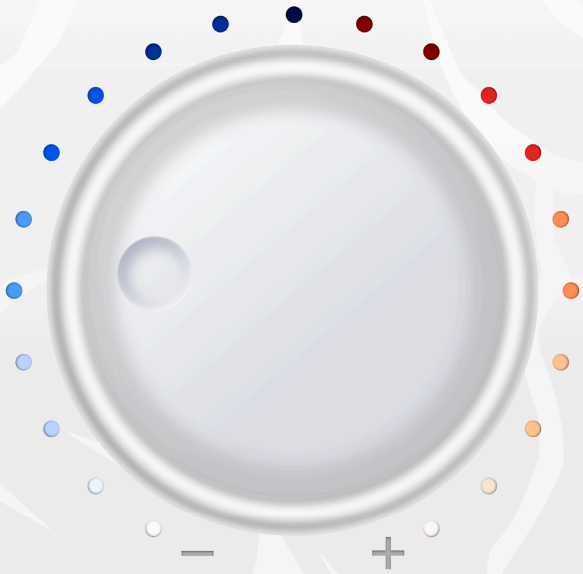
Gaining Control

The Neural Basis of Proactive Inhibition



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The Neural Basis of Proactive Inhibition

Het Verkrijgen van Controle

De Neurale Basis voor Proactieve Inhibitie

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General Introduction

On the subject of inhibition

This thesis ventures into the subject of inhibition. We will focus specifically on behavioral inhibition, i.e., the suppression of motor responses. This type of inhibition relies on an intricate brain network encompassing cortical and subcortical structures, that enables us to incorporate information from past and present events. Humans have the capacity to employ forethought and anticipation to aid the navigation of the world around them – we do not operate in a vacuum. Our actions and inactions are shaped by the constant bombardment of stimuli that we either consciously or subconsciously process. Regarding inhibition, this means that instead of a purely reactive process, we often form expectations on what behavioral response may be warranted in a particular situation. The ability to incorporate these expectations into inhibitory control proactively is thought to rely on specific connections between cortical and subcortical areas. These connections are still in development throughout adolescence and malformations of these connections are associated with the occurrence of certain psychiatric disorders. This thesis aims to identify the brain regions associated with proactive inhibition, the connections between them, and find links with behavioral control in daily life.

What is inhibition

We can view inhibition as suppressing the execution of an action by some degree of restraint, for instance not taking another snack or trying to not look at your phone. This ability relies not only on your body functioning correctly in the biological sense, but also requires a level of cognitive control over your actions. In biology, physiology and fundamental neuroscience, inhibition can have various meanings ranging from inhibition at a synaptic and cellular level, to reflexive behaviors causing limbs to retract from a stimulus. In this thesis inhibition simply refers to the stopping of a planned or already initiated movement, and possibly preceding preparatory processes. There is some debate on how response inhibition relates to cognitive control, and how issues with basic response inhibition affect things like attention and impulsivity (Aron, 2016; Kenemans et al, 2005; Lansbergen et al., 2007). While this thesis investigates how inhibition relates to broader cognitive development, it specifically does this in terms of the anticipatory mechanisms preceding inhibition. These mechanisms allow us to prepare in advance and gain more control over the environment around us. This does not imply we gain more 'free

will', but instead of succumbing to the reactive tendencies our environment provokes, we can direct our resources towards more long-term goals.

Reactive and proactive

Whereas reactive inhibition can be seen as the pure suppression of an initiated movement - reactive, this suppression ordinarily does not come out of the blue. In daily life we are able to navigate our environment successfully by anticipating what will happen in the future, either due to actions of ourselves or others. This anticipation can lead to us exhibiting a level of restraint in our actions, in order to be ready for what may cross our path. Whereas the suppression of initiated movement can be viewed as a reactive process – reacting to a stimulus – the anticipation of having to suppress provides us with proactive control. Proactive inhibition is a fundamental hallmark of higher-order cognitive control, and it serves to improve performance and aid survival. By becoming more careful and delaying a response, the chance that the response can either be inhibited successfully, or alternative action can be taken is increased (Logan & Cowan, 1984).

How do we measure inhibition?

In this thesis the most common task used to measure inhibition is the stop-signal anticipation task. Using this paradigm, it is possible to measure both reactive and proactive inhibitory control. The task features a moving bar and a target, and the goal is to stop the bar when it reaches this target by pressing a button – a simple feat that even young children are able to accomplish. The difficult part is that the bar, on occasion, will stop before it reaches the target line. To perform the task well, you have to refrain from pressing the button when this happens. To make things a bit simpler, cues are presented to give an indication of how likely the bar will stop on its own (in which case you should not press the button). After a couple of minutes of performing the task, we will end up with data on how fast and accurate you are at inhibiting responses, and how much you slow down when stopping is likely.

First, your reactive inhibition is defined by how close to the target you are still able to inhibit a response successfully. You can imagine that it is easy to suppress a response when you are warned well in advance, but that it gets more difficult with seconds to spare. It is of course not easy to measure the speed at which someone is inhibiting a response, because successful inhibition means there will

not be a response to measure. The theoretical model used to define inhibition speed (stop-signal response speed, or SSRT) is shown in **figure 1**. It employs the so-called horse-race model. The graph shows a hypothetical distribution of an individual's reaction time on trials where a button was pressed. In trials where a stop-signal is given, the time from the 'go' stimulus presentation to the stop-signal presentation is called the stop-signal delay (SSD). The task monitors outcomes and adjusts each individual's SSD so that the probability of inhibition (P(Inhibit | Signal)) and the probability of responding (P(RespondlSignal)) are equal (i.e., both approximately 50%). In other words, this is the time of presenting the participant with a stop-signal at which inhibition is successful in still half the times.

Next to reactive measurements, we can look at how much people slow down their responses when expecting the occurrence of a full-stop. On trials with a high likelihood, people will generally perform much slower than on trials with a low or no likelihood of a stop at all. This slowing down can be used as a measurement of proactive inhibition.

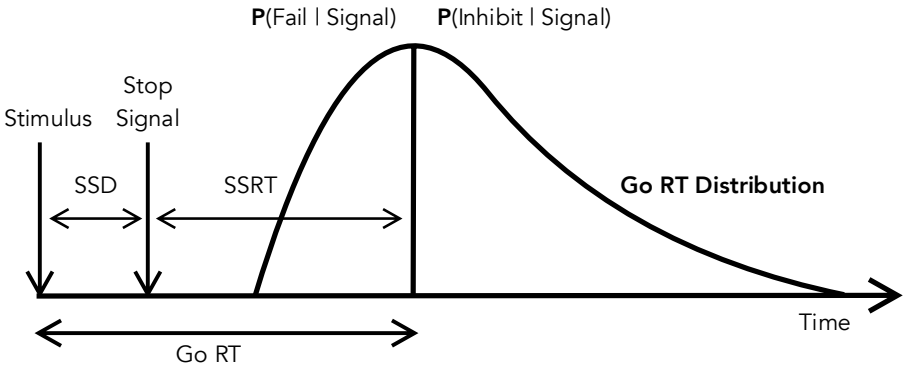

Figure 1. The theoretical model used to compute the SSRT *Adapted from Evans & Hampson (2015).*

Inhibition and the brain

In the brain, inhibition involves activity in a network associated with stopping, consisting of the striatum, motor and pre-motor cortex, right frontal and parietal cortical areas (Vink et al., 2005; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Chikazoe, Jimura, Hirose, et al., 2009; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Zandbelt & Vink, 2010; Duque, Labruna, Verset, Olivier, & Ivry, 2012; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2013;

van Belle, Vink, Durston, & Zandbelt, 2014). Specifically, the striatal area has been identified as a crucial region in inhibition. Its exact role is still unclear, and it has been implicated in both proactive processes leading up to response inhibition as well as reactive inhibition. It has been suggested that striatal activation during reactive inhibition is, in part, related to prior anticipatory processing of contextual cues (Vink et al. 2015; Pas et al., 2017, 2019).

Notably, these regions go through an important transition during adolescence. In the brain, structural as well as functional changes occur that parallel the development of higher-order cognitive functions. The rate of development differs across the brain: subcortical regions such as the amygdala and striatum are thought to follow a different developmental trajectory than the frontal cortex. This may result in a temporary functional imbalance within frontostriatal and frontolimbic circuits, which may give rise to impulsivity and risk-taking behavior typical for adolescents. It has been proposed that high rates of risk-taking in adolescence are partly attributable to these patterns of neurobiological development that promote an increase in sensation-seeking tendencies at a time when impulse control is still developing. On the one hand an increase in impulsive and risk-taking behavior can lead to unfavorable outcomes like accidents, substance abuse or sexually transmitted diseases. On the other hand, this propensity to exhibit more explorative and adventurous behavior can have its benefits, in that it may lead to adolescents acquiring new experiences (Crone and Dahl, 2012; Steinberg, 2008).

Techniques used in this Thesis

Functional MRI

The majority of the articles in this thesis use functional magnetic resonance imaging (fMRI) to investigate which parts of the brain are associated with inhibitory control. This technique allows for the non-invasive measurement of blood oxygenation in the brain, from which we derive where activation is higher or lower when performing a certain task compared to baseline. The degree to which activity in specific brain regions was associated with inhibitory control was tested using a general linear model. Resulting parameter estimates convey how much fluctuations in blood oxygenations are associated with task conditions. As variation in the signal derived from fMRI is only partially caused by brain activity, around three percent, we therefore need a large number of similar

measurements to derive a reliable estimation. This means that subjects performing a certain task will need to execute the same response multiple times. The difficulty lies in keeping subjects, both young and old, motivated enough throughout the task to acquire a sufficient number of measurements. In this thesis fMRI is also used to measure the similarity of brain activity in two separate regions. This is done by testing the coherence of the signal over time, resulting in a measure of functional coupling of two regions. Separate regions of the brain that show similarities in signal in terms of time and magnitude, are presumed to be connected.

Electroencephalography

Another technique used in this thesis is electroencephalography (EEG). As opposed to functional MRI which measures blood oxygenation, EEG measures the actual firing of neurons in the brain. The particular technique used in chapter 7 is a wavelet analysis, which uses a frequency transformation of the signal over time to deduce whether cortical regions become more or less active. As cortical activation increases, for instance in the pre-motor cortex during movement preparation, the coherence of neural activation decreases. Whereas the BOLD signal measured with fMRI is a slow metabolic process that relies on oxygenated blood traveling to areas of the brain, the EEG signal is derived directly from the firing of neurons. This means that with EEG we can measure at a much higher temporal resolution. The downside is that because electrodes are placed on the scalp, and due to the propagation of electrical signals, the spatial resolution is much poorer compared to fMRI.

Aim and outline

The aim of this thesis is to describe the brain regions and neural correlates that are associated with inhibitory control, and how those regions interact with each other. **Chapter 2** begins by exploring the broader function of the striatal area of the brain using functional MRI and a learning task. We found that activation in parts of the striatum is associated with within-subject variations in learning performance, and that this region appears to play a vital role in learning by adjusting behavior based on feed-back. **Chapter 3** focusses on activation in the striatum during reactive inhibition, and how this activation is associated with the ability to predict the occurrence of a stop in advance. **Chapter 4** shifts towards proactive inhibitory control, and how striatal, frontal- and parietal-cortical

activation preceding inhibition is dependent on the degree to which stops are expected. In **Chapter 5** we employ EEG to investigate proactive inhibitory control with a high temporal precision, and find an association with beta-band desynchronization. In **Chapter 6** we investigate how self-regulation in children relates to brain activity and functional coupling during inhibition.

Chapter 2

Ventral striatum is related to within-subject learning performance

Matthijs Vink, Pascal Pas, Erik Bijleveld, Ruud Custers, Thomas E. Gladwin

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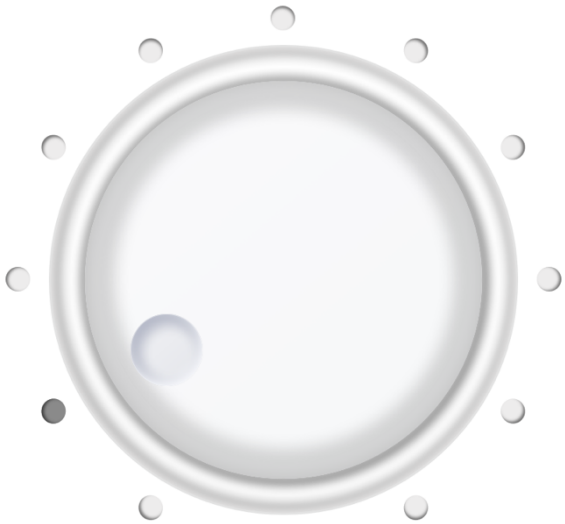

Abstract

Learning from feedback involves a network of various cortical and subcortical regions. Although activation in this network has been shown to be especially strong in successful learners, it is currently unclear which of these regions are related to within-subject variation in learning performance. To this aim, 21 subjects performed a probabilistic feedback-learning task consisting of multiple independent Learning blocks and non-learning Control blocks, while functional magnetic resonance imaging data were acquired. In agreement with previous studies, activation in anterior, lateral, and medial left prefrontal cortex, insula and superior and inferior parietal cortical regions were found when contrasting Learning and Control blocks. Furthermore, activation in the supplementary motor area, anterior cingulate cortex and bilateral striatum was associated specifically with the learning phase and not the application phase during Learning blocks. Finally, activation only in the ventral striatum was associated with within-subject learning performance across the Learning blocks. Taken together, these latter two results are argued to provide the answer to the main research question: ventral striatum activation is associated with within-subject variations in learning performance. The ventral striatum appears to play a vital role in learning by adjusting behavior based on feedback.

Introduction

For any organism that needs to engage in adaptive goal-directed behavior, the ability to learn from feedback is crucial. Specifically, feedback learning allows organisms to use previous experiences to make predictions about the consequences of their actions. This process is often conceptualized as consisting of three steps: encoding the current state, selecting a response, and adjusting subsequent selection based on the outcome (Bunge, 2004, Seger, 2008). In humans, previous research has pinpointed several brain regions involved in this learning cycle. The ventromedial prefrontal cortex (PFC) appears to be involved in encoding the reward value associated with states (Blair et al., 2006). Punishment results in increased activation in the insula and anterior cingulate cortex (ACC) (Ullsperger and von Cramon, 2003) and may result in deactivation in the ventral striatum (Becerra et al., 2001). The basal ganglia are particularly important in selecting responses based on expected outcomes, given the current state. These regions appear to be essential for the use of value information for the selection of goal-directed responses (O'Doherty et al., 2007, Brovelli et al., 2008, Shohamy et al., 2008). Subsequently, they shape responses by biasing response competition in the supplementary motor area (SMA) (Seger, 2008, Vink et al., 2005a, Zandbelt and Vink, 2010, Zandbelt et al., 2012a). After response selection, feedback is used to fine-tune existing stimulus–response mappings, and, when necessary, to learn novel ones (Boettiger and D'Esposito, 2005). Prediction errors related to the expectation versus the receipt of rewarding outcomes have been disentangled and shown to be associated with activation in the ventral striatum and medial PFC, respectively (Knutson and Wimmer, 2007). In turn, adjustments of behavior in response to changes in reward likelihood are associated with activation in the ventral PFC and ventral striatum (Delgado et al., 2005, Day and Carelli, 2007, Van Hell et al., 2010). Finally, the ACC has been argued to integrate input signaling prediction errors, and use this information to select responses (Holroyd and Coles, 2008). Moreover, the functional role of the ACC is not merely restricted to processing errors, but instead is related to behavioral adjustments based on evaluative functions, in order to avoid losses (Magno et al., 2006).

Previous studies have shown relationships between individual differences in learning performance and activation in the striatum and ACC (Schonberg et al., 2007, Santesso et al., 2008). These studies mark an important step in the understanding of the neural underpinnings of feedback learning, as they

pinpoint the brain mechanisms that are most proximally involved in shaping learning performance. It is important to note, though, that these studies investigated between-subject differences in learning behavior. In the present research, complementing previous studies, we explore which brain regions covary with performance within individuals. Specifically, by comparing multiple independent learning periods within subjects, we examine which brain regions are associated with fluctuations of individual learning performance over time.

Subjects performed a probabilistic feedback-learning task that consisted of multiple independent Learning blocks and non-learning Control blocks, while being scanned with functional magnetic resonance imaging (fMRI). In each Learning block, subjects had to learn the rule describing which button (left, right) was associated with a particular-colored cue (two colors per block). As there were multiple independent Learning blocks (each with new color cues), the learning process could be measured repeatedly. To identify regions associated with learning, intended to provide a basic verification that the task activated learning-related regions as expected, we contrasted activation during Learning blocks to that of Control blocks. Next, we contrasted trials at the beginning of each Learning block to those at the end (controlled for the same within-block contrast in Control blocks), so we could identify regions associated with learning the stimulus–response rule (Learning phase) as compared to applying that rule (Application phase). Since subjects had to establish a new stimulus–response rule in each Learning block, each block could be assigned a score for performance reflecting the successful acquisition of that rule. This allowed us to determine activation related to the within-subject variation in learning performance across the experiment as a predictor for brain activation. Note, importantly, that it is the combination of the two contrasts described above that will provide the essential information on learning-related activation. In the Learning phase versus Application phase contrast, activation during the Learning phase will covary with learning-related processes, but also with lower accuracy and more negative feedback. In the final, parametric, contrast, higher activation will again covary with learning-related processes, but now with higher accuracy and more positive feedback. So, if activation turns out to be present in both contrasts, this indicates that the activation that is found is related to learning, rather than to the valence of feedback.

Experimental procedures

Participants

Twenty-one right-handed subjects (10 male, mean age 22, standard deviation 2 years) were tested. Informed consent was obtained from all subjects and the study was approved by the local ethics committee of the UMC Utrecht, the Netherlands.

Task

The feedback-learning task (see **figure 1**) consisted of 12 Control and 12 Learning blocks, presented in alternation with the exception of the first two blocks that were both Control blocks. Each block had a duration of 20 s (20 trials), and began with a small central fixation square and two empty squares (left and right of the screen). In Control blocks, one of the peripheral squares changed color, whereas in Learning blocks, the central fixation square changed color, indicating to the subject that a response had to be made. Responses were given using the right thumb and had to be made within 700 ms after stimulus onset. Immediately following the response, feedback was presented up to 900 ms after stimulus onset. Next, the display was cleared for 100 ms until the next trial. During Control blocks, indicated by a gray-colored central fixation square, subjects had to press the response button corresponding to the location of the stimulus (left or right). Feedback in this condition was either neutral or negative: after a correct response, a green '+0' was shown, otherwise a red '−1'. During Learning blocks, the central fixation square was filled by one of two colors. These were determined pseudo-randomly per block, such that they were easy to distinguish. Subjects then had to learn which response (either left or right) was associated with that particular color. Feedback followed immediately after responding. After a correct response, a green '+1' was presented; an incorrect response was followed by a red '−1' in the square corresponding to the pressed button. Feedback was based on a probabilistic model. That is, feedback was provided according to the proper mapping on 75% of the trials, and according to the reverse mapping in 25% of the trials. Trials with feedback according to the reverse mapping were distributed randomly across the 20 trials of each block. As a result, pressing the correct response resulted in positive feedback on three out of four trials (i.e. 75%).

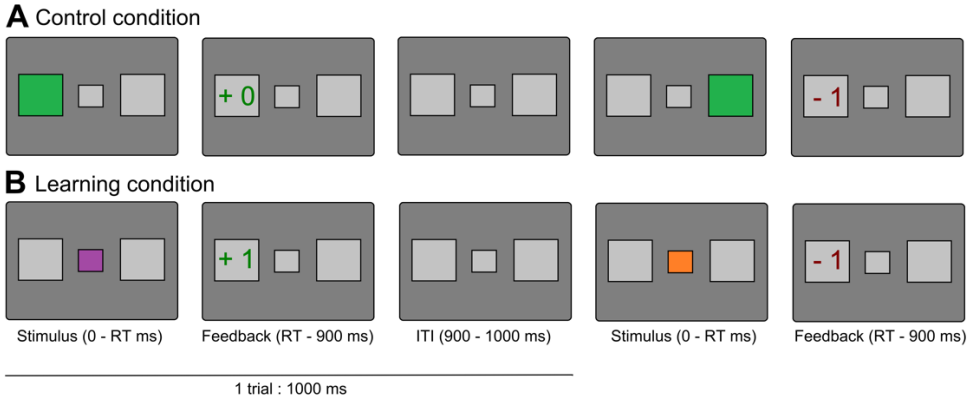

Figure 1. Schematic representation of the probabilistic feedback-learning task. *The task consisted of 12 non-learning Control blocks and 12 Learning blocks of 20 trials each. (A) In the Control condition, each trial started with the presentation of a green square either on the left or right side of the screen. Subjects were instructed to press either the left or right button corresponding to the location of the green square. Immediately after responding, feedback was presented in the square corresponding to the response. If the response was correct, a green '+0' appeared, otherwise a red '−1' appeared. (B) In the Learning condition, each trial started with the presentation of a colored cue in the center of the screen. Subjects had to learn which button to press (left or right) in response to that cue. In each Learning block, there were two colors used as cue, and these were different for each block. Feedback was given in a similar fashion as for the non-learning Control condition.*

Prior to the fMRI session, subjects were trained to become familiar with the task. First, they performed a simplified version of the task in which feedback was deterministic: a stimulus was associated with a response, and if and only if that response was given the resulting feedback was positive. Then, they performed the task with probabilistic feedback (75% valid), but were informed of the correct response on each trial. This was done to acquaint subjects with the concept of probabilistic feedback. Finally, subjects performed the task using only feedback to determine correct responses. This latter task was identical to the task used in the fMRI session, although it featured different colors. Note that subjects did not learn the set of stimulus–response mappings per se, but were only acquainted with the task. In this way, we could identify neural correlates of the acquisition of

new stimulus–response mappings during the fMRI session, for each of the 12 Learning blocks separately.

Behavioral analysis

In Learning blocks, subjects responded according to an implicit stimulus–response mapping, based on the color of the central fixation square. The stimulus–response mappings were different for each Learning block. Learning blocks were divided into Learning and Application phases based on the last switch between stimulus–response mappings evidenced by the responses. That is, Learning phase ended when the subject started to consistently respond according to one stimulus–response mapping. Control blocks were also divided into two phases, based on the average trial duration of these phases in Learning blocks. Accuracy and reaction time were calculated for and compared between these two phases of Control and Learning blocks.

Image acquisition

Data were acquired on a 3T Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). Foam padding was used to restrict head motion. Functional scans were acquired using a two-dimensional echo-planar imaging (2D-EPI) sequence and SENSE factor 2.4 (anterior–posterior), with the following parameters: TE = 23 ms, TR = 1600 ms, voxel size = 4 mm isotropic, flip angle = 72.5°, reconstructed matrix = 64 × 64, 36 axial slices per volume, field of view 192 × 256 × 96. A total of 225 functional volumes were acquired in about 8 min.

fMRI analysis

Preprocessing and statistical analyses were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Functional scans were realigned using rigid-body transformation. The anatomical scan was co-registered to the functional scans, and both the anatomical and functional scans were normalized to match the MNI-152 T1-template. Finally, the functional scans were smoothed using a full-width-half-maximum 8-mm Gaussian kernel. For each individual subject, regression-coefficients for each voxel were obtained from a General Linear Model (GLM) regression analysis using a factor matrix that contained the factors modeling activation during the two phases of the Control and Learning blocks (four factors). To obtain activation related to fluctuations in individual performance across blocks, a parametric factor modeling the accuracy during

each Learning block was also included. Low-frequency drifts were controlled for using a high-pass filter (discrete cosine functions) with a cutoff of 128s. Motion parameters from the realignment procedure were included as regressors of no interest to account for residual effects of head motion.

The strategy for group-wise analyses was as follows. First, to obtain basic activation associated with Learning versus Control blocks, a whole-brain group-wise paired-samples *t*-test was performed to test the difference in activation between Learning blocks and Control blocks. Next, to identify regions associated with the initial Learning phase of Learning blocks, where the stimulus–response rule had to be determined as compared to the subsequent application of the rule, a whole-brain group-wise paired-samples *t*-test was performed to test Learning versus Applying phases during Learning blocks. By contrasting this to the same contrast in Control blocks (early phase versus late phase during Control blocks), we corrected for the potential confound of time-in-block. Finally, a whole-brain group-wise one-sample *t*-test was performed to identify activations associated with within-subject performance (accuracy) variations across blocks. The accuracy of each Learning block as a whole was determined and used as a parametric modulator of the activation during the Learning phase of each of the 12 Learning blocks, per subject. This yielded a regression-coefficient map per subject indicating where activation was related to fluctuations in Learning accuracy across the 12 Learning blocks. These maps were used in a group-wise one-sample *t*-test to reveal brain regions that consistently (over all subjects) showed higher activation when subjects performed relatively well. All group maps were tested for significance at a family-wise error (FWE) corrected cluster level of $p = 0.05$ (cluster-defining threshold of $p = 0.001$, critical cluster size of 28 voxels).

Results

Behavioral results

The average number of trials in the Learning phase of Learning block (i.e. at the beginning of each Learning block) was 10 (standard error 1). After this Learning phase, in the remainder of the trials in each Learning block, the stimulus–response rule is applied during the Application phase. Thus, on average, both the Learning and Application phases consisted of about 10 trials for each Learning block. These trial numbers were also used to divide Control blocks into

two phases. Performance data are presented in **figure 2**. Mean accuracy was 95% (SD 2.3) and 98% (SD 1.2) for Control blocks, and 46% (SD 5.9) and 73% (SD 3.1) for Learning blocks, respectively. Note that given a 75% validity of feedback, an accuracy of 73% in the Application phase of Learning blocks reflects an almost perfect application of the stimulus–response mappings. Mean reaction time was 431 ms (SD 14.3) and 420 ms (SD 16.8) for Control blocks, and 452 ms (SD 21.4) and 478 ms (SD 18.5) for Learning blocks, for the Learning and Application phases, respectively.

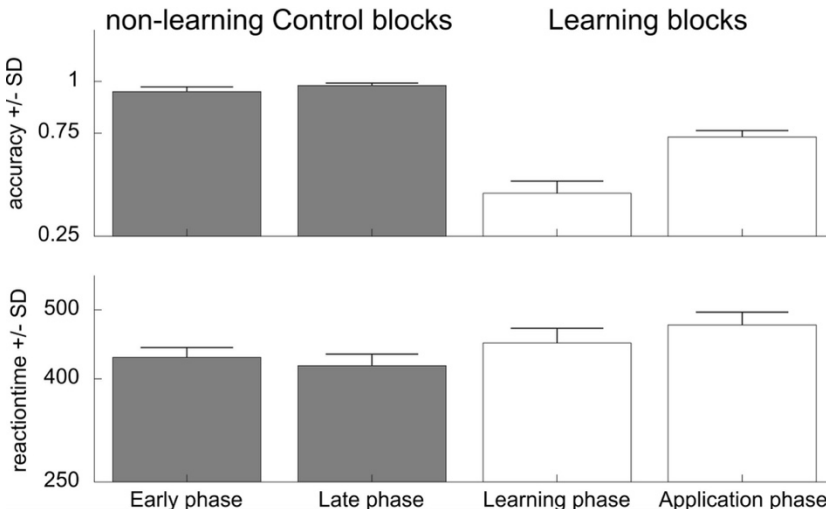

Figure 2. *Accuracy (top) and reaction time (bottom) data for non-learning Control blocks (black bars) and Learning blocks (white bars). Accuracy and reaction times for Learning blocks were calculated for the Learning phase (first 10 trials of Learning blocks) and during the Application phase (last 10 trials of Learning blocks). Non-learning Control blocks were also split into two phases similar to Learning blocks to investigate potential within-block effects.*

fMRI results

As shown in Fig. 3a, activation associated with Learning versus Control blocks was found in a network consisting of ACC, SMA, left precentral gyrus, bilateral middle frontal gyrus (BA10), insula, inferior parietal cortex, and bilateral precuneus, and thalamus (**Table 1**). The contrast Learning versus Application phase revealed activation in the left and right ventral striatum, and SMA and ACC (**Fig. 3b**; **Table 1**), indicating that these areas are significantly involved in

acquiring and adjusting of stimulus–response mapping based on feedback. Finally, and most relevant to the aim of the present study, activation related to within-subject performance variations across blocks was found only in the ventral striatum, bilaterally (**Fig. 3c**; **Table 1**). Even upon lowering the threshold to $p < 0.001$ uncorrected for multiple comparisons, no additional activations appeared. There were no areas showing a significant negative relation with within-subject performance variations across blocks.

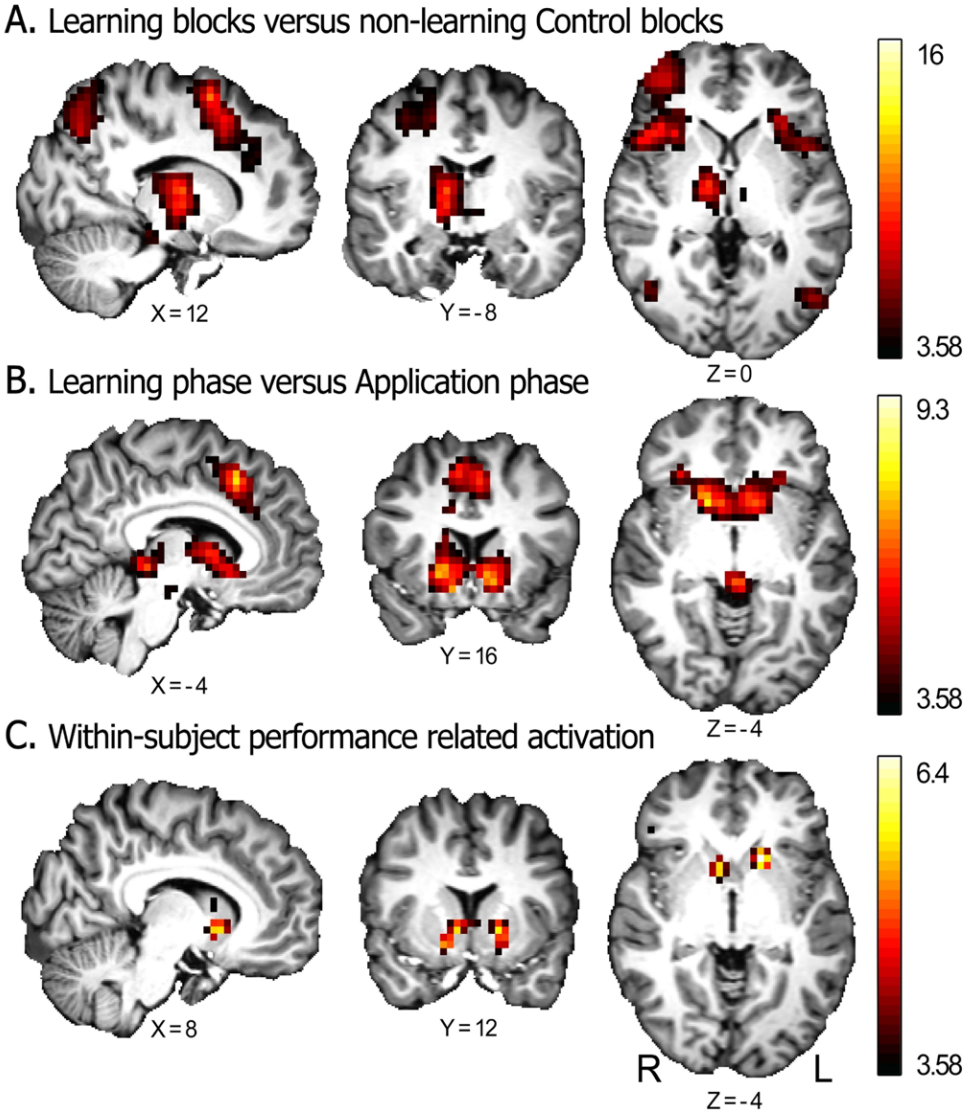

Figure 3. Imaging results for depicting various aspects of the learning network. All brain activation maps are thresholded at a family-wise error- corrected cluster level of $p < 0.05$. For details see Table 1. (A) Brain activation for the contrast of Learning blocks versus non-learning Control blocks. (B) Brain activation for the contrast of the Learning phase (first 10 trials of Learning blocks) versus the Application phase (last 10 trials of Learning blocks). This was contrasted against the same contrast for non-learning Control blocks to eliminate possible within-block effects (see methods). (C) Brain activation associated with fluctuations in within-subject learning success across the 12 Learning blocks in the experiment.

Table 1. Overview of activations

Region	BA	Side	Number of voxels	*X*	*Y*	*Z*	Max *t*-value
Learning blocks versus non-learning Control blocks							
IFG/insula	47	L	89	44	20	0	6.38
MFG	8/9/10	L	273	39	8	44	6.14
		R	34	−44	52	20	4.27
Occipital lobe	19/37	R	58	43	15	22	5.82
DLPFC	10/46	L	229	42	44	22	6.50
SPL	7	L	595	55	−40	40	16.21
		R	219	−40	−48	48	8.48
IPL	40	L	253	41	−47	39	6.49
SMA	6	L	64	0	16	52	4.97
Thalamus		R	289	12	−8	8	5.71
Learning phase versus Application phase							
Ventral Striatum		L/R	473	16	24	−12	9.34
				−12	16	−12	7.19
SMA/anterior cingulate	6	L/R	182	−4	20	44	7.75
Superior Colliculus		L/R	47	0	−32	−4	6.51
Within-subject performance related activation							
Ventral striatum		L	32	16	12	−12	5.31
		R	34	−16	16	−4	6.42

Note: All results are significant at a family-wise error corrected cluster level of $p < 0.05$; L, left; R, right; X Y Z refer to the center of mass; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; SPL, superior parietal lobe; IPL, inferior parietal lobe; SMA, supplementary motor area.

Discussion

In the current study, subjects performed a feedback-learning task, in which simple stimulus–response mappings had to be learned based on probabilistic feedback (75% valid). Increased activation was found in frontal (inferior and dorsolateral PFC, ACC and SMA and parietal (superior and inferior) cortex (Fig. 2a) when contrasting Learning blocks with non-learning Control blocks. Activation in bilateral dorsal and ventral striatum, as well as the SMA and the ACC was more prominent during the Learning phase at the beginning of each Learning block, compared to later on in the block with the mere application of stimulus–response rule (Fig. 2b). Finally, and of most interest with regard to the main research aim, individual within-subject fluctuations in performance in Learning blocks were associated with activation solely in the bilateral ventral striatum (Fig. 2c). Taken together, these data suggest that learning involves an intricate network of cortical and subcortical regions. These data replicate and extend previous between-subject learning studies by showing that the ventral striatum plays a particularly pivotal role in learning as it is related to within-subject learning success.

Learning blocks versus non-learning Control blocks

As expected, the contrast between Learning and Control blocks showed brain activation in a network of regions associated with general goal-directed behavior. Activation in the dorsolateral PFC may be due to increased working memory demands in Learning blocks. In Control blocks, a response (pressing left or right button) was directly indicated by the stimulus (presented on either the left or right side of the screen), whereas in Learning blocks, responses were based on arbitrary task demands (i.e. the color of a centrally presented stimulus indicated a response). This is consistent with the literature linking the dorsolateral PFC to establishing high-level rules guiding response selection (Koechlin et al., 2003, Hamidi et al., 2009, Kehagia et al., 2010). Furthermore, activation of the SMA throughout Learning blocks agrees with the idea that the SMA is sensitive to response conflict (Zandbelt et al., 2012b). Even after a stimulus–response mapping has been established, there will still be more response conflict than in the Control condition, as stimulus–response compatibility was always higher in this condition. Finally, we found parietal activation. As the parietal cortex is associated with visual short-term memory (Vink et al., 2005a, Kawasaki et al., 2008) and sensorimotor transformations (Grol et al., 2006, Chong et al., 2008,

Coulthard et al., 2008), activation during Learning blocks could be explained by an increase in attention to the color of the central cue and the direction of responses.

Learning versus applying stimulus–response mappings

Next, we focused on those regions showing activation more specifically related to feedback learning, by separating the acquisition and adjustment of mappings based on feedback (i.e. Learning phase of individual Learning blocks) from the application of learned stimulus–response mappings (i.e. Application phase). To correct for general time-in-block effects, we corrected for the same contrast (using the first 10 trials versus last 10 trials) in Control blocks. Our results are consistent with those reported by Eliassen et al. (2012), who reported higher activations in striatal and frontal regions during the early phases of learning as compared to the subsequent application phase. Specifically, we found increased activation during the Learning phase versus the Application phase in the bilateral striatum, and SMA extending to the ACC. The SMA and striatum are closely interconnected. The striatum is the main subcortical input region of the medial motor loop and has been associated with the initiation as well as the inhibition of movements (Vink et al., 2006, Vink et al., 2005b, Zandbelt and Vink, 2010, Zandbelt et al., 2011). The SMA is the main cortical region of the medial motor loop (Alexander and Crutcher, 1990). The relationship between the SMA and response conflict (Zandbelt et al., 2012b) may also explain its activation during the Learning phase as compared to the Application phase of Learning blocks (versus the same contrast in Control blocks). In the Learning phase, at the start of Learning blocks, response conflict is high because neither response (left or right button press) has yet a clear advantage, whereas in the Application phase at the end of the block such an advantage has developed based on feedback. The difference in ACC activation found between the early and late phases of the blocks may reflect increased performance monitoring during the initial learning phase (Ridderinkhof et al., 2004), and the need to update responses based on punishment (Ullsperger and von Cramon, 2003). This explains why such activation is absent during the late application phase of stimulus–response mappings, as there is no longer a need to adjust behavior based on feedback. The involvement of the ventral part of the striatum in learning from feedback was expected based on its association with the processing of prediction errors (Becerra et al., 2001, Knutson and Cooper, 2005, O'Doherty et al., 2007, Brovelli et al., 2008) and adjustment of behavior based on feedback (Delgado et al.,

2005, Tricomi et al., 2006, Day and Carelli, 2007; for an overview see Bornstein and Daw, 2011). Activation in the ventral striatum has been found to reflect prediction errors in both Pavlovian (i.e. stimulus > outcome) and operant conditioning (i.e. response > outcome, given the stimulus) (O'Doherty et al., 2007, Brovelli et al., 2008). In contrast, the dorsal striatum appears to be involved with biasing response probabilities during operant conditioning (Vink et al., 2005a, Vink et al., 2005b, O'Doherty et al., 2007, Zandbelt and Vink, 2010). In addition we did not find ventral striatum activation in the Learning versus Control contrast, suggesting the ventral striatum is only active during either learning or adjusting stimulus–response mappings (Learning phase), and does not play a role during the Application phase.

Within-subject learning performance

Finally, we found activation in the ventral striatum to covary with within-subject performance across the 12 Learning blocks, with higher activation when learning was more successful. This is consistent with findings from Schonberg et al. (2007) and Santesso et al. (2008) who showed in a between-subject design that more successful learners also showed higher activation in the ventral striatum. We extend these findings by showing this effect in individual subjects using a within-subject design. Combined with the data from the Learning versus Application contrast described above, we take our results to suggest that this ventral striatum activation reflects the use of feedback in creating and adjusting stimulus–response mappings. Indeed, as the task involved only simple stimulus–response mappings, the primary factor determining learning success was whether mappings were correctly established based on probabilistic feedback (75% correct feedback). This interpretation is consistent with results from Seger and Cincotta (2006) and Tricomi et al. (2006) who also used within-subject blocked designs similar to our setup to investigate the regions involved in learning. However, whereas they reported activation in the dorsal caudate nucleus to be responsive to feedback during learning, we found the ventral but not the dorsal striatum to be associated with within-subject variations in learning performance. We did find activation in the dorsal striatum, but only when contrasting the Learning phase with the Application phase Learning blocks.

Limitations

There are alternative accounts that could be argued to explain our findings. One could argue that the current results were due to a lower incidence of rewarded

responses in low-accuracy blocks, leading to lower ventral striatum activation in those blocks. However, the ventral striatum also showed increased activation in the Learning phases of Learning blocks independent of performance (Fig. 3b), which contained more punished than rewarded trials compared to the later phase of these Learning blocks, when subjects performed at their maximum. We therefore argue that the correlation between activation in the ventral striatum and learning success is not likely to reflect effects of reward alone (see also Schonberg et al., 2007, Santesso et al., 2008), and that this activation is largely linked to the creation and adjustment of stimulus–response mappings. Furthermore, it has been argued that activation in the ventral striatum is associated with occurrence of prediction errors. Indeed, Schonberg et al. (2007) reported higher prediction error-related activation in the ventral striatum in subjects who were good learners compared with subjects who were poor learners. It may very well be the case that successful learners are successful because of this increased response to prediction errors, and this heightened response serves to adjust behavior accordingly. In our design we tested for within-subject effects, so that individual differences (being either a good or poor learner) cannot explain our results. In addition, in blocks in which learning was more successful there were fewer prediction errors than during lower accuracy blocks, perhaps arguing against the idea that prediction errors are the primary process driving activation in the ventral striatum.

It should be noted, that given our blocked design we are unable to determine the individual contributions from stimulus-cue, response, or outcome evaluation processes to the patterns of brain activations, or effects of feedback valence. Even using a trial-by-trial design, it is difficult to disentangle these processes given the temporal resolution of fMRI. Techniques such as EEG do provide this temporal resolution, but lack spatial resolution. One way of measuring ventral striatum activation with a high temporal resolution is via electrodes such as those used for deep-brain stimulation (Cohen et al., 2011).

Finally, we note that in the control blocks we attempted to remove either positive or negative feedback. However, the +0 feedback indicating no change in score was positive relative to the punishment for making an error. However, the accuracy in this condition was very high and, essentially, required no feedback learning, so that we expect the effects of the feedback to have been minimal relative to the effects in Learning blocks.

Further research is needed to determine whether these results generalize. For instance, it may be that increasing the complexity by increasing the number of stimulus–response mappings would lead to Learning phase-related activation in other regions such as the dorsolateral PFC. Furthermore, we note that subjects were under relatively high time pressure to respond (700 ms from stimulus onset). This may have influenced the activation in the striatum and SMA, as these regions are sensitive to time pressure (Forstmann et al., 2008). A further fundamental question is via which mechanisms relationships between stimuli, responses and outcomes are encoded, as opposed to where in the brain. The presence of widespread changes in phase relations related to stimulus–response mapping (Gladwin and de Jong, 2005, Gladwin et al., 2008) provides tentative evidence for phase coding playing a role in the implementation of goal-directed behavior (Roelfsema et al., 1997). Finally, a potentially important question is whether fluctuations in performance in patient groups are also found to be associated with the ventral striatum, or whether other regions and hence component processes might be more relevant in those populations. For example, obsessive–compulsive disorder is known to be associated with deficient ventral striatum processing during reward (Figee et al., 2011, Figee et al., 2013).

Summary and conclusion

In conclusion, learning by establishing stimulus–response mappings is a prerequisite of adaptive goal-directed behavior. In a task with multiple independent Learning blocks per subject, the process of creating and adjusting stimulus–response mappings based on feedback involved the SMA, ACC and striatum. In addition, both activation in the ACC and the ventral striatum was only found to be significantly associated with learning the stimulus–response rules, and not with their application when the rule was successfully learned. Finally, and most notably, only the ventral striatum was found to be associated with within-subject variation in learning success. The combination of these results provides a novel kind of support for the central role of the ventral striatum in adjusting behavior using feedback, and suggests that individual fluctuations in learning performance over time may be related to processes in the ventral striatum.

Chapter 3

Striatal activity during reactive inhibition is related to the expectation of stop-signals

Running title: Striatal activity and the expectation of stop-signals

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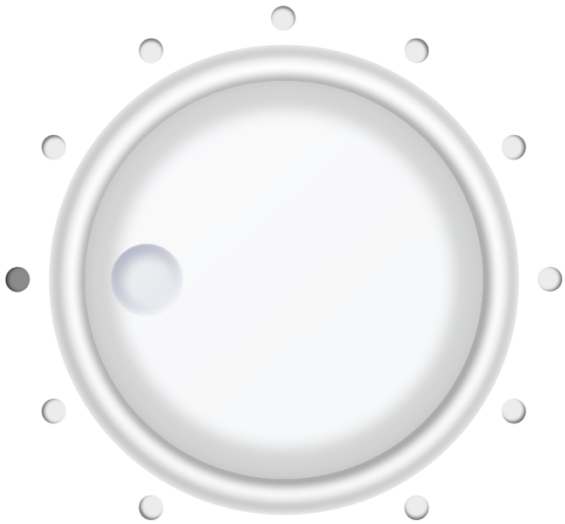

Abstract

Successful response inhibition relies on the suppression of motor cortex activity. The striatum has previously been linked to motor cortex suppression during the act of inhibition (reactive), but activation was also seen during anticipation of stop signals (proactive). More specifically, striatal activation increased with a higher stop probability. Here we investigate for the first time whether activation in the striatum during reactive inhibition is related to previously formed expectations. We used a modified stop-signal response task in which subjects were asked trial by trial, after being presented a stop-signal probability cue, whether they actually expected a stop to occur. This enabled us to investigate the subjective expectation of a stop signal during each trial. We found that striatal activity during reactive inhibition was higher when subjects expected stop signals. These results help explain conflicting findings of previous studies on the association between striatal activation and inhibition, since we demonstrate a crucial role of the subjects' expectation of a stop signal and thus their ability to prepare for a stop in advance. In conclusion, the current results show for the first time that striatal contributions to reactive response inhibition are, in part, related to subjective anticipation.

Introduction

To successfully navigate the world, people often need to control habitual actions or stop them altogether. Broadly speaking, the inhibition of responses can be divided into reactive and proactive (Aron, 2011). Reactive inhibition describes the direct inhibitory response to a stimulus, while proactive inhibition involves the anticipation of having to stop in advance. This anticipation can be derived from past experiences or external cues (Chikazoe et al., 2009; Verbruggen and Logan, 2009; Vink et al., 2014; 2015b), and ordinarily leads to the slowing down of responses (Logan and Cowan, 1984). This interplay of expectancy and inhibition develops throughout childhood (Vink et al., 2014), and has been shown to be impaired in several psychiatric disorders, such as schizophrenia (Vink et al., 2015a).

Functional imaging studies have demonstrated that proactive inhibition involves activity in a network associated with stopping, including the supplementary motor area, dorsal premotor cortex, parietal cortex, right inferior frontal gyrus and the striatum (Vink et al., 2006; Chikazoe et al., 2008; 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010; Duque et al., 2012; Zandbelt et al., 2012). The corpus striatum has been identified as a crucial region in inhibition. Its exact role is still unclear, as it has been implicated in both proactive processes leading up to response inhibition as well as reactive inhibition. Specifically, reactive inhibition during a stop-signal paradigm has been associated with increased activation in the striatum when comparing successful inhibition to failed inhibition trials (Vink et al., 2005). However, this activity has also been linked to an increase in stop-signal probability, with more activation when the probability of a stop-signal occurring was high (Zandbelt and Vink, 2010). Vink and colleagues (2015b) suggest that striatal activation during reactive inhibition is, in part, related to prior anticipatory processing of contextual cues.

To determine whether the striatum is more involved in reactive stopping or anticipatory processes preceding inhibition, it is necessary to investigate them separately. It is difficult to separate these two processes, as many tasks used in inhibition experiments rely on a single outcome measure, pressing a button or refraining from doing so, without taking the subjects' interpretation of a given cue into account. This makes it difficult to attribute a more specific role to the striatum, delineating effects stemming from formed expectations and successful

performance on the task. For instance, subjects may interpret cues indicating chances of having to stop differently, depending on success or fail in previous trials. After a number of high-probability trials in succession without an actual stop-cue, the subsequent high-probability cue may hold more weight for a participant. People are known to be bad at predicting random events, known as naive statistics and the gambler's fallacy (Clotfelter and Cook, 1993). The current study aims to investigate the role of the striatum during reactive response inhibition, and test whether its activation may in part reflect anticipatory processing triggered by previous contextual cues (Zandbelt and Vink, 2010). To achieve this we have modified a standard stop-signal response task (Vink et al., 2015b). A subjective measurement was added to the task after subjects were presented with the cue indicating stop-signal probability. Subjects were asked whether they expected a stop-signal to occur, using "yes", "no" or "don't know". With this subjective measurement, we could investigate the effect on proactive inhibition of both an objective stop-signal probability and the participant's interpretation of these cues. We previously found that subjective expectation yielded differences in striatal activation during the anticipatory period when presented with a cue indicating the probability of having to stop, with more striatal activity when subjects expected a stop-signal to subsequently occur (Vink et al., 2015b). Expecting stop-signals was also shown to aid successful inhibition, with a higher accuracy during expected stops. In our current study, we will use the same paradigm to investigate the role of the striatum during the response period of the task. This enables us to not only separate correct and incorrect responses, but also to differentiate expected and unexpected stops.

25 Healthy volunteers (20 males) performed a modified delayed-response stop-signal anticipation task while being scanned with functional MRI (Zandbelt et al., 2012). At the beginning of each trial, a cue is presented indicating stop-signal probability (0% or 50%), and subjects are asked to indicate whether or not they expect a stop-signal to occur (yes/no/don't know). We chose a 50% stop-signal probability to ensure a sufficiently high number of stops. After a variable delay following the cue, a stimulus is presented either requiring subjects to respond (go trials) or refrain from responding (stop trials). The effect of stop-signal probability and stop-signal expectation on brain activation during the stimulus-response period is investigated for both go trials and stop trials in the left and

right striatum, and motor cortex, with regions of interest taken from (Zandbelt et al., 2011).

Hypotheses

Similar to previous work on inhibition performance on similar tasks (Zandbelt and Vink, 2010; Zandbelt et al., 2011), we expect to find differences in striatal and motor cortex activation when comparing correct and incorrect stops. Striatal activity during inhibition has been associated with accuracy (Vink et al., 2005; Zandbelt and Vink, 2010), and we have previously found that the subjective expectation of stop-signals also leads to higher striatal activation during the cue period (Vink et al., 2015b). In the current study, we will focus on the response period. With expected stops, subjects will rely on proactive processes that involve the striatum, better preparing them for response inhibition and slowing down their responses. We therefore anticipate finding more striatal activation when subjects expect a stop to occur, compared to unexpected stops. As the striatum is thought to modulate motor cortical responses, we also predict a corresponding diminished motor cortex activation for expected stops, compared to unexpected stops (Zandbelt and Vink, 2010).

Experimental procedures

Subjects

Twenty-five healthy volunteers (Age M=21.6 years, SD=2.7; 5 females) participated in the experiment. All subjects were right-handed, reported no history of psychiatric or neurologic disorders and gave written informed consent. The study was approved by the ethics committee of the University Medical Center Utrecht. This study conformed to the 2013 WMA Declaration of Helsinki.

Stop-Signal Anticipation Task

Subjects performed a modified stop-signal anticipation task, in order to measure proactive and reactive inhibitory control (see **figure 1**). The task and experimental procedures were as described before (Vink et al., 2015b). In short, subjects are instructed to make timed responses to a moving bar (referred to as go trials). In some trials, the bar stops on its own (referred to as the stop-signal) and subjects have to refrain from responding. A cue is presented at the start of each trial indicating the probability that the bar will stop, either a '0' indicating no chance of a stop-signal occurring, or '*' indicating the possibility that a stop-signal could

occur. Subjects were asked immediately after the cue to answer the question: 'Do you expect a stop-signal?' by pressing a button corresponding to 'yes' or 'no'. This provided us with information concerning the subjects' subjective stop-signal expectation. If subjects failed to respond within 1000 ms, the trial was coded as 'don't know'. Also, if subjects thought that the chance that the bar would stop was 50%, i.e. if they had no expectation at all, they were allowed to refrain from making a choice and the trial would continue in the same fashion. In total, 180 trials were presented, 60 trials with 0% stop-signal probability and 120 trials with a 50% stop-signal probability. These trials were ordered in a pseudo-random sequence that was fixed across subjects. Task difficulty was managed in a stepwise fashion, with a varying delay between the stop cue and the target depending on correct or incorrect trials. This ensured overall stop accuracy to be around 50% for each individual participant. The duration between stop-cue and target at which the participant is able to attain a 50% accuracy is known as the Stop-Signal Response Time (SSRT) (Logan and Cowan, 1984), and used as a measurement of inhibition performance.

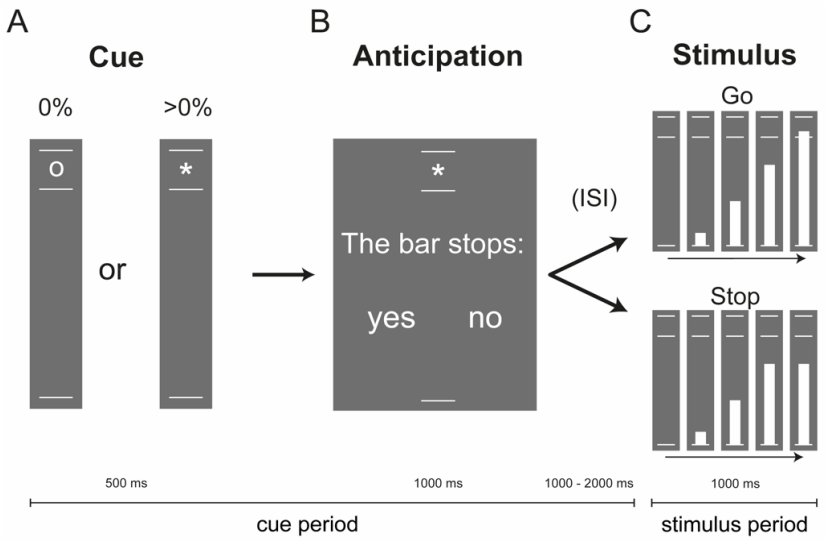

Figure 1. Delayed-response stop-signal anticipation task. *On each trial, a bar moves at constant speed from the bottom line to the upper line, reaching the middle white line in 800 ms (C). The aim is to stop the moving bar as close to the middle white line as possible by pressing a button with the right thumb during the stimulus period (Go trials). In some trials, the bar stops moving*

automatically before reaching the middle white line (stop), and subjects have to refrain from responding. The stop-signal delay (SSD) between de target line and the stopped bar is initially set at 550 ms and is varied in steps of 33 ms according to a tracking procedure (SSD is increased after a successful stop trial making it more difficult, and decreased after stop-trials in which subjects fail to inhibit, in order to achieve 50% accuracy). At the beginning of each trial, the stop-signal probability is indicated by a cue (the exact stop-signal probability is not visible for the subjects) (A). Immediately after this cue, subjects indicate whether they expect a stop in the upcoming trial by pressing a button (yes/no) (B). The task continues after 1000 ms regardless of a response. ISI, inter-stimulus interval. The inter-trial interval (not pictured) varies from 1000 to 2000 s.

Data acquisition

Imaging was performed on a 3.0 T Achieva whole-body magnetic resonance imaging scanner (Philips Medical Systems, Best, The Netherlands) at the University Medical Center Utrecht. The image acquisition parameters were identical to those described in (Vink et al., 2015b). In short, functional (T2*-weighted) echo planar images with blood oxygen level-dependent contrast oriented in a transverse plane tilted 20° over the left–right axis were obtained in a single run (683 volumes; 30 slices per volume; voxel size, 4 mm isotropic; repetition time, 1600 ms; echo time, 23 ms). A whole brain T1-weighted structural image (185 slices; repetition time, 8.4 ms; echo time, 3.8 ms; flip angle, 8°; field of view, 252 X 185 X 288 mm; voxel size, 1 mm isotropic) was acquired for within-subject registration purposes.

Analyses

Behavior

We calculated the percentage of trials in which subjects expected a stop-signal. We did this separately for trials with a 0% stop-signal probability and for trials with a 50% stop-signal probability. In addition, we analyzed the influence of stop-signal expectation on accuracy and response times. The impact of stop-signal expectation on the speed of inhibition was measured by the stop-signal reaction time, computed according to the integration (Logan and Cowan, 1984). The stop trial accuracy was also determined for both stop-signal expectation conditions.

Imaging

Image data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing and first-level analyses were performed as described before (Vink et al., 2015b). In brief, preprocessing involved slice timing correction, realignment correcting for motion, spatial normalization to the Montreal Neurological Institute template brain, and smoothing (8mm FWHM) to correct for inter-individual anatomical differences.

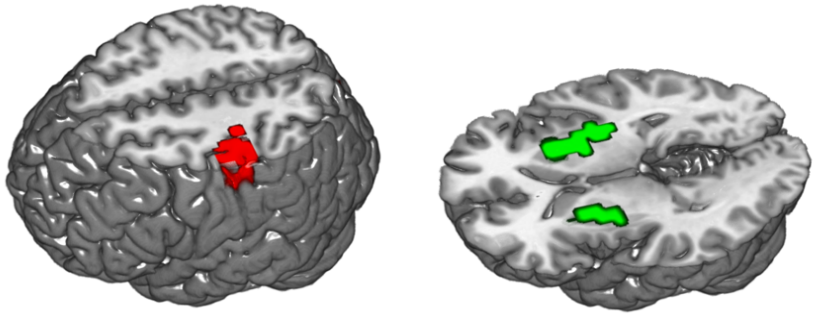

Figure 2. *Regions of interest for the motor cortex (left) and the left and right striatum (right), based on (Zandbelt et al., 2011).*

Functional images were submitted to a general linear model regression analysis. Activation time-locked to the stimulus response period was modelled based on stop-signal probability and stop-signal expectation. This resulted in contrasts for expected/unexpected and correct/incorrect trials. Trials in which a participant did not indicate an expectation were combined into a nuisance factor. Furthermore, trials with no stop-signal probability where subjects nonetheless expected a stop and incorrect go trials were considered as errors and added to the nuisance factor. Stimulus-related activation was modelled as an epoch of 1000 ms. On average the inter-trial interval was 1000 ms (ranging from 500 to 1500 ms), and served as an implicit baseline. Six realignment parameters were added as regressors of no interest to correct for head motion. All data were high-pass filtered with a cutoff of 128 s to control for low-frequency drifts. We investigated the effect of stop-signal probability and expectation during the stimulus-response period in predefined ROIs of the motor cortex, left and right striatum taken from (Zandbelt et al., 2011). Mean activation level, expressed as

percentage of signal change between each of the aforementioned contrasts, was calculated per participant for each ROI.

Results

Behavior

An overview of the percentage of trials in which a stop-signal was expected is presented in **table 1**. In the baseline condition with a 0% stop-signal probability, subjects indicated in 2% of the trials that they expected a stop-signal and in 95% that they did not expect a stop-signal, and did not respond in 3% of the trials. In the 50% stop-signal probability, subjects indicated in 48% of the trials that they expected a stop-signal to occur, in 45% that they did not, and in 7% of the trials subjects did not respond. Overall, subjects did not provide an answer in 10% of the trials, indicating that in those trials they did not have a clear inclination for choosing between expecting or not expecting a stop cue or simply were too slow to respond.

Accuracy and response times are presented in **table 2**. Accuracy on go trials was close to 100% for all conditions. Overall accuracy on stop trials was 52.43 % (SD = 3.14). As the task uses a stepwise performance adjustment, accuracy on stop trials for each individual participant should lie around 50%. Subjects performed significantly better on trials with expected stops (M = 58.61, SD = 7.41) than with unexpected stops (M = 46.26, SD = 8.53), [t(24) = 4.2, p < 0.01].

Table 1. Percentage of stop-signal anticipation per trial type

	0%	>50%	Paired samples T-test
Stop-signal expected	2 ± 5	48 ± 14	t(25) = -14,34, p < 0.001
Stop-signal not expected	95 ± 5	45 ± 12	t(25) = 16,88, p < 0.001
No expectation indicated	3 ± 2	7 ± 14	t(25) = -1,79, p = 0.09

We replicated our previous findings (Vink et al., 2015b), showing that subjects responded more slowly on trials where a stop-signal could occur but none was expected, with RTs for 0% stop signal probability trials shorter (M = 807, SD = 17) than for those with a 50% probability (M = 845, SD = 26), [t(24) = 9.6 p < 0.01]. During the trials with a 50% stop probability, subjects where even slower when they also expected a stop to occur, with RTs shorter when a stop signal was not expected (M = 845, SD = 26) than when a stop was expected (M = 857, SD = 24), [t(24) = 3.66, p < 0.01]. Observing this effect of slowing down on trials

with a stop probability, and even slower responses when stops were expected, validates/confirms that subjects understood the task.

Table 2. Accuracy and response times per trial type. *Values ± SEM. Test values and P-values result from repeated-measures analyses. RT, reaction time on go trials; SSRT, stop-signal reaction time.*

		50% probability			
Trial type	**0% probability**	**Not expected**	**Expected**	**Test value**	**P-value**
Go					
Accuracy (%)	95 ± 5	98 ± 3	97 ± 4	$F_{2,23}$= 3.60	0.044
RT (ms)	807 ± 17	845 ± 26	857 ± 24	$F_{2,23}$= 57.6	< 0.0001
Stop					
Accuracy (%)		46 ± 8	58 ± 7	t(24) = 4.2	< 0.0001
SSRT (ms)		231 ± 18	226 ± 22	t(24) = 1.1	0.28

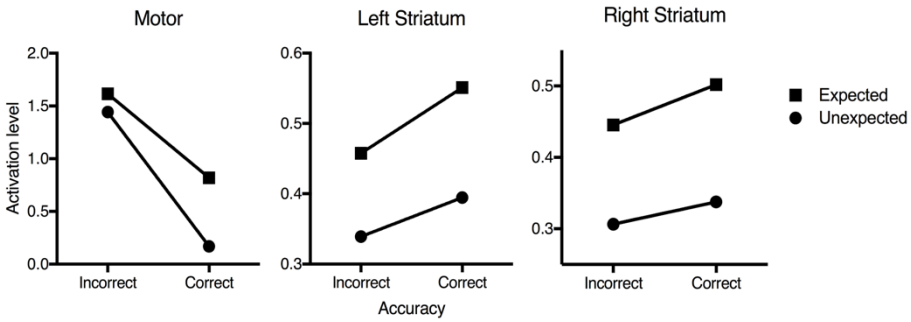

Figure 3. *Estimated marginal means for activation in the motor cortex, left and right striatum, for unexpected/expected and incorrect/correct stops.*

Imaging data

To test the effects of expectancy and accuracy on the striatum, a GLM repeated measures was conducted on the stop trials. For the left striatum there was a main effect of expectancy [F(1,24) = 6.22, p = 0.02], but not for accuracy [F(1,24) = 0.09, p = 0.77], and no interaction effect [F(1,24) = 0.02, p = 0.70]. For the right striatum there was an effect of expectancy as well [F(1,24) = 6.47, p = 0.02], but again not for accuracy[F(1,24) = 0.20, p = 0.66], nor was there an interaction effect [F(1,24) = 0.04, p = 0.83]. This effect of expectancy on striatal activation is visualized in **figure 3**.

A similar analysis was conducted for the motor cortex ROI. There was a main effect of expectancy [$F(1,24) = 4.25$, $p = 0.05$], and for accuracy [$F(1,24) = 19.59$, $p < 0.01$], but no interaction effect [$F(1,24) = 2.47$, $p = 0.13$].

Discussion

The current study is the first to investigate the role of the striatum during outright stopping and to take into account the influence of participants' trial by trial subjective expectation of stop signals. Using a modified stop-signal anticipation task, subjects were asked on each trial after having seen the cue, whether they expected a stop to occur or not. This additional measurement allowed us to separate effects of expectation from the act of stopping in itself. The current study shows for the first time that striatal activation during reactive inhibition is associated with the pre-existing subjective expectation of having to stop. This finding is in line with our previous findings on proactive inhibition and the striatum, and findings on striatal contributions to stopping.

In our task, there was significantly more bilateral activation in the striatum during stopping when subjects already expected the stop-signal to occur. There was no difference in activation between correct and incorrect stops, as we had found previously when we did not correct for expectation (Vink et al., 2005; Zandbelt and Vink, 2010). Similar to earlier findings (Zandbelt and Vink, 2010; Vink et al., 2014; 2015b), subjects slowed down their responses when the cue showed a high probability of a stop-signal, and slowed down even more when they also indicated that they expected a stop-signal. The link between expectation of stop signals and the striatum is in line with studies that have reported striatal activity when the occurrence of a stop-signal was highly predictable (Vink et al., 2005; Zandbelt and Vink, 2010). These results allow us to explain why not all response-inhibition paradigms find striatal activation during inhibition. Striatal involvement may rely on subjects being able to anticipate the occurrence of stop signals.

The basal ganglia are presumed to mediate behavioral control arising from frontal cortical areas (Alexander and DeLong, 1986). Recent work suggests that the dysfunction in the striatal area found in schizophrenia results in an inability to adequately incorporate cues to prepare for upcoming events (Vink et al., 2015a). In the context of an expected stop in the current task, heightened striatal activity may therefore reflect the early preparation of resources for a change in

behavior, in this case inhibition. Since the striatum has been implicated in the suppression of motor responses (Vink et al., 2005; Aron, 2006a; Zandbelt and Vink, 2010), it possibly exerts this proactive role by modulating the response threshold in the motor cortex (Lo and Wang, 2006; Forstmann et al., 2008; Jahfari et al., 2010). In macaque monkeys, response suppression indeed correlated with activity of interneurons in the putamen (Lee et al., 2005), while oscillations in the putamen were tuned to rhythmical movement (Bartolo et al., 2014), suggesting that putamen activity is associated with the internal representation of sensorimotor states.

Motor cortex activation was lower for successful stops, but contrary to our expectation we did not find lower motor cortex activation when those stops were expected. This finding could be the result of a late-breaking mechanism that halts the motor response at the last minute (Kühn et al., 2009). Suppression of an already initiated response depends partly on the ability of the subthalamic nucleus (STN) to suppress thalamocortical output. Activity in the STN in humans has been linked to breaking or inhibiting go responses (Aron, 2006b), and stimulation of the STN has been demonstrated to facilitate basic motor control in patients with Parkinson Disorder (Favre et al., 2012; Obeso et al., 2013). Excitation of the STN in rats was shown to be largely related to stop cues, whereas striatal activity depended on movement-related inhibition (Schmidt et al., 2013). Within our current paradigm, the STN could be key in understanding to what degree inhibitory processes are affected by expectations.

It is unclear whether striatal activation during reactive inhibition and earlier during proactive inhibition represents one continuous or two separate processes. Timing and type of response seem crucial for distinguishing the many different roles of the striatum, such as in anticipation, learning and effort. For example, the striatum also has been reported to be involved in cue-learning paradigms (Vink et al., 2013), to signal prediction errors (Eshel et al., 2016), and invested effort (Pas et al., 2014). Kimura and colleagues (2003) found a differentiation between the caudate nucleus and putamen of macaque monkeys during go signal responses and reward anticipation. Rat research has shown important distinctions in basal ganglia structures involved in responses to unexpected stimuli (Watson et al., 2015). A closer look at striatal subsystems and

their involvement in the expectation of inhibitory control seems therefore warranted as well.

Notably, activity in the striatum during the response period did not directly correlate with accuracy, even though expectancy was both associated with striatal activity and accuracy. Accuracy for expected stops were significantly higher, presumably because subjects slowed down more and therefore had more time to inhibit their response. A stop signal was expected in about half of the trials where one could occur, but the actual rate at which they occurred was not known to them. Expecting a stop signal was therefore not directly related to one actually appearing, and it did only indirectly benefit accuracy on the task. Stop trials that were expected and where a stop signal did end up appearing, were more often correct, simply because subjects slowed down their responses. Therefore, the relationship between striatal activity and accuracy exists only indirectly and possibly is not strong enough to be significant.

Conclusion

Our current findings stress the important role of the striatum in expectation. We have demonstrated the involvement of the striatum in forming expectations during proactive inhibition, and its subsequent contribution to reactive inhibition. For the first time we show how this involvement is exhibited during actual stopping, with greater striatal activation for expected stops when compared to unexpected stops. These findings support previous research implicating the striatum in proactive inhibition when dealing with cues indicative of stop-signal probability. It suggests that the striatum not only plays a role during the initial phase of assessing probability of inhibition, but continues this involvement during actual stopping. Specifically, this role might be to prepare the individual for a behavioral change by suppressing response-activation in the motor cortex. These results allow us to build towards a more complete model of response inhibition, delineating the roles of reactive and proactive processes in the brain. Furthermore, shedding light on the contribution of the striatum to response inhibition allows for a better understanding of psychopathology revolving around striatal dysfunction, such as seen in schizophrenia, impulsivity, or addictive behaviors. Even during normal brain development, imbalances in prefrontal and striatal development can lead to more impulsive and disinhibited behaviors (Casey and Caudle, 2013). Investigating striatal contributions to

inhibition therefore enables us to better understand how a developing brain is more prone to risk taking, and where development is most vulnerable. Future research can further delineate the specific functions of the striatum, possibly dependent on striatal subdivisions, and their contribution to behavioral control.

Chapter 4

Using subjective expectations to model the neural underpinnings of proactive inhibition

Running title: Modelling foundations of proactive inhibition

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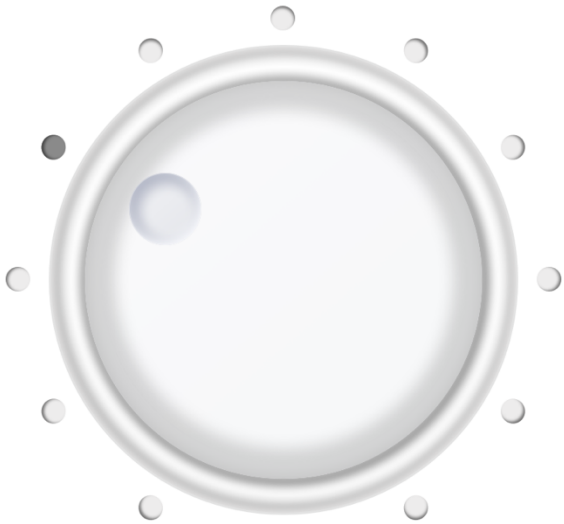

Abstract

Proactive inhibition – the anticipation of possibly having to stop a response - relies on objective information contained in cue-related contingencies in the environment, as well as on the subjective interpretation derived from these cues. To date, most studies of the brain areas underlying proactive inhibition have exclusively considered the objective predictive value of environmental cues, by varying the probability of stop-signals. However, only taking into account the effect of different cues on brain activation, the subjective component of how those cues affect behavior is ignored. We used a modified stop-signal response task that included a measurement for subjective expectation, to investigate the effects of both objective probability and subjective interpretation. After presenting a cue indicating the probability that a stop-signal will occur during the task, subjects were asked whether they actually expected a stop-signal to occur. Response time was used to retrospectively model brain activation during the cue. The results show that activation in the right striatum, right frontal cortex and right parietal cortex is significantly linked to the subjective expectation of a stop-signal. Our study is the first to demonstrate that the subjective expectation of having to inhibit a response is sufficient to evoke activation in key regions associated with inhibition.

Introduction

Efficient goal-directed behavior relies on the ability to anticipate future events, allowing us to proactively adjust our response tendencies. This anticipation can be derived from consistent patterns of events involving environmental cues. These patterns reflect some objective probability of what is likely to happen contingently on the cues, but the decision to change our behavior depends on the subjective estimation of that probability. Inhibition is rarely a simple reaction to a stop cue, as it relies on the correct anticipation of the probability of having to stop a response in advance. For example, slowing down when cycling through a busy street will increase the chances of successfully coming to a stop when someone crosses the road. This type of anticipation is commonly referred to as proactive inhibition (Chikazoe *et al.*, 2009; Verbruggen & Logan, 2009; Zandbelt *et al.*, 2012; Vink *et al.*, 2014; 2015). Proactive inhibition can facilitate behavioral control by delaying a response, and thereby increasing the chance that the response can be inhibited successfully, or alternative action can be taken (Logan & Cowan, 1984).

Tasks that are designed to engage proactive control typically use cues at the start of each trial. These cues indicate to the subject the likelihood of having to stop or withhold a response. While these cues objectively represent a stop-signal likelihood, subjects can vary in their subjective expectation whether or not a stop-signal will occur, for example, based on the occurrence of stop-signals in previous trials. Subjects make a prediction based on a cue, and subsequently use that information to improve their prediction. Therefore, we argue that investigating proactive inhibitory control relies upon the adequate characterization of the role of both objective cue information and subjective expectation. To date, most studies investigating the neural components of proactive inhibitory control have solely relied on varying the objective probability of a cue. Our previous research, (Vink *et al.*, 2015), was the first to incorporate a subjective measurement.

Traditional functional imaging studies have demonstrated that proactive inhibition involves activity in a network associated with stopping, consisting of the striatum, supplementary motor area (SMA), dorsal premotor cortex (PMd), right inferior frontal gyrus (rIFG) and right inferior parietal cortex (rIFC) (Vink *et al.*, 2005; Chikazoe *et al.*, 2007; 2008; Jahfari *et al.*, 2010; Zandbelt & Vink, 2010;

Duque *et al.*, 2012; Zandbelt *et al.*, 2013; van Belle *et al.*, 2014). By disentangling the processing of objective cue information and subjective stop-signal expectation, we (Vink *et al.*, 2015) were able to show for the first time that activation in the striatum, SMA, PMd and midbrain was related to subjective expectation.

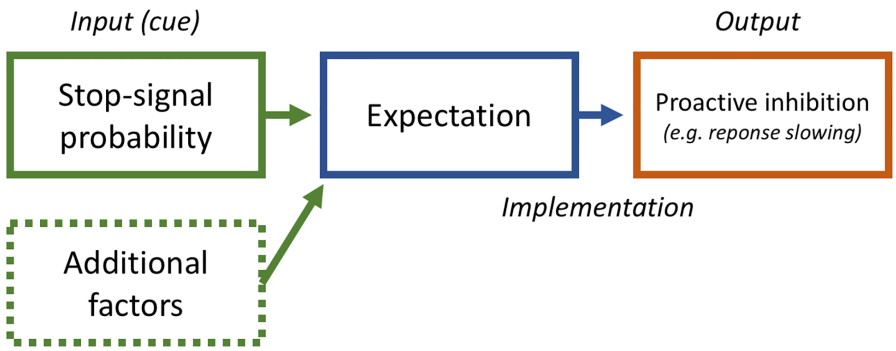

Figure 1. Schematic representation of the processes that lead up to proactive inhibition. *Proactive inhibition is defined behaviorally as slowing down responding in anticipation of having to stop a response. This slowing is based on whether or not, and to which degree, the subject expects a stop-signal to occur. In turn, this subjective expectation is based in part on the cue, which indicates stop-signal probability. However, as we have shown before, subjects vary in their subjective expectation on a trial-by-trial basis. From this simplified scheme, it follows that investigating neural underpinnings of proactive inhibition should not be based on cues indicating stop-signal probability, but rather on the actual subjective expectation. In the current study, we measure this subjective expectation in two ways: [a] subjects indicate their expectation of a stop occurring (yes/no) via button press, [b] response speed is taken as an indicator of subjective expectation, which slower responses indicating a higher level of stop-signal expectation, and thus more proactive inhibition.*

However, forcing subjects to rate their subjective expectations into two categories of 'expected' and 'unexpected stops' ignores possible individual variation in their assessments. On each trial, the same kind of cue can be processed differently by the subject and consequently elicit a different response (see **figure 1**). To better quantify the subjective component in cue processing,

we will take into account the effect of these cues on subsequent response times. A consistent finding from studies on proactive inhibition is that an increase in stop-signal probability is accompanied by a slowing of responses (Vink *et al.*, 2005; 2006; Verbruggen & Logan, 2008; Zandbelt & Vink, 2010; Jahfari *et al.*, 2012; Zandbelt *et al.*, 2013). In addition, subjects also slow down even more when they also expect a stop to occur (Vink *et al.*, 2015). In our current experiment, we will use this effect of slowing down to infer whether or not subjects actually expected a stop to occur, and use this to more accurately model their responses.

Materials and methods

Subjects

Twenty-five volunteers (Age M=21.6 years, SD=2.7; 5 females, 20 males) participated in the experiment. All subjects were right-handed, reported no history of psychiatric or neurologic disorders and gave written informed consent. The study was approved by the ethics committee of the University Medical Center Utrecht. This study conformed to the 2013 WMA Declaration of Helsinki.

Stop-Signal Anticipation Task

Subjects performed the stop-signal anticipation task (Zandbelt *et al.*, 2013), a stop-signal task designed to measure proactive and reactive inhibitory control. The task and experimental procedures were adapted from (Vink *et al.*, 2015), see **figure 2** for an overview. In short, subjects were instructed to stop a moving bar on the screen (referred to as go trials). In some trials, the bar stops moving on its own (referred to as the stop-signal) and subjects have to refrain from responding. At the beginning of each trial, a cue indicates the probability that the bar will stop: either a '0' indicating no chance of a stop-signal occurring, or a '*' indicating the possibility that a stop-signal could occur. Subjects were asked immediately following the cue to answer the question: 'Do you expect a stop-signal?' by pressing a button corresponding to 'yes' or 'no'. This provided us with information concerning the subjects' subjective stop-signal expectation. If subjects did not respond within 1000 ms, the trial was coded as 'don't know'. Also, if subjects had no expectation at all, they were allowed to refrain from making a choice and the trial would continue in the same fashion. In total, 180 trials were presented, 60 trials with 0% stop-signal probability and 120 trials with

a 50% stop-signal probability. These trials were ordered in a pseudo-random sequence that was fixed across subjects.

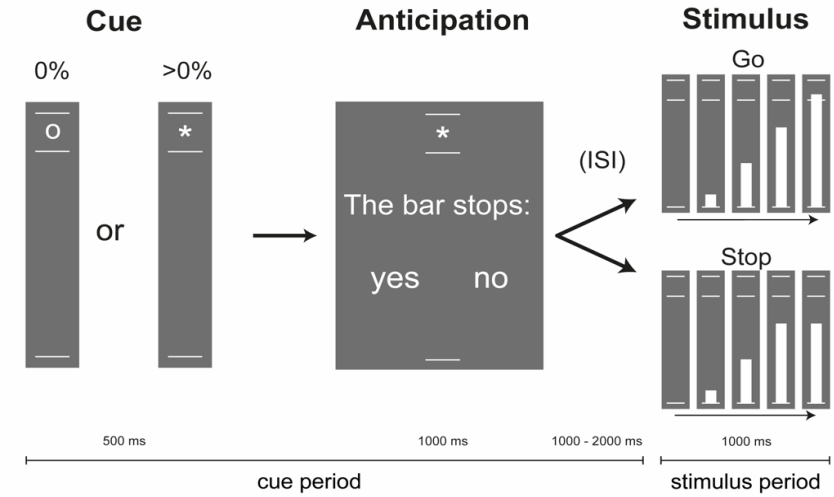

Figure 2. Delayed-response stop-signal anticipation task. *On each trial, a bar moved at constant speed from the bottom line to the upper line, reaching the middle white line in 800 ms (C). The aim is to stop the moving bar as close to the middle white line as possible by pressing a button with the right thumb. These trials are referred to as go trials. In some trials, the bar stops moving automatically before reaching the middle white line (stop), indicating that subjects have to refrain from reacting. The stop-signal delay (SSD) was initially set at 550 ms and was varied in steps of 33 ms according to a tracking procedure (SSD is increased after a successful stop trial; SSD is decreased after stop-trials in which subjects fail to inhibit). At the beginning of each trial, the stop-signal probability was indicated by a cue (the exact stop-signal probability was not visible for the subjects) (A). Immediately after this cue, subjects indicated whether they expected a stop-signal in the upcoming trial by pressing a button (yes/no) (B). They were not forced to make a decision; the task continued after 1000 ms regardless of a response. ISI, inter-stimulus interval. The inter-trial interval (not pictured) varied from 1000 to 2000 s.*

Data acquisition

Imaging was performed on a 3.0 T Achieva whole-body magnetic resonance imaging scanner (Philips Medical Systems, Best, the Netherlands) at the

University Medical Center Utrecht. Functional (T2*-weighted) echo planar images with blood oxygen level-dependent contrast oriented in a transverse plane tilted 20° over the left–right axis were obtained in a single run (683 volumes; 30 slices per volume; voxel size, 4 mm isotropic; repetition time, 1600 ms; echo time, 23 ms). A whole brain T1-weighted structural image (185 slices; repetition time, 8.4 ms; echo time, 3.8 ms; flip angle, 8°; field of view, 252 X 185 X 288 mm; voxel size, 1 mm isotropic) was acquired for within-subject registration purposes.

Analyses

The percentage of trials was calculated where subjects expected a stop to occur. This was done separately for trials with a 0% stop-signal probability and for trials with a 50% stop-signal probability. In addition, the effect of stop-signal expectation on accuracy and response times was assessed. The impact of stop-signal expectation on the speed of inhibition was measured by the stop-signal reaction time, computed according to the integration (Logan & Cowan, 1984). The stop trial accuracy was also determined for both stop-signal expectation conditions.

Imaging

Image data were analyzed using SPM. Preprocessing involved slice timing and correction, spatial normalization to the MNI template brain, and smoothing (8mm FWHM) to correct for inter-individual differences. Functional images were submitted to a general linear model regression analysis. Activation time-locked to the presentation of the cue and to the stimulus response period was modelled based on stop-signal probability and stop-signal expectation. Trials in which a participant did not indicate an expectation, trials with zero stop-signal probability where subjects nonetheless expected a stop and incorrect go trials were considered as errors and added to the nuisance factor. Stimulus-related activation was modelled as an epoch of 1000 ms. On average the inter-trial interval was 1000 ms (ranging from 500 to 1500 ms), and served as an implicit baseline. Six realignment parameters were added as regressors of no interest to correct for head motion. All data were high-pass filtered with a cutoff of 128 s to control for low-frequency drifts.

To investigate the brain regions associated with proactive inhibition, we performed three whole brain analyses during the cue period. First, we contrasted

activation in the brain for cues indicating the possibility of a stop-signal, and those without. Second, for the cues with a stop-signal probability of 50% we contrasted those cues where subjects expressed actually expecting a stop to occur, with those in which they did not. Last, we looked at brain activity for the trials in which a stop-signal could occur, with subjects' subsequent response times included as a parametric modulator in a separate model. For this, the hemodynamic response function is convolved with a signal containing delta peaks multiplied by the response times, as we expect more brain activation during the cue period when subjects slowed down afterwards.

Results

Behavior

An overview of the percentage of trials in which a stop-signal was expected is presented in **Table 1**. Accuracy and response times are presented in **Table 2**. Accuracy on go trials was close to 100% for all conditions. Overall accuracy on stop trials was 52% (SD = 3). Subjects performed significantly better on trials with expected stops (M = 59, SD = 7) than trials with unexpected stops (M = 46, SD = 9, $t(25) = 4.2$, $p < 0.001$).

Table 1. *Stop-signal anticipation per trial type as mean (± SD) percentage of trials.*

	0% probability	>50% probability	Paired samples t-test
Stop-signal expected	2 ± 5	48 ± 14	$t(24) = -14.3$, $p < 0.001$
Stop-signal not expected	95 ± 5	45 ± 12	$t(24) = 16.9$, $p < 0.001$
No expectation indicated	3 ± 2	7 ± 14	$t(24) = -1.8$, $p = 0.09$

Table 2. *Mean (± SD) accuracy and response times per trial type.*

		50% probability			
Trial type	**0% probability**	**Not expected**	**Expected**	**Test value**	**P-value**
Go					
Accuracy (%)	95 ± 5	98 ± 3	97 ± 4	$F_{2,23} = 3.6$	0.044
RT (ms)	807 ± 17	845 ± 26	857 ± 24	$F_{2,23} = 57.6$	< 0.001
Stop					
Accuracy (%)		46 ± 9	59 ± 7	$t(24) = 4.2$	< 0.001
SSRT (ms)		231 ± 18	226 ± 22	$t(24) = 1.1$	0.28

In line with previous findings (Zandbelt *et al.*, 2013; Vink *et al.*, 2015) subjects responded slower on trials where a stop-signal could occur $t(24) = 10.1$, $p < 0.001$. When we only included trials where subjects did not expect a stop, subjects were again slower on trials where a stop could occur $t(24) = 9.6$, $p < 0.001$. Finally, when subjects expected a stop, their responses slowed down even more $t(24) = 3.7$, $p = 0.001$. This effect of response slowing is visible in **figure 3**.

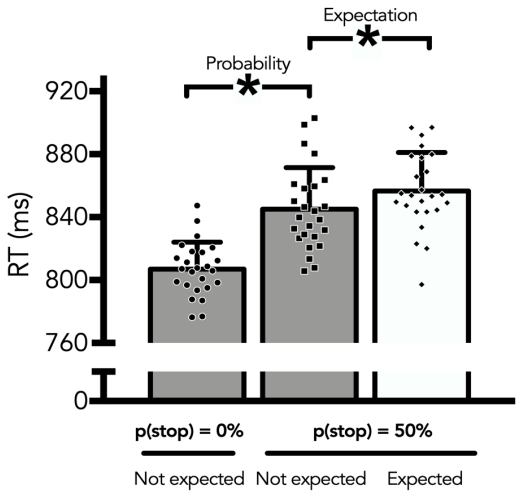

Figure 3. Response times for all conditions. *Subjects were slower on trials with a stop-signal probability of 50%, and even slower when they also expected one to occur. *p < 0.001.*

Imaging

See our supplemental materials for a replication of our previous study (Vink et al., 2015), using pre-defined regions of interest. When contrasting the cues indicating a stop-signal probability of 50% with those indicating 0% stop-signal probability, we found activation in medial and inferior frontal gyrus, inferior parietal lobe and putamen (**figure 4.A**), indicating that these areas are involved with the possible inhibition of a future response or the processing of environmental cues. Our second analyses contrasted the cues with a stop-signal probability where subjects expected a stop, with those in which they did not expect one. This analysis yielded again significant activation in the medial frontal gyrus, parietal lobe and in the occipital gyrus (**figure 4.B**). Finally, we modelled activation during the cue period using subsequent response time as a parametric modulator. We found that activation in the mid frontal gyrus, inferior parietal lobe and right putamen positively correlated with response time (**figure 4.C**).

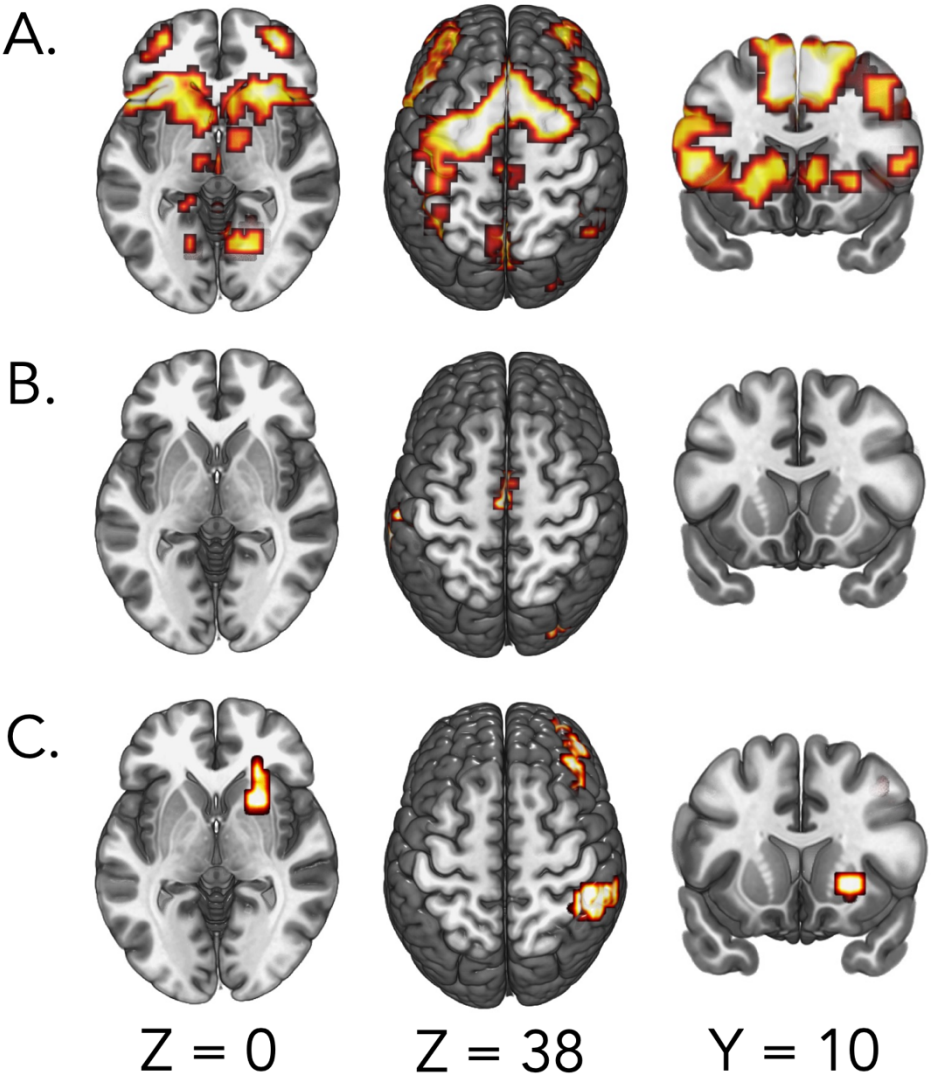

Figure 4. Imaging results for the three whole-brain analyses. *All brain activation maps are thresholded at a family-wise error- corrected cluster level of p < 0.05, with cluster sizes determined with the CorrClusTh script (http://www.sph.umich.edu/~nichols/JG5/CorrClusTh.m). For details see Table 3.* ***A:*** *Brain activation for the contrast of trials with a stop-signal probability of 50% vs 0%.* ***B:*** *Brain activation for the contrast of the cues with a stop-signal probability of 50% where subjects expected one to occur vs where they did not.* ***C:*** *Brain activation during the cue period modulated by subsequent response times.*

Discussion

Our current results show that both subjective expectation and objective stop-signal processing underlie proactive inhibitory control processes. In line with our previous study, subjects slowed down their responses when there was a cued probability that a stop-signal would occur, and slowed down even more when they actually expected a stop-signal. As subjects consistently slow down when expecting a stop to occur, we used response time as an additional objective and continuous measurement of stop expectancy. Activation in the putamen, inferior parietal lobe and mid frontal gyrus during the cue period correlated positively with response time, and was therefore linked to actual subjective expectation.

These results replicate earlier findings, where activation in the striatum was shown to depend on subjective anticipation of stop-signals (Vink *et al.*, 2015). Furthermore, a recent study found that striatal activation during reactive inhibition also depended on subjects expecting the stop in advance (Pas *et al.*, 2017). In addition, response inhibition studies have commonly reported striatal activity when the occurrence of a stop-signal was highly predictable (Vink *et al.*, 2005; Aron & Poldrack, 2006; Vink *et al.*, 2006; Zandbelt & Vink, 2010; Zandbelt *et al.*, 2011). Our results are also supported by studies implicating the striatum in the control over actions (Kimura, 1992; Chen *et al.*, 2010; Watanabe & Munoz, 2010; Duque *et al.*, 2012; Zandbelt *et al.*, 2013).

Functionally, the striatum is closely connected with the motor cortex (Vink *et al.*, 2005; Forstmann *et al.*, 2008; Duann *et al.*, 2009; Zandbelt & Vink, 2010; Vergani *et al.*, 2014), and consequently involved in basic motor inhibition and response switching (Forstmann *et al.*, 2008). The corpus striatum itself has been identified as a crucial region in inhibition. And while its exact role is unclear, it has been implicated in both proactive processes leading up to response inhibition as well as in reactive inhibition (Vink *et al.*, 2005). In addition, the basal ganglia have been hypothesized to act as a gatekeeper, preventing execution of conflicting motor responses (Mink, 1996; Friend & Kravitz, 2014). A more overarching role of the striatum is likely the selection of responses based on prior reinforcement (Vink et al., 2013).

Our current results show that this area is involved in the process of proactive inhibition. Indeed, striatal activity has been linked to the expectation of higher

effort demands (Pas *et al.*, 2014). Activation has also been demonstrated to increase during cue-learning paradigms; being linked to the formation of stimulus-response associations (Vink *et al.*, 2013; Diederen *et al.*, 2016). During our task, subjects constantly have to ascribe a subjective weight to the cue they are given – what do they actually believe is going to happen. This can therefore be seen as comparable to the learning phase of a cue-learning paradigm. (Tricomi *et al.*, 2006) showed that striatal activation was linked to the incorporation of feedback in a learning task, and data by (Seger, 2005) reaffirms its role in identifying the behavioral context for selection of an appropriate strategy. Striatal contributions to proactive inhibition could therefore lie in selecting the optimum response, and linking cues with the appropriate behavior.

Another important role in inhibition is played by the right inferior frontal cortex (Aron *et al.*, 2003; Rubia *et al.*, 2003). An increase in functional connectivity between this area and the basal ganglia has been shown to increase response inhibition efficiency (Xu *et al.*, 2016) and right frontal cortex activity has been correlated with stopping speed (Whelan *et al.*, 2012). A prominent line of reasoning is that this region is critical in the act of stopping itself (Aron, 2011), functioning as a breaking mechanisms halting or slowing down responses (Aron *et al.*, 2014; Cai *et al.*, 2014). Hampshire and colleagues (Hampshire, 2015) propose the alternative view that recruitment is related to detection of important cues, instead of to the subsequent suppression of motor responses. Indeed, cognitive control was primarily engaged for contextual cue monitoring instead of the actual stopping, during a response inhibition task (Chatham *et al.*, 2012). Findings from the psychiatric field support this theory as well. For example, in patients suffering from post-traumatic stress disorder, impaired right inferior frontal cortex (rIFC) functioning has been directly linked to the processing of contextual cues (van Rooij *et al.*, 2014). In line with this, reduced activation in the rIFG and temporoparietal junction was accompanied by impairments in the processing of cues aiding proactive inhibition in schizophrenia patients (Zandbelt *et al.*, 2011). The rIFC directs attentional processes (Baldauf & Desimone, 2014), with differential roles in attention and inhibition depending on subareas within the rIFC (Sebastian *et al.*, 2015). Therefore, involvement of the right frontal cortex in cue processing might be mediated by increased attention to these cues. This attentional account for the role of the IFG is supported by studies that compared brain activation in response to unexpected stimuli and stopping per

se (Sharp *et al.*, 2010). Hypoactivation of the right inferior frontal cortex (rIFC) in patients with ADHD has been linked to impaired response inhibition (Morein-Zamir *et al.*, 2014). Taken together with our results, this places the rIFG in a multiple demand network (Kolodny *et al.*, 2017).

Activation in the right inferior parietal lobe has been linked to self-initiated as opposed to triggered or automatic responses (Kühn *et al.*, 2009). Kühn and colleagues suggest that this region plays a role in inhibitory processes when voluntary suppression of a response requires more selection effort or attention. Other research has linked the right inferior parietal cortex (rIPC) to the storage of acquired motor skills (Niessen *et al.*, 2014), as lesions to this region disrupt the ability to perform previously learned actions (Halsband *et al.*, 2001), and has demonstrated its involvement in response selection processes (Dippel & Beste, 2015). Together with our findings, this suggests that the rIPC could be involved in preparing for an alternative motor response when the probability of having to change the response, e.g., on encountering a stop-signal, is high.

Limitations

Our task repeatedly asks subjects whether they expect a stop-signal or not, based on a single cue. It may very well be that subjects' reported expectation is not fully correlated with their internal subjective expectation. However, it is not necessarily relevant whether our measurement was actually able to capture our subjects' expectations, or whether choosing 'yes' or 'no' steered their behavior accordingly. Nevertheless, the self-report would appear to have at least face validity and our results show an effect of this reported expectation on both behavioral measurement and in brain activation. By using response times as a parametric modulator of brain activation during the preceding cue period, we have also included an objective measurement of proactive inhibition.

Conclusion

Proactive inhibition cannot be investigated by solely looking at objective cue information, and our results establish the necessity of taking into account the variability of the effect that a cue has on a subjects' behavior. Tasks solely relying on objective information derived from cues are missing an important factor when interpreting the results, namely how those cues are truly processed and interpreted. With our current experiment, we have used this subjective

component to demonstrate that activation in the striatum, right frontal cortex and right parietal cortex were related to the expectation of having to inhibit a response, i.e. proactive inhibition. These results allow us to build towards a more complete model of response inhibition, delineating the roles of objective and subjective information.

Supplemental materials

The following serves as a replication analysis of our previous research (Vink *et al.*, 2015). Here, our task was set up with multiple levels of stop-signal probability, and therefore the level of subjective expectation was related to objective stop-signal probability. The task contained two levels of stop-signal probability (25% and 34%), and subjects indicated that they expected a stop-signal in 25% and 75% of the trials, respectively. Although we grouped together the two levels of stop-signal probability to minimize the impact of the potential confound, these results needed to be replicated in an unbiased design. Therefore, we now used a single stop-signal probability level of 50% to allow the unbiased disentangling of brain activations related to subjective expectations and the processing of objective stop-signal probabilities.

To replicate our previous results, we investigated the effect of stop-signal probability and expectation during the cue and stimulus-response period in predefined regions of interest (ROIs). These ROIs were based on activation patterns from a previous study in which sample of healthy participants performed the delayed-response stop-signal anticipation task (Zandbelt et al., 2013b). For the cue period, we looked at the striatum, SMA, left PMd and midbrain. For the stimulus-response period the ROIs included the rIFG and rIPC. Mean activation level, expressed as percentage of signal change, was calculated per participant for each ROI. Identical to the previous study, paired-sampled t-tests were used to investigate differences in activation between conditions.

Imaging data

Cue period

Figure 5 shows activation in the ROIs during the cue period. Activation in the striatum $t(24) = 3.7$; $p = 0.001$, SMA $t(24) = 5.4$; $p < 0.001$ and PMd $t(24) = 5.3$; $p < 0.001$ was higher in trials with 50% stop-signal probability compared to trials with 0% probability, regardless of expectation. No such effect was observed in the midbrain region $t(24) = 1.739$; $p = 0.095$. Next, we looked at activation in these regions for trials with 0% vs. 50% stop-signal probability while subjects did not expect a stop-signal. These analyses showed a significant difference in activation for the striatum $t(24) = -2.4$; $p = 0.022$, SMA $t(24) = -4.2$; $p < 0.001$ and PMd $t(24) = -3.0$; $p < 0.01$. Again, no difference was found in the midbrain

region t(24) = -1.2; p = 0.30. Finally, we looked at the difference in trials where subjects did versus did not expect a stop-signal to occur, in the context of 50% probability. For trials in which subjects expected a stop to occur, activity in the striatum t(24) = -2.2; p = 0.035, SMA t(24) = -2.3; p = 0.028 and PMd t(24) = -3.9; p < 0.001 was higher than when they did not expect one. Again, there were no significant differences in the midbrain region t(24) = 1.1; p = 0.27.

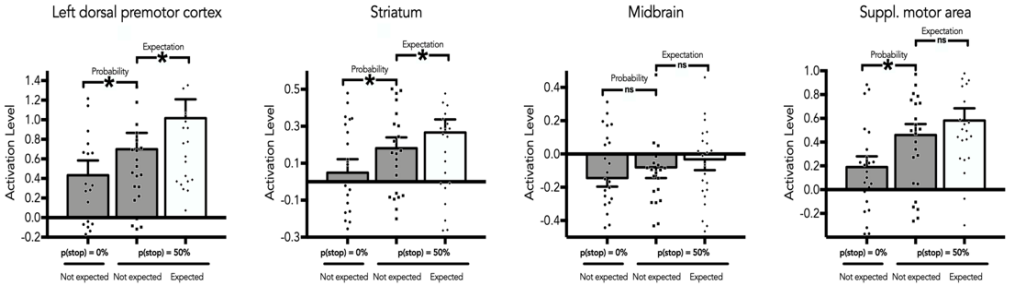

Figure 5. *Activation as percent signal change in the selected ROIs during the cue period across conditions. Center coordinates for left PMd -24,10,54; Striatum -8,12,0; Midbrain -5,-31,-18 and SMA -8,5,50. *P < 0.05.*

Stimulus and response period

Figure 6 shows activations in the ROIs during the stimulus and response period. Similar to previous studies (Zandbelt *et al.*, 2013; Vink *et al.*, 2015), we found heightened activation in both the rIFG t(24) = 4.5; p < 0.001 and rIPC t(22) = 6.6; p < 0.001 when stop-signal probability was 50% compared to 0%, regardless of stop-signal expectation. In addition, we examined the effect of stop-signal expectation by examining a subset of trials where subjects indicated not expecting a stop-signal. There was significantly more activation in both the rIFG t(24) = -4.2; p < 0.001 and rIPC t(22) = -6.3; p < 0.001 in trials with 50% compared to 0% stop probability. Finally, we examined the effect of subjective expectation in the context of 50% stop-signal probability. There was no significant effect for stop-signal expectation on activation in the rIFG t(24) = 1.2; p = 0.23 and rIPC t(22) = -0.4; p = 0.68.

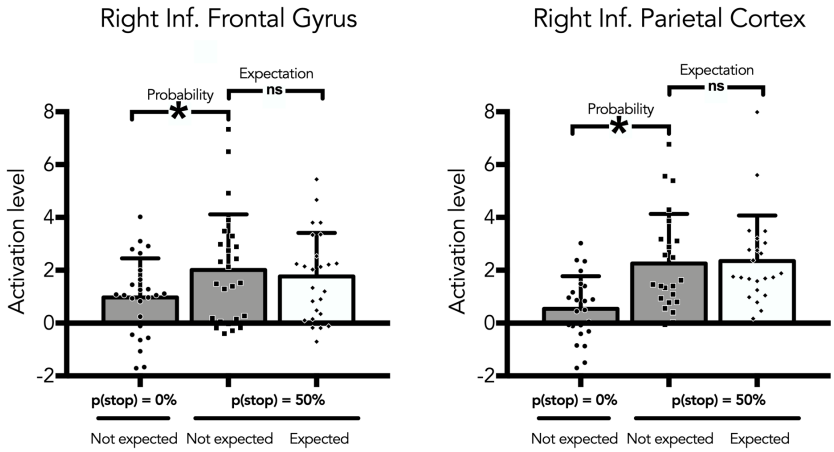

Figure 6. *Activation as percent signal change in the selected ROIs during the response period across conditions. Center coordinates for rIFG 50,10,29, and rIPC 59,-40,30. *P < 0.05*

Chapter 5

Beta-band event-related desynchronization in the motor cortex predicted by slowing due to proactive inhibition

Running title: Beta-band desynchronization predicted by proactive response slowing

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Submitted

Abstract

Proactive inhibitory control refers to our ability to slow down our behavioral responses in anticipation of an impending stop. In the brain, this involves activity in a network associated with stopping, but more specifically relies on connections between cortical and subcortical structures. These connections are not yet fully developed until late adolescence and are underdeveloped in some psychiatric illnesses. Previous studies have used electroencephalography (EEG) to identify event-related oscillations that may be associated with proactive inhibition, by showing differences corresponding to stop-signal likelihood. Our aim was to demonstrate that these differences can be linked to the process of slowing down in anticipation of a stop-signal, rather than solely to the likelihood of the stop-signal itself. To this aim we have used a stop-signal anticipation task (SSAT) with cues indicating the stop-signal probability at the beginning of each trial. Since responses slow down in anticipation of a stop-signal, we used this slowing-down to retrospectively identify proactive inhibitory brain activity preceding the response. We measured event-related beta desynchronization (beta-band ERD) at a central sensorimotor cluster of electrodes. Our analysis showed that beta-band ERD was more pronounced during go-trials with a 50% stop-signal probability as compared to those with a 0% probability. Notably, during those trials with a 50% stop-signal probability where participants slowed down their responses most, beta-band ERD was significantly more pronounced than during trials with faster responses or with a 0% stop-signal probability. This is the first study that uses behavioral effects of proactive inhibition to identify neural correlates with EEG.

Introduction

The ability to inhibit prepotent responses allows human beings to navigate a world filled with complex stimuli. Without inhibitory control, we would be left at the mercy of our environment and the reactive tendencies it provokes. The anticipation of future events can greatly assist us in our inhibitory needs. To achieve this, we need to take into account the probability of such future events occurring, and regulate our behavior accordingly – for instance, by delaying a response. Such a delay increases the odds that a response can be successfully inhibited if needed, or that alternative action can be taken (Logan & Cowan, 1984). This type of anticipation is commonly referred to as proactive inhibition (Chikazoe et al., 2009; Verbruggen & Logan, 2009; Vink, Kaldewaij, Zandbelt, Pas, & Plessis, 2015; Kenemans, 2015).

The neural underpinnings of proactive inhibition have been extensively mapped using functional magnetic resonance imaging (fMRI). This network consists of a frontostriatal network, spanning the supplementary motor area, dorsal pre-motor cortex, right inferior frontal gyrus, and right inferior parietal cortex (Chikazoe et al., 2009; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Duque, Labruna, Verset, Olivier, & Ivry, 2012; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Pas, Plessis, van den Munkhof, Gladwin, & Vink, 2019; Pas, van den Munkhof, Plessis, & Vink, 2017; van Belle, Vink, Durston, & Zandbelt, 2014; Vink et al., 2005; Zandbelt & Vink, 2010; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013). This frontostriatal network remains under construction throughout childhood, due to different rates of maturation across the brain: subcortical regions such as the striatum are thought to mature sooner than cortical structures (Casey, Jones, & Hare, 2008; Casey, Jones, & Somerville, 2011). During this developmental phase, children gradually become more skilled in their inhibitory control (Vink et al., 2014). This improvement is associated with the rise of proactive response strategies that allow for more efficient processing by engaging inhibitory functions prior to the actual appearance of a stop-signal (Zandbelt & Vink, 2010). These behavioral changes are paralleled by functional and structural changes in the brain, facilitating the transition from childhood to adulthood. Specifically, developmental improvements in proactive inhibition are accompanied by increases in activation and functional connectivity of the frontostriatal network (Vink et al., 2014).

Connections between these regions can also be studied using EEG, for instance by measuring oscillations in the signal. These oscillations are said to reflect cortical activation in respect to a host of cognitive functions (Pfurtscheller & Lopes da Silva, 1999; Schnitzler & Gross, 2005). Changes in these oscillations occur when synchronization in one particular frequency band arises accompanied by de-synchronization in another, reflecting a change in the state of brain activity (Steriade, Contreras, Amzica, & Timofeev, 1996). These phenomena are commonly called event-related synchronization or de-synchronization (ERD), and are temporally precise means for cortical functional measurements (Neuper & Pfurtscheller, 2001). ERD specifically has proven itself as a strong indicator of motor planning, with desynchronization occurring in the beta frequency band (17-20 Hz) during anticipation and execution of movements and synchronization afterwards (Alegre et al., 2003; Gladwin, Lindsen, & de Jong, 2006; Hari et al., 1998; McFarland, Miner, Vaughan, & Wolpaw, 2000; Stancák & Pfurtscheller, 1995). The degree of desynchronization has also been shown to relate to motivational aspects driving the inhibitory action (Gable, Threadgill, & Adams, 2015; Meyniel & Pessiglione, 2014). Considering that this pattern has been found in the motor area in relation with response preparation, response inhibition, and response uncertainty (Pfurtscheller et al., 2013), beta-band ERD offers itself as a possible functional EEG measure of proactive inhibition.

While the onsets of beta-band ERD and motor preparation have been linked (Alegre et al., 2003; Kaiser, Birbaumer, & Lutzenberger, 2001; Kilner, Bott, & Posada, 2005), it is less clear what factors determine its amplitude. A number of studies have found that neither direction of movement, level of executed force, or speed seem to affect beta-band ERD amplitude (Stancàk & Pfurtscheller, 2011; Tombini et al., 2009; Waldert et al., 2008). However, Tzagarakis et al. (2010) found that directional uncertainty related to which hand would need to be used on a task, did predict the power of beta-band activity during motor preparation. More recently, Liebrand (2018) found stronger beta-band ERD in the sensorimotor cortex during a stop-signal task for those trials where a stop-signal could occur than for those where none could occur.
Proactive inhibition is defined by the slowing down of responses in anticipation of a possible stop-signal. In previous research, we have mapped proactive inhibition in the brain using participants' subjective expectations in addition to

stop-signals (Pas et al., 2017; 2019; Vink et al., 2015). More recently, we have used the slowing down of responses towards a possible stop-signal to be indicative of participants' actually expecting a stop-signal to appear (Pas et al., 2019). Our current goal is to link beta-band ERD to proactive inhibition, by focusing on the behavioral effect of slowing down. We expected to find beta-band ERD in trials with a 50% stop-signal probability, as opposed to those with a 0% probability. Using reaction time, we tested whether this effect is specifically related to response slowing in anticipation of a stop-signal. To do that, we used a modified delayed-response stop-signal anticipation task (SSAT) with simultaneous EEG recordings. At the beginning of each trial, a cue indicates the stop-signal probability (0% or 50%), and after a variable delay (ranging from 1,000 to 2,000ms), the stimulus is presented, requiring participants to respond (go-trials) or refrain from responding (stop-trials). Beta-band ERD is calculated for the period between cue and stimulus, recorded from a cluster of sensorimotor electrodes, and compared between the two cue types and subsequently for fast and slow responses within those conditions respectively.

Methods

Participants

Fifty-four healthy volunteers (mean age 21 years, range 18-26; 13 males) participated in the experiment in exchange for study credit. The participants were recruited by way of a convenience sample. All participants were right-handed, had normal or corrected-to-normal vision. Furthermore, all gave written informed consent, and the study was approved by the local ethical committee.

Stop-Signal Anticipation Task

Participants performed the stop-signal anticipation task (Zandbelt et al., 2013), a stop-signal task designed to measure both proactive and reactive inhibitory control. The task and experimental procedures were adapted from Vink et al. (2015), see **figure 2** for an overview. In short, participants were instructed to stop a rising green bar nearby a stop line by pressing the spacebar (go-trials). In some trials, the rising bar turns red before reaching the top line and in this case participants have to refrain from responding (stop-signal). At the beginning of each trial, a cue represents the probability that a stop-signal will occur: either an 'H' or an 'O', one indicating no chance of a stop-signal occurring (0% probability) and the other representing the possibility that a stop-signal could occur (50%

probability). This approach ensures a sufficiently high number of stops (Pas, van den Munkhof, du Plessis, & Vink, 2017). The meaning of the cues 'H' and 'O' was counterbalanced between participants. During the task, participants had to alternate their left and right hand for pressing the spacebar. Which hand the participants had to start with was counterbalanced as well. Task difficulty was adjusted to performance in a stepwise fashion, with a varying delay between the stop-signal and the target (i.e. the stop-line) depending on the success of the previous trial. This adjustment tuned the overall stop accuracy to around 50% for each individual participant. In total, 416 trials were presented, 208 trials with 0% stop-signal probability and 208 trials with a 50% stop-signal probability. These trials were ordered in a pseudo-random sequence fixed across participants. According to Wagner et al. (2018), the large number of participants (54) and the number of stop-trials (104) together are sufficient for detecting a significant beta band power effect related to inhibitory control. See **figure 1** for an overview of the task setup.

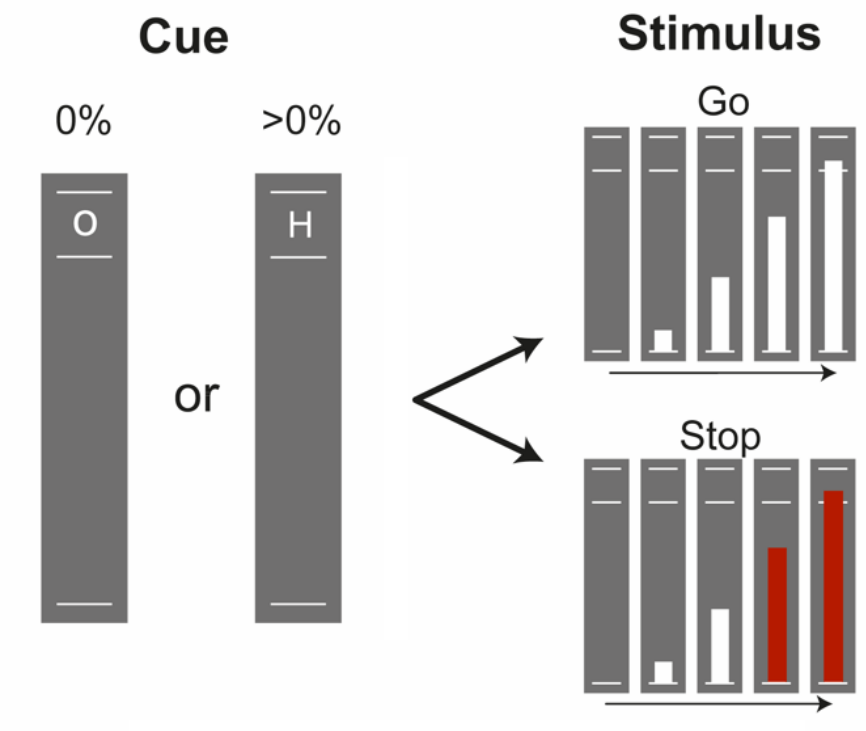

Figure 1. Delayed-response stop-signal anticipation task. *On each trial, a green bar moves at constant speed from the bottom line to the top line, reaching the white middle line at 800ms. The goal is to stop the moving bar as close to the middle line as possible by pressing the space bar with the thumb. These trials are referred to as go-trials. In stop-trials, the bar turns red before reaching the middle line, indicating that participants have to refrain from pressing the space bar. The stop-signal delay (SSD) is initially set at 550ms and subsequently varies in steps of 33ms according to a tracking procedure (SSD is increased after a successful stop-trial, and decreased after stop-trials in which participants fail to inhibit). At the beginning of each trial, the stop-signal probability is indicated by a cue. After 1500 ms the bar animation will begin after which participants have a maximum of 1000 ms to press the space bar. After the animation a feedback screen appears for 500 ms followed by a 750 ms inter-trial-interval.*

Measurements

EEG was recorded from 32 scalp locations using the International 10–20 EEG System with Ag–AgCl-tipped electrodes. The electro-oculogram was recorded from bipolar montages above and below the right eye and the outer canthi of the eyes. Raw EEG recordings were made with the ActiveTwo system (BioSemi, Amsterdam, The Netherlands) relative to the common mode sense. Ocular artifacts were removed using the Gratton et al. algorithm (1983). All data were recorded with a sampling rate of 2,048 Hz.

Processing of the EEG-data

Data were low-pass filtered at 30 Hz and down-sampled to 512 Hz to prevent memory and computational problems during the analysis. The wavelet transformation was done on the entire time series without any filtering or artefact rejection before cutting it into trial epochs of 5 seconds (3.75 seconds as the trial duration, and 1.5 seconds before the cue). The transformation was done by implementing a wavelet time-frequency transformation (using Morlet wavelets) based on multiplication in the frequency domain. The chosen frequencies were 17–20 Hz, in steps of 0.1 Hz. In order to increase the signal-to-noise ratio, we averaged the power spectra measured at electrodes around the sensorimotor cortex. We combined Cz, C3, C4, CP1, CP2 and Pz to form a central sensorimotor cluster, similar to the approach of Liebrand et al. (2017). Relative de-

synchronization was calculated by dividing the signal by the mean signal before the cue (-1500 ms: 0 ms) to allow for comparison between conditions.

Analysis

For the analysis comparing the two types of cues, we subjected the mean power of 100ms-intervals between 500ms and 1500ms to paired-sample t-tests. This interval length was taken from Liebrand et al. (2018), as a tradeoff between providing a fair temporal resolution while limiting the number of statistical tests. The temporal position of this interval is assumed to span the entire period of cue-processing, as we do not expect the effect of a cue on brain activity to be instantaneous, and we expect the cue-processing to be ended by the start of the bar-animation in the task. A false discovery rate (FDR) method with a q-value of 0.05 was used to correct for multiple testing.

Results

Behavior

Participants were slower to push the space bar in trials with a 50% stop-signal probability than in those with a 0% probability, with a mean of 861 ms (SD = 32) versus a mean of 820 ms (SD = 22), $t(55) = 10.89$, $p < 0.0001$. When considering the most extreme 30% of the fastest and the slowest responses for either of the cues respectively, we see that participants slow down more extremely during the trials with a 50% stop-signal probability condition than during those with a 0% probability. A repeated measures analysis on these four categories confirms this, showing a significant effect for speed $F(54,1) = 229.91$, $p < 0.0001$ and a significant interaction of speed and cue $F(54,1) = 26.62$, $p < 0.0001$. See **figure 2** for an overview of the distribution of response times.

EEG

To test whether inverse beta power reflects proactive inhibitory control, we first contrasted go-trials with a 0% stop-signal probability with go-trials with a 50% stop-signal probability. We performed ten paired-sample t-tests on the mean signal in intervals of 100 ms over the time span between 500 ms and 1500 ms after the cue. After FDR correction, nine paired-sample t-tests were significant. The maximum t-value was between 1200 ms and 1250 ms after the cue, with $t(54) = 4.21$ and $p = 0.001$. This result revealed that the sensorimotor beta-ERD was more pronounced during trials with a chance of a stop-signal occurring.

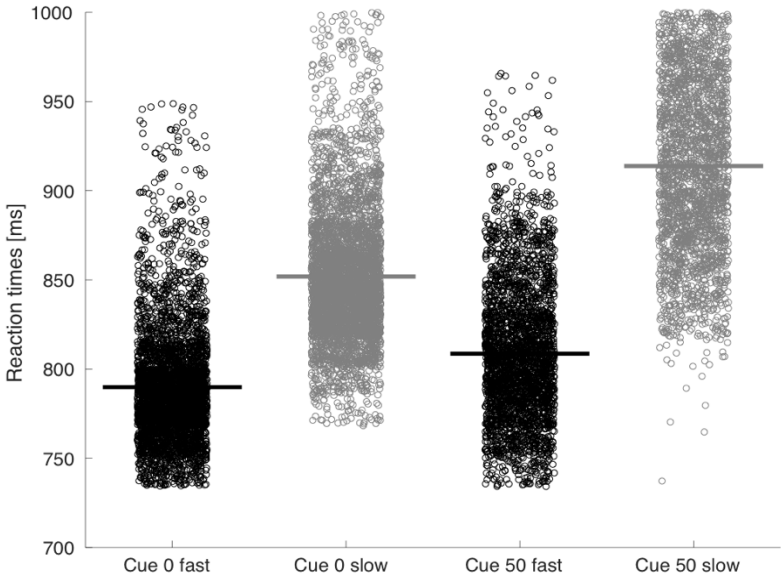

Figure 2. *Distribution plots of response times for the two cues, divided into the 30% fastest and slowest responses for all participants. Note that the slowest trials for some participants can still be faster than fast trials for other participants.*

Our aim was to directly link sensorimotor beta-ERD to the goal-directed slowing-down of the motor reaction in anticipation of a stop-signal. We therefore performed a repeated measures analysis on the same 100ms intervals as before, but only using the most extreme 30% of the slowest and fastest trials per cue. Our interest here concerned the interaction effect of cue with speed, as we only expected beta-ERD to be associated with slowing down in the condition with a 50% stop-signal probability. Of the ten tests, eight were significant with a maximum F-value between 900 ms and 950 ms after the cue, with $F(53,2) = 13.83$ and $p < 0.001$ (corrected with an FDR of 0.05). See **figure 3** for the beta-band time courses, and supplementary material for ERP graphs of the sensorimotor electrodes over the same time courses.

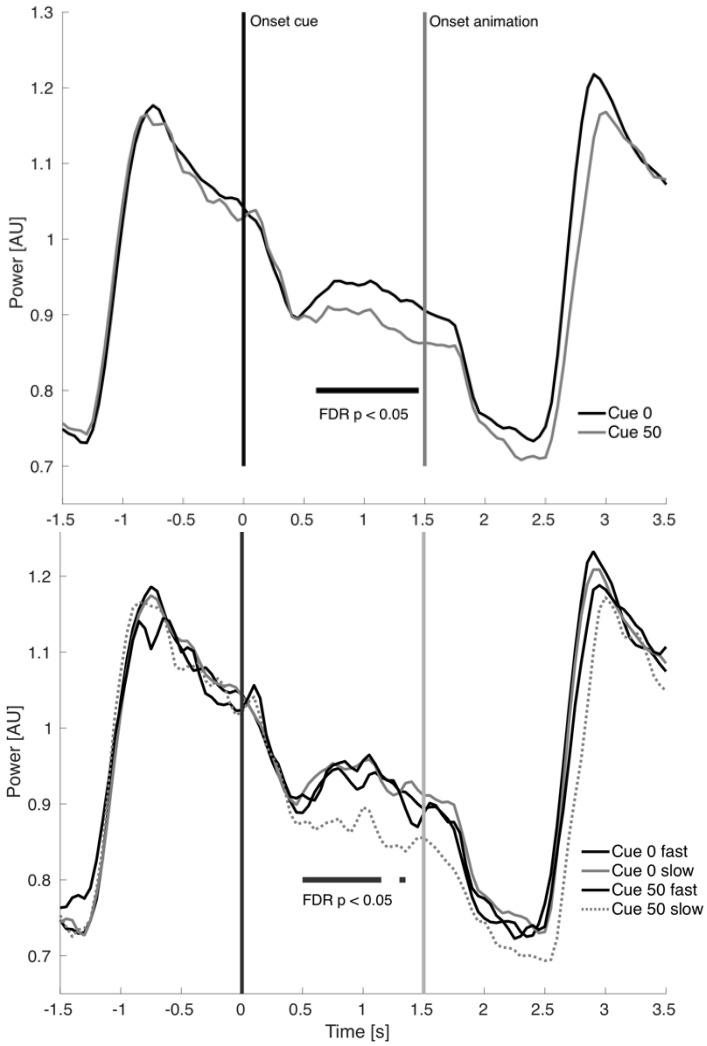

Figure 3. *TOP: Average beta-ERD per cue type, BOTTOM averages plotted for the most extreme 30% of the slowest and fastest responses per cue type. Time series were transformed to give relative values by dividing the time series by mean power of the time span between 1500 ms and 500 ms before the cue. T-tests were performed between 500 ms and 1500 ms after the cue, in segments of 100 ms, with the horizontal black line indicating an FDR-corrected significant difference of $p < 0.05$.*

Discussion

In the present study we validated beta-band ERD as an EEG-marker of proactive inhibition. More specifically, we investigated whether the beta-band effect is related to the anticipation of a stop-signal, and whether the effect is more pronounced when responses are slowed down. In line with previous research (Liebrand, Kristek, Tzvi, & Krämer, 2018; Tzagarakis et al., 2010), there was more sensorimotor beta-band ERD during trials with a 50% stop-signal probability, compared to those with a 0% stop-signal probability. Furthermore, this effect showed to be correlated with the trials in which participants slowed down their responses. These results link beta-band ERD to the intentional goal-directed slowing down of responses in anticipation of a stop-signal, and hence validate beta-band ERD as an EEG-marker of proactive inhibitory control. Where previous research was unable to link beta-band ERD amplitude to speed of movement (Stancàk & Pfurtscheller, 2011; Tombini et al., 2009), we demonstrate that it is not mere speed of movement but the purposeful slowing down in anticipation of stopping that affects amplitude.

Behavior

In line with our previous experiments using the SSAT paradigm (Pas et al., 2017; Vink et al., 2014; 2015), participants slowed down their responses in trials where a stop-signal could occur. In a previous study, we used this effect of proactive slowing to model differences in brain activation using trial-by-trial variances in response times as a behavioral marker (Pas et al., 2019). This enabled us to identify activation in certain brain regions specifically associated with proactive response slowing. The current experiment used the same behavioral effect to validate beta-band ERD as an EEG-marker of proactive inhibition.

Sensorimotor beta power

Beta desynchronization over the motor cortex typically occurs during movement preparation (Pfurtscheller et al., 1997; Neuper et al., 2006; Tzagarakis et al., 2014). This decrease in power is thought to stem from a synchronization between the motor cortex and the basal ganglia (Brown, 2000). Our study demonstrated that sensorimotor beta-band ERD was specifically linked to the intentional goal-directed slowing down in anticipation of a stop-signal. During proactive inhibition, subcortical areas such as the striatum are thought to modulate the response threshold of the motor cortex (Aron & Poldrack, 2006; Forstmann et

al., 2008; Jahfari et al., 2010; Lo & Wang, 2006; Vink et al., 2005; Zandbelt & Vink, 2010). Dopamine release in the striatum is presumed to help with the filtering of cortical input, and desynchronization of basal ganglia output (McIntyre and Hahn, 2010), which subsequently affects beta oscillations in the motor circuits (Meyniel & Pessiglione, 2014). Our previous study on the role of the motor cortex in proactive inhibition failed to find an effect of the expectation of stop-signals on brain activation in this region (Pas et al., 2017). It was hypothesized that this was due to the motor cortex being part of a mechanism that halts the motor response at the last minute (Kuhn et al., 2009). However, the current EEG experiment demonstrates that anticipatory motor control can be linked to a change in sensorimotor activity. It may be that the increased temporal resolution of EEG allows us to detect these more subtle effects, that would have otherwise remained hidden using fMRI.

Future research

An EEG-marker of proactive inhibition opens doors for new insights in developmental neuroscience. While children at the end of childhood can successfully inhibit prepotent responses, they gradually become more skilled in fine-tuning their inhibitory control during childhood and adolescence (Vink et al., 2014). This shift towards proactive response strategies is facilitated by developmental changes that are accompanied by an increase in activation of the frontostriatal network and in functional connectivity within this network. With the use of EEG, the development of these networks can be investigated from an earlier age, where the use of fMRI is not always allowed or appropriate due to its more invasive nature. In addition, early detection of abnormalities in proactive inhibition enabled by our EEG-marker could help to identify the onset of disorders such as schizophrenia and target interventions early-on, as these disorders often go hand in hand with impaired development of proactive inhibitory control (Hughes, Fulham, Johnston, & Michie, 2012; Vink et al., 2016). Lastly, the mobility that comes with using EEG instead of fMRI, enables us to combine measurements with virtual reality – furthering ecological validity (see for example Tromp et al. (Tromp, Peeters, Meyer, & Hagoort, 2018).

Limitations

The current task demands the stopping of a motor response when a stop-signal appears. However, this type of inhibition is not as relevant to some real-life

situations as the switching of one motor response to another, such as ceasing to push the gas pedal while instead simultaneously pushing the break (Liebrand, 2018). Hence, to expand our understanding of real-life preparatory motor control, future research should investigate whether the neural processes that we associated with response inhibition alone may also underlie response switching (Boecker, Gauggel, & Drueke, 2013). Studies using task-switching paradigms have previously investigated different forms of motor preparation and context to examine their effects on cortical oscillatory activity (de Jong, Gladwin, & 't Hart, 2006; Gladwin et al., 2006). However, we note that the "pure" inhibition of motor responses without necessarily switching to a different response would appear to be potentially relevant to the fundamental defensive response of freezing (R. J. Blanchard, Blanchard, Rodgers, & Weiss, 1990; Bradley, Codispoti, Cuthbert, & Lang, 2001; Fanselow, 1994; Gladwin, Hashemi, van Ast, & Roelofs, 2016).

Conclusion

In conclusion, we showed that sensorimotor beta-band ERD is linked to the goal-directed slowing down in anticipation of a stop-signal and thus of proactive inhibition. Our study replicates previous results linking beta-band ERD and preparatory motor inhibition, and serves as a solid stepping-stone towards further study, such as mapping the development of proactive inhibition in children.

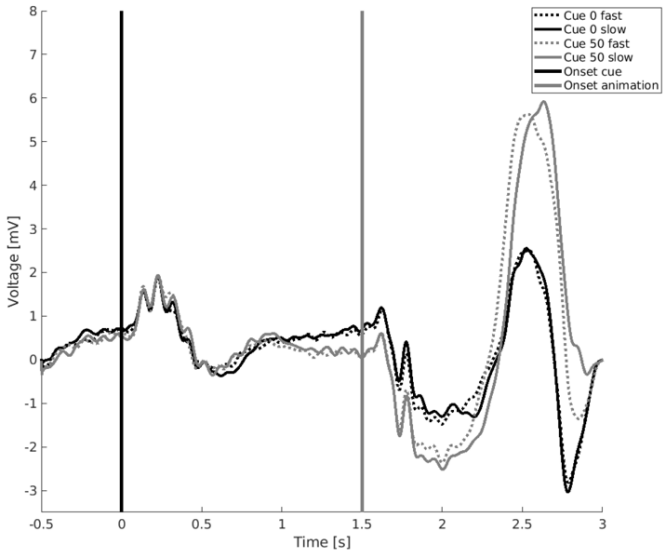

Figure S1. Event-related potentials. *Separate plots for the 30% slowest and fastest responses per cue type.*

Chapter 6

Self-regulation in the Pre-Adolescent Brain

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Introduction

To function adequately in everyday life, the ability to effectively exert control over your emotions, behavior, and impulses is crucial. This capacity is commonly referred to as self-regulation. Self-regulation has been defined as the ability to monitor and modulate emotions, behavior, and cognition, that in turn allows us to achieve goals and adapt to changing circumstances (Berger et al., 2007). This capacity develops from early infancy until well into adulthood. Where goals early in life are concrete and focused on direct rewards, e.g. food and nurture, there is a shift in adolescence where the ability arises to forgo immediate gratification and goals gradually become more abstract and long-term (Mischel et al., 1989).

Self-regulation can be studied across development in terms of executive functions (Vink et al., 2020). Inhibition can be seen as a low-level executive function, and develops in infancy and preschool years (Diamond, 2013). During middle childhood, children develop high-level executive functions, such as planning, problem solving, information processing and cognitive flexibility (Rosario Rueda et al., 2019). These high-level executive functions are founded on the integration of low-level functions. Then, during adolescence, the various executive functions start becoming integrated to support high-level executive control, also called cognitive control (Anderson et al., 2001). Executive control refers to the coordination of previously acquired low- and high-level executive functions such as working memory, inhibition, mental shifting, and information processing, which are then called upon as needed (Friedman et al., 2008; Best et al., 2011).

In the case of inhibition, it has been shown that while children at the end of childhood can inhibit prepotent responses, a low-level executive function, they further develop this skill during adolescence (Vink et al., 2014). This improvement is associated with the rise of proactive response strategies that allow for more efficient processing by engaging inhibitory functions prior to the actual inhibition, leading to the anticipatory slowing down of responses (Zandbelt and Vink, 2010; Pas et al., 2017; Pas et al., 2019). The true progress across childhood and adolescence is not better executive functions in itself, but rather more effective use of these functions due to their integration with other high-level executive functions such as planning. As such, the development of self-

regulation is supported by the development of low-level executive functions early in life, and their subsequent integration later on (Vink et al., 2020).

This integration of executive functions, which allows for proactive inhibitory control, has been theorized to depend upon the establishment of frontal control over the rest of the brain, in particular subcortical regions (Cools, 2011; Vink et al., 2014; Insel et al., 2017). The shift from low-level reactive to more higher-level proactive inhibition strategies has previously been linked to increased frontal activation as well as increased functional coupling between frontal and subcortical regions (Vink et al., 2014; Van den Bos et al., 2015).

However, these previous studies included adolescents and young adults, and we therefore do not yet know how and if individual differences in the state of executive function development and brain maturation pre-adolescence are linked to levels of self-regulation. It may very well be that children who show higher levels of self-regulation are better able to engage relevant brain regions. This may be coupled with increased functional coupling between regions that will begin to form brain networks. For instance, stronger frontostriatal connections have been linked to better delay of gratification (Achterberg et al., 2016). Consequently, measurements at this period in development may provide predictors of progress in adolescence and possibly outcome in adulthood. There have been some studies linking inhibitory control in children to brain measures, but their sample sizes are either relatively small (Durston et al., 2002; Schel et al., 2014; Steinbeis et al., 2015; Liuzzi et al., 2020), focused on inhibition and unhealthy eating (English et al., 2019; Van Meer et al., 2016), or used samples of at-risk children (Ware et al., 2015; Réveillon et al., 2016; Van Hulst et al., 2018; Meldrum et al., 2018; Cope et al., 2020).

Our aim is to investigate whether there are associations between self-regulation and brain measures in a large cohort of typically developing children. We will assess children's self-regulatory abilities in daily life via questionnaires. These data will be combined with self-regulatory measures from an inhibition task and accompanying functional MRI measures, that include both low-level reactive inhibition and higher-level anticipatory processes. This allows us to investigate to what degree individual differences in the brain areas underlying inhibitory control exist, whether they are linked to self-regulation in daily life, if this changes with age and whether this is different for boys and girls.

The central hypothesis is that children who show high levels of self-regulation in daily life will already show higher levels of reactive and proactive inhibitory control. Behaviorally, we expect children scoring higher on self-regulation, to demonstrate more proactive inhibitory control during the task, resulting in the slowing down of responses in anticipation of a stop-signal on go trials (Pas et al., 2019; Vink et al., 2014). In the brain, we expect this measure to be associated with the establishment of frontal control over the rest of the brain (Cools, 2011). This is expected to result in higher levels of activation in the right mid frontal cortex (Pas et al., 2019), and increased functional coupling between cortical and subcortical regions. Specifically, between the right frontal cortex and the striatum during proactive inhibition, and the left-motor cortex during reactive inhibition (Vink et al., 2014).

Materials and Methods

Participants

We requested the largest available data sample from the YOUth cohort study (Onland-Moret et al., 2020, www.uu.nl/en/research/youth-cohort-study), which provided us with a total of 798 subjects. There is currently no data available from children performing our current fMRI inhibition task that allows us to perform a power analysis. However, we opted for this considerable number because functional MRI in children can lead to moderately reliable results, due to suboptimal task-compliance and movement (see Buimer et al., 2020), and a higher number allows us to investigate subtle differences in brain activation. Of all subjects a complete anatomical and functional scan was available, as well as data from the task. The study was approved by the ethics committee of the University Medical Center Utrecht.

Self-regulation Questionnaire

The full-scale Early Adolescent Temperament Questionnaire-Revised Short Form for parents (EATQ-R-SF: translated in Dutch by C.A. Hartman) is used to obtain a measure of self-regulatory capabilities (Ellis and Rothbart, 2001). This questionnaire was filled out by one of the parents on their child's behavior. Items on the 'inhibitory control' subscale were scored from a 1-5, where the final score was an average of all the items, with higher scores implying more inhibitory control. The mean score of the sample was 3.61 (SD = 0.54), with the values having a slight negative skew (-0.24) but normal distribution.

Pubertal development

The Pubertal development questionnaire (PDS) (Carskadon and Acebo, 1993) was used to get an indication of general levels of pubertal development in our sample. The cumulative score for girls (M = 5.4, SD = 1.8) was higher than for boys (M = 4.1, SD = 1.3), $t(464) = 8.9$, $p < 0.001$. As expected, the overall distribution of scores was positively skewed (1.71), with the majority of children falling in the pre- and early pubertal category (338 against 130).

Self-regulation functional MRI Task

We will use behavioral measures and functional MRI data acquired while subjects perform the Stop-Signal Anticipation Task (SSAT; see Onland-Moret et al., 2020). The SSAT provides us with several measures: inhibition speed and accuracy, identification of the regions associated with inhibitory control, a measure of relative activation in those regions, and the ability to measure functional coupling between those regions (Zandbelt and Vink, 2010), see **fig. 1**. Subjects are presented with three parallel horizontal lines. On each trial, a bar moves at a constant speed from the lower line towards the upper line, reaching the middle line in 800 milliseconds. The main task is to stop the bar as close to the middle line as possible, by pressing a button with the right thumb (i.e. Go trial). Stop trials are identical to Go trials, except that the bar stops moving automatically before reaching the middle line, indicating that a response has to be suppressed (i.e. stop-signal). The probability that such a stop-signal will appear is manipulated across trials and can be anticipated based on three different cues; '0' indicating 0% chance, '*' 22 percent and '**' 33 percent chance the bar will stop on its own. Task difficulty is adjusted to performance in a stepwise fashion, with a varying delay between the stop-signal and the target (i.e. the stop-line) depending on the success of the previous trial, thereby keeping the number of failed and successful trials comparable between subjects and sessions. This allows for a fair comparison between children that may possess varying levels of inhibitory control (Telzer et al., 2018). There were 256 trials in total presented in pseudorandom order: 85 trials with 0% probability, 86 trials with a 22% probability and 85 trials with a 35% probability.

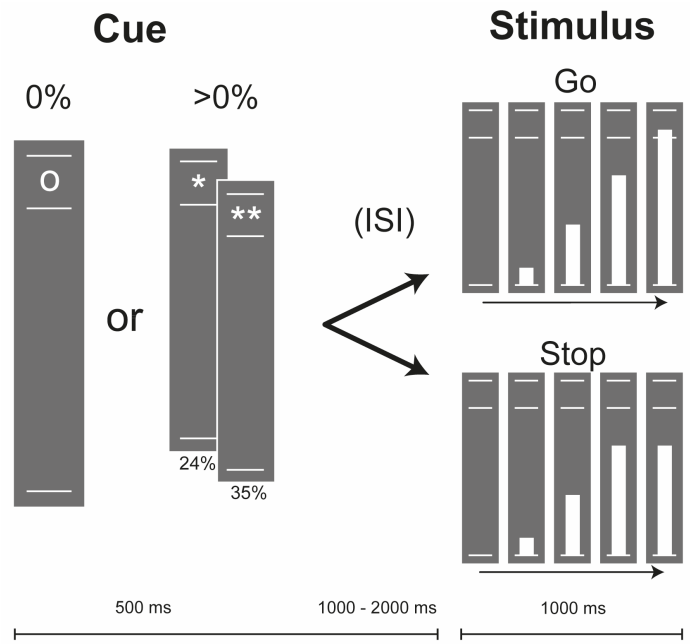


Figure 1. Stop signal anticipation task. Trials begin with the presentation of a cue (0, * or **), representing the stop-signal probability (0, 24 and 33% respectively). Permanently visible are three horizontal white lines, goal is to stop a rising bar as close to the middle line as possible (target) by pressing a button, but refrain from pressing the button when the bar stops on its own (stop signal).

Behavioral analysis

Reactive inhibition was measured by the latency (stop-signal response time; SSRT) and success of stopping on stop trials. The SSRT was computed according to the integration method (Logan and Cowan, 1984) and pooled across all stop-signal probability levels. This measure has been used as a behavioral indicator of inhibitory control (Fogel et al., 2019), and has been shown to be increased in children with inhibition problems, such as ADHD (Slusarek et al., 2001). Proactive inhibition was measured as the effect of stop-signal probability on go-signal response time. Adults subjects tend to slow down their responses as the probability of a stop becomes more likely (Vink et al., 2005). For all measures, the effect of age was estimated using a regression analysis with age as a continuous regressor and sex as a between-subject variable.

Image acquisition

The experiment was performed on a Philips (Philips medical systems, Best, the Netherlands) Ingenia 3.0 T MRI scanner at the UMC Utrecht. Functional images consisted of whole-brain, T2*-weighted echo planar images with blood oxygen-dependent contrast [repetition time 1000 ms, echo time 25 ms, flip angle 65, 2.5 x 2.5 in-plane resolution, 2.5 mm slice thickness, 51 slices per volume, SENSE factor, 1.8 (anterior–posterior) and multiband factor 3] in a single run of 595 dynamic scans. A T1-weighted image from the same session was used for within-subject registration purposes.

fMRI Analysis

Preprocessing

Image data were processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included realignment to correct for head motion, where the time-series were registered by a least-square approach and a rigid-body transformation. Then slice timing correction was applied by interpolating all slices in time to the center slice. Even with short repetition times and multiband, slice timing correction has been demonstrated to benefit results (Parker, 2019). Spatial normalization was done to the Montreal Neurological Institute template brain, and smoothing was applied (8 mm full width at half maximum) to correct for inter-individual differences.

Subject exclusion

A number of subjects were excluded based solely on a fixed fMRI signal threshold, as the threshold for generating brain masks (default of 80% of global signal) can result in holes inside the mask for some subjects. This was due to either significant movement (possibly exasperated by the multiband sequence), or general scanner artefacts. It is difficult to assess retrospectively whether signal artefacts are primarily due to scanner issues or motion artefacts. Subjects with voxels below the signal threshold within the brain, excluding cerebellum, were removed from the analysis. The total number of subjects excluded with this method was 151 (82 boys, mean age 9.6 years), leaving a dataset of 645 children (278 boys, mean age 9.5 years). During the subsequent analyses, 5 children were excluded from the dataset by being either an outlier in terms of signal (n = 2) or behavior (n = 3), leaving a final dataset of 640 children. There were 86 left-handed children in our sample, however all were instructed to perform the task using the right hand. As we did not have specific hypotheses on how handedness

affects inhibitory motor control during the task, we did not exclude these participants from our analyses. We have rerun all analyses with right-handed children only to ensure that left-handedness did not change the significance of our main findings. These analyses are added as a supplemental material. See **table 1** for an overview of our sample, and **table 2** for an overview of the measures taken from the subjects.

Table 1. overview of the sample after exclusion of outliers, with a paired-samples t-test for sex differences

	Boys	Girls	Total	t	p
Participants n	278	362	640		
Age in years, mean (sd)	9.51 (.87)	9.50 (.83)	9.50 (.85)	.11	.91
Righthanded n (%)	232 (83%)	322 (89%)	554 (87%)		
EATQ-R mean (sd), n	3.57 (.55), 238	3.64 (.52), 304	3.61 (.54), 542	1.5	.13
PDS mean (sd), n	1.15 (.36), 208	1.38 (.49), 260	1.28 (.45), 468	5.5	< 0.0001

EATQ-R = Early Adolescent Temperament Questionnaire-Revised Short Form
PDS = Pubertal development questionnaire

Individual analyses

Functional images were submitted to a general linear model. Activation was time-locked to the presentation of the cue and to the stimulus response period was modeled based on stop-signal probability and stop-signal expectation. On average the inter-trial interval was 1,000ms (ranging from 500 to 1,500ms), and served as an implicit baseline. Six realignment parameters were added as regressors of no interest to correct for residual signal changes related to head motion. All data were high-pass filtered with a cut-off of 128 s to control for low-frequency drifts. For each participant, we computed two contrast images: (1) activation during successful stop trials versus failed stop trials (reactive inhibition), (2) activation during go trials with a stop-signal probability versus trials without (proactive inhibition). In the latter, the probability of a stop-signal appearing is expected to lead to the anticipatory slowing down of responses (Pas et al., 2019; Vink et al., 2015).

Group analysis

The two contrast images per subject were subjected to a one-sample t-test group-level analysis, resulting in two group-level brain maps. To investigate

potential activation patterns outside the predefined ROIs, a whole-brain analysis was performed with significance testing using voxel-wise inference. Due to our large sample size, we opted for a FWE (Bonferroni) correction for multiple testing, $p < 0.05$.

Region of interest analyses

To determine effects of sex and age on activation in these contrasts, regression analyses were performed on predefined regions of interest (ROIs), created using the MarsBaR toolbox (Brett et al., 2002; http://marsbar.sourceforge.net). For proactive inhibition the regions are based on the activation patterns in young adults from Pas et al. (2019), resulting in three regions; the right mid frontal cortex, the right parietal cortex and the right putamen. The reactive inhibition ROIs were based on activation in young adults from Pas et al. (2017), and consisted of the left motor cortex, and the bilateral striatum. From these ROIs, we extracted the mean activation level for each participant for the two contrasts of interest. Mean activation levels of all ROI were analyzed using a regression analysis with age as predictor, and sex as a between-subject variable.

Functional coupling

Functional coupling analyses were performed using psychophysiological interaction (PPI) (Friston et al., 1997) to investigate the effect of age and sex on the coupling between ROIs of the frontostriatal network. These measures serve as an indication of similarity in activation of two different regions in the brain. The seed was defined as a 6-mm-radius sphere around the center-of-mass of the right striatum (MNI coordinates [20, 12, 0]). This seed was taken from Vink et al. (2014) in which a similar analysis was conducted. A PPI analysis was performed to investigate the functional coupling on the contrast of go trials with stop-signal probability 0% against go trials with >0% stop-signal probability. Functional coupling was investigated between the seed and the right mid frontal cortex, and the parietal cortex. For reactive inhibition, functional coupling was investigated during successful stop trials versus unsuccessful stop trials (i.e., psychological factor) between the seed and the left motor cortex.

For each participant, the first eigenvariate of the BOLD signal for the seed region was calculated and adjusted for average activation during the task and head motion. The interaction between activity within the seed region and the psychological factor was then calculated, for both positive as well as negative

relationships. The resulting individual contrast images were entered into a second-level analyses to test for the effect of sex and age on functional coupling.

Table 2. Overview of measures in the analysis

Measures	Type	Source	Description
Self-regulation	Questionnaire	EATQ-R[1]	Score of self-regulation
Pubertal Development	Questionnaire	PDS[2]	Indication of pubertal development
SSRT	Behavior	Task	Reactive inhibition speed
Accuracy	Behavior	Task	Reactive inhibition accuracy
Response slowing	Behavior	Task	Proactive response slowing
ROI Brain activation	Neuroimaging	Task fMRI	Mean activation levels in predefined regions of interests during reactive and proactive inhibition
Psychophysiological interactions	Neuroimaging	Task fMRI	Measure of functional coupling between ROI regions during reactive and proactive inhibition

In this paper we will use the EATQ-R questionnaire as a measure of self-regulation in daily life. We will link this measure to measures of inhibitory control from the task and the associated brain measures.

1. *The full-scale Early Adolescent Temperament Questionnaire-Revised Short Form for parents (EATQ-R-SF: translated in Dutch by C.A. Hartman) (Ellis and Rothbart, 2001).*
2. *Pubertal development scale questionnaire (PDS) (Carskadon and Acebo, 1993)*

Results

Confounds

First, we tested for age and sex-related effects on motion during the task using a regression analysis. This revealed no main effect of sex $F(1,633) = 0.73$, $p = 0.39$, but did show an effect of age $F(1,636) = 19.37$, $p < 0.001$, with motion being significantly lower in older than younger children. We performed additional Pearson's correlation tests to see whether movement during the task was related to our behavioral measures of reactive and proactive inhibition, or scores of self-regulation. Such an association was found in a previous fMRI study investigating inhibitory control (Stange et al., 2018), and this would present a possible confound for our current study. However, the resulting correlation coefficients ranged from -0.06 to 0.13, and none were significant. The tests were also run with the excluded subjects re-added to the sample, but the correlation coefficient ranged from -0.08 to 0.10.

Behavior

We then assessed effects of sex and age on reactive and proactive behavioral measures from the task. We found that reactive inhibition latency (SSRT) was significantly associated with age $F(1,636) = 104.84$, $p < 0.001$ ($r = -0.38$), but not with sex $F(1,637) = 3.08$, $p = 0.08$, indicating that older children where faster at inhibiting responses than younger children. Inhibition accuracy also improved with age $F(1,636) = 26.67$, $p < 0.001$, regardless of sex $F(1,636) = 1.00$, $p = 0.32$. Slowing down responses in anticipation of a stop-signal is a measure of proactive inhibition. Participants slowed their responses more with increasing stop-signal probability, $F(2,638) = 248.71$; $p < 0.001$, regardless of sex, $F(2,638) = 2.52$, $p = 0.11$. This proactive response slowing was not associated with age $F(1,636) = 2.97$, $p = 0.09$, nor with sex $F(1,637) = 0.48$, $p = 0.49$. While older children were both significantly faster and more accurate in response inhibition than younger children, they did not show an increase in response slowing.

The 'inhibitory-control scale' of the EATQ served as a proxy of more general self-regulation abilities of the children. There was no effect of age on the scores, $F(1,536) = 2.57$, $p = 0.11$; nor sex, $F(1,536) = 2.59$, $p = 0.11$; nor an interaction effect, $F(1,536) = 0.92$, $p = 0.34$. To test our hypothesis that children scoring higher on this scale show better inhibitory control during the task, a regression analysis was conducted for reactive and proactive measures of inhibition. There was no significant main effect of the scores on SSRT (e.g. reactive inhibition), $F(1,536) = 0.43$, $p = 0.51$. However, we did find a significant relation between self-regulation and proactive response slowing on the task, $F(1,533) = 6.48$, $p = 0.01$, regardless of sex $F(1,533) = 0.54$, $p = 0.46$.

Activation

Whole Brain

To explore brain regions associated with reactive and proactive response inhibition outside of our predefined regions of interest, two whole brain analyses were conducted. During reactive inhibition we found significant clusters of activation in the bilateral putamen, superior temporal gyrus and the precuneus. Deactivation was found in the cerebellum, cingulate and postcentral gyrus left insula. For proactive inhibition we found significant activation clusters in the right mid. Frontal gyrus extending into the putamen, cerebellum, bilateral inferior parietal lobes and bilateral temporal gyri, with significant deactivation in the

cuneus and anterior cingulate. See **figure 3** and **table 3** for an overview of activation clusters. An extra figure for illustrative purposes was added as a supplemental material that shows our predefined ROIs displayed on top of our whole-brain results.

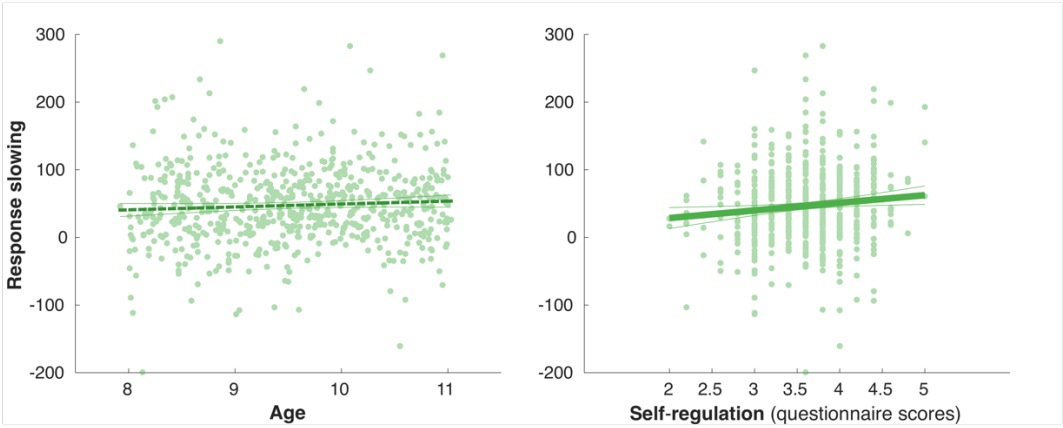


Figure 2. Proactive response slowing against age and self-regulation scores. LEFT: *Scatter plots of response slowing on the task plotted against age, not significant; RIGHT: scores on the self-regulation scale of the EATQ questionnaire as a function of age (with linear trend line and 95% confidence interval).*

Region of interests

A one-sample t-test was used to test for significant activation in the selected ROI. For reactive inhibition we found significant deactivation in the left motor cortex in the contrast of successful stop trials versus failed stop trials, $t(639) = -2.39$, $p = 0.02$, indicating suppression of the motor cortex during successful inhibition. In addition, there was significant bilateral activation in the striatum, left $t(639) = 10.67$, $p < 0.001$, and right $t(639) = 10.65$, $p < 0.001$. For proactive inhibition, there was significant activation in the network associated with proactive inhibition: the mid frontal cortex, $t(639) = 9.11$; $p < 0.001$, the right parietal cortex, $t(639) = 6.90$; $p < 0.001$, and the right putamen $t(639) = 4.42$; $p < 0.001$. There were no significant effects of age and sex on these ROI, see the supplemental materials for a detailed analysis.

Table 3. Overview of activations

Region	BA	Side	No. of voxels	X	Y	Z	Max t-value
Reactive inhibition							
Positive							
Putamen		L	347	-24	8	-4	13.79
Putamen		R	1618	24	12	0	13.66
Superior Temporal Gyrus	22	L	75	-64	16	0	6.46
Precuneus	31	L	83	-24	-36	28	5.84
Negative							
Cerebellum		L	379	-32	-52	-20	13.63
Cerebellum		R	264	-32	-56	-16	12.22
Cingulate Gyrus	32	L/R	89	0	24	28	8.40
Postcentral gyrus	1	L	60	-52	16	-20	8.19
Insula	13	L	141	-44	8	-4	6.79
Proactive Inhibition							
Positive							
Mid. frontal gyrus	9	R	1183	48	36	24	10.15
Inf. Parietal lobe	40	R	692	48	-44	52	11.94
Inf. Parietal Lobe	40	L	615	-44	-36	44	8.86
Cerebellum		L/R	483	-8	-80	-32	8.48
Mid. Temporal gyrus	37	R	139	48	-68	0	8.75
Mid. Temporal gyrus	37	L	72	-44	-72	4	8.52
Negative							
Cuneus	18	L/R	1869	8	-92	24	16.41
Anterior Cingulate	24	L/R	155	0	28	-8	7.37

All results are significant at a voxelwise FWE correction of $p < 0.05$, height threshold $T = 4.33$; L, left; R, right; X Y Z refer to the center of mass.

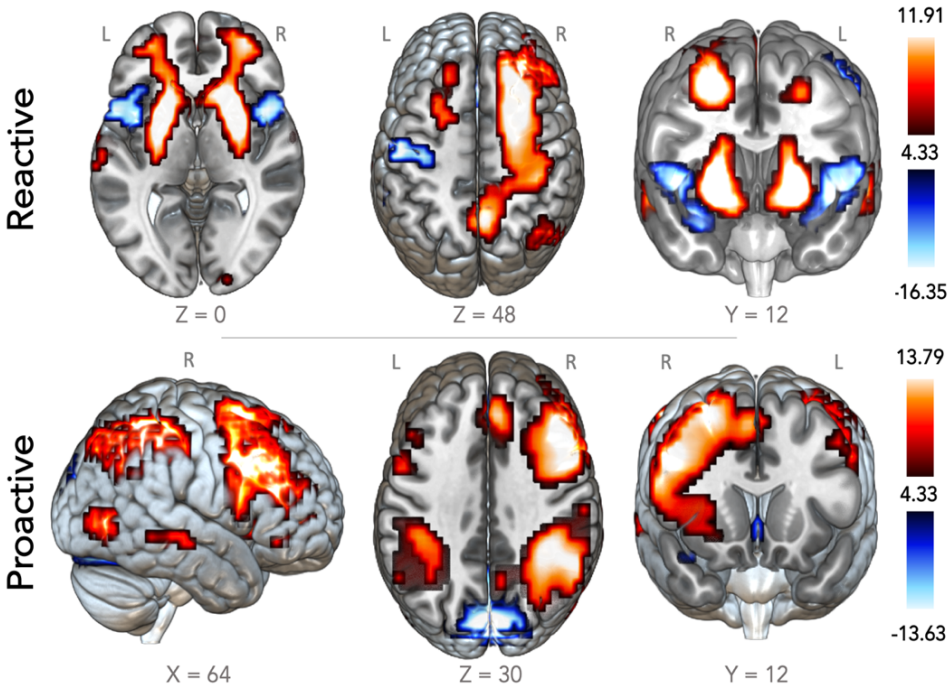


Figure 3. Significant activation clusters during reactive and proactive inhibition. *Above 'Reactive inhibition': correct versus incorrect stop trials. Significant clusters of positive activation include the bilateral putamen, superior temporal gyrus and the precuneus. Deactivation occurred in the bilateral cerebellum, cingulate and postcentral gyrus and the left insula. Below 'Proactive inhibition': Go trials with >0% stop-signal probability versus 0%. Significant clusters of activation include the right mid frontal cortex, the right parietal cortex and the right putamen. Deactivation was found bilaterally in the cuneus and the anterior cingulate cortices (FWE corrected at $p < 0.05$, height threshold $T = 4.33$).*

We expected children scoring higher on self-regulation to exhibit more activation in the frontal cortex. We found that activation in the right mid frontal cortex during proactive inhibition was associated with self-regulation, $F(1,536) = 6.37$, $p = 0.01$ ($r = 0.11$), with no interaction effect for sex $F(1,536) = 0.07$, $p = 0.79$ (corrected for multiple comparisons for the three ROI, with $p < 0.05 / 3 = 0.016$) (Fig. 4).

Functional Coupling

To investigate the degree to which areas of the brain are functionally connected, we tested for effects of sex and age on functional coupling between cortical and subcortical ROI of the brain. During reactive inhibition, there was an effect of age on functional coupling between the right striatum and the left motor cortex, $F(1,636) = 4.93$, $p = 0.03$. There was no effect of sex, $F(1,633) = 1.71$, $p = 0.19$, though there was an interaction effect between sex and age, $F(1,636) = 4.66$, $p = 0.03$. A post-hoc regression analysis revealed that this association with age, was specifically present for girls $F(1,361) = 10.52$, $p < 0.01$ ($r = 0.17$), but not for boys $F(1,277) = 0.01$, $p = 0.92$ ($r = 0.01$); (Bonferroni corrected for multiple comparisons at $p < 0.05/2 = 0.025$). An additional analysis splitting the two sexes in groups based on pubertal development, revealed that boys with mid pubertal characteristics had significantly more coupling between the two ROI, than boys in pre- and early puberty $t(205) = 2.95$, $p < 0.01$. There was no such difference for girls.

During proactive inhibition, regression analyses showed that activation in the striatum was more strongly coupled with the mid frontal cortex for older than younger children, $F(1,636) = 7.21$, $p = 0.01$. There was no effect for sex $F(1,633) = 2.13$, $p = 0.14$, but there was an interaction effect between sex and age,

F(1,636) = 10.26, p < 0.001 (Fig. 4). A post-hoc regression analysis revealed that the association with age was specifically present for boys F(1,277) = 15.56, p < 0.001 (r = 0.23), but not for girls F(1,361) = 0.03, p = 0.85 (r = -0.01); (Bonferroni corrected for multiple comparisons at p < 0.05/2 = 0.025). There was no difference in coupling based on pubertal development, for either sex. For the right parietal cortex, there were no effects of age and sex altogether.

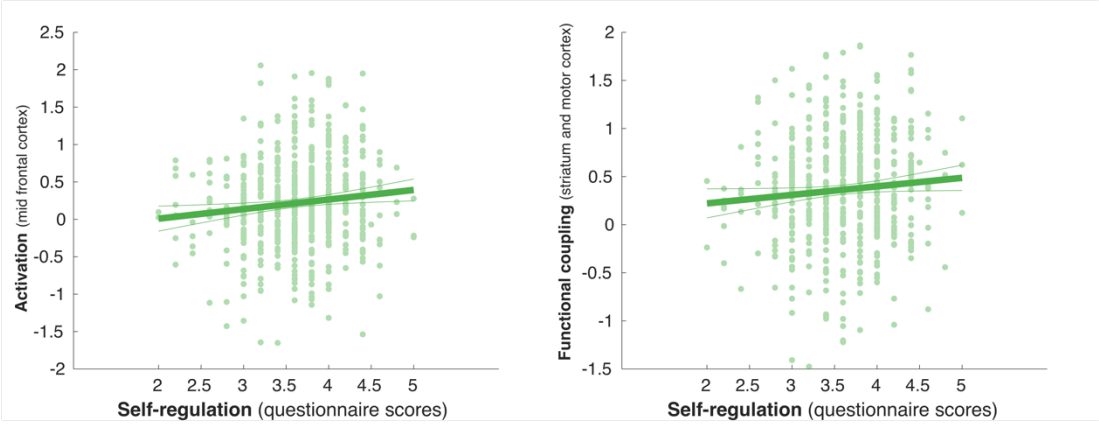


Figure 4. Self-regulation scores against brain activation and functional coupling. *Scatter plot of activation in the mid frontal cortex during proactive inhibition against self-regulation scores (LEFT) and functional coupling between the right striatum and left motor cortex during reactive inhibition as a function of self-regulation scores (RIGHT) (with linear trend line and 95% confidence interval).*

Our final hypothesis was that increases in self-regulation would be paralleled by more functional coupling between subcortical and cortical areas of the brain. For reactive inhibition, we found a moderate relationship of self-regulation scores and coupling between the left motor cortex and the right striatum, F(1,536) = 4.18, p = 0.04; but no interaction with sex, F(1,536) = 3.08, p = 0.08. There was no effect of the scores on frontostriatal coupling during proactive inhibition, F(1,536) = 0.81, p = 0.37; and no interaction with sex, F(1,536) = 1.34, p = 0.25.

Discussion

In this study, we investigated whether self-regulatory abilities in children are reflected in brain measures. We present data on the relationship between self-regulation and neural correlates of reactive (i.e., outright stopping), and

proactive inhibition (i.e., anticipation of stopping) in a cohort of 640 healthy children aged 8.5–11.5 years. Behaviorally, we find that even in the narrow age-range spanning 3 years, there are advances in inhibitory control speed and accuracy. Both boys and girls slowed down their responses in anticipation of a stop, demonstrating that proactive inhibitory control is already present. Notably, we found that an independent measure of self-regulation was associated with the amount of proactive response slowing on the task. In the brain, we found significant activation in brain regions associated with reactive and proactive inhibition. During reactive inhibition, there was increased activation in the bilateral striatum and a decrease in the left motor cortex. During proactive inhibition, there was increased activation in the right mid frontal gyrus, the right inferior parietal lobe and the right putamen. Activation in these regions was not associated with age and did not vary between boys and girls. However, self-regulation scores were positively associated with activation in the frontal cortex during proactive inhibition. Finally, we found several age-related changes that differed between the sexes. In girls, functional coupling between the right striatum and the left motor cortex increased with age during reactive inhibition. In boys, proactive inhibition fronto-striatal functional coupling (between the right striatum and the mid frontal cortex) increased with age.

In our sample, reactive inhibition improved significantly in terms of speed and accuracy in the span of three years. Both older boys and girls are more skilled at inhibiting responses than their younger counterparts, in line with other studies (Bedard et al., 2002; Durston et al., 2002; Tamm et al., 2002; Rubia et al., 2013; Velanova et al., 2009; Van de Laar et al., 2011). Notably, our data shows that even young children around the age of nine already exhibit proactive response slowing. This effect of responses becoming slower with increasing stop-signal probability has been consistently established in adults (Vink et al., 2005, 2006; Chikazoe et al., 2009; Verbruggen and Logan, 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010; Zandbelt et al., 2011; Vink et al., 2015; Pas et al., 2017; Pas et al., 2019), with some evidence showing that adolescents also exhibit this feature (Vink et al., 2014). Where recent studies have looked at proactive inhibitory control in younger children in terms of performance monitoring (Hadley et al., 2019), or differences in proactive inhibition between ADHD and healthy control children (van Hulst et al., 2018) - our study is the first to investigate sex and developmental effects on both reactive and proactive

inhibition in a sample of children at a young age.
In line with previous research, we found deactivation in the left motor cortex during successful inhibition (Chikazoe et al., 2009; Vink et al., 2005; Zandbelt and Vink, 2010; Pas et al., 2017). This deactivation did not increase with age, nor did it differ for boys and girls. Bilateral activation of the striatum was also associated with reactive inhibition. This region has been consistently associated with the suppression of motor responses (Vink et al., 2005; Aron and Poldrack, 2006; Zandbelt and Vink, 2010), and modulating the response threshold (Lo and Wang, 2006; Forstmann et al., 2008; Jahfari et al., 2010). Previous research link striatal activation during reactive inhibition to the prior anticipatory processing of contextual cues (Vink et al., 2015; Pas et al., 2017). This makes it difficult to pin-down its specific role, where effects stemming from formed expectations and successful performance on the task may intertwine. The level of activation was not associated with age, nor did it differ for the two sexes. Some studies have pointed to a decrease in striatal activation with age during reactive inhibition (Casey et al., 1997; Durston et al., 2002; Rubia et al., 2007). A previous study with a sample of adolescents also failed to find an association with age – albeit in a much smaller sample (Vink et al., 2014). It may be that a decrease in striatal activation during reactive inhibition is paralleled by an increase during proactive inhibition, but that this shift relies on the relative maturation of frontostriatal networks. This is akin to the temporal shift in striatal activation from actual reward receival to the anticipation of the reward (Schultz et al., 1997). When rewards can be predicted by a cue, striatal activation increases in anticipation and less as a reaction to receiving of the reward. Previous research has shown that this shift develops throughout adolescence (Bjork et al., 2010; Hoogendam et al., 2013; Vink et al., 2014). This is supported by research showing that the striatum is associated with the learning of stimulus-response associations, but not with their application (Vink et al., 2013).

Next to activation in our predefined regions of interest, our whole-brain analyses revealed additional brain areas where significant activation occurred. These activation patterns are in line with literature on response inhibition and motor control, specifically for the Superior Temporal Gyrus (Horn et al., 2003), and the Precuneus (Wenderoth et al., 2005). We also found significant deactivation of the bilateral insula, implicated in motor preparation (Hester et al., 2004).
Functional coupling between the left motor cortex and the right striatum

increased with age, specifically for girls. Among boys, those further along in pubertal development also exhibited more functional coupling. This is in line with previous research showing a positive association between functional coupling and age in adolescents (Vink et al., 2014). This difference for the two sexes points to possible distinct developmental trajectories. It may be that boys already show higher levels of coupling at a younger age and therefore have less room for increases, although this difference was not significantly present in our sample.

During proactive inhibition, children in our sample predominantly exhibited activation in cortical areas such as the right parietal cortex and right mid frontal cortex, with the activation cluster extending into the striatum. Response inhibition studies have commonly reported an association between striatal activation and the anticipation of stop-signals (Aron and Poldrack, 2006; Vink et al., 2005, 2006; Vink, de Leeuw, et al., 2015; Hu and Li, 2011; Vink, et al., 2015; Zandbelt et al., 2011; Zandbelt and Vink, 2010). The broader area of the basal ganglia has been hypothesized to act as a gatekeeper, preventing execution of conflicting motor responses (Friend and Kravitz, 2014; Mink, 1996), and incorporating prior reinforcement (Vink et al., 2013). In addition to the striatum, the right mid frontal cortex has long been recognized as playing an important role in proactive inhibition (Aron et al., 2003; Rubia et al., 2003; Vink, de Leeuw, et al., 2015; Vink, et al., 2015). An increase in functional connectivity between this area and the basal ganglia has been shown to increase response inhibition efficiency (Xu et al., 2016). In contrast, hypoactivation of the right frontal cortex in patients with ADHD has been linked to impaired response inhibition (Morein-Zamir et al., 2014).

The largest cluster of activation during proactive inhibition was present in the right parietal cortex. Activity in this area has been linked to self-initiated as opposed to triggered or automatic responses (Kuhn et al., 2009), the storage of acquired motor skills (Halsband et al., 2001; Niessen et al., 2014), involvement in response selection (Dippel and Beste, 2015). The parietal cortex and mid temporal gyrus were found to be bilaterally activated, with a large cluster of deactivation centered around the cuneus. Deactivation of the cuneus has previously been found during go/no-go tasks. One theory is that this deactivation may resemble a task demand sensitive cross-modal inhibition

mechanism that optimizes performance by reducing potentially distracting neural processes (Laurienti et al. 2002; Talanow et al., 2020).
We saw a significant association with age and functional coupling of the right striatum and the right mid frontal cortex, specifically for boys. Previous research has shown increases in functional connectivity between these regions in an older sample of children (Vink et al., 2014). During adolescence, maturation of brain regions varies spatiotemporally over the brain, with subcortical regions related to motivation maturing before prefrontal development (Casey et al., 2008; Casey, 2015; Gladwin et al., 2011). Our data shows that a degree of variability exists between the sexes regarding functional coupling, though it is not clear whether these differences will persist throughout development or are temporary. Sex differences have been found in brain volume, with a larger increase in white matter for males compared than females (Giedd et al., 1999; De Bellis et al., 2001; Lenroot et al., 2007). Research into sex differences in the brain during inhibition has also pointed to differences in frontostriatal activation (Rubia et al., 2013).

Our aim was to determine whether children who show high levels of self-regulation also show high levels of reactive and proactive inhibitory control. We found that children with higher self-regulation scores demonstrated more response slowing during the task. It is presumed that the improvement in self-regulation in adolescence is in part due to the effective integration and coordination of executive functions, leading to the rise of proactive response strategies that allow for a more efficient processing by engaging inhibitory functions prior to having to inhibit responses (Zandbelt and Vink, 2010; Vink et al., 2020). In terms of brain activation, self-regulation was positively associated with activation in the right mid frontal cortex during proactive inhibition. This finding is in line with the notion that proactive inhibitory control relies on the establishment of frontal control over the rest of the brain, in particular subcortical regions (Cools, 2011; Vink et al., 2014). The right frontal cortex has long been recognized as playing an important role in proactive inhibition (Aron et al., 2003; Rubia et al., 2003; Vink et al., 2015; Pas et al., 2019). Finally, self-regulation scores were also correlated with functional coupling between the right striatum and the left motor cortex. On the one hand functional coupling between these two regions may point to an increase in efficiency of motor inhibition, and that this is reflected in the general ability of inhibitory control in daily life. For

instance, the ability to suppress automatically elicited responses may help in controlling eating behavior (Fogel et al., 2019). Alternatively, the increase in functional coupling during reactive inhibition may not be limited to our selected ROI, and reflect a more general trend of increasing connectivity between subcortical and cortical structures (Duijvenvoorde et al., 2019).

Limitations

A number of limitations need to be considered. First, our results are based on an fMRI paradigm in children. In an adult sample this specific task has a moderate reliability (Buimer et al., 2020), and data from children will generally be more confounded due to issues of head motion or task compliance (Greene et al., 2018). We chose to employ strict objective parameters for subject exclusion, resulting in 151 children being left out of our analysis. While our remaining sample size was large enough to test our main hypotheses, we lack the power to reliably investigate individual differences and must stick to general group characteristics. In addition, the fact that we did not have questionnaire data from all children results in smaller subgroups.

Head motion can produce spurious signal fluctuations that may confound measures of functional coupling (Ciric et al., 2018). While we have taken measures of reducing head motion issues, some residual effects will remain present in the data. Due to the head moving from a fixed origin (the neck) the strength of short-range connections can increase as they are more similar in their timing of movement, as opposed to long-range connections that become weaker (Satterthwaite et al., 2014). In terms of our functional coupling results, the main effects were significantly different between the sexes whereas movement did not differ.

Conclusion

Our data shows for the first time in children, that self-regulation is related to behavioral and neural correlates of inhibitory control. First, we showed that even children at a young age exhibit proactive inhibitory control over their actions, while reactive inhibition improved with age. Children scoring higher on self-regulation demonstrated more proactive inhibitory control in terms of slowing down their responses, higher activation in the mid frontal cortex and more functional coupling between subcortical and cortical areas. This paper does not provide a definitive answer to how increases in self-regulation during childhood

relate to changes on a neural level, however, it does shed light on a number of neural correlates that are of importance in development. The associations between self-regulation and neural underpinnings in our sample undoubtably are limited in size, as such this data may benefit from optimizing methods of reducing noise that may be present in both questionnaire and brain data. When cohort data from a second wave will be made available, future research can employ longitudinal designs to further investigate the neural aspects of self-regulation. In theory, the state of self-regulation in the brain at a young age could subsequently be used to make predictions on well-being, school results and drug usage in adolescence.

Supplemental Materials

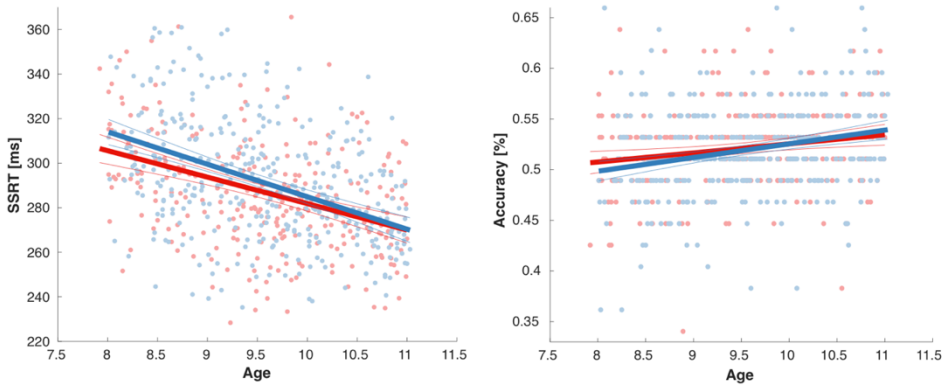


Figure S1. Behavioral measures of reactive inhibition. *Data for response latency (SSRT) on the left, and inhibition accuracy on the right, for boys (red) and girls plotted against subject age (with linear trend line and 95% confidence interval).*

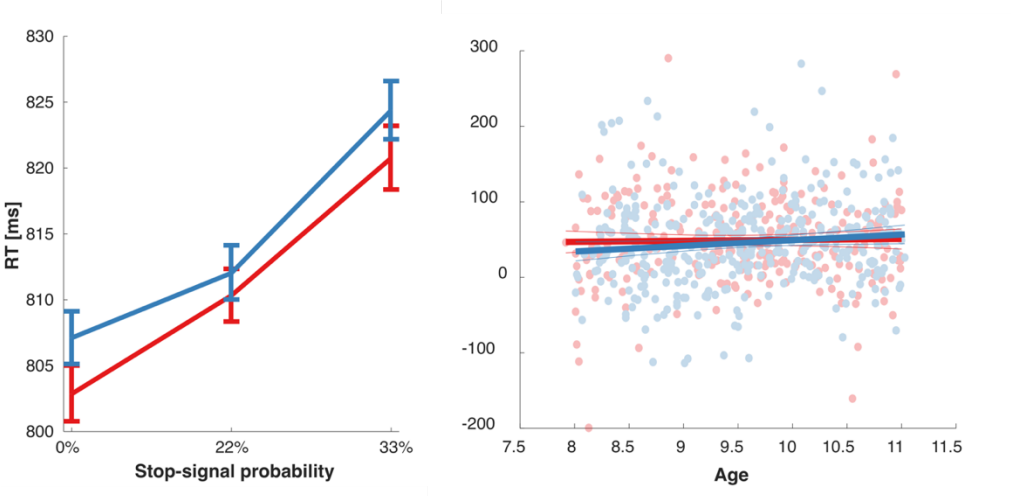


Figure S2. Behavioral measures of proactive inhibition. *On the left response time for boys (red) and girls during each stop-signal probability condition. On the right the amount of response slowing as a function of age.*

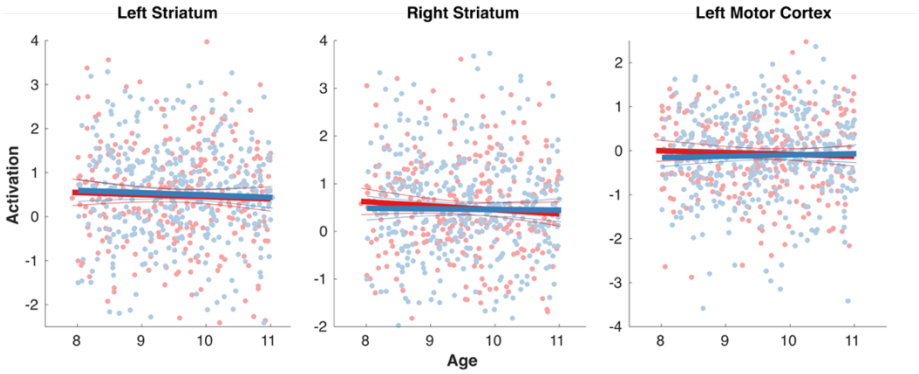


Figure S3. Mean activation levels for reactive inhibition per ROI. *Scatter plots (regression coefficients) as a function of age (with linear trend line and 95% confidence interval).*

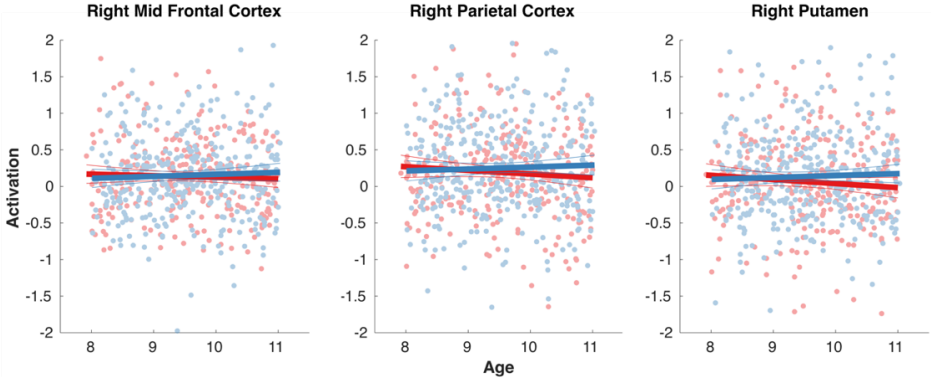


Figure S4. Mean activation levels for proactive inhibition per ROI. *Scatter plots (regression coefficients) as a function of age (with linear trend line and 95% confidence interval).*

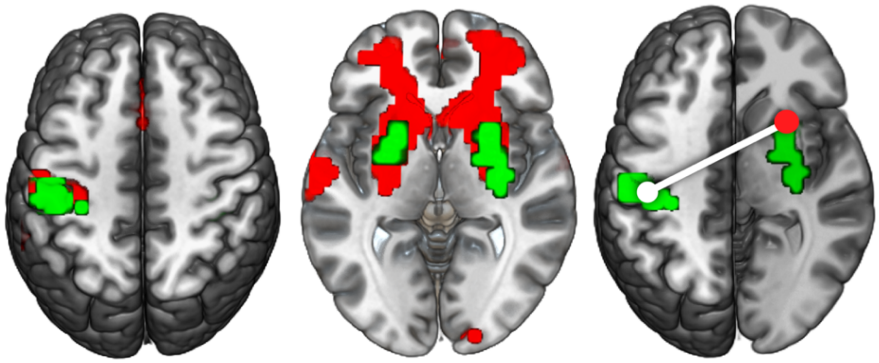


Figure S5. ROI for reactive inhibition. *On the left shown in green the ROI of the left-motor cortex on top of the whole-brain deactivation pattern in red, middle the bilateral striatum ROI in green on top of the activation pattern - of the current sample when contrasting correct versus incorrect stop trials. On the right image the connection is visualized that we test in the functional coupling analysis, between the left motor cortex and the right striatum with in red the PPI VOI seed.*

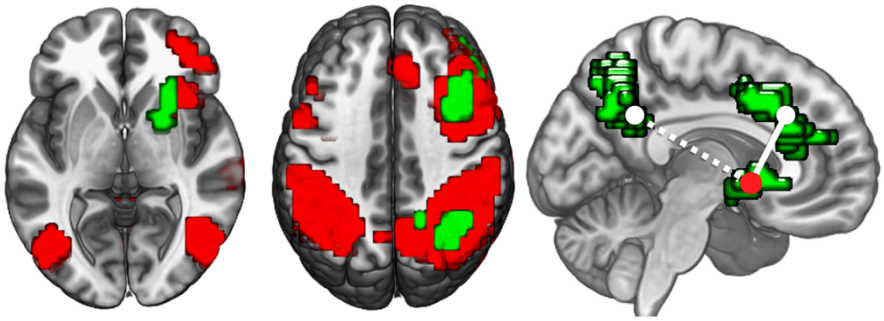


Figure S6. ROI for proactive inhibition. *The two images on the left show In green the ROI on top of the whole-brain activation pattern of the current sample when contrasting Go trials with >0% stop-signal probability versus 0%. These are the mid frontal cortex, the right parietal cortex and the right putamen. On the rightmost image the two connections are visualized that we test in the functional coupling analysis, frontostriatal (solid) and between the striatum and parietal cortex (dotted), with in red the PPI VOI seed.*

ROI analyses

Subsequent regression analyses for both proactive and reactive inhibition showed that this activation was not associated with age nor sex. Specifically, for

the right mid frontal cortex, there was no effect of sex $F(1,633) = 0.81$, $p = 0.37$, age $F(1,633) = 0.10$, $p = 0.75$ ($r = -0.01$), nor an interaction $F(1,637) = 2.02$, $p = 0.16$. For the right parietal cortex there again were no effects of sex $F(1,637) = 1.63$, $p = 0.20$, age $F(1,633) = 0.23$, $p = 0.63$ ($r = -0.02$), nor an interaction $F(1,637) = 1.49$, $p = 0.22$. Finally for the right putamen, there again was no main effect for sex $F(1,637) = 4.37$, $p = 0.14$, and age $F(1,633) = 0.24$, $p = 0.63$ ($r = -0.02$), nor an interaction effect $F(1,637) = 0.69$, $p = 0.41$.

Functional Coupling

During reactive inhibition, there was an effect of age on functional coupling between the right striatum and the left motor cortex, $F(1,636) = 4.93$, $p = 0.03$. There was no effect of sex, $F(1,633) = 1.71$, $p = 0.19$, though there was an interaction effect, $F(1,636) = 4.66$, $p = 0.03$. A post-hoc regression analysis revealed that this association with age, was specifically present for girls $F(1,361) = 10.52$, $p < 0.01$ ($r = 0.17$), but not for boys $F(1,277) = 0.01$, $p = 0.92$ ($r = 0.01$); (Bonferroni corrected for multiple comparisons at $p < 0.05/2 = 0.025$). An additional analysis splitting the two sexes in groups based on pubertal development, revealed that boys with mid pubertal characteristics had significantly more coupling between the two ROI, than boys in pre- and early puberty $t(205) = 2.95$, $p < 0.01$. There was no such difference for girls.

During proactive inhibition, regression analyses showed that across development activation in the striatum became more strongly coupled with the mid frontal cortex, $F(1,636) = 7.21$, $p = 0.01$. There was no effect for sex $F(1,633) = 2.13$, $p = 0.14$, but there was an interaction effect, $F(1,636) = 10.26$, $p < 0.001$. A post-hoc regression analysis revealed that the association with age was specifically present for boys $F(1,277) = 15.56$, $p < 0.001$ ($r = 0.23$), but not for girls $F(1,361) = 0.03$, $p = 0.85$ ($r = -0.01$); (Bonferroni corrected for multiple comparisons at $p < 0.05/2 = 0.025$). There was no difference in coupling based on pubertal development, for either sex. For the right parietal cortex, there were no effects of age and sex altogether.

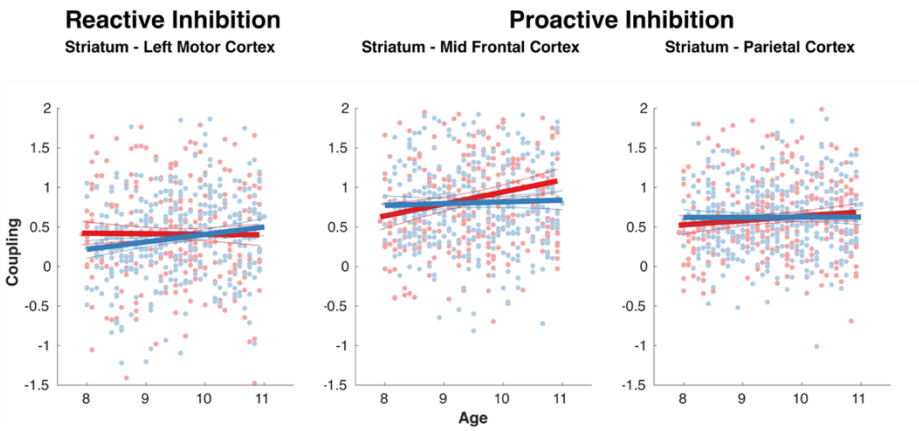


Figure S7. *Scatter plots of the level of functional coupling (regression coefficients) for the left-motor cortex (LEFT) during reactive inhibition, and right mid frontal cortex (MIDDLE) and the right parietal cortex (RIGHT) during proactive inhibition, with the right striatum as a seed, plotted against age (with linear trend line and 95% confidence interval), for boys (red) and girls.*

For reactive inhibition, there also was a relationship between SSRT (measurement of reactive inhibition speed) and coupling between the left motor cortex and the right striatum, $F(1,636) = 8.04$, $p < 0.001$; but no interaction with sex, $F(1,636) = 0.00$, $p = 0.97$. There was no association between response slowing on the task (measurement of proactive inhibition) and frontostriatal coupling, $F(1,636) = 1.42$, $p = 0.23$; nor an interaction with sex, $F(1,636) = 0.56$, $p = 0.46$.

Handedness

Our main regression analyses were rerun with all left-handed children excluded. The relationship between self-regulation and proactive response slowing on the task remained significant, $F(1,459) = 6.23$, $p = 0.01$, regardless of sex $F(1,459) = 0.49$, $p = 0.48$. The relationship between self-regulation and activation in the frontal cortex remained significant as well, with $F(1,459) = 4.51$, $p = 0.03$, regardless of sex, $F(1,459) = 0.20$, $p = 0.65$. Then finally the relationship between self-regulation and functional coupling. This association remained significant as well with $F(1,459) = 3.50$, $p = 0.03$, with no effect of sex, $F(1,459) = 2.51$, $p = 0.08$.

Additional information on whole-brain analysis

For the whole-brain analyses the estimated FWHM by SPM12 was 20.2mm x 19.1mm x 15.4mm (5.1x4.8x3.9 voxels), with a search volume of 1373568 mm3 (21462 voxels, 198.7 resels; corresponding to 0.01 resels-per-voxel). In addition, as spatial smoothing can introduce a bias in the localization of reward-related brain activity (Sacchet & Knutson, 2014), we have calculated the mean resels-per-voxel specifically for the striatal area. This was done using a mask based on the activation patterns from the 'correct-versus-incorrect stops' contrast, created using the MarsBaR toolbox (Brett et al., 2002; http://marsbar.sourceforge.net), and produced a mean statistic of 0.015 resels-per-voxel.

References

Sacchet, M. D., & Knutson, B. (2013). Spatial smoothing systematically biases the localization of reward-related brain activity. NeuroImage, 66, 270-277. https://doi.org/10.1016/j.neuroimage.2012.10.056

Chapter 7

Summary and General Discussion

Key findings

- Activation in the ventral striatal part of the brain is related to learning performance.
- Striatal activation is only associated with the inhibition of a response when the stop was anticipated.
- Height of striatal activation is linked to the anticipatory slowing down in anticipation of a stop, i.e. proactive inhibition.
- Proactive inhibition is specifically associated with activation in the striatum, right-frontal, and right-parietal cortex.
- Proactive inhibition is measurable using EEG and represented by beta-band desynchronization over the motor cortex.
- Children with higher levels of self-regulation employ more proactive inhibition.
- During proactive inhibition, 9-year-olds show brain activation in the same areas of the brain as adults.
- Children with more self-regulation exhibit more cortical-subcortical coupling (i.e. activation becoming more synchronized over time).

Summary of findings

The main goal of this thesis was to investigate the neural underpinnings of proactive inhibitory control in the brain. We started with an experiment investigating a key brain area that had been consistently linked to proactive inhibition, the striatum. In **chapter 2** we found that activation in this area was related to the creation and updating of stimulus-response mappings. Of interest was the fact that activation in the ventral striatum was only related to the learning of stimulus-response associations, and not to their application. Furthermore, individual variation in this activation was linked to success of learning from feedback during the task. These results led to the hypothesis that the striatal activation commonly found during motor inhibition could also be linked to a process like feedback learning. In **chapter 3** we indeed found that striatal activation during reactive motor inhibition was only present when the stop had been anticipated in advance by the subject. In **chapter 4** we used subjects' slowing down when anticipating the need for a stop to investigate the brain areas involved in proactive inhibition. Instead of purely relying on task manipulation, we used behavioral observations to reduce noise in our data. This method

revealed that the striatum and parts of the right frontal and parietal cortex were specifically linked to anticipating an upcoming stop, a fundamental principle of proactive inhibitory control. In **chapter 5** we used electroencephalography to investigate proactive inhibition with an increased temporal resolution. We found that when subjects slowed down their responses in anticipation of a stop, desynchronization in the beta-band frequencies occurred over the frontal cortex, indicative of the occurrence of motor planning. Finally, in **chapter 6** we used the regions we identified in **chapters 3** and **4** to investigate inhibitory control in children and see whether there is a link with self-regulation in daily life. We found that children around the age of 9 years already show activation patterns similar to those in adults when exerting reactive and proactive inhibitory control. Furthermore, we found that activation in the frontal cortex during proactive inhibition, and functional coupling between cortical and subcortical areas was related to a measure of self-regulation.

Discussion

The striatum and learning

We expected a link between activation in the striatum and learning based on its association with the processing of prediction errors (Becerra et al., 2001, Knutson and Cooper, 2005, O'Doherty et al., 2007, Brovelli et al., 2008) and adjustment of behavior based on feedback (Delgado et al., 2005, Tricomi et al., 2006, Day and Carelli, 2007). Striatal activation has been linked to both Pavlovian and operant conditioning (O'Doherty et al., 2007, Brovelli et al., 2008). In **chapter 3** we specifically did not find ventral striatum activation when contrasting the Learning versus Control condition. This supports the notion that this part of the striatum is only active during either the formation or adjustment of stimulus–response mappings (Learning phase) and is not involved during their subsequent application. In general, activation in the striatum has consistently been linked to response inhibition (Vink et al., 2005; Aron, 2006a; Zandbelt and Vink, 2010). This role in the suppression of motor responses is possibly due to modulation of the response threshold in the motor cortex (Lo and Wang, 2006; Forstmann et al., 2008; Jahfari et al., 2010). Our results linking the striatum to the formation and updating of stimulus-response mappings may elucidate its role in response inhibition. As the task employed in **chapter 3** consisted of only simple stimuli and accompanying behavioral response mappings, the primary factor determining learning success was whether mappings were correctly established based on

probabilistic feedback (consistent with Seger and Cincotta (2006) and Tricomi et al. (2006)). Anticipation that is formed based on a cue, is met with either an expected or unexpected outcome. In response inhibition, the striatum should therefore only accompany responses that were anticipated in advance and therefore allow for the updating of stimulus-response associations.

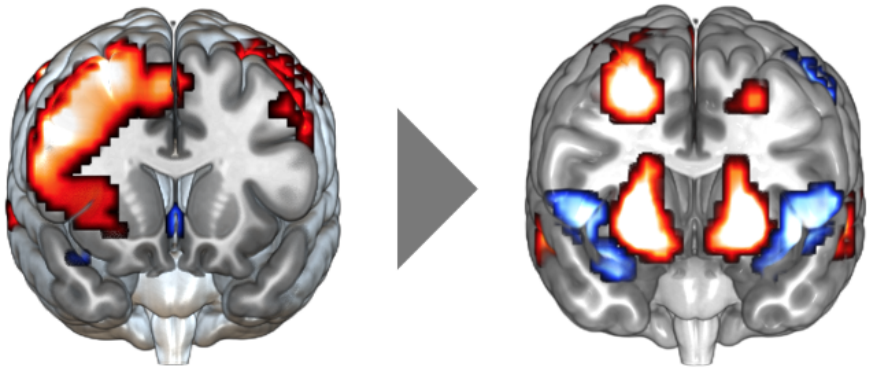


Figure 1. *On the left, activation during proactive inhibition, consisting of cortical areas extending into the putamen. On the right activation during reactive inhibition with peak activation clusters in the bilateral striatum. Activation patterns taken from the results of* ***chapter 6****.*

The striatum and anticipation

Previous studies have linked striatal activity to inhibition when stop-signals where predictable (Vink et al., 2005; Zandbelt and Vink, 2010). This may mean that striatal involvement is dependent on subjects being able to anticipate the occurrence of stop signals. In **chapter 4** we tested this hypothesis by designing a stop-signal task in which subjects were asked whether they expected a stop to occur based on a preceding probabilistic cue.

The basal ganglia are presumed to mediate behavioral control arising from frontal cortical areas (Alexander and DeLong, 1986). For instance, the dysfunction in the striatal area found in schizophrenia results in an inability to adequately incorporate cues to prepare for upcoming events (Vink et al., 2015a). In the context of an expected stop in the current task, heightened striatal activity

may therefore reflect the early preparation of resources for a change in behavior, in this case inhibition. Since the striatum has been implicated in the suppression of motor responses (Vink et al., 2005; Aron, 2006a; Zandbelt and Vink, 2010), it possibly exerts this proactive role by modulating the response threshold in the motor cortex (Lo and Wang, 2006; Forstmann et al., 2008; Jahfari et al., 2010). See **figure 1** for a side-by-side of activation during proactive and reactive inhibition.

The striatum is not a homogeneous cluster of neurons in the brain. Functionally it can be divided into a ventral and dorsal part. The ventral part houses the nucleus accumbens and is associated with processing reward-related information. The dorsal part consists of the caudate nucleus and the putamen, associated with sensorimotor processing (Voorn et al., 2004). In terms of motor inhibition, the ventral system is assumed to play a role primarily in the prediction and anticipation phase, whereas the dorsal striatum is associated with action outcome (O'Doherty et al., 2004). This translates to the proactive and reactive phases, respectively, of inhibition in this thesis.

Individual variability

The research in this thesis predominantly revolves around the testing and comparing of group-based results. In neuroscience it is common practice to almost exclusively report averaged group results and rely on aggregate statistics. This is often done under the assumption that there is uniformity in the spatio-temporal dynamics of brain functions in a population. The blood-oxygen-level-dependent (BOLD) signal derived via functional MRI (fMRI) can be viewed as a robust surrogate for neuronal activity. However, this signal has been shown to vary substantially across subjects, brain regions, and repetitive measurements (Lin et al., 2018). Within-subject variability will simply end up as noise in the statistical model, as individual activation maps are averaged to a single group map. This means that any information on variation of BOLD activation within and across individuals is lost. Variability can be seen as a generally overlooked dimension of neuroimaging results. Studies that have focused on individual variability in fMRI signal patterns have shown that these can vary greatly within a single task, sometimes even lacking any overlap between paradigms (Miller et al., 2009). Several studies have found unique and systematic individual patterns of brain activity across different tasks (Bolt, Nomi, Bainter, Cole, & Uddin, 2019; Bolt, Nomi, Yeo, & Uddin, 2017; Gratton et al., 2019; Miller, Donovan, Bennett,

Aminoff, & Mayer, 2012). Research into variability has demonstrated that small fluctuations of neural activity can even be more informative than peak or mean BOLD activation (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Nomi, Bolt, Ezie, Uddin, & Heller, 2017). Furthermore, variability in brain activation in terms of resting-state connectivity was shown to be, for a large part, heritable (Teeuw et al., 2019).

Especially when dealing with large samples such as the one used in **chapter 6**, it could be considered a waste to overlook individual variability in the data. With the proper tools and statistics, this may enable researchers to reduce unexplained noise and increase reliability. There is ample evidence showing a developmental shift from variable to more focused and consistent activation patterns in the brain (Dehaene-Lambertz, Monzalvo, & Dehaene, 2018; Durston et al., 2006). Ignoring such a shift may become problematic when interpreting longitudinal data. As individuals mature, neural computations underlying task-specific actions become more consistent, and therefore be less variable over time (Koolschijn et al., 2011). Ultimately, variability can increase again due to age-related decline in dopamine levels leading to noisier signal processing (Samanez-Larkin et al., 2010). Previous research found high between-subject variability regarding BOLD hemodynamic response shape related to aging and physiological characteristics (Aguirre, Zarahn, & D'esposito, 1998; Jacobs et al., 2008; Kannurpatti, Motes, Rypma, & Biswal, 2010). A decrease in BOLD variability has also been linked to creativity (Roberts, Grady, & Addis, 2020), memory performance (Protzner, Kovacevic, Cohn, & McAndrews, 2013), and intelligence (Boylan et al., 2020; Hilger, Fukushima, Sporns, & Fiebach, 2019; Jiang, 2019).

The waste of movement

Functional MRI allows for the us to pinpoint the location of brain activation in a relatively high spatial resolution. The technique is non-invasive and safe to use in children. However, data acquisition, especially from children, is often hindered by excessive movement of the subject during scanning. Not only does moving around in the scanner result in a physical shift of location, but movement also results in local signal-changes and changes in signal-to-noise ratio. Subject movement remains the foremost cause of low reliability of fMRI signals (Gorgolewski et al., 2013b), and it has been shown that even motion correction is not sufficient in removing contamination (Power et al., 2012). For example, the

technique used to acquire fMRI is called echo-planar imaging. This means that the brain is divided into a number of slices going from top to bottom. These slices are not read-out simultaneously, and there is a delay between exciting the atoms and reading out the signal. This means the signal-changes are not linear to the movement, and signal will be lost that cannot be fully recovered. Moreover, when movement is excessive, the MRI images can be distorted to such a degree that aligning them to the rest of the series is no longer possible. In addition, subject movement may be related to variables of interest such as age or have a genetic component (Achterberg & Van der Meulen, 2019; Teeuw et al., 2019). Participants with such excessive amounts of movement during acquisition are typically excluded from subsequent analysis. As was the case in **chapter 6**, a considerable number of children participating in fMRI studies end up being excluded (Greene et al., 2018). Techniques that can be used to deal with noisy resting-state fMRI scans, for instance a split-session approach (Teeuw et al., 2021), are not always suitable for task-fMRI that utilize complex paradigms. With children participating in more and more task-based fMRI studies, the necessity of developing better approaches to deal with movement during the scanning of task paradigms become even more urgent.

Reproducibility

In part due to the effects of movement on the signal, fMRI results are rarely high in reliability and reproducibility. While the number of published fMRI studies is high, a meta-analysis in 2010 found only 13 fMRI studies between 2001 and 2009 on reproducibility. These studies reported ICCs values in a range from 0.16 to 0.88, with an average reliability of 0.50 (Bennett and Miller, 2010). Reliability will especially become problematic when dealing with low sample sizes, or with groups where movement is expected to be above average (e.g. children). This thesis contains articles that suffer from both these hindrances. The samples in **chapter 2, 3 and 4** are meager in size. The approach was to therefore limit ourselves to the testing of predefined regions of interest, and operated within the constraints of our hypotheses. For example, in **chapter 4** we found an association between three regions and anticipatory slowing down of responses. These regions, specifically the striatum and mid frontal cortex, were in line with previous literature. In a separate study, we found the reliability of the fMRI tasks used in **chapter 6** to be reasonable (Buimer et al., 2020). As the sample in this chapter consisted of children between the age of 9 and 11, we chose to be more

conservative in the tests to run. While we did report more explorative whole-brain statistics, our main results were based on hypotheses founded on previous literature.

Future Directions

The YOUth Cohort Study aims to explain inter-individual variation that is driven by the interplay between biological, psychological, and environmental processes (Onland-Moret et al., 2020) – and this data was used in **chapter 6**. A possibility of having such a rich data set is that it may allow us to identify children at increased risk of having developmental problems later in life, ranging from learning disabilities, substance dependence or abuse, to the development of psychiatric disorders. Such a characterization of development can for instance be made by the estimation of a 'biological age' with the use of brain measures (Brouwer et al., 2021). Reliable brain age predictors may lead to the detection of individual variations in the developmental state of the brain, allowing for precision strategies targeted to the individual child. However, the value often lies in simply knowing variability in development exists, and regarding children as a homogeneous entity will inevitably leave some children behind. These goals depend on collecting a large amount of high-quality data, enabling researchers to uncover new links between environment, neuroscience, and daily-life functioning. This thesis serves as a prelude to what may be possible with such a wealth of information. With the addition of additional waves to the cohort, the developmental trajectories of a healthy brain can be described in further detail. In addition, studies using twin-designs can offer insight into the genetic influences on normative brain development (Van Soelen et al., 2012; Koenis et al., 2015).

Conclusion

The goal of this thesis was to investigate the neural underpinnings of proactive inhibition. Via a number of separate experiments, the key regions associated with this process have been identified in this thesis. Furthermore, functional aspects of these regions have been linked to processes in daily life. These results add new insights on when we view a brain as fully matured, and how we deal with the trajectory leading up to adulthood. It has long been known that the regions of the brain dealing with impulse control, inhibition and learning do not fully develop in parallel. We have found indications in the brain that this imbalance

may, for example, lead to an excess of risk-seeking behaviors we associate with adolescence. In this thesis a focus was put on brain activity during specific tasks. What may shed new light on these processes in the future is the ability to combine these findings together with a large amount of data from different modalities, to understand why some children experience more problems growing up than others into adulthood. Most importantly, the human brain is not a detached entity that can be fully understood in isolation. The increasing amount of data available allows us to investigate how individual factors, environmental processes, and their intricate interplay shape who we are.

Chapter 8

Nederlandse Samenvatting

Over inhibitie

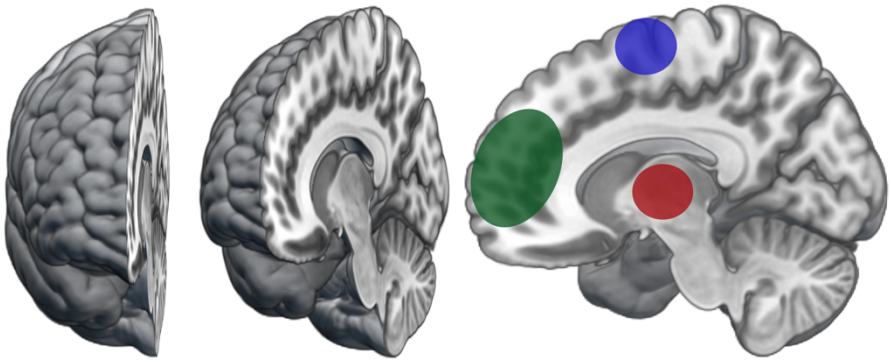
Inhibitie is een breed concept dat op verschillende niveaus gebruikt kan worden. Binnen dit proefschrift hebben we het voornamelijk over motorische inhibitie. Dit verwijst naar ons vermogen om een eenmaal ingezette handeling weer te stoppen. Bijvoorbeeld een ingezette grijpbeweging waarbij je de hand op het laatste moment weer stopt of terugtrekt. Inhibitie kan echter ook verwijzen naar het stoppen van een handeling al voordat de beweging is ingezet. Denk hierbij aan kunnen afblijven van aanlokkelijk etenswaar voor je op tafel. De verleiding is soms zo groot dat je, zonder je vermogen tot inhibitie, voortdurend op deze prikkels uit je omgeving zou reageren.

Motorische inhibitie bevat twee componenten. Enerzijds is er een reactief deel, dat verwijst naar het simpelweg onderdrukken van een actie. Anderzijds is er een proactief deel, wat inhoudt dat er rekening wordt gehouden met de mogelijkheid dat een handeling onderdrukt moet worden. In de praktijk is het lastig om reactieve en proactieve inhibitie los van elkaar te zien – we zijn onophoudelijk bezig met het anticiperen op veranderingen in onze omgeving. Proactieve inhibitie zorgt ervoor dat wanneer we de kans achten ons te moeten inhouden, we hier dan ook rekening mee houden. We worden op die momenten bijvoorbeeld voorzichtiger en vertragen ons gedrag. Als we op het laatst toch moeten ingrijpen zijn we beter voorbereid en vergroot dit onze kans van slagen.

Inhibitie en het brein

Inhibitie is terug te leiden naar een aantal hersengebieden. Centraal in ons brein liggen de basale kernen, en een onderdeel hiervan is het striatum. Dit gebied is betrokken bij motivatie en motorische processen. In andere woorden, dit gebied bepaalt hoe beloningsprikkels uit onze omgeving ons beïnvloeden, en hoe dit vervolgens ons gedrag stuurt en vormt. Daarbij is het striatum sterk verbonden met de motorische hersenschors. Hierdoor speelt het striatum bijvoorbeeld een rol bij het leggen van associaties tussen een beloningsprikkel en een handeling, zodat we op die manier automatismen kunnen aanleren. Het alleen al zien van een snack laat je hand er bijna automatisch naar toe grijpen. Dit is in de eerste levensjaren een prima eigenschap, waarbij de volwassenen simpelweg de filter kunnen zijn op wat de peuter wel of niet in zijn of haar mond stopt. Op een gegeven moment ontstaat echter de behoefte aan een 'zelfregulerend' vermogen. Zeker als het kind gaat kruipen en lopen dient er een rem te komen op waar allemaal naar gegrepen wordt. Bij voorkeur is dit een rem die op basis

van aanleren ontstaat en verder gevormd wordt. Deze remmende activiteit vindt plaats in de frontaalschors. Zie **figuur 1** voor een weergave van de gebieden.



Figuur 1. *Dwarsdoorsnede van het brein met de rechterhersenhelft zichtbaar. Met groen de frontaalschors gemarkeerd aan de voorkant, met blauw de motorische schors, en met rood het striatum.*

Gedurende de ontwikkeling van de hersenen zijn het striatum en de frontaalschors functioneel niet volledig met elkaar in balans. Richting de puberteit ontstaat er een disbalans waarbij de frontaalschors relatief ten opzichte van het striatum minder actief is. Dit hangt samen met een periode waarin tieners wat impulsiever worden, en meer risico's opzoeken. Aan de ene kant zorgt deze impulsiviteit wellicht voor ongunstig gedrag zoals een toename in ongelukken, of heeft het mogelijke gevolgen als drugsgebruik of het oplopen van seksueel overdraagbare aandoeningen. Echter kan gesteld worden dat deze neurobiologische verandering ook een positieve kant heeft. Het drijft adolescenten ertoe nieuwe, eigen ervaringen op te doen en de wereld verder te verkennen.

Het meten van inhibitie

Om de hersenprocessen in kaart te brengen die ten grondslag liggen aan inhibitie hebben we een manier nodig om dit gedrag in de scanner te ontlokken. Hiervoor gebruiken we taken die een deelnemer laten reageren op een dusdanige manier dat zowel proactieve als reactieve processen aangeroepen worden. In deze thesis is hiervoor een zogenaamde stopsignaal taak gebruikt.

Deelnemers voeren een simpele repetitieve handeling uit, waarbij deze handeling soms op het laatste moment gestopt dient te worden. Hoe accuraat iemand is in dit stoppen verwijst naar het vermogen om reactieve inhibitie toe te passen. Sommige mensen zullen 200 milliseconden (0,2 seconden) voor een stopsignaal nog kunnen reageren, waar anderen simpelweg meer tijd nodig hebben. Deze reactieve inhibitie is, onder andere, afhankelijk van verbindingen tussen de basale kernen en de motorische schors. Daarnaast is in deze taak ook een element verwerkt waardoor deelnemers de kans in kunnen schatten dat een handeling gestopt moet gaan worden. Bij een grote stopkans zullen mensen doorgaans voorzichter worden en hun reacties vertragen. Moet dan op het laatste moment ingehouden worden, is de kans groter dat dit ook daadwerkelijk lukt. Dit proactieve proces is afhankelijk van de ontwikkeling van, en verbindingen tussen, de frontaalschors en het striatum.

Technieken

In deze thesis is zowel functionele MRI als EEG gebruikt om de hersenprocessen in kaart te brengen die geassocieerd zijn met inhibitie. Voor beide technieken is het noodzakelijk om het gedrag dat gemeten moet worden zo vaak mogelijk te herhalen. Enerzijds doordat er bij deze technieken inherent te maken hebben met veel ruis in het signaal, anderzijds komt er ruis voort uit de variatie in de reactie van de deelnemer. De reactie van de deelnemer kan bijvoorbeeld afhangen van de moeilijkheid van de taak, de afwezigheid van comfort bij het liggen in een scanner, de verveling of vermoeidheid vanwege het onderworpen worden aan allerlei testen. Alles draagt bij aan extra ruis in de meting, waarbij het toepassen van zo veel mogelijk herhalingen een van de oplossingen is om hier tegenwicht aan te bieden.

MRI staat voor *magnetic resonance imaging*, en hierbij liggen deelnemers tijdens het doen van de taak in een scanner waar ze blootgesteld worden aan een aan sterk passief magneetveld. Aangezien hemoglobine in ons bloed magnetische eigenschappen heeft, kan met het gebruik van kleinere wisselende magneten en radiogolven worden afgeleid waar meer of minder zuurstofrijk bloed stroomt in het brein. Deze techniek meet dus niet daadwerkelijke hersenactiviteit, maar een afgeleide hiervan. Hierbij moet ook gezegd worden dat de snelheid waarmee bloed naar een bepaalde plek in het brein stroomt een limiet legt op de temporele resolutie. Dit betekent dat er effectief een vertraging van een aantal seconden tussen hersenactiviteit en het functionele MRI-signaal.

EEG, ofwel *electroencephalografie*, is een techniek om wel het directe vuren van neuronen te meten. Dit gebeurt met een soort muts gevuld met elektrodes die op het hoofd wordt aangebracht. De temporele resolutie van EEG is een stuk hoger dan die van functionele MRI – met EEG kijken we als het ware zonder vertraging naar de hersenactiviteit. Hierbij is echter wel de limitatie dat we enkel meten aan de oppervlakte van de schedel, en we een stuk minder kunnen zeggen over de precieze bron van de activiteit. De specifieke EEG-techniek in **hoofdstuk 5** gebruikt een wavelet-transformatie om af te leiden of een deel van het brein meer of minder actief wordt over tijd.

Doel van de thesis

Het doel van dit proefschrift was om de hersengebieden te beschrijven die betrokken zijn bij inhibitie. In **hoofdstuk 2** zijn we begonnen om naar de bredere functie van het striatum te kijken, en welke rol dit gebied speelt in het aanleren van gedrag. We vonden dat de hoogte van activiteit in het striatum samenhangt met leerprestaties op een taak. Deze bevindingen resulteerde in de hypothese dat het gebied een rol speelt bij het gebruik van feedback om gedrag bij te sturen. In **hoofdstuk 3** keken we naar de specifiekere rol van het striatum binnen motorische inhibitie. Eerder onderzoek liet zien dat het striatum betrokken was bij zowel reactieve als proactieve inhibitie. Wij vonden dat, in lijn met de hypothese vanuit **hoofdstuk 3**, het striatum alleen betrokken was bij inhibitie als de deelnemer de stop van tevoren kon anticiperen. In **hoofdstuk 4** gebruikten we het idee dat wanneer deelnemers de verwachting hebben zich te moeten inhouden, ze hun gedrag vertragen. We vonden dat de hoogte van activiteit in onder andere het striatum en de frontaalschors samenhing met de mate van vertraging in reactiesnelheid. In **hoofdstuk 5** hebben we EEG gebruikt om met een hogere temporele resolutie naar de hersenprocessen onderliggend aan proactieve inhibitie te kijken. We vonden dat wanneer deelnemers vertraagden in anticipatie op een stopsignaal, desynchronisatie van frequenties in de bèta-band plaatsvond in het frontale-motorische gebied – een indicatie van motorische voorbereiding. Uiteindelijk hebben we de gebieden die we in **hoofdstukken 3** en **4** hebben gevonden, gebruikt om inhibitie te onderzoeken in pre-adolescente kinderen. We vonden dat sommige kinderen al hersenactiviteit vertoonden in dezelfde gebieden als volwassenen bij het anticiperen op en onderdrukken van impulsen. Daarnaast werd gevonden dat de hoogte van

activatie in de frontaalschors, en verbindingen tussen corticale en subcorticale gebieden, samenhing met gedragsbeheersing in het dagelijks leven.

Concluderend

Met een aantal verschillende experimenten hebben we in dit proefschrift de hersenprocessen in kaart proberen te brengen die onderliggend zijn aan gedragsinhibitie. De resultaten geven nieuwe inzichten over wanneer we het brein als volgroeid kunnen beschouwen, en hoe we omgaan met het pad richting volwassenheid. Het is al langer bekend dat de gebieden die geassocieerd zijn met gedragsbeheersing, inhibitie en leren niet gelijktijdig ontwikkelen. In deze thesis ligt de focus op specifieke geïsoleerde handelingen binnen een taak. Het gebruik van deze taken in combinatie met individuele kenmerken en omgevingsfactoren kan helpen bij het begrip van inhibitie in een ruimer verband. Op die manier kunnen we onderzoeken waarom sommige kinderen uiteindelijk problemen met gedragscontrole ondervinden, en anderen niet. Het brein is wellicht in isolatie te onderzoeken, maar niet te begrijpen zonder bredere context. De toename van grote datasets van bijvoorbeeld cohortstudies maakt een koppeling mogelijk tussen neurobiologische, psychologische en omgevingsdata. Dit staat ons toe te onderzoeken hoe een samenspel van biologische en omgevingsfactoren ons vormen tot wie we zijn.

Chapter 9

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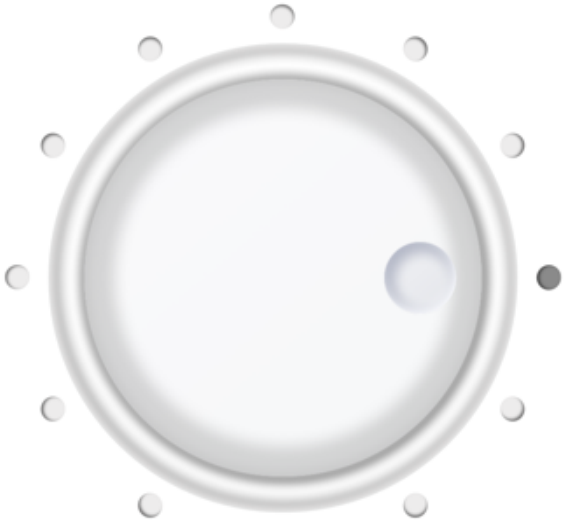

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Chapter 10

Dankwoord

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Chapter 11

List of publications

About the author

List of Publications

Published

Vink, M., **Pas, P.**, Bijleveld, E., Custers, R., & Gladwin, T. E. (2013). Ventral striatum is related to within-subject learning performance. Neuroscience, 250(C), 408–416. http://doi.org/10.1016/j.neuroscience.2013.07.034

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[1] Shared first author

Submitted

Pas, P., Gladwin, T.E., Angerer, E., Bik, A., Soethoudt, N. & Vink, M. Beta-band event-related desynchronization in the motor cortex predicted by slowing due to proactive inhibition

About the Author

Pascal Pas was born august 9th, 1987 in Doetinchem. He obtained his VMBO and HAVO diplomas, 2003 and 2005 respectively, at Ulenhof College in Doetinchem. After a year of studying Built Environment at the HAN University of Applied Sciences of Arnhem, he switched to Human Resource Management at the Saxion University of Applied Sciences in Deventer and obtained his propaedeutic exam. In 2007 he began studying for a bachelor's degree in psychology at Utrecht University and graduated in 2010. He subsequently graduated cum laude from a master's in social psychology and a research master's in Social and Health Psychology (2011 and 2013 respectively). During the final year of the research master programme, he spent half a year at University College London at the Department of Experimental Psychology.

Pascal started working as a research assistant at Utrecht University during his research master's programme and continued at the University Medical Hospital Utrecht after obtaining his degree. After initially assisting in multiple neuroimaging research projects and intermittently working on own research, he officially started his own PhD project in 2016 under de supervision of Prof. dr. Hulshoff Pol.