree of response slowing that occurs when people respond to an imperative stimulus in a context where they might suddenly need to stop the initiated response compared to a context in which they do not need to stop. To test which neurocognitive mechanisms underlie the proactive preparation to stop we performed two studies with transcranial
magnetic stimulation (TMS) while additionally re-analyzing data from a prior study (Aron, Behrens, et al., 2007), with functional magnetic resonance imaging. This study was supervised by Prof. Dr. Adam R. Aron, and conducted in his lab at the University of California San Diego (UCSD).

Chapter four converges findings from chapter two and three by showing that proactive response inhibition (when there is no signal to stop) relies on the very same network that is used for full reactive response inhibition (i.e., when there is an unexpected signal to stop). Moreover, this chapter examines how the advance preparation to stop (proactive response inhibition) modulates the need for fronto-subcortical control when a signal to stop is actually given.

In chapter five, the focus is shifted towards the initiation and selection of action plans. Here, we argue that during perceptual decision-making, more often than not, sensory information has to be transformed into a deliberate and goal-oriented motor plan. This chapter establishes the importance of fronto-basal ganglia routes in action selection, and furthers our understanding of how information from sensory regions is integrated into this circuit to facilitate response selection.

In the last research chapter, chapter six, we step away from the brain to establish experimentally how changes in the motivation to respond with a deadline, and information available to make decisions, affect both response selection and inhibition. We address this question in a series of seven behavioral studies (wrapped into three larger experiments) where we manipulate the quality of sensory information provided, or foreknowledge about the stimuli that are yet to come.

Finally, in chapter seven, I will summarize and interpret the obtained results, discuss limitations, and outline possible future directions.
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**Described work**

**Chapter two**

**Chapter three**

**Chapter four**

**Chapter five**

**Chapter six**
Other work


