MOTIVATIONAL AND NEUROMODULATORY INFLUENCES ON PROACTIVE AND REACTIVE COGNITIVE CONTROL

Hanne Schevernels

Promotor: Prof. Dr. C. Nico Boehler
Copromotor: Prof. Dr. Patrick Santens

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# TABLE OF CONTENTS

## ACKNOWLEDGEMENTS

## CHAPTER 1 INTRODUCTION

- What is under control? Refining the concept control
  - Reactive and proactive control
  - Structural and neuromodulatory systems involved in control
  - An example: proactive and reactive inhibitory control
- Why is it under control? The role of motivation
  - Neural basis of reward processing
  - Reward and effort
  - Motivation triggers cognitive control
- When is it under control? Using event-related potentials

## CHAPTER 2 TASK PREPARATION PROCESSES RELATED TO REWARD PREDICTION PRECEDE THOSE RELATED TO TASK-DIFFICULTY EXPECTATION

- Introduction
- Materials and Methods
  - Participants
  - Stimuli and procedure
  - EEG acquisition and preprocessing
  - EEG analyses
- Results
  - Behavioral results
  - ERP results: cue-locked
  - ERP results: target-locked and feedback-locked
- Discussion
- Conclusions

## References
CHAPTER 5 THE EFFECT OF VAGUS NERVE STIMULATION ON RESPONSE INHIBITION

Introduction 166
Materials & methods 170
Participants 170
VNS apparatus 171
Stimuli and procedure 171
Electrophysiological recordings and preprocessing 173
Statistical analyses 175
Results 177
Behavior 177
Event-related Potentials 179
Discussion 181
Conclusion 186
Acknowledgements 187
References 188
Appendix I 198

CHAPTER 6 GENERAL DISCUSSION

Results: an overview 199
Mental preparation as an important proactive control function 199
Neuromodulatory and reward influences in reactive control 202
Theoretical implications and discussion 205
The anticipation of cognitive and physical effort 205
Reward and punishment as motivators 207
The direction of the link between reward and effort 209
Electrophysiology in the stop-signal task 212
Clinical implications 214
Future research 216
Conclusion 217
References 218

CHAPTER 7 NEDERLANDSE SAMENVATTING

Introductie 231
Empirische studies 234
Algemene discussie 239
Conclusie 242
Referenties 243
APPENDIX DATA STORAGE FACT SHEETS
ACKNOWLEDGEMENTS

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CHAPTER 1
INTRODUCTION

“Goals transform a random walk into a chase.”
Mihaly Csikzentmihalyi

Imagine you are on your way to an important job interview (or a PhD defense) which you obviously don’t want to be late for. Of course it turns out that the road you wanted to take is blocked. Chances are that you will not wait until the situation is resolved and you decide to take a different route. This is an example of how in daily life we need to be able to flexibly adapt our behavior to environmental changes while keeping our internal goals in mind. In psychology this capability has been referred to as cognitive control. Hence, cognitive control is a very broad concept that involves a large scope of executive processes like updating and maintaining task goals, attention, working memory, response inhibition and performance monitoring. These control-related functions are thought to mainly rely on processes in prefrontal brain areas (Miller, 2000) and cognitive control has usually been seen as a higher-order voluntary process (Miller & Wallis, 2009). Although they have been largely studied separately for a long time, today the importance of motivation in cognitive control has generally been recognized (Botvinick & Braver, 2014). Motivation can trigger control in the sense that goals are prioritized in function of the value of their outcome. For example, you might be particularly eager to get to that job interview (in time) because this new job would considerably increase your salary. In the current dissertation we aim at investigating the underlying processes of different forms of control and their potential interaction with motivation.
Reactive and proactive control

In some situations cues can warn us about an upcoming event so that we can already optimize cognitive and motor systems to deal with it in a way that is consistent with our goals. For example, when riding a two-way bike lane and seeing another biker coming from the opposite direction, we can prepare to safely pass each other by keeping right and slowing down in order to continue our way. On the other hand, sometimes situations do not allow us to anticipate and thus we need to be able to immediately deal with the situation when it occurs. Coming back to our biking example, if we reach an intersection where the view is blocked and suddenly another biker is coming from that direction we have to hit the brakes instantly to avoid a crash. In the present work we distinguish these two forms of cognitive control, referring to the first as proactive control and the latter as reactive control (along the lines of the dual mechanism of control theory by Braver, 2012; Braver et al., 2007).

Proactive control supports the processing of and dealing with an upcoming event by active preparation. This could involve active rehearsing and maintaining task goals, changes in resource allocation and the implementation of general task strategies. Reactive control triggers task-specific cognitive processes only when they are really needed and thus functions more as a late correction mechanism. Hence, one major difference between proactive and reactive control relates to the time of their involvement, i.e. when control processes are implemented. This temporal
separation also means that proactive and reactive control can interact to optimize behavioral performance and outcomes.

**Structural and neuromodulatory systems involved in control**

As previously stated, the prefrontal cortex (PFC) is supposed to be critically involved in cognitive control (Miller, 2000). Yet, also other regions seem to be included, forming a network of cortical (e.g. PFC, anterior cingulate cortex, pre-supplementary and premotor cortex), and subcortical regions (like the insula, thalamus, caudate and putamen) that interact to implement control (e.g. Cole & Schneider, 2007; Niendam et al., 2012). More specifically, proactive cognitive control is thought to be mostly characterized by sustained brain activation in PFC, possibly driven and maintained by activity in the dopaminergic system (Boehler et al., 2011; Braver, 2012). In contrast, reactive control is believed to typically implicate late enhanced brain activation patterns that are specifically related to the actual performance of the task. Importantly, the dopaminergic system seems to be less involved in reactive control (at least concerning reactive control in a given situation rather than learning from it, which could also be considered a reactive form of control and features significant dopaminergic involvement, see e.g. Jocham & Ullsperger, 2009). For instance, concerning neuromodulatory influences, response inhibition, which has been typically considered a reactive control function (see below), has been found to be mainly affected by the noradrenergic modulatory system and not the dopaminergic system (Bari et al., 2009; for an overview see Eagle et al., 2008; but see Robertson et al., 2015).

Although the points above suggest not only neurochemical but also structural difference between reactive and proactive control, we note that
during preparation also task-related brain regions have been found to be activated (e.g. Duque et al., 2012; Vink et al., 2015) as a function of proactive control. Moreover, dopaminergic regions have also been shown to be involve in reactive functions like performance monitoring, as evident from attenuated error negativities that reflect error processing (Falkenstein et al., 1991, 2000; Gehring et al., 1993) through a drug-induced increase in dopamine levels (for an overview see Jocham & Ullsperger, 2009). Thus, although there could be some differences in the systems involved, the distinction between proactive and reaction control made here is mostly conceptual and to a lesser extent systematical.

An example: proactive and reactive inhibitory control

A central cognitive control function is response inhibition (Aron, 2007; Verbruggen & Logan, 2008), which is the ability to withhold a predominant or already-initiated motor action when it is not or no longer appropriate. One of the main paradigms that have been used to investigate this function (also in the current dissertation) is the stop-signal task. In this task subjects need to rapidly cancel a response when an infrequent stop signal occurs shortly after the presentation of a go stimulus (see figure 1). Whether inhibition is successful or not is thought to be defined by a race between a go process and a stop process that are triggered by the respective stimuli and for the most part proceed independently from each other (Logan & Cowan, 1984; Logan et al., 1984). Functional Magnetic Resonance Imaging (fMRI) studies in humans using the stop-signal task have shown that response inhibition primarily involves activity in (pre)frontal regions (like the right inferior frontal gyrus and/or the pre-supplementary motor area) and in basal ganglia circuits (e.g. Aron et al., 2014; Aron & Poldrack, 2006).
Typically, in the stop-signal task reactive inhibitory control is studied, implicating immediate stopping when the stop signal is observed, the occurrence of which cannot be predicted. The speed of this process is reflected by the stop-signal reaction time (SSRT) which is a measure for how long it takes to inhibit a response from the moment the stop signal is presented (Verbruggen & Logan, 2008). Given that performance in the stop-signal task depends on a race between going and stopping, successful inhibition can likely also be promoted by inserting control processes or strategies before the onset of the trial or stop signal that bias this race. This has been labeled as proactive inhibition (e.g. Aron, 2011; Verbruggen & Logan, 2009) and one of its prime illustrations is proactive slowing in which responses are given more slowly in task contexts with a high probability of full response inhibition being necessary, likely relating to response thresholds being increased in order to improve successful stopping (Verbruggen & Logan, 2009). Proactive response inhibition might be engaged via the use of knowledge about the upcoming event as indicated by cues or contextual information (Swann et al., 2013; Verbruggen & Logan, 2009). This means that proactive adjustments can be made flexibly between trials. This was shown in a previous study of Chikazoe et al. (2009) who found response slowing in go trials in which the color of the go stimuli indicated that stopping might be required compared to certain going. Moreover, imaging results implied that when a cue signals the need for inhibition, a typical stopping-related brain network is already activated thereby suggesting that stopping is being prepared (see also e.g. Vink et al., 2014, 2015; Zandbelt & Vink, 2010; Zandbelt et al., 2013). Furthermore, inhibitory cognitive control can also be implemented in the span of several trials, which was demonstrated by the finding that the response threshold was increased in blocks with relevant stop-signals compared to blocks in
which stop signals can be ignored (Verbruggen & Logan, 2009). Proactive and reactive inhibitory control do not need to be mutually exclusive and can even work together to reach optimal stopping performance. For example, Chikazoe et al. (2009) found that increased slowing (i.e. preparation cost) in go trials was correlated with decreased SSRTs and reduced reactive inhibitory control activity.

Figure 1. Example of the stop-signal task. In the stop-signal task most trials are go trials in which subjects have to press a button (left or right) as fast as possible according to the direction of the go stimulus (‘>’). However, occasionally they have to suppress this response when the stop signal rapidly follows the presentation of the go stimulus. The stop signal is visual (‘V’) in the visual stop-signal task and auditory (a tone) in the auditory stop-signal task.

**WHY IS IT UNDER CONTROL?**

**THE ROLE OF MOTIVATION**

‘What guides behavior?’ This is a question that has attracted a lot of attention over many years in different fields. Our everyday behavior can be driven by both intrinsic, e.g. internal goals, and extrinsic factors, e.g. reward
and punishment (see also the self-determination theory, Deci & Ryan, 1985). In the current work we focused on extrinsic motivators (mostly reward). People and other animals strive to increase positive outcomes like reward and decrease negative outcomes like punishment. Although we focus on monetary reward (and punishment) as motivators, we do not presume that results are restricted to reward and thus similar findings could be obtained by manipulating other types of motivators.

**Neural basis of reward processing**

Many years of research in humans and animals have successfully shown the significance of the dopaminergic neuromodulatory system in reward-related processes. Importantly, it was found that in monkeys dopaminergic neurons in the ventral tegmental area (VTA) do not only fire when receiving a reward but also during reward prediction when a stimulus consistently precedes the reward (Mirenowicz & Schultz, 1994; Schultz, 1998; Schultz et al., 1997, 1998). A similar involvement of the dopaminergic system in reward anticipation has been shown in humans, usually by fMRI studies that implemented a monetary incentive delay (MID) task (Knutson et al., 2000). In this task a cue informs subjects whether correct performance in the upcoming trial will be rewarded/punished or not (see figure 2). Accordingly, when comparing neural activity during preparation when cues signal reward (or punishment) versus no-reward, mainly increased hemodynamic activation is observed in the ventral striatum and the dopaminergic midbrain (e.g. Knutson et al., 2000, 2005b; Knutson & Cooper, 2005a; Schott et al., 2008; Wittmann et al., 2005).
In real life, reward is usually not the sole factor that is guiding behavior. Since reward is often not readily available, one also needs to take into account the amount of effort needed to obtain the valuable outcome or in general to achieve the goal. Effort can be related to either physical or mental effort and reflects the degree of engagement in a physically or mentally demanding task (Westbrook & Braver, 2015). Given that cognitive control is a complex function, cognitive effort is bound to be involved in control processes when trying to reach a goal (e.g. Shenhav et al., 2013).

In general, it is assumed that animals and humans tend to avoid effortful actions (Kool et al., 2010) and according to the effort-discounting principle the net value attached to a reward depends on the amount of effort.
required, defining effort in terms of a cost. Specifically, if a reward can be obtained easily it is valued more than when it is only achieved through a lot of effort (see e.g. Botvinick et al., 2009; Westbrook et al., 2013). However, humans also have a tendency to engage in challenging tasks, for example to achieve long-term goals (Duckworth et al., 2007), and some people are inclined to do this more than others (need for cognition, see Cacioppo & Petty, 1982; Cacioppo et al., 1984, 1996).

The dopaminergic system originating in the midbrain (from the substantia nigra pars compacta and the ventral tegmental area) and its main subcortical and cortical target areas like the striatum and the anterior cingulate cortex (ACC) have been supposed to play a key role in this link between reward and effort. As such, some studies have proposed that these regions encode the net value, i.e. the subjective value of reward in which effort is discounted from the reward, suggested by increased activation in these regions when anticipating/choosing less effortful performance in rewarded conditions (Botvinick et al., 2009; Croxson et al., 2009). Yet, it has also been suggested that the dopaminergic system and the ACC are particularly implicated in overcoming effort costs to acquire a desired goal (Kurniawan et al., 2011). Moreover, in contrast to the discounting principle, studies have shown that similar regions (including the dopaminergic midbrain and ACC) are related to effortful motivated cognitive preparation with increased activity when preparing for a highly demanding task (e.g. Boehler et al., 2011; Krebs et al., 2012; Kurniawan et al., 2013; Vassena et al., 2014).

We note that usually in these previous studies effort is related to action execution and a Pavlovian link has been assumed between action and reward since humans and animals are more likely to engage in approach
behavior when being rewarded (or preparing for reward), in contrast to avoidance behavior when being punished (for evidence see Guitart-Masip et al., 2011, 2012b, 2014). Together these results imply a tight coupling between reward and effort when an action is (to be) performed.

**Motivation triggers cognitive control**

Typically reward has beneficial effects on a wide variety of cognitive functions. For example, reward seems to positively influence cognitive control indicated by improved task-switching (e.g. Umemoto & Holroyd, 2014), working memory performance (e.g. Jimura et al., 2010; Taylor et al., 2004), response inhibition (e.g. Boehler et al., 2012; Rosell-Negre et al., 2014), goal-driven attentional control (e.g. Kiss et al., 2009; Padmala & Pessoa, 2011; Pessoa & Engelmann, 2010), and even memory formation (Wittmann et al., 2005, 2008). Moreover, these studies typically show that enhanced motivation is associated with increased activation in networks that underlie (task-specific) cognitive control functions (Boehler et al., 2014; Jimura et al., 2010; Pochon et al., 2002; Taylor et al., 2004) and thus it is likely that reward can trigger or energize boosted control in order to optimize performance and obtain goals (Kouneiher et al., 2009).

**Motivation and proactive control**

Reward is especially believed to promote a sustained proactive mode of cognitive control (Braver, 2012; Braver et al., 2007), in line with the observation that both motivation and proactive control implicate the dopaminergic system and dopamine release in the prefrontal cortex (see also Chiew & Braver, 2014). This hypothesis was supported by studies using the AX-continuous performance task (AX-CPT) task in which subjects are instructed to press one button every time a probe (‘X’) is preceded by a
specific cue (‘A’) and another button for all other stimuli. This task involves several cognitive functions like goal representation, goal maintenance and sustained attention. In a proactive control state one would be primarily focused on the cue (‘A’), while in a reactive control state one would be rather attending the probe (‘X’) (Braver et al., 2009). In line with a proactive cognitive control mode, it was found that reward enhanced performance in ‘AX’ trials while it had detrimental effects in ‘AY’ trials, in which the cue falsely led subjects to expect a probe (Locke & Braver, 2008; see also Strang & Pollak, 2014). Moreover, fMRI results displayed more sustained activation triggered by the cue in regions related to cognitive control in the reward context (Locke & Braver, 2008; Strang & Pollak, 2014).

Given this link between proactive control and reward, motivational effects have mainly been shown in tasks using reward context (blocks) and cueing paradigms (e.g. Padmala et al., 2011; Pochon et al., 2002; Rosell-Negre et al., 2014). As such, Jimura et al. (2010) observed that in a reward block, consisting of reward trials and no-reward trials, working memory performance was enhanced even (and particularly) for no-reward trials, which seemed to profit from the reward context. Sustained activation in the right lateral PFC confirmed that the reward context created a shift to a proactive control mode that influenced all trials (including no-reward trials). Along similar lines, Soutschek et al. (2014) showed that manipulating congruency expectancy in a Stroop task, which modulates proactive control, decreased the Stroop effect under low motivation but not in highly motivating conditions. This suggests that both factors influence the same proactive control processes and thus no additional advantage of congruency expectancy could be detected when subjects were highly motivated. Yet, motivation did not affect the level of conflict adaptation (i.e. reduced conflict
after incongruent trials), a form of reactive control adjustments. Hence, all these aforementioned results point in the direction of a large influence of motivation in (preparatory) proactive control processes.

**Motivation and reactive control**

In contrast to Soutschek et al. (2014), other researchers did detect motivational effects on reactive conflict adjustments. More specifically, it was usually observed in this line of research that conflict adaptation increased after reward feedback when contingent upon task performance (Braem et al., 2012; Stürmer et al., 2011; see also Braem et al., 2014). This might indicate increased attention to task-relevant information after conflict detection, possibly via the strengthening of associations (Braem et al., 2012). Moreover, in a number of studies by Krebs et al. (2010, 2011, 2013) it was shown that reward can also have an impact on control processes when the reward information is linked to a target feature instead of being cued, thus limiting the role of preparatory control. Here, interference was reduced when reward was associated to the task-relevant dimension (i.e. color of the word) of a target in a Stroop task, implicating enhanced reactive control processes as demonstrated by boosted activation in lateral prefrontal areas (Krebs et al., 2011). However, in case reward information was implicitly linked to the task-irrelevant dimension (i.e. word meaning, which itself was both task- and reward-irrelevant) interference was enhanced. These results suggest that reward information can influence attention thereby being able to both promote and hinder behavioral performance (Krebs et al., 2011, 2013; see also Anderson, 2013). Furthermore, Boehler et al. (2012, 2014) found that reward can improve response inhibition in a similar set-up, presumably via enhanced reactive control. To summarize, even though findings are less clear
and less numerous it seems that motivation can also influence reactive cognitive control in some situations.

**WHEN IS IT UNDER CONTROL? USING EVENT-RELATED POTENTIALS**

In all of our studies we measured electrical brain activity from the surface of the scalp, i.e. an electroencephalography (EEG), while subjects performed a cognitive task. The EEG is mostly generated by the summation of synchronized post-synaptic activity in a large number of neurons in the brain (mainly the cortex). Importantly, electrical activity is measured with only a slight delay which is considered the main advantage of EEG. In case EEG signals are recorded while subjects perform a task, event-related potentials (ERPs) can be derived which represent neural activity time-locked to a certain event (e.g. a stimulus or response). Thus, related to this event several ERP components can be observed that reflect certain neurocognitive processes elicited by an event. The high temporal resolution of this technique allows us to identify exactly when activity occurs. This temporal precision was one of the key reasons to use EEG in our studies given that we generally discriminate proactive and reactive processes as a function of time. Hence, we can investigate proactive and reactive functions in the same task and establish possible interactions. For instance, we can examine both preparatory functions during cue-target intervals and task-related reactive processes evoked by the target.

A component that has been used to investigate proactive control is the contingent negative variation (CNV) (e.g. Killikelly & Szücs, 2013; van Wouwe et al., 2011; Vanderhasselt et al., 2014). This is a slow negative-
going wave that is typically observed during cue-target intervals at frontocentral electrodes. The CNV starts to appear around 1 second before the (cued) presentation of a target stimulus and is supposed to reflect orienting towards and preparation for the upcoming target, including attentional and response preparation/readiness (Connor & Lang, 1969; Tecce, 1972; van Boxtel & Brunia, 1994). Many studies have established the role of the CNV in effortful cognitive preparation and top-down attentional orienting (Ansari & Derakshan, 2011; Falkenstein et al., 2003; Gómez et al., 2007; Grent-’t-Jong & Woldorff, 2007; Rösler et al., 1997; Wild-Wall et al., 2007).

Proactive control might not only be reflected in cue-evoked preparatory potentials like the CNV, but also in target-evoked components like the sensory N1 that reflects (top-down guided) attentional processing of the related stimulus (Hopf et al., 2002; Luck et al., 1990; Vogel & Luck, 2000). Before the start of each trial or block strategic adjustments can be made in line with a flexible control system. These proactive changes likely involve shifts in selective attention to stimuli that would result in fluctuations of the target-locked N1 amplitude. For example, in a magnetic electroencephalography (MEG) study of Boehler et al. (2009) using the stop-signal task this idea was supported since they found that enhanced magnetic N1 amplitudes for go stimuli predicted facilitated action execution and increased stop-locked N1 amplitudes were associated with successful inhibition. Hence, it was suggested that the N1 component indexed dynamic adjustments in the strategic allocation of attentional resources.

On the other hand, the N2 and/or P3 components (also label the N2/P3 complex) in the go/no-go and stop-signal task have been typically thought to reflect reactive response inhibition (e.g., Bekker et al., 2005; Bokura et al.,
2001; Eimer, 1993; Huster et al., 2011; Kok et al., 2004; Schmajuk et al., 2006; van Gaal et al., 2011). Hence, reactive processes might be revealed by target-evoked ERP components that are typically related to the performance of the task. To conclude, EEG can be a powerful tool in distinguishing reactive and proactive processes and establishing a potential interaction.

**OUTLINE OF THE PRESENT DISSERTATION**

In the current dissertation we aimed at defining processes underlying proactive and reactive control and the influence of motivation therein. Given the assumed fast temporal succession of different operations, we were particularly interested in the temporal dynamics of these processes, which is why all empirical chapters report studies using EEG.

In the first two empirical chapters (**CHAPTER 2** and **CHAPTER 3**) we investigated an important function of proactive control: effortful cognitive preparation for the upcoming target. Given the strong link between proactive control and motivation, in **CHAPTER 2** we examined whether reward influences preparation via top-down attention or whether the related processes can be temporally distinguishable. This work was based on a previous fMRI study of Krebs et al. (2012) in which the authors sought to determine distinct and shared brain regions in the anticipation of reward and task difficulty in a cued-attention paradigm. Importantly, besides some specific brain activation, expected value and task-difficulty evoked highly overlapping brain activity and an interaction was observed in dopaminergic regions with maximal activation for cues predicting difficult yet rewarding trials. Hence, a cortico-subcortical circuit and the dopaminergic system are supposed to interact to allocate additional resources in highly demanding
tasks when it is particularly worth the effort. Since the expectation of reward and task demands evoke similar brain activity, reward seems to act via strategic attention (for a discussion see also Maunsell, 2004). Yet, because of the low-temporal resolution of fMRI it is not known whether effects of attention and task-difficulty are triggered at the same point in time. Thus, we implemented the paradigm in an EEG setting and explored ERP components evoked by the cue (reflecting both early cue evaluation and later preparatory phases), target and feedback. We were mainly interested in the cue-evoked CNV since this component is supposed to reflect effortful cognitive preparation. This chapter indicated selective influences of reward in cue-evaluation and preparatory processes that are temporally distinguishable from top-down attentional effects. Yet, they also seem to interact in a later preparation phase indicative of the integration of both factors.

Given this significant role of reward (and the dopaminergic system) in effortful preparation, in CHAPTER 3 we tried to refine the interpretation of a series of recently-published studies employing an anticipated motivated orthogonalized go/no-go task (Guitart-Masip et al., 2011, 2012a, 2014). The goal of Guitart-Masip and colleagues was to test the Pavlovian hypothesis that reward is closely coupled to action execution while punishment engages avoidance or action inhibition. Hence, these authors designed a paradigm in which both action and valence were crossed during anticipation, resulting in four types of cues: go to win, go to avoid losing, no-go to win and no-go to avoid losing. In go trials subjects had to press a left or right button according to the location of a target circle on the screen, while subjects had to withhold a response in no-go trials. Behaviorally, results showed that performance in go trials was improved in reward compared to punishment conditions suggesting a link between action execution and reward. Surprisingly, using
fMRI they found increased activation in the typical ‘reward network’, like the striatum and dopaminergic SN/VTA regions, when preparing for action over inhibition, which was furthermore mostly independent from anticipated valence (reward or punishment). They concluded that these regions predominantly encode the anticipation of action execution rather than reward. However, as already noted, previous work of our group has shown that these dopaminergic regions are also implicated in the effortful control of resources during preparation (Krebs et al., 2012), even in the absence of reward or punishment (Boehler et al., 2011). Therefore, the difference in action-related activation during preparation in the dopaminergic midbrain that was indicated by Guitart-Masip et al. (2011, 2012a) might be explained by variations in cognitive preparatory effort. The study presented in CHAPTER 3 explores this hypothesis, again mainly via investigating modulations in CNV amplitude.

These previous studies of Guitart-Masip et al. (2011, 2012a, 2014) also suggested a behavioral link between reward/dopamine and action execution and as described in the introduction (and established by the results of CHAPTER 2) motivation seems to enhance task performance mostly via proactive preparatory processes. However, it has been shown that action inhibition can also profit from reward, not only when reward information is cued (Rosell-Negre et al., 2014) but also in a non-cueing design without the engagement of global preparatory processes (Boehler et al., 2012). Boehler et al. (2012) found that when the color of a visual stop signal in the stop-signal task signaled that correct stopping would be rewarded in the current trial, inhibition was improved (shorter SSRTs). In a follow-up fMRI study this positive reward effect was explained in terms of enhanced reactive control since increased activation in regions typically related to reactive
inhibition was observed in reward-related trials (Boehler et al., 2014). Although these results implied boosted reactive control, in CHAPTER 4 we investigated the possibility that latent proactive control processes might still contribute to the favorable impact of reward. Specifically, proactive control could be employed in the form of a sustained attentional proactive control mode induced by a reward context (Jimura et al., 2010; Locke & Braver, 2008) and/or via a more selective proactive control process in which subjects strategically screened for the reward-related color. Accordingly, in CHAPTER 4 we conducted an ERP study in which subjects performed the rewarded stop-signal task (reward block) of Boehler et al. (2012, 2014), intermixing reward and no-reward trials, and an identical stop-signal task in which none of the trials were rewarded (no-reward block). This allowed us to establish the impact of reward on both proactive and reactive control functions in the stop-signal task.

Although beneficial effects of reward on response inhibition could be related to changes in the dopaminergic neuromodulatory system, at least in task contexts that allow for enhanced proactive control, earlier research suggested that response inhibition itself is mainly modulated by the noradrenergic system. As such, people with attention-deficit hyperactivity disorder (ADHD) who are impaired in stopping performance (Lijffijt et al., 2005; Murphy, 2002; Senderecka et al., 2012) generally show improved inhibition after administering medication that increases noradrenaline concentrations (Aron et al., 2003; Chamberlain et al., 2007; Overtoom et al., 2003). Moreover, in healthy animals and humans particularly drugs that affect noradrenaline levels (like selective noradrenaline reuptake inhibitors) seemed to enhance action-cancellation abilities in the stop-signal task (Bari et al., 2009; Humby et al., 2013; Linssen et al., 2012; see also Eagle et al.,
Therefore, in **CHAPTER 5** we tested whether vagus nerve stimulation (VNS) in epileptic patients would affect response inhibition, since VNS is thought to excite noradrenergic neurons in the locus coeruleus (Fornai et al., 2011). Again surface ERPs were recorded in order to examine underlying brain processes. As indicated in the previous chapter and earlier studies (Bekker et al., 2005a, 2005b; Boehler et al., 2009), it seems that stopping performance might also depend on perceptual processes, like detecting the stop signal, which has been referred to as a proactive control function (Verbruggen et al., 2014). Hence, additional to stopping performance, the influence of VNS on these proactive sensory (N1) and reactive inhibitory (P3) processes was assessed in this chapter.

In the last section of this dissertation, the **GENERAL DISCUSSION**, we provide an overview of the results and relate our findings to the existing literature. Subsequently, we discuss the generalizability and overall implications of these results. General strengths and weakness of our studies are mentioned and we suggest some future research ideas.
REFERENCES


Recently, attempts have been made to disentangle the neural underpinnings of preparatory processes related to reward and attention. Functional magnetic resonance imaging (fMRI) research showed that neural activity related to the anticipation of reward and to attentional demands invokes neural activity patterns featuring large-scale overlap, along with some differences and interactions. Due to the limited temporal resolution of fMRI, however, the temporal dynamics of these processes remain unclear. Here, we report an event-related potentials (ERP) study in which cued attentional demands and reward prospect were combined in a factorial design. Results showed that reward prediction dominated early cue processing, as well as the early and later parts of the contingent negative variation (CNV) slow-wave ERP component that has been associated with task-preparation processes. Moreover these reward-related electrophysiological effects correlated across participants with response time speeding on reward-prospect trials. In contrast, cued attentional demands affected only the later part of the CNV, with the highest amplitudes following cues predicting high-difficulty potential-reward targets, thus suggesting maximal task preparation when the task requires it and entails reward prospect. Consequently, we suggest that task-preparation processes triggered by reward can arise earlier, and potentially more directly, than strategic top-down aspects of preparation based on attentional demands.

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Everyday human behavior is guided by internal states and objectives that interact with external factors. Central among these external influences are reward and reward prediction. The dopaminergic midbrain is known to play a critical role in these reward-related processes and to be central to reinforcement learning (e.g., Glimcher, 2011; Wise & Rompre, 1989). It has been shown that stimuli predicting the possibility to obtain a reward invoke neuronal activity that is similar to that triggered by the reward itself in both animal (e.g., Mirenowicz & Schultz, 1994; Schultz et al., 1997) and human research (e.g., D’Ardenne et al., 2008; Knutson & Cooper, 2005; Knutson et al., 2005; Schott et al., 2008; Zaghloul et al., 2009). This process is believed to simultaneously energize cognitive and motor processes that may help to successfully obtain the reward (Salamone & Correa, 2012). Along such lines, the anticipation of reward has been shown to enhance a wide range of cognitive operations, including memory and novelty processing (e.g., Adcock et al., 2006; Krebs et al., 2009; Wittmann et al., 2005, 2008), perceptual discrimination (e.g., Engelmann & Pessoa, 2007; Engelmann et al., 2009), cognitive flexibility (e.g., Aarts et al., 2010) and conflict resolution (e.g., Padmala & Pessoa, 2011; Stürmer et al., 2011).

Effects of reward and attention have largely been considered as distinct phenomena, and they therefore have been investigated mainly in separate fields. However, it has been pointed out that most studies are not able to distinguish direct reward effects from effects of voluntary attentional enhancement (Maunsell, 2004). Previous studies have shown that attention and reward clearly interact: visual attention is more efficient when conditions or stimuli are motivationally significant (Engelmann & Pessoa,
and rewarded stimulus aspects draw more attention (Krebs et al., 2010, 2013). These studies, however, have generally not been able to differentiate between more direct low-level influences of reward versus indirect strategic attentional effects, although some recent studies have shown that reward associations can have a direct impact on early stages of visual, cognitive, and oculomotor processes, without the mediation of strategic attention (Della Libera & Chelazzi, 2006; Hickey and van Zoest, 2012; Hickey et al., 2010). These early-stage effects are thought to rely on the direct association between task-relevant stimulus features and reward, and hence do not reflect preparatory or strategic effects that require a cue-target sequence. Baines et al. (2011), in turn, investigated the dynamics of spatial attention and motivation in an event-related-potentials (ERP) study, but also focused on effects of target processing. They showed that motivation and attention had early independent effects when visually processing the target stimulus, with interactions only arising later.

Whereas the above studies thus tried to dissociate influences of reward and attention largely during target discrimination processes, the possible dissociations of attention and reward prospect during task preparation have received little attention so far. Yet, effective preparatory brain mechanisms can be crucial for successful task performance. Moreover, it has been suggested that the dopaminergic system plays an important role in improving task performance mostly in proactive/preparatory contexts (Braver et al., 2007). Importantly, the dopaminergic response that is typically related to reward anticipation is usually assumed to be only elicited by extrinsic factors (but see Salamone & Correa, 2012). However, in a recent paper by our group (Boehler et al., 2011) this idea was challenged. In this fMRI study, a visual discrimination task was performed in which a cue informed participants of
the task demands (high or low) for the upcoming trial. Despite the absence of reward or any other immediate extrinsic motivator, the dopaminergic midbrain showed enhanced activity for high compared to low task demands. Thus, anticipation of attentionally demanding tasks, independent of any extrinsic factor, can invoke neural processes that resemble the anticipation of reward, suggesting that the dopaminergic midbrain is more generally engaged in flexible resource allocation processes to meet situational requirements for which it can be recruited in different ways (see also Nieoullon, 2002; Salamone et al., 2005).

To further investigate the overlap and distinctiveness of the neural networks related to reward-dependent and reward-independent recruitment of neural processing resources Krebs et al. (2012) systematically crossed reward and attentional demand prediction in a subsequent fMRI study. Both factors activated selective but also similar neural networks with mostly additive effects, but also interactions for some areas, including the dopaminergic midbrain, with maximal activity in response to cues that predicted difficult potential-reward trials. These findings were taken to support the view that the dopaminergic midbrain plays a role in a broader network that is involved in the control of neuro-cognitive processing resources to optimize behavior when it is particularly worthwhile. Importantly, the above task required attentional orienting and task preparation immediately in response to the cue, which sets it apart from typical neuroeconomic experiments that emphasize evaluative processes and have conceptualized task demands as costs that get discounted from the possible reward (Croxson et al., 2009; McGuire & Botvinick, 2010). There are however important questions that cannot be addressed with fMRI because of the slow characteristics of the hemodynamic response. Most
Importantly, studies using fMRI are not able to distinguish processing stages related to cue evaluation and task-preparation processes in general, as well as potential differences in the temporal dynamics of such processes related to the processing and anticipation of reward and task demands. The present study was performed to tackle these questions of timing by using ERPs in an adapted version of the study by Krebs et al. (2012).

Our central aim was to systematically investigate how the prediction of attentional demands and reward availability is registered over time, and leads to adjustments in preparatory activity preceding the target stimulus onset. After the initial registration of the relevant features, we expected differential effects on neural markers of task preparation and attentional orienting. An ERP component that is particularly interesting in this regard is the contingent negative variation (CNV), which is a central slow negative brain wave that has been typically observed between a warning (cue) and imperative stimulus (target). This ERP wave has been shown to reflect the anticipation of or orienting to the upcoming stimulus and response preparation, and has been related to preparatory attention, motivation and response readiness (Grent’-t-Jong & Woldorff, 2007; Tecce, 1972; van Boxtel & Brunia, 1994; Walter et al., 1964). We expected that cue information about reward availability and task demands could lead to dissociations of processes related to the interpretation of the cue information and subsequent task preparation not only in amplitude but also in time. These two manipulations could start to influence brain processes at a different point in time, with reward effects potentially arising earlier since reward is known to be a salient stimulus feature that can even modify early visual processes directly (e.g., Hickey et al., 2010) and because a reward-
CHAPTER 2

predicting cue can become an inherently motivating stimulus (Bromberg-Martin & Hikosaka, 2009; Mirenowicz & Schultz, 1994).

MATERIALS AND METHODS

Participants

Twenty-two healthy right-handed participants with normal color vision participated in the present study (three male; mean age 20, range 18-23). The study was approved by the local ethics board and written informed consent was obtained from all participants according to the Declaration of Helsinki prior to participation. Participants were compensated at 15€ per hour plus an additional performance-based bonus between 4 and 8€.

Stimuli and procedure

The present experiment was based on an earlier fMRI study (Krebs et al., 2012), by using a very similar version of the paradigm with some adjustments related to electroencephalography (EEG) methodology (Fig. 1). A central gray fixation square (0.5°) and two placeholder frames, one in the left and right visual field (6° lateral from fixation and 6° below fixation), were continuously present on a black background throughout the experiment. Each trial started with a centrally presented arrow cue (400 ms duration) predicting the target location (left or right), as well as reward availability and task difficulty. With respect to reward likelihood, cue color was either green or blue, indicating whether a fast correct answer was going to be rewarded or not. In addition, white or black squares in the center of these arrows specified the difficulty (high or low) of the upcoming task trial. Colors predicting reward (green and blue) and task difficulty (white and
black) were counterbalanced across participants. To enable links to some earlier studies in this attentional-cueing field (e.g., Grent-'t-Jong & Woldorff, 2007), catch cues trials were also included (where the cue was gray upward-oriented arrows, enclosing a little dark gray square, indicating no target would follow); these trials were, however, ultimately not used for the present analysis.

After a variable inter-stimulus interval (ISI) of 1100 ms to 1600 ms the target stimuli were presented in the placeholder frames for 100 ms, whereas catch cues were followed at that time point by another cue that started a new trial. Targets were gray circles (radius 1°), interrupted by two opposing gaps. The participants were asked to respond only to the covertly attended stimulus at the cued location, while ignoring the stimulus in the opposite hemifield, by indicating which gap was larger (index versus middle finger of the right hand for larger gap at the bottom versus the top, respectively). On low-difficulty trials, one of the gaps was clearly larger than the other, with gap angles of 90° versus 20°. On high-difficulty trials, the two gaps were more similar, with gap angles of 40° versus 20°, and were thus harder to discriminate. A response time-out was adjusted after every high-difficulty trial to obtain a constant ratio of 75% correct versus 25% error or missed trials thereby ensuring that the task was similarly difficult for all participants. This variable response time-out was used during task performance to adjust visual feedback. Yet, it was not applied when analyzing behavioral data and cue- and target-related ERPs.

A feedback display was presented after a varying ISI of 900 to 1300 ms. In potential-reward trials, four cents could be won or lost, indicated by a display above the standard fixation square of ‘+4’ after correct and fast responses and ‘-4’ after incorrect or too-slow responses. To preserve trial
structure similarity, in no-reward trials feedback comprised of a ‘+0’ or ‘-0’ for correct and incorrect/missed trials, respectively. The feedback stimulus was displayed for 400 ms, followed by an inter-trial interval of 600-1000 ms. Additionally, after each experimental run the total gained amount was presented.

The participants started with a short practice run to get acquainted with the task. After practice, three runs of 200 trials each were performed. In every run, the factors of reward and task difficulty were crossed and shown in randomized order, resulting in 20 trials per condition (high-difficulty reward, low-difficulty reward, high-difficulty no-reward, low-difficulty no-reward) per target side (left vs. right) plus 40 catch trials. This resulted in a total of 60 trials per active-attention condition (120 when combining data for left- and rightward cues), and 120 catch trials. The participants sat in a shielded room and were monitored with a camera. They were asked to sit in a relaxed position, limit blinking, and fixate on the fixation square throughout the task. In each run five 20-second breaks were inserted in which the participants could move and relax their eyes.
Figure 1. Paradigm. In active-attention trials cues indicated the target location (direction of arrow), availability of reward (color of arrow) and task difficulty (color of fixation square). After a variable ISI a target was presented and participants had to indicate whether the top or bottom gap was larger. Subsequent feedback indicated the amount of money won or lost (4 eurocents for reward trials or 0 eurocents for no-reward trials).

**EEG acquisition and preprocessing**

EEG activity was recorded with a Biosemi ActiveTwo measurement system (BioSemi, Amsterdam, Netherlands) using 64 Ag-AgCl scalp electrodes attached in an elastic cap, arranged according to the standard international 10-20 system. Four external electrodes were additionally attached to the head: left and right mastoids, which were used for later offline re-referencing to the average of these two channels, and a bilateral
electro-oculogram (EOG) electrode pair next to the outer canthi of the eyes referenced to each other to measure horizontal eye movements. Signals were amplified and digitized with a sampling rate of 1024 Hz.

EEG data was processed using EEGLAB (Delorme & Makeig, 2004) and the ERPLAB plugin (http://erpinfo.org/erplab), running on MATLAB. Trials with blink artifacts were corrected by independent component analysis (ICA). Epochs were created time-locked to the onset of the relevant stimulus (cue, target or feedback), including a 200 ms pre-stimulus period, that was used for baseline correction. The total time window of the epoched ERPs varied according to the kind of stimulus, with the post-stimulus length equal to the duration of the stimulus presentation plus the time window of the shortest ISI. Epochs with horizontal eye movements detected by a step function (with threshold 60μV and moving window of 400 ms in the bipolar EOG channel) were rejected. We also rejected trials with drifts larger than -/+ 200 μV in any scalp electrodes. For cue-related data, this led to the rejection of 6% of epochs on average for the different cueing conditions, for which rejection rates were very similar (ranging from 5.6% to 7.2%). For the targets, on average 4.5% of the epochs were excluded, with minimal differences between conditions (range 4.2% to 4.8%). On average 5.6% of the correct feedback epochs were rejected, again with similar percentages for all conditions (ranging from 5.1% to 6.2%). Next, EEG epochs were averaged across participants according to the different conditions.

**EEG analyses**

Although we were mostly interested in the cue phase activity, ERP responses to the target and feedback stimuli were also analyzed to investigate the possible effects of preparation on target and feedback
processing. Analyses of the cue data included all trials, while analyses of the target and feedback stimuli were limited to trials with correct responses. Although it would also be interesting to look at error responses and negative feedback, we did not analyze this data. The main reason is that there are not enough error trials for a reliable ERP analysis, in particular when dissociating trials with incorrect responses from trials with correct responses that were given too late.

Mean amplitudes were derived for time-windows averaged across electrodes within a region of interest (ROI). Time windows and ROIs of components were defined by ERP waveforms and topographic maps collapsed across conditions. Thus, the channel and time-window selection was orthogonal to the conditions of interest. Based on this approach, the cue-related P1 was quantified at posterior electrodes PO7, PO8, PO3, PO4, O1 and O2 between 70 and 130 ms. This component was followed by a negative wave (N1) over the same posterior brain area from 130 to 180 ms. A P2 with a central positive deflection at electrode sites C1, C2, Cz and CPz from 200 to 250 ms was detected, followed from 250 to 300 ms by a negative anterior (electrodes FC1, FC2, F1, F2, FCz and Fz) deflection in the N2 range. A clear P3 component was observed at occipito-parietal electrode sites (P1, P2, PO3, PO4, Pz and POz) and quantified between 300 and 500 ms. The CNV, a late negative-going wave for active-attention cues, was detected within a central ROI (C1, C2 and Cz) between 700 and 1500 ms (earliest onset of the target). Consistent with earlier studies (Broyd et al., 2012; Connor & Lang, 1969; Goldstein et al., 2006; Jonkman et al., 2003) this large time window was divided in two parts: 700-1100 ms and 1100-1500 ms, resulting in an early and late CNV component.
For targets, the P1 was quantified over lateral posterior sites (PO7, PO8, PO3, PO4, O1 and O2) between 70 and 130 ms, followed by a negative N1 in a time window of 150-200 ms over those same sites. From 180 to 230 ms post-target onset a P2 component was present and maximal at central electrode sites C1, C2, Cz and CPz. The N2 amplitude was analyzed on frontal electrode sites (F1, F2, FC1, FC2, FCz and Fz) between 250 and 300 ms. A late target P3 was visible from 300 ms to 600 ms in parietal regions (P1, P2, Pz and POz). A feedback-related component was observed over central parietal electrodes (CP1, CP2 and CPz) starting around 200 ms after feedback presentation, which was quantified between 200 and 400 ms.

Amplitudes were examined using a repeated-measures analysis of variance (rANOVA) with factors reward (reward, no-reward) and task difficulty (high, low). Results are generally reported without strict Bonferroni correction for multiple testing when multiple ERP components were considered to avoid over-correction, thereby potentially manufacturing false negatives. However, we are also referring to the corrected p-values when interpreting the results of the rather exploratory early and mid-range potentials (P1, N1, P2, N2 and P3) in the cue and target phase (yielding a corrected value of p<0.01).

RESULTS

Behavioral results

Response times (RTs) were shorter in trials with potential reward (M = 514.96 ms, SD = 50.69 ms) versus those without (M = 526.28 ms, SD = 54.43 ms), as indicated by a main effect of reward (F(1,21)=22.81, p<0.001, see table 1). There was also a significant main effect of task difficulty
(F(1,21)=109.36, p<0.001) with faster responses for low-difficulty trials (M = 491.29 ms, SD = 50.13 ms) than for high-difficulty trials (M = 549.95 ms, SD = 57.47 ms). The interaction of reward and task difficulty approached significance (F(1,21)=4.02, p=0.058) explained by a larger RT difference between high-difficulty and low-difficulty trials for reward trials compared to no-reward trials.

Analyses of the accuracy data yielded a main effect of reward (F(1,21)=14.03, p=0.001) with more correct responses for reward trials (M = 90 %, SD = 4 %) as compared with no-reward trials (M = 87 %, SD = 4 %). Unsurprisingly, accuracy was higher when the discrimination task was easy (M = 95 %, SD = 5 %) than when it was difficult (M = 81%, SD = 3 %; F(1,21)=234.38, p<0.001). No significant interaction of reward and task difficulty was found for task accuracy (F(1,21)=1.689, p=0.27). All these results are in line with the behavioral effects of the previous fMRI version of this task (Krebs et al., 2012).

<table>
<thead>
<tr>
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<th>High-difficulty</th>
<th>Low-difficulty</th>
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<tbody>
<tr>
<td>Reward</td>
<td>546 (58)</td>
<td>484 (46)</td>
</tr>
<tr>
<td></td>
<td>83 (6)</td>
<td>97 (3)</td>
</tr>
<tr>
<td>No-reward</td>
<td>554 (58)</td>
<td>499 (54)</td>
</tr>
<tr>
<td></td>
<td>79 (6)</td>
<td>94 (4)</td>
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<tr>
<td>RT (ms)</td>
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<tr>
<td>Correct (%)</td>
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Table 1. Behavioral results. Response times in milliseconds (ms) and percentage correct responses in all four main conditions with corresponding standard deviations in brackets.
**ERP results: cue-locked**

**Early and mid-range potentials**

None of the early sensory components elicited by the cues (P1 and N1) were modulated by our task manipulation (all p>0.1). The cue-related P2 component had a larger amplitude for reward cues than for no-reward cues, as indicated by a main effect of reward (F(1,21)=13.09, p=0.002; see figure 2A). Task difficulty did not influence the amplitude of this component (F(1,21)=1.65, p=0.21), and there was no significant interaction between the two factors (F(1,21)=0.14, p=0.71). The mean amplitude of the N2 component showed a trend-level main effect of reward (F(1,21)=3.63, p=0.07), with a larger amplitude for no-reward cues. No main effect of reward nor an interaction between reward and task difficulty was observed on this component (F(1,21)<1). Since the N2 follows the P2 very quickly, modulations of those components are not easily distinguishable. However, the most important finding here is that the reward availability is detected as early as 200 ms post-cue (P2 effect). The subsequent P3 amplitude was larger for reward cues compared to no-reward cues (F(1,21)=22.07, p<0.001; see figure 2B). No significant main effect of task difficulty (F(1,21)=2.86, p=0.11) or interaction (F(1,21)<1) was found for the P3 response.
Figure 2. Mid-range cue-related potentials. (A) Grand average ERPs elicited by cues in all four conditions at electrode sites C1, C2, Cz and CPz between 200 and 250 ms, and a topographic map reflecting the difference in P2 amplitude between reward-predicting cues and trials without reward prediction (electrodes of interest are indicated by white markers). (B) Grand average ERPs locked to the onset of the cue at electrode sites P1, P2, PO3, PO4, Pz and POz between 300 and 500 ms, reflecting P3 amplitudes in all conditions, and a topographic plot for reward condition versus no-reward condition.

Contingent Negative Variation (CNV)

For the early part of the CNV an enhanced amplitude was found for reward-predicting cues (F(1,21)=19.41, p<0.001), while no main effect of task difficulty nor interaction between reward and task difficulty was observed (both F(1,21)<1; see figure 3B). Reward also modulated the late
part of the CNV (F(1,21)=22.88, p<0.001), again with larger amplitudes for reward trials. Yet, this later main effect was modulated by an interaction between reward and task difficulty (F(1,21)=4.32, p=0.05; see figure 3C). This interaction resulted from the difference between high-difficulty and low-difficulty cues being larger for reward trials than for no-reward trials, with the largest late CNV deflection for high-difficulty reward trials.

To fully capture this result pattern (see Nieuwenhuis et al., 2011), a 3-way rANOVA with the additional factor time (early vs. late CNV) was implemented. A main effect of time was present (F(1,21)=75.44, p<0.001), with a higher level of negative-polarity activity in the later window. Again, larger CNV amplitudes were observed for reward cues compared to no-reward cues, resulting in a main effect of reward across both time periods (F(1,21)=22.95, p<0.001). There was also a significant interaction between time and task difficulty (F(1,21)=10.85, p=0.003), due to a larger difference between high-difficulty and low-difficulty trials in the late phase, with high-difficulty trials being more negative. Moreover, a marginally significant three-way interaction between time, task difficulty and reward was observed (F(1,21)=3.52, p=0.075). This 3-way interaction pattern was due to the interaction between task difficulty and reward only arising at a later stage of the preparation process.

Finally, this difference in CNV amplitude in the late time interval between high-difficulty and low-difficulty cues in reward trials was related to performance during target processing in that it correlated with the high-versus-low difficulty difference in the RTs to the following potentially rewarding target (r=-0.5, p=0.017; see figure 3C). In contrast, the difference in late CNV amplitude between high-difficulty and low-difficulty cues without a potential reward and the corresponding difficulty effect in RTs to
the target was not significant (p=0.7). Moreover, no significant correlation was found between reward and no-reward differences for RTs and early and late CNV amplitude (respectively p=0.76 and p=0.38).

Figure 3. Contingent Negative Variation. (A) Electrophysiological waveform indicating the CNV, with an early (700-1100 ms) and late (1100-1500 ms) phase at electrode sites C1, C2 and Cz. (B) Topographic maps resulting from condition-wise contrasts in the early and late time window of the CNV (ME = main effect). (C) Correlation between difficulty effect in the reward condition on the late CNV amplitude and target RTs (high minus low task difficulty, respectively).
ERP results: target-locked and feedback-locked

Albeit of subordinate priority, we also analyzed the ERPs elicited by the target stimuli. No significant differences between conditions were detected in the mean amplitudes of the early P1 and N1 components (all p-values>0.1). A significant interaction (F(1,21)=4.88, p=0.04) was obtained for the P2 component. This interaction is explained by a larger difference between high-difficulty and low-difficulty targets in reward trials (with a more positive wave for low-difficulty reward trials) compared to the same contrast for no-reward trials. However, this interaction effect related to P2 amplitude should be viewed as more exploratory considering that it would not survive a Bonferroni correction that takes all five ERP components into account that were analyzed here (resulting in a threshold of p<0.01). Subsequently, a more negative N2 deflection was observed for targets in no-reward trials, revealed by a main effect of reward (F(1,21)=11.31, p=0.003). The main effect of task difficulty (F(1,21)=1.61, p=0.22) and the interaction (F(1,21)<1) did not reach significance for these components. For the P3 component, a main effect of reward was observed (F(1,21)=23.65, p<0.001, see figure 4A), with a larger amplitude for targets in reward trials compared to no-reward trials. Additionally, the P3 amplitude was larger for low-difficulty targets than for high-difficulty targets, reflected statistically by a main effect of task difficulty (F(1,21)=32.86, p<0.001). No significant interaction of reward and task difficulty was observed for the P3 (F(1,21)=2.36, p=0.14).

A prominent feedback-related component that was visible over posterior central electrode sites showed a significant main effect of reward (F(1,21)=105.33, p<0.001), with larger positive amplitudes for the reward condition compared to the no-reward condition. The main effect of task
difficulty was also highly significant ($F(1,21)=127.99$, $p<0.001$) due to more positive amplitudes for high-difficulty than low-difficulty trials. Moreover, a highly significant interaction was observed ($F(1,21)=29.82$, $p<0.001$), explained by a larger amplitude difference in high-difficulty versus low-difficulty trials in the reward condition compared to the no-reward condition (see figure 4B).

Figure 4. Target- and feedback-related potentials. (A) Grand average ERPs indicating target P3 amplitudes at parietal electrode sites P1, P2, Pz and POz between 300 and 600 ms and a topographic map reflecting the average of all four main conditions, with the ROI being indicated by white electrode markers. (B) Electrophysiological waveforms time-locked to the onset of the feedback electrodes CP1, CP2 and CPz (from 200 to 400 ms) and a topographic map averaging the four main conditions.
DISCUSSION

In the present study the participants performed a cued visual discrimination task in which the targets were preceded by cues that indicated not only the target location but simultaneously the level of task difficulty and the possibility to receive a monetary reward in case of a correct and fast response. Krebs et al. (2012) already demonstrated the utility of this task to assess cognitive processes related to the prospect of reward and task demands. Again, in the current study the experimental manipulations were proven successful in that reward improved discrimination performance (more accurate and faster responses), which furthermore interacted with the manipulation of task difficulty.

The central aim of the present study was to explore neural activity related to the anticipation of both reward and attentional demands (i.e., discrimination difficulty), and more specifically, the respective time course of such activity. The present results support the idea that these processes can be dissociated temporally during task preparation. In this preparation phase reward availability modulated the processing of the cue starting from 200 ms post cue onset, with larger P2 amplitudes for potential-reward trials compared to no-reward trials. In addition, the main effect of reward was prevalent in all later ERP components of the cueing phase. The impact of reward on the amplitude of later components of warning stimuli, particularly on the P3, has been shown in previous studies (Goldstein et al., 2006; Hughes, et al., 2012). In contrast, reports on how reward availability impacts the anticipatory CNV component are rather inconsistent. Some researchers have reported variable CNV amplitudes depending on the rewarding characteristics of the warning stimulus (Hughes et al., 2012; Pierson et al.,
Another anticipatory slow-wave component that is similar to the CNV is the stimulus-preceding negativity (SPN) which reflects anticipatory attention (disentangled from motor preparation; van Boxtel and Böcker, 2004; Brunia & van Boxtel, 2001; Brunia et al., 2011). The SPN has also been shown to be affected by the motivational relevance of a stimulus, more precisely, and in line with the current results, a more negative SPN amplitude is observed when a rewarding event is expected (Brunia et al., 2011; Fuentemilla et al., 2013). Hence, in agreement with previous reports, the present study clearly supports the notion that reward can influence the attentional anticipation of, and the preparation for, an upcoming target.

On the other hand, and more importantly, task-difficulty effects arose only later in the preparation phase, as reflected by an interaction effect in the late CNV component. Specifically, CNV differences following cues predicting high-difficulty versus low-difficulty targets were more apparent in reward trials compared to no-reward trials, but only in the late part of the CNV. As a consequence, the most negative going wave was observed for high-difficulty reward trials. Importantly, this difference in task preparation indeed affected subsequent target-discrimination performance, indicated by the fact that participants with a larger difference in late CNV amplitude between high-difficulty and low-difficulty cues in the reward condition also showed faster responses for high-difficulty reward targets compared to low-difficulty reward ones. Such correlations between CNV amplitude and behavioral performance have been shown before (Birbaumer et al., 1990; Fan et al., 2007; Haagh & Brunia, 1985; Wascher et al., 1996) and correspond to the notion that the CNV reflects both motor preparation and attention or stimulus anticipation (Connor & Lang, 1969; Rohrbaugh et al., 1987), which however others have failed to find (Goldstein et al., 2006; Sobotka et al., 1992).
1976; Tecce, 1972; van Boxtel & Brunia, 1994). It has to be noted that reward and task-difficulty might influence both kinds of processes in a different way, but it is not possible to distinguish attentional orienting from motor preparation in the current experiment.

Although a main effect of task-difficulty was found for RTs, there was no clear difference between CNV amplitudes in high-difficulty no-reward trials and low-difficulty no-reward trials. This might be explained by a motivational account, in which additional strategic attention is employed only when it is worth the effort. Therefore, no extra preparation processes will be triggered by high-difficulty cues in situations without the potential of being rewarded. The current finding is probably context-dependent, since participants usually also engage attentional resources in difficult tasks that lack (the prospect of) reward. In the current experiment, however, no-reward trials could be seen as disappointing leading to a lack of motivation to spend processing resources on these trials. Alternatively, control processes elicited by task difficulty might be qualitatively different in the reward condition and the no-reward condition along the lines of a proactive vs. reactive distinction (e.g., Braver, 2012). Specifically, high task-difficulty in a reward context clearly engage proactive control mechanisms, as indexed here be the CNV. In contrast, different levels of task difficulty in the no-reward condition of the current experiments might have invoked different levels of reactive control (i.e., during target processing), which could be difficult to detect in the target-related ERPs. A final option would be that the participants did not invoke any additional control processes, neither pro- nor reactively, for high-difficulty trials as compared to low-difficulty trials in the no-reward condition. The current ERP data cannot adjudicate between these alternatives.
Patient research and studies with healthy individuals have indicated that the CNV might be related to the dopaminergic system (e.g., Amabile et al., 1986; Gerschlager et al., 1999; Linssen et al., 2011). Consequently, the observed interaction between task difficulty and reward in this component appears to be consistent with the results of the previous fMRI study of Krebs et al. (2012) showing a very similar interaction pattern in the dopaminergic midbrain with highest activation levels in respond to cues that predicted both reward and high difficulty. Of course, it should be noted that ERP measurements will not directly reflect activity in deep brain structures such as the dopaminergic midbrain (Cohen et al., 2011), but only through cortical consequences of its involvement. This possible link to the dopaminergic system raises another alternative, or possibly supplementary, interpretation for the current results. With higher levels of (reward) uncertainty, slower sustained activations of the dopaminergic system have been shown to increase (Fiorillo et al., 2003; Preuschoff et al., 2006). The current results related to late CNV amplitude are in line with this finding. The amplitude is lowest for cues that do not predict reward. Not only do these trials not feature reward, but reward uncertainty is also lowest here (for both high-difficult and low-difficult trials). In reward trials, reward uncertainty is present in both conditions, but most pronounced when cues predict a high-difficulty trial; correspondingly the largest CNV amplitude has been detected in this condition. However, considering the established characteristics of the CNV as a typical preparatory component reflecting anticipatory attention and motor preparation, this uncertainty-based interpretation appears less likely as the full explanation of the data pattern than the task-preparation-related account.
The central finding of the current study is the temporal dissociation between processes related to the anticipation of potential reward and attentional demands. The earlier and more pronounced effect of reward compared to task difficulty appears to suggest that reward might influence visual processing of the cue stimuli in a more bottom-up way, while anticipated attentional demands seem to trigger a more voluntary (top-down) influence that arises later. This might relate to the idea that there could be different routes by which the dopaminergic system is recruited that has been previously suggested by other researchers (e.g., Salamone et al., 2005). Also, in patients with Parkinson’s disease, which is characterized by major disturbances of the dopaminergic system, voluntary attention mechanisms are affected while performances and processes in automatic attention tasks can remain intact (Brown and Marsden, 1988; Brown and Marsden, 1990; Yamaguchi and Kobayashi, 1998). Other studies have shown that reward associations, especially for task-irrelevant stimulus aspects, can distract participants from the task-relevant aspects and have a detrimental effect on performance (e.g., Hickey et al., 2010; Krebs et al., 2010, 2011, 2013), which also adds evidence in favor of potential automatic influences of reward on task processes. We suggest that reward influences cue-related processes relatively directly, while strategically implemented attentional orienting plays a role only later in processing in an attempt to optimize performance according to the situational circumstances.

Another key aspect is that temporal information provided here by the ERP measures also enables the dissociation of processes related to cue evaluation from the preparatory processes it triggers. Specifically, our data indicates that early cue evaluation is particularly sensitive to possible reward availability, whereas cued task demands do not play a major role until late in
the actual task-preparation process as the target is about to occur. Furthermore, the finding that the late CNV amplitude, which has been consistently linked to task preparation, was maximal for high-difficulty reward trials, speaks to an additional critical issue. Specifically, as alluded to in the introduction, neuroeconomic experiments usually conceptualize high task demands as costs that get discounted (e.g., Croxson et al., 2009; McGuire & Botvinick, 2010). This should even more so be the case in the present experiment, as reward probability was lower in high-difficulty than low-difficulty trials. Even in this situation, we found the largest CNV amplitude in high-difficulty reward trials. If this had been merely an effect of expected reward value, the low-difficulty reward trials should have triggered the largest CNV wave. An important difference to the earlier neuroeconomic experiments was that in the present study participants had to start preparing for the upcoming task in response to the cue, which in our opinion relies on a neural network that overlaps with reward-related processes (see also Stoppel et al., 2011).

Subsequent to the preparation phase, the early perceptual processing of the target was not affected by the reward or difficulty manipulation, which is consistent with earlier reports (Baines et al., 2011; Hughes et al., 2012) that could not find an early reward impact in the target P1-N1 component in their cueing paradigms. The earliest manipulation effects in the current study were observed 200 ms after target onset. In particular, the P2 amplitude was largest for low-difficulty reward trials and for the N2 and the P3 components a main effect of reward was observed, with an enhanced positive wave for reward trials. These findings match with the results of several recent ERP studies investigating reward, suggesting that attention to or attentional capture by rewarding or affective stimuli was increased (e.g., Baines et al.,
The amplitude of the P3 in the present study was also larger in the low-difficulty condition compared to the high-difficulty condition, perhaps due to reward expectancy being higher in the low-difficulty trials (Goldstein et al., 2006; Gruber & Otten, 2010; Wu & Zhou, 2009). Also, similar results have been found in other discrimination tasks, showing a diminished visual or auditory evoked P3 amplitude in difficult discrimination trials (Hoffman et al., 1985; Palmer et al., 1994; Polich, 1987; Senkowski & Herrmann, 2002). This has been related to decreased decision certainty (i.e. ‘equivocation’), since confidence in the decision made is reduced when discriminations are more difficult (Palmer et al., 1994; Ruchkin & Sutton, 1978). Moreover, both the reward and difficulty main effect might be partly explained by the relation of the target P3 to response execution (Doucet & Stelmack, 1999), with larger P3 amplitudes for faster responses. Hughes et al. (2012) also showed that the target-locked P3 amplitude was larger for easy compared to difficult detected target pictures in a rapid serial visual presentation task and results suggested that the P3 amplitude on single trials reflected the confidence in detecting a target. Hence, the P3 modulation probably reflects a combination of reward expectancy, confidence in correct responding, and facilitated response execution.

Targets were followed by a feedback presentation, for which we had to limit our analysis to correct feedback due to trial-number limitations. The feedback elicited a broad centro-parietal component, which probably reflects a feedback-related P3 component. The response to the different kinds of positive feedback in the present experiment displayed sensitivities to reward in general, as well as to the difficulty of the task. The P3 component is generally known to be sensitive to expectancy (Courchesne et al., 1977;
Johnson & Donchin, 1980; Núñez Castellar et al., 2010) and more specifically with regard to feedback, the P3 amplitude has been observed to be larger for unpredicted outcomes compared to predicted outcomes (Hajcak et al., 2005, 2007). Since in the current experiment correct feedback is more unexpected in high-difficulty trials than in low-difficulty trials, the main effect of task-difficulty might reflect this subjective expectation. The current findings related to reward are also consistent with previous reports showing larger P3 amplitude following reward feedback than no-reward feedback (Hajcak et al., 2007), which might indicate higher motivational significance of reward feedback (see Sato et al., 2005). Finally, the response also displayed an interaction pattern, wherein the difference between low- and high-difficulty trials was larger for rewarded trials. This latter interaction seems to represent a combination of performance monitoring of correct performance on the one hand, and of reward outcome evaluation on the other.

**Conclusions**

To summarize, in the present study we investigated the time course of task preparation as a function of anticipated reward and anticipated attentional task demands. While preparing for the target, reward influenced neural processes more rapidly, with large effects in both the early and late stages of preparation. In contrast, it seems that processing resources were only later allocated in a strategic fashion that also incorporated anticipated task difficulty. These findings provide evidence that effects of voluntary attentional demands and reward can be temporally dissociated, not only during task execution but also during task preparation.
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References


CHAPTER 3
PREPARING FOR (VALENCED) ACTION – THE ROLE OF DIFFERENTIAL EFFORT IN THE ORTHOGONALIZED GO/NO-GO TASK

Associating reward to task performance has been shown to benefit scores of cognitive functions. Importantly, this typically entails associating reward to the execution of a response, hence intertwining action-related processes with motivational ones. However, recently, preparatory action requirements (go/no-go) and outcome valence (reward/punishment) were elegantly separated using a cued orthogonalized go/no-go task. Functional magnetic resonance imaging results from this task showed that typical areas of the ‘reward network’ like the dopaminergic midbrain and the striatum predominantly encode action rather than valence, displaying enhanced activity when preparing for action (go) compared to inaction (no-go). In the current study we used event-related potentials (ERPs) to probe for differences in preparatory state related to cognitive effort in this task, which has similarly been linked to “reward-network” activity. Importantly, the contingent negative variation (CNV), which is linked to effortful cognitive preparation processes during cue-target intervals, was clearly observed in go trials but not in no-go trials. Moreover, target-locked ERP results (N1 and P3) suggested that attention to the target was enhanced when an action had to be performed (go trials), and typical inhibition-related ERP components were not observed in no-go trials, indicating a lack of active response inhibition. Finally, feedback P3 results suggested that correct feedback was valued more in motivated go trials, again implying that more effort was required to correctly perform the task. Together, these results indicate that the anticipation of action compared to inaction simultaneously entails differences in mental effort, highlighting the need for further dissociation of these concepts.

1 Schevernels, H., Bombeke, K., Krebs, R. M., Boehler, C. N. Preparing for (valenced) action – the role of differential effort in the orthogonalized go/no-go task. Manuscript submitted for publication.
INTRODUCTION

Everyday behavior requires flexible behavioral control that is sensitive to changes in the environment. When the environment or context suggests the availability of reward or punishment, people strive for minimization of punishment and the maximization of reward. As such, it has been shown that the prospect of reward enhances performance in a wide range of behavioral tasks (Adcock et al., 2006; Beck et al., 2010; Etzel et al., 2015; Locke & Braver, 2008; Padmala & Pessoa, 2011). However, in these tasks usually a predefined motor response has to be executed in order to receive a reward, thereby coupling reward to action execution (and the respective anticipation thereof). Hence these studies cannot distinguish valence (i.e. reward vs. punishment) and action effects (i.e. action execution vs. inhibition) and their underlying neural substrates. This is of particular importance considering that in Pavlovian control valence and action are inherently linked since stimuli that are appetitive (either in nature or via classical conditioning) automatically invigorate approach behavior or action and aversive stimuli promote withdrawal or inhibition. This relation between reward and the execution of a motor response (go) and between punishment and the inhibition of motor actions (no-go) has also been suggested in previous studies investigating learning and decision making (Chiu et al., 2014; Frank et al., 2004; Freeman et al., 2015; Gray & Mcnaughton, 2000).

One group of studies (Cavanagh et al., 2013; Guitart-Masip et al., 2011, 2012a, 2012b; Richter et al., 2014) that has elegantly investigated the effects of action requirements and reward value and their interaction has crossed both factors in a cue-based paradigm (the so-called ‘orthogonalized
go/no-go task’). This led to four conditions indicated by different cues: go to win, go to avoid losing, no-go to win and no-go to avoid losing, which were used to compare differential anticipatory neural activity related to action and valence (Guitart-Masip et al., 2011, 2012a). The behavioral data favored an inherent association between reward and go indicated by an interaction between action and valence. Nevertheless, functional magnetic resonance imaging (fMRI) results mostly demonstrated a main effect of action, in particular in parts of the typical “reward network” including the substantia nigra/ventral tegmental area (SN/VTA) and striatum that were found to predominantly encode action anticipation irrespective of valence (Guitart-Masip et al., 2011, 2012a).

However, recent evidence shows that the same neural system is also involved in effort-based management of neural resources. For example, Boehler et al. (2011) found that even in the absence of reward or any other type of direct extrinsic motivator the dopaminergic midbrain is more active when subjects prepare for a cognitively demanding task compared to a less demanding task. Moreover, it has been found that the dopaminergic midbrain regions and important dopaminergic target areas like the anterior cingulate cortex (ACC) and striatum are not only activated during the anticipation of reward but also during the anticipation of (cognitive and physical) effort in a perceptual task (Krebs et al., 2012), a cognitive task (Vassena et al., 2014) and a physical instrumental task (Kurniawan et al., 2013). Hence these results suggest that the dopaminergic midbrain is not only involved in the processing of reward but also in the control of cognitive processing resources (see also Nieoullon, 2002; Salamone et al., 2005). As such, it is important to note that the action manipulation as described in the studies of Guitart-Masip and colleagues seems to simultaneously entail
differences in mental effort. More specifically, in go trials mental preparation is likely pronounced since subjects have to attend to the upcoming target in order to perform the task correctly (and quickly), which is not the case for no-go trials. Hence, activity enhancements of the striatum and dopaminergic midbrain during action-related preparation can alternatively or additionally represent changes in preparatory state.

In order to probe whether different levels of task preparation might have contributed to the results by Guitart-Masip’s group (2011, 2012a, 2014) in the current study we recorded electroencephalographic (EEG) activity while participants performed the orthogonalized go/no-go task of Guitart-Masip et al. (2011, 2012a). To further test whether there is any preparatory effort during anticipation of no-go trials, we also included cued catch trials in which participants knew that no target would be presented (see also Grent-’t-Jong & Woldorff, 2007). Moreover, two other baseline conditions were included, i.e. neutral go and neutral no-go, in which trials were never rewarded or punished.

One event-related component that is particularly interesting with regard to the goal of the current study is the contingent negative variation (CNV) since it is supposed to reflect changes in preparatory activity (Walter et al., 1964). The CNV is a fronto-central negative-going component observed between a warning and imperative stimulus that starts to appear around 1 sec preceding target presentation and is supposed to reflect processes related to anticipatory attention, motor preparation and arousal (Birbaumer et al., 1990; Connor & Lang, 1969; Tecce, 1972; van Boxtel & Brunia, 1994). In a number of studies the CNV was investigated using a cued go/no-go paradigm and they found that the CNV is larger when anticipating go trials compared to no-go trials suggesting enhanced
preparatory cortical activity (e.g. Filipović et al., 2001; Funderud et al., 2012; Rosahl & Knight, 1995). Moreover, the CNV has been shown to be sensitive to the anticipation of different levels of task demands or cognitive effort (Ansari & Derakshan, 2011; McEvoy et al., 1998; Schevernels et al., 2014; but see Vuillier et al., 2015), which may again largely reflect differences in preparatory state or the amount of resources allocated to a cognitive process (see also Rösler et al., 1997). Therefore, if different levels of task preparation are involved, we would expect larger CNV amplitudes in anticipated go trials than in no-go trials (as suggested by previous studies). Since the CNV has been shown to be affected by extrinsic motivation (Hughes et al., 2012; Pierson et al., 1987; Schevernels et al., 2014; van den Berg et al., 2014; but see Goldstein et al., 2006; Sobotka et al., 1992), we also expected a larger CNV amplitude in go to win and go to avoid losing trials (which may or may not differ from each other) compared to go neutral trials. We also investigated the cue-evoked parietal P3 (which largely precedes the CNV) since this component has been shown to be affected by reward anticipation, suggesting its role in motivated attention (Goldstein et al., 2006, 2008; Hughes et al., 2012; Kohls et al., 2011; Schevernels et al., 2014).

The level of preparation should also affect processing of the subsequent target and thus we also investigated target-evoked event-related potentials (ERPs) related to early visual processing and attention. Moreover, it is unclear how much active response inhibition precued no-go trials require (since the tendency to initiate a motor response is preempted by the cue) in which case one should not observe typical inhibition-related ERP effects, like modulations of the frontal target-evoked frontal N2 and P3 in no-go trials (Bokura et al., 2001; Bruin et al., 2001; Eimer, 1993; Falkenstein
et al., 1999; Gajewski & Falkenstein, 2013; Pfefferbaum et al., 1985; van Boxtel et al., 2001). Finally, the P3 related to positive feedback has been shown to be larger in high-demand tasks and thus it has been suggested that reward feedback is more valued when subjects had to put in a lot of effort (Ma et al., 2014; Schevernels et al., 2014). Thus, we expected larger P3 amplitudes evoked by correct feedback in go trials than in no-go trials. Together, with this study we sought to use ERPs related to the cue, target and feedback to investigate whether the action-dominated activity as found by Guitart-Masip et al. (2011, 2012a) might also partly arise from differences in preparatory mental effort.

MATERIALS & METHODS

Participants

Twenty-one subjects participated in the experiment (17 women, mean age = 25.2 years, SD = 5.4 years). They were all right-handed, had correct or corrected-to-normal vision and reported no history of psychiatric or neurological disorders. Prior to participation written informed consent was obtained according to the procedure approved by the local ethics committee. After finishing the task, each subject received a financial compensation of 25€ plus an additional bonus depending on their task performance (maximal 10€).

Paradigm

In the present study we used a modified version of the orthogonalized go/no-go task of Guitart-Masip et al. (2011). In this experiment cues indicate whether the upcoming trial will be a go or no-go trial. In go trials subjects
have to respond as quickly as possible according to the location of the target (left or right), while in no-go trials no button has to be pressed when the target appears. Cues also indicate the potential valence of the trial (i.e., the outcome depending on task performance). In addition to the two original valence-related cues (reward and punishment) we included neutral cues in which performance outcome was not related to reward or punishment to be able to further investigate motivational effects by comparing against a neutral baseline. Moreover, we implemented cued catch trials in which participants knew that no target was presented, and which therefore should not trigger any preparatory activity. Except for catch trials, participants received feedback about the outcome at the end of each trial. Stimulus presentation durations and timing differed from the original experiment since they were optimized for an EEG setting (see Figure 1). In contrast to the studies of Guitart-Masip et al. (2011, 2012a), who used 50% cue-only trials in order to disentangle hemodynamic activity related to cue processing from subsequent processes, the high temporal resolution of EEG (combined with the relatively slow succession of events) allows us to distinguish motor-related from preparatory-related activity directly, hence largely abolishing the need for this procedure.

Different fractal images (5°x7°) served as cues indicating the trial type. We kept the four conditions implemented in the study of Guitart-Masip et al. (2011): respond quickly and correctly to obtain a reward (go to win), respond quickly and correctly to avoid punishment (go to avoid losing), do not respond to obtain a reward (no-go to win) and do not respond to avoid punishment (no-go to avoid losing). Furthermore three other trial types were included serving as baseline conditions: respond quickly and correctly although there is no prospect of reward or punishment (go neutral), do not
respond although there is no prospect of reward or punishment (no-go neutral), and attentively wait for the next cue since no target will appear (cued catch). Hence, in total there were seven different fractal images. Each fractal cue was presented for 800 ms and occurred for an equal number of times.

After a variable delay of 1200 to 1500 ms (only showing a fixation cross) the next cue appeared in cued catch trials and a target was presented for 1000 ms in non-catch trials. Targets were circles (radius 3°) that were randomly displayed on the left or right side (5°) of a central fixation cross. In go trials subjects had to press the letter ‘A’ with their left index finger when the circle was displayed on the left side of the screen while they had to press the letter ‘L’ with their right index finger when the circle was shown on the right side of the screen (QWERTY-layout keyboard). Moreover, in go trials responses had to be made quickly since a fixed response time-out was implemented (which was not the case for no-go trials). This time-out varied between subjects since it was based on their performance in the second training run (see below). More specifically, the maximal time to respond in go trials was defined by taking the average of response times on correct go trials in this training run plus 50 ms².

At the end of each non-catch trial feedback was presented for 800 ms following a varying interstimulus interval of 300 to 800 ms. A green upward pointing arrow indicated a gain of 10 eurocents, a red downward pointing arrow signaled a 10 eurocents loss and a yellow horizontal bar was shown.

² We implemented this subject-based time-out instead of a fixed maximum response time of 700 ms (Guitart-Masip et al., 2011), which turned out to be too long during piloting this task, in order to assure that similar accuracy levels would be reached as in the study of Guitart-Masip and colleagues.
when subjects did not lose or win any money. This outcome was dependent on the trial type as well as on the subject’s performance. However, in win and avoid losing conditions the outcome was furthermore probabilistic in the sense that even when subjects performed the task correctly only 70% of correct reactions in win trials were rewarded and only 70% of correct reactions in avoid losing trials were not punished (consistent with the paradigm of Guitart-Masip et al., 2011, 2012a). Hence, in 70% of the trials subjects would gain a reward in win trials and avoid punishment in avoid losing trials when they gave a fast and accurate response in go conditions and withheld their response in no-go conditions. In neutral task conditions a horizontal bar was always presented indicating that no money had been won or lost.

Before starting the experiment, task requirements were explained and subjects were instructed to minimize eye movements and blinking. Subjects were explicitly told that they could win extra money contingent on their task performance and they were informed about the probabilistic feedback. Furthermore subjects had to memorize the meaning of all seven cues, which was also repeated at the beginning of every experimental run. To ensure that subjects had learned the cue meanings, we implemented a first practice session including 10 trials per condition (70 trials in total), in which neither a response time-out nor a probabilistic outcome was applied, and the Dutch words ‘goed’ (correct) or ‘fout’ (incorrect) were presented to provide additional feedback. In case accuracy was worse than 75% in one of the conditions we restarted this practice block. Subsequently, subjects performed a second practice run in which trials were presented in the same way as in the experimental task (with probabilistic outcome). In the experimental session seven runs of 70 trials were performed with 10 trials per condition
presented equally often in a randomized order. This resulted in a total of 490 trials with 70 trials per condition. In each run a self-paced break was implemented after 35 trials. Moreover, after every run subjects were informed about the amount of money they had already won. Two versions of the experiment were created to counterbalance the meaning of the fractal cues across participants.

Figure 1. Task procedure. At the start of each trial a cue signaled the possible value of the trial (win, avoid losing or neutral) and indicated whether the subject would have to respond (go trials) or not (no-go trials) to the upcoming target. In go trials subjects had to press a button according to the location of the target. In cued catch trials subjects knew that no target would be presented after the cue. At the end of each non-catch trial feedback was presented dependent on the trial type and performance. A green arrow pointing upwards meant that subjects won 10 eurocents, while a red arrow pointing downwards indicated a 10 eurocents loss. A yellow horizontal bar signaled that no money was won or lost. The feedback was probabilistic so that only 70% of correct and fast responses in go trials and 70% of correct withholding responses in no-go trials were rewarded (win trials) or not punished (avoid losing trials).

**EEG acquisition and preprocessing**

EEG signals were recorded using a Biosemi ActiveTwo system (CLS-DRL reference) and sampled at 256 Hz. Data were recorded from 64 Ag-
AgCl scalp electrodes positioned according to the international 10-20 location configuration. External electrodes were attached to the left and right mastoid for offline re-referencing. Horizontal and vertical eye movements were measured using electrodes placed at the external canthus of the left and right eye and directly above and below the left eye, respectively. Subjects were tested in a dimly-lit electrically-shielded room.

A combination of EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) was used to analyze the collected EEG data. As a first step, we re-referenced the data to the average of the left and right mastoid. Subsequently, data was low-passed filtered (30 Hz) and eye blinks were removed using independent component analysis. Channels that were very noisy were interpolated (only 6 channels in total across all datasets). Baseline-corrected epochs were created time-locked to the onset of the cue, target and feedback with a time window of -200 ms to 2300 ms, -200 ms to 1000 ms and -200 ms to 800 ms, respectively. Epochs containing eye movements (step function with threshold 60 μV and window size 400 ms in the bipolar HEOG channel) and extreme values in scalp electrodes (> +150 μV) were automatically removed and afterwards all epochs were visually inspected for possible additional missed artifacts. This resulted on average in 4.4% rejected cue-locked epochs, 2.4% rejected target-locked epochs and 1.9 % rejected feedback-locked epochs.

**Data analysis**

**Behavior**

Accuracy, i.e. a correct button press within the response time-out window in go trials and not responding in no-go trials, was investigated using a repeated-measures ANOVA (rANOVA) with within-subject factors
action (go/no-go) and valence (win/avoid losing/neutral). In case Mauchly’s test indicated that the assumption of sphericity did not hold, degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity. The number of reactions that exceeded the response time-out and reaction times in correct go trials (i.e. only including reaction times within the response window) were analyzed using paired-sample t-tests. If tests were significant we also report effect sizes (Cohen’s d and partial eta squared, $\eta^2_p$).

**ERPs**

For both cue-locked and target-locked ERPs mean amplitude measurements were derived within a specific time range and region of interest. ERPs related to cues and targets only included trials in which subjects responded accurately (i.e. within time-out window for go trials). Feedback-related analyses included trials in which responses and feedback were correct (no incorrect feedback). All analyses were performed on 30 Hz low-passed filtered data, but for illustration purposes a 15 Hz low-pass filter was applied in the figures. Amplitudes were analyzed using rANOVAs with the factors action (go/no-go) and valence (win/avoid losing/neutral) and applying the Greenhouse-Geisser degrees of freedom correction whenever necessary. Hence, in case Mauchly’s test of sphericity was significant we report uncorrected F-values, Greenhouse-Geisser corrected p-values and Epsilon ($\varepsilon$). Post-hoc tests were performed to further investigate significant effects. Effect sizes (Cohen’s d and partial eta squared) are reported when statistical results were significant. ERPs related to cued catch trials were not included in the statistical analyses but they are displayed in the figures as a reference.
The parietal cue-evoked P3 was maximal at electrode sites Pz, P1 and P2 between 400 and 600 ms after cue onset (mainly for go trials). Subsequently a large negative component, i.e. the CNV, was detected between 1000 and 2000 ms (earliest onset of the target) mainly in go conditions at frontocentral locations (FCz, FC1, FC2, Cz, C1 and C2). Consistent with earlier studies (Broyd et al., 2012; Goldstein et al., 2006; Jonkman et al., 2003; Schevernels et al., 2014) this prolonged negativity was separated in an early and late CNV from 1000 to 1500 ms and 1500 to 2000 ms, respectively.

Since we were also interested in early effects of different kinds of cues on visual processing of the target circle we also analyzed different target-related components. Early positive (P1) and negative waves (N1) were maximal in posterior regions on the contralateral side of target presentation. Hence P1 and N1 components were observed in PO7 when the circle was presented on the right and in PO8 when the circle was presented on the left side of the screen, within a time-window of 80 to 120 ms for P1 and 140 to 180 ms for N1. Also a clear broad centroparietal P3 was quantified between 250 and 450 ms on electrode sites Pz, P1 and P2. The processing of correct feedback gave rise to a prominent P3 that was maximal between 300 and 450 ms at parietal electrode sites (Pz, P1, P2, POz, PO3, PO4).

**RESULTS**

**Behavior**

Analyses related to behavioral accuracy revealed a significant main effect of action (F(1,20)=42.48, p<0.001, \( \eta^2_p = 0.68 \)) showing higher
accuracy for no-go trials compared to go trials. However, although reaching similar overall accuracy rates, we failed to replicate an important feature of the behavioral results of (Guitart-Masip et al., 2011) in that we neither found a significant main effect of valence nor a significant interaction (both p’s>0.15). This pattern also didn’t change when including responses that exceeded the response-time out window seeing that the number of go trials that exceeded the maximal response time was similar for different types of valence conditions (p’s>0.2; average: 7.4 ±0.6). In contrast, in correct go trials subjects did respond slower in the neutral condition compared to the avoid losing (t(20)=2.95, p=0.008, d=0.64) and win condition (t(20)=4.63, p<0.001, d=1.01), but reaction times in the latter two conditions did not differ (p>0.4). These behavioral results are summarized in table 1.

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<th>Table 1. Behavioral performance.</th>
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<td>Mean values and standard errors of the mean (SEM) are shown for all conditions.</td>
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**ERPs**

**Cue-locked ERPs**

The cue-locked P3 amplitude was considerably larger for cues signaling go trials (F(1,20)=57.36, p<0.001, $\eta_p^2=0.74$; see Figure 2). Also, a
main effect of valence was observed (F(2,40)=4.26, p=0.021, $\eta^2_p=0.18$), but valence also significantly interacted with action (F(2,40)=3.67, p=0.048, $\epsilon=0.77$, $\eta^2_p=0.16$) due to a larger P3 amplitude in go to win trials compared to go to avoid losing trials (t(20)=4.07, p=0.001, d=0.89) and go neutral trials (t(20)=3.31, p=0.004, d=0.72) but a similar P3 amplitude in the different no-go conditions (see Figure 2B). Both early and late CNV amplitude showed a clear main effect of action (F(1,20)=11.8, p=0.003, $\eta^2_p=0.37$ and F(1,20)=20.07, p<0.001, $\eta^2_p=0.52$) with larger negative-going waves for cues signaling go trials (see Figure 2), whereas neither the main effect of valence nor the interaction between the factors was significant (all p’s>0.1).
Figure 2. Cue-locked ERP results. (A) Topographical maps reflecting the P3, early CNV and late CNV in go and no-go trials and the corresponding differences indicating the main effect of action. Note that the topographical maps of the (early and late) CNV in go and no-go trials reflect the difference between go or no-go trials on one hand and cued catch trials (which should not induce any preparatory activity) on the other hand. Go trials elicited larger positivities than no-go trials between 400 and 600 ms (P3). Moreover, in go trials a clear (early and late) CNV is observed, which is not the case for no-go trials. (B) Grand-average ERP waves locked to the cue over electrode sites Pz, P1 and P2 show larger P3 amplitudes in go trials and especially in go to win trials compared to go to avoid losing and neutral trials. Moreover, grand-average waveforms over fronto-central sites (FCz, FC1, FC2, Cz, Z).
C1 and C2) are depicted for each condition, reflecting the early and late CNV component in go trials. Frames indicate the time range of the different components (as included in the analyses).

**Target-locked ERPs**

The posterior target-locked P1 did not show any significant differences (p-values>0.2), but the visual N1 was larger in go trials compared to no-go trials (F(1,20)=11.48, p=0.003, $\eta^2_p=0.37$; see Figure 3A). We did not find a significant main effect of valence (p>0.4) nor a significant interaction (p>0.1) related to the N1 component. The target-locked parietal P3 amplitude showed a large main effect of action (F(1,20)=161.03, p<0.001, $\eta^2_p=0.89$) and an interaction between action and valence (F(2,40)=3.88, p=0.029, $\eta^2_p=0.16$). Figure 3A illustrates that these effects reflect significantly larger P3 amplitudes in go trials and especially in go to win and go to avoid losing trials, while there was no difference between the no-go conditions.

**Feedback-locked ERPs**

The feedback-evoked P3 showed a significant main effect of the factors action (F(1,20)=9.55, p=0.006, $\eta^2_p=0.32$) and valence (F(2,40)=39.19, p<0.001, $\eta^2_p=0.67$), but also a significant interaction (F(2,40)=3.92, p=0.028, $\eta^2_p=0.16$). As can be observed in Figure 3B, win feedback (arrow pointing upwards) elicited the largest P3s when subjects had to perform an action (go trials). Moreover, the P3 amplitude related to
positive feedback was significantly larger in go compared to no-go trials not only in the win condition (arrow pointing upwards) but also in the avoid losing condition (horizontal bar) (both tests: $t(20)=2.93, p=0.008$, $d=0.64$). On the other hand, the P3 was smallest for correct feedback in neutral trials and it did not significantly differ between neutral go and no-go trials ($p>0.1$).

Figure 3. (A) Target-locked ERPs. Waveforms averaged over PO7 for targets presented on the right side of the screen and PO8 for targets presented on the left side of the screen, showing enhanced target-locked N1 in go trials (left panel). Grand-average target-locked ERPs over parietal regions (Pz, P1 and P2) reflecting the target P3 between 250 and 450 ms, illustrating enhanced P3 amplitudes in go trials and especially in go to win and go to avoid losing trials (right panel). (B) Correct feedback-locked ERPs. Over parietal regions (Pz, P1, P2, POz, PO3 and PO4) grand-average ERPs show more positive P3 components evoked by correct feedback in go trials compared to no-go trials only in the go to win and avoid losing conditions. Frames indicate the time range of the different components (as included in the analyses).
DISCUSSION

The goal of the current study was to investigate differential involvement of (preparatory) mental effort in the orthogonalized go/no-go task of Guitart-Masip et al. (2011, 2012a) using ERPs. In line with the idea that preparing for a go trial is more demanding than preparing for a no-go trial, we found diminished cue-evoked P3 amplitudes and an absence of the preparation-related CNV component for the expectation of no-go targets. Moreover, visual attention to the target was decreased in no-go trials as indicated by smaller N1 and P3 amplitudes. Finally, the P3 amplitude related to correct feedback was significantly larger in go trials, which might suggest more positive subjective appraisal of correct feedback for a more effortful task. All these results together point in the direction of differential cognitive resource engagement during preparation, task performance and feedback evaluation in anticipated go trials compared to anticipated no-go trials.

Main effects of action and effort anticipation

The key focus of our experiment lies in the manipulation of action and in line with the effect found by Guitart-Masip et al. (2011, 2012a) we observed higher accuracy in no-go trials (nearly 100% correct) suggesting that these trials were less difficult than go trials. Importantly, the cue-locked P3 as well as the CNV component showed highly significant effects of action with larger amplitudes for the anticipation of go trials compared to no-go trials. The P3 has been suggested to reflect activity in the locus coeruleus-norepinephrine (LC-NE) system that is involved in stimulus
evaluation and decision making thereby guiding attention allocation in favor of goal-relevant stimuli (Nieuwenhuis et al., 2005). Hence, the large difference in P3 amplitude between go and no-go trials might suggest that go trials are identified as being more task-relevant promoting more attention to the go stimuli.

More importantly, we did find a substantially larger early and late CNV in go trials than in no-go trials. For the latter we in fact found that the CNV was practically absent (compared to catch trials), in line with previous findings showing a significant cue-related action effect (Filipović et al., 2001; Funderud et al., 2012; Randall & Smith, 2011; Rosahl & Knight, 1995). This difference probably entails more motoric preparation but also more cognitive preparation in go trials considering that it has been shown that the CNV also or mainly reflects effortful cognitive preparation processes, and that participants in the current task cannot prepare for a specific response yet (Ansari & Derakshan, 2011; Cui et al., 2000; Falkenstein et al., 2003; Gómez et al., 2007; Lorist et al., 2000; Rösler et al., 1997; Wild-Wall et al., 2007). Hence, these results are in favor of our hypothesis that no-go cues differ from go cues in mental preparatory activation going beyond merely motor preparation. Importantly, this effect could very well link back to the action-dominated activity in the dopaminergic source and target regions found by Guitart-Masip et al. (2011, 2012a) given evidence for a link between the CNV and central dopaminergic activity\(^3\) (Amabile et al., 1986; Fan et al., 2007; Gerschlager et al., 1999; Linssen et al., 2011; Oishi et al., 1995), and the fact that these areas have

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\(^3\) Of course, the CNV does not directly signal subcortical dopamine release (Cohen et al., 2011) but it could rather reflect its effects on cortical brain areas via dopaminergic pathways.
been found to be sensitive to differences in preparatory effort (e.g., Boehler et al., 2011; see also below).

The target-related ERPs provided further evidence for differences in effort-related processes. Specifically, we found a diminished contralateral posterior N1 component in no-go trials, implying decreased early visual attention to the circle target when subjects did not have to perform an action (and thus did not need to discriminate the target’s location; see e.g., Vogel & Luck, 2000). In addition, the subsequent parietal P3 amplitude was enhanced in go trials compared to no-go trials consistent with ERP results found in studies using the go/no-go task showing a more parietal scalp distribution for go trials (Bokura et al., 2001; Bruin & Wijers, 2002; Liu et al., 2011; Tekok-Kilic et al., 2001). The parietal go P3 component has been distinguished from the frontal no-go P3 (Bokura et al., 2001; Pfefferbaum & Ford, 1988; Tekok-Kilic et al., 2001) with the first being more similar to the classical P300, likely reflecting target detection and evaluation, response production, and executive control processes (Eimer, 1993; Liu et al., 2011; Pfefferbaum et al., 1985; Tekok-Kilic et al., 2001). Remarkably, in no-go trials we did not observe any typical inhibition-related components like the no-go related frontal N2 or frontocentral P3 (Bokura et al., 2001; Bruin et al., 2001; Eimer, 1993; Falkenstein et al., 1999; Gajewski & Falkenstein, 2013; Kok, 1986; Pfefferbaum et al., 1985; Randall & Smith, 2011; Smith et al., 2008), suggesting that there is little active inhibition involved in cued no-go trials. Moreover, correct feedback4 elicited a parietal P3 which was more positive in go trials than in no-go trials in both win and avoid losing conditions but not in neutral conditions, which implies an effect of action when motivation

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4 Error feedback was not analyzed due to very low error rates, especially in no-go trials.
is high. Considering that the feedback P3 is involved in high-level affective evaluation of the outcome (Nieuwenhuis et al., 2005; Wu & Zhou, 2009; Zhou et al., 2010), studies that found enhanced correct-feedback P3 amplitudes in more difficult tasks have explained this in terms of more positive evaluation of the feedback stimulus after one had to put in more effort to correctly perform the task (Ma et al., 2014; Schevernels et al., 2014), which is again consistent with the notion that effort differed between cued go and no-go trials in the present experiment.

Thus, the enhanced activity in the SN/VTA and the striatum in expected go trials compared to no-go trials that was found by Guitart-Masip et al. (2011, 2012a) might not only represent anticipated action effects but also differences in anticipated mental effort or resource allocations. This is in line with previous findings demonstrating dopaminergic and striatal involvement in the (preparatory) control of cognitive resources in order to achieve goals and optimize behavioral outcomes (Boehler et al., 2011; Krebs et al., 2012; Nieoullon, 2002; Plichta et al., 2013; Vassena et al., 2014). Related to this idea, Kurniawan et al. (2013) implemented a very similar paradigm but they orthogonalized physical effort and valence in a pure go-trial context by showing fractal cues that indicated the required force with

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5 The feedback-related P3 amplitude has also been shown to be enhanced when events are unlikely or unexpected (Bellebaum & Daum, 2008; Hajcak et al., 2005, 2007; Wu & Zhou, 2009). In the current task accuracy was lower in go trials compared to no-go trials and thus correct feedback could be experienced as more unexpected. However, the correct-feedback P3 did not significantly differ between go trials and no-go trials in neutral conditions for which the frequency proportion is similar as in win and avoid losing conditions. Furthermore, the subjective frequency difference might have been reduced given that 30% of correct responses were not rewarded or punished in both go and no-go trials (probabilistic feedback). Hence, we favor the stimulus-evaluation over the expectancy account to explain the action-related differences in correct feedback-P3 amplitudes in the current task.
which subjects had to squeeze a handgrip (high effort or low effort) and the probability to win or lose money. They found increased BOLD signals when anticipating higher effort in the ACC and the dorsal striatum, two typical reward-related brain areas. Although in the current study we investigate mental effort and not physical effort (as in the study of Kurniawan et al., 2013), it has been shown that they partly rely on similar underlying mechanisms and brain structures (like the ventral striatum) that motivationally drive both task-specific systems (Schmidt et al., 2012). Also, in many studies it has been advocated that dopaminergic activity is involved in motivated behavior and specifically in the exertion of effort to overcome work-related requirements or costs (Kurniawan et al., 2011; Salamone & Correa, 2012; Salamone et al., 2005, 2007). However, whether this link between dopamine and effort can only be established when an action is required or whether it also plays a role in action inhibition or withdrawal is not clear. Hence, it would be interesting to manipulate (preparatory) task demands. Yet, in the current basic task design there seems to be no feasible way to create more difficult anticipated no-go trials without lowering stopping probability below 100%.

The contribution of effort-related processes aside, a direct coupling between action and valence could of course still exist (in which dopamine might be involved, see also Frank et al., 2004, 2007). This has also been suggested by other previous studies investigating instrumental learning, where it was shown that subjects were more successful in learning to withhold a response (no-go) when anticipating punishment and to actively respond (go) when anticipating reward (Cavanagh et al., 2013; Chowdhury et al., 2013; Guitart-Masip et al., 2012b, 2014; Richter et al., 2014). Nevertheless, in the current study action and effort are clearly intertwined
and anticipation of no-go does not necessarily induce (preparation for) active inhibition or withdrawal, but rather altogether diminished (preparatory) cognitive resources devoted to the task.

**Effects of valence and interaction effects**

Behaviorally, we did not replicate the asymmetrical valence effect in that there was no significant difference in accuracy levels or reaction times between go to win and go to avoid losing conditions (although numerically going in the expected direction). This might be due to an overall difference in reaction time, since in the current experiment subjects responded on average approximately 200 ms faster compared to the studies of Guitart-Masip et al. (2011, 2012a). The generally slower response speed in the previous studies might be explained by the fMRI versus EEG scanning environment, differences in task instructions, task design or training levels of subjects. Moreover, differences in response time-out might be relevant. In particular, our time-out procedure might have been too strict and could have pushed subjects to respond very fast and therefore leaves a smaller margin for improvements over conditions. Moreover the implementation of a neutral condition might have increased the motivational value of the avoid losing condition to a similar level as the win condition which is suggested by smaller reaction times on both go to win and go to avoid losing trials compared to go neutral trials. Of note, similar behavioral results for potential monetary gain and potential monetary loss have been found previously (Carter et al., 2009; Engelmann et al., 2009; but see Ivanov et al., 2012; Paschke et al., 2015; Potts, 2011). Given these differences, our failure to replicate the asymmetrical valence effect on go accuracy might very well not translate into a challenge of its validity (also note that on the neural level we did observe some interactions between action and valence, see below).
The cue-locked P3 amplitude in go trials was increased for win trials compared to avoid losing and neutral trials, thereby confirming the sensitivity of this component to reward (Goldstein et al., 2006, 2008; Hughes et al., 2012; Pfabigan et al., 2014; Schevernels et al., 2014), particularly in cues signaling go trials (Kohls et al., 2011). However, although we expected to find a motivational effect on the preparatory CNV component (mainly in go trials), we did not find a significant amplitude difference between anticipated gain, loss and neutral trials. However, results of previous studies investigating the role of reward and/or punishment during target preparation are also inconsistent, with some studies reporting a lack of motivational influences on the CNV amplitude (Broyd et al., 2012; Goldstein et al., 2006; Sobotka et al., 1992) but others finding larger CNV amplitudes for cues indicating reward and/or punishment availability (Hughes et al., 2012; Pfabigan et al., 2014; Schevernels et al., 2014; Vuillier et al., 2015). In contrast to the current paradigm, these previous studies however usually investigated reward effects on the CNV amplitude in classic monetary incentive delay tasks that always involve the execution of an action.

Regarding target processing, the current study shows that the target-evoked go P3 is also affected by motivation, with larger amplitudes in both punishment and reward conditions compared to neutral conditions. The target P3 has been previously shown to be sensitive to reward likely reflecting increased attention to the target when it is highly significant or motivationally relevant (Baines et al., 2011; Hughes et al., 2012; Krebs et al., 2013; Schevernels et al., 2014). Turning to feedback processing, the parietal P3 evoked by correct feedback showed a main effect of valence with a decrease in P3 amplitudes from win trials to avoid losing trials to neutral trials. This is consistent with previous studies that have observed larger P3
amplitudes for reward compared to no-reward feedback (Bellebaum et al., 2010; Hajcak et al., 2007; Sato et al., 2005; Schevernels et al., 2014) illustrating this component’s sensitivity to the magnitude of the reward outcome and thus suggesting its involvement in motivated significance (for an overview see San Martín, 2012).

CONCLUSIONS

Together, the present behavioral and ERP results pattern points in the direction of effort-related differences between go and no-go trials in the orthogonalized go/no-go paradigm of Guitart-Masip (2011, 2012a). Most importantly, the absence of a CNV in no-go trials suggests a lack of involvement of preparatory cognitive processes. In turn, early and late visual attention during target processing was decreased and no typical inhibition-related components were detected after no-go cues. Finally, even the feedback-related ERP results implied a role of effort in that correct feedback seemed to be valued more positively in go trials. Therefore we conclude that the established dominance of anticipated action (over valence) in typical reward-related brain networks simultaneously entails differences in mental effort engagement. From a more general perspective, our results suggest that action- and effort-related factors are difficult to disentangle and raise the question whether action effects would still hold when the amount of (anticipated) effort is held constant.


of mental versus physical effort. PLoS Biology, 10(2), e1001266. doi:10.1371/journal.pbio.1001266


sensori-motor association and expectancy in the human brain. 

on cognitive task preparation as reflected by event-related potentials. 
Clinical Neurophysiology, 118(3), 558–569. 

Wu, Y., & Zhou, X. (2009). The P300 and reward valence, magnitude, and 
doi:10.1016/j.brainres.2009.06.032

FRN and P300 effects in outcome evaluation. Neuropsychologia, 
48(12), 3606–3613. doi:10.1016/j.neuropsychologia.2010.08.010
CHAPTER 4
ELECTROPHYSIOLOGICAL EVIDENCE FOR THE INVOLVEMENT OF PROACTIVE AND REACTIVE CONTROL IN A REWARDED STOP-SIGNAL TASK

Reward availability is known to facilitate various cognitive operations, which is usually studied in cue-based paradigms that allow for enhanced preparation in reward-related trials. However, recent research using tasks that signal reward availability via task-relevant stimuli suggests that reward can also rapidly promote performance independent of global strategic preparation. Notably, this effect was also observed in a reward-related stop-signal task, in which behavioral measures of inhibition speed were found to be shorter in trials signaling reward. Corresponding fMRI results implied that this effect relies on boosted reactive control as indicated by increased activity in the ‘inhibition-related network’ in the reward-related condition. Here, we used EEG to better characterize transient modulations of attentional processes likely preceding this ultimate implementation of response inhibition. Importantly, such modulations would probably reflect enhanced proactive control in the form of more top-down attention to reward-related features. Counter to the notion that behavioral benefits would rely purely on reactive control, we found increased stop-evoked attentional processing (larger N1 component) on reward-related trials. This effect was accompanied by enhanced frontal P3 amplitudes reflecting successful stopping, and earlier and larger ERP differences between successful and failed stop trials in the reward-related condition. Finally, more global proactive control processes in the form of a reward context modulation of reward-unrelated trials did not have an effect on stopping performance but did influence attentional processing of go stimuli. Together, these results suggest that proactive and reactive processes can interact to bring about stimulus-specific reward benefits when the task precludes differential global preparation.

INTRODUCTION

In everyday life it is important to adapt behavior to changing situational demands, a function that has been broadly labeled cognitive control. A central component thereof is the ability to rapidly withhold an already-initiated motor action when needed. This inhibition process has been investigated frequently using the stop-signal task, in which responses to a go stimulus occasionally have to be cancelled upon the rapidly following presentation of a stop signal (Logan, 1994; Logan & Cowan, 1984). The processes underlying this task are usually explained by the well-validated horse-race model which assumes that the behavioral outcome (successful or unsuccessful stopping) is determined by a race between a go and a stop process, that are largely independent (Logan & Cowan, 1984, see also Boucher et al., 2007). Based on this model a measure for the duration of the implementation of response inhibition can be derived, the so-called stop-signal response time (SSRT), which has been shown to be prolonged in several neuropsychiatric disorders such as attention-deficit hyperactivity disorder, obsessive-compulsivity disorder and schizophrenia (Bekker et al., 2005b; Chamberlain et al., 2006a; Lijffijt et al., 2005; Lipszyc & Schachar, 2010).

While different cognitive functions, including cognitive control, are usually studied in settings devoid of explicit extrinsic motivation, it has been shown that reward prospect can have beneficial effects on a range of cognitive functions like working memory (Beck et al., 2010; Gilbert & Fiez, 2004), memory formation (Adecock et al., 2006), and attention (Krebs et al., 2009; Padmala & Pessoa, 2011; Schevernels et al., 2014; Stoppel et al.,
In these studies, motivation is usually implemented using a cue indicating that a reward can be obtained if the upcoming task is performed correctly (monetary incentive delay task; Knutson, Westdorp, Kaiser & Hommer, 2000). Hence, reward effects have usually been investigated with respect to preparatory proactive processes showing that reward prospect improves behavioral performance largely via enhanced top-down preparatory control (Chelazzi et al., 2013; Pessoa & Engelmann, 2010). The few studies that have looked at reward effects on response inhibition thus far have used such task contexts that allow for differential preparation by implementing cues indicating reward availability (e.g., Greenhouse & Wessel, 2013; Rosell-Negre et al., 2014; Scheres et al., 2001). Breaking with this traditional setup, we have recently shown that reward can also influence response inhibition without the involvement of global preparatory functions (Boehler et al., 2012b, 2014, but see also Wilbertz et al., 2014). Instead of pre-cueing reward prospect, the color of the stop signal itself indicated whether successful stopping would be rewarded. Despite the fact that participants could not globally prepare for rewarded trials in advance, response inhibition was facilitated (shorter SSRTs) for reward-related trials. Moreover, functional magnetic resonance imaging (fMRI) results suggested that this behavioral benefit was due to enhanced reactive control mechanisms as indicated by reward-related enhancements in right-lateralized medial and lateral prefrontal brain regions that are considered to be central to response inhibition in general (Boehler et al., 2014).

Yet, it is possible that this enhanced control was not completely independent of additional proactive processes. Specifically, although global proactive control enhancements were precluded because reward-related trials were unpredictable, stimulus-specific proactive control could still have been
involved if observers strategically screened for the reward-related color. This may have increased the sensory response to the reward-related stop signal. Given the tight timing of different processing stages in this task, it is quite possible that fMRI would not be sensitive to transient changes in attentional processes. Here, methods with higher temporal resolution like electroencephalography (EEG) or magnetoencephalography (MEG) might be more suitable, and have in fact already been used to establish a general role of attentional processes in the dynamics of the processes underlying the stop-signal task. Specifically, it has been demonstrated that the size of the sensory stop signal-locked N1 component is related to ultimate stopping success, with larger N1 amplitude being found for successful stop trials (Bekker et al., 2005a; Boehler et al., 2009). This effect likely indicates that more attention was devoted to the stop-stimulus, possibly at the cost of paying less attention to the preceding go-stimulus, and that the distribution of attentional resources is likely under active top-down control (Boehler et al., 2009). In line with this notion, in a recent study of Greenhouse and Wessel (2013) that implemented a paradigm in which cues indicated the relative value of stopping and going, it was observed that the N1 component was enhanced when cues emphasized stopping over going. In this case N1 amplitudes were enhanced for successful and unsuccessful stop trials implying a generally enhanced deployment of top-down visual attention to the stop signal in this condition. Hence, in the current study we implemented our previous rewarded stop-signal paradigm (Boehler et al., 2012b, 2014) in an EEG setting to be able to identify transient modulations of attention that might precede the implementation of response inhibition. More specifically, we expected an enhanced stop-locked N1 component in successful stop trials in line with previous studies (Bekker et al., 2005a; Boehler et al., 2009). Furthermore, if the current event-related reward manipulation
induced changes in proactive attentional control (in the form of enhanced
top-down attention) we expected larger stop-evoked N1 amplitudes in stop
trials that signal reward availability.

Besides the possible role of stimulus-specific attentional control,
global preparatory control processes could still generally occur in our task.
Specifically, even though our task equates such processes between reward-
related and reward-unrelated trials, global preparation can play a role in the
form of a general context effect in the current task. For example, Jimura and
colleagues (2010) showed that when reward-unrelated trials were intermixed
with reward-related trials (which triggered a proactive control mode),
working memory improved also for reward-unrelated trials. Moreover, other
studies have shown that behavioral measures for cognitive functions, like
conflict adaptation (Braem et al., 2012) and action-effect binding (Muhle-
Karbe & Krebs, 2012), can be altered for reward-unrelated trials in a
rewarded context. These results suggest that a reward context can create a
global state of sustained strategic proactive control (see also Locke &
Braver, 2008). In order to investigate whether such global processes also
occur in our task and whether they influence response inhibition, in the
present study we added a control block in which none of the trials were
associated with reward. Behaviorally this context effect should show up
when comparing inhibition-related parameters, in particular the SSRT, in no-
reward trials from the no-reward block with no-reward trials from the reward
block. Specifically, if the reward-unrelated trials in the reward block would
benefit from being in a rewarded task context, we should also find improved
behavioral performance in these trials (compared to trials in the no-reward
block). Given that the introduction of different contexts or blocks can create
changes in the sustained attentional state that might affect the processing of
all stimuli including go signals, we also explored the early attention-related go-locked N1, which has been related to strategic deployment of visual attention to the go stimulus (Boehler et al., 2009).

In addition to the specific interest in attentional components possibly reflecting proactive control, EEG offers a rich view on the process dynamics in the stop-signal task, allowing us to also study possible modulations of later, presumably control-related, components in relation to the reward availability and context manipulation. Most studies using event-related potentials (ERPs) in the stop-signal and go/no-go task, have focused on the frontal N2 and P3, labeled the N2/P3 complex (e.g. Bekker et al., 2005a; Bokura et al., 2001; Eimer, 1993; Huster et al., 2010, 2011; Kok et al., 2004; Ramautar et al., 2006a; Schmajuk et al., 2006; van Boxtel et al., 2001; van Gaal et al., 2011). Recent studies have found that the N2 is usually larger in unsuccessful than in successful stop trials suggesting a general role in response control, conflict monitoring and error processing (Dimoska et al., 2006; Enriquez-Geppert et al., 2010; Greenhouse & Wessel, 2013; Huster et al., 2013). In contrast, particularly the frontal P3 has been argued to reflect actual reactive inhibition in the stop-signal task (e.g. Bekker et al., 2005a; Dimoska et al., 2006; Enriquez-Geppert et al., 2010; Lansbergen et al., 2007). Thus, in line with these previous studies, we expected larger N2 amplitudes in unsuccessful stop trials and larger P3 amplitudes in successful stop trials (e.g. Dimoska et al., 2006; Greenhouse et al., 2013; Senderecka et al., 2012). Moreover, concerning reward modulations, the aforementioned study by Greenhouse and Wessel (2013) showed that the frontal stop-evoked P3 was larger when stopping was successful compared to unsuccessful, and that this difference was larger when stopping was rewarded over going. Hence, boosted reactive control in reward-related stop trials, as indicated by
our previous fMRI study (Boehler et al., 2014), might be mainly reflected by modulations of the stop P3 component. Also previous studies have observed earlier peak latencies for the N2 and P3 components (Kok et al., 2004) and earlier onsets of the P3 (Wessel & Aron, 2014) in successful compared to failed stop trials, suggesting that an earlier implementation of the internal response to the stop signal increases the likelihood of successful stopping. Therefore, reward-related differences in reactive response inhibition could also entail latency differences of the successful and unsuccessful stop-related N2 and P3. Hence, the overall aim of the current study was to investigate reactive control processes that have been shown to be susceptible to reward manipulations in a broader mechanistic context which includes a possible role of transient and sustained attentional processes.

**MATERIALS & METHODS**

**Participants**

Twenty healthy right-handed students were recruited for the experiment (6 males, mean age = 22 years, range = 18-26 years). Subjects had normal or corrected-to-normal vision and no history of psychiatric or neurological disorders. Prior to participation they all gave written informed consent. After finishing the experimental task of approximately one hour, participants received a compensation of 20€ and an additional performance-dependent bonus between 2.5 and 4€.

**Stimuli and procedure**

For the present study we used a modified version of the rewarded stop-signal paradigm previously used in Boehler et al. (2012, 2014). In
contrast to that earlier work, we optimized the experiment for an EEG setting, and added a no-reward block to be able to investigate reward context effects (see figure 1). Throughout the experiment a black rectangular box and a white fixation dot were presented centrally on a gray background. As in a typical stop-signal task (Logan, 1994; Logan & Cowan, 1984), subjects had to perform a simple discrimination task on most trials (go trials), but were asked to inhibit their response to the go stimulus whenever an infrequent stop signal was presented shortly thereafter (stop trials). Go stimuli were green traffic light symbols pointing to the left or the right. The target go stimulus was presented centrally above the fixation dot and surrounded by 2 additional green traffic symbols on both sides that were to be ignored. Participants were asked to respond rapidly with the index finger (left mouse button) or middle finger (right mouse button) of their right hand according to the orientation of the central go traffic sign. A typical ‘don’t-walk’ traffic sign was used as a stop stimulus, and importantly the color of this signal could either be blue or pink with a matching number of occurrences. In both go and stop trials the total stimulus presentation duration was 600 ms, followed by a variable inter-stimulus interval of 1000 to 1400 ms (randomly distributed). Participants had to complete two blocks, a reward block and a no-reward block. Only in the reward block the color of the stop signal was relevant, since it indicated whether a correct stop would be rewarded or not.

Participants started with a short practice run to get acquainted with the task. This session included 34 go trials and 20 stop trials with 10 blue stop signals and 10 pink stop signals. In stop trials the interval between a go and stop stimulus (go-stop delay) was constantly adapted to create a 50% proportion of correct stopping. To this end, a staircase procedure was
implemented in which the go-stop delay was increased by 34 ms after a successful stop trial (SST) and decreased by 34 ms after an unsuccessful stop trial (UST), with a minimum of 34 ms and a maximum of 567 ms delay (initial value: 200 ms). Pink and blue stop trials shared the same staircase, thereby controlling the stopping-success rate over all stop trials within a block. Reward was only assigned to one of the two colors of the stop signal at the start of the reward block. The order of the reward and no-reward blocks (reward block first or no-reward block first) and the color of reward-predictive stop signals (pink or blue) were counterbalanced across subjects, and only two long blocks were used to minimize carry-over effects related to reward-related colors. Both the experimental reward and no-reward block consisted of 5 runs of 100 trials, yielding a total of 320 go trials and 180 stop trials (90 trials for each color) for each block. In the reward block participants could win points if inhibition was successful in reward-related stop trials, but not in reward-unrelated stop trials. At the end of every run the amount of points gathered in that run was shown. Participants were also explicitly told that these points would be added up at the end of the block resulting in an extra bonus of between 0€ and 6€ depending on their performance in reward-related stop trials, and they were informed about the exact transformation from points to money. Subjects were also asked to respond as fast as possible and not to slow down their responses during the experiment. Additionally, to further prevent slowing, we told participants that the collected points in that run would be set to zero in case they responded too slowly on average in a given run. Since this procedure turned out to be quite effective, this latter correction was never actually used.
Figure 1. Procedure rewarded stop-signal task. In most of the trials participants had to press left or right according to the direction of the central go stimulus (go trials). However, occasionally a stop signal was presented shortly after a go stimulus with a variable go-stop delay indicating that the response had to be withheld (stop trials). The color of the stop signal was either pink or blue. In the reward block the reward-related (RR) color indicated that successful stopping would be rewarded, while in reward-unrelated (RU) stop trials no reward could be earned. In the no-reward block the color of the stop signal had no additional meaning since no money could be won for either of the two kinds of trials (both RU stop trials). The order of the blocks and the reward color were counterbalanced across participants. R block: reward block; NR block: no-reward block; RR: reward-related; RU: reward-unrelated; ISI: inter-stimulus interval.

Electrophysiological recordings and preprocessing

EEG data was collected with a Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands) using 64 Ag-AgCl scalp electrodes positioned according to the standard international 10-20 system. In addition to these
scalp electrodes external electrodes were attached to the left and right mastoid. Moreover, to monitor horizontal and vertical eye movements electrodes were placed at the outer canthi of both eyes and directly above and below the left eye. Signals were recorded with a sampling rate of 256 Hz. Because of a relatively high number of missed go trials, which were furthermore unbalanced over the two blocks, the data of one participant were excluded.

Data was processed and analyzed using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014). Data was re-referenced offline to the average of the left and right mastoid and a low-pass FIR filter was applied at 30 Hz (-6 dB attenuation at 33.7 Hz) was applied. Moreover, blinks were removed using independent component analysis. Epochs were created locked to all relevant stimulus types, with a time window from -200 (for baseline correction) to 1000 ms for go-locked epochs and a time window of -200 to 1500 for stop-locked epochs. Automatic artifact rejection was performed on these epochs with a subsequent visual inspection to reject missed artifacts. The automatic rejection involved removing trials with extreme values (larger than +/- 150μV) in the EEG signal of the 64 scalp electrodes. Furthermore, epochs including horizontal eye movements were detected by a step function in the bipolar eye channel (with a threshold of 60μV, window size of 400 ms and window step of 10 ms). Together, this resulted in on average 5.4% rejected epochs locked to the go stimulus and 5.1% removed stop-locked epochs in stop trials.

In a stop trial the presentation of the go stimulus is usually very rapidly followed by the stop signal (typically around 200 ms after go-stimulus onset). One apparent problem that arises when using the stop-signal task in an EEG setting is that the processing of the go-stimuli is still ongoing
when the stop stimulus is presented. In particular, the signal overlap will differ for conditions that feature different go-stop delays, as is the case for successful and unsuccessful stop trials. As a consequence this overlap coming from the go stimulus should be removed to be able to examine processing that is specifically related to the stop signal. To this end, a difference wave was created by subtracting overlapping go ERP components from the stop-locked ERPs based on a procedure introduced by de Jong et al. (1990) and Kok et al. (2004)\(^2\) (that was also successfully implemented by Krämer et al. 2011, 2013 and Ramautar et al. 2004, 2006a). First, since the overlap depends on the stimulus onset asynchrony between go and stop stimulus and the stop signal usually follows the go stimulus slightly more quickly in successful than failed stop trials, we matched go-stimulus trials in terms of the go-stop delays of stop-signal trials in the reward and no-reward block. Hence, in go trials we set a mock S2 event that is matched in time with regard to the stop-signal delay of the stop ERP which the go activity is subtracted from. This means that for each delay separately we subtracted the delay-matched go-trial activity. Second, it is important to realize that not only stimulus-based processes differ across the different conditions, but

\(^2\) Another technique that has been used to remove go-processing overlap from stop trials is ADJAR (Woldorff, 1993) (e.g. Bekker et al., 2005a, 2005b; Lansbergen et al., 2007; Schmajuk et al., 2006). While more finessed approaches might also allow for an adaptive adjustment of the go-stop delay, typically ADJAR involves a systematic jittering between the two successive events it separates (here, go and stop). In contrast, here we used a simple adaptive procedure (i.e. a dynamic staircase procedure including a fixed number of go-stop delays) without additional temporal jittering in order to stay close to our earlier studies investigating the present reward effect on response inhibition (Boehler et al., 2012b, 2014). In general this dynamic procedure of adjusting the go-stop delay is preferable since it brings all participants’ stopping success rate to approximately 50%, which furthermore helps to reliably estimate the SSRT.
likely also response-based ones. Specifically, since a horse-race model is assumed to underlie the stop signal task, motor response buildup in USTs correspond more closely to fast go trials, whilst SSTs correspond to go trials with slow responses. Therefore we matched go and corresponding stop trials according to their reaction time distribution (e.g. Kok et al., 2004; Ramautar et al., 2004, 2006a). Hence, slow and fast go trials were created for every go-stop delay according to the proportion of successful and failed stops per participant and accordingly subtracted (UST-go fast and SST-go slow) separately for the reward and no-reward block.

In addition to the temporal overlap of go- and stop-related signals, visual inspection of the stop-locked signals also suggested spatial overlap. Some components were not clearly distinguishable since they arose in relative close proximity of each other at similar points in time, like the visual posterior N1 and the frontocentral N2 and the frontocentral stop P3a and parietal P3b. To disentangle these components we applied a Laplacian filter to the stop-locked data using the CSD toolbox (Kayser, 2009; Kayser & Tenke, 2006) thereby enhancing the spatial resolution and intensity of ERP components. Two recent studies (Krämer et al., 2013; Rangel-Gomez et al., 2015) have also successfully applied surface Laplacian transformation to stop-locked ERPs that were corrected for residual go activity using a similar subtraction method as the one used here. Specifically, they have shown the value of this technique for separating stopping-related frontal and occipito-parietal negativities. More generally, Kayser and Tenke (in press) have also demonstrated that Laplacian transformation is useful to dissociate P3a and P3b components. Using this Laplacian transformation, current source densities (CSDs) were calculated according to the spherical spline algorithm of Perrin et al. (1989), using a default smoothing constant of 1.0-5 and a
head radius of 10 cm. Note that transformation via CSDs results in reference-free ERP data. Although stop-locked ERPs refer to CSDs, for simplicity reasons we speak of the related components without always explicitly mentioning the underlying transformation.

**Analyses**

The SSRT was measured using the integration approach, which has been shown to be the most reliable approach in particular in the presence of non-identical stopping-success rates across different conditions (Boehler et al., 2012a; Logan & Cowan, 1984; Verbruggen & Logan, 2009a; Verbruggen et al., 2013). In this method go-trial reaction times are rank-ordered and the reaction time (RT) corresponding to the percentage of failed stop trials is identified for each run and each subject separately. Next, the average duration of the go-stop delay for both kinds of stop trials (blue and pink) in each run is subtracted from this percentile-based go-RT value. Accuracy, RTs, and SSRTs were analyzed using paired sample t-tests and repeated-measures analyses of variance (rANOVAs). All statistical tests were performed two-tailed unless stated otherwise.

All analyses related to the EEG signal of the unsuccessful stop condition exclusively included trials with “correct” responses to the go stimulus to avoid additional error-related signals. ERP measurements locked to the go stimulus focused on stop trials and were limited to the N1 because this component occurs clearly before the average onset of the stop signal, thus influences from processing the stop signal will be minimal, and has been shown before to play a role in stopping performance (Boehler et al., 2009; Knyazev et al., 2008). Time points and a region of interest for each component were defined based on the average ERP over all conditions in
waveforms and topographical maps. Mean amplitudes and local peak latencies (over ±11.7 ms and using an absolute peak in case no local peak is found) were measured at this location and within this given timeframe.

In stop trials the N1 component that was time-locked to the go stimulus preceding the stop signal peaked over bilateral posterior regions (channels PO7 and PO8) between 140 and 180 ms. A rANOVA was performed on the amplitude and latency of this go-locked component related to stop trials with factors success (UST, SST), which indicates whether a given stop trial was ultimately successful or not, and block (no-reward, reward). Turning to the processing of the stop stimulus, stop-locked P1 was quantified between 90 and 130 ms at PO7 and PO8, whilst N1 amplitude was observed at PO7 and PO8 between 160 and 210 ms. The frontocentral stop-related N2 occurred at FCz at distinctively different time points for SST and UST and consequently amplitudes were analyzed between 140 and 180 ms for SST and 150 and 230 ms for UST. A subsequent frontocentral positivity clearly peaked at FCz, extending from 230 to 370 ms for SST and from 270 to 410 ms for trials in which stopping failed. No evidence was found for general reward context effects in behavior (i.e. no difference between reward-unrelated trials in the reward and no-reward block, see section 5.1), which mostly speaks to the specificity of the event-related reward effect (i.e. the influence of the reward-related stimulus color) and implies that reward-unrelated trials in the reward block provide a good baseline condition to identify these specific reward-related effects. Hence to prevent an unnecessary increase in the complexity of the results and a decrease of the sensitivity to detect event-related reward effects, we only investigated ERPs for stop signals in the reward block. Therefore, components were analyzed using a rANOVA with factors success (UST,
SST) and reward (reward-related, reward-unrelated) in the reward block. However, in figures we do illustrate ERPs locked to stop signals in the no-reward block for reference.

In keeping with the notion that response-inhibition processes are probably more (efficiently) involved in successful than in failed stop trials, we contrasted ERP waveforms from successful and unsuccessful stop trials in reward-related and reward-unrelated conditions to be able to investigate differential inhibition-related activity (ERPs related to trials in the no-reward block were again included in the figure as a visual reference). This identified a large positivity over electrode site FCz between 100 and 350 ms. Moreover, we performed a two-tailed permutation test based on the tmax statistic (Blair & Karniski, 1993) using the Mass Univariate ERP Toolbox (Groppe et al., 2011) to be able to detect when ERPs related to SSTs differ reliably from USTs waveforms both for trials locked to reward-related stops and to reward-unrelated stops in the reward block. To limit the number of comparisons and increase power we downsampled the data to 128 Hz and tested all time points between 100 and 350 ms at electrode FCz, resulting in a total of 33 comparisons. The null distribution was derived from 2500 within-subject random permutations. It has to be noted that this permutation test strongly controls the familywise-error rate and consequently is one of the best methods to establish the onset of an effect since a significant outcome at a certain time point is quite reliable. However, this also means that it has less statistical power compared to other related techniques (like cluster-based permutations tests) and thus likely provides slightly delayed onset measures (for a more detailed discussion see Groppe et al., 2011).
RESULTS

Behavior

Accuracy

The percentage of correct responses on go trials did not differ significantly between the no-reward and reward block ($t(18)=0.42$, $p=0.68$). Also, the number of successful stop trials did not differ overall between blocks ($t(18)=1.29$, $p=0.21$). Importantly, results showed significantly more successful stops for reward-related than reward-unrelated stop trials ($t(18)=2.88$, $p=0.005$, one-tailed) within the reward block (see table 1). A slightly different stopping-success rate in the two types of stop trials is possible due to the joint staircase procedure, which only controls the overall stopping-success rate (50%) and was expected based on our earlier work (Boehler et al., 2012).

Reaction times and SSRTs

Correct RTs in go trials were similar in the reward block compared to the no-reward block ($t(18)=1.79$, $p=0.091$). In line with previous results and the horse-race model, participants responded significantly faster in USTs compared to go trials ($F(1,17)=268.49$, $p<0.001$, see table 1). In contrast, there was no effect of reward color in the reward block for UST reaction times ($t(18)=0.49$, $p=0.63$). Importantly, we found faster inhibition in the reward-related stop condition compared to the reward-unrelated stop condition ($t(18)=2.15$, $p=0.023$, one-tailed) corroborating the differential stopping-success rate which implies a faster stopping process for reward-related trials, thereby replicating the behavioral findings of Boehler et al. (2012, 2014). The SSRT in reward-unrelated stop trials in the reward block,
in turn, did not differ from the SSRT in the no-reward block (t(18)=0.65), indicating the absence of a behavioral context effect in which stop trials could have globally benefited from the context of reward-related trials.

<table>
<thead>
<tr>
<th>go trials</th>
<th>R block</th>
<th>NR block</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT</strong></td>
<td>426.5 ms (±9.5)</td>
<td>420.3 ms (±8.6)</td>
</tr>
<tr>
<td><strong>accuracy</strong></td>
<td>96.6 % (±1.1)</td>
<td>96.9 % (±0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>stop trials</th>
<th>RR</th>
<th>RU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT</strong></td>
<td>376.2 ms (±8.4)</td>
<td>378.2 ms (±9.2)</td>
</tr>
<tr>
<td><strong>success rate</strong></td>
<td>52.8 % (±1.1)</td>
<td>46.9 % (±1.0)</td>
</tr>
<tr>
<td><strong>go-stop delay</strong></td>
<td>243.5 ms (±11.8)</td>
<td>245.1 ms (±12.1)</td>
</tr>
<tr>
<td><strong>SSRT</strong></td>
<td>168.4 ms (±4.9)</td>
<td>175.0 ms (±5.9)</td>
</tr>
</tbody>
</table>

Table 1. Summary of behavioral results (average ± SEM). R block: reward block; NR block: no-reward block; RR: reward-related; RU: reward-unrelated; RT: reaction time, SSRT: stop-signal response time. Visual Cues. Five possible cues were presented to the participant.

**Event-related Potentials**

**Go-locked ERPs**

Regarding the go stimulus only the N1 was analyzed which appears before the average go-stop delay and has been shown to be relevant for stopping performance (Boehler et al., 2009; Knyazev et al., 2008). As is evident in figure 2, the amplitude of the N1 component time-locked to the go stimulus in stop trials was larger in the reward block compared to the no-reward block (F(1,18)=13.52, p=0.002). Furthermore there was a trend towards an effect of success (F(1,18)=3.69, p=0.072) suggesting larger go-induced N1 amplitudes in trials resulting in a failed stop.
Figure 2. Go-locked N1 in stop trials. Grand-average ERP waveforms time-locked to the onset of the go stimulus in stop trials averaged over electrodes PO7 and PO8 are shown. Go-locked N1 amplitudes are clearly larger in the reward block compared to the no-reward block, as is depicted in the topographic map reflecting the related reward difference between 140 and 180 ms. Positive plotted upwards; R: reward block; NR: no-reward block; SST: successful stop trial; UST: unsuccessful stop trial.

Stop-locked CSDs

Bilateral visual P1 components did not show any significant effects in amplitude (all p-values>0.1), nor in latency (all p-values>0.15). The stop-evoked N1 amplitude was larger for USTs compared to SSTs in the reward block (F(1,18)=5.4, p=0.032). Interestingly within the reward block, reward-related stop-stimuli elicited larger N1s than reward-unrelated ones (F(1,18)=5.39, p=0.032). We found no significant interaction effect between the factors reward and success (F(1,18)=0.46, p=0.5). Although there was no significant effect of overall stopping success on latency over the two kinds of blocks, within the reward block N1s appeared slightly earlier in SSTs than in USTs (F(1,18)=4.82, p=0.041). These effects are displayed in figure 3.
Figure 3. Stop-locked early visual components. Event-related CSDs elicited by stop signals related to the different conditions over posterior electrodes PO7 and PO8, depicting P1 and N1. Topographic maps of the N1 component on the right result from condition-wise contrasts from 160 to 210 ms showing an effect of the reward-signaling color of the stop signal and a main effect of stopping success. Positive plotted upwards; R: reward block; NR: no-reward block; SST: successful stop trial; UST: unsuccessful stop trial; RR: reward-related; RU: reward-unrelated.

Figure 4A shows that the frontocentral stop-related N2 peaks (and turns towards a positive polarity probably due to P3 overlap\(^3\)) substantially earlier in time in SSTs compared to USTs in the reward block, with peaks appearing around 160 ms for SSTs and 200 ms for USTs trials (F(1,18)=39.06, p<0.001). Therefore, comparing amplitudes between these types of trials requires considering different time windows (140-180 ms for SSTs and 150-230 ms for USTs). This strongly limits the comparability between amplitudes of SSTs and USTs, since they might be related to

\(^3\) Although with the CSD analyses we tried to disentangle different components, the frontal stop-locked N2 and P3 appeared in very close proximity to each other, both in time and space, and are thus hard to separate. The N2 latency effect showing earlier peak latencies in successful stop trials might thus be due to an earlier onset of the overlapping P3.
distinctive underlying processes, but not between trial types within these two conditions (reward-related SSTs vs reward-unrelated SSTs and reward-related USTs vs reward-unrelated USTs). When nevertheless comparing the values from these different time windows, N2 amplitudes showed significant stopping-success effects (F(1,18)=10.47, p=0.005) with larger negativities in USTs (see figure 4A). The frontocentral P3 appeared considerably later when inhibition failed, peaking around 300 ms for SSTs and 340 ms for USTs (F(1,18)=45.43, p<0.001). Amplitudes (over different time-windows for USTs and SSTs) revealed a significant main effect of stopping success (F(1,18)=14.12, p=0.001) and a marginally significant main effect of reward (F(1,17)=4, p=0.061) implying a larger positivity in SSTs and in reward-related trials in the reward block respectively. Interestingly, reward and stopping success significantly interacted (F(1,18)=22.13, p<0.001) indicating that the stop P3 amplitude difference between reward-related and reward-unrelated trials was opposite in SSTs compared to USTs (see figure 4A) with larger amplitudes for reward-related than reward-unrelated stop trials when stopping was successful (t(18)=3.55, p=0.002) and the other way around for USTs (t(18)=-2.4, p=0.03).

To further investigate inhibition-related processes we subtracted ERPs of stop trials that were unsuccessful from waveforms related to successful stopping. As is shown in figure 4B this resulted in a frontocentral positivity comparable to the P3a discussed above that is larger for reward-related stop trials compared to reward-unrelated stop trials (t(18)=3.9, p=0.001). Moreover, a tmax permutation test showed that the difference between USTs and SSTs exceeds the critical t-value earlier and more extended in time in reward-related stop trials (around 172-313 ms) compared to reward-unrelated stop trials (around 211-290 ms) in the reward block (see first two
rows of the raster diagram in figure 4B). Furthermore, when directly comparing the difference wave in reward-related and reward-unrelated stop trials this double difference reaches significance after approximately 211 ms (see last row of the raster diagram in figure 4B).

Figure 4. Stop-locked frontocentral components. (A) Event-related CSDs locked to the stop signal at electrode site FCz for all conditions, showing an earlier stop N2 and P3 peak for successful (solid line) compared to failed stop trials (dashed line). The topographic map on the right indicates that the stop P3 component is larger when the color of the stop signal is indicative of reward in SST in the reward block during the SST timeframe (between 230 and 370 ms). (B) Grand average SST-minus-UST difference waveforms at electrode FCz and the topographic map of this difference between 100 and 350 ms (average over all conditions), showing its frontocentral location. Moreover, a raster diagram illustrates different time points at which the t-value of the differences between SST and UST reaches significance.
according to a tmax permutation test, showing an earlier significant difference in reward-related stop trials (top row) compared to reward-unrelated stop trials (second row) in the reward block. In the third row of the diagram the results of directly subtracting the stopping-success difference in the reward-related and reward-unrelated stop trials are depicted. Positive plotted upwards; R: reward block; NR: no-reward block; SST: successful stop trial; UST: unsuccessful stop trial; RR: reward-related; RU: reward-unrelated.

**DISCUSSION**

The current study examined the temporal dynamics of motivational effects on inhibition-related processes using ERPs in a rewarded stop-signal task. Our behavioral results confirm that reward can facilitate response cancellation as indicated by a larger percentage of successful stops and shorter SSRTs on reward-related stop trials. Although our ERP results were less clear concerning inhibition-related components, we did find some evidence for a reward-related facilitation effect on inhibition in the form of larger stop-locked P3 amplitudes in successful stop trials and a larger, also seemingly earlier, frontocentral positivity reflecting the difference between successful and failed stop trials in the reward-related condition. Importantly, this effect was preceded by a larger stop-evoked bilateral posterior N1 component for the reward-related color. We think that this modulation likely reflects enhanced top-down attention to the reward-related feature, which likely aids later processes that implement response inhibition. Finally, being in a reward-related task context did not seem to generally benefit response inhibition, whereas visual processing of go stimuli was generally enhanced as indicated by a larger posterior go N1 component in the reward block.
Reward effects on response inhibition

In the current study we replicated the behavioral results of our previous studies (Boehler et al., 2012, 2014; but see also Wilbertz et al., 2014), showing that reward can accelerate motor cancellation even in the absence of classic preparatory control since reward prospect was not precued. Although we focus our discussion on reward effects, we do note that reward might not affect results in a unique and direct way in this context. Rather, we assume that reward increases extrinsic motivation and that it is likely that alternative motivational manipulations would yield similar results. Given the fact that response inhibition in the stop-signal task is traditionally considered a reactive control function (Aron, 2011), we expected our ERP results to corroborate boosted reactive inhibitory control in reward-related stop trials corresponding to our previous fMRI results (Boehler et al., 2014). To this end we focused mainly on the frontal N2 and P3 since these components are supposed to reflect brain activity linked to response inhibition (e.g. Bekker et al., 2005a; Ramautar et al., 2006a; Schmajuk et al., 2006; van Boxtel et al., 2001). To isolate processes specifically triggered by the stop signal, like inhibition-related brain responses, we temporally removed residual go-related ERP waveforms and we minimized spatial overlap through a CSD analysis. Both the frontal N2 and P3 peaked earlier for successful stop trials than unsuccessful stop trials, which was also found in some previous studies (Dimoska et al., 2003; Kok et al., 2004; Ramautar et al., 2004) and is in line with the horse-race model assuming that when the inner stop process occurs early it is more likely to finish before the go process (resulting in a successful stop).

We did not find a differential effect of reward-related stop trials in the stop N2 component. Furthermore, the stop-N2 amplitude was larger when
stopping failed, although this comparison was based on different time-ranges and thus might reflect fundamentally different process dynamics. This amplitude difference has been observed previously (Dimoska et al., 2003, 2006; Greenhouse & Wessel, 2013; Krämer et al., 2011; Ramautar et al., 2004, 2006a, 2006b; Senderecka et al., 2012; but see Liotti et al., 2007, 2010; Schmajuk et al., 2006), and recent studies suggest that the N2 component is involved in monitoring of stopping performance, conflict monitoring and error processing (Dimoska et al., 2006; Enriquez-Geppert et al., 2010; Greenhouse & Wessel, 2013; Huster et al., 2013; Krämer et al., 2011). Additionally, we found that the frontal stop-evoked P3 did not only peak earlier, but was also more pronounced when inhibition was successful, in line with previous studies suggesting that in particular the P3 reflects reactive motor inhibition processes (Bekker et al., 2005a; de Jong et al., 1990; Dimoska et al., 2003, 2006; Enriquez-Geppert et al., 2010; Greenhouse & Wessel, 2013; Huster et al., 2013; Lansbergen et al., 2007; Overtoom et al., 2002; Ramautar et al., 2004; Senderecka et al., 2012). In the current study, we observed larger P3s in reward-related successful stop trials, which might indicate enhanced reactive control in this condition. In conflict with this interpretation, however, one should note that this frontal positivity peaks after the completion of the stopping process as indicated by the SSRT (also noted by e.g. Dimoska et al., 2003 and Huster et al., 2013). Nevertheless, the stop P3 in successful trials can still reflect the outcome of the inhibition process, like inhibitory effects on motor cortex (Band & van Boxtel, 1999), or the evaluation of stopping (Bruin et al., 2001). It has also been shown that differences in early P3 amplitude and onset might reflect the implementation of inhibition (Greenhouse & Wessel, 2013; Kok et al., 2004; Lansbergen et al., 2007; Wessel & Aron, 2014).
Evidence for enhanced response inhibition in reward-related stop trials is also suggested by the present ERP difference between successful and failed stop trials. This difference resulted in a frontocentral positive component that peaked around 250 ms, encompassing larger positivities in successful stop trials overlapping with the stop-evoked N2 and P3 component. This component was also described in earlier studies (e.g. de Jong et al., 1990; Greenhouse & Wessel, 2013) and was shown to be larger for controls compared to people with attention-deficit hyperactivity disorder who have problems with inhibitory control (Bekker et al., 2005b; Overtoom et al., 2002; Senderecka et al., 2012). Yet, although probably implying enhanced inhibition, we note that larger positivities for successful stop trials might also reflect differences in error- and motor-related brain activity. This difference component showed larger amplitudes for reward-related stop trials and results indicated that the stopping-success difference appeared earlier and was more extended in reward-related compared to reward-unrelated stop trials in the reward block. More specifically, the SST-minus-UST component was significantly different from zero starting around 170

Specifically, failed stop trials also evoke error-related activity (like the frontocentral error-related negativity) in contrast to successful stop trials. Moreover, to remove overlap from the go stimulus we subtracted delay-matched ERPs related to slow go trials from ERPs related to trials in which stopping was successful. However, go trials contain an executed motor response while motor activation is not completed in successful stop trials, thus the subtraction procedure likely introduced a polarity-inverted (positive) motor component in successful stop trials (see also Kok, 1986). Ideally, in successful stop trials only the build-up of motor processes and not the activity related to the actual execution of the motor response is to be subtracted, which unfortunately is not easily implemented. Yet, we did try to limit the influence of motor-related processes by also taking go-trial response speed into account (fast and slow go trials subtracted from unsuccessful and successful stop trials respectively).
ms for reward-related trials and around 210 ms for reward-unrelated trials in the reward block. Since we used a tmax permutation statistic, which strongly controls the familywise-error rate, the actual onset latency of this stop-evoked component is probably earlier (Groppe et al., 2011). Also electrophysiological research with animals studying inhibition of saccades and modeling studies have shown that neuronal activity on inhibition trials differs from activity on no-stop trials only immediately before the end of the SSRT (see Boucher et al., 2007). Hence the onset of this component could be early enough to reflect the implementation of response inhibition.

As can be seen in figure 4, both the successful stop P3 and SST-minus-UST wave indicate that processing of the rewarded stop signal is special since it is different from reward-unrelated trials in the reward and no-reward block, with no obvious difference between the latter two. This was expected based on our behavioral data showing facilitated inhibition in reward-related trials, but not for reward-unrelated trials in the reward versus the no-reward context. Hence, the observed reward effect in these components may suggest earlier and enhanced inhibition processes in reward-related stop trials. Although both effects have a very similar topography (as can be observed in figure 4) they might also (partially) reflect differential underlying mechanisms and brain activity. For example, the difference in P3 amplitude between reward-related and reward-unrelated successful stop trials might also relate to differences in the evaluation of the stimulus or response, which could e.g. originate from more ventromedial areas. However, based on the present EEG data, we cannot easily investigate this issue.

In our previous fMRI study brain regions that were more active in reward-related trials in both successful and unsuccessful stop trials within
the stopping network were taken to represent enhanced inhibitory control independent of the behavioral outcome. In the current results however, we only observed enhanced stop P3 amplitudes for reward-related trials when stopping was successful. This suggests that fMRI results might be more sensitive to detect generally boosted reactive control processes since it has a better spatial resolution, while ERPs might reveal more information related to the timing of inhibitory control processes. Also beyond the description of subtle and transient modulations of neural activity like the ones described here, fMRI seems limited concerning its ability to separate go-related and stop-related processes. One way of separating such processes is to look at proactive inhibition wherein response inhibition is studied indirectly during go trials under different stopping probabilities. Although this is an interesting research line that has generally shown overlap between proactive and reactive inhibition (e.g. Aron et al., 2014; Chikazoe et al., 2009), there is still debate on which processes are exactly reflected in different brain areas during proactive inhibition (e.g. Vink et al., 2015; Zandbelt et al., 2013) and the details of this topic are beyond the scope of our work here.

The role of reward in visual processing of the stop stimulus

Importantly, in addition to the modulations of the N2 and P3 discussed above, our Laplacian-transformed ERP results clearly showed larger posterior N1 amplitudes in response to reward-related stop-stimuli. This suggests that the actual implementation of response inhibition is preceded by enhanced visual attention for the reward-related color. Such N1 modulations in response to the stop stimulus have been suggested before to reflect strategic orienting of attention (Bekker et al., 2005a; Boehler et al., 2009; Pessoa, 2009), and have been found to be enhanced when the value of stopping is increased (Greenhouse & Wessel, 2013; see also Krebs et al.,
2013). Given that in the present data the N1 modulation was specific for the reward-related condition, we take this to suggest that participants strategically screened for this feature in a voluntary top-down, and hence proactive fashion. One should note, however, that there is the alternative possibility that the enhanced sensory response to the reward-related stop-stimulus reflects enhanced non-strategic bottom-up saliency of a feature that is consistently (Anderson et al., 2011a, 2012; Krebs et al., 2013; Theeuwes & Belopolsky, 2012) or previously paired with reward (Hickey & van Zoest, 2012; Hickey et al., 2010). Although in these studies reward information is usually task-irrelevant and not in line with subjects’ goals, reward does influence task performance and stimulus processing in an involuntary way. However, many of these studies mainly investigated effects of reward feedback on subsequent target selection in a visual search tasks and although paradigmatical differences are quite pronounced, EEG work investigating the automatic influence of reward on visual attention has documented effects on the P1, for which we did not find any significant effects (Hickey et al., 2010). Also, other studies have shown that reward effects (even in the extrastriate visual cortex) can be under top-down attentional control (Buschschulte et al., 2014; Engelmann & Pessoa, 2007). Both the strategic top-down and involuntary bottom-up account would predict better behavioral performance because reward information is also relevant to task goals in the current study. Although the current paradigm is not set up to dissociate these alternative underlying mechanisms, here we consider the strategic top-down modulation as the more likely explanation since the stop-evoked N1 modulations as observed in the stop-signal task have usually been explained in terms of strategic attentional control. We think that in the current task sustained proactive control interacts with and possibly supports
reactive (inhibitory) control mechanisms by strategically screening for a reward-related feature and thereby enhancing its processing.

Surprisingly, not only the color of the stop signal, but also stopping success was reflected in the amplitude of the stop-evoked N1 with larger negativities for trials in which response suppression was eventually unsuccessful. This is opposed to what has been found previously in ERP and MEG studies (Bekker et al., 2005a, 2005c; Boehler et al., 2009; Dimoska & Johnstone, 2008; Lansbergen et al., 2007). Mostly this has been explained by assuming that more pronounced sensory processing of or increased visual attention to the stop signal will more likely result in successful stopping. Interestingly, the study of Greenhouse and Wessel (2013) investigating the role of reward-related preparation in stopping showed that the visual N1 was larger when correct stopping was rewarded over going, but did not find statistical differences between successful and unsuccessful stop trials in both conditions. Hence, our stopping-success effect on the N1 amplitude is not in line with previous findings, whereas a slightly earlier peak for successful stopping seems to be in line with the general notion of enhanced attention to the stop-stimulus in successful trials. Importantly, no difference between successful and failed stop trials was observed for trials in the no-reward block. A possible hypothesis is that the stopping-success effect found in the N1 actually reflects activity from the stopping-success effect in the frontocentral N2 that is leaking into the N1 because they could not be clearly separated in time and space, which EEG will be more susceptible to than MEG (see Boehler et al., 2009, which featured the most comparable paradigm). Yet, based on the present data, we can also not rule out that the stopping-success effect on the N1 amplitude is valid and reflects some
interaction between reward information and the process dynamics of attention and response inhibition.

**Context effects**

Previously it has been shown that changes in motivational state can alter sustained brain activity and influence processing of all stimuli even when they are not motivationally relevant themselves (Jimura et al., 2010; Locke & Braver, 2008). In our study SSRTs did not differ significantly between reward-unrelated stop trials in the reward block and in the no-reward block, thus behaviorally there was no indication of a global reward effect on inhibitory control. On the other hand, we found a larger visual posterior go-evoked N1 component\(^5\) in the reward context compared to the no-reward context, so it seems that visual attention is generally boosted when the task context is motivationally relevant. This suggests that a rewarded or motivationally relevant context likely triggered changes in sustained proactive control as suggested previously (Jimura et al., 2010; Locke & Braver, 2008). Thus, although there is evidence for changes in sustained motivation, stopping probably can’t be globally enhanced easily, which could relate to the very small amount of time that is available for bringing about any enhancements (around 200 ms). This also suggests that enhanced processing of the reward-related color specifically, as was described above, might be particularly important in this task.

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\(^5\) We note that this posterior negativity might also represent (at least in part) a selection negativity (SN) instead of a N1 component; yet, even if true, this does not substantially changes the interpretation of the results because the selection negativity is also believed to reflect attentional target-processing (e.g. Hillyard & Anllo-Vento, 1998).
The idea that visual processing of the go stimulus can be under (partial) top-down proactive control was already introduced by Boehler et al. (2009). In this previous MEG study it was shown that the go-locked N1 in future stop trials was more pronounced when stopping would be unsuccessful. Although only marginally significant, we replicated this effect in this ERP study. Moreover, in the MEG study it was found that trial-by-trial adjustments likely reflecting strategic top-down control modulations (Botvinick et al., 2001; Fecteau & Munoz, 2003; Laming, 1979), like reaction time slowing to go trials after stop trials, was reflected in the go N1 with smaller negativities in go trials following stop trials compared to go trials. It was concluded that the amount of resources are devoted strategically to visual processing of a stimulus and changes can be made within and between trials (see also Barceló et al., 2000; Hopf et al., 2002). Given that larger go N1s make ultimate stopping success less likely, the present reward modulation seems a bit counter-intuitive. At the same time, participants were not allowed to strategically slow down their go responses, so that the overall N1 effect probably relates to a state of generally heightened attention that is not necessarily directly helpful in stopping.

**CONCLUSION**

To summarize, the current behavioral results show selective motivational effects on inhibitory control restricted to trials in which the stop stimulus really signaled reward prospect, which was also hinted at by our ERP results. Specifically, there were subtle modulations of ERP components that are typically associated with (reactive) response inhibition. Importantly, this facilitation was preceded by enhanced selective attention
to, and thus more profound visual processing of, the stop stimulus for reward-related trials. This implies that the sensory processing of the reward-related feature is increased probably by proactively screening for this feature, which consequently might assist reactive inhibitory control. Furthermore, ERP-related block effects showed that being in a rewarded context already influences visual processing of go stimuli in stop trials. Hence, a motivationally significant environment might introduce changes in the global state, perhaps towards a sustained strategic proactive control mode (Locke & Braver, 2008), thereby having an impact on all stimuli and trials that are comprised in this environment. Yet, this global effect did not seem to be able to facilitate response inhibition in general, suggesting that context does not always exclusively influence the potentially rewarded process (here stopping).
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REFERENCES


Hickey, C., Chelazzi, L., & Theeuwes, J. (2010). Reward changes salience in human vision via the anterior cingulate. The Journal of
Electrophysiological evidence for the involvement of proactive and reactive control in a rewarded stop-signal task

Neuroscience, 30(33), 11096–11103. doi:10.1523/JNEUROSCI.1026-10.2010


CHAPTER 5
THE EFFECT OF VAGUS NERVE STIMULATION ON RESPONSE INHIBITION

Previous research has suggested that the noradrenergic system plays an important role in the ability to withhold a response, usually by pharmacologically increasing extracellular noradrenaline (NA) concentrations. In the current study we explored whether vagus nerve stimulation (VNS) in epileptic patients, which is believed to increase NA levels via activation of the locus coeruleus, would also positively affect response inhibition. Moreover, we tried to identify the dynamics of the underlying neural processes by also investigating event-related potentials (ERPs). Patients performed an auditory stop-signal task once when stimulation was switched on and once when the vagus nerve was not stimulated. This task allows us to estimate the stop-signal response time (SSRT), which is a measure for how rapidly an already-initiated motor response can be cancelled. The results show that the behavioral SSRT benefit (i.e. the amount of SSRT reduction in VNS ON compared to VNS OFF) was correlated with the percentage of seizure reduction. Hence, patients who clinically profit more from VNS treatment show a larger advantage, in terms of faster inhibition, when the vagus nerve is being stimulated, probably due to more effectively boosted NA. Furthermore, ERP results implied earlier sensory processing of the stop signal and more pronounced reactive inhibition (or the evaluation thereof) when stimulation was switched on, which however was independent of the individual amount of seizure reduction. We conclude that these results further support the significant involvement of the noradrenergic system in response inhibition, and identify enhanced response inhibition as a possible positive neurocognitive effect of VNS.

INTRODUCTION

For obvious reasons, it is important for successful navigation of everyday life situations to be able to rapidly inhibit a response when environmental stimuli indicate that the current action is no longer appropriate or even deleterious. In psychological research, response inhibition has frequently been investigated using the stop-signal task (Logan et al., 1984). In this task a go stimulus is usually presented to which subjects have to respond quickly by pressing a button. However, occasionally a stop signal is displayed rapidly after the go stimulus in which case responses are to be withheld. Hence, in stop trials action-related processes that were already initiated by the go stimulus need to be suppressed. Importantly, by implementing this task one can estimate the stop-signal reaction time (SSRT), which is a measure for how long a participant needs to inhibit a response. This estimation is usually based on a horse-race model that assumes that there is a competition between two parallel processes (going and stopping) and whichever finishes first will determine the behavioral outcome (Logan & Cowan, 1984; Logan, 1994; see also Boucher et al., 2007). Studies have found longer SSRTs and/or decreased stopping success in people with attention-deficit hyperactivity disorder (ADHD) (e.g. Lijffijt et al., 2005; Murphy, 2002; Senderecka et al., 2012), Parkinson’s Disease (Gauggel et al., 2004) and obsessive compulsive disorder (Menzies et al., 2007). In parallel, research has begun to identify the neuroanatomical networks that underlie inhibitory control, and the consensus seems to be that prefrontal areas in the right inferior frontal gyrus (IFG) and/or the pre-supplementary motor area (pre-SMA) interact with motoric parts of the basal
ganglia in order to cancel a motor response (Aron & Poldrack, 2006; Aron et al., 2014; Chambers et al., 2009).

In addition to the neuroanatomical substrates, research has investigated which neurotransmitters play a modulating role in response inhibition. Here, particularly noradrenaline (NA; also called norepinephrine) has been shown to play a significant role (for an overview see Eagle et al., 2008). Specifically, performance in the stop-signal task in both animals and humans has been found to profit from medication that increases extracellular levels of NA, like the NA reuptake inhibitors atomoxetine (Bari et al., 2009; Chamberlain et al., 2006b; Humby et al., 2013; Robinson et al., 2008) and methylphenidate (Linssen et al., 2012). Moreover, patients with ADHD, who generally are impaired in inhibition capabilities and are assumed to suffer from insufficient NA levels, show improved response inhibition when medicated with drugs that boost NA (again through reuptake inhibition), like desipramine and methylphenidate (Aron et al., 2003; Overtoom et al., 2003). Similarly, certain doses of guanfacine impair stopping probably via engagement of presynaptic $\alpha_2$-receptors that ultimately decreases NA release (Bari et al., 2009, 2011; but see Müller et al., 2005). However many of these drugs also affect the levels of other neurotransmitters, in particular dopamine (DA) (Bymaster et al., 2002) but also serotonin, acetylcholine and histamine (Ding et al., 2014; Horner et al., 2007; Tzavara et al., 2006). Yet, results of recent studies suggest that inhibitory performance in the stop-signal task is mostly sensitive to fluctuations in NA levels (Bari & Robbins, 2013; Bari et al., 2009, 2011; Eagle et al., 2008).

In the current study the involvement of NA in response inhibition was further investigated by indirectly manipulating NA levels in patients that are treated with vagus nerve stimulation (VNS). VNS is applied in suitable
patients with drug-resistant epilepsy. It entails a spiral electrode that is wrapped around the vagus nerve in the neck and connected to and controlled by a pulse generator that is implanted below the skin. In about 50% percent of the patients VNS successfully reduces the amount of seizures by a significant degree (≥ 50%) (Englot et al., 2011). Although it is not clear how VNS works exactly to achieve this, experimental evidence suggest that the noradrenergic system plays an important role, consistent with the fact that vagus nerve fibers connect via the nucleus of the solitary tract to the locus coeruleus (LC) which is the main source for NA in the forebrain (see Fornai et al., 2011). Accordingly, animal studies have found that VNS enhances NA concentrations in several brain areas like the cortex, nucleus accumbens and hippocampus (Manta et al., 2013; Raedt et al., 2011; Roosevelt et al., 2006). Moreover, although results are not conclusive, VNS can also have positive effects on cognitive functions that are likely similarly related to changes in NA levels (Vonck et al., 2014). Thus we assume that in line with previous studies that have manipulated NA levels using drugs, response inhibition will benefit when the noradrenergic system is triggered via stimulation of the vagus nerve.

Here, we did not only investigate behavioral measures of response inhibition like the SSRT, but also studied electroencephalographic (EEG) signals related to response inhibition given that event-related potentials (ERPs) have generally been shown to be sensitive to VNS (Brázdil et al., 2001; De Taeye et al., 2014; Neuhaus et al., 2007; but see Hammond et al., 1992). Studies applying EEG in the stop-signal task usually mainly investigate the stop N2 component, which peaks around 200 ms after the stop-signal at frontal electrodes, and the stop-evoked frontocentral P3 that is maximal at approximately 300 ms. Usually the stop N2 has been related to
error detection and performance monitoring, given that the N2 amplitude has been found to be larger in unsuccessful stop trials compared to successful stop trials (Dimoska et al., 2006; Enriquez-Geppert et al., 2010; Greenhouse & Wessel, 2013; Huster et al., 2013, but see Rangel-Gomez et al., 2015; Schmajuk et al., 2006). It is typically found that it is the dopaminergic system that is involved in behavioral and error monitoring (Bari & Robbins, 2013; Barnes et al., 2011; Holroyd & Coles, 2002), but recently it was pointed out that also other neurotransmitters including NA might play a role in performance monitoring (Jocham & Ullsperger, 2009). Hence, it is not clear whether VNS will affect the stop-evoked N2. In contrast to the N2, in the stop-signal task the frontal P3 is increased in successful stop trials and supposed to reflect actual response inhibition and/or the evaluation thereof (Bekker et al., 2005a; Dimoska et al., 2006; Enriquez-Geppert et al., 2010; Lansbergen et al., 2007; Wessel & Aron, 2014). Hence, given the previously mentioned involvement of NA in response inhibition, we expected that VNS would have an influence in particular on P3 amplitudes. Both the N2 and P3 components have also been shown to peak earlier when stopping was successful suggesting an earlier internal response to the stop signal (Kok et al., 2004; Ramautar et al., 2004, 2006a) and therefore we also analyzed peak latencies.

Furthermore, response inhibition performance might not only be dependent on reactive inhibitory processes but also on the attentive processing of the task-relevant stimuli. Therefore, we investigated N1 components related to the processing of both the visual go stimulus and the auditory stop signal. The amplitude of the stop-evoked N1 has been found to be increased in stop trials that end up being successful, implicating varying levels of attention directed to the stop signal in stopping success (Bekker et
al., 2005a, 2005c; Boehler et al., 2009; Lansbergen et al., 2007). While Bekker et al. (2005b) showed that this difference could not be observed in adults with ADHD, indicating that disrupted attentional processing might also contribute to impaired stopping in these patients, Overtoom et al. (2009) found that such a relationship could be restored by administering methylphenidate. In addition, the N1 related to processing of the go stimulus has been observed to be enhanced in unsuccessful stop trials suggesting that more attention to the go stimulus is more likely to result in later unsuccessful stopping (Boehler et al., 2009). Boehler et al. (2009) concluded that changes in resource allocation can be made within and between trials and that stopping success is thus dependent on attentional resources devoted to the go stimulus and the stop signal in each trial. Since the noradrenergic system is supposed to be involved in attention and sensory processing (Berridge & Waterhouse, 2003), N1 components might also be sensitive to changes in NA levels induced by VNS. Hence, in the current study we compared behavioral and ERP results in the stop-signal task in epileptic patients that were implanted with VNS when stimulation was switched on versus off, as an indirect way to further explore the role of the noradrenergic system in response inhibition.

MATERIALS & METHODS

Participants

After giving written informed consent, twenty patients with refractory epilepsy (8 males, mean age = 44 years, range = 21-66 years) participated in the current experiment. The study was approved by the ethics board of Ghent University Hospital. All patients were treated with VNS stimulation for at
least 18 months and had an IQ score of 70 or more on the Wechsler Adult Intelligence Scale. Seizure reduction was calculated by subtracting the number of seizures during 3 consecutive months preceding the test period (after VNS implantation) from the number of seizures before VNS implantation, divided by the total number of seizures before VNS (baseline). A detailed description of this and other patient characteristics is provided in Appendix I. We note that the current study was part of a set of experiments that were performed consecutively by all patients (see De Taeye et al., 2014, for an additional report on the same cohort).

**VNS apparatus**

All patients had been previously implanted with a VNS device (Cyberonics, Houston, TX, USA) containing 2 electrodes at the left vagus nerve and a pulse generator positioned below the left collarbone. Each participant performed the task once when stimulation was on and once when stimulation was off, the order of which was counterbalanced. After performing the first session the VNS device was switched on or off and a break of at least 20 minutes was included before starting the second task session. When stimulating the vagus nerve the duty cycle was set to 7 seconds ON / 18 seconds OFF, while other device settings could vary between patients depending on clinical effectiveness (see Appendix I).

**Stimuli and procedure**

In the present study a typical stop-signal task with visual go stimuli and auditory stop stimuli was implemented. Most trials (67%) were go trials

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2 In case the number of monthly seizures decreased by more than 50% after VNS implantation, patients were considered responders to the VNS therapy (n=10).
in which patients had to respond quickly to a central go stimulus, which was a green traffic-light sign. More specifically, participants had to press the left or right mouse button according to the orientation of a central green traffic light (left or right, with equal probability; response time-out of 1600 ms). The central go stimulus was always displayed directly above a fixation dot and the target was flanked by two additional green traffic light symbols on each side (one pointing in the same direction and the other in the opposite direction, and the opposite side displaying the mirror image so that overall congruency was always the same) that were to be ignored. In 33% of the trials a tone (514 Hz, 200 ms) was presented (stop trial). Upon the presentation of this auditory stop signal patients had to try to withhold the go-trial response they were about to give.

Visual go stimuli were displayed on the screen for 1000 ms. In stop trials the tone was presented at a varying stimulus-onset asynchrony (i.e. go-stop delay). Specifically, a staircase procedure was applied in order to create a 50% stopping-success rate. To this end, if stopping was successful the go-stop delay was increased resulting in a reduced chance of successful response inhibition, whereas the go-stop delay was decreased after unsuccessful stop trials thereby increasing the likelihood of successful inhibition on the next trial. The delay was increased or decreased by 50 ms in the first 10 stop trials and by 17 ms in the remaining stop trials (with a minimum of 70 ms and a maximum of 800 ms). The inter-trial interval varied randomly between 1800 and 2200 ms.

Before starting the experiment, task instructions were given and patients were asked to try to respond as fast as possible, to limit eye blinking and to keep their eyes on the fixation dot. First, patients completed a training run of 60 trials (40 go trials and 20 stop trials) to get acquainted with the task. Subsequently, two experimental runs, one run ON VNS and one run
OFF VNS, were performed. Each experimental run included a total of 160 go trials and 80 stop trials, that were randomly presented, and a short break of 10 seconds was implemented after every 60 trials.

**Electrophysiological recordings and preprocessing**

EEG data was collected with a Micromed System Plus (Micromed, Mogliano, Italy) containing 61 Ag/AgCl electrodes, mounted in an electrode cap (WaveGuard EEG cap system), that were positioned on the head according to the extended international 10-20 system. During recording data was referenced to electrode site CPz, while channel AFz was used as a ground. Signals were amplified and digitized with a sampling rate of 1024 Hz, an anti-aliasing filter of 250 Hz, a gain of 50 dB and a resolution of 16 bits.

We used EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) to preprocess and analyze the data. First, data was down-sampled offline to 256 Hz and re-referenced to the average of all channels (reinstating channel CPz). Subsequently, a 30 Hz low-pass filter (-6 dB attenuation at 33.7 Hz) was applied and we corrected for eye blinks using independent component analysis (ICA). Epochs were then created from -200 to 600 ms locked to the onset of the go stimulus and from -200 to 800 ms locked to the onset of the stop signal. These epochs were baseline corrected using the 200 ms pre-stimulus period. We automatically rejected epochs including extreme values (> +/- 150μV) and additionally visually inspected EEG signals for any missed artifacts.

Given that the auditory stop signal is presented rapidly after the go stimulus, ERPs locked to the stop signal might in part reflect continuing processing of the preceding go stimulus. Hence, to be able to investigate
activity exclusively related to the processing of the stop signal, we removed
temporal overlap coming from the go stimulus by applying a subtraction-
based correction procedure (see also de Jong et al., 1990; Kok et al., 2004;
Krämer et al., 2011, 2013; Ramautar et al., 2004, 2006). Specifically, we set
a mock S2 event in go trials and accordingly subtracted ERPs locked to this
event from stop-locked ERPs in stop trials. Before performing this
subtraction two things were taken into consideration. Firstly, the go-related
overlap varies according to the go-stop delay. This means that the overlap is
different for successful and failed stop trials given that in successful stop
trials the stop signal is usually presented more quickly after the go stimulus
than in unsuccessful stop trials. Thus, we inserted an artificial S2 event in
correct go trials that were matched for the go-stop delays of the stop trials
before subtraction. Secondly, since a horse-race model is assumed to
underlie the stop-signal task, motor responses in unsuccessful stop trials are
more comparable to those in fast go trials, while the motor build-up in
successful stop trials more closely resembles that in slow go trials (seeing
that a successful and failed stop trial would have been respectively a slow
and fast go trial if no stop signal would have been presented). Hence, for
each patient (separately for ON and OFF VNS) fast and slow go trials were
created for each go-stop delay according to the proportion of unsuccessful
and successful stop trials, respectively, in the go reaction-time distribution.
Thus, we subtracted delay-matched fast go trials from unsuccessful stop
trials and delay-matched slow go trials from successful stop trials.

However, different components related to the processing of the stop
signal (like the auditory N1 and stop N2 and the anterior inhibition-related
P3a and parietal P3b) also spatially overlap. Therefore, we applied a surface
Laplacian filter to the stop-locked EEG signals in order to disentangle these
components. Recently, studies have shown that Laplacian transformations can successfully separate P3a and P3b components (in a typical oddball task, Kayser & Tenke, in press) and distinguish components in the stop-signal task (e.g. Krämer et al., 2013; Rangel-Gomez et al., 2015). Hence, in the current study we calculated Laplacian-transformed current source densities (CSDs) using the CSD toolbox for EEGLAB (Kayser & Tenke, 2006; Kayser, 2009). The spherical spline algorithm of Perrin et al. (1989) was applied with a default smoothing constant of $1.0^{-5}$ and a head radius of 10 cm resulting in reference-free CSDs. To simplify, we speak of the related stop-locked components without always explicitly referring to the underlying Laplacian transformation.

### Statistical analyses

In total, data of four participants had to be removed (R1, R3, R8, NR4). One dataset (R8) was not included because the patient showed less than 50% correct in-time go-trial responses. Data of patient R3 was rejected given that she had an implausible SSRT probably because of approximately 40 unsuccessful stop trials in a row (including 25 trials with the minimal go-stop delay). Furthermore, two other datasets (R1, NR4) were excluded because of very noisy EEG data. Hence, data of sixteen patients (6 males, mean age = 42 years, range = 21-66 years) were included in the analyses.

### Behavior

Our main variable of interest was the SSRT, which was calculated using the integration method that has been shown to yield reliable SSRT estimates, especially when the stopping-success rate differs between conditions (Boehler et al., 2012a; Logan & Cowan, 1984; Verbruggen & Logan, 2009a; Verbruggen et al., 2013). Hence, following this procedure for
each participant and each session (ON and OFF VNS) reaction times on go trials are rank-ordered and missed go trials are assigned the maximal response-time value (1600 ms). Subsequently, the average go-stop delay is subtracted from the \( n \)th reaction time that corresponds to the percentage of unsuccessful stop trials. A repeated-measures analysis of variance (rANOVA) was performed with SSRT as a dependent variable and factor VNS (ON, OFF) and covariate (percentage of) seizure reduction\(^3\). Furthermore, go-trial accuracy, reaction times in correct go trials and go-stop delays in stop trials were also analyzed with a rANOVA including factor VNS (ON, OFF) and covariate seizure reduction. In case effects including the covariate seizure reduction were at least borderline significant, we further explored the direction of this effect using a Kendall’s tau (\( \tau \)) correlation coefficient since data was not fully normally distributed, and contained some patients with the same values (since more than one patient had 100% and 0% seizure reduction, respectively).

**Event-related potentials**

We exclusively studied electrophysiological data in stop trials (both go-stimulus-locked and stop-stimulus-locked components). Unsuccessful stop trials included stop trials in which participants pressed the correct mouse button. For each component we defined a region of interest and time window based on topographical maps and previous related studies. Mean amplitude measurements and local peak latencies (over \( \pm 11.7 \) ms) were analyzed using a rANOVA with factors success (unsuccessful stop trials,

\(^3\) We preferred to include the covariate seizure reduction instead of the dichotomous variable responder (responder, non-responder; see e.g., De Taeye et al., 2014) since this is a more fine-grained measure of the subject-dependent effect of VNS treatment and avoids a possibly arbitrary dichotomy.
successful stop trial), VNS (ON, OFF) and the covariate seizure reduction. If we observed a significant effect of seizure reduction, Kendall’s tau correlational analysis was performed to establish the direction of the effect given that the covariate seizure reduction did not show a normal distribution. 15 Hz low-pass filtered data are displayed in all figures for illustration purposes, but the statistical analyses were performed on data that were only low-pass filtered with 30 Hz.

In stop trials the go-locked visual N1 peaked between 160 to 200 ms at electrode sites PO7 and PO8. This component is related to visual processing of the go stimulus and arises clearly before the subsequent stop signal (average go-stop delay = 382 ms) and should hence not be affected by it. Turning to the processing of the stop stimuli, CSDs evoked by the stop signal showed a clear bilateral auditory N1 at central electrode sites (C3, C4, C5, C6, FC3, FC4, FC5 and FC6) between 110 and 160 ms. The frontal stop N2 was quantified at electrode FCz from 160 to 220 ms. Moreover, the inhibition-related frontal P3 was observed mainly in successful stop trials at the same electrode site (FCz) starting at 250 ms until 350 ms.

RESULTS

Behavior

Accuracy and reaction times in go trials did not differ significantly between the VNS ON and VNS OFF condition (p’s>0.8), nor was there a significant main effect of seizure reduction or interaction (p’s>0.26). In stop trials, stop-signal delays and the percentage of successful stop trials were similar in all conditions independent of seizure reduction (p’s>0.36). Importantly, SSRTs were not significantly decreased when the vagus nerve
was stimulated \((F(1,14)=1.28, p=0.28)\), but it did marginally significantly interact with seizure reduction \((F(1,14)=3.27, p=0.092\), see table 1 for an overview of behavioral results). We further explored this effect by correlating the amount of seizure reduction with the SSRT benefit, i.e. the SSRT difference between VNS ON and VNS OFF (negative values reflect the expected decrease in SSRT when VNS was switched on) using a one-tailed Pearson-correlation test, based on the a-priori hypothesis that patients that profit more from the VNS treatment should also show a larger behavioral benefit. Seizure reduction significantly correlated with SSRT benefit scores \((\tau=-0.34, p=0.037)\) indicating that a larger seizure reduction after VNS implantation was associated with an increased benefit for stopping speed in terms of SSRT when VNS was switched on compared to off (see figure 1).

<table>
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<th>table 1. Behavioral results</th>
<th>VNS ON</th>
<th>VNS OFF</th>
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<tr>
<td><strong>go trials</strong></td>
<td></td>
<td></td>
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<tr>
<td>(RT)</td>
<td>661.4 ms (± 43.6)</td>
<td>673.8 ms (±35.8)</td>
</tr>
<tr>
<td>(accuracy)</td>
<td>93.4 % (±2.3)</td>
<td>90.6 % (±3.2)</td>
</tr>
<tr>
<td><strong>stop trials</strong></td>
<td></td>
<td></td>
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<tr>
<td>(RT)</td>
<td>571.7 ms (±33.7)</td>
<td>566.1 ms (±31.7)</td>
</tr>
<tr>
<td>(success rate)</td>
<td>50.6 % (±2.3)</td>
<td>53.2 % (±1.1)</td>
</tr>
<tr>
<td>(go-stop delay)</td>
<td>381 ms (±43.3)</td>
<td>382.4 ms (±36)</td>
</tr>
<tr>
<td>(SSRT)</td>
<td>274.8 ms (±24.3)</td>
<td>281.9 ms (±30.2)</td>
</tr>
</tbody>
</table>
Figure 1. Correlational analysis. A negative correlation between the variables seizure reduction and SSRT benefit was found reflecting that patients with a higher percentage of seizure reduction (i.e. a decreased amount of seizures) after VNS implantation also show more reduced SSRTs when VNS is on compared to off.

**Event-related Potentials**

We analyzed ERPs using a rANOVA with factors VNS (ON, OFF), success (unsuccessful stop trials, successful stop trial) and the covariate seizure reduction, both regarding amplitude and latency. Given the behavioral results, we again suspected effects of VNS to depend on the percentage of seizure reduction, indicated by an interaction between VNS and seizure reduction. In stop trials, the go-locked posterior N1 amplitude did not show a significant main effect of success (F(1,14)=0.98, p>0.3) nor of VNS (F(1,14)=1.7, p>0.2), and also no effect of seizure reduction or any interactions (p’s>0.25). For go-evoked N1 latency we did not find any effects (all p’s>0.1) except for a significant main effect of seizure reduction (F(1,14)=4.62, p=0.049) indicating later go N1 peaks when subjects responded more to VNS treatment (τ=0.36, p=0.06). The amplitude of the
auditory N1 time-locked to the stop signal was similarly large in successful and unsuccessful stop trials (F(1,14)=1.3, p>0.25), also no other main or interaction effects were detected (p’s>0.2). The N1 peaked slightly earlier when VNS was switched on compared to off, but this effect was only marginally significant (F(1,14)=3.44, p=0.085). All other results did not reach significance levels (p’s>0.1). The frontal stop N2 amplitude only showed a borderline significant main effect of success (F(1,14)=3.48, p=0.083), but success also interacted with VNS (F(1,14)=3.76, p=0.073) indicating a similar N2 amplitude in successful and unsuccessful stop trials in VNS ON conditions but a larger amplitude in unsuccessful stop trials in VNS OFF conditions (see figure 2). Concerning the latency of the N2, we observed a main effect of success (F(1,14)=4.93, p=0.043) with an earlier N2 peak in successful stop trials (183.6 ms) compared to failed stop trials (187.9 ms). Yet, success also marginally significantly interacted with VNS (F(1,14)=3.97, p=0.066) suggesting that the stop N2 peaked earlier in successful stop trials compared to unsuccessful stop trials only when VNS was switched off (see figure 2). Moreover, a marginally significant interaction between success and seizure reduction was observed (F(1,14)=3.78, p=0.072) implying larger success effects (unsuccessful-minus-successful) in peak latencies in patients that do not respond highly to VNS treatment (τ=-0.38, p=0.053). Other results related to N2 latency were not significant (p’s>0.1). The stop-locked frontal P3 amplitude was larger (and more clearly detected) in successful stop trials than in unsuccessful stop trials (F(1,14)=11.54, p=0.004, see figure 2). Moreover, the P3 was enhanced in case VNS was on compared to off (F(1,14)=7.03, p=0.019, see figure 2), but there was no interaction between VNS and seizure reduction (F(1,14)=2.4, p=0.15) or any other effect (p’s>0.5). We did not observe any significant results related to stop P3 latencies (p’s>0.13).
DISCUSSION

The central goal of this study was to investigate effects of VNS on inhibitory performance and its underlying mechanisms using ERPs. Behaviorally, we found that the size of the SSRT difference between VNS ON and VNS OFF conditions correlated with the percentage of seizure reduction. Specifically, patients that showed a larger therapeutic effect of VNS (i.e. more seizure reduction after VNS implantation) were also able to faster inhibit responses when VNS was switched on. ERP results were less clear given that no interaction between VNS and seizure reduction was found. We observed some general VNS effects (independent of seizure reduction) including earlier stop-evoked N1 peaks and larger stop P3 amplitudes when the vagus nerve was stimulated. Also, related to the stop
N2, VNS seemed to influence the difference between successful and unsuccessful stop trials implying changes in performance monitoring.

In line with studies that reported improved inhibition performance when drugs increased NA levels (see e.g. Eagle et al., 2008; Ilieva et al., 2015), results indicated beneficial effects of VNS on SSRTs in subjects that responded more to VNS treatment while go accuracy and reaction times remained similar, speaking to the specificity of the effect. Given that VNS likely reduces seizures by activating the LC-NA system (Fornai et al., 2011; Krahl et al., 1998), NA concentrations are probably more enhanced in patients that show more seizure reduction. This is consistent with the observation that NA effects in pharmacological studies arise mainly for higher doses of NA-related medication. For example it has been shown that only relatively large doses of such pharmaceuticals result in significantly reduced SSRTs compared to placebo, while stopping performance after administering lower doses is not statistically different from that in placebo conditions (Linssen et al., 2012; Overtoom et al., 2009; Robinson et al., 2008; but see Humby et al., 2013, for a more complex pattern possibly indicating an inverted U relation). However, we do note that the correlation between seizure reduction and SSRT benefit is also driven by patients that do not have a clinical VNS treatment effect (seizure reduction of 0%) who seem to show a reversed pattern in SSRT performance, i.e. slightly increased SSRTs in VNS ON compared to VNS OFF conditions. It is not clear how stimulation of the vagus nerve might induce a detrimental effect on response inhibition in these patients, hence interpretation should be taken with care, and more data would be helpful to confirm this correlational pattern.

In the EEG data we did not find an effect that mimicked the behavior results (i.e. no interaction between the factors VNS and seizure reduction).
However, the stop-locked N1 seemed to peak slightly earlier when VNS was on compared to off, possibly suggesting earlier processing of the auditory stop signal in this condition. Such a head-start could be behaviorally relevant given the dynamic nature of the horse-race model that describes the underlying processes. Furthermore, in addition to the expected enhancement of the frontal inhibition-related P3 amplitude in successful stop trials (e.g. Greenhouse & Wessel, 2013; Lansbergen et al., 2007; Ramautar et al., 2004, 2006), we also found larger P3 amplitudes when stimulation was switched on. Hence, although these effects did not interact with seizure reduction, they might reflect a generally favorable impact of VNS on response inhibition that cannot be detected in behavioral performance. These findings imply that VNS-induced boosted NA might result in earlier attentive sensory processing of the stop signal and enhanced (evaluation of) reactive response inhibition. Although it might seem implausible that patients without seizure reduction show VNS effects as well, having no treatment effect does not necessarily mean that stimulation has no influence at all on different processes in the brain (like NA transmission). Rather, these neurophysiological effects might not (reach a certain threshold to) translate into seizure reduction.

Some of the current ERP results however are not in line with previous studies. For one, in contrast to the results of the MEG study of Boehler et al. (2009) that showed an increased go N1 in unsuccessful stop trails and an enhanced stop N1 in successful stop trials, in the present study we failed to detect a success effect in both the visual go-locked N1 amplitude and auditory stop N1 amplitude. Moreover, the overall N1 amplitude and the relation between successful and failed stop trials were not dependent on the activation of VNS in the current manuscript. Hence, a simple model in
which attention is globally boosted by VNS seems unlikely to explain the
data in their entirety. Overtoom et al. (2009) reported that the difference in
stop P3 amplitude between successful and unsuccessful stop trials was
reduced in people with ADHD receiving methylphenidate. On the other
hand, Logemann et al. (2013) showed that this success effect in stop P3
decreased when NA transmission was attenuated via clonidine (partial α2-
recepter agonist). However, VNS-induced DA levels did not affect the
success effect in the stop P3 amplitude here. Of course there are a number of
differences between the design of the current study and these previous
studies that limit comparability. For example, Overtoom and colleagues
tested people with ADHD who have difficulties with response inhibition to
begin with (e.g. Lijffijt et al., 2005; Murphy, 2002; Senderecka et al., 2012),
which to our knowledge is not the case for epileptic patients. Moreover,
these researchers did not apply a Laplace transformation and quantified the
stop N1 at central electrode sites (and thus stop N1 and N2 components
might be difficult to disentangle). The main limitation of the current study,
that also played a role in some of these previous studies and might
particularly affect the reliability of the ERP results, is the relatively small
sample size (n=16) which reduces the signal-to-noise ratio and the chance of
finding significant correlations. In the current design however we tried to
restrict the influence of other confounds like variation in age, type of
epilepsy, anti-epileptic drugs (AEDs), location of the seizures and brain
lesions, by comparing the same subject in VNS ON and VNS OFF
conditions thereby keeping patient characteristics constant.

Although the current ERP results imply earlier processing of the stop
signal and enhanced reactive control in case the vagus nerve was stimulated
in epileptic patients, we could not detect a general improvement in inhibitory
behavioral performance when stimulation was on compared to off (independent of seizure reduction). This might in part be due to processes that are only accessory to response inhibition, like impaired monitoring functioning as suggested by the stop N2. More specifically, the larger amplitude (and earlier peak) when stopping is unsuccessful compared to successful that is usually observed in the stop-evoked N2 component (e.g. Dimoska et al., 2006; Krämer et al., 2011; Ramautar et al., 2004; but see Schmajuk et al., 2006) was only detected when stimulation was off. Also the peak difference in successful compared to failed stop trials was larger when patients responded more to VNS treatment. These findings might imply diminished error/conflict detection or performance monitoring with increasing levels of NA. Thus far the role of the noradrenergic system in performance monitoring has not been extensively studied (Jocham & Ullsperger, 2009), yet Riba et al. (2005) reported that enhanced NA release by administering yohimbine (that blocks α2-noradrenergic receptors) increases the error negativity (Ne), which is supposed to reflect error processing and response monitoring (Falkenstein et al., 1991, 2000; Gehring et al., 1993) and in the stop-signal task might (partly) overlap with the unsuccessful stop N2 (also suggested by e.g. Greenhouse & Wessel, 2013; Ramautar et al., 2006). Hence, it does not seem likely that larger NA levels interfere with response monitoring. However, many other neurotransmitters, in particular dopamine but also serotonin and GABA (see Jocham & Ullsperger, 2009), are probably engaged in human action monitoring. Given that VNS also has been shown to affect these other neurotransmitters (although maybe to a lesser extent) (Ben-Menachem et al., 1995; Manta et al., 2013; Nemeroff et al., 2006), especially dopamine increase in prefrontal cortex (Manta et al., 2013) or a complex interplay between different neurochemical systems might result in decreased monitoring functions
(Jocham & Ullsperger, 2009). Furthermore, we note that although VNS might also induce changes in other neurotransmitters and mainly in serotonin because of enhanced firing of serotonergic neurons in the raphe nucleus (Dorr & Debonnel, 2006; Manta et al., 2013; Nemeroff et al., 2006), the positive effects of VNS on response inhibition are most likely due to modulations of NA release given that in particular boosted NA and not serotonin has been found to decrease SSRTs in the stop-signal task (Bari et al., 2009; Clark et al., 2005; Drueke et al., 2010; Eagle et al., 2009).

**CONCLUSION**

In summary, behaviorally response inhibition seemed to benefit from VNS but only in the epileptic patients that showed the largest seizure reduction after VNS treatment. Given that response inhibition is a central cognitive-control ability, this finding represents an important neurocognitive benefit of the procedure, albeit being limited to patients for whom it is also clinically particularly effective. Although ERP results were more difficult to interpret they suggest that performance monitoring (stop N2) could be impaired but the auditory stop signal is detected and processed earlier (stop N1 latency) and reactive inhibition processes are boosted (stop P3) in case the vagus nerve was stimulated. These results further support the hypothesis that NA plays a significant role in response inhibition.
ACKNOWLEDGEMENTS

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Ding, Y.-S., Naganawa, M., Gallezot, J.-D., Nabulsi, N., Lin, S.-F., Ropchan, J., … Laruelle, M. (2014). Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports:


THE EFFECT OF VAGUS NERVE STIMULATION ON RESPONSE INHIBITION


Krämer, U. M., Solbakk, A.-K., Funderud, I., Løvstad, M., Endestad, T., & Knight, R. T. (2013). The role of the lateral prefrontal cortex in...
inhibitory motor control. Cortex, 49(3), 837–849. doi:10.1016/j.cortex.2012.05.003


**Appendix I**

### Table 1. Patient characteristics

<table>
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<tr>
<th>Responders</th>
<th>Patient Sex</th>
<th>Age (years) reduction (%)</th>
<th>Seizure year</th>
<th>VNS Implantation (year)</th>
<th>Output (mA)</th>
<th>Freq (Hz)</th>
<th>Pulsewidth (μs)</th>
<th>VNS parameters</th>
<th>HEZ Lobe</th>
<th>Side</th>
<th>AEDs</th>
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<tr>
<td>R1 M</td>
<td>52</td>
<td>100.0</td>
<td>1995</td>
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<th>Freq (Hz)</th>
<th>Pulsewidth (μs)</th>
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<td>30</td>
<td>500</td>
<td>FL</td>
<td>Left</td>
<td>VPA, LEV, PB, LCZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td>44</td>
<td>14.2</td>
<td>2.3</td>
<td>26</td>
<td>413</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Appendix I.** Patient characteristics. Patients of which data were removed from the analyses are displayed in light grey font color. VNS = vagus nerve stimulation; M = male; F = female; Impl = implantation; Freq = frequency; HEZ = hypothesized epileptogenic zone; FL = frontal lobe; TL = temporal lobe; PL = parietal lobe; OL = occipital lobe; AEDs = anti-epileptic drugs; CBZ = carbamazepine; CLB = clobazam; CZP = clonazepam; LCZ = lacosamide; LTG = lamotrigine; LEV = levetiracetam; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PGB = pregabalin; RG = retigabine; VPA = valproic acid; VGB = vigabatrin.
CHAPTER 6
GENERAL DISCUSSION

The central goal of the current research project was to dissociate processes related to proactive and reactive control in different motivational task contexts. This dissociation was largely accomplished by describing different temporal dynamics, which was possible through the use of EEG because of its high temporal precision. Moreover, we explored the impact and functioning of reward, an important motivator for the implementation of cognitive control, on functional processes related to both types of control. In the first two chapters we mainly focused on effortful cognitive preparation (which represents a principal function of proactive control) and its relation to reward and (indirectly) to the dopaminergic system. In the last two chapters the emphasis was placed primarily on (the systems involved in) response inhibition as a form of reactive control and the potential interaction with proactive control via global and selective attention.

RESULTS: AN OVERVIEW

Mental preparation as an important proactive control function

Reward-triggered preparation, anticipation of task-demands (reflecting top-down attentional preparation) and proactive cognitive control have all been related to the dopaminergic system (see CHAPTER 1, introduction). This suggests that reward and top-down attentional processes might be linked by effortful resource allocation during preparation in function of optimizing performance especially when the outcome is valuable. In
CHAPTER 2, reward and task demands were therefore systematically crossed by the implementation of a cued attentional paradigm with different levels of anticipated target-discrimination difficulty and availability of reward (see also Krebs et al., 2012) while simultaneously EEG was recorded. Results indicated that the expectancy of reward influenced relatively early evaluation processes of the cue (like the P2 and P3). Furthermore, effortful cognitive and response preparation as reflected by the CNV was also mainly dominated by reward. Nevertheless, in later preparatory stages reward and task difficulty interacted with maximal CNV amplitudes in difficult reward-anticipation trials while amplitudes were similarly lower in easy and difficult trials when motivation was low (i.e. cues indicated no reward could be won). Also, in line with previous studies (e.g. Birbaumer et al., 1990; Fan et al., 2007; Wascher et al., 1996), the difference in late CNV amplitude between easy and difficult trials in the reward condition correlated with the same difference in reaction time.

These results stress the importance of effortful preparation for subsequent target-discrimination performance. Also, reward effects seem to be (temporally) distinguishable from task-difficulty effects during cue-target intervals and thus likely cannot be reduced to top-down attentional mechanisms involved in task-difficulty preparation. Rather, reward already affected the evaluation of the cue consistent with a more bottom-up impact of reward on attention (possibly in line with studies suggesting enhanced non-strategic saliency of features that are consistently or previously coupled to reward; e.g. Anderson et al., 2011; Hickey et al., 2010; Krebs et al., 2013). Yet, in a late preparation phase reward and task-difficulty information are integrated implying more effortful preparatory control when the task will be difficult, particularly when correct performance will be rewarded.
Furthermore, the finding that the modulation of CNV amplitude was primarily driven by reward information in the cue confirms the important link between reward (motivation) and effortful preparatory control.

In a series of previous studies using an orthogonalized go/no-go task it was suggested that the dopaminergic midbrain is predominantly engaged in preparing for action execution over inhibition rather than reward anticipation. Yet, in CHAPTER 3 we tested the potential involvement of effortful preparation in this task, inspired by the findings in the previous chapter and the idea that dopaminergic activity might particularly signal the willingness to overcome effort (e.g. Kurniawan et al., 2011; Treadway et al., 2012) and motivated resource allocation during preparation (e.g. Boehler et al., 2011; Krebs et al., 2012). We implemented the orthogonalized go/no-go task of Guitart-Masip in an EEG setting and added three baseline conditions. Importantly, the CNV was only observed when cues indicated subjects would have to perform an action (press left or right) upon target presentation (go trials). On the other hand, if cues signaled that no response had to be made (no-go trials) the CNV component was not detected, similar to catch trials in which no target would be presented, implying a lack of task preparation. The even earlier cue-evoked parietal P3 also showed clearly larger amplitudes in go trials compared to no-go trials and catch trials indicating increased attention to/more profound processing of go stimuli probably because they are recognized as particularly task-relevant. In subsequent target processing an enhanced visual N1 component illustrated that top-down attention was increased to circle targets in go trials (compared to no-go trials). Furthermore, as expected, no reactive inhibitory processes seemed to be engaged in no-go trials indicated by the absence of the
inhibition-related anterior N2/P3 complex that is typical observed in no-go trials (e.g. Bokura et al., 2001; Eimer, 1993; Gajewski & Falkenstein, 2013).

Together these findings speak against the notion that active (preparing for) target processing and response inhibition is involved in anticipated no-go trials. Thus, people might only mentally prepare for an upcoming target when they really need to process it (in order to correctly perform the task). To conclude, in this chapter we have successfully shown that effortful cognitive preparation can be an additional or alternative explanation for the increased dopaminergic activation when anticipating action (Guitart-Masip et al., 2011, 2012a), in line with previous studies linking effort and dopamine (e.g. Boehler et al., 2011; Kurniawan et al., 2011). Hence, it is not clear whether the dopaminergic dominance of action execution over inhibition would persist when the amount of (anticipated) effort would be matched.

**Neuromodulatory and reward influences in reactive control**

In the studies of Guitart-Masip and colleagues an asymmetric link between action and valence was also suggested since in go trials performance was enhanced when cues signaled reward compared to punishment (Guitart-Masip et al., 2012a) and learning to go was shown to be improved when anticipating reward while learning to withhold responses was more successful when anticipating punishment (e.g. Cavanagh et al., 2013; Guitart-Masip et al., 2012b). Yet, recently response inhibition has also been shown to benefit from reward (Rosell-Negre et al., 2014) even when reward information is not cued and thus global preparatory changes are not possible (e.g. Boehler et al., 2012, 2014). We showed that the latter finding was related to boosted reactive control as specified by increased activity in
the ‘inhibition network’ upon the presentation of a rewarded stop signal (Boehler et al., 2014). Given the important link between reward and proactive processes, in **CHAPTER 4** we explored whether these reward effects on response inhibition were solely related to reactive processes or whether variations in latent proactive control might also be involved. As predicted, when the color of the stop signal indicated reward could be won in case stopping was successful in the current trial (reward-related stop trial), reactive inhibition was enhanced implied by shorter SSRTs and also by enhanced successful stop P3 amplitudes and an increased (as well as earlier) frontocentral positivity reflecting the difference between successful and unsuccessful stop trials. More importantly, we furthermore found boosted stop-elicited N1 amplitudes in reward-related stop trials, likely reflecting proactive attentional screening for the reward-signaling color. Furthermore, stopping performance in reward-unrelated stop trials was not affected by the mere presence of a reward context, i.e. similar SSRTs in reward-unrelated trials in a reward block and no-reward block. Nonetheless, go-evoked N1 amplitudes were larger in the reward block compared to the no-reward block, which demonstrates that being in a reward context might not always exclusively influence the rewarded behavior but that it might create a sustained proactive control mode as suggested previously (Jimura et al., 2010; Locke & Braver, 2008) thereby affecting the processing of all stimuli within the context. Yet, behaviorally, such an effect was not detected in our study, possibly due to the fact that in the stop-signal task, going and stopping stand in opposition, so that a global performance-enhancing effect might not clearly manifest for either process, depending on its exact nature.

Hence, although at first glance reward effects might exclusively be due to reactive processes, given that there was no possibility to differentially
prepare for different conditions in a global fashion as in pre-cueing designs, it is important to acknowledge that latent proactive processes can still be engaged for example via specific strategic attention or in general via sustained activity dynamics triggered by the context. These proactive processes might consequently also support reactive control in order to optimize performance and reach predefined goals.

In **CHAPTER 5** we further explored processes underlying response inhibition. Evidence supports a rather specific role of the noradrenergic system in response cancellation (see Eagle et al., 2008). This has usually been demonstrated by the finding that drug-induced increase of noradrenaline concentrations results in improved stopping (e.g. Bari et al., 2009; Chamberlain et al., 2006; Overtoom et al., 2003; Robinson et al., 2008). To further support this hypothesis we explored the impact of vagus nerve stimulation (VNS) in epileptic patients on response inhibition given that VNS is believed to increase noradrenaline levels via indirect projections to the locus coeruleus, which is probably also a critical mediator in the reduction of seizures in these patients (Fornai et al., 2011). Most notably, we found that the percentage of seizure reduction (which indicates whether VNS treatment is effective for a given patient) was correlated with the amount of reduction in SSRT when VNS was switched on compared to off. More specifically, patients with an increased treatment effect showed more improvement in response inhibition in terms of SSRTs when the vagus nerve was stimulated. To be able to more closely examine (proactive and reactive) mechanisms involved in this effect we also analyzed ERPs. These results were less straightforward but seemed to indicate slightly earlier attentional processing of the auditory (earlier N1 latency) in VNS ON compared to VNS OFF conditions, which could be potentially relevant given the assumed
race between going and stopping. Moreover, enhanced reactive response inhibition was suggested by increased P3 latency when the stimulator was on. Since these effects of VNS were irrespective of the percentage of seizure reduction, they suggest a general influence of VNS that did not translate directly into behavioral performance benefits. Furthermore, these positive effects might be opposed by decreased performance monitoring (indicated by the stop N2) when stimulation was on.

Though some caution should be taken when interpreting these results because there were some limitations to this study (like noisy ERPs and seemingly detrimental inhibition effects of stimulation for patients that did not clinically profit from the VNS treatment), the findings of **CHAPTER 5** were in line with studies suggesting a role of the noradrenergic system in response inhibition. Also, they point in the direction of a possible cognitive advantage of VNS in particular in patients that already benefit most in terms of reduced seizures.

**THEORETICAL IMPLICATIONS AND DISCUSSION**

**The anticipation of cognitive and physical effort**

The concept of cognitive effort is believed to reflect the level of cognitive engagement in a certain task (Westbrook & Braver, 2015). If one puts more effort into a task, this probably translates into increased engagement of top-down attentional processes and might consequently also improve behavioral performance. In **CHAPTER 2** and **CHAPTER 3**, we showed the importance of cognitive effort during preparation and results of **CHAPTER 2** indicated that increased motivation can lead to enhanced levels of preparatory cognitive effort. Yet, it is not clear whether these effects
would extent to (the anticipation of) physical effort, which refers to the degree of muscle activity that one has to exert in a task. Schmidt et al. (2012) directly compared brain regions involved in physical and mental effort during task execution. These authors showed that although they mostly engage distinct task-specific brain activity, mental and cognitive effort seem to rely on a common motivational center, specifically the ventral striatum.

During preparation phases, the anterior cingulate cortex (ACC) and striatum (which are both important target regions of the dopaminergic system) have been shown to be involved in the anticipation of physical effort with more activation when preparing for highly demanding physical tasks (e.g. Kurniawan et al., 2013). Importantly, anticipation of increased mental effort has been related to similar brain regions (e.g. Boehler et al., 2011; Krebs et al., 2012; Vassena et al., 2014). Also Kurniawan et al. (2011) suggested based on several studies that the ACC and basal ganglia (in relation to the dopaminergic pathways) play an important role in anticipating, choosing or executing effortful actions. In line with this idea we assume that these regions are engaged as a general motivator to sustain effortful preparation (or task execution) independent of whether this effort is physical or cognitive in nature.

Interestingly, Kurniawan et al. (2013) explored anticipation of physical effort using a design that was based on the orthogonalized go/no-go task of Guitart-Masip et al. (2011) and thus was very similar to the procedure that we used in CHAPTER 3. In the fMRI study of Kurniawan et al. (2013) fractal cues similarly indicated the valence of the upcoming trial, but instead of action anticipation these cues additionally signalled the amount of physical effort one would have to exert in the upcoming trial. They only found main effects of task difficulty during anticipation with increased ACC
and striatal activity when preparing for higher physical effort. Given that in Chapter 3 we found evidence for the idea that the anticipation of no-go trials could also involve a lack of cognitive effort, this could be related to ACC activity (as indicated by studies suggesting the ACC, as part of a thalamocortical circuit, could be a generator of the CNV; see e.g. Nagai et al., 2004) and thus possibly also relate back to the ACC as a general node for effortful preparation.

**Reward and punishment as motivators**

In the current work the emphasis was mostly placed on reward (in the form of gaining money) and how it affects proactive and reactive control. Yet, we argue that the observed effects are likely not specific to reward given that we assume a more strategic attentional role of reward in all our studies. Consistent with this idea Maunsell (2004) stated that reward effects can be established via enhanced top-down attention and that in many previous studies these factors cannot be clearly distinguished. Hence, it is conceivable that other motivators such as punishment could use the same route (i.e. via strategic attentional control). Alternative manipulations like punishment (and even intrinsic goals) would thus probably similarly boost or energize control processes. As such, (the avoidance of) punishment has also been shown to enhance cognitive control, mostly in the same extent as reward (Engelmann & Pessoa, 2007; Engelmann et al., 2009; Krawczyk & D’Esposito, 2013; Savine et al., 2010; Small et al., 2005), and also similarly enhance brain networks related to top-down attention (Engelmann et al., 2009; Krawczyk & D’Esposito, 2013; Small et al., 2005). Interestingly, Krawczyk performed two very similar studies in which working memory was tested: in one of the studies a cue indicated the amount of money that could be won in case a correct response was given (Krawczyk et al., 2007),
in the other study the amount of money that someone could avoid losing was cued (Krawczyk & D’Esposito, 2013). When a cue predicted the potential of losing money, enhanced activity in the striatum and amygdala was detected consistent with potential monetary gains (but see Knutson et al., 2001). Moreover, in reward conditions and avoiding punishment conditions respectively, encoding of information was improved via top-down effects (indicated by boosted activity in the prefrontal cortex) by increasing attention towards relevant stimuli. Furthermore, Carter et al. (2009) showed that brain areas that typically respond to the anticipation of gains (like the ventral tegmental area and nucleus accumbens) were also enhanced when anticipating losses. Together these results suggest that (the anticipation of) reward and punishment serve as motivators that can drive control processes through very similar mechanisms. Yet, we note that although punishment and reward can have similar effects on behavior and control-related networks, these influences could also possibly be obtained via different routes (Small et al., 2005).

In the design described in CHAPTER 2 cues actually both signaled reward and punishment since correct fast performance was rewarded and incorrect or too slow responses were punished (similar manipulation see e.g. Taylor et al., 2004). The results are thus related to enhanced motivation probably due to both reward and punishment expectation, yet we described reward as a key concept in this study. Specifically, participants not only knew that a certain compensation for participation would be paid independent of task performance, but also that the reward procedure would in any case lead to an additional monetary bonus, so that the overall expectation was clearly one of receiving additional reward of a variable amount, of which only the size depended on their performance. In CHAPTER
we implemented a study that included both anticipated reward (‘win cues’) and punishment (‘avoid losing cues’). Reward and punishment avoidance did not seem to influence preparatory effort in a different way (i.e. similar CNV amplitudes, see also Broyd et al., 2012; Pfabigan et al., 2014). However, during cue evaluation P3 amplitudes were particularly increased when cues signaled reward in comparison to punishment and neutral conditions. A particular sensitivity of the cue P3 to the anticipation of gain over the anticipation of loss has been reported before (Broyd et al., 2012; Pfabigan et al., 2014) and could be related to increased saliency of/attention to the reward stimulus. These results suggest that reward and punishment can slightly differently affect cue evaluation, yet it seems that they usually do not affect proactive processes in a substantially different way.

**The direction of the link between reward and effort**

Motivation is easily thought of as a mediator of effort in the sense that when one is motivated to succeed in a task, one is probably more likely to engage more effort. This idea is in line with the ERP results mentioned in **CHAPTER 2** in that more preparatory effort is exerted in case correct performance of the upcoming task is particularly worthwhile. Unexpectedly, in **CHAPTER 3** we did not find modulations in go CNV amplitudes in reward/punishment trials compared to neutral trials. There might be a number of reasons why this motivational effect was not observed. For example, the go task (pressing left or right according to the location of a circle) might have been too easy so that differential preparation might not be considered necessary (and thus performance could possibly mostly rely on reactive control processes). Also the employed probabilistic feedback might support this effect since subjects were informed about this probability feature and thus they might have assumed that negative feedback was always
misleading rather than being due to too slow performance. Furthermore, in the literature mixed findings are reported with some studies showing an effect of reward/punishment on CNV amplitudes (e.g. Hughes et al., 2012; Pfabigan et al., 2014; van den Berg et al., 2014) whereas others do not (e.g. Broyd et al., 2012; Goldstein et al., 2006). This might be related to certain task features as described above, yet future studies are necessary to confirm this effect.

According to the effort-discounting principle effort is inherently negative and thus reward is devaluated when high effort is required to achieve it. In humans mainly dopaminergically-innervated subcortical and cortical regions (like the striatum and the ACC), as well as possibly the dopaminergic source regions themselves, have been supposed to reflect the net value of reward indicated by increased activity when less effort is required to obtain a similar rewarding outcome (Botvinick et al., 2009; Croxson et al., 2009). Also Prévost et al. (2010) suggested that these regions coded for the devaluation of reward. This is in contrast to studies that have found increased activation in these dopamine-related brain structures when high effort needs to be engaged implying a role of motivated resource allocation to overcome effort to achieve goals (e.g. Boehler et al., 2011; Krebs et al., 2012; Vassena et al., 2014; see also Kurniawan et al., 2011).

In our work, results were consistent with the latter idea rather than supporting the discounting principle. This is, in **CHAPTER 2** we found maximal CNV amplitudes in reward trials when subjects anticipated a high-difficult trial (requiring more cognitive effort) instead of a low-difficult trial. This reflects the involvement of motivated anticipatory processes even more so given that low-difficult trials are more likely to be performed correctly and thus be rewarded. Also in **CHAPTER 2** and **CHAPTER 3**, we observed
enhanced feedback-related P3 components in hard (high-difficult and go trials respectively) compared to easy trials (low-difficult and no-go trials respectively) especially in highly motivating conditions (reward and reward/punishment respectively). This could imply that subjects value correct feedback more when they have put a lot of effort into correctly performing the task, particularly in motivationally significant conditions (see also Ma et al., 2014) which is in line with the effort justification hypothesis (see the cognitive dissonance theory of Festinger, 1957).

Finding evidence in favor of effort discounting or motivated effort engagement might depend on certain task-related characteristics. As such, some studies have investigated the relation between reward and effort in decision-making tasks. In this line of research it is explored how willing humans or animals are to engage in highly demanding tasks. Thus, in these paradigms subjects can freely choose the difficulty level of the upcoming trial in anticipation of potential differential rewards (see e.g. Kurniawan et al., 2010; Prévost et al., 2010; Westbrook et al., 2013). However, different results could be observed when implementing no-choice tasks (e.g. Krebs et al., 2012) as also suggested by Schouppe et al. (2014) who found differential effort-related striatal activity in choice and no-choice tasks). Importantly, motivated effort engagement might be particularly relevant in a phase were subjects can actively prepare for the upcoming target in a way that improves performance and is contingent upon task performance (in contrast to non-contingent rewards, see e.g; Botvinick et al., 2009), as was the case in CHAPTER 2. Hence, dopaminergically-innervated brain regions might be involved in both effort discounting and motivated resource allocation dependent on the phase/context animals or humans are in.
Electrophysiology in the stop-signal task

In CHAPTER 4 and CHAPTER 5 control processes related to response inhibition were examined in the stop-signal task. In this regard ERPs are very useful given that they provide additional information on the timing and nature of the underlying processes that might support behavioral performance. Given that components in the stop-signal task have been thought to reflect specific functions (such as more proactive attention-related N1 components and reactive N2 and inhibitory P3 components), this paradigm was particularly useful to investigate reactive and proactive control. However, there are also some complications when investigating ERPs in the stop-signal task. As such, given that they are presented close in time, stop-evoked signals suffer from temporal overlap of the go stimulus, which furthermore can differ between conditions, and several stop-evoked components also overlap in space (like the frontal stop P3 and parietal go P3). We tried to deal with these issues by correcting for both types of overlap. This might limit the comparability of results over studies that use different overlap-removal techniques or studies that only correct for one type of overlap or apply no correction.

This might be one of the reasons why in some research the stop N2 was observed over right frontal electrodes (e.g. Logemann et al., 2013; Schmajuk et al., 2006) while other authors reported a frontocentral stop N2 component (Kok et al., 2004; Ramautar et al., 2006a). These components might reflect different functions with the right N2 being more related to reactive inhibition in the right inferior frontal gyrus (rIFG) since the right N2 is larger in successful stop trials (Schmajuk et al., 2006). On the other hand, seeing that the central N2 is enhanced in unsuccessful stop trials, this component might be more related to conflict detection and performance
monitoring (e.g. Dimoska et al., 2006; Greenhouse & Wessel, 2013; Kok et al., 2004; Ramautar et al., 2006a) in the ACC and/or inferior frontal gyrus (Enriquez-Geppert et al., 2010; Ramautar et al., 2006b). In CHAPTER 4 and CHAPTER 5 we observed the typical frontocentral N2 that was usually larger for unsuccessful stop trials. Yet, when in epileptic patients the vagus nerve was stimulated this difference between successful and unsuccessful stop trials in N2 amplitude could not be detected signifying decreased monitoring in this condition (see CHAPTER 4).

Furthermore, although previous work has noted that the stop P3 might appear too late to reflect the initiation of reactive inhibition (Dimoska et al., 2003; Huster et al., 2013), many studies have suggested that the P3, which shows larger amplitudes on successful stop trials, most likely reflects reactive inhibitory processes (Bekker et al., 2005a; de Jong et al., 1990; Dimoska et al., 2003, 2006; Enriquez-Geppert et al., 2010; Greenhouse & Wessel, 2013; Lansbergen et al., 2007; Overtoom et al., 2002; Ramautar et al., 2004; Senderecka et al., 2012). Moreover, Wessel and Aron (2014) have shown that the P3 onset is typically still in time to reflect response inhibition. Results of CHAPTER 4 and CHAPTER 5 suggest that the P3 might indeed be related to reactive inhibition since they are consistent with (although not identical to) effects observed in SSRTs. As such, we found amplified successful P3 amplitudes in reward-related stop trials (CHAPTER 4) and enlarged P3 components when vagus nerve stimulation was switched on (CHAPTER 5), suggesting improved reactive response inhibition.

ERPs in these chapters also allowed us to investigate N1 components as a function of proactive control. Recently, it has been emphasized that attentional processing of the stop signal is a significant aspect in (successful) stopping (Verbruggen et al., 2014). Boehler et al. (2010) found larger
activation in the occipital cortex for visual stop signals in successful stop trials compared to unsuccessful stop trials, which might indicate more profound processing of the stop stimulus. Also previous results highlighted the role of the go and stop N1 in successful stopping performance (Bekker et al., 2005a; b; Boehler et al., 2009). However, in CHAPTER 4 and CHAPTER 5 we failed to detect enhanced stop N1 amplitudes in successful stop trials. We speculate that this effect might be quite sensitive to task manipulations or that there might be subtle individual differences in (the intensity/frequency of) the use of attentional adjustments. Still, effects in N1 amplitude in CHAPTER 4 showed that top-down attention to the reward-related color of the stop stimulus was increased and general attention (to the go stimulus) was boosted in the reward block.

In CHAPTER 4 and CHAPTER 5 we successfully demonstrated neuromodulatory and motivational influences on reactive and proactive inhibitory control. Thus, although there are some (largely technical) difficulties related to it, investigating ERPs in the stop-signal task might be particularly valuable to detect the role of underlying proactive and reactive process within the same trial that might otherwise not be revealed.

**CLINICAL IMPLICATIONS**

The findings presented in the current thesis contribute to the knowledge about neural mechanisms underlying motivation and control processes. This is of particular interest not only to gain insights into healthy brain functioning, but also to neurological disorders that show difficulties with one (or both) of these functions. As such, the dysregulation of motivation is critically involved in several disorders like depression (e.g.
Yang et al., 2014), attention-deficit hyperactivity disorder (ADHD; e.g. Cubillo et al., 2012), Alzheimer disease (e.g. Landes et al., 2001), schizophrenia (e.g. Strauss et al., 2014) and Parkinson’s disease (e.g. Pagonabarraga et al., 2015). Also cognitive control functions are diminished in, for example, people with Huntington and Parkinson’s disease (e.g. Brown & Marsden, 1990; Lawrence et al., 1996; Sawamoto et al., 2008), schizophrenia (e.g. Lesh et al., 2011), depression (e.g. Austin, 2001) and patients with frontal lobe damage (e.g. Stuss & Benson, 1984); for an overview see also Elliott (2003). More specifically, reactive response inhibition has been shown to be affected in people with ADHD (Barkley, 1997; Chambers et al., 2009; Lijffijt et al., 2005; Murphy, 2002; Senderecka et al., 2012), obsessive compulsive disorder (Menzies et al., 2007), Parkinson’s Disease (Gauggel et al., 2004) and ADHD (Barkley, 1997; Chambers et al., 2009). In our work (see CHAPTER 4 and CHAPTER 5) we have demonstrated that reactive inhibitory control can be supported by proactive processes and thus that stopping possibly also depends on sensory and attentional processes. Hence, studies could further reveal the influence of these processes in the inhibitory impairments that are observed in these studies (see for example Bekker et al., 2005b). Moreover, in CHAPTER 5 it was suggested that the noradrenergic system could also play an important role in reactive response inhibition and VNS could improve stopping performance. Regarding proactive processes, the CNV was found to be attenuated in patients with Parkinson’s disease (Gerschlager et al., 1999; Lukhanina et al., 2006; Wascher, 1997), implicating the relation between this component and the dopaminergic system (see also Linssen et al., 2011) and decreased cognitive and motor preparation in these patients. Hence, defining the processes affecting the CNV (like in CHAPTER 2 and CHAPTER 3) might also have further implications for these patients.
FUTURE RESEARCH

In the current dissertation we have shown that proactive and reactive control are important functions that can both be affected by motivation. Although we found that proactive and reactive control can be engaged in the same task, and have speculated that they can interact with each other, more research is needed to confirm whether there is a direct link between these two control functions and how exactly it operates under different conditions. Moreover, although EEG has high temporal precision, its spatial resolution is rather low. Thus, combined EEG and fMRI could provide more insight into the brain activation pattern that is associated with proactive and reactive control. Also, more clarity is needed to define the interplay between proactive and reactive control given that some researchers have proposed that enhanced proactive control alleviates the need for reactive control processes indicated by reduced activity in reactive control regions during task execution (Chikazoe et al., 2009; Padmala & Pessoa, 2011), while other results suggested that proactive control can actually boost reactive control networks (Rosell-Negre et al., 2014).

As already stated in the previous sections, the current findings are particularly related to mental effort and reward. Future studies should provide more evidence for the idea of a single node for (preparatory) effort by simultaneously investigating physical and mental effort and how this might be reflected by the CNV component. Also, the possibly unique as well as shared mechanisms and influences of reward, punishment and even intrinsic motivation in energizing different control functions could be further explored. Moreover, although a coupling was supposed between action execution and reward and action inhibition/withdrawal and punishment
(Guitart-Masip et al., 2011, 2012b, 2014), we have shown that reactive response inhibition can also benefit from reward. Hence, it would be interesting to also include punishment in a stop-signal paradigm and investigate its impact on reactive and proactive processes and capture whether these are comparable to reward effects. Furthermore, in our work reward information is always tied to a feature of the cue or target. Although ERP results mainly suggested higher functions of reward in the form of motivation, rewarded features have also been suggested to engage more automatic processes (Hickey & van Zoest, 2012; Hickey et al., 2010). To confine these bottom-up attentional influences it would be interesting to have reward availability communicated by an additional stimulus that is not task-relevant.

**CONCLUSION**

In the current dissertation we have shown that proactive and reactive control are important functions that can both be affected by motivation (likely via fluctuations in the dopaminergic system), while the noradrenergic modulatory system seems be particularly involved in reactive response inhibition. Moreover, our results suggest that both forms of cognitive control are not mutually exclusive since they can be engaged within the same trial, raising the possibility that they furthermore interact with each other in order to optimally tweak performance under varying motivational and situational settings.
REFERENCES


The Journal of Neuroscience, 31(13), 4955–4961. doi:10.1523/JNEUROSCI.4845-10.2011


signal paradigm. Biological Psychiatry, 54(12), 1345–1354. doi:10.1016/S0006-3223(03)00703-0


Hickey, C., Chelazzi, L., & Theeuwes, J. (2010). Reward changes salience in human vision via the anterior cingulate. The Journal of
Neuroscience, 30(33), 11096–11103. doi:10.1523/JNEUROSCI.1026-10.2010


Krebs, R. M., Boehler, C. N., Roberts, K. C., Song, A. W., & Woldorff, M. G. (2012). The Involvement of the Dopaminergic Midbrain and Cortico-Striatal-Thalamic Circuits in the Integration of Reward
Prospect and Attentional Task Demands. Cerebral Cortex, 22(3), 607–15. doi:10.1093/cercor/bhr134


psychophysiological study of the stop task. Biological Psychiatry, 51(8), 668–676. doi:10.1016/S0006-3223(01)01290-2


noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology, 33(5), 1028–1037. doi:10.1038/sj.npp.1301487


CHAPTER 7
NEDERLANDSE SAMENVATTING

INTRODUCTIE

Het is uiterst belangrijk dat we ons in het dagelijkse leven kunnen aanpassen aan onze omgeving op een manier die consistent is met onze vooropgestelde doelen. Deze vaardigheid wordt in de psychologie *cognitieve controle* genoemd en is een centraal begrip in deze onderzoeksthes. Cognitieve controle is een concept dat verschillende processen omvat (zoals werkgeheugen, selectieve aandacht, responscontrole en responsinhibitie) en is voornamelijk gelinkt aan activatie in de prefrontale cortex (Miller, 2000). We maken een onderscheid tussen twee vormen van cognitieve controle: proactieve en reactieve controle (gebaseerd op een theorie van Braver namelijk ‘the dual mechanism of control theory’, zie Braver, 2012; Braver et al., 2007).

*Proactieve controle* houdt in dat we dankzij een bepaalde context of cue ons mentaal en/of fysiek reeds kunnen voorbereiden op een nakende gebeurtenis zodat we onze doelen (beter) kunnen bereiken. Bijvoorbeeld, stel dat je als autobestuurder iets verder een voetganger de weg ziet oversteken dan kan je hierop anticiperen door reeds te vertragen (het gaspedaal los te laten). Verschillende cognitieve functies kunnen hierbij een rol spelen, zoals het actief herhalen en bijhouden van doelen, wijzigen van de aandachtsfocus en het invoeren van strategieën. *Reactieve controle* daarentegen treedt op als een laattijdig correctiemechanisme in situaties waarbij we niet kunnen anticiperen op een gebeurtenis. Bijvoorbeeld, veronderstel dat je even niet
aan het opletten bent tijdens het autorijden en plots steekt een voetganger de weg over, dan moet je onmiddellijk de rem kunnen indrukken. Dus, bij reactieve controle worden processen die specifiek gerelateerd zijn aan het uitvoeren van de taak slechts geactiveerd wanneer ze noodzakelijk zijn. Bijgevolg zijn deze twee vormen van cognitieve controle voornamelijk te onderscheiden in functie van tijd, dit wil zeggen wanneer de controleprocessen ingevoerd worden.

Hoewel ze langdurig afzonderlijk werden bestudeerd, wordt tegenwoordig het belang van de interactie tussen motivatie en cognitieve controle erkend (Botvinick & Braver, 2014). Cognitieve controle wordt immers gedreven door motivationele factoren, dit wil zeggen dat wanneer iemand meer gemotiveerd is om een bepaald doel te bereiken zal hiervoor ook meer controle uitgeoefend worden. Verschillende soorten motivators kunnen leiden tot veranderingen in cognitieve controle. In de studies beschreven in het huidige werk werd voornamelijk de rol van beloning als een motivator voor controle onderzocht gezien mensen en dieren inherent streven naar het maximaliseren van positive resultaten (zoals beloning) en het minimaliseren van negatieve resultaten (zoals straf).

Het is algemeen geweten dat de neurotransmittor dopamine een belangrijke rol speelt in beloningsgerelateerde processen. Schultz en zijn collega’s kwamen tot de cruciale bevinding dat dopaminerge neuronen in apen niet enkel actief zijn bij het krijgen van een beloning, maar ook bij het zien van een bepaalde stimulus die een beloning voorspelt (Mirenowicz & Schultz, 1994; Schultz et al., 1997, 1998). Dit werd later bevestigd bij mensen door studies gebruik makend van functionele magnetische resonantie beeldvorming (fMRI) waarin verhoogde activatie in dopaminerge hersenregio’s gevonden werd wanneer cues voorspelde dat een geldbeloning
gewonnen kon worden bij het correct uitvoeren van de taak (zie Knutson et al., 2000). Dopamine lijkt echter ook voornamelijk een rol te spelen wanneer een *inspanning* geleverd moet worden om een beloning te verkrijgen (Kurniawan et al., 2011). Deze inspanning kan zowel fysiek als mentaal zijn en beschrijft in welke mate iemand geëngageerd is om een moeilijke taak uit te voeren (Westbrook & Braver, 2015). Aangezien cognitieve controle een complexe functie is, vereist deze mentale inspanning om zo het vooropgestelde doel te kunnen bereiken.

Beloning heeft doorgaans een positieve invloed op cognitieve functies zoals bijvoorbeeld werkgeugen (Jimura et al., 2010; Taylor et al., 2004), responsinhibitie (Boehler et al., 2012; Rosell-Negre et al., 2014), aandacht (Kiss et al., 2009; Padmala & Pessoa, 2011; Pessoa & Engelmann, 2010) en langetermijn geheugen (Wittmann et al., 2005). Meestal worden deze positieve gedragseffecten gevonden in situaties waarbij men zich kan voorbereiden of een verandering in aandachtsfocus kan implementeren, zoals in paradigma’s die gebruik maken van een belonende cue of context (Jimura et al., 2010; Padmala & Pessoa, 2011; Pochon et al., 2002; Rosell-Negre et al., 2014). Dit impliceert een sterke link tussen beloning en proactieve controle (zie ook Braver, 2012). Echter, er zijn ook enkele studies die aantonen dat beloning een gunstige impact kan hebben op reactieve controleprocessen, dit wil zeggen wanneer er geen voorbereiding kan plaatsvinden, bijvoorbeeld wanneer beloning gekoppeld wordt aan een taak-relevante stimulus (Boehler et al., 2012, 2014; Krebs et al., 2010, 2011).

In dit proefschrift onderzoeken we de onderliggende processen gerelateerd aan proactieve en reactieve controle (en hun potentiële interactie) en de rol van motivatie hierin. Aangezien we proactieve en reactieve controle voornamelijk onderscheiden in functie van tijd, is elektro-
encephalographie (EEG) een interessante methode omwille van zijn hoge temporele precisie. Indien EEG gemeten wordt terwijl een taak wordt uitgevoerd, kunnen we ‘event-related potentials’ (ERPs) bestuderen. Deze ERPs bestaan uit verschillende componenten die onderliggende elektrische hersenactiviteit (en dus cognitieve functies), uitgelokt door een bepaalde stimulus of respons, reflecteren.

EMPIRISCHE STUDIES

In de eerste twee empirische studies (zie hoofdstuk 2 en hoofdstuk 3) bestudeerden we voornamelijk een belangrijke proactieve controlefunctie, namelijk cognitieve voorbereiding, en welke invloed motivatie hierop kan hebben. De mate van cognitieve (en motorische) voorbereiding op een taak wordt voornamelijk weergegeven door de ‘contingent negative variation’ (CNV), dit is een component die optreedt in het cue-target interval vanaf ongeveer 1 seconde voordat de door de cue voorspelde target verschijnt (Connor & Lang, 1969; Tecce, 1972; van Boxtel & Brunia, 1994).

De studie omschreven in hoofdstuk 2 is gebaseerd op het idee dat een beloning voorbereidingsprocessen beïnvloedt via top-down aandachtsprocesses (zie ook Maunsell, 2004). Immers, een eerdere fMRI studie van Krebs et al. (2012) toonde aan dat het anticiperen van beloning en taakmoeilijkheid grotendeels gelijkaardige hersengebieden activeert. Bovendien werd er in sommige regio’s, zoals de dopaminerge middenhersen, een interactie gevonden met maximale activatie wanneer de cue zowel een beloning als een moeilijke trial voorspelde. Echter, gezien fMRI een lage temporele resolutie bevat, is het moeilijk om vast te stellen op welk moment hersenprocessen geactiveerd zijn en dus mogelijks is er een
onderscheid in wanneer de manipulaties in beloning en taakmoeilijkheid een effect hebben. Bijgevolg registreerden we EEG-signalen terwijl proefpersonen het paradigma van Krebs et al. (2012) uitvoerden waarin een cue voorspelt hoe moeilijk de taak zal zijn en of er een mogelijkheid is om een beloning te winnen bij een correct antwoord. De resultaten impliceerden dat tijdens het cue-target interval processen eerder worden gestuurd door beloning dan door taakmoeilijkheid. Immers, zowel de evaluatie van de cue als vroege cognitieve voorbereiding (vroege CNV) werden enkel beïnvloed door beloning. Bovendien observeerden we een interactie in late voorbereidingsfases met maximale late CNV amplitudes in moeilijke doch belonende condities. We concludeerden dat motivatie een belangrijke impact kan hebben op proactieve voorbereidingsprocessen die waarschijnlijk niet beperkt zijn tot top-down aandachtsmechanismen zoals betrokken in de voorbereiding op een moeilijke taak. Echter, in latere stadia van het voorbereidingsproces worden belonings- en moeilijkheidsinformatie geïntegreerd opdat er enkel meer cognitieve voorbereiding voor een moeilijke trial zou worden geïmplementeerd wanneer dit de moeite waard is (belonend).

Het lijkt er dus op dat beloning (en bijgevolg hoogstwaarschijnlijk ook het dopaminerge systeem) een belangrijke rol kan spelen in het gemotiveerd toewijzen van cognitieve bronnen tijdens de voorbereidingsfase om optimaal doelen te kunnen bereiken. In hoofdstuk 3 gaan we hierop verder door het belang van mentale voorbereiding als een alternatieve of aanvullende verklaring voor te stellen voor de resultaten uit een reeks recent gepubliceerde papers van Guitart-Masip et al. (2011, 2012, 2014). Deze auteurs vertrokken van het Pavloviaanse idee dat beloning inherent gekoppeld is aan benadering of het uitvoeren van actie, terwijl straf
gekoppeld is aan vermijding of actie-inhibitie. Bijgevolg stelde zij een design op waarbij een cue de valentie (straf of beloning) en actie (executie/go of inhibitie/no-go) van de trial aangaf (d.i. de ‘orthogonalized go/no-go taak’). Er werd een gedragsmatige link gevonden tussen beloning en het uitvoeren van actie gezien er meer correcte antwoorden werden gegeven in go trials wanneer de cue beloning voorspelde. Belangrijker echter is dat in deze studie onverwachts werd geobserveerd dat tijdens de voorbereidingsfase de activatie van de dopaminerge gebieden voornamelijk gedomineerd werd door actie, met grotere activatie wanneer men zich voorbereidde op een go trial (actie) dan op een no-go trial (inactie), in plaats van door beloning. Gezien andere studies van onze onderzoeksgroep hebben aangetoond dat deze zelfde dopaminerge gebieden ook actief zijn tijdens het voorbereiden op een moeilijke taak (Boehler et al., 2011; Krebs et al., 2012), stellen we dat verschillen in geanticipeerde go en no-go trials ook verklaard kunnen worden door veranderingen in actieve mentale voorbereiding op de taak en niet enkel door actievoorbereiding. In de studie omschreven in hoofdstuk 3 lieten we daarom proefpersonen de orthogonalized go/no-go taak (met enkele extra basiscondities) uitvoeren terwijl we hersenactiviteit vastlegden aan de hand van EEG. Zoals verwacht konden we enkel een duidelijke CNV observeren in geanticipeerde go trials en niet in no-go trials. Bovendien suggereerden ERP componenten gerelateerd aan de target (cirkel links of rechts op het scherm) dat er meer visuele aandacht aan de target werd besteed in go trials en dat er geen actieve responsinhibitie aanwezig was in no-go trials. Dus, deze resultaten bevestigden onze hypothese dat wanneer iemand anticipeert op het uitvoeren van een actie in plaats van het weerhouden ervan, brengt dit (ook) meer non-motorische mentale voorbereiding met zich mee. De toename in activatie in het dopaminerge
systeem in geanticipeerde go trials (zie Guitart-Masip et al., 2011) kan dus hoogstwaarschijnlijk ook te wijten zijn aan meer cognitieve voorbereiding.

In de laatste twee empirische studies (hoofdstuk 4 en hoofdstuk 5) lag de nadruk grotendeels op reactieve controleprocessen in de vorm van reactieve responsinhibitie. Dit is de vaardigheid om een respons te kunnen onderdrukken of annuleren wanneer deze niet langer adequaat is gezien de omstandigheden. Reactieve responsinhibitie wordt voornamelijk onderzocht aan de hand van de stop-signaal taak. Hierbij worden vooral go trials gepresenteerd waarbij zo snel mogelijk een vooropgestelde respons moet gegeven worden bij het zien van de go-stimulus. Echter, af en toe wordt er kort na de go-stimulus een stop-signaal weergegeven en moet men trachten om de door de go-stimulus uitgelokte actie tijdig te onderdrukken (en dus geen respons te geven), dit is een zogenaamde stop trial. De stop-signaal reactietijd (SSRT) is een belangrijke maat voor reactieve responsinhibitie gezien deze aangeeft hoe lang het duurt om het actieproces te annuleren vanaf het verschijnen van het stop-signaal.

Zoals we reeds aanhaalden wordt beloning voornamelijk gelinkt aan het uitvoeren van een actie (Guitart-Masip et al., 2014) en aan proactieve controle (zie inleiding en hoofdstuk 2). Echter, in een recente studie toonden we aan dat beloning ook een positieve invloed kan hebben op reactieve responsinhibitie (in een situatie waarbij geen cues betrokken zijn). Hierbij vonden we snellere responsinhibitie (verminderde SSRTs) wanneer de kleur van het stop-signaal te kennen gaf dat er geld kon gewonnen worden bij het succesvol weerhouden van een respons (Boehler et al., 2012). Bovendien verhoogde de activatie in het ‘responsinhibitienetwerk’ in deze beloningsgerelateerde stop trials. Hoewel dit duidt op toegenomen reactieve
controle, gingen we in **hoofdstuk 4** verder na of onderliggende proactieve controleprocessen effectief uitgesloten zijn in dit paradigma. Hiervoor registreerden we EEG terwijl proefpersonen een belonende stop-signaal taak uitvoerden waarin belonende stops afgewisseld werden met niet-belonende stops (belonend blok) en een gelijkvaardige stop-signaal taak waarin geen enkele trial beloond werd (niet-belonend blok). We vonden evidentie voor het idee van toenemende reactieve controle in belongingstials, maar ook bleek dat een proactieve strategie werd geïmplementeerd waarin proefpersonen strategisch zochten naar de beloningsgerelateerde kleur en dat algemene proactieve aandacht gestegen was in het belonend blok. Dus, we concludeerden dat proactieve controleprocessen ook een rol kunnen spelen wanneer er geen cue aanwezig is en dus mogelijks reactieve controleprocessen ondersteunen om tot een optimaal resultaat te komen.

In **hoofdstuk 5** gingen we verder met het bestudeerden van de onderliggende processen van responsinhibitie. Voornamelijk de neurotransmittor noradrenaline zou een belangrijke rol spelen in het annuleren van een actie. Zo werd aangetoond dat wanneer noradrenerge concentraties in het brein werden verhoogd door middel van medicatie, dan verbeterde ook de inhibitiegerelateerde performantie in de stop-signaal taak (Bari et al., 2009; Humby et al., 2013; Linssen et al., 2012; see also Eagle et al., 2008). We trachtten deze hypothese verder te onderbouwen door epileptische patiënten met een ‘vagus nerve stimulator’ (VNS) de stop-signaal taak te laten uitvoeren. VNS zou immers het aantal epileptische aanvallen verminderen voornamelijk door het activeren van noradrenerge neuronen in the locus coeruleus (Fornai et al., 2011). We vonden dat patiënten die het meeste effect hadden van de behandeling (grootste vermindering in het aantal aanvallen na VNS implantatie) ook de grootste
voordelige effecten in inhibitie (vermindering in SSRTs) vertoonden wanneer VNS was ingeschakeld. Bovendien impliceerde de elektrofysiologische data dat stop-signalen iets eerder visueel verwerkt werden en meer reactieve inhibitie betrokken was wanneer de vagus zenuw gestimuleerd werd. Deze resultaten bieden verdere evidentie voor de rol van noradrenaline in responsinhibitie en duiden op een potentieel positief neurocognitief effect van VNS voornamelijk bij patiënten die reeds het meest therapeutische voordeel hebben.

**ALGEMENE DISCUSSIE**

In het huidige proefschrift trachtten we de onderliggende processen betrokken in reactieve en proactieve controle te onderscheiden aan de hand van EEG. Bovendien bestudeerden we de effecten van motivatie op beide cognitieve processen. In de eerste twee studies benadruktten we het belang van cognitieve voorbereiding als een functie van proactieve controle en toonden we aan dat beloning hier positieve effecten op kan hebben. Verder bevestigden we de rol van noradrenaline en beloning in responsinhibitie en toonden we aan dat proactieve en reactieve controle waarschijnlijk kunnen samenwerken om vooropgestelde doelen zo goed mogelijk te bereiken.

In onze studies manipuleerde we motivatie voornamelijk door middel van beloning (geld). Echter, we gaan ervan uit dat andere motivators zoals straf (en ook intrinsieke factoren) kunnen leiden tot vergelijkbare effecten. Zo is reeds aangetoond dat het vermijden van straf ook een positieve invloed kan hebben op cognitieve controle, vaak in gelijkaardige mate als beloning (Engelmann & Pessoa, 2007; Engelmann et al., 2009; Krawczyk & D’Esposito, 2013; Savine & Braver, 2010; Small et al., 2005). Bovendien
wordt de anticipatie van straf en beloning gerelateerd aan activatie in zeer gelijkaardige hersengebieden (Carter et al., 2009; Krawczyk & D’Esposito, 2013). Dus zowel (de anticipatie van) beloning als straf kunnen fungeren als motivators om meer controle uit te voeren waarschijnlijk via zeer gelijkaardige mechanismen (zoals het verhogen van top-down aandacht). Verder vermoeden we ook dat het effect van motivatie niet beperkt is tot mentale inspanning (zie hoofdstuk 2 en hoofdstuk 3) maar waarschijnlijk ook betrekking heeft op fysieke inspanning. Dit komt overeen met een studie van Schmidt et al. (2012) die suggereert dat cognitieve en fysieke inspanning beroepen op een gemeenschappelijk motivationeel centrum (zoals het striatum en/of de anterieure cingulate cortex) dat vervolgens taak-specifieke hersenregio’s aanstuurt.

De resultaten van hoofdstuk 2 impliceren dat wanneer iemand meer gemotiveerd is om een taak tot een goed einde te brengen deze hiervoor ook meer moeite zal doen. Bovendien vonden we in hoofdstuk 2 en hoofdstuk 3 elektrofyisologische evidentie voor het idee dat correcte feedback meer geapprecieerd wordt in een moeilijke taak en dit voornamelijk wanneer de uitkomst positief is, d.i. beloning gewonnen of straf vermeden kan worden (zie ook Ma et al., 2014), consistent met de ‘effort justification hypothesis’ (zie de cognitieve dissonantie theorie van Festinger, 1957). Deze bevindingen zijn overeenkomstig met studies die hebben aangetoond dat dopaminegerelateerde subcorticale en corticale gebieden een verhoogde activatie vertonen wanneer iemand meer inspanning moet leveren om zijn of haar doelen te bereiken (e.g. Boehler et al., 2011; Krebs et al., 2012; Kurniawan et al., 2011; Vassena et al., 2014). Dit is echter tegengesteld aan het ‘effort-discounting’ idee waarbij wordt verondersteld dat inspanning negatief is en beloning wordt gedevalueerd naar mate men er meer
inspanning voor moet leveren. Dit principe werd ondersteund door studies die vonden dat dopaminegerelateerde corticale en subcorticale hersengebieden meer geactiveerd zijn wanneer minder inspanning nodig is om eenzelfde beloning te verkrijgen (e.g. Botvinick et al., 2009; Croxson et al., 2009). Of er evidentie gevonden wordt voor effort-discounting of voor gemotiveerde inspanning hangt waarschijnlijk af van bepaalde factoren, waarbij gemotiveerde inspanning voornamelijk een rol speelt op het moment dat men zich kan voorbereiden voor een bepaalde taak, waarbij deze voorbereiding bepalend is voor het bereiken van een doel en dus het resultaat afhangt van de prestatie op de taak (zoals in hoofdstuk 2).

In hoofdstuk 4 en 5 konden we dankzij elektrofysiologische data aantonen dat zowel proactieve als reactieve controle van belang zijn binnen eenzelfde paradigma. Proactieve controleprocessen in de stop-signaal taak worden gereflecteerd door de mate van aandacht voor of verwerking van de stimulus. Zo werd reeds geïmpliceerd dat wanneer het stop-signaal beter verwerkt wordt er meer kans is op succesvolle inhibitie (Bekker et al., 2005; Boehler et al., 2009; Verbruggen et al., 2014). Wij vonden echter niet dat er een verschil was in sensorische verwerking van het stop-signaal in succesvolle en gefaald stop trials. Wel werd het stop-signaal beter verwerkt wanneer motivatie hoog was (zie hoofdstuk 4) en iets eerder verwerkt wanneer VNS ingeschakeld was (zie hoofdstuk 5). Hoewel er wat onduidelijkheid bestaat over welke ERP componenten nu precies reactieve responsinhibitie reflecteren, tonen onze resultaten aan dat een specifieke component (de frontale stop P3) gelijkaardige (maar niet identieke) resultaten vertoont als de gedragsmatige reactieve inhibitiemaat (SSRT) en deze suggereerden dat meer reactieve inhibitie geïmplementeerd wordt.
wanneer iemand gemotiveerd is (hoofdstuk 4), en ook wanneer noradrenalineconcentraties verhoogd zijn door VNS (hoofdstuk 5).

Hoewel we aantoonden dat proactieve en reactieve controle in dezelfde taak een rol kunnen spelen (zie hoofdstuk 4), blijft het noodzakelijk om een directe link tussen beide vormen van controle vast te stellen. Bovendien is het nog steeds onduidelijk op welke manier proactieve en reactieve controle interageren. Zo werd er enerzijds verondersteld dat wanneer meer proactieve controle uitgeoefend wordt minder reactieve controle nodig is tijdens het uitvoeren van de taak (Chikazoe et al., 2009; Padmala & Pessoa, 2011) en anderzijds zou meer proactieve controle kunnen leiden tot meer activatie in het reactieve controlenetwerk om tot optimale resultaten te komen (Rosell-Negre et al., 2014; zie ook hoofdstuk 4). Toekomstig onderzoek is dus nodig om een antwoord op deze fundamentele vragen te kunnen bieden.

**Conclusie**

In dit proefschrift toonden we aan dat proactieve en reactieve controle belangrijke functies zijn die beide beïnvloed kunnen worden door motivatie (waarschijnlijk via fluctuatiën in het dopaminerge systeem). Het noradrenerge modulatorische systeem lijkt echter voornamelijk betrokken in reactieve responsinhibitie. De resultaten impliceren bovendien ook dat beide vormen van cognitieve controle elkaar niet uitsluiten en waarschijnlijk zelfs samenwerken om het beste resultaat te kunnen bereiken.


APPENDIX
DATA STORAGE FACT SHEETS

1. Contact details
   ________________________________________________________________
   1a. Main researcher
       ____________________________________________________________
       - name: Hanne Schevemels
       - address: Henri Dunantlaan 2, 9000 Gent
       - e-mail: hanne.schevemels@ugent.be
   1b. Responsible Staff Member (ZAP)
       ____________________________________________________________
       - name: C. Nico Boehler
       - address: Henri Dunantlaan 2, 9000 Gent
       - e-mail: nico.boehler@ugent.be

   If a response is not received when using the above contact details, please send an email to data.pd@ugent.be or contact Data Management, Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2, 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies
   ======================================================================
   * Reference of the publication in which the datasets are reported

   * Which datasets in that publication does this sheet apply to?:
     The sheet applies to all data reported in the study (chapter 2)

3. Information about the files that have been stored
   ======================================================================
   3a. Raw data
       ____________________________________________________________

   * Have the raw data been stored by the main researcher?
     [x] YES    [ ] NO
   If NO, please justify:

   * On which platform are the raw data stored?
     - [x] researcher PC
     - [x] research group file server
     - [ ] other (specify): ...


* Who has direct access to the raw data (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [x] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): ...

3b. Other files
   -----------------------------------------------------------------

* Which other files have been stored?
  - [x] file(s) describing the transition from raw data to reported results. Specify. See methodology and results section in the article
  - [x] file(s) containing processed data. Specify. Pivot tables and figures are available on my personal computer
  - [x] file(s) containing analyses. Specify. See results section in the article (Chapter 2)
  - [ ] file(s) containing information about informed consent.
  - [x] a file specifying legal and ethical provisions. Specify. Documents submitted to the Ethical Committee as well as their letter of approval are saved on my personal computer
  - [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify. ...
  - [ ] other files. Specify. ...

* On which platform are these other files stored?
  - [x] individual PC
  - [ ] research group file server
  - [ ] other: ...

* Who has direct access to these other files (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [x] all members of the research group
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v0.2
% Data Storage Fact Sheet
% Name/identifier study: Preparing for (valenced) action -
the role of differential effort in the orthogonalized go/no-go task
% Author: Hanne Schevernels
% Date: 16 May 2015

1. Contact details

1a. Main researcher

- name: Hanne Schevernels
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: hanne.schevernels@ugent.be

1b. Responsible Staff Member (ZAP)

- name: C. Nico Boehler
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: nico.boehler@ugent.be

If a response is not received when using the above contact details,
please send an email to data.pp@ugent.be or contact Data Management,
Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2,
9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:

* Which datasets in that publication does this sheet apply to?
The sheet applies to all data reported in the study (chapter 3)

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher?
  [x] YES / [] NO
  If NO, please justify:

* On which platform are the raw data stored?
  - [x] researcher PC
  - [x] research group file server
  - [] other (specify): ...
* Who has direct access to the raw data (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): ...

3b. Other files

* Which other files have been stored?
  - [x] file(s) describing the transition from raw data to reported results. Specify. See methodology and results section in the article.
  - [x] file(s) containing processed data. Specify. Pivot tables and figures are available on my personal computer.
  - [ ] file(s) containing analyses. Specify. See results section in the article (Chapter 3).
  - [ ] file(s) containing information about informed consent.
  - [x] a file specifying legal and ethical provisions. Specify.
  Documents submitted to the Ethical Committee as well as their letter of approval are saved on my personal computer.
  - [x] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: ...
  - [ ] other files. Specify: ...

* On which platform are these other files stored?
  - [x] individual PC
  - [ ] research group file server
  - [ ] other: ...

* Who has direct access to these other files (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): ...

4. Reproduction

* Have the results been reproduced independently? [ ] YES / [x] NO

* If yes, by whom (add if multiple):
  - name:
  - address:
  - affiliation:
  - e-mail:

v0.2
% Data Storage Fact Sheet
% Name/identifier study: Electrophysiological evidence for the
involvement of proactive and reactive control in a rewarded
stop-signal task
% Author: Hanne Schevernels
% Date: 16 May 2015

1. Contact details
=================================================================

1a. Main researcher
=================================================================
- name: Hanne Schevernels
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: hanne.schevernels@ugent.be

1b. Responsible Staff Member (ZAP)
=================================================================
- name: C. Nico Boehler
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: nico.boehler@ugent.be

If a response is not received when using the above contact details,
please send an email to data.pp@ugent.be or contact Data Management,
Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2,
9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies
=================================================================
* Reference of the publication in which the datasets are reported:

* Which datasets in that publication does this sheet apply to?
The sheet applies to all data reported in the study (chapter 4)

3. Information about the files that have been stored
=================================================================

3a. Raw data
=================================================================
* Have the raw data been stored by the main researcher?
  [x] YES / [ ] NO
  If NO, please justify:

* On which platform are the raw data stored?
  - [x] researcher PC
  - [x] research group file server
  - [ ] other (specify) ...
* Who has direct access to the raw data (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): …

3b. Other files

* Which other files have been stored?
  - [x] file(s) describing the transition from raw data to reported results. Specify. See methodology and results section in the article
  - [x] file(s) containing processed data. Specify. Pivot tables and figures are available on my personal computer
  - [x] file(s) containing analyses. Specify. See results section in the article (chapter 4)
  - [ ] file(s) containing information about informed consent
  - [x] a file specifying legal and ethical provisions. Specify
  Documents submitted to the Ethical Committee as well as their letter of approval are saved on my personal computer
  - [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: …
  - [ ] other files. Specify: …

* On which platform are these other files stored?
  - [x] individual PC
  - [ ] research group file server
  - [ ] other: …

* Who has direct access to these other files (i.e., without intervention of another person)?
  - [x] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): …

4. Reproduction

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* If yes, by whom (add if multiple):
  - name:
  - address:
  - affiliation:
  - e-mail:

v0.2
1. Contact details

1a. Main researcher

- name: Hanne Schevermels
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: hanne.schevermels@ugent.be

1b. Responsible Staff Member (ZAP)

- name: C. Nico Boehler
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: nico.boehler@ugent.be

If a response is not received when using the above contact details, please send an email to data.pp@ugent.be or contact Data Management, Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2, 9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

Reference of the publication in which the datasets are reported:

* Which datasets in that publication does this sheet apply to?
The sheet applies to all data reported in the study (chapter 5)

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher?
  [x] YES / [ ] NO
  If NO, please justify:

* On which platform are the raw data stored?
  - [x] researcher PC
  - [x] research group file server
  - [x] other (specify): personal computer of Leen De Taeye
256  APPENDIX

* Who has direct access to the raw data (i.e., without intervention of another person)?
  - [ ] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): Leen De Taeye

3b. Other files

* Which other files have been stored?
  - [ ] file(s) describing the transition from raw data to reported results. Specify: See methodology and results section in the article
  - [ ] file(s) containing processed data. Specify: Pivot tables and figures are available on my personal computer
  - [ ] file(s) containing analyses. Specify: See results section in the article (chapter 5)
  - [ ] file(s) containing information about informed consent
  - [ ] a file specifying legal and ethical provisions. Specify: Documents submitted to the Ethical Committee as well as their letter of approval are saved on my and L. Detayos personal computer
  - [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: ...
  - [ ] other files. Specify ...

* On which platform are these other files stored?
  - [ ] individual PC
  - [ ] research group file server
  - [ ] other: ...

* Who has direct access to these other files (i.e., without intervention of another person)?
  - [ ] main researcher
  - [ ] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
  - [ ] other (specify): ...

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  - address
  - affiliation
  - e-mail: