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The effect of neuromodulators on cognitive control

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CHAPTER 1

INTRODUCTION

We are frequently confronted with situations in which multiple responses seem feasible, yet just one is appropriate. If the appropriate response is more obvious than the others, there is no problem. A problem arises, however, when the appropriate response is less obvious than the other ones. How does our brain then understand which response to execute? The mere fact that there are multiple options alerts the brain (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Verguts & Notebaert, 2008, 2009). Because we become more alert, activation increases in specific brain regions, which helps us to choose the appropriate response. Simultaneously, it might be that we learn from the current situation which response we should choose the next time. Learning might occur because the confusion -due to the multiple response options- also elevates the release of the brain chemical dopamine. We hypothesize that dopamine makes the connections between the situation-related neurons and the response-related neurons stronger. The next time that we are in such a situation the appropriate response seems more obvious, because we learned that this is the right thing to do. There is another brain chemical, norepinephrine, which seems to have a similar role in choosing the appropriate response. The current dissertation investigates whether dopamine and norepinephrine indeed improve the ability to select the appropriate response in an ambiguous situation. The introduction will first provide a more elaborate overview of the relevant literature, before introducing the experimental techniques that are used, and the studies we executed.

Theoretical background

The ability to suppress an obvious but incorrect response in favor of a less obvious but appropriate action is called cognitive control (Norman & Shallice, 1986; Verguts & Notebaert,

2008, 2009). Cognitive control is a complex behavior, based on several lower level compounds. A long recognized aspect of cognitive control is working memory (WM), as updating and maintaining the appropriate action goal is essential for optimal cognitive control (Baddeley & Della Sala, 1996; Norman & Shallice, 1986). Another essential aspect is an evaluative system that is triggered by the increased need for cognitive control (Shenhav, Botvinick, & Cohen, 2013). Over the years, several possible triggers for the need of increased cognitive control have been proposed. One possible trigger (and very popular in the literature) is response conflict (Botvinick et al., 2001), meaning that more than one response is simultaneously activated. However, other potential triggers have been proposed, including error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993), error likelihood (Brown & Braver, 2005), volatility (Rushworth & Behrens, 2008), and prediction error (Alexander & Brown, 2011; Silvetti, Seurinck, & Verguts, 2011). Regardless of the exact nature of the trigger, all proposals agree that the anterior cingulate cortex (ACC) evaluates the need for increased cognitive control (Shenhav et al., 2013). This need can be met by recruiting additional resources to overcome a behavioral impasse. The ACC projects to both the midbrain ventral tegmental area (VTA; Devinsky, Morrell, & Vogt, 1995; Geisler, Derst, Veh, & Zahm, 2007) and the midbrain locus coeruleus (LC; Aston-Jones & Cohen, 2005; Jodo, Chiang, & Aston-Jones, 1998), which release dopamine (DA) and norepinephrine (NE), respectively. Both DA and NE might serve to provide such additional resources. According to the adaptation-by-binding model (Verguts & Notebaert, 2008, 2009) the effect of DA and NE is implemented by Hebbian learning (Hebb, 1949). Hebbian learning entails that the connection (synaptic efficiency) between neurons that fire together, is strengthened. Recent research shows that Hebbian learning is implemented by long-term potentiation (LTP; Lisman, Grace, & Duzel, 2011) and that both DA and NE improve LTP (Lisman et al., 2011; Sara, 2009). In a situation that requires cognitive control, the neurons that fire together are typically the stimulus-related neurons and the response-related neurons; according to the model, they become more strongly connected as a consequence. When the same or a similar situation is encountered again and the stimulus-related neurons are again active, the appropriate response will be more strongly activated as a result of this learning process. In other words, one role for Hebbian learning in cognitive control might be that response selection in future situations is improved due to learning of response selection in the

current situation. The current dissertation investigates whether DA and NE indeed improve the ability to select the appropriate response in an ambiguous situation.

Cognitive control is experimentally studied by congruency tasks such as the Stroop task (Stroop, 1935), the Simon task (Simon, 1969), and the flanker task (Eriksen & Eriksen, 1974). In congruency tasks two conditions are compared. One condition consists of trials that require increased cognitive control (incongruent condition; simulating the ambiguous situation mentioned in the previous paragraph); one condition consists of trials that do not require increased cognitive control (congruent condition). In the current dissertation only the flanker task is used, although in different versions in different chapters. In each trial in the flanker task, five figures are shown, the middle being the target, the two on the left and the two on the right being the flankers. In the arrow flanker task, the figures are left- and right-pointing arrows, and the corresponding responses are a left or right key press, respectively. In congruent trials all arrows point in the same direction. In incongruent trials, the flanker arrows point opposite to the direction of the target, therefore inducing a need for increased cognitive control.

As pressing left for a left-oriented arrow and pressing right for a right-oriented arrow are over-learned stimulus-response (SR) mappings, we developed a new version of the flanker task, to investigate cognitive control in novel situations, requiring new SR binding. Similarly to the arrow flanker task, in each trial of the novelty flanker task five figures are shown. The middle figure again is the target; the two figures left and right are the flankers. Different from the arrow flanker task that had just two figure options (left and right arrow), the novelty flanker task has four figure options. As all the flanker figures in one trial are all identical, this results in 16 different stimuli, four of which are congruent and 12 incongruent. Congruent and incongruent trials are presented in equal proportions (50%) and in a randomized order.

The efficiency of cognitive control can be determined by comparing the behavioral response to the congruent and incongruent condition. As the incongruent trials evoke both the appropriate and the inappropriate response, selecting the appropriate response is more difficult, resulting in prolonged reaction times (RTs). The difference in RT between the congruent and incongruent conditions indexes the ability to suppress the interference evoked by conflicting or distracting stimuli (congruency effect). It is typically found that interference suppression following an incongruent trial is improved compared to interference suppression following a

congruent trial. In particular, the congruency effect is smaller after an incongruent than after a congruent trial (Gratton effect; Gratton et al., 1992). This Gratton effect is typically interpreted as expressing how well the previously experienced conflicting situation (previous trial) adapts us for dealing with the current situation (current trial) Therefore, it is sometimes called post-conflict adaptation.

We hypothesize that both interference suppression and post-conflict adaptation are modulated by neuromodulators like DA and NE. Therefore we will measure and manipulate both DA and NE in multiple ways and investigate their effect on interference suppression and post-conflict adaptation. The initial proposal for this dissertation was to scan LC activity on a trial-to-trial basis and analyze whether LC activation predicted interference suppression. The LC is located in the brain stem, close to the fourth ventricle, it has an intersection of approximately a square millimeter, and a length of approximately a centimeter (Keren, Lozar, Harris, Morgan, & Eckert, 2009; Nieuwenhuis & Jepma, 2011). Particularly the first three characteristics make it difficult to scan the LC by functional magnetic resonance imaging (fMRI). Our aim was initially even more ambitious, as we intended to investigate whether previous trial LC activation predicted current trial interference suppression. Whilst preparing this study I often wondered, like Boromir reflected on the Ring: “It is a strange fate that we should suffer so much fear and doubt over so small a thing. Such a little thing.” (from The Lord of the Rings: The Fellowship of the Ring). It took a while, but eventually we realized that scanning the LC to predict interference suppression on the next trial was a kind of a hopeless quest. However, we found alternative routes to accomplish our quest of investigating the effect of neuromodulators in cognitive control, which resulted in three experimental studies. As the studies use many different experimental techniques, I will first provide an overview of the techniques that were used.

Experimental techniques

The first experimental technique that was used, is pupil dilation. Pupil dilation is a non-invasive technique that measures both phasic and tonic NE release (Nieuwenhuis & Jepma, 2011). The LC controls pupil dilation as the LC projects via two intermediate synapses to both the sphincter and dilator muscle of the iris (Samuels & Szabadi, 2008). Hence, increased NE release will dilate the pupil, whereas decreased NE will constrict the pupil. This has been experimentally demonstrated in rodents: Clonidine (a NE agonist) dilates the pupil, whereas yohimbine (a NE antagonist) reduces pupil size (Koss, 1986). Pupil dilation can be measured using eye track recordings.

As a non-invasive technique to measure DA release we recorded eye blinks. Eye blinking as a measure of DA activity is typically used to investigate tonic DA activity. The average number of blinks per minute (eye blink rate (EBR)) in humans is increased after administering a DA agonist (apomorphine; Blin, Masson, Azulay, Fondarai, & Serratrice, 1990). Clinical studies in DA-related diseases provide further evidence. Parkinson patients (with impaired DA functioning) show decreased EBR (Deuschl & Goddemeier, 1998) and patients diagnosed with schizophrenia (with increased DA uptake in the striatum) show elevated EBR (Freed et al., 1980; Karson et al., 1983). The correlation between DA and eye blinks is further confirmed by examining EBR in users of illegal substances (Colzato, van den Wildenberg, & Hommel, 2008; Kowal, Colzato, & Hommel, 2011). Eye blinks are typically recorded with the ocular electrodes in an EEG set-up. As we investigated eye blinks simultaneously with pupil dilation, eye blinks were derived from eye track recordings.

In addition to recording measures of endogenous DA and NE, we experimentally manipulated NE. The LC can be stimulated to release NE by vagus nerve stimulation (VNS). VNS is an electrical device implanted under the collar bone, and connected by a wire to an electrode around the vagus nerve. As the vagus nerve ends at the brainstem, close to the LC, stimulating the vagus nerve activates the LC, thus releasing NE (Hassert, Miyashita, & Williams, 2004; Raedt et al., 2011; Roosevelt, Smith, Clough, Jensen, & Browning, 2006). VNS is applied in pharmaco-resistant patients with epilepsy as it reduces mean monthly seizure frequency and

increases quality of life in many of them (Ben-Menachem, 2002; DeGiorgio et al., 2000; Weinshenker & Szot, 2002). Thirty-five to 59% of the VNS patients benefits from the therapy (responders), as they exhibit a 50 to 100% reduction in mean monthly seizure reduction. In contrast, others hardly benefit from the therapy (De Herdt et al., 2007; non-responders, with 50% to 0% mean monthly seizure reduction; DeGiorgio et al., 2000).

Our final methodology was a pharmacological manipulation of both DA and NE. To investigate the effect of DA and NE we selected two agents that in single-dose intake would enhance selective neuromodulator release. To account for the placebo effect, participants not only were administered with the DA and NE agent, but also with a placebo. Both agents should have an activating effect and have similar pharmacokinetic properties. This required careful consideration as some agents have a different effect in single-dose application compared to their therapeutical (long-term) use (Jocham, Klein, & Ullsperger, 2011). Considering the above, our DA agent of choice was amisulpride, and our NE agent of choice reboxetine. The individual response to a DA agent depends on the subject's working memory (WM) performance (Cools & D'Esposito, 2011). The WM span test examines how many 'chunks of information' can be kept active in WM and manipulated at the same time. Similarly, the individual response to an NE agent depends on trait personality (Itoi & Sugimoto, 2010; Ressler & Nemeroff, 2000). A less anxious personality predicts an enhanced response to the NE drug, whereas a high anxious personality predicts a decreased response (De Rover et al., 2012). Prior to executing the study, many more aspects than just pharmacokinetic agent properties required consideration. Participants' safety required developing questionnaires serving as a first examination whether drug intake was safe to them. The questionnaire was based on the known contra-indications and side-effects of amisulpride and reboxetine.

The previously described techniques have been applied in a set of three experiments. The remainder of this chapter provides a brief preview of the three studies that are reported in chapter two to four.

Outline of the dissertation

In chapter two we investigated how endogenous DA and NE influence cognitive control in a well-known situation. Being in a situation that requires cognitive control might activate nuclei like the VTA and LC to release neuromodulators such as DA and NE. We hypothesized that both DA and NE improve post-conflict adaptation. To investigate the effect of DA and NE we needed a measure to indicate neuromodulator release on a trial-to-trial basis. As previously discussed, scanning the LC using fMRI was not an option. Fortunately, the eye is not only the mirror of the soul, but the mirror of brain activity as well. DA release can be measured (indirectly) by increased eye blinking, and NE release can be measured (indirectly) by increased pupil dilation (see above). Eye track recordings provide us with pupil size measurements on a millisecond scale. From this measure, both eye blinks and pupil dilation can be derived. Participants executed the arrow version of the flanker task whilst pupil size was recorded by eye tracking. The arrow flanker task investigates effectiveness of cognitive control in a well-known situation. Measuring DA and NE release on a trial-to-trial basis allowed us to investigate whether stimuli-evoked DA and/or NE release is sufficient to enhance post-conflict adaptation.

In chapter three we investigated how experimentally manipulated NE influences cognitive control in a well-known situation. Pupil dilation as an index of NE release is only an indirect measure. Directly manipulating NE and investigating its effect on cognitive control would provide additional evidence for the effect of NE in cognitive control. We therefore investigated the effect of NE by VNS in cognitive control. VNS patients executed the arrow flanker task twice, once on VNS and once off VNS. Our patient sample consisted of both responders and non-responders. Hence we could compare cognitive control during increased NE level relative to baseline NE level in a well-known situation. We hypothesized that increased NE would improve cognitive control. We further hypothesized that cognitive control during VNS would be improved in responders, but not in non-responders.

In the fourth chapter we investigated the effect of pharmacologically manipulated DA and NE in cognitive control, both in a well-known and in a novel situation. The study in chapter three only manipulated NE, but also manipulating DA would provide complementary proof.

Furthermore, both studies described in chapter two and three only tested the effect of DA and/ or NE in a well-known situation. Cognitive control in novel situations might depend on different processes of resource allocation. Therefore participants did not only execute the arrow flanker task, but the novelty flanker task as well. Participants were extensively screened, both by a general medical doctor and by a psychiatrist, before being included in the study sample. Based on their pharmacokinetic properties amisulpride was chosen to manipulate DA and reboxetine (brand name Edronax) was chosen to manipulate NE. Both agents have successfully been used before. As it is known that individuals respond differently to DA and NE agents, we added individual difference indices. To account for DA-related individual differences, the WM span task of the Wechsler adult intelligence scale III-NL (WAIS-III-NL; Klinkenberg & Kooij, 2005) was administered. Furthermore, to account for NE-related individual differences, the Liebowitz social anxiety scale (LSAS; Heimberg et al., 1999; Van Balkom, De Beurs, Hovens, & Van Vliet, 2004) was administered.

Together, the studies described in chapter two to four provide a broad sample of the effect of DA and NE in both well-known and novel situations. Both endogenously evoked neuromodulators as well as experimentally manipulated effects can be compared. As the individual studies are described in chapter two to four, in the fifth chapter I will subsequently summarize the findings of the studies. This would hopefully lead to a unified view on the effect of DA and NE in cognitive control and point to future directions in research.

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CHAPTER 2

BLINKING PREDICTS ENHANCED COGNITIVE CONTROL[1]

Recent models have suggested an important role for neuromodulation in explaining trial-to-trial adaptations in cognitive control. The adaptation-by-binding model (Verguts & Notebaert, Psychological review, 115(2), 518–525, 2008), for instance, suggests that increased cognitive control in response to conflict (e.g., incongruent flanker stimulus) is the result of stronger binding of stimulus, action, and context representations, mediated by neuromodulators like dopamine (DA) and/or norepinephrine (NE). We presented a flanker task and used the Gratton effect (smaller congruency effect following incongruent trials) as an index of cognitive control. We investigated the Gratton effect in relation to eye blinks (DA related) and pupil dilation (NE related). The results for pupil dilation were not unequivocal, but eye blinks clearly modulated the Gratton effect: The Gratton effect was enhanced after a blink trial, relative to after a no-blink trial, even when controlling for correlated variables. The latter suggests an important role for DA in cognitive control on a trial-to-trial basis.

[1] Van Bochove, M. E., Van der Haegen, L., Notebaert, W., & Verguts, T. (2013). Blinking predicts enhanced cognitive control. *Cognitive, Affective, and Behavioral Neuroscience, 13*, 346-354, doi: 10.3758/s13415-012-0138-2.

Introduction

Much of our behavior is driven by routines. However, when an unexpected situational change occurs, we are able to overcome our automatic response in favor of a more appropriate one. This is referred to as cognitive control. For example, when our familiar road to home is blocked, we can suppress our urge to drive as usual and take the advised alternative route. The next day, taking the detour is already easier, perhaps due to the already formed association between the roadblock and the detour.

According to extant models, a behavioral impasse, like the roadblock, constitutes a trigger for cognitive control (e.g., conflict-monitoring model, Botvinick, Braver, Barch, Carter, & Cohen, 2001; error likelihood model, Brown & Braver, 2005; supervisory attentional system model, Norman & Shallice, 1986). For example, in the conflict-monitoring model, cognitive control is triggered by conflict between simultaneously active responses, addressing the issue of how the cognitive system knows when cognitive control is needed. The adaptation-by-binding model (Verguts & Notebaert, 2008, 2009) further specifies the mechanism of how such control may be implemented and addresses how the cognitive system learns to select the correct response. This model proposes that cognitive control emerges from fast binding between stimulus, action, and context events. Furthermore, the model proposes that such stimulus–action–context binding is modulated by salient (arousing) stimuli that arrive simultaneously. In the context of a flanker task (Eriksen & Eriksen, 1974; see Fig. 1), for instance, the response conflict caused by incongruent flankers increases binding between task demand representations, target stimulus, and response. The implementation of cognitive control upon the detection of conflict is typically considered as a reactive form of control, since one reacts upon the detection of difficulties. Other models describe how the system can be optimized in anticipation of difficulties, which is referred to as proactive control (Braver, 2012).

A frequently used index of cognitive control is the Gratton effect. It means that the congruency effect (difference in response time (RT) between incongruent and congruent stimuli) is smaller after incongruent than after congruent trials (Gratton, Coles, & Donchin, 1992). It has been argued by Hommel, Proctor and Vu (2004) and Mayr, Awh and Laurey (2003) that the Gratton effect is due to mere feature integration or repetition effects, respectively. However, recent research provides evidence that the effect is at least partly driven by cognitive control

(Notebaert & Verguts, 2007; Ullsperger, Bylsma, & Botvinick, 2005). The model accounts for the Gratton effect, since it proposes that active representations (generally, task-relevant associations) are bound together after conflict. This will result in a stronger focus on task-relevant information because top-down control (dorsolateral prefrontal cortex) is increased, and target–response connections are strengthened. Although the model explains the Gratton effect by means of stronger connections, it does capture the generality of the effect, as long as the same relevant dimension is used. When the task-relevant dimension changes between two trials, the model explains no or a reversed Gratton effect. This has indeed been empirically observed (Notebaert & Verguts, 2008).

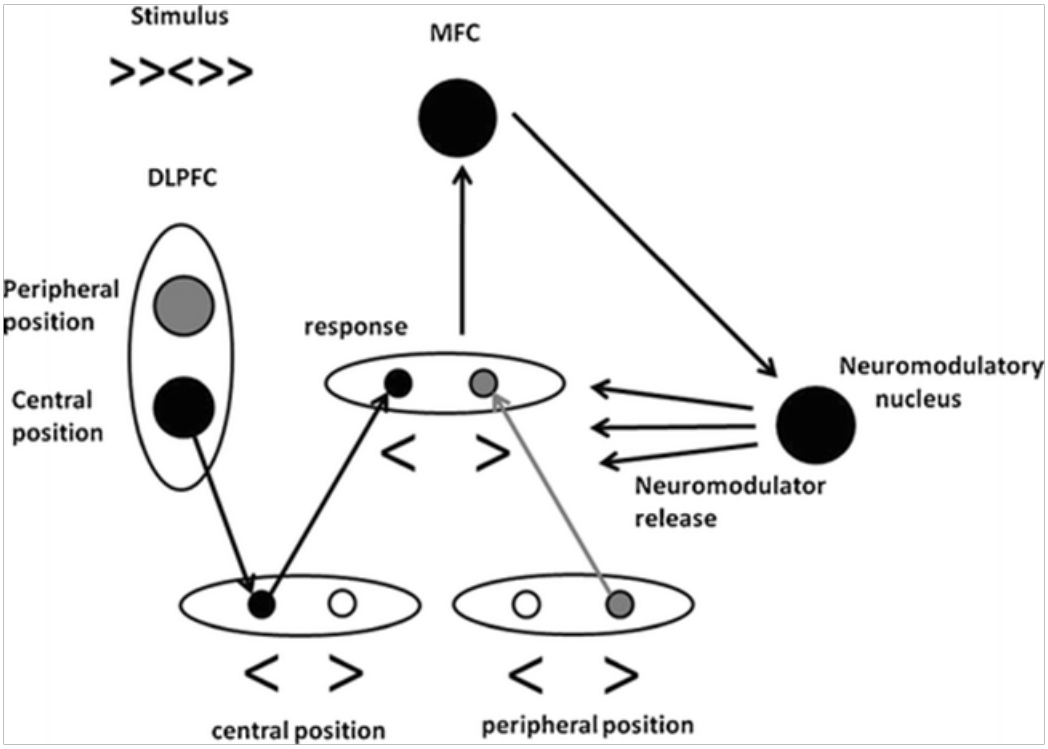

Figure 1

Schematic model (after Verguts & Notebaert, 2009) for the flanker task (incongruent stimulus, presented upper left). There are two visual input layers, representing input from the central position and the peripheral position. The dorsolateral prefrontal cortex (DLPFC) represents task demands. When instructed to respond to the central position (central arrow of the flanker stimulus), this dimension is prioritized due to the top-down influence of the DLPFC. Because of the activation of the peripheral position, the incorrect answer also becomes slightly activated. This simultaneous activation at the response layer is registered as conflict in the medial frontal cortex (MFC). The MFC consequently activates the neuromodulatory nucleus to release the neuromodulator. The neuromodulator increases binding between the most active representations, which results in increased task-relevant connections

There is good support for the hypothesis that conflict is detected in the medial frontal cortex (MFC; Botvinick et al., 2001). In the adaptation-by-binding model, this triggers the norepinephrine (NE) system in the locus coeruleus (LC), leading to increased binding in the cortex and hippocampus. This theory is consistent with the fact that (1) the MFC projects to the LC (Jodo, Chiang, & Aston-Jones, 1998; see Aston-Jones & Cohen, 2005, for a review), (2) arousal enhances memory representations (e.g., McGaugh, 2006), (3) NE has been described as a "now print" signal (Harley, 2004; Livingston, 1967; Sara, 2009), (4) NE enhances binding by modulating Hebbian learning (Harley, 2004), and (5) Hebbian learning can develop rather quickly (e.g., within five trials, the smallest number tested in the paradigm reviewed in Weinberger & Bakin, 1998). However, dopamine (DA) is also described as a major learning signal in the brain (Reynolds, Hyland, & Wickens, 2001) and is also related to Hebbian learning. In vivo recordings in rodents show that DA (via D1 receptors) plays an essential role in both early and late long-term potentation in learning. In particular, DA may interact with the NMDA receptor, which is thought to implement Hebbian plasticity at the cellular level (Granado et al., 2008; see Lisman, Grace, & Duzel, 2011, for a review). FMRI research in humans shows that VTA activation, which suggests DA release, activates cortical areas related to cognitive control and predicts enhanced cognitive control in a task-switching paradigm (Savine & Braver, 2010). Similar to NE, DA is released after arousing events (see Bromberg-Martin, Matsumoto, & Hikosaka, 2010, for a review). Moreover, binding between a visual stimulus and a subsequent action is suggested to be mediated by DA (Colzato, van Wouwe, & Hommel, 2007; Colzato et al., 2012; Schnitzler & Gross, 2005) via the D1 receptor (Colzato & Hommel, 2008). Besides the D1 receptor type, there is the D2 receptor type, which is involved in cognitive flexibility (Van Holstein et al., 2011). In the present article, we address only D1 receptor type modulation.

Hence, either NE or DA (or both) could be the relevant neuromodulator for implementing cognitive control. Consistent with a role for DA (related to reward processing; e.g.,Schultz, 1998), Braem, Verguts, Roggeman, and Notebaert (2012) found that reward on a (correct) previous trial increases the Gratton effect, especially in highly reward-sensitive persons (but see Stürmer, Nigbur, Schacht, & Sommer, 2011; Van Steenbergen, Band, & Hommel, 2009). Here, we follow a complementary approach: Instead of presenting affective stimuli, we measure markers of the autonomic nervous system to investigate its modulation of the Gratton effect. To investigate the role of NE in cognitive control, we measure pupil dilation on a trial-to-trial basis.

Pupil dilation provides a measure of both tonic and phasic LC activation in humans (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; see Nieuwenhuis & Jepma, 2011, for a review). The LC is the main source of NE in the brain (Sara, 2009) and is connected via two intermediate synapses to both the sphincter and dilator muscle of the iris (Samuels & Szabadi, 2008). Moreover, NE agonists (e.g., clonidine) dilate the pupil, whereas NE antagonists (yohimbine) reduce pupil size (Koss, 1986). Hence, pupil dilation can act as an indirect measure of NE release. At the same time, to investigate the role of DA, we measure eye blinks on a trial-to-trial basis. Support for the assumption that eye blinks are related to DA processing comes from investigations of eye blink rate (EBR). DA increases the EBR, in both humans and rats (Blin, Masson, Azulay, Fondarai, & Serratrice, 1990; Taylor et al., 1999). Furthermore, Parkinson patients (with impaired DA functioning) exhibit decreased EBR (Deuschl & Goddemeier, 1998), and patients diagnosed with schizophrenia (with increased DA uptake in the striatum) show elevated EBR (Freed et al., 1980; Karson et al., 1983). Also, recreational cocaine users exhibit a reduced EBR, consistent with their reduced D2 receptor density (Colzato, van den Wildenberg, & Hommel, 2008). Similarly, there is a decreased EBR in chronic cannabis users (Kowal, Colzato, & Hommel, 2011). Moreover, a link between EBR, DA, and cognitive control was established by Dreisbach et al. (2005), demonstrating an influence of EBR on perseveration and distractibility, which was modulated by DRD4 polymorphism.

The adaptation-by-binding model (Verguts & Notebaert, 2008, 2009) proposes that the Gratton effect results from binding. Together with the reviewed literature on Hebbian learning and neuromodulation, the model motivates our hypotheses that NE and DA, as they relate to binding, might play a role in conflict adaptation. Accordingly, we investigated the modulatory influence of pupil dilation (putative marker of NE) and eye blink (putative marker of DA) on the Gratton effect. More specifically, we tested whether congruency predicts increased pupil dilation and blinking and whether pupil dilation and/or blinking predicts increased adaptation (larger Gratton effect) from trial to trial.

Method

Participants

Forty-eight students participated for a monetary reward of 8 Euros (mean age = 22.1 years [range, 18–33], 38 female, 46 right-handed). All participants gave their written informed consent.

Apparatus

Eye data were recorded using an Eye Link 1000 Tower Mount (SR Research, Ontario, Canada) eye tracker. Sample rate was 500 Hz. Responses were collected with a Microsoft SideWinder ® Plug & Play Game Pad.

Stimuli

The stimuli on each trial of the flanker task consisted of five arrows (e.g., >><>>). The middle arrow was the target stimulus; the two arrows left and right of the target arrow were flanker arrows. Arrows were oriented left (<) or right (>). This resulted in four different stimuli, since both target directions had congruent and incongruent flankers. The stimuli were presented in a random order in equal proportions. The arrows were presented in black on a white background. All stimuli had the same luminance to prevent luminance confounds on the pupil dilation recordings. An error was followed by a low tone.

Procedure

Participants were instructed to respond to the direction of the target arrow by pressing the left or right button with their left or right index finger, respectively. In order to acquire enough trials with pupil dilation data, we asked participants to blink less than usual, but not to refrain from blinking. If they experienced dry eyes, they were encouraged to blink during drift correction or breaks. Calibration and validation of gaze position were carried out with a 9-point grid. Viewing was binocular throughout the experiment, but pupil dilation was recorded for the right eye only. A chinrest and a brace at forehead height were used to restrict head movements. Participants

executed a training block consisting of 20 trials; then they performed eight test blocks consisting of 100 trials each. In both the training block and the test blocks, each trial started with stimulus presentation for 200 ms. In the case of a correct response, the stimulus was followed by a fixation cross during 2,000 ms. An incorrect response was followed by a low tone for 250 ms, after which again a fixation cross was presented during 4,000 ms. To ensure accurate eye data collection, we applied drift correction for gaze position every tenth trial. In order to investigate a possible effect of luminance, half of the participants (n = 22) executed the experiment in a brightly lit room, and the other half of the participants (n = 26) in a dimly lit room. Within each group, we held luminance constant. The experiment lasted for approximately an hour.

Data analysis

Only correct trials were analyzed, with RT as the dependent variable. Since only incorrect trials were followed by feedback, trials of interest contained no feedback. The data were analyzed with both repeated measures ANOVA and hierarchical generalized linear modeling (HGLM) applying the "summary statistic" approach (Lorch & Myers, 1990; Notebaert & Verguts, 2007). When the dependent variable was continuous, the first-level model was linear (so HGLM was actually just a hierarchical linear model); when the dependent variable was binary (i.e., in the case when blink was the dependent variable), the first-level model was logistic. The HGLM procedure allows taking into consideration several correlated factors simultaneously by including them as regressors. For instance, we expect that pupil dilation will be affected by congruency. Therefore, the factor previous pupil dilation will be correlated with the factor previous congruency. Hence, if we want to show that previous pupil dilation modulates the Gratton effect, it is important to show that this effect is not caused by previous congruency. HGLM will reveal unique variance that is explained by each factor independently. In this way, HGLM is complementary to the more standard ANOVA approach. Results that turn out to be consistent across analyses can be considered robust. In the HGLM analyses, for each individual participant separately, we applied linear (or logistic in the case in which blink was the dependent variable) regression, including each trial as one data point. Incorrect trials were not included, nor were trials following errors in the n−1 regressors included. The regression coefficients (betas) for the different regressors from the individual-subject analyses were subsequently investigated with one-sample t-tests, testing whether they deviated from zero at the group level.

Trials with missing pupil data were considered blink trials (containing one or more blinks) and, accordingly, were included in the blink analysis. Since we asked participants to blink less than usual, but not to refrain from blinking, there was, on average, an equal number of blink and pupil trials. In the HGLM analysis, the regressors were congruency (Cn), previous-trial congruency (Cn−1), interaction between congruency and previous-trial congruency (i.e., the Gratton effect; Cn*Cn−1), blink (Bn), previous-trial blink (Bn−1), Cn*Bn−1, and finally Cn*Cn−1*Bn−1. Both congruency and blink were modeled with dummy variables (congruent = 0, incongruent = 1; no blink = 0, blink = 1). Since there was a small break after every tenth trial to perform drift correction, every tenth trial was excluded from all previous-trial regressors.

For the pupil analyses, raw pupil data was preprocessed using MATLAB 7.9. Only trials without blinks were included in the pupil dilation analysis. From each trial, a window of 2 s starting at stimulus presentation was analyzed. As baseline, we took pupil dilation at the start of each trial (first three samples). Analyses based on data with just the first sample of each trial as baseline yielded very similar results. Baseline pupil dilation at the start of each trial was subtracted from maximum pupil dilation within a trial to prevent an influence of drift. This defined pupil size on each trial. For the ANOVA, a pupil was defined as large if it was in size percentile 50 or more for that subject, and as small otherwise. In the HGLM analysis, the regressors were similar to those for the blink analyses, except that pupil size on the current (Pn) and previous trial (Pn−1) replaced the blink variables. Congruency was again modeled with a dummy variable, but pupil dilation was continuous (the larger the number [scale in arbitrary units], the larger the pupil). As in the blink HGLM analysis, every tenth trial was excluded from previous-trial regressors.

Results

Pupil data were collected on 52 % of the trials. Blinking occurred on 42 % of the trials. The average error rate was 6 %.

Before the main analysis, we first checked whether congruency on the current trial predicts blink on the current trial with an HGLM analysis with congruency on the current trial as regressor. This was indeed the case, $t(47) = 1.878$, $SE = .041$, $p = .034$, one-sided, indicating that blinking increases on incongruent trials, as compared with congruent trials.

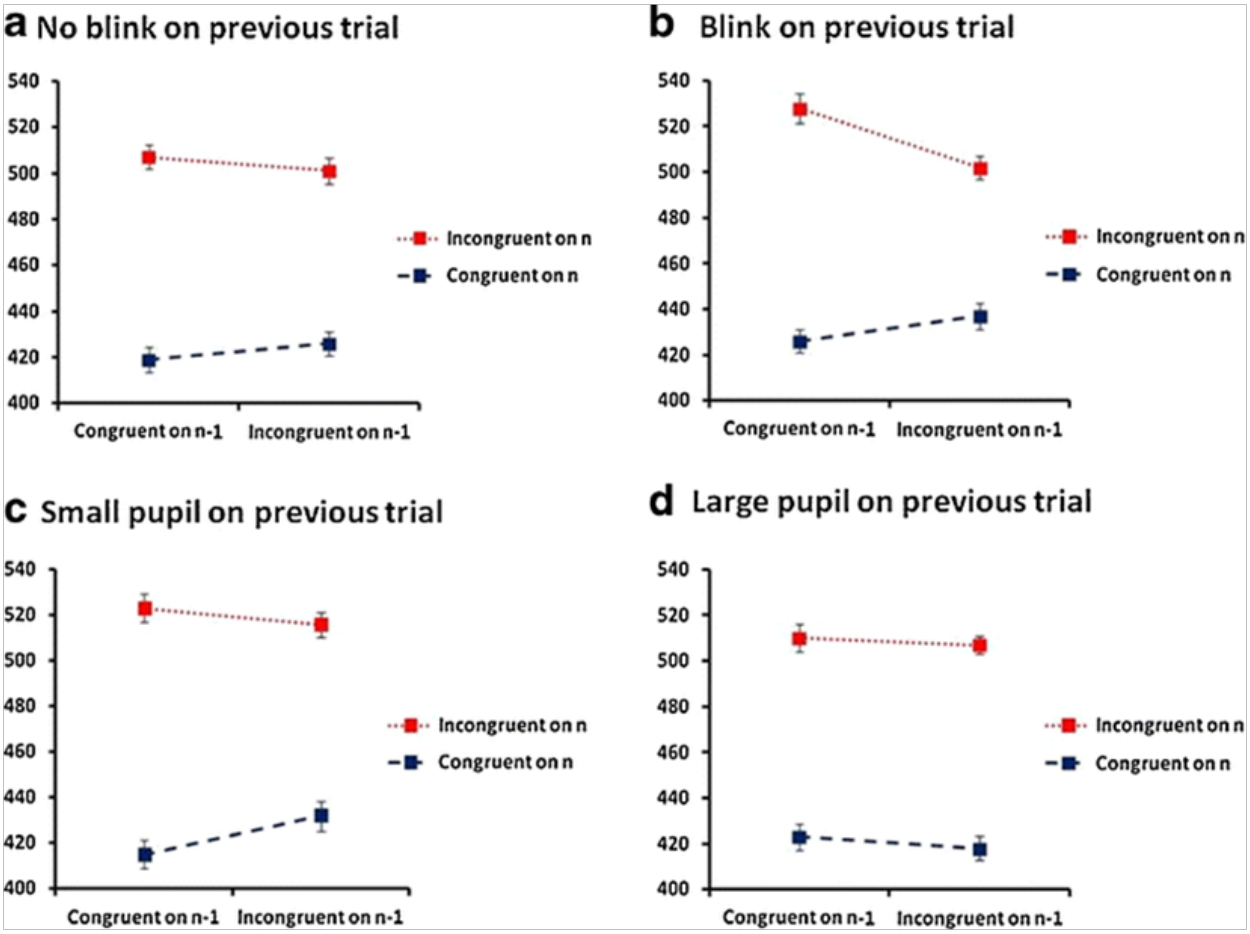

Figure 2

The Gratton effect after a no-blink trial (a), after a blink trial (b), after a small pupil trial (c), and after a large pupil trial (d). The y-axis shows average RTs; for each average, the confidence interval is depicted

We applied a blink ANOVA on RTs, with congruency on the current trial, congruency on the previous trial, and blink (yes / no) on the previous trial as independent variables. We found a significant main effect for congruency on the current trial, $F(1, 47) = 693$, $MSE = 938$, $p < .001$,

indicating that congruent trials are faster (see Fig. 2a, b). We also obtained a significant main effect for congruency on the previous trial, $F(1, 47) = 5.13$, $MSE = 238$, $p = .03$, replicating earlier reports of postconflict slowing (Verguts, Notebaert, Kunde, & Wühr, 2011). There was a significant two-way interaction between congruency on the current trial and congruency on the previous trial, $F(1, 47) = 37.5$, $MSE = 383$, $p < .001$, indicating an overall Gratton effect. The three-way interaction between congruency on the current trial, congruency on the previous trial, and blink on the previous trial was also significant, $F(1, 47) = 16.4$, $MSE = 206$, $p < .001$, indicating a larger Gratton effect after a blink trial, as compared with after a no-blink trial (see Fig. 2a, b). Post hoc tests revealed that participants had a Gratton effect after a blink, $F(1, 47) = 43.4$, $MSE = 365$, $p < .001$, but also after a no-blink trial, $F(1, 47) = 8.53$, $MSE = 223$, $p = .005$. We also found a significant main effect for blink on the previous trial, $F(1, 47) = 5.80$, $MSE = 1{,}592$, $p = .02$, and a significant two-way interaction between congruency on the previous trial and blink on the previous trial, $F(1, 47) = 6.43$, $MSE = 243$, $p = .02$.

In the HGLM blink analysis (see Table 1), we found a significant main effect for congruency (Cn), $t(47) = 18.4$, $p < .001$, $\beta = 90.3$, indicating that participants were slower on incongruent trials. We found a significant two-way interaction between congruency on the current and the previous trials (Cn*Cn−1), $t(47) = -3.32$, $p = .002$, $\beta = -14.6$, indicating an overall Gratton effect. Importantly, and consistent with the blink ANOVA, we found a significant three-way interaction between congruency on the current trial, congruency on the previous trial, and blink on the previous trial (Cn*Cn−1*Bn-1), $t(46) = -2.22$, $p = .03$, $\beta = -11.4$, indicating a larger Gratton effect on trials following a blink trial, as compared with trials following a no-blink trial (cf. Fig. 2). This shows that blinking on the previous trial has a significant effect on cognitive control even after controlling for the effect of congruency on the current and previous trials. We also found a significant main effect for blink on the current trial (Bn), $t(46) = 2.21$, $p = .03$, $\beta = 5.98$. There were no significant differences between the groups (tested under bright vs. dimmed light conditions; all two-sample $ts < 1.48$, all $ps > .15$).

Table 1

Blink analysis: coefficients of the HGLM analysis with response time as dependent variable

Predictor	Cn	Cn-1	Bn	Bn-1	Cn*Cn-1	Cn*Bn-1	Cn*Cn-1*Bn-1
Beta	90.3	5.70	5.98	-1.83	-14.6	3.93	-11.4
SE	4.91	3.05	2.71	3.24	4.38	5.24	5.13
Sig.	.000	.07	.03	.58	.002	.46	.03
T stat.	18.4	1.87	2.21	-.564	-3.32	.750	-2.22
Df.	47	47	46	46	47	46	46

Note. Predictors were congruency on the current trial (Cn), congruency on the previous trial (Cn−1), blink on the current trial (Bn), blink on the previous trial (Bn−1), two two-way interaction terms, and a three-way interaction term. All p values are two-sided. A negative beta value indicates a faster response

To examine the role of pupil dilation, before the main analysis, we first checked whether congruency on the current trial predicts pupil dilation with an HGLM analysis with congruency on the current trial as regressor, and it did, $t(47) = 5.14$, $SE = 6.60$, $p < .001$. This indicates that pupil dilation increases more on incongruent trials, as compared with congruent trials.

We then applied a pupil dilation ANOVA on RTs, with congruency on the current trial, congruency on the previous trial, and pupil dilation (large/small) on the previous trial as independent variables. We found a significant main effect for congruency on the current trial, $F(1, 47) = 857$, $MSE = 958$, $p < .001$, indicating that congruent trials are faster (Fig. 2c, d). We found a significant two-way interaction between congruency on the current trial and congruency on the previous trial, $F(1, 47) = 9.30$, $MSE = 365$, $p = .004$, indicating an overall Gratton effect. The three-way interaction between congruency on the current trial, congruency on the previous trial, and pupil dilation on the previous trial was also significant, $F(1, 47) = 11.2$, $MSE = 360$, $p = .002$. However, this indicated that participants had a larger adaptation effect after a small pupil size than after a large pupil on the previous trial. Post hoc tests revealed that participants had a significant adaptation effect after a small pupil size, $F(1, 47) = 25.6$, $MSE = 289$, $p < .001$, but not after a large one, $F(1, 47) = .032$, $MSE = 436$, $p = .86$. We also found a significant main effect for pupil dilation on the previous trial, $F(1, 47) = 13.5$, $MSE = 339$, $p = .001$.

In the HGLM pupil dilation analysis (see Table 2), we found a significant main effect for congruency (Cn), $t(47) = 7.17$, $p < .001$, $\beta = 74.4$, indicating that incongruent trials were slower. We also found a significant main effect for pupil dilation (Pn), $t(47) = 3.53$, $p = .001$, $\beta = .086$, indicating that pupil dilation leads to a longer RT. Importantly, the near zero value of the nonsignificant three-way interaction regression parameter indicates that the modulation by pupil size suggested by the pupil dilation ANOVA and visual inspection of Fig. 1c, d could be due to confounding variables. This indicates that we cannot draw any conclusions about the effect of pupil dilation on cognitive control. There was no difference between the two groups (tested under bright vs. dimmed light conditions; all two-sample $ts < 1.17$, all $ps > .25$).

Table 2

Pupil size analysis: coefficients of the HGLM Analysis with response time as dependent

Predictor	Cn	Cn-1	Pn	Pn-1	Cn*Cn-1	Cn*Pn-1	Cn*Cn-1*Pn-1
Beta	74.4	12.8	.086	-.023	-15.0	-.046	-.001
SE	10.4	10.0	.024	.022	12.8	.025	.052
Sig.	.000	.21	.001	.32	.25	.08	.98
T stat.	7.17	1.27	3.53	-1.01	-1.17	1.82	-.021
Df.	47	47	47	47	47	47	47

Note. Predictors were congruency on the current trial (Cn), congruency on the previous trial (Cn−1), pupil dilation on the current trial (Pn), pupil dilation on the previous trial (Pn−1), two two-way interaction terms, and a three-way interaction term. All p values are two-sided. A negative beta value indicates a faster response

Discussion

First, we found that congruency on the current trial predicts both pupil dilation and blink on the current trial, consistent with findings of Siegle, Ichikawa, and Steinhauer (2008). More broadly, our findings on pupil dilation and blinking suggest that incongruent stimuli can trigger the

autonomic system (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Kobayashi, Yoshino, Takahashi, & Nomura, 2007).

Next, in our main analysis, we investigated the modulatory effect of pupil dilation (NE related) and eye blink (DA related) on the Gratton effect. We found a significant modulation of the Gratton effect by eye blink on the previous trial, even when we controlled for the effect of congruency on the current and previous trials. We failed to find a similar modulatory effect for pupil dilation.

Modulation of the Gratton effect by neuromodulatory markers is predicted by the adaptation-by-binding model (Verguts & Notebaert, 2008). This model proposes that the traditional roles of these neuromodulators in learning (Berridge & Waterhouse, 2003; Lisman et al., 2011) and cognitive control are not two separate functions but, instead, are strongly related. In particular, the DA burst underlying the blink may increase binding between stimulus, action, and more general task-relevant context elements. The modulatory role of DA in cognitive control is well-established in both computational models (e.g., Braver & Cohen, 2000; O'Reilly & Frank, 2006) and empirical studies (see Cools & D'Esposito, 2011, for a review). In particular, DA is involved in working memory (Brozoski, Brown, Rosvold, & Goldman, 1979) and has been proposed to be involved in regulating different computational trade-offs, such as flexibility versus stability (Cools & D'Esposito, 2011; Hazy, Frank, & O'Reilly, 2007). Dreisbach et al. (2005) observed that elevated DA levels increased distractibility; Dreisbach and Goschke (2004) found that positive affect (presumably triggering DA) had the same effect. In contrast, we find that a phasic burst of DA increases control. This is not necessarily in contradiction. First, in the task used by Dreisbach and colleagues, a task switch situation (switching between different goals) was implemented, in contrast to ours, where the goal was always the same. Also, the data pattern of Dreisbach and colleagues was modulated by DRD4 genotype (D4 being a D2-like receptor), whereas our effect is presumably D1-receptor dependent (see above). However, the exact relationships between these tasks and data remain to be determined. Similarly, theoretical and modeling accounts of NE in cognitive control focused on its role in regulating exploration versus exploitation (Aston-Jones & Cohen, 2005; Jepma & Nieuwenhuis, 2011), although empirical validation remains currently mixed (e.g., Jepma, Te Beek, Wagenmakers, Van Gerven, & Nieuwenhuis, 2010).

Since we find that blink, but not pupil dilation, modulates the Gratton effect, it is possible that specifically reward, not generally arousal, drives DA bursts in the current task. Reward is intimately connected to the dopaminergic system (Lisman et al., 2011; Schultz, 1998), and it may be more rewarding to execute an incongruent trial than a congruent trial (Molapour & Morsella, 2011; Schouppe et al., submitted; Silvetti, Seurinck, & Verguts, 2011). Incongruent trials themselves are aversive (Dreisbach & Fischer, 2012; Schouppe, De Houwer, Ridderinkhof, & Notebaert, 2012; Van Steenbergen et al., 2009), but successfully executing such difficult trials may be more rewarding than executing the easier congruent trials (Schouppe et al., submitted). This reward by self-evaluation may influence performance on the next trial(s) and improve binding between task-relevant representations (Waszak & Pholulamdeth, 2009). Also, in a Stroop task in which some stimuli are rewarded and others not, reward decreases the congruency effect (Krebs, Boehler, & Woldorff, 2010). Finally, reward increases the Gratton effect when reward is performance related, especially in reward-sensitive subjects (Braem et al., 2012). Of course, we cannot unambiguously equate the current DA modulation as a reward modulation phenomenon, given that different DA neurons have different functional characteristics (e.g., sensitivity to reward vs. novelty; see Bromberg-Martin et al., 2010, for a review). This needs to be further investigated with the current behavioral paradigm.

We expected to find a similar effect for pupil dilation, since NE was proposed to be the relevant neuromodulator by Verguts and Notebaert (2009). However, because of the inconsistency between the ANOVA and HGLM analysis, no strong conclusions can be drawn from the present data with respect to NE. The inconsistent outcomes of the ANOVA and the HGLM analysis may be due to the fact that the factors in the analyses are not orthogonal, since congruency causes pupil dilation. It may be possible that we did not find an effect for pupil dilation because trait anxiety determines the direction of the effect of NE release (De Rover et al., 2012). Another possibility is that the null effect for pupil dilation in the HGLM analysis is due to the fact that NE is released only in the early trials of the experiment when there is a high uncertainty in how to respond (Aston-Jones, Rajkowski, & Cohen, 1999; Dayan & Yu, 2006; Yu & Dayan, 2005). Since we used a congruent arrow flanker task (press left button for left arrow), the task may have been (over)learned rather quickly. Future research is needed to investigate the modulatory roles of eye blink and pupil size in more novel tasks.

We presently investigated cognitive control and found a phasic influence of DA. It would be of interest to see whether tonic and phasic DA would have different effects on proactive and reactive control, respectively (Braver, 2012). In addition, since eye blink and pupil dilation are only indirect measures of DA and NE, respectively, direct neuroimaging and pharmacological manipulations are needed to investigate the roles of DA and NE nuclei in early and late stages of cognitive control.

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CHAPTER 3

INCREASED COGNITIVE CONTROL DURING NOREPINEPHRINE RELEASE THROUGH VAGUS NERVE STIMULATION[1]

Cognitive control is supposed to be supported by increased norepinephrine (NE) release. This might be implemented by either learning or by generally alerting the cognitive system. In the current study we manipulated NE levels during the administration of a flanker task. Nineteen epilepsy patients who were chronically treated with vagus nerve stimulation (VNS) executed the task twice, once during VNS on and once during VNS in the off condition. It has been suggested that VNS increases NE in patients who respond well to the therapy (responders). We used the congruency effect and the Gratton effect as indices of cognitive control and investigated whether these indices were modulated by VNS. We further examined whether the VNS induced modulation depended on how well patients responded to the therapy. We expected a modulation in patients who respond well, but not in patients who hardly benefit from the therapy. For responders, stimulation generally improved response selection but deteriorated conflict adaptation. This corresponds to the hypothesis that NE has a general impact on the cognitive system. This might be related to the moderate level of NE release that is evoked by VNS.

[1] Van Bochove, M.E., De Taeye, L., Vonck, K., Raedt, R., Meurs, A., Boon, P., Dauwe, I., Notebaert, W., & Verguts, T. (manuscript in preparation). Increased cognitive control during norepinephrine release through vagus nerve stimulation

Introduction

In situations that evoke multiple and contradictory responses, the brain is able to select and execute the appropriate response most of the time. This ability is referred to as cognitive control, the ability to suppress an obvious but incorrect response in favor of a less obvious but appropriate action (Norman & Shallice, 1986; Verguts & Notebaert, 2008, 2009). Research on cognitive control builds on several models assuming that working memory (WM) plays a central role in updating and maintaining the appropriate action goal (Baddeley & Della Sala, 1996; Norman & Shallice, 1986). However, it has to be specified when (and when not) cognitive control needs to be triggered. Several possible triggers for cognitive control have been proposed, including conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001), error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993), error likelihood (Brown & Braver, 2005), volatility (Rushworth & Behrens, 2008), and prediction error (Alexander & Brown, 2011; Silvetti, Seurinck, & Verguts, 2011). Irrespective of its exact nature, many of these proposals agree that the anterior cingulate cortex (ACC) detects the need for cognitive control. According to the adaptation-by-binding model the ACC consequently recruits neuromodulatory systems in the brainstem (e.g.dopamine (DA) system, norepinephrine (NE) system; Verguts & Notebaert, 2008, 2009). Previous research suggests that the release of phasic DA in previously encountered conflicting situations increases our ability to adapt to the current conflicting situation. It is thought that the released DA strengthens binding between active stimulus and response representations which enables us to select the appropriate response in the current situation (Van Bochove, Van der Haegen, Notebaert, & Verguts, 2013). A similar role for NE was predicted by the adaptation-by-binding model (Verguts & Notebaert, 2009), but has not been confirmed in our previous experimental research (Van Bochove et al., 2013). However, in the previous study, we only measured (rather than manipulated) NE, and in an indirect way (via pupil size). The current study was designed to further investigate the proposed role of NE in cognitive control by addressing these issues. We investigated the effect of vagus nerve stimulation (VNS) in patients with epilepsy on the flanker task and compared on stimulation (increased NE) with off stimulation (baseline NE).

In epilepsy activating the NE system plays a role in the reduction of seizure frequency (Weinshenker & Szot, 2002). This may be because epileptic patients show reduced NE receptor

density (Briere et al., 1986; see Giorgi, Pizzanelli, Biagioni, Murri, & Fornai, 2004, for a review), reduced α1-adrenoceptor signaling in the epileptic focus (Dubeau & Sherwin, 1989), or reduced cortical NE (Pacia, Doyle, & Broderick, 2001). Although the mechanism of action is not entirely clear, increased brain NE leads to seizure suppression in rats (Raedt et al., 2011). In humans not only seizure reduction as main effect but also increased quality of life and increased alertness are reported as positive side effects of NE therapy in epilepsy (Ergene, Behr, & Shih, 2001; Kossoff & Pyzik, 2004).

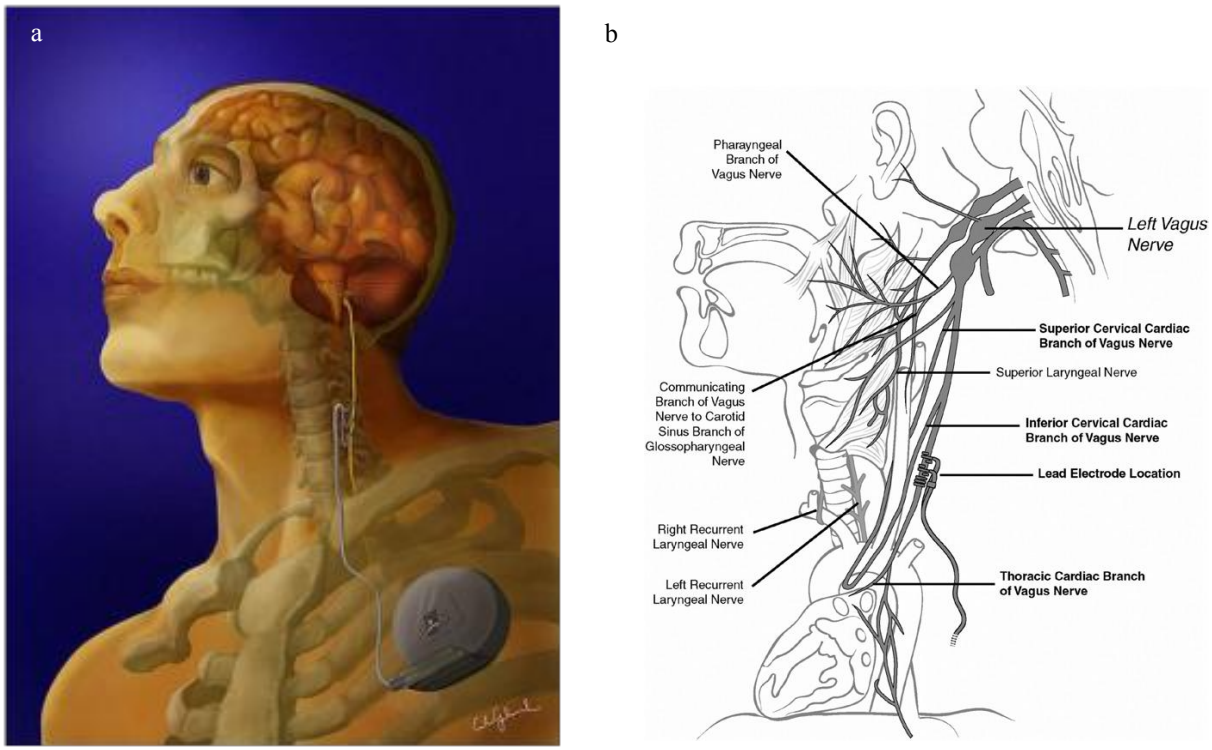

Figure 1

a Stimulator and wire attached to the vagus nerve. **b** Schematic diagram showing the local anatomy and nerves related to the left vagus nerve with attached VNS device wires. Copyright Dramatic First Words Spoken in 2 Children After Vagus Nerve Stimulation Marie F. Grill, MD, and Yu-tze Ng, MD, FRACP 2010

In most cases of epilepsy therapy consists of medication. For pharmaco-resistant epileptic patients there is the possibility of VNS therapy (Fornai, Ruffoli, Giorgi, & Paparelli, 2011). Patients receive an implant under the collarbone, which is connected by a wire to an electrode

placed around the left vagus nerve in the neck (see Figure 1A). This cranial nerve consists of 20% efferent (motor) fibers and 80% afferent (sensory) fibers. The afferent fibers end at the brainstem close to the locus coeruleus (LC) and the dorsal raphe nucleus (DRN; see Figure 1B). The LC is the main source of NE in the brain (Sara, 2009). Research in mice shows that the relative tonic and phasic firing of the LC is related to the release of NE (Carter et al., 2010). Acute stimulation of the vagus nerve consequently activates the LC to release NE. As rodent research shows, VNS therapy causes a significant increase of NE in the hippocampus (Raedt et al., 2011), basolateral amygdala (Hassert, Miyashita, & Williams, 2004) and cortex (Roosevelt, Smith, Clough, Jensen, & Browning, 2006). Several studies report seizure reduction due to VNS (Ben-Menachem, 2002; DeGiorgio et al., 2000; Weinshenker & Szot, 2002). As NE is not only related to seizure reduction, but also to cognition (Sara & Bouret, 2012; Sara, 2009), both improved memory (Clark, Naritoku, Smith, Browning, & Jensen, 1999) and improved language abilities (Grill & Ng, 2010) are reported as positive side effects of VNS therapy on cognitive functions.

Although VNS is a generally successful therapy in epilepsy (Ben-Menachem, 2002; DeGiorgio et al., 2000; Weinshenker & Szot, 2002), not all VNS patients benefit from the therapy. A VNS patient is medically considered a responder when there is a monthly seizure frequency reduction of at least 50% compared to pre VNS therapy. A study of 195 VNS patients shows a responder rate of 35% (DeGiorgio et al., 2000), and another study (N = 138) shows a responder rate of 59% (De Herdt et al., 2007). In the latter study 19% of the patients had no seizure frequency reduction at all and 7% had an increase in seizure frequency. It is yet unknown why some patients benefit from VNS while others don't. It might be that not all epileptic patients have reduced NE release due to their illness. One study finds in one type of epilepsy (neocortical temporal lobe epilepsy) reduced NE as in another type (mesial temporal lobe epilepsy) increased NE (Pacia et al., 2001). As responder status might be an indication of NE functioning, we will include this as a factor in our analyses. We expect neither a modulation of the congruency effect nor the Gratton effect in non-responders compared to responders.

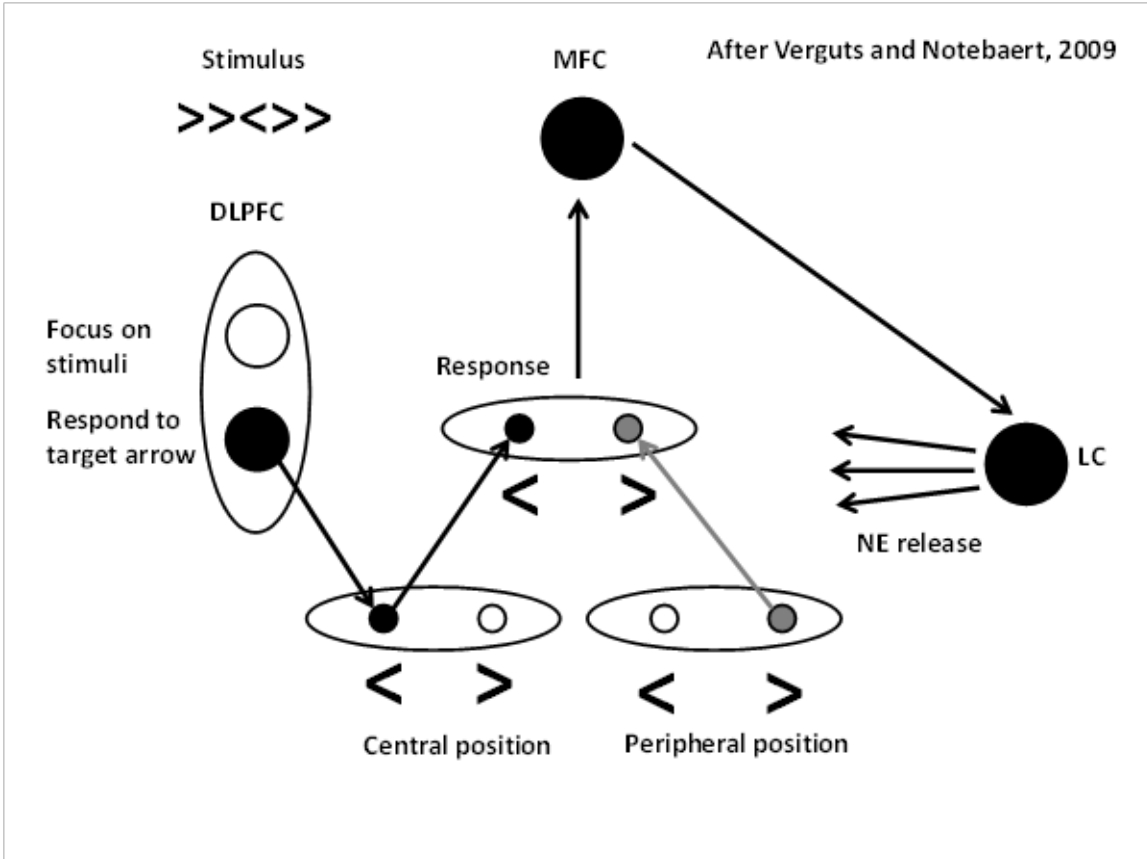

Figure 2

Schematic model (after Verguts & Notebaert, 2009) for the flanker task for incongruent trials (represented upper left). There are two visual input layers, representing input from the central position (represented lower left) and the peripheral position (represented lower right). The dorsolateral prefrontal cortex (DLPFC, represented middle left) represents task demands. The instruction to respond to the arrow in the central position prioritizes this dimension due to the top-down influence of the DLPFC. Due to the activation of the peripheral position, the incorrect response also becomes activated, but as this dimension is not prioritized by the DLPFC, this dimension is less activated. The simultaneous activation at the response layer activates the MFC, which in its turn activates the LC to release NE (represented in the middle right). The released NE might increases binding between the most active representations, which are the task relevant representations (NE-learning account). Alternatively, the released NE might have a general alerting function to increase performance (NE-performance account)

Patients with VNS provide us with a unique opportunity to investigate the role of NE in cognitive functioning. Cognitive control is often studied with tasks like the flanker task (Eriksen & Eriksen, 1974) and the Stroop task (Stroop, 1935) in which incongruent stimuli (evoking

contradictory responses) and congruent stimuli (evoking no contradictory responses) are presented intermixed. Two indices of cognitive control are derived from these tasks, the congruency effect and the Gratton effect (Gratton, Coles, & Donchin, 1992). The congruency effect is the difference in reaction time (RT) between congruent and incongruent trials. A smaller congruency effect is considered to indicate that the participant can ignore the strong but irrelevant stimulus dimension and is hence an index of cognitive control. The Gratton effect is the difference in congruency effect after an incongruent versus after a congruent trial. The congruency effect following an incongruent trial is smaller. Particularly, a congruent trial following an incongruent trial evokes a slower response, compared to a congruent trial following a congruent trial; but an incongruent trial following an incongruent trial evokes a faster response compared to an incongruent trial following a congruent trial. The size of the Gratton effect expresses how the previously encountered situation enables us to adapt better to the current situation[3]. A larger Gratton effect expresses increased post-conflict adaptation.

Several models hold an important function for NE in cognitive control processes but differ in the precise role NE takes (Aston-Jones & Cohen, 2005; Nieuwenhuis & Jepma, 2011; Verguts & Notebaert, 2008, 2009). Broadly speaking, we can dissociate models that propose a learning role for NE from models that propose a performance role for NE. The adaptation-by-binding model proposes that NE modulates cognitive control through Hebbian learning. The theory holds that incongruent stimuli increase the need for cognitive control to deal with the behavioral impasse. This is detected by the medial frontal cortex (MFC; Botvinick et al., 2001) which according to the adaptation-by-binding model activates the LC to release NE (Verguts & Notebaert, 2009). Incongruent trials indeed evoke higher arousal (Kobayashi, Yoshino, Takahashi, & Nomura, 2007), and consequently a larger pupillary response (Laeng, Ørbo, Holmlund, & Miozzo, 2011), pupil dilation being an index of NE activity. The released NE then increases binding between stimulus, response and context representations in the cortex, which enables adaptation in the next trial (see figure 2). The adaptation-by-binding model is supported by evidence as the MFC projects to the LC (Aston-Jones & Cohen, 2005; Jodo, Chiang, & Aston-Jones, 1998). Further, NE is known to improve memory (McGaugh, 2006) and has been

[3] An alternative explanation for the Gratton effect is that it is a confound of stimulus and/or response repetitions, rather than a cognitive control phenomenon (Hommel, Proctor, & Vu, 2004; Mayr, Awh, & Laurey, 2003), but these accounts are demonstrably at least incomplete (Notebaert & Verguts, 2007; Ullsperger, Bylsma, & Botvinick, 2005).

described as a "now print" signal (Harley, 2004; Livingston, 1967; Sara, 2009). In vitro research shows that NE is involved in long-term potentiation (Tully, Li, Tsvetkov, & Bolshakov, 2007), and a neuroimaging study in humans shows increased connectivity between brain regions during an attention task trough NE (Coull, Büchel, Friston, & Frith, 1999). More specifically, NE is known to enhance binding in Hebbian learning (Harley, 2004), which is tested to develop rather fast (e.g. within five trials, the lowest number tested in Weinberger & Bakin, 1998). The increased stimulus-response binding enables faster responses in incongruent trials, as through learning you are better skilled to ignore the distracting flankers. This consequently leads to a reduced congruency effect. As a consequence, the congruency effect will be smaller as a result of a boost of the NE system, for example due to VNS stimulation. The Gratton effect in its turn will be larger as a result of boosting the NE system. See Figure 3 for formal modeling predictions and Appendix ("NE-learning model") for detailed modeling description.

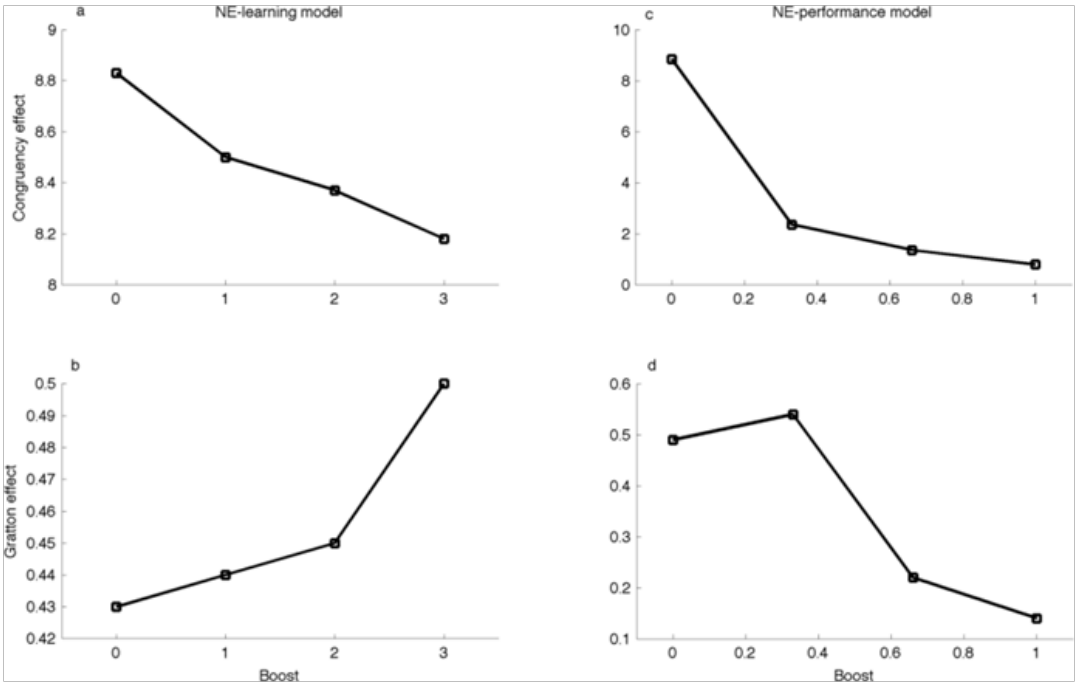

Figure 3

Predicted effects for the indices of cognitive control given the boost-size for both the NE-learning model (left) and the NE-performance model (right). The congruency effect for the NE-learning model (a), the Gratton effect for the NE-learning model (b), the congruency effect for the NE-performance model (c), and the Gratton effect for the NE-performance model (d).

Alternatively, other models propose that NE is important for cognitive control through general performance increase (Aston-Jones & Cohen, 2005; Nieuwenhuis & Jepma, 2011). Indeed, NE is related to arousal (Sara & Bouret, 2012) and is thought to change the signal to noise ratio of cortical neurons (Aston-Jones & Cohen, 2005), enabling faster response selection and execution. As the LC fires depending on the complexity of stimuli and responses (Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004), incongruent trials evoke more NE than congruent trials. Furthermore, NE increases responsiveness to sensory information, enabling rodents to respond better to target stimuli (Devilbiss, Page, & Waterhouse, 2006). In this case, we would predict a smaller congruency effect and a smaller Gratton effect as a result of boosting the NE system; see Figure 3 for modeled prediction.

Although our prediction that NE modulates both the congruency and the Gratton effect is well grounded in rodent and human research, a previous attempt to test modulation of cognitive control by the NE system provided only partial confirmation. Increased pupil dilation does not enhance the Gratton effect , but blinking (which is DA related; Blin, Masson, Azulay, Fondarai, & Serratrice, 1990; Taylor et al., 1999) does (Van Bochove et al., 2013). This might be due to methodological reasons. Pupil dilation indeed is a measure of NE activity (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Koss, 1986; Nieuwenhuis & Jepma, 2011; Samuels & Szabadi, 2008), but only an indirect measure. Besides that, as the pupillary response is rather slow, it takes approximately a second for the pupil to dilate and another second to return to baseline- pupil dilation research requires rather long trials (2.5 sec per trial). This might cause the failure of a previous trial NE boost to influence current trial RTs. In addition, in the previous study we measured but did not manipulate NE, requiring sophisticated statistical machinery to disentangle the contributions of different sources of variance.

To sum up, it is proposed that NE mediates cognitive control. Furthermore, VNS therapy is suggested to increases NE in epileptic patients, but only in patients that respond well to the therapy. We therefore compared cognitive control indices (congruency and Gratton effect) between on and off VNS therapy, in both responders and non-responders. If NE release modulates cognitive control by binding (NE-learning model), we expect a reduced congruency effect and an enhanced Gratton effect during stimulation, compared to no stimulation, but only in responders. However, if NE release modulates cognitive control by generally improving

performance through alerting the cognitive system (NE-performance model), we expect both a reduced congruency and a reduced Gratton effect during stimulation, compared to no stimulation, and only in responders.

Method

Participants

Nineteen VNS patients participated in this study; two patients could not complete the study due to fatigue (mean age = 43 years [range, 21-66], 11 female, 15 right-handed). All patients gave their written informed consent. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local university hospital ethics committee. Nine patients were VNS therapy responders, which means that they had a more than 50% reduction in mean monthly seizure frequency compared to pre-VNS therapy. Three of these patients were seizure-free. The remaining eight patients had a less than 50% reduction in seizure frequency (non-responders), of whom five patients had no seizure reduction at all. One of the patients that could not complete the study was a responder, the other was a non-responder. Most patients, even the responders, are not able to have a job, although one patient is a full-time college student.

Apparatus

All patients were implanted with a VNS device (Cyberonics, Webster, TX, USA). Therapeutic stimulation parameters ranged between 0.75 – 3.00 mA output current, 20-30 Hz frequency, and pulse width of 250-500 μs. For the experimental protocol stimulation was programmed to the maximum duty cycling of the device (7s on and 18s off) for the VNS 'on' condition, compared to no stimulation for the VNS 'off' condition.

Stimuli were presented on a DELL laptop and responses were collected with a QWERTY keyboard.

Stimuli

In each trial of the flanker task, a series of five arrows were presented (e.g., >><>>). The central arrow was considered the target; the two arrows left and right were flanker arrows. The arrows were oriented left (<) or right (>). As both target directions had congruent and incongruent flankers, this resulted in four different stimuli. Each of the four stimuli were presented in equal proportions and in a random order. The stimuli were presented in black on a white background. In case an error was committed, the stimulus was followed by a low tone.

Procedure

Participants were instructed to respond to the central arrow, pressing with their left or right index finger corresponding to the direction of the arrow. With their left index finger they had to press the f key, with their right index finger they had to press the j key. Both keys are to be recognized by the tactile marker on the key.

Patients executed a training block consisting of 20 trials; they consequently executed 4 test blocks, each consisting of 80 trials. In both the training block and the test blocks all trials had the same sequence of events. The trial starts with a fixation cross for 200 ms. Then the stimulus was presented upon response, followed by another fixation cross. The total duration of a trial was 1450 ms. Incorrect responses were followed by a low tone.

Data analysis

Only correct trials were included for analysis. Data were analyzed using linear mixed models (LMM) in R. In an LMM analysis all single trials are included in a linear regression analysis, rather than the averages over trials per participant. In all analyses RT was the dependent variable (continuous) and subject was random variable (nominal). Predictors were congruency status on the current trial (Cn), congruency status of the previous trial (Cn-1), VNS condition (Cond.), and responder status (Resp.). The predictors were dummy coded: congruency (congruent = 0, incongruent = 1), VNS condition (no stimulation = 0, stimulation = 1), and responder (no responder = 0, responder = 1). A negative beta indicates faster RTs.

Results

We consecutively executed four LMM analyses. In the first analysis (see Table 1) we tested whether the congruency effect was relatively more reduced in responders on stimulation (see Figure 4). The significant main effect for congruency shows that congruent trials lead to faster RTs compared to incongruent trials ($t(9506) = 7.63$, $p < .001$, $\beta = 45.0$). We found a marginally significant effect for responder status ($t(15) = 2.02$, $p = .06$, $\beta = 183.4$), showing that responders have slower overall RTs compared to non-responders. There was a significant two-way interaction for condition by responder status ($t(9506) = -10.3$, $p < .001$, $\beta = -85.0$), showing that overall RTs are relatively reduced in the stimulation condition for responders compared to non-responders. And finally there was a significant three-way interaction between congruency, condition and responder status ($t(9506) = -2.18$, $p = .03$, $\beta = -17.9$), showing that the congruency effect is relatively reduced for responders in the stimulation condition.

Table 1

Modulation of the congruency effect by condition and responder status: LMM analysis with RT as dependent variable

Predictor	Cn	Cond.	Resp.	Cn*Cond	Cn*Resp	Cond*Resp	Cn*Cond*Resp
Beta	45.0	-4.01	183.4	.629	1.776	-85.0	-17.9
SE	5.90	5.90	90.9	5.90	8.24	8.24	8.23
Sig.	.000	.497	.06	.92	.83	.000	.03
T stat.	7.63	-.680	2.02	.107	.213	-10.3	-2.18
Df.	9506	9506	15	9506	9506	9506	9506

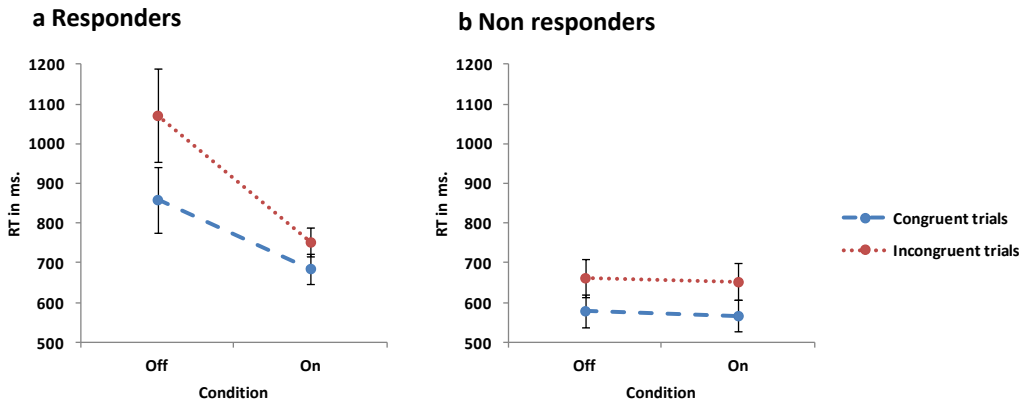

Figure 4

The congruency effect for responders (a) and non-responders (b) compared for off stimulation (left) and on stimulation (right). The y-axis shows average RTs. For each average error bars are depicted, note that the error bars depict variability and not significance

In the second analysis (see Table 2) we investigated whether the modulation of the congruency effect by condition still holds if only responders are included in the analysis. It would show whether the three way interaction between congruency, condition and responder in the first analysis is a mere effect of group, or truly the effect of condition. Note that this analysis includes only nine patients. We found a significant main effect for congruency ($t(4897) = 6.23$, $p < .001$, $\beta = 46.8$). The significant main effect for condition shows that stimulation leads to faster overall RTs compared to no stimulation ($t(4897) = -11.9$, $p < .001$, $\beta = -89.0$). The significant interaction term shows that the slowing in incongruent trials is less in the stimulation condition compared to the no stimulation condition ($t(4897) = -2.32$, $p = .02$, $\beta = -17.3$).

Table 2

Modulation of the congruency effect by condition in the VNS responder patients only: LMM analysis with RT as dependent variable

Predictor	Cn	Condition	Cn*Condition
Beta	46.8	-89.0	-17.3
SE	7.47	7.46	7.46
Sig.	.000	.000	.02
T stat.	6.23	-11.9	2.32
Df.	4897	4897	4897

In the third analysis (see Table 3) we investigated whether not only the congruency effect, but also the Gratton effect, was modulated by condition and responder status. We found a significant modulation for a smaller congruency effect due to NE release (see Figure 5). There was a significant main effect for congruency ($t(8857) = 14.0$, $p < .001$, $\beta = 43.4$), and condition ($t(8857) = -12.2$, $p < .001$, $\beta = -37.6$), and a marginal significant effect for responder status ($t(15) = 1.88$, $p = .08$, $\beta = 77.4$). There also was a significant two-way interaction between congruency on the current trial and congruency on the previous trial ($t(8857) = -3.88$, $p < .001$, $\beta = -12.0$), indicating a standard Gratton effect. There were two more significant two-way interactions, one between congruency on the current trial and condition ($t(8857) = -2.58$, $p = .01$, $\beta = -7.98$), and another one between condition and responder status ($t(8857) = -11.1$, $p < .001$, $\beta = -34.5$). There was a significant three-way interaction between congruency on the current trial, condition, and responder status ($t(8857) = -2.45$, $p = .01$, $\beta = -7.56$), like in the first analysis. Finally, the four-way interaction between congruency on the current trial, congruency of the previous trial, condition, and responder status was significant and in the direction predicted by the NE-performance model ($t(8857) = 2.02$, $p = .04$, $\beta = 6.23$), indicating a smaller Gratton effect for responders in the stimulation condition.

Table 3

Modulation of the Gratton effect by condition and responder status: LMM analysis with RT as dependent variable

Predictor	Cn	Cn-1	Cond.	Resp.	Cn*Cn-1	Cn*Cond.	Cn-1*Cond.	Cn*Resp	Cn-1*Resp.	Cond.*Resp.
Beta	43.4	-1.77	-37.6	77.4	-12.0	-7.98	-2.94	.882	1.85	-34.5
SE	3.09	3.09	3.10	41.3	3.09	3.09	3.09	3.09	3.09	3.10
Sig.	.000	.57	.000	.08	.0001	.01	.34	.78	.66	.000
T stat.	14.0	-.573	-12.2	1.88	-3.88	-2.58	-.96	.286	.438	-11.1
Df.	8857	8857	8857	15	8857	8857	8857	8857	8857	8857

Predictor	Cn*Cn-1*Cond.	Cn*Cn-1*Resp	Cn*Cond.*Resp	Cn-1*Cond.*Resp.	Cn*Cn-1*Cond.*Resp.
Beta	4.26	-3.48	-7.56	-.08	6.23
SE	3.09	3.09	3.09	3.09	3.09
Sig.	.17	.26	.01	.98	.04
T stat.	1.38	-1.13	-2.45	-.03	2.02
Df.	8857	8857	8857	8857	8857

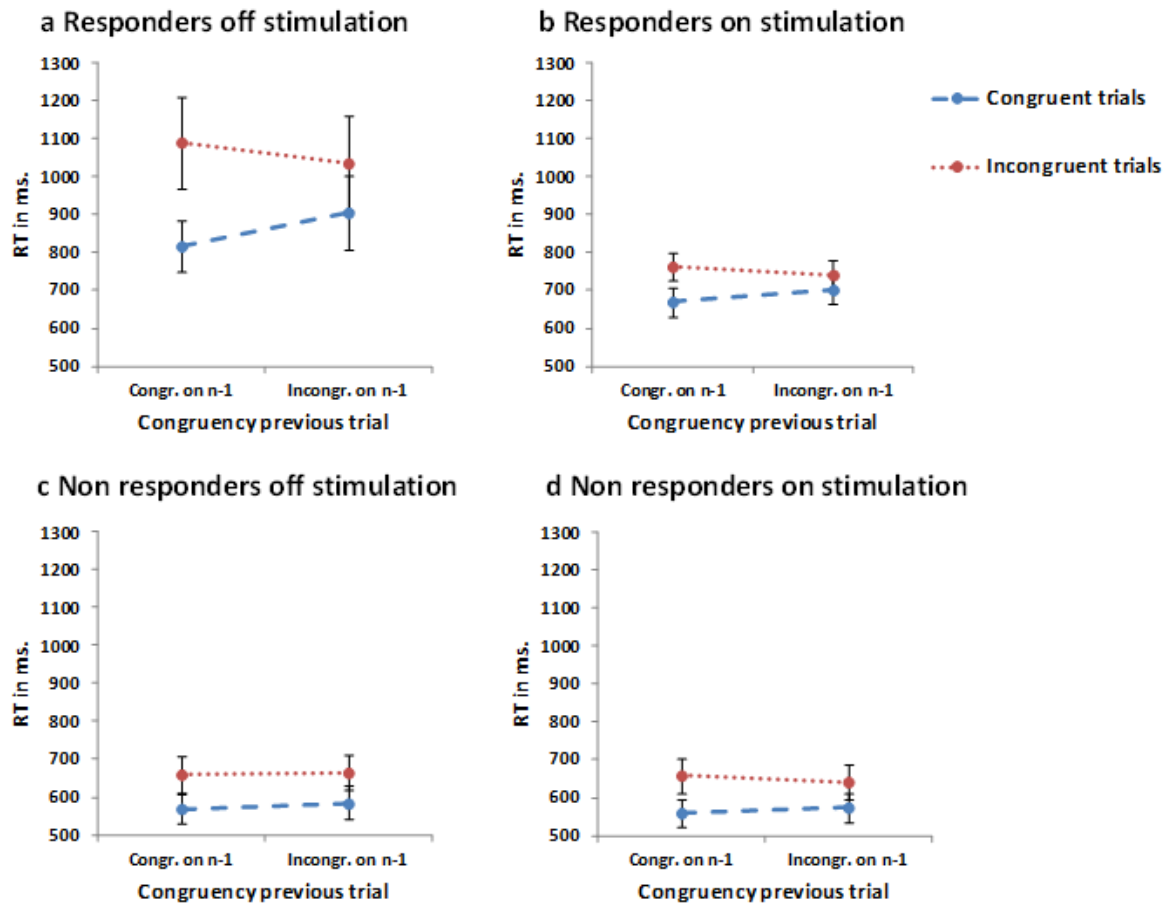

Figure 5

The Gratton effect for responders off stimulation (a), responders on stimulation (b), non-responders off stimulation (c), and non-responders on stimulation (d). The y-axis shows average RTs. For each average error bars are depicted, note that the error bars depict variability and not significance

In the fourth and last analysis (see Table 4) we investigated whether the modulation of the Gratton effect by condition still holds if only responders are included in the analysis. Note again that this analysis includes only nine patients. There was a significant main effect for congruency ($t(4827) = 7.15$, $p < .001$, $\beta = 46.1$), and condition ($t(4827) = -12.9$, $p < .001$, $\beta = -83.2$). There was a significant two-way interaction between congruency on the current trial and congruency on the previous trial ($t(4827) = -3.07$, $p = .002$, $\beta = -19.7$), indicating a standard Gratton effect. There was another significant two-way interaction, between congruency on the current trial and condition ($t(4827) = -2.99$, $p = .003$, $\beta = -19.2$). The three-way interaction of

interest between congruency of the current trial, congruency of the previous trial condition was significant ($t(4827) = 1.65$, $p = .049$ (one sided), $\beta = 10.6$).

Table 4

Modulation of the Gratton effect by condition in the VNS responder patients only: LMM analysis with RT as dependent variable (* one sided)

Predictor	Cn	Cn-1	Cond.	Cn*Cn-1	Cn*Cond.	Cn-1*Cond.	Cn*Cn-1*Cond.
Beta	46.1	8.8	-83.2	-19.7	-19.2	-5.73	10.6
SE	6.44	6.43	6.44	6.44	6.44	6.43	6.44
Sig.	.000	.17	.000	.002	.003	.37	.049*
T stat.	7.15	1.37	-12.9	-3.07	-2.99	-.892	1.65
Df.	4827	4827	4827	4827	4827	4827	4827

Discussion

We found that VNS stimulation in responders reduces the congruency effect, suggesting that NE reduces the behavioral slowing induced by incongruent stimuli. This was confirmed by a first analysis of the data of both responders and non-responders for the interaction between congruency, condition and responder status; and a second analysis of only the responder data for the interaction between congruency and condition. Both analyses hold similar and significant results. There is no reduction of the congruency effect for non-responders. We also found a modulation of the Gratton effect during stimulation, only for responders. The modulation by condition holds in the responders only analysis, proving that the effect of condition is not driven by mere group differences. We expected a larger Gratton effect during stimulation according to the NE-learning model and a smaller Gratton effect during stimulation according to the NE-performance model. Consistent with the latter, we found a smaller Gratton effect during stimulation. This is inconsistent with our earlier report (Van Bochove et al., 2013) where we found no NE-ergic modulation of the Gratton effect.

The modulation of the congruency effect by NE consistent with the NE-performance model suggests that increased NE is beneficial in overcoming the behavioral impasse inflicted by incongruent stimuli. In general, it confirms the role of NE in cognitive control. Similar results were found as NE increased preparedness to respond to salient stimuli, enabling rodents to respond better to target stimuli (Devilbiss et al., 2006), leading to a more stable system, better prepared to perform optimally. This might be related to moderate levels of NE, improving WM function in the prefrontal cortex (PFC) via the α2A receptor type (Li & Mei, 1994; see Arnsten, 2011, for a review). Due to improved WM functioning it is easier to focus on the target stimuli and ignore the distracters.

It is striking how severely RTs are extended in responders without stimulation; the difference with RTs of non-responders is close to significant. Epilepsy is known to influence cognition, although the underlying mechanism is unclear, as it is unclear why it affected the responder sample and not the non-responder sample. Several studies report reduced cognitive functioning in epileptic patients correlating with repeated seizures. In fact even one single seizure (lifetime) has a significant influence on one's quality of life (Modi et al., 2009). A study of 94 patients shows a negative correlation between the number of seizures and IQ (see Aldenkamp & Bodde, 2005, for a review; Dodrill, 1986) and another study reports verbal memory problems for patients with temporal lobe epilepsy, particularly those with a high seizure frequency (Hendriks et al., 2004). Not only epileptic discharges during convulsive seizures but also during nonconvulsive seizures (e.g. absence seizures) are shown to influence alertness as measured by simple RTs and memory (Aldenkamp & Arends, 2004; Aldenkamp et al., 2001). Given the fact that both the modulation of the congruency effect and the Gratton effect hold in the responders only analyses, the found effects cannot be driven by group differences due to eventual reduced cognitive functioning in the responder sample.

Interpreting the modulation of the congruency effect by VNS also requires considering which particular nucleus is stimulated. The vagus nerve ends at the brainstem, close to the LC, which is close to the DRN as well. Acute VNS therapy only increases NE release, while chronic VNS therapy increases both NE and serotonin (5-HT; Dorr & Debonnel, 2006). All patients in the current study have VNS for at least 18 months and chronic effects of VNS therapy. As the 5-HT response to VNS is slow, it will not respond to the interruption in the off condition.

Consequently, 5-HT levels in both conditions are equal and will have equal effects on RTs. However, the NE response to VNS is fast, resulting in different levels of NE in the on and off condition. We therefore assume that in the current experimental set-up, only differences in NE levels will influence behavior.

The current data do not support the predictions of the NE-learning account (e.g., adaptation-by-binding) in the sense that for responders, a smaller Gratton effect was observed ON stimulation. However, it is possible that binding (hence, learning) is increased with even higher levels of NE. NE release has different effects depending on which NE receptor type it binds to (Arnsten, 2000). The preferred receptor type for NE is the α2A type (Arnsten, 2000, 2011). If only moderate levels of NE are released it will only bind to this receptor type. The effect is that WM functioning improves, but at the same time, α2A receptor type activation prevents binding (Arnsten, 2000; Genkova-Papazova, Petkova, Lazarova-Bakarova, Boyanova, & Staneva-Stoytcheva, 1997; Sirviö, Riekkinen, Vajanto, Koivisto, & Riekkinen, 1991). To achieve binding the NE β receptor type needs to be activated, which only occurs when high amounts of NE are released (Arnsten, 2000, 2011). As our patients did receive VNS stimulation, but did not seem agitated, we can safely assume that they only received moderate NE release rather than high levels of NE, which is unlikely to effectuate binding. This leaves room for an NE-learning modulation of the Gratton effect in situations that evoke higher levels of NE up to the level that the β receptor type is activated. Not finding confirmation for the NE-learning account might also have more methodological reasons. In responders we saw that the congruency effect was dramatically reduced during stimulation. As the Gratton effect is a further modulation of this effect, it might be that the size of the congruency effect during stimulation was too small to be further reduced by the effect of previous trial congruency. In other words, it might be a ceiling effect.

Although we cannot be entirely sure in rejecting the NE-learning account due to methodological reasons mentioned above, the modulation of the Gratton effect we found does match with the NE-performance hypothesis. It shows that NE acts at a more general level boosting speed in all conditions (congruent and incongruent) alike, which results in minimizing the differences between reaction times of the different conditions. This coincides with the above given description of the effect of NE by receptor types. We argued before that there might be

α2A receptor activation which is related to improved WM functioning (Arnsten, 2000, 2011). Increased WM functioning would support better and faster response selection and suppression of the response tendencies evoked by the distracting flankers.

Previously we did not find a modulation of the Gratton effect by NE (Van Bochove et al., 2013). We applied a similar arrow flanker task and recorded pupil dilation as measure of NE. NE release was related to trial characteristics, incongruent trials evoked more NE than congruent ones. This phasic NE manipulation did not modulate the Gratton effect. We argued that there might not be enough NE release after incongruent stimuli as NE is only released in situations in which correct response selection is highly uncertain or when stimuli are salient, threatening or unexpected (Aston-Jones & Cohen, 2005; Aston-Jones, Rajkowski, & Cohen, 1999; Dayan & Yu, 2006; Yu & Dayan, 2005). Likewise in volatile situations there is increased learning caused by increased NE (Silvetti, Seurinck, Van Bochove, & Verguts, 2013). As we used a congruent flanker task (press the left button for a leftward pointing arrow) the task might have been overlearned rather quickly. In the current study, there certainly was NE release due to stimulation, and it modulated the Gratton effect. So NE can modulate the Gratton effect, but the phasic release evoked by an overlearned task might not be sufficient.

There are other candidates to modulate adaptation including DA, and 5-HT. DA has the characteristics to improve adaptation as it is known to improve learning (Lisman, Grace, & Duzel, 2011) and response vigor (Niv, Daw, Joel, & Dayan, 2007). A similar role is recently proposed for 5-HT (Boureau & Dayan, 2011; Cools, Nakamura, & Daw, 2011). Phasic DA as measured by blinking during the previous trial of a flanker task improves the Gratton effect in the current trial (Van Bochove et al., 2013). Depressed mood linked to reduced 5-HT similarly evokes a larger conflict adaptation effect (van Steenbergen, Booij, Band, Hommel, & van der Does, 2012). Future research should focus on the integration of the knowledge of the separate neuromodulaters that might play a role in cognitive control, especially as the neuromodulatory systems are not as separate as is often thought. In particular as the Ventral Tegmental Area (VTA, DA related), LC (NE related) and DRN (5-HT related) are interconnected (El Mansari et al., 2010) and project all to the PFC (Chandler, Lamperski, & Waterhouse, 2013), influencing cognitive control.

From the current and previous study we gained coherent elementary insight concerning the effect of NE and DA in cognitive control. Although the phasic NE release in a overlearned congruency task did not evoke sufficient NE to modulate the Gratton effect (Van Bochove et al., 2013), continuous moderate levels of NE release do modulate both the congruency and Gratton effect in a NE-performance manner. It enables faster reactions, better response selection and suppression of environmental distracters. Phasic DA has a complementary role as it enables improved behavioral adaptation even in situations that are over learned (Van Bochove et al., 2013).

The current study also shows that epilepsy patients may benefit from VNS in more than one way. The most obvious effect of course is seizure frequency reduction. Another known effect is mood improvement (Elger, Hoppe, Falkai, Rush, & Elger, 2000), but we currently show that also response selection and response vigor improve. As epilepsy often decreases self-confidence through the unexpected and paralyzing nature of seizures, regaining control through VNS will contribute to improved well-being of these patients.

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Appendix *Model architecture*

The model is similar to the one reported in Verguts & Notebaert (2008), and in particular the version reported in Blais & Verguts (2012). Most specifications here are taken from the latter paper. Time in a trial is indexed by *t*; the cascade rate of activation in a trial is denoted by τ. At input, a target and flanker layer are implemented (see Figure A1). The activation equation for an arbitrary input unit *i* (either in the target or flanker layer) is:

$$x_i^{in}(t+1) = (1-\tau)x_i^{in}(t) + \tau I_i(t). \quad \text{(A1)}$$

$I_i(t)$ is an indicator function equal to 1 if the stimulus corresponding to that unit *i* is presented at time *t*, and zero otherwise. To implement residual activation from earlier trials, activation of input units at the start of trial *n* was set to 40% of the value at the end of trial *n* – 1. This residual activation causes the Gratton effect (see Blais & Verguts, 2012, for explanation).

Input units send activation to response units. The activation equation for a response unit *j* is:

$$x_j^{res}(t+1) = (1-\tau)x_j^{res}(t) + \tau\left(\sum_i w_i^{ir} x_i^{in}(t)\left(C + \sum_{k=1}^{2} w_{ki}^{ti}(n)x_k^{td}(n)\right) + w^{inh}\sum_{k\neq j} x_k^{res}(t)\right). \quad \text{(A2)}$$

The matrix $\boldsymbol{w}^{ir}$ contains bottom-up weights from the input layers to the response layer. The term $\left(C + \sum_{k=1}^{2} w_{ki}^{ti}(n)x_k^{td}(n)\right)$ implements top-down attentional weighting from the two DLPFC units (flanker, target; see Figure 1) to the input layers by weight matrix $\boldsymbol{w}^{ti}$ which is adaptively changed across trials *n*. The term $w^{inh}\sum_{k\neq j} x_k^{res}(t)$ reflects response competition. The summation $-w^{inh}\sum_j\sum_{k\neq j} x_j^{res}(t)x_k^{res}(t)$ over response units represents the total amount of response conflict (response conflict unit in Figure 1; Botvinick et al., 2001).

The activation equation for the control unit equals:

$$x^{con}(n+1) = \lambda_{con}x^{con}(n) + (1-\lambda_{con})\left(-w^{inh}\sum_j\sum_{k\neq j} x_j^{res}x_k^{res} + \beta_{con}\right). \quad \text{(A3)}$$

This equation is applied at the end of each trial *n*. Finally, weights are adapted according to a conflict-modulated Hebbian learning rule:

$$w_{ki}^{\mathrm{ti}}(n+1) = \lambda_w w_{ki}^{\mathrm{ti}}(n) + (1-\lambda_w)\left(\alpha \times f + \beta_w\right). \tag{A4}$$

The term *f* implements the conflict-modulated Hebbian term:

$$f = (x^{\mathrm{con}}(n) - \overline{x^{\mathrm{con}}})x_i^{\mathrm{in}}(t)\left(x_k^{\mathrm{ti}}(n) - 1/2\right), \tag{A5}$$

where $\overline{x^{\mathrm{con}}}$ denotes the mean activity of the control unit up to trial *n*. When both difference terms in (A5) are negative, the equation is set to zero. Weights w^{ti} are only adapted between attentional units and their corresponding input layer units and are restricted to be non-negative.

Parameters were taken from Blais & Verguts (2012). They were as follows: $\tau = 0.1$, $w^{\mathrm{inh}} = -0.5$, $C = 0.7$, $\lambda_{\mathrm{con}} = 0.8$, $\beta_{\mathrm{con}} = 1$, $\lambda_{\mathrm{w}} = 0.2$, $\alpha = 20$, $\beta_{\mathrm{w}} = 0.5$. The activation of the target attention unit was set at 1, that of the flanker attention unit at 0.3. The initial strength of each attention unit to its corresponding input units (i.e., initial entries in matrix $\boldsymbol{w}^{\mathrm{ti}}$) was 0.5. The strength of input-response connections for the target layer equals 1 (e.g., from number 1 to response "1"; matrix $\boldsymbol{w}^{\mathrm{ir}}$); the strength of input-response connections for the flanker layer equals 1.1. In each trial, activation of the input and response units was updated according to Equations (A1) and (A2) until one of the response units reached a threshold value of 0.6. The corresponding response was taken to be the model's response choice and the time needed to reach that unit was taken to be the model's response time. The qualitative pattern of results was robust to changes in these parameters.

NE-learning model

The factor *f* in Equation (A5) was augmented with a percentage of *n*% (*n* = 0, 100, 200, or 300). Congruency effects are plotted in Figure A1a across different values of *n*. This plot (like all other plots) shows the average difference across three runs of the simulation; results were very similar across replications. As can be seen, congruency effect decreases with increasing learning. The Gratton effects are plotted in Figure A1b. In this case, the effects increase with increasing "boost".

NE-performance model

In this case, the response unit x^{res} received an extra boost (after application of Equation (A2)) of 0, 33, 66, or 100% after every update step. As a result, it reached its threshold value more quickly. Congruency effects are plotted in Figure A1c. Just like in the NE-learning model, congruency effect becomes smaller with increasing "boost". However, the Gratton effect (Figure A1d) shows a different pattern: Here, the effect typically becomes smaller with increasing boost. Hence, this effect is diagnostic for differentiating the NE-learning versus NE-performance model.

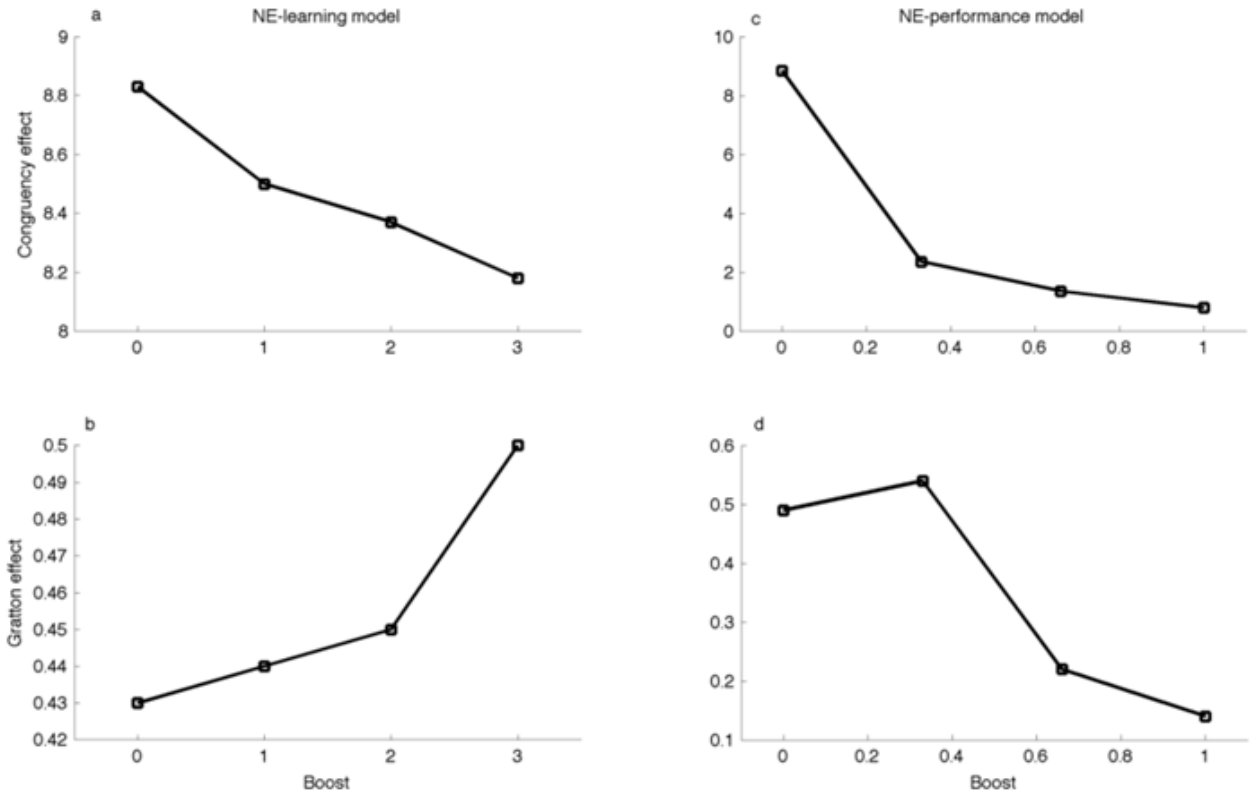

Figure A1.

Congruency and Gratton effects for NE-learning model (a, b) and NE-performance model (c, d).

CHAPTER 4

AMISULPRIDE, BUT NOT REBOXETINE MODULATES COGNITIVE CONTROL[1]

Cognitive control depends on the rapid allocation of additional resources. The need for additional recourses is thought detected by the anterior cingulate cortex (ACC). The ACC consequently might activate either the ventral tegmental area (VTA) or the locus coeruleus (LC) to release dopamine (DA) or norepinephrine (NE). Both neuromodulators might improve cognitive control by means of increasing the signal-to-noise ratio (SNR) and/ or long-term potentiation (LTP). The current study pharmacologically manipulated both DA and NE release to investigate their effect in cognitive control. Twenty participants executed two versions of the flanker task, the arrow flanker and the novelty flanker task. The arrow flanker task investigates cognitive control in a well-known situation, whereas the novelty flanker task investigates cognitive control in a novel situation. Both interference suppression (congruency effect) and post-conflict adaptation (Gratton effect), were investigated on reaction times (RTs) and accuracy. To account for individual differences in DA and NE agent response we included a working memory span task and a trait anxiety questionnaire. Amisulpride (DA agent) but not reboxetine (NE agent) improved post-conflict adaptation in accuracy in the novelty flanker task. Interference suppression and post-conflict adaptation in the arrow flanker task were not modulated by amisulpride or reboxetine. The current study provides further support that DA is involved in post-conflict adaptation.

[1] Van Bochove, M. E., Van Heeringen, K., Silvetti, M., Colzato, L.S., Notebaert, W., & Verguts, T. (manuscript in preparation). Amisulpride, but not reboxetine modulates cognitive control.

Introduction

In an ambiguous and complex environment selecting an appropriate response out of many possible responses is often challenging, but hesitating might be costly. Therefore extra cognitive resources should rather be rapidly allocated, which is one way of exerting cognitive control (Norman & Shallice, 1986; Verguts & Notebaert, 2008, 2009). The need for additional resources to overcome a behavioral impasse is thought to be detected by the anterior cingulate cortex (ACC; Alexander & Brown, 2011; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Brown, 2013; Shenhav, Botvinick, & Cohen, 2013; Silvetti, Seurinck, & Verguts, 2011). The ACC is connected to the ventral tegmental area (VTA; Devinsky, Morrell, & Vogt, 1995; Geisler, Derst, Veh, & Zahm, 2007) and the locus coeruleus (LC; Aston-Jones & Cohen, 2005; Jodo, Chiang, & Aston-Jones, 1998), so activating the ACC might consequently activate the VTA or the LC to release dopamine (DA) or norepinephrine (NE), respectively, which might serve to recruit such additional resources (e.g. Verguts & Notebaert, 2008). The benefits of these resources might be twofold. First, in the current situation DA and NE might help to suppress interference of an obvious yet inappropriate response or any other distracter. Both DA and NE are known to increase the signal-to-noise ratio (SNR), which enhances target detection and reduces noise from distracting stimuli (Aston-Jones & Cohen, 2005; Lisman, Grace, & Duzel, 2011). Second, for future situations there might be a benefit from DA and NE as both neuromodulators enhance learning by inducing long-term potentiation (LTP; Lisman et al., 2011; Tully, Li, Tsvetkov, & Bolshakov, 2007). In this case, connections between stimulus-related and response-related neurons might become stronger, thus to ameliorate response selection in future situations. This learning effect of DA and NE in cognitive control was previously proposed by the adaptation-by-binding model (see Figure 1; Verguts & Notebaert, 2008, 2009).

Such ambiguous situations that evoke multiple responses are experimentally studied using congruency tasks like the flanker task (Eriksen & Eriksen, 1974) and the Stroop task (Stroop, 1935). For example, in the flanker task, in the incongruent condition target stimuli are presented simultaneously with flanking distracter stimuli. Reaction times (RTs) in this condition are slower compared to RTs in the congruent condition in which flanking stimuli are the same as the target stimuli. The difference score between these conditions (congruency effect) is interpreted as the effectiveness of interference suppression, meaning how well we are able to

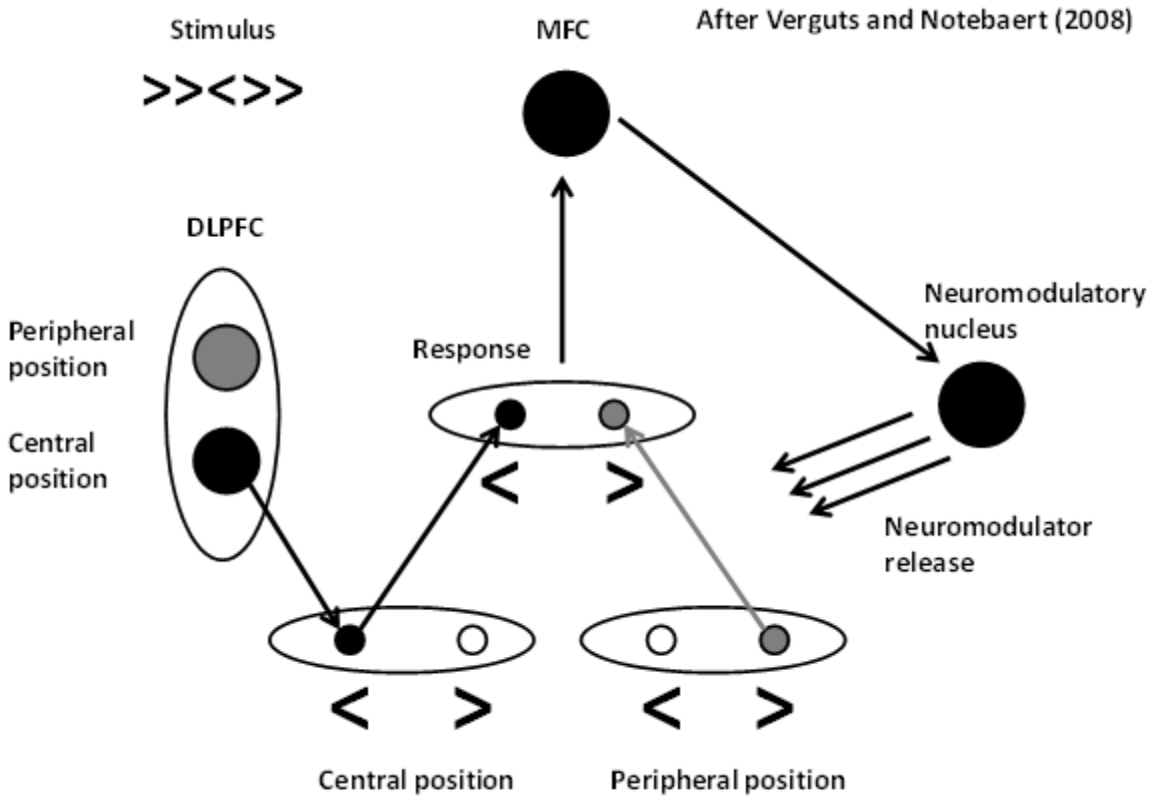

Figure 1.

Schematic model (after Verguts & Notebaert, 2009) for the flanker task for incongruent trials (represented upper left). There are two visual input layers, representing input from the central position (represented lower left) and the peripheral position (represented lower right). The dorsolateral prefrontal cortex (DLPFC, represented middle left) represents task demands. The instruction to respond to the arrow in the central position prioritizes this dimension due to the top-down influence of the DLPFC. Due to the activation of the peripheral position, the incorrect response also becomes activated, but as this dimension is not prioritized by the DLPFC, this dimension is less activated. The simultaneous activation at the response layer activates the MFC, which in its turn activates the VTA or LC to release DA or NE (represented in the middle right). The released DA or NE might increases binding between the most active representations, which are the task relevant representations (increased LTP account). Alternatively, the released DA or NE might increase the SNR which enhances target detection (increased SNR account)

suppress irrelevant information. Interference suppression is improved after an incongruent trial, compared to a congruent trial. The difference score between the congruency effect following an incongruent trial and a congruent trial (Gratton effect) is interpreted as the effectiveness of post-conflict adaptation, meaning how well previously experienced conflict adapted us for the current situation (Gratton, Coles, & Donchin, 1992). As both interference suppression and post-conflict adaptation may be different in well-known situations and novel situations, we consider two versions of a congruency task. The arrow flanker task will test both indices for well-known situations, as pressing left for a left oriented arrow and right for right oriented arrow are over-learned responses. In the novelty flanker task participants have to execute a flanker task in which they are confronted with 4 new stimuli, each stimulus with its own appropriate response. Consequently 4 new stimulus-response (SR) mappings have to be learned in an environment that requires interference suppression and post-conflict adaptation.

Both interference suppression and post-conflict adaptation are thought to be modulated by DA and NE. Endogenous variation in DA (measured indirectly using eye blinks) improved post-conflict adaptation in a simple congruency task (Van Bochove, Van der Haegen, Notebaert, & Verguts, 2013). A DA overdose disrupted post-conflict adaptation (Duthoo et al., 2013). Increased NE through vagus nerve stimulation (VNS) in epileptic patients disrupted post-conflict adaptation in an arrow flanker task, but it improved interference suppression (Van Bochove, De Taeye, Vonck, Raedt, Meurs, Boon, Dauwe, Notebaert, & Verguts, in preparation). Likewise a DA-related manipulation such as reward (Lisman et al., 2011; Schultz, 1998) linked to specific stimuli enhances interference suppression (Krebs, Boehler, & Woldorff, 2010) and post-conflict adaptation (Braem, Verguts, Roggeman, & Notebaert, 2012) for these stimuli. Despite the known effect of NE in LTP, no improved post-conflict adaptation by NE was found (Van Bochove et al., 2013). Except for the VNS study, all other mentioned studies utilized either an indirect way of measuring DA and NE release, or an indirect way of manipulating them. Manipulating both neuromodulators pharmaceutically and systematically would provide more direct evidence for their role in cognitive control.

We previously stated that the effect of DA and NE on cognitive control might be mediated by two distinct mechanisms, increasing the SNR and/ or enhancing LTP. Computational modeling demonstrates that a neuromodulatory boost implemented by increased

SNR versus increased LTP, can have distinct effects on the two aspects of cognitive control, namely interference suppression and post-conflict adaptation (see Figure 2; Van Bochove et al., in preparation). For interference suppression, there is no difference in outcome whether the effect of the neuromodulators modulates interference suppression via increased SNR or via enhanced LTP. In both cases a neuromodulatory boost will enhance interference suppression, which is expressed in a decreased congruency effect. For post-conflict adaptation, it does make a difference whether the effect of the neuromodulatory boost is effectuated via increased SNR or via enhanced LTP. In case the neuromodulatory boost is effectuated via increased SNR there will be deteriorated post-conflict adaptation, expressed in a decreased Gratton effect. However, if the neuromodulatory boost is effectuated via enhanced LTP, there will be improved post-conflict adaptation, expressed in an increased Gratton effect.

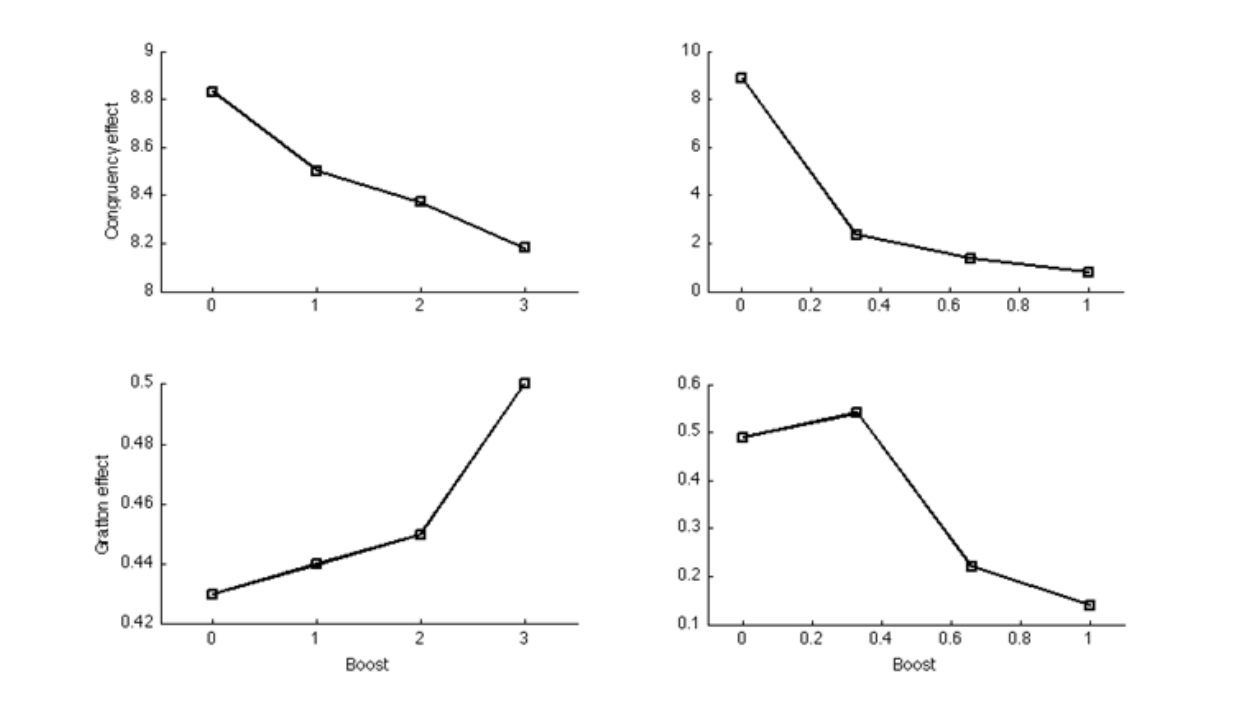

Figure 2.

Modeled predictions for the influence of a neuromodulatory boost on the congruency effect (upper panel), and Gratton effect (lower panel), modulated by either increased LTP (left panel) or increased SNR (right panel).

Both DA and NE can be pharmaceutically manipulated by several drugs. The drugs of choice for the current study required several pharmacokinetic similarities. Both should have an activating effect, similar intake to peak period, and similar half-life's. The drugs meeting these criteria are Amisulpride as a DA agent and Reboxetine (brand name Edronax) as an NE agent. Amisulpride is a D2 selective antagonist but in low dose might affect the D1 receptor. Amisulpride has successfully been used in a probabilistic learning paradigm (Jocham, Klein, & Ullsperger, 2011). Reboxetine is a selective NE reuptake inhibitor which affects the increase of NE in the cortex, and simultaneously affects a decrease in the firing rate of the LC by the auto-inhibitory effect by α2 receptors (Szabo & Blier, 2001). The cumulative effect of reboxetine on the cortex and the LC results in dose dependent increased extracellular NE in the frontal cortex (Page & Lucki, 2002). Reboxetine has been shown to improve interference suppression (Wagner et al., 2010) and target detection for emotional stimuli (De Martino, Strange, & Dolan, 2008).

How participants respond to DA and NE drugs, depends on individual difference characteristics. The response to a DA drug is modulated by working memory (WM) span storage and processing capacity. A lower WM span capacity predicts an enhanced response to the drug, whereas a high WM span predicts a decreased response (Cools & D'Esposito, 2011; Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). WM span functioning is determined by individual baseline DA levels, and consequently WM span performance mirrors a person's baseline DA level. Similarly the response to a NE drug is modulated by trait anxiety. A less anxious personality predicts an enhanced response to the NE drug, whereas a high anxious personality predicts a decreased response. Trait anxiety mirrors individual baseline NE levels (Itoi & Sugimoto, 2010; Ressler & Nemeroff, 2000). As both WM span capacity and trait anxiety may induce noise to the behavioral response to the DA and NE drugs, we will include indices for both characteristics to our experimental design. WM span capacity will be measured by the WM span subscale from the Wechsler Adult Intelligence Scale III-NL (WAIS-III-NL; Klinkenberg & Kooij, 2005). Trait anxiety will be measured by the Liebowitz Social Anxiety Scale (LSAS; Heimberg et al., 1999; Van Balkom, De Beurs, Hovens, & Van Vliet, 2004) as was previously done by De Rover et al. (2012). Summarizing, we studied the effects of DA and NE in interference suppression and post-conflict adaptation by manipulating them experimentally (pharmaceutically). We studied these effects in both well-known and novel situations, by using the arrow flanker task and the novelty flanker task, respectively. To account for individual

differences concerning responses to the pharmacological manipulation, we administered a WM span task and the LSAS anxiety questionnaire. We investigated the effect of a single acute dose of amisulpride and reboxetine in a randomized, placebo-controlled, double-blind design on the behavioral effects in interference suppression and post-conflict adaptation in an arrow flanker task and a novelty flanker task.

Method

Subjects

Twenty healthy college students participated in the study (mean age = 23 years, 13 females, 3 left handed). Females were only allowed to participate if they used an oral contraceptive to avoid menstrual cycle-dependent interactions (Becker & Cha, 1989; Becker, Robinson, & Lorenz, 1982; Creutz & Kritzer, 2004; Moldovanova et al., 2008). Participants were only included after medical and psychiatric examination by a medical doctor and a psychiatrist, respectively. Participants were instructed to abstain from alcohol 24 hrs. prior to each test session. They were also instructed to abstain from coffee, tea, cola, energy drinks, chocolate and nicotine 5 hrs. prior to each test session. They could not have used any illegal drugs within a year prior to testing. All participants provided written informed consent and received a monetary compensation ranging from 190 to 205 euro, depending on performance on the cognitive tests. The study was approved by the medical ethical committee of the Ghent University hospital and by the Belgian federal agency for drugs and health products (FAGG, Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten).

Screening

Prior to medical and psychiatric screening, participants underwent a telephone interview, consisting of questions to exclude participants at risk for known contraindications and side effects to the use of amisulpride and reboxetine. If passed successfully, participants underwent a

medical examination at the Drug Research Unit Ghent (D.R.U.G. unit) at Ghent University hospital. This included a urine sample test, a blood sample test, an electrocardiogram (ECG), heart rate (HR) measurement, blood pressure (BP) measurement, and a pregnancy test for females. If passed successfully, participants underwent a psychiatric screening at the Psychiatry Unit of the Ghent University hospital, consisting of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Participants were screened on current occurrence and on any history of psychiatric disorders. Only participants who passed all tests were included in the study.

Pharmacological design

Participants were tested on three separate occasions, once on placebo, once on a single oral dose of the DA agent amisulpride (200 mg), and once on a single oral dose of the NE agent reboxetine (brand name Edronax 4 mg). All testing occasions were separated by one week to assure complete washout of the drug before the next measurement. The order of administration was counterbalanced. Seven participants received amisulpride in week 1; reboxetine in week 2; and placebo in week 3. Seven participants received reboxetine in week 1; placebo in week 2; and amisulpride in week 3. Finally, six participants received the placebo in week 1, amisulpride in week 2, and reboxetine in week 3. On each occasion participants arrived at 08.00 hrs. for HR and BP measurements. All HR and BP measurements were taken in resting position after a 5 minutes rest. At 09.00 hrs. the substance (either placebo, amisulpride or reboxetine) were taken with 240 ml. water. Substance intake was double-blind. Participants were blindfolded during substance intake, to avoid visual detection of differences in outer appearance of the substances. Participants then stayed until 11.30 hrs. in a recreation room where they could study, read a book, watch television or do other quiet activities. Between 11.30 and 12.00 hrs. a lunch was served. The waiting period was intended for the active substances to reach peak blood levels. From 12.00 hrs. on there were 4 cycles that each started with a 10 minute resting period for HR and BP measurements and was followed by a 20 minute test session for a cognitive computer task. After 4 cycles with HR and BP measures and cognitive tasks, participants underwent their final HR and BP check after which they filled out a post-session questionnaire. The questionnaire covered all possible side effects that could be induced by either amisulpride or reboxetine. All observations were analyzed by a medical doctor who consequently decided whether participants

were dismissed or needed further medical observation. All adverse events were logged in an adverse events log. Most reported adverse events were drowsiness or mild palpitations, one participant reported mild visual dissociations.

Cognitive tasks

Participants executed 4 cognitive computer tasks, two of which are reported in the current article. These tasks are the arrow flanker task and the novelty flanker task. Both tasks are adaptations of the original flanker task developed by Eriksen and Eriksen (1974). In the arrow flanker task, each trial presents a stimulus consisting of 5 arrows oriented left or right. The middle arrow is the target to which should be responded with a left or right button press for a left or right arrow, respectively. The two arrows left and right of the target are flankers. In each stimulus, all flankers are identical (either left or right pointing) to each other. The flankers can either be identical to the target (congruent condition), or non-identical to the target (incongruent condition), which results in 4 different stimuli. The incongruent flankers interfere with the appropriate response to the target. All stimuli are presented in randomized order and in equal proportions.

In the novelty flanker task, each trial presents a stimuli consisting of 5 square-like figures. Each figure looks like a square that misses one side, resulting in 4 different figures. Each figure is arbitrarily related to one response button, which requires 4 response buttons. Responses are made with the left and right index finger and the left and right middle finger. Each stimulus of 5 figures contains a target, the middle figure, and 2 flanker figures left and right from the target. In each stimulus all flanker figures are identical to each other. The flankers can be congruent or incongruent to the target, which results in 16 different stimuli (see Figure 3). All stimuli were presented in randomized order, and congruent trials and incongruent trials were presented in equal proportions. As there were less possible stimuli in the congruent condition (4 stimuli) than in the incongruent condition (12 stimuli), contingencies for individual congruent stimuli (12.5%) differed from individual incongruent stimuli (4.17%).

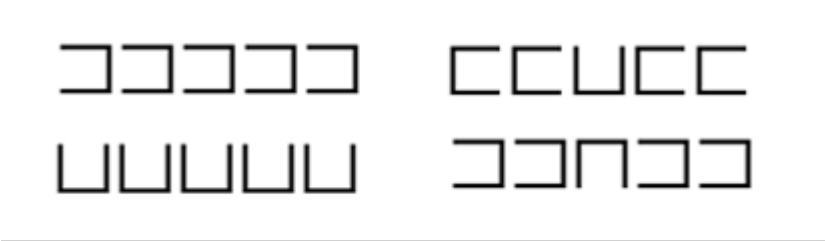

Figure 3.
Four examples of novelty flanker stimuli.

Data analysis

Only correct trials were included for analysis. RT data were analyzed using linear mixed model (LMM) analysis in R (nlme package), accuracy data were analyzed using logistic nonlinear mixed model (nLMM) analysis in R (lme4 package). In a mixed regression model analysis (either linear or nonlinear (logistic)) all single trials are included in a regression analysis, rather than the averages over trials per participant. The advantage of applying (n)LMM over standard RM-ANOVA's is that including the individual trials of all participants can strongly increase power. This approach has previously shown its use in a data set in which noise and a limited sample size caused a standard RM-ANOVA to fail (van bochove et al, in prep). As it is previously shown that there is much noise in pharmacological data, too (cools, 2008, 2009, 2011; van schouwenburg, 2013), for the current data set (n)LMM seemed the preferable method again. In RT data analyses, RT on individual trials was the dependent variable; in accuracy data analyses, accuracy (0 = error, 1 = accurate) on individual trials was the dependent variable. In both analyses (RT and accuracy) subject was random variable. Predictors were congruency status on the current trial (Cn), congruency status of the previous trial (Cn-1), pharmaceutical condition (Condition), WM span score (WM), and trait anxiety score (LSAS). The predictors Cn, Cn-1, and Condition were dummy coded: Cn (congruent = 0, incongruent = 1), Cn-1 (previous congruent = 0, previous incongruent = 1), Condition (placebo = 1, DA = 2, NE = 3). A helmert contrast was applied to all categorical predictors, before entering them into a mixed regression model. The predictors WM span score and LSAS score were continuous; a higher score indicates a higher WM span capacity or a more anxious personality, respectively. The dependent variables were RT or accuracy. RT was a continuous variable, a higher score indicates a slower RT. Accuracy was a categorical variable (inaccurate response = 0, accurate response = 1).

Although (n)LMM has major benefits, for the current data set it has one limitation. The categorical predictor Condition has three levels. A (n)LMM analysis will consequently not analyze the overall effect of Condition. In contrast, it will define two regression weights for Condition. The first regression weight indicates whether the effect of condition two significantly differs from the effect of condition one. The second regression weight indicates whether the effect of condition three significantly differs from the average effect of condition one and two. In the current data set, this means that first the effect of DA is compared to the placebo condition and second the effect of NE is compared to the average effect of the placebo and DA. This similarly applies to all interaction terms with Condition.

For the RT data, we will apply the analysis of variance function from the R nlme package, which tests whether a set of regressors improves fit of the model, similar to standard ANOVA (bates, 2010). This function provides an estimation of the overall effect of condition. However, unlike standard ANOVA, this analysis is still based on the LMM model (i.e., individual trial as unit of measurement). This function is not available for nLMM and is hence not applied to the accuracy (error) data.

Results

Results are described in three parts. First, we report LMM analyses on the RT data of the arrow flanker task and the novelty flanker task. Second, we report nLMM analyses on the error data of both tasks. In the third and final part, we include the individual difference scores (WM span and LSAS) to the RT analyses of both tasks. Error data did not allow including WM span and LSAS scores as the estimation algorithm did not converge with WM span and LSAS included. . This indicates that the accuracy data did not contain enough data points (information) to allow estimation of the contribution of the predictors. Note that (denominator) degrees of freedom in our analyses are typically larger than in standard t- and F-tests because individual trial rather than subject is the unit of measurement.

RT

Arrow flanker task. In the first analysis we tested the effect of Cn and Condition on RTs in the arrow flanker task. We first applied an analysis of variance on the LMM fitted parameters. The significant main effect for congruency (see Figure 4) showed that congruent trials lead to faster RTs compared to incongruent trials ($F(1,35969) = 3091$, $p < .001$). The significant main effect for Condition (see Figure 5) showed that pharmaceutical condition changes RTs ($F(2,35969) = 54$, $p < .001$). However, the non-significant interaction showed that the congruency effect is not modulated by the pharmaceutical condition ($p = .87$). Additionally, the LMM analysis showed that incongruent trial are slower compared to congruent trials (congruency effect), ($t(35969) = 55.5$, $p < .001$, $\beta = 33.0$). RTs in the DA condition were slower than in the placebo condition ($t(35969) = 2.51$, $p = .01$, $\beta = 1.83$). RTs in the NE condition were slower than in the (average of the) placebo and DA condition ($t(35969) = 2.25$, $p < .001$, $\beta = 10.1$). The congruency effect was not modulated by DA nor by NE (both p's > .59).

The second analysis investigated the effect of Cn, Cn-1 and Condition on RTs in the arrow flanker task. We first applied an analysis of variance on the LMM fitted parameters. The analysis revealed a standard congruency effect ($F(1,33482) = 2809$, $p < .001$) and a main effect for Condition ($F(2,33482) = 56.6$, $p < .001$). The interaction between Cn and Cn-1 showed a standard Gratton effect ($F(1,33482) = 4.96$, $p = .03$). All other predictors and interactions were non-significant (all p's > .01). Additionally, the LMM analysis showed a standard congruency effect ($t(33482) = 52.6$, $p < .001$, $\beta = 32.3$). RTs in the DA condition were slower than in the placebo condition ($t(33482) = 2.41$, $p = .01$, $\beta = 1.82$). RTs in the NE condition were slower than in the (average of the) placebo and DA condition ($t(33482) = 10.1$, $p < .001$, $\beta = 4.37$). The analysis revealed a standard Gratton effect ($t(33482) = -2.21$, $p = .03$, $\beta = -1.36$).

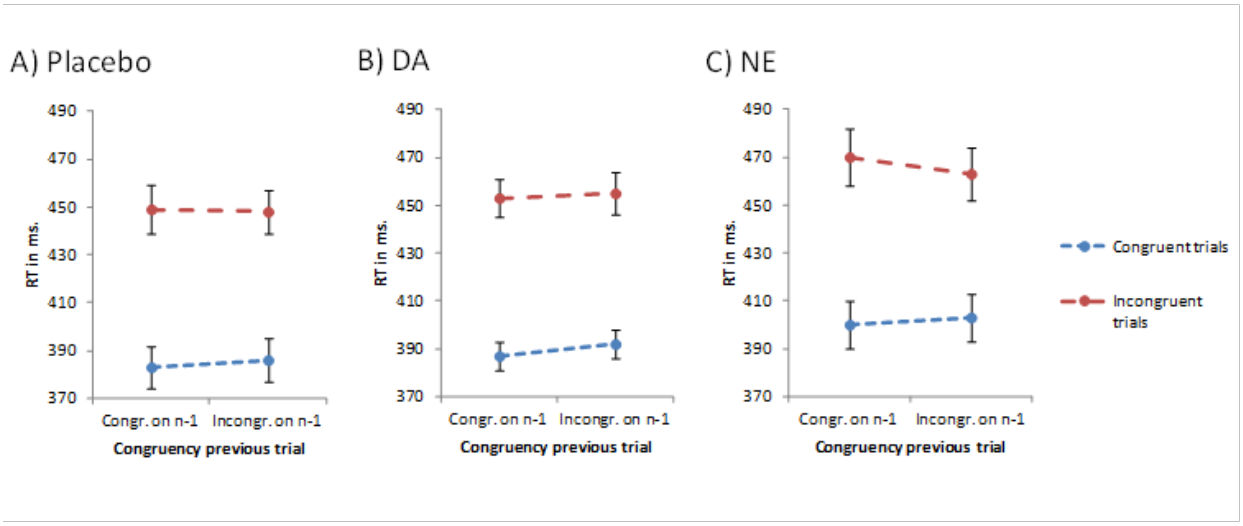

Figure 4.

RT data arrow flanker task for placebo, DA and NE condition.

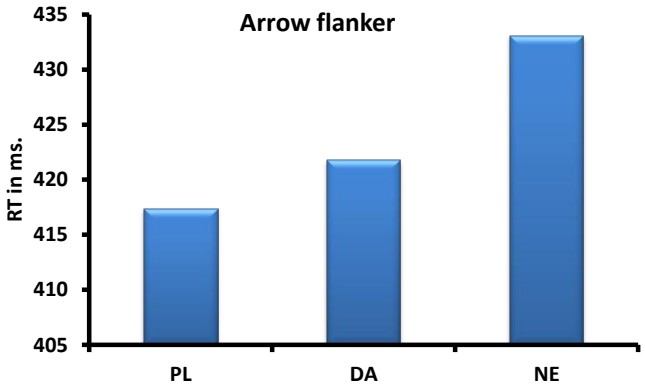

Figure 5.

RT by condition for the arrow flanker task

Novelty flanker task. The third analysis investigated the effect of Cn and Condition on RTs in the novelty flanker task. We first applied an analysis of variance on the LMM fitted parameters. There was a main effect for current trial congruency (see Figure 6; $F(1,37036) = 138$, $p < .001$). There was no main effect for Condition (see Figure 7), nor an interaction effect between Cn and Condition (all p's > .53). Additionally, the LMM analysis showed a standard congruency effect ($t(37036) = 11.7$, $p < .001$, $\beta = 17.3$).

The fourth analysis investigated the effect of Cn, Cn-1 and Condition on RTs in the novelty flanker task. We first applied an analysis of variance on the LMM fitted parameters. There was a main effect for Cn ($F(1,33887) = 140$, $p < .001$) and for Condition ($F(2,33887) = 3.55$, $p = .03$). There were no other significant main or interaction effects (all p's $> .08$), indicating that there was not even a standard Gratton effect ($p = .25$). Additionally, the LMM analysis showed a standard congruency effect ($t(33887) = 11.9$, $p < .001$, $\beta = 17.7$). Concerning the significant main effect for Condition, the LMM analysis showed that RTs in the DA condition did not differ significantly from the placebo condition (p = .33), but RTs in the NE condition were significantly slower than in the (average of the) placebo and DA condition ($t(33887) = 2.48$, $p = .01$, $\beta = 2.60$).

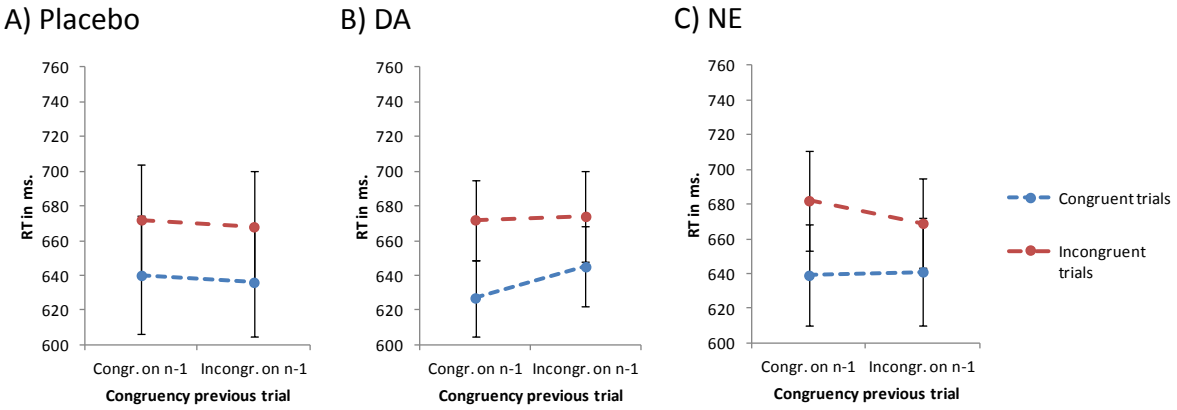

Figure 6.

RT data novelty flanker task for placebo, DA and NE condition

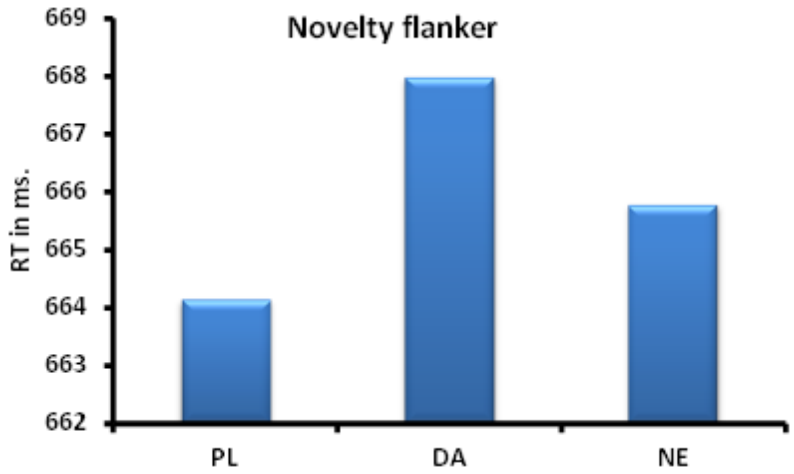

Figure 7.
RT by condition for the novelty flanker task

Accuracy

Arrow flanker task. The fifth analysis investigated the effect of Cn and Condition on accuracy in the arrow flanker task. The nLMM analysis showed a standard congruency effect (see Figure 8; z = -33.3, p < .001, β = 1.08). Accuracy in the DA condition (see Figure 9) differed significantly from accuracy in the placebo condition (z = -2.09, p = .03, β = -.08), and accuracy in the NE condition differed significantly from (the average of the) accuracy in the placebo and DA condition (z = 3.28, p = .001, β = .08). There were no significant interactions between Cn and Condition (all p's > .13).

The sixth analysis investigated the effect of Cn, Cn-1 and Condition on accuracy in the arrow flanker task. The nLMM analysis showed a standard congruency effect (z = -30.6, p < .001, β = -1.05), indicating decreased accuracy in the incongruent condition. Previous trial congruency influenced accuracy significantly (z = 5.72, p < .001, β = .20), indicating increased accuracy following a previously incongruent trial. Accuracy was decreased in the DA condition, compared to the placebo condition (z = -1.96, p = .05, β = -.07), but accuracy was increased in the NE condition, compared to the (average of the) DA and placebo condition (z = 3.21, p = .01, β = .08). The interaction term between Cn and Cn-1 showed a marginally significant standard Gratton effect (z = 1.91, p = .06, β = .07). All other interaction terms were non-significant (all p's

> .19), indicating no modulation by pharmaceutical condition of either the congruency effect or Gratton effect.

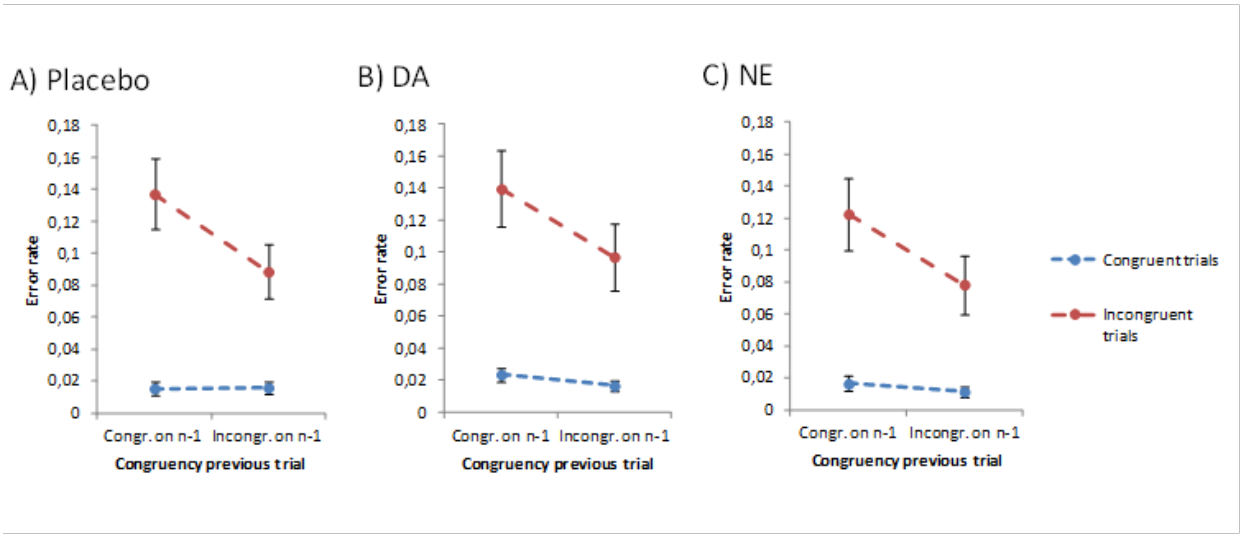

Figure 8.

Accuracy data arrow flanker task for placebo, DA and NE condition.

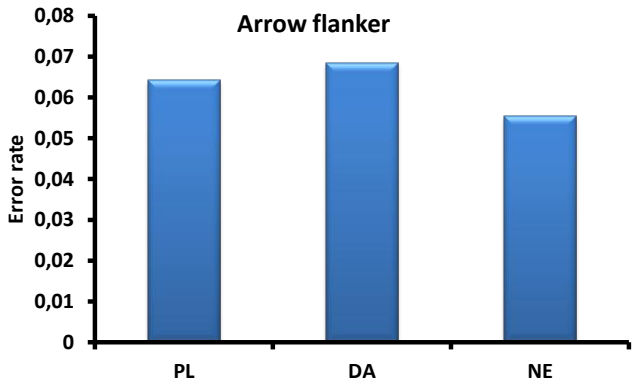

Figure 9.

Error rate by condition for the arrow flanker task

Novelty flanker task. The seventh analysis investigated the effect of Cn and Condition on accuracy in the novelty task. The nLMM analysis showed a standard congruency effect (see Figure 10; z = -2.32, p = .02, β = -.04). Accuracy was decreased in the DA condition (see Figure 11), compared to the placebo condition (z = -6.44, p < .001, β = -.143), but increased in the NE condition compared to the (average of the) DA and placebo condition (z = 5.86, p < .001, β = .08). The interaction terms between Cn and Condition (DA and NE) were both non-significant (all p's > .56) indicating that the congruency effect was not modulated by either DA or NE.

The eighth analysis investigated the effect of Cn, Cn-1 and Condition on accuracy in the novelty flanker task. The nLMM analysis showed a standard congruency effect (z = -2.19, p = .03, β = -.04). Previous trial congruency influenced accuracy significantly (z = 2.31, p = .02, β = .05) indicating increased accuracy following a previously incongruent trial. Accuracy was decreased in the DA condition, compared to the placebo condition (z = -6.33, p < .001, β = -.15), but accuracy increased in the NE condition compared to the (average of the) DA and placebo condition (z = 5.69, p < .001, β = .08). The interaction term between Cn and Cn-1 showed a significant standard Gratton effect (z = -4.10, p < .001, β = -.08). The significant three-way interaction between Cn, Cn-1 and DA indicated enhanced post-conflict adaptation due to DA (z = 2.83, p = .005, β = .07). However, the three-way interaction between Cn, Cn-1 and NE was not significant (p = .78), indicating that contrary to DA, NE did not enhance post-conflict adaptation. All other interaction terms were non-significant (all p's > .18).

The ninth analysis was similar to the eighth analysis, except that all trials containing feature repetitions were removed. The nLMM analysis showed no effect for congruency (see Figure 12; p = .97), contrary to the eighth analysis with feature repetition trials. The effect of previous trial congruency was now only marginally significant (z = 1.94, p = .05, β = .06). Accuracy was again decreased in the DA condition, compared to the placebo condition (z = -2.97, p = .002, β = -.11) and again increased in the NE condition compared to the (average of the) DA and placebo condition (z = 4.94, p < .001, β = .11). The interaction term between Cn and Cn-1 showed again a significant standard Gratton effect (z = -2.62, p = .008, β = -.08). The significant three-way interaction between Cn, Cn-1 and DA indicated enhanced post-conflict adaptation due to DA (z = 3.19, p = .001, β = .12). This demonstrated that the modulation of the post-conflict adaptation that was found in the eighth analysis was not driven by feature

repetitions. Similar to the eighth analysis, there was no modulation of post-conflict adaptation by NE (p = .24), and again all other interaction terms were non-significant (all p's > .10).

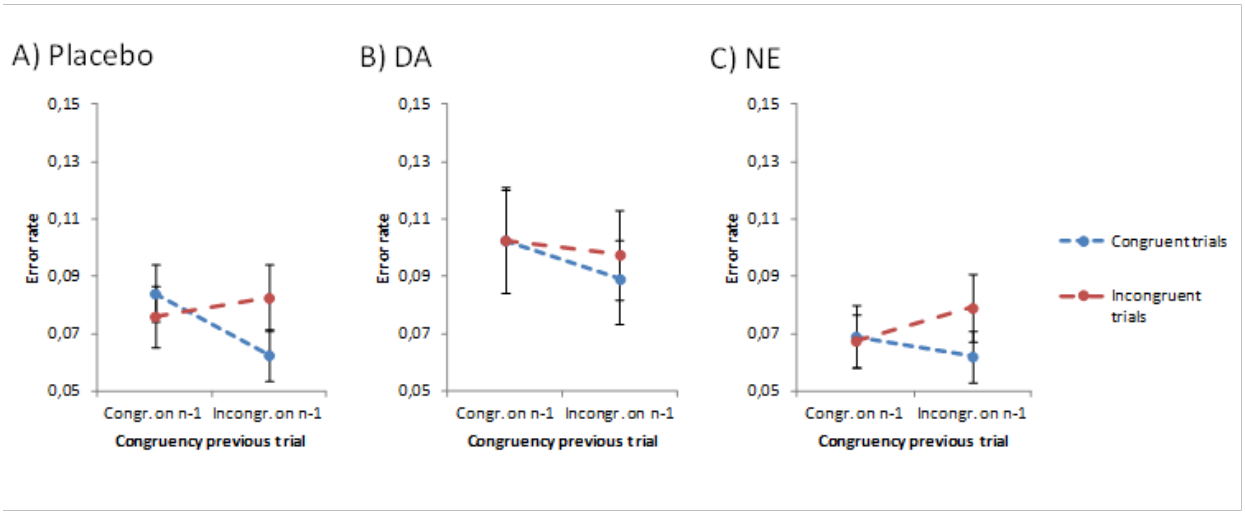

Figure 10.

Accuracy data novelty flanker task, including feature repetition trials, for placebo, DA and NE condition

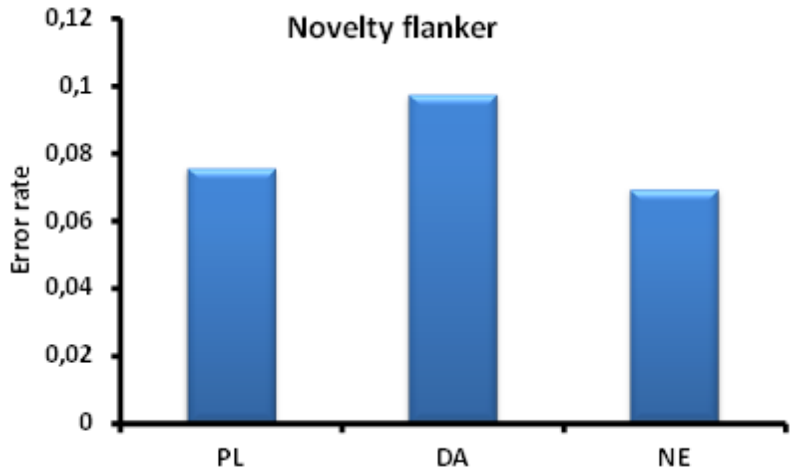

Figure 11.

Error rate by condition for the novelty flanker task

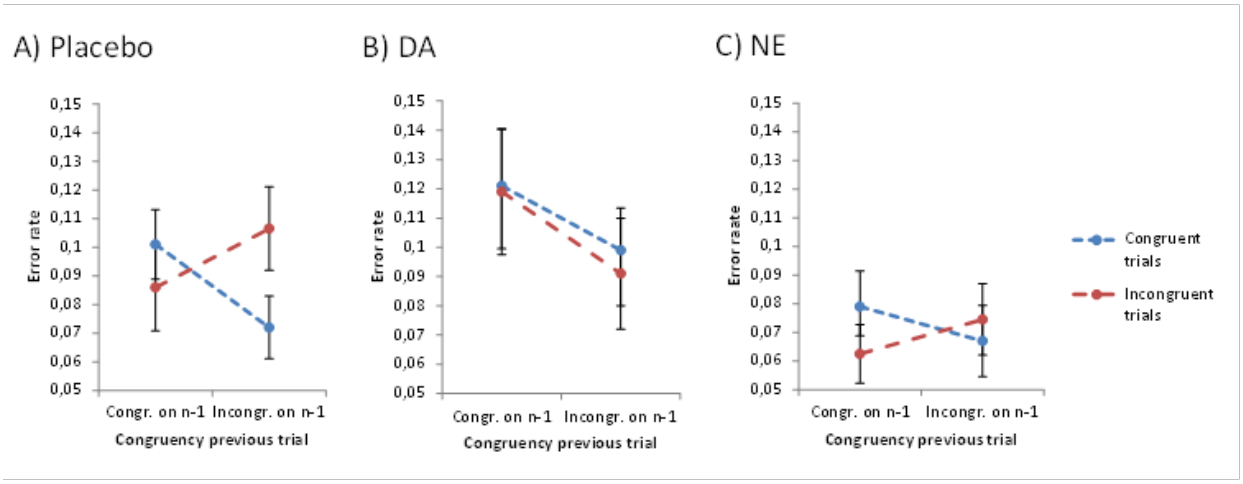

Figure 12.

Accuracy data novelty flanker task, without feature repetition trials, for placebo, DA and NE condition

RT results with WM span and LSAS included

Arrow flanker task. In the tenth analysis we again investigated the effect of Cn, Cn-1 and Condition on RTs in the arrow flanker task. However, this time we also added WM span score and LSAS score as predictors. We first applied an analysis of variance on the LMM fitted parameters. There was a significant main effect for congruency ($F(1,33449) = 2825$, $p < .001$) and Condition ($F(2,33449) = 56.9$, $p < .001$). There were four significant two-way interactions, between Cn and Cn-1 ($F(1,33449) = 4.99$, $p = .03$), between Condition and WM span score (see Figure 13; $F(2,33449) = 14.8$, $p < .001$), between Condition and LSAS score ($F(2,33449) = 5.38$, $p = .005$), and between WM span score and LSAS score ($F(1,16) = 4.51$, $p = .0498$). There were four significant three-way interactions, between Cn, Cn-1 and WM span score ($F(1,33449) = 10.9$, $p < .001$), between Cn, Cn-1 and LSAS score ($F(1,33449) = 3.85$, $p < .0499$), between Cn, WM span score, and LSAS score ($F(1,33449) = 5.31$, $p = .02$), and between Condition, WM span score, and LSAS score ($F(2,33449) = 71.7$, $p < .001$). None of the four-way interactions nor the five-way interaction were significant (all p's > .28).

Additionally the LMM analysis showed only a marginally significant congruency effect ($t(33449) = 1.86$, $p = .06$, $\beta = 17.1$). RTs in the DA condition were faster than in the placebo condition ($t(33449) = -6.96$, $p < .001$, $\beta = -78.5$), and RTs in the NE condition were slower than in the (average of the) DA and the placebo condition ($t(33449) = 10.4$, $p < .001$, $\beta = 67.7$).

Contrary to the analysis of variance, the LMM did not hold a significant Gratton effect (t(33449) = 1.49, p = .14, β = 13.7). The effect of DA and WM span on RTs showed that the higher the WM span score the more DA had a slowing effect (t(33449) = 7.85, p < .001, β = 5.77). In contrast, the effect of NE and WM span showed that the higher the WM span score the more NE had a speeding effect (t(33449) = -10.2, p < .001, β = -4.32). The effect of DA and LSAS score showed that the higher the LSAS score the more DA leads to slowing (t(33449) = 6.54, p < .001, β = 4.28). In contrast, the effect of NE and LSAS score showed that the higher the LSAS score, the more NE leads to speeding (t(33449) = -9.18, p < .001, β = -3.46). The interaction between WM span score and LSAS score was marginally significant (t(16) = 2.12, p = .05, β = .80). Contrary to the analysis of variance, the three-way interaction between Cn, Cn-1 and WM span score was not significant in the LMM (p = .15), as was the case for the three-way interaction between Cn, Cn-1 and LSAS score (p = .59). The three-way interaction between Cn, WM span score and LSAS score was significant, but hard to interpret, given the small number of participants at each level of WM span score and LSAS score (t(33449) = -2.31, p = .02, β = -.08). Similarly the three-way interactions between DA, WM span score, and LSAS score (t(33449) = -7.33, p < .001, β = -.32) and NE, WM span score, and LSAS score (t(33449) = 9.59, p < .001, β = .24) were significant, but hard to interpret, given the small number of participants at each level of WM span score and LSAS score.

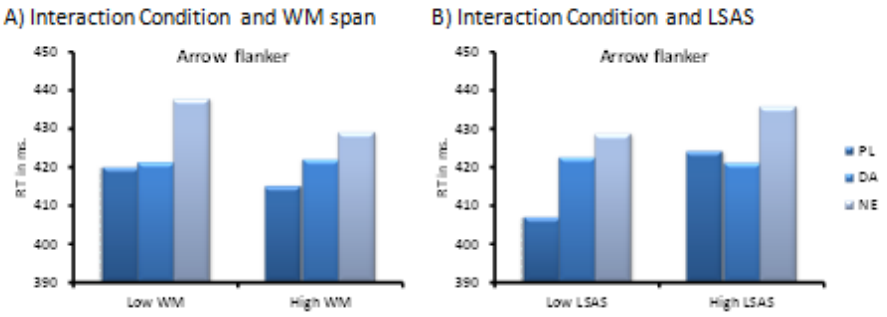

Figure 13.

RT data arrow flanker task, interactions of Condition by WM span (A), and LSAS (B)

Novelty flanker task. In the eleventh analysis we again investigated the effect of Cn, Cn-1, and Condition on RTs in the novelty flanker task, whilst adding WM span score and LSAS score. We

first applied an analysis of variance on the LMM fitted parameters. There was a significant main effect for congruency ($F(1,33854) = 144$, $p < .001$) and Condition ($F(2,33854) = 3.63$, $p = .03$). There were two significant two-way interactions, between Condition and WM span score ($F(2,33854) = 61.0$, $p < .001$) and between Condition and LSAS score (see Figure 14; $F(2,33854) = 108$, $p < .001$). However, there was no significant interaction between Cn and Cn-1 ($p = .25$), indicating that there was not significant standard Gratton effect. There were two significant three-way interactions, between Cn, WM span score and LSAS score ($F(1,33854) = 4.09$, $p = .04$), and between Condition, WM span score and LSAS score ($F(2,33854) = 214$, $p < .001$). All other interaction terms were non-significant (all p's > .07).

Contrary to the analysis of variance, the LMM analysis showed a non-significant congruency effect (p = .32). RTs in the DA condition were faster than in the placebo condition ($t(33854) = -11.0$, $p < .001$, $\beta = -310$), however, RTs in the NE condition were slower than in the (average of the) DA and placebo condition ($t(33854) = 23.1$, $p < .001$, $\beta = 373$). The effect of DA and WM span on RTs showed that the higher the WM span score the more DA leads to slowing ($t(33854) = 11.3$, $p < .001$, $\beta = 20.7$). In contrast, the effect of NE and WM span showed that the higher the WM span score the more NE leads to speeding ($t(33854) = -21.3$, $p < .001$, $\beta = -22.3$). The effect of DA and LSAS score showed that the higher the LSAS score the more DA leads to slowing ($t(33854) = 9.76$, $p < .001$, $\beta = 15.9$). In contrast, the effect of NE and LSAS score showed that the higher the LSAS score the more NE leads to speeding ($t(33854) = -20.6$, $p < .001$, $\beta = -19.3$). The three-way interaction between Cn, WM span score and LSAS score was significant, but hard to interpret, given the small number of participants at each level of WM span score and LSAS score ($t(33854) = -2.04$, $p = .04$, $\beta = -.18$). Similarly the three-way interactions between DA, WM span score, and LSAS score ($t(33854) = -10.0$, $p < .001$, $\beta = -1.08$) and NE, WM span score, and LSAS score ($t(33854) = 18.0$, $p < .001$, $\beta = 1.11$) were significant, but hard to interpret, given the small number of participants at each level of WM span score and LSAS score.

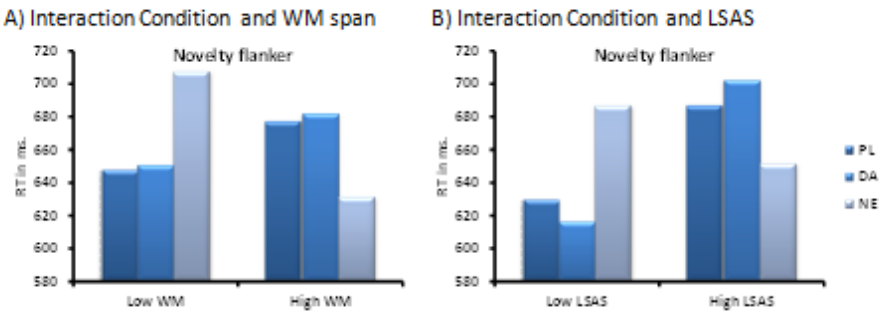

Figure 14.

RT data novelty flanker task, interactions of Condition by WM span (A), and LSAS (B)

Discussion

The current article investigated the effect of both DA and NE in cognitive control. The effect of both neuromodulators was pharmacologically manipulated. As DA agent, amisulpride was administered; and as NE agent, reboxetine was administered. Their effect in cognitive control was investigated in both a well-known and a novel situation, by administering the arrow flanker task and the novelty flanker task, respectively. Amisulpride modulated post-conflict adaptation in accuracy, but not in RTs in the novelty flanker task. It did not modulate interference suppression in the novelty flanker task. Furthermore, in the arrow flanker task, amisulpride modulated neither interference suppression nor post-conflict adaptation. Reboxetine did not modulate any index of cognitive control in either the arrow flanker task, or the novelty flanker task. Although there was no modulation of both cognitive control indices by either amisulpride or reboxetine in the arrow flanker task, the effects of both agents on RTs were modulated by both WM span and trait anxiety. Similarly, the effect of both agents on RTs in the novelty flanker task was modulated by both WM span and trait anxiety.

Our main result was obtained in the novelty flanker task. We observed a modulation by DA of the Gratton effect in the accuracy data, not in the RT data. This restriction to accuracy

data is not without precedence: The effect of cortisol (manipulated by stress) on cognitive control (in particular, Gratton effect) was located in earlier research to accuracy data, too (Plessow, Fischer, Kirschbaum, & Goschke, 2011). The precise reason for this pattern, however, is currently unclear.

In the placebo condition, we found reversed Gratton effects, meaning a smaller congruency effect following congruent trials, compared to incongruent trials. This finding is also not without precedents (e.g. Jiang, Bailey, Chen, Cui, & Zhang, 2013). According to (Mordkoff, 2012) the reason for the reversed Gratton effect in accuracy data of four-alternative choice data is due to the use of 50% congruent stimuli. In his experiment, Mordkoff (2012) explicitly compared a 25% congruent condition (i.e., the "natural" condition when stimuli are sampled at random in a four-alternative design) with a 50% congruency condition (as in our experiment), and found a reversed Gratton effect in the accuracy data in the 50% congruent condition exclusively. Also here, the reason for the precise pattern is unclear. However, whatever the reason for obtaining this pattern in the placebo (baseline) condition, it is still the case that this pattern is modulated by DA (three-way interaction Cn, Cn-1, and condition). In particular, the reversed Gratton effects seems to be abolished by DA medication. This pattern is in line with that reported by Duthoo et al. (2013), who found that the standard Gratton effect in Parkinson patients was abolished after DA medication.

After removing feature repetitions, typically Gratton effects diminish or sometimes even disappear (Mayr, Awh, & Laurey, 2003). It is argued by these authors that the effect that is interpreted to be conflict adaptation, is actually merely the result of short-term SR integration (Hommel, Proctor, & Vu, 2004). Removing trials that contain feature repetition would then lead to a diminished or vanished Gratton effect. In our case, it was opposite, with stronger (reversed Gratton) effects after feature repetition removal in the placebo condition. A natural interpretation would be that feature repetitions lead to a standard Gratton effect, so if this tendency is removed, the reversed Gratton effect becomes more pronounced.

All effects on the congruency effect and the Gratton effect were specific to DA. The absence of an effect for NE may have been due to our drug of choice for manipulating NE, namely reboxetine. There were good reasons for our initial choice for reboxetine (see introduction); however, in retrospect, reboxetine might not be the best drug to induce effects that

are detectable by cognitive behavioral tasks (Jepma, Te Beek, Wagenmakers, Van Gerven, & Nieuwenhuis, 2010; Siepmann, Mück-Weymann, Joraschky, & Kirch, 2001). Atomoxetine is often used to manipulate NE (e.g. Chamberlain et al., 2009; Graf et al., 2011). However, we refrained from using it because even a single dose of atomoxetine may induce a suicide attempt (Bangs et al., 2008; but see Monte, Ceschi, & Bodmer, 2013).

Although we included two individual difference indices, even more indices are known to mediate the response to neuromodulatory drugs. For instance the relationship between DA and reversal learning depends on striatal dopamine synthesis (Cools et al., 2009). Similarly, the effect of DA drugs on attention and cognition are mediated by anatomical fronto-striatal connection strength (Van Schouwenburg et al., 2013). It was beyond the scope of the current article to include the required positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) data to account for these individual difference indices. At the same time, not including these indices might explain some of our results.

To measure trait anxiety we applied the LSAS, as was previously done by De Rover and colleagues (2012). Future research may consider using instead the state-trait anxiety inventory (STAI; Spielberger & Sydeman, 1994). The STAI is generalized to all aspects of anxiety, whereas the LSAS only measures social anxiety.

Although WM span capacity was selected to account for individual difference in responding to DA drugs (Cools & D'Esposito, 2011; Cools et al., 2008), NE is known to influence WM span capacity as well (Arnsten, 2000, 2011; Avery, Dutt, & Krichmar, 2013; Chamberlain, Müller, Blackwell, Robbins, & Sahakian, 2006). Similarly, trait anxiety was selected to account for individual differences in the response to NE drugs (De Rover et al., 2012; Mizuki, Suetsugi, Ushijima, & Yamada, 1996). However, it may be that trait anxiety appears to be related to DA as well (Gregory & Eley, 2007; Kienast et al., 2008). Finally, there may be an interaction between anxiety and WM span capacity, as rumination increases due to high WM span capacity (Curci, Lanciano, Soleti, & Rimé, 2013). These intertwined relationships between DA, NE, WM and anxiety might explain why in our analyses WM span not only interacts with the DA condition, but also with the NE condition. Similarly it might explain why trait anxiety not only interacts with the NE condition but also with the DA condition.

The interactions between condition, WM span and trait anxiety further show that the effect of individual difference indices depends on task characteristics. Most striking in the current data set is the differential effects that both indices have on reboxetine in the arrow flanker task and the novelty flanker task. In the arrow flanker task, reboxetine increases RTs both in people with a high WM span capacity and in people with high trait anxiety. In contrast, in the novelty flanker task reboxetine decreases RTs both in people with high WM span and in people with high trait anxiety. So for the same group of people, the group with a high WM span, reboxetine is beneficial in the more complex novelty flanker task, but detrimental in the simpler arrow flanker task. This seems in line with the inverted u-shape function that NE has in WM (ref). However, this does not resolve why reboxetine deteriorates RTs in people with low WM span capacity in both the arrow flanker task and the novelty flanker task. In the group of high anxious group, reboxetine is beneficial in the novelty flanker task, but detrimental in the arrow flanker task. This raises the question why increased NE is beneficial in highly anxious people, particularly when they execute a complex task.

To sum up, in a pharmacological manipulation design we observed an effect of DA, but not NE medication, on standard indices of cognitive control. Although this is a promising methodology, the specificity of the findings clearly indicates a need for future research.

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CHAPTER 5

GENERAL DISCUSSION

The current dissertation investigated the effect of neuromodulators in cognitive control. In particular, the effects of dopamine (DA) and norepinephrine (NE) are studied in interference suppression and post-conflict adaptation. Both the effects of endogenously evoked as well as experimentally manipulated neuromodulators are studied. Furthermore the effects in well-known and novel situations are studied. Before unifying the findings on the experimental studies, this chapter will provide a brief summary of the studies reported in chapter two to four.

The study in chapter two started off with investigating the effect of endogenously evoked DA and NE in a well-known situation. The well-known situation was experimentally simulated by the arrow flanker task. DA and NE release were indexed by eye blink and pupil dilation, respectively. We found that both eye blinks and pupil dilation increase in the incongruent relative to the congruent condition. This suggests that in situations requiring increased cognitive control, both DA and NE are allocated rather quickly to serve as additional resources. Further analysis confirmed that increased DA release on the previous trial predicted increased post-conflict adaptation in the current trial. This is consistent with a proposed learning effect that DA was hypothesized to have in cognitive control. The data did not reveal a similar pattern for NE. A similar learning effect was hypothesized for NE (based on Verguts & Notebaert, 2009), but not confirmed. The finding that situations that require increased cognitive control do indeed evoke more NE, yet the increased NE does not improve post-conflict adaptation was quite puzzling. However, it is known that increased trial length decreases post-conflict adaptation (Egner, Ely, & Grinband, 2010). It might be that due to the rather long trials (2.5 sec) that were required for pupil dilation recording, partially caused the missed effects of pupil dilation.

The experimental manipulation of NE by means of vagus nerve stimulation (VNS) in patients with epilepsy as described in chapter three was therefore an excellent opportunity to further investigate the effect of NE in cognitive control. As VNS stimulates the locus coeruleus (LC) to release NE, we were able to compare cognitive control during VNS (increased NE) to

cognitive control without VNS (baseline NE). We further compared the effect of responders (50 to 100% average monthly seizure frequency reduction) to non-responders (49% or less monthly seizure frequency reduction). We tested the effect of NE in a well-known situation, simulated by the arrow flanker task. We found increased interference suppression (smaller congruency effect) in responders during VNS compared to responders without VNS. In non-responders there was no improved interference suppression due to VNS. Furthermore post-conflict adaptation was modulated in responders during VNS. However, post-conflict adaptation was deteriorated (smaller Gratton effect), instead of improved. Again in non-responders there was no modulation due to VNS. This pattern of improved interference suppression and deteriorated post-conflict adaptation is in line with the increased signal-to-noise ratio (SNR) account of the effect of NE in cognitive control (Aston-Jones & Cohen, 2005).

In the third experimental study, described in the fourth chapter, both DA and NE were experimentally studied by a single dose of a DA agent and a NE agent. As DA agent amisulpride was administered and as NE agent reboxetine was administered. The effects on cognitive control both in a well-known situation and a novel situation were tested, simulated by the arrow flanker task and the novelty flanker task, respectively. In the novelty flanker task we found amisulpride modulated post-conflict adaptation in accuracy but not in reaction times (RTs). Amisulpride did not modulate interference suppression in the novelty flanker task. Reboxetine did not modulate interference suppression or post-conflict adaptation in the novelty flanker task. In the arrow flanker task there was no modulation of either interference suppression or post-conflict adaptation by either amisulpride or reboxetine. Taken together this shows that DA modulates post-conflict adaptation. Although there was no modulation of cognitive control indices by amisulpride or reboxetine in the arrow flanker task, the effect of both agents was modulated by both working memory (WM) span capacity and trait anxiety. In the novelty flanker task we also found modulations of the effect of both agents by WM capacity and trait anxiety. However, these modulations differed between the arrow flanker task and the novelty flanker task. The most striking difference is that reboxetine increases RTs both in people with a high WM span capacity and in people with high trait anxiety when they execute the arrow flanker task. In contrast, when executing the novelty flanker task, reboxetine decreases RTs both in people with high WM span and in people with high trait anxiety. Finally it is noteworthy that WM span capacity as individual difference index for DA modulates not only the effect of amisulpride, but also the

effect of reboxetine. Similarly, trait anxiety, which was included as individual difference score for NE, modulated not only the effect of reboxetine, but also the effect of amisulpride.

Comparisons across studies show some coherent and some less coherent effects of both DA and NE in cognitive control. Both in the first study (chapter two) and the third study (chapter four), DA modulates post-conflict adaptation. This underlines the effect that DA has in cognitive control. Neither the first nor the third study provided evidence for a role of NE in cognitive control. Although it might be telling that both studies fail to find an effect, in both studies this might be due to methological limitations. Contrary to the first and the third study, the second study does find an effect of NE in cognitive control. Increased NE improves interference suppression (smaller congruency effect), but deteriorates post-conflict adaptation (smaller Gratton effect). This pattern is in line with the effect that NE has by increased SNR. Taken together these studies seem to point out that in the current situation (e.g., the current trial), increased NE release improves the ability to ignore distractors and execute the appropriate response. However, for future situations (e.g., later trials) there are benefits from DA release in the current situation, as DA increases learning (possibly via long-term potentiation) to select the appropriate response next time.

Although the results from the three studies seem quite coherent, questions remain. In the second paper on the adaptation-by-binding model (verguts & notebaert, 2009), the Hebbian learning effect that was hypothesized to underpin cognitive control was attributed to NE. None of the past three studies found an effect on Hebbian learning in cognitive control by NE. In contrast, the Hebbian learning effect that we did find, was due to DA. Can these three studies conclusively state that there is no hebbian learning effect of NE in cognitive control? We do not think so. As argued before, there are methodological limitations in all three studies. In the first study there is the extended trial length. This was needed for pupil dilation recordings, but might have prevented us from finding the pupil dilation dependent effect. In the second study, there was a huge decrease of interference suppression due to VNS, which might have left no room for further modulation by previous-trial congruency. In the third study we chose to manipulate NE by administering reboxetine for pharmacokinetic reasons. Like many other drugs applied in cognitive neuroscience, reboxetine does interact with behavioral outcomes in some studies (De Martino, Strange, & Dolan, 2008; Wagner et al., 2010), but fails to interact in other studies

(Jepma, Te Beek, Wagenmakers, Van Gerven, & Nieuwenhuis, 2010; Siepmann, Mück-Weymann, Joraschky, & Kirch, 2001). Failing to find a modulation by reboxetine might not necessarily be due to the fact that there is no effect from NE, but may instead be due to the drug of choice (reboxetine) itself.

In addition to the methodological limitations of the previous studies, there are concerns that arise when considering the literature by Arnsten (2000, 2011). There are at least three important NE receptor types, alpha1, alpha2, and beta. The influence of NE on LTP is thought to occur via the β receptor type (Arnsten, 2000). However, NE binds preferentially to the α2 receptor type (Arnsten, 2000). Only when NE is released in high amounts it will bind to the β receptor and possibly increase LTP. It can be argued that in none of the three studies NE release was high. In the first study increased NE release was either due to spontaneous fluctuations in the arrow flanker task, or evoked by incongruent stimuli of that task. We showed that perceiving five arrows that evoke multiple response tendencies, indeed increases NE release. However, possibly neither spontaneous fluctuations during the task, nor the task itself were sufficiently arousing to evoke sufficiently high amounts of NE. In the second study NE release was increased by VNS, yet patient care requires that NE release should not evoke a constant state of agitation. Consequently VNS in patients may only evoke moderate levels of NE, not enough to bind to the β receptor type. In the third study NE release was increased by reboxetine intake. Reboxetine was administered in a standard therapeutic dose, which again for patient cares' sake is not likely to evoke high levels of NE. Consistently, the behavioral outcomes of an increased RT (1.6 ms and 15.7 ms in the arrow flanker task and the novelty flanker task, respectively), suggest that it is unlikely that NE release was elevated to high levels. Revealing the proposed binding effect by NE in post-conflict adaptation might require manipulations that do evoke high levels of NE. We will elaborate on this issue at the end of the chapter, where we unfold our suggestions for future research.

Another open question is why the three studies show inconsistent effects of NE in cognitive control. NE modulated post-conflict adaptation in the second study as predicted by the SNR account, but this effect was not revealed in the first and third study. Similarly the effect of NE in interference suppression is found in the second study, but not replicated in the third. On the other hand both studies that investigated an effect by DA, found the effect. Could it be that

that it is more challenging to investigate the NE system? Nieuwenhuis and Jepma (2011) state that although a theoretical framework on the role of NE in cognition exists from 2005 on (Aston-Jones & Cohen, 2005), until 2011 any empirical testing of this framework in humans is lacking. As an explanation why the empirical testing is still lacking, they point out that investigating the NE system in humans "poses considerable challenges". The small size and the position of the LC make it virtually impossible to scan the LC by functional magnetic resonance imaging (fMRI). They further state that development of non-invasive indirect measures of NE is promising, but in its infancy. For instance pupil dilation might be used as a physiological measure, but unless other physiological methods like EEG, there are not yet standards, manuals or ready-to-use programs like Brain Vision Analyzer or EEGLAB for pupil dilation data analysis. In contrast, for DA the theoretical framework based on macaque research dates already from more than twenty years ago, elucidating the effect of DA in reward prediction error (for a review see Schultz, Dayan, & Montague, 1997). Concurrently, within the field of artificial intelligence a temporal difference learning algorithm was developed (Sutton & Barto, 1998) that nicely matched the findings of the animal research (Montague, Dayan, & Sejnowski, 1996). This raised a vast amount of literature on the role of DA in human cognition (Schultz, 2007). As the ventral tegmental area (VTA), one of the nuclei in humans that releases DA, is substantially larger than the LC, for instance fMRI research on the VTA-behavior relationship in humans is much more feasible. As the DA nuclei in animals are also substantially larger than the LC, single-cell recordings in VTA or other DA nuclei are much more common than in the LC (but see Sara & Bouret, 2012; Rajkowski, 2000, cited in Aston-Jones & Cohen, 2005). Taken together the lack of support in two of the three studies reported in the current dissertation could be at least partially due to limited accessibility and hence knowledge of the LC-NE system.

Although we found coherent evidence for the role of DA in post-conflict adaptation, questions remain here, too. In the first study the arrow flanker task was administered. In the third study, both the arrow flanker task as well as the novelty flanker task were administered. DA release did improve post-conflict adaptation in the arrow flanker task in the first study, but failed to do the same in the arrow flanker task in the third study. However, in the third study DA did modulate post-conflict adaptation, at least in the novelty flanker task. Two questions remain, however. First, what are the crucial differences between the conditions of the arrow flanker task in the first and third studies; and second, how did the novelty flanker task in the third study

compensate for what lacked in the arrow flanker task in the third study. Answering the first question requires some explanation about the situation in which both data sets were acquired. During the first study, participants were seated with their chin on a chinrest and their forehead to a forehead brace. They had to remain seated in this uncomfortable position for the duration of the task, which lasted an hour. To acquire enough trials in which participants did not blink, participants were instructed to blink less than usual. Several participants reported that it took some effort to blink less than usual and to remain focused on reducing the blink rate throughout the experiment. This might have created a kind of dual task situation. Participants not only executed the arrow flanker task, but simultaneously focused on reducing their blink rate. On the other hand, during the execution of the arrow flanker task in the third study, participants were comfortably seated in a normal chair behind a desk on which a laptop was placed. Task execution took approximately 17 minutes and there was no need to focus on reducing their blink rate, as there was no eye track recording. It might be that the conditions of the first study increased task demands sufficiently to create a situation in which the modulating effect of DA could be found. This also might relate to the second question, as one of the differences between the novelty flanker task and the arrow flanker task is increased task difficulty. The increased difficulty might be due to two factors. The first factor is that there is no need to memorize a response mapping prior to executing an arrow flanker task. Subjects automatically remember to press left for a left oriented arrow and right for a right oriented arrow. In contrast, mapping four novel figures to four arbitrary response buttons requires some rehearsal and practice. Although this argument has some face validity, it does not answer the question completely. Increased set size, e.g. the number of SR mappings, is known to decrease post-conflict adaptation (Blais & Verguts, 2012). The novelty flanker task has an increased set size (4 SR mappings), compared to the arrow flanker task (2 SR mappings). As increased set size decreases post-conflict adaptation, it is an open question why DA modulates post-conflict adaptation in the task with the larger set size, but not in the task with the smaller set size. This needs further investigation, particularly as the effect of set size in Blais and Verguts (2012) was studied in a congruency task in which the difficulty of the SR mappings was kept constant and only the set size was manipulated. In contrast, in the two flanker tasks used in the studies reported in the current dissertation, not only set size but also SR mapping difficulty differed.

The two versions of the flanker task were administered as we hypothesized that DA would improve post-conflict adaptation in a well-known situation, whereas NE would improve post-conflict adaptation in novel situations. Our aim was to differentiate the use of DA in cognitive control from the use of NE in cognitive control. From the first and third study it can be concluded that DA can improve post-conflict adaptation, both in well-known and in novel situations, but only if the complexity of the task indeed requires increased recourses to overcome the behavioral impasse. The fact that DA can modulate post-conflict adaptation when a task is executed under demanding circumstances, suggests that complexity is not necessarily defined by task characteristics, but also by the circumstances under which the task is executed. This also suggests that it is a simplification to state that DA improves post-conflict adaptation at all times. It seems to do so only when increased resources are truly needed. This further underlines the evaluative nature of cognitive control (Shenhav, Botvinick, & Cohen, 2013).

As we previously showed that the search for the effect by NE in cognitive control is limited by lack of detailed information of the effect of NE on cognition in general, I would like to suggest another NE-related study. The binding effect by NE is β receptor dependent (Arnsten, 2000), and therefore requires high levels of NE. High levels of NE are at the same time highly arousing (Aston-Jones & Cohen, 2005). The proposed effect of increased SR binding by high NE levels would be decreased RTs for response execution, whereas arousal may actually increase RTs. These effects might abolish one other. We therefore suggest to execute a study in two sessions, in which the binding effect is evoked in the first session and tested in the second session. Testing the binding effect in the second session has the advantage that the arousal from the first session is faded, and only the binding effect remains. We previously used vagus nerve stimulation (VNS) in patients with epilepsy as a manipulation. A similar, but non-invasive, device is transcutaneous vagus nerve stimulation (t-VNS; Stefan et al., 2012). The device is placed in the outer ear, where a branch of the vagus nerve ends. Via the electrode placed in the ear, the LC can be stimulated, similar to the mechanism of action of VNS. We suggest to test 3 samples of healthy participants twice. The first sample will execute the novelty flanker task in the first session with t-VNS, and in the second session without t-VNS. The second sample will execute the novelty flanker without t-VNS and the second session with t-VNS. The third sample will execute the novelty flanker task in both sessions without t-VNS. We predict a smaller congruency effect in the t-VNS condition, due to increased interference suppression. We predict

a larger Gratton effect in the second session for the sample that started in the t-VNS condition, compared to the second session of the sample that executes the task twice without t-VNS.

Another open question was which factors define the complexity of the situation that requires cognitive control. Possible factors are the number of SR mappings, e.g. set size (Blais & Verguts, 2012), or the familiarity of the SR mappings. We would suggest to compare two types of flanker task, the novelty flanker task that we used before, and the letter flanker task. The letter flanker task should be executed on a standard QWERTY/AZERTY keyboard to enable the use of the highly familiar SR mappings of the letters on the keyboard. The suggested letters for the task are D, F, J, and K, as these letters allow the use of the keys with the tactile markers, F and J. At the same time, the visual difference between these letters allows accurate target detection. Both tasks could be compared between full set size (4 SR mappings) and partial set size (2 SR mappings). In this way, we can investigate the effects of set size (2, 4) and familiarity (well-known, novel). Comparing average RT and accuracy across conditions reveals overall difficulty differences of those conditions. Comparing congruency effect on RTs and accuracy per condition, would show the effect of set size and familiarity in interference suppression. Finally, comparing the Gratton effects of the different tasks would show the effect of set size and familiarity in post-conflict adaptation.

The open question I finally would like to address is that of the particular role of DA and NE in cognitive control. In our third study we aimed to investigate how these two neuromodulators relate to each other in their effect in cognitive control. However, the difference between the arrow flanker task and the novelty flanker task didn't help us to disentangle their unique contribution. It might be that using one task, but two indices is a more fruitful approach. When we used eye blinks and pupil dilation as indices for DA and NE respectively (chapter 2), we analyzed pupil dilation only in trials without blinks (Siegle, Ichikawa, & Steinhauer, 2008). As participants blinked a lot in the first half of the experiment, a lot of information on the role of NE in this part of the learning process was lost. Deriving both indices for all trials might reveal when DA and NE play their specific role in cognitive control. This can be done either in a novelty flanker task or the letter flanker task mentioned above

The adaptation-by-binding model (Verguts & Notebaert, 2008, 2009) has led to the studies executed for this dissertation. The model was an adaptation on the conflict monitoring

model (CMM; Botvinick, Braver, Barch, Carter, & Cohen, 2001). The adaptation-by-binding model started from the conflict detection mechanism, and added Hebbian learning. However, the 2008 paper on the adaptation-by-binding model already speculates that the anterior cingulate cortex not only transmits conflict signals to subcortical structures, but also other evaluative signals. This is in line with more recent proposals arguing for different evaluative signals calculated in (dorsal) anterior cingulate (Alexander & Brown, 2011; Shenhav et al., 2013; Silvetti, Seurinck, & Verguts, 2011). Still, the adaptation-by-binding model needed adaptation itself. Although the 2008 paper suggests both DA and NE as possible candidates for adaptation-by-binding, at the start of the first study we were solely focused on the role of NE by binding in cognitive control. At some point, I realized that DA-mediated blinks might have the effect in cognitive control that we were looking for. The effect of the third study further underlines the learning effect of DA in cognitive control. As such, the NE-learning adaptation-by-binding model may have to be adapted to a DA-learning-based model.

The three studies have triggered another adaptation of the model, too. At the start of the first model we solely focused on the learning-mediated effect, based on Hebbian learning and LTP. As the first study did show that NE release increased in trials that need increased control, but that the released NE did not result in (LTP-mediated) improved cognitive control, we had to reconsider whether the effect of neuromodulators in cognitive control was only mediated by learning. Studying the NE literature redirected our attention to the role NE has in increasing the SNR. We realized that the effect of neuromodulators in cognitive control might be two-fold, both by learning and by increasing SNR. Hence, the adaptation model was prepared for the next adaptation as the second study suggested that the effect that NE has in cognitive control is in line with the SNR account. The new resulting model might trigger as much adaptations as its predecessor adaptation-by-binding, as the above clearly shows that lots of questions remain.

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NEDERLANDSTALIGE SAMENVATTING

Stel u voor dat u op weg bent vanaf uw werk om naar huis te gaan. De route is u vanzelfsprekend zeer bekend. U nadert de afslag van de snelweg die u moet nemen om thuis te komen en tot uw verrassing ziet u een oranje bord met daarop het opschrift ‘omleiding’. Hoe sterk de neiging om hier de afslag te nemen ook is, u bent prima in staat om uw geautomatiseerde gedrag te onderdrukken en de weg te vervolgen zoals het op de borden staat aangegeven. Echter, hoezeer u ook in staat bent uw gedrag razendsnel aan te passen, u zult ook merken dat wanneer u de volgende dag weer op hetzelfde punt belandt, u al veel makkelijker uw neiging om af te slaan kunt onderdrukken. Dit suggereert dat u hebt geleerd van uw ervaring van gisteren. Dit is een uitstekend voorbeeld van het soort gedrag dat we in het onderzoek voor deze dissertatie hebben onderzocht. Dit type gedrag wordt cognitieve controle genoemd. Het wordt omschreven als de mogelijkheid om vanzelfsprekend, maar ongewenst gedrag te kunnen onderdrukken, om in de plaats daarvoor minder voor-de-hand-liggend, maar gewenst gedrag te kunnen uitvoeren. Door middel van ons onderzoek hebben we willen bepalen hoe we in staat zijn om in een ogenblik te bepalen wat in de gewijzigde situatie het gewenste gedrag is.

Omdat er in het dagelijks leven altijd meer aspecten meespelen dan de aspecten die specifiek zijn voor cognitieve controle, zijn er computertaken ontwikkeld die deze situaties simuleren. Zulke taken worden congruentie taken genoemd. Een voorbeeld van een congruentie taak is de Stroop taak (spreek uit als stroep taak). In deze taak zie je steeds kleurwoorden op het beeldscherm, zoals bijvoorbeeld ‘rood’ en ‘blauw’. Nu is het niet de bedoeling dat je de woorden hardop uitspreekt, maar de inktkleur waarin de woorden zijn weergegeven. U zult merken dat wanneer de inktkleur identiek is met het kleurwoord, bijvoorbeeld het woord ‘rood’ afgedrukt in de kleur rood, dat u heel snel de inktkleur kunt benoemen. Daarentegen, wanneer de inktkleur niet identiek is met het kleurwoord, bijvoorbeeld het woord ‘rood’ afgedrukt in de kleur blauw, dat het een beetje langer duurt voordat u de inktkleur kunt benoemen. Proefbeurten waarin het kleurwoord en de inktkleur overeen komen, worden congruent genoemd; proefbeurten waarin het kleurwoord en de inktkleur niet overeen komen worden incongruent genoemd.

De reden waarom we iets langzamer reageren in de incongruente proefbeurten, is omdat het lezen van woorden een veel meer geautomatiseerd gedraging is dan het benoemen van kleuren. We lezen dagelijks, maar na de kleuterklas gebeurt het zelden meer dat iemand ons vraagt “welke kleur is dit?”. Daarmee is deze taak dus een prima simulatie van cognitieve controle. We moeten onze geautomatiseerde reactie om het woord voor te lezen onderdrukken, om de minder voor-de-hand-liggende, maar juiste actie uit te voeren. Tijdens het onderzoek dat hier beschreven wordt, is steeds gebruik gemaakt van een andere congruentie taak, de flanker taak. In de flanker taak ziet u in elke proefbeurt steeds vijf pijltjes op het beeldscherm. Het middelste pijltje geeft aan welke actie u moet uitvoeren. Als het middelste pijltje naar links wijst, drukt u zo snel mogelijk de linker knop in; als het middelste pijltje naar rechts wijst, drukt u zo snel mogelijk de rechter knop in. De twee pijltjes links en rechts geven geen extra informatie over de actie die u moet uitvoeren. Zij worden de flankers genoemd, vandaar de naam ‘flanker taak’. In een congruente proefbeurt wijzen de flanker pijltjes dezelfde kant op als het middelste pijltje. Zij leiden u dus niet af van uw doel om zo snel mogelijk op de knop te drukken die hoort bij de richting van het middelste pijltje. Daarentegen in een incongruente proefbeurt wijzen de flanker pijltjes in de richting die tegengesteld is aan het middelste pijltje. Ook al is het alleen het middelste pijltje waarop u uw reactie moet bepalen, onbewust verwarren de flanker pijltjes u toch, waardoor u net wat langzamer reageert op incongruente proefbeurten. Dat u in incongruente proefbeurten trager reageert wordt het congruentie effect genoemd. Het geeft aan hoe goed u de afleidende informatie van de flankers kunt onderdrukken. Uit eerder onderzoek is gebleken dat het congruentie effect na een incongruente proefbeurt kleiner is dan na een congruente proefbeurt. Dat effect wordt het Gratton effect genoemd. Het congruentie effect na een incongruente proefbeurt is waarschijnlijk kleiner, omdat u een beetje alerter wordt van het uitvoeren van een incongruente proefbeurt. Doordat u wat alerter bent kunt u een incongruente proefbeurt wat sneller uitvoeren. Daarentegen bent u iets te alert geworden voor het uitvoeren van een congruente proefbeurt, waardoor u wat trager reageert. Het verschil tussen uw reactie op incongruente en congruente proefbeurten wordt dus kleiner. Dit Gratton effect geeft aan hoeveel u van de vorige proefbeurt hebt geleerd, waardoor u zich beter kunt aanpassen in de huidige proefbeurt.

Om te begrijpen hoe onze hersenen onze handen zo goed kunnen aansturen om steeds de goede keuze te maken, worden vaak modellen gemaakt. Waarschijnlijk het bekendste model

betreffende cognitieve controle is het conflict monitoring model (botvinick, 2001). In het model wordt uitgelegd dat in situaties die extra cognitieve controle nodig hebben meerdere reacties geactiveerd worden in de hersenen. Omdat het bekend is dat er maar één reactie uitgevoerd moet worden, wordt er in de hersenen een alarmsignaal gegeven. Dat wordt gedaan door de anterieure cingulate cortex (ACC) een deel dat in de voorste hersenen zit. Dit alarmsignaal wordt doorgegeven aan het werkgeheugen, waardoor we ons beter kunnen concentreren op ons doel en ons minder laten afleiden door de flanker pijltjes. Nu verklaart dit model wel hoe onze hersenen weten wanneer er extra cognitieve controle nodig is, maar niet hoe onze hersenen weten wat nu precies de goede reactie is. Daarom is er een nieuw model ontwikkeld, het adaptatie-door-binding model (verguts & notebaert, 2008, 2009). In dit model wordt op een iets andere manier uitgelegd wat er in onze hersenen gebeurt wanneer er extra cognitieve controle nodig is, en daardoor kan het wel verklaren hoe onze hersenen weten wat de goede reactie is. In het adaptatie-door-binding model wordt ook verondersteld dat de ACC een alarmsignaal afgeeft als er meerdere reacties worden geactiveerd in de hersenen terwijl bekend is dat er maar een moet worden uitgevoerd. Maar dit signaal wordt volgens het adaptatie-door-binding model niet doorgegeven aan het werkgeheugen, maar aan zeer kleine gebiedjes diep in de hersenstam, zoals het ventrale tegmentale gebied (Engelse afkorting: VTA) en de locus coeruleus (LC). Als de VTA een alarmsignaal ontvangt zal het de stof dopamine afgeven, en wanner de LC een alarmsignaal ontvangt, zal het de stof norepinephrine (ook wel noradrenaline genoemd) afgeven. Beide stoffen zorgen ervoor dat een signaal beter kan worden doorgegeven van de ene hersencel naar de andere hersencel en dat hersencellen sterker met elkaar verbonden raken. Deze stofjes zorgen er dus voor dat het signaal van de goede reactie versterkt wordt, waardoor de hersenen makkelijker de goede reactie van de verkeerde reactie kunnen onderscheiden. Daarnaast zorgen ze er ook voor dat de hersencellen die de situatie weergegeven en de hersencellen die de reactie weergeven, sterker met elkaar verbonden raken. Dat is een vorm van leren. Daardoor weten we de volgende keer beter wat de goede reactie is, want we hebben geleerd van de huidige situatie. Nu lijkt het heel waarschijnlijk dat dit een goed model is, omdat het gebaseerd is op feiten die we weten over de ACC, VTA, LC, dopamine en norepinephrine. Maar of deze hersengebieden en hersenstofjes echt zo samenwerken in het geval van cognitieve controle, was nog niet onderzocht. Deze dissertatie beschrijft drie studies die zijn uitgevoerd om te onderzoeken of

dopamine en norepinephrine echt de rol spelen in cognitieve controle die wordt voorgesteld door het adaptatie-door-binding model.

Het is uiteraard onmogelijk is om de hersenen te openen om precies te zien wanneer de VTA en de LC hun stofjes afgeven en wat het effect van de stofjes op de hersencellen is. Nu kun je tegenwoordig heel goed hersenscans uitvoeren met functionele magnetische resonantie afbeeldingen (Engelse afkorting: fMRI). Het probleem voor de LC is alleen dat die zo klein is, dat het nagenoeg onmogelijk is om de LC te scannen. De doorsnede van de LC is slechts een vierkante millimeter bij een lengte van een centimeter. We hebben dus andere methoden gebruikt om te weten wanneer er norepinephrine wordt afgegeven door de LC en wat het effect daarvan is.

In de eerste studie hebben we deelnemers een flankertaak laten uitvoeren, terwijl er een filmpje van hun rechter oog werd gemaakt. Als er norepinephrine afgegeven wordt door de LC, wordt ook automatisch de pupil groter. Door van milliseconde tot milliseconde te kijken naar de grootte van de pupil, kunnen we afleiden wanneer er norepinephrine wordt afgegeven. Van hetzelfde oogfilmpje kunnen we ook afleiden wanneer de VTA dopamine afgeeft, omdat we dan knipperen, en knipperen wordt in de literatuur gerelateerd aan dopamine. Uit onze gegevens konden we afleiden dat mensen meer knipperen tijdens incongruente proefbeurten en dat de pupil groter wordt tijdens incongruente proefbeurten. Dit suggereert dat tijdens incongruente proefbeurten meer dopamine en norepinephrine vrijkomt. Verder konden we afleiden dat het congruentie effect na een incongruente proefbeurt waarbij dopamine vrijkomt nog kleiner wordt dan normaal na een incongruente proefbeurt. Het Gratton effect wordt dus sterker als er dopamine vrijkomt. Dat suggereert dat dopamine ons helpt om de volgende keer ons beter aan te passen in een situatie waarin cognitieve controle nodig is. We hadden verwacht dat we hetzelfde effect ook konden vinden voor pupilgrootte en norepinephrine, maar dat was van onze gegevens niet af te leiden.

In de tweede studie hebben we daarom speciaal het effect van norepinephrine onderzocht. Door de vagus zenuw te stimuleren, dat is een zenuw in de nek, kan de LC gestimuleerd worden om meer norepinephrine af te geven. Dit wordt gebruikt bij patiënten met epilepsie, die niet reageren op medicatie. Zij krijgen een stimulator, VNS genoemd, onder hun schouderbeen geïmplanteerd, die met een draad verbonden is met een elektrode rond de vagus zenuw. Het

effect van VNS is dat er meer norepinephrine afgegeven wordt in de hersenen, waardoor de patiënten minder epileptische aanvallen hebben. De patiënten hebben twee keer de flanker taak uitgevoerd, een keer terwijl VNS ingeschakeld was, en een keer terwijl VNS uitgeschakeld was. Hierdoor konden we het congruentie effect uit een situatie met extra norepinephrine vergelijken met het congruentie effect in een situatie zonder extra norepinephrine. Hetzelfde konden we doen voor het Gratton effect. Uit de gegevens konden we afleiden dat het congruentie effect kleiner wordt als de taak wordt uitgevoerd als VNS is ingeschakeld. Dat suggereert dat norepinephrine ons helpt om sneller op ons doel te reageren en ongewenste reacties te onderdrukken. Echter, ook het Gratton effect werd kleiner na een incongruente proefbeurt als de taak werd uitgevoerd als VNS was ingeschakeld. Dat wijst erop dat norepinephrine ons niet helpt om de volgende keer ons beter aan te passen in een situatie waarin cognitieve controle nodig is.

Omdat in studies met patiënten ook altijd factoren meespelen die je niet precies kent, omdat niet precies bekend is wat alle gevolgen van de ziekte zijn, kunnen we op grond van de voorgaande studie niet met zekerheid zeggen wat het effect van norepinephrine is. In de derde studie hebben we daarom nog eens het effect van norepinephrine onderzocht. Tegelijkertijd wilden we het effect van dopamine nog eens onderzoeken. In de eerste twee studies hebben we cognitieve controle onderzocht met een flankertaak waarin u op pijltjes moet reageren. Nu is links drukken als u een pijltje dat naar links wijst iets wat u allang hebt geleerd. We hebben daarom een nieuwe variant van de flankertaak gemaakt, waarin nieuwe figuurtjes worden getoond. Net als in de pijltjes flankertaak moet een deelnemer op het middelste van vijf figuurtjes letten. Maar in deze taak met nieuwe figuurtjes zijn er wel vier verschillende mogelijkheden voor het middelste figuurtje. Voor elk figuurtje moet een andere knop worden ingedrukt. Voordat de taak wordt uitgevoerd, moet dus worden geleerd welke knop voor elk figuurtje moet worden ingedrukt. De flanker figuurtjes kunnen weer congruent en incongruent zijn. Met deze taak wilden we onderzoeken hoe cognitieve controle wordt toegepast in situaties die nieuw voor ons zijn. In deze studie hebben we het effect van dopamine en norepinephrine onderzocht door mensen een medicijn te geven voorafgaand aan het uitvoeren van de taak. We gebruikten daarvoor het medicijn amisulpride, dat er voor zorgt dat er wat meer dopamine in de hersenen is. Het tweede medicijn was reboxetine, dat ervoor zorgt dat er wat meer norepinephrine in de hersenen is. Vervolgens gebruikten we ook een placebo, omdat we weten dat mensen zich anders gaan gedragen als ze weten dat ze een medicijn hebben geslikt. Vooraf

werden de deelnemers uitgebreid onderzocht om na te gaan of ze veilig aan het onderzoek konden deelnemen. Voor de studie moesten de deelnemers vervolgens drie dagen naar het ziekenhuis komen, steeds met een week ertussen. Op elke dag kregen ze een van de twee medicijnen of de placebo toegediend, tot ze beide medicijnen en de placebo ingenomen hadden. Op elke dag voerden de deelnemers beide versies van de flankertaak uit, de pijltjes versie en de versie met de nieuwe figuurtjes. Zo konden we het effect van zowel dopamine als norepinephrine op beide taken vergelijken. Uit de gegevens konden we afleiden dat tijdens het uitvoeren van de pijltjes flankertaak noch dopamine noch norepinephrine een effect hadden gehad op het congruentie effect en het Gratton effect. In de flankertaak met de nieuwe figuurtjes vonden we dat beide stofjes geen effect hebben op het congruentie effect, maar dat dopamine wel invloed heeft op het Gratton effect. Samengevat, de gegevens van de derde studie suggereren dat we in een bekende situatie dopamine en noreinephrine niet gebruiken om afleiding te negeren en beter op ons doel te focussen, maar in een nieuwe situatie gebruiken we dopamine wel.

De gegevens van de drie studies samen suggereren dat dopamine ons helpt om te leren welke actie we moeten uitvoeren, als we weer in een situatie zijn waarin cognitieve controle nodig is. Norepinephrine lijkt ons te helpen om afleiding beter te negeren in situaties waarin cognitieve controle nodig is. Er blijven nog wel vragen over. Bijvoorbeeld, waarom hielp dopamine wel in de pijltjes flankertaak uitgevoerd tijdens de eerste studie, maar niet bij dezelfde taak in de derde studie? Een verschil tussen de eerste en de derde studie is dat de derde studie onder makkelijke omstandigheden werd uitgevoerd. De deelnemers van de eerste studie zaten achter een apparaat dat het oogfilmpje maakte. Daarvoor moesten ze gedurende een uur doodstil in een ongemakkelijke houding zitten, en erop letten dat ze niet teveel knipperden, terwijl ze de pijltjes flankertaak uitvoerden. Tijdens de derde studie zaten de deelnemers in een comfortabele stoel, met op de tafel voor hen een laptop waarop ze gedurende slechts 17 minuten de pijltjes flankertaak uitvoerden. De omstandigheden tijdens de eerste studie waren dus zwaarder dan in de derde studie, waardoor dopamine wel hielp om te leren om het gewenste gedrag uit te voeren.

Alleen in de tweede studie hebben we gevonden dat norepinephrine ons helpt om afleiding te negeren als we ons in een situatie bevinden waarin cognitieve controle nodig is. Het is mogelijk dat norepinephrine niet zo'n grote rol speelt in cognitieve controle. Anderzijds is het ook mogelijk dat we geen effect van norepinephrine hebben gevonden omdat er in het algemeen

veel minder bekend is over het effect van norepinephrine in hersenfuncties. De werking van dopamine wordt al decennia lang onderzocht, terwijl norepinephrine nog veel korter wordt onderzocht. De relatieve onbekendheid van norepinephrine kan eraan bijgedragen hebben dat we weinig effect van norepinephrine hebben gevonden. Het is daarom belangrijk dat we verder gaan met het onderzoeken van het effect van norepinephrine op de hersenen. Het kan ertoe bijdragen dat we het effect van norepinephrine op ons gedrag beter kunnen onderzoeken.