The price of learning good from bad: motivational costs and benefits in cognition and affect

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The price of learning good from bad: motivational costs and benefits in cognition and affect

Goed of slecht? Motivationele kosten en baten in cognitie en affect
(met een samenvatting in het Nederlands)

Proefschrift

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Door

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Voor Menno en Meike……

Voor inspiratie, kracht en hoop.....

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Chapter **1**

General Introduction

Chapter 1: General Introduction

A major theme in understanding human behavior is the question how rewards and punishments motivate and shape behavior and influence cognition. Reward, in the broadest sense, means any change in situation that improves well-being or is experienced as pleasant by an organism in a given state (e.g. food delivery, availability of a sexual mate, the relief of pain, or for some species the collection of secondary valuables such as money). In direct contrast, punishment can be defined as any change in situation that threatens well-being or is experienced as aversive (e.g. painful stimulation, loss of money, or the absence of an expected reward). The survival of an organism is highly dependent on whether rewards can be successfully obtained and punishment (or threats) can be avoided. Therefore it is thought that phylogenetically old neural mechanisms have developed that subserve the direction of behavior towards reward pursuit (appetitive motivational drive) and punishment avoidance (aversive motivational drive) (Ernst & Fudge, 2009). The "Triadic model" developed by Ernst and colleagues poses that the appetitive motivational drive is supported by the ventral striatum (mainly the nucleus accumbens), while the aversive motivational drive is supported by the amygdala (Ernst, Pine, & Hardin, 2006). Goal-directed behavior results from the balance between these two motivational drives and the regulation thereof by frontal cortical brain areas.

Related to this conceptualization, the reinforcement sensitivity theory by Gray proposes that reward related behavior is supported by the behavioral activation system (BAS), which consists of the mesolimbic (including the ventral tegmentum and nucleus accumbens) and mesocortical dopamine (DA) pathways. The behavioral inhibition system (BIS) is thought to inhibit ongoing goal-directed behavior when confronted with signals of threat or punishment, and is thought to consist of the septo-hippocampal complex and its cortical efferents (Gray, 1987; Gray & McNaughton, 2003). The balance between appetitive and aversive drives in behavior is thought to be at the basis of individual differences in behavior and decision making. When multiple action options are present at the same time, a decision needs to be made as to what action is the most advantageous. Individuals with a strong appetitive drive are more likely to choose actions that are associated with high rewards, even if potential punishments are also high. This leads to risky, impulsive choices (risk-taking). On the other hand, when the aversive drive is

dominant, avoidant behavior will be more likely to occur. The functioning of the aversive circuitry is thought to be related to experience of negative feelings such as fear and anxiety.

The studies presented in this thesis are focused on the interaction between motivational drives (appetitive/aversive) and cognitive functions. Whereas cognition and motivation have long been studied in relative separation, in the recent decades a flourishing field of research on the interaction between motivation/emotion and cognition, or so called "hot" cognition, has emerged. In analogy, the term "cool" cognition is often used to refer to the study of cognitive processes without specific focus on the interaction with motivational drives. Different aspects of the motivation-cognition interaction will be addressed in the three sections in which this thesis is divided. This introduction is dedicated to the theoretical outlines of these three approaches. The next section will describe a theoretical frame work pertaining to the influence of motivational drives on learning processes. This frame work was the original basis of this PhD project. Two further sections describe research from avenues that have been explored along the way, and have proven rather fruitful. Specifically, the second section describes a series of experiments on the influence of emotion/motivation on attention. In the third section two studies on the effect of prolonged cognitive performance on motivation and cognition will be discussed

1.1. Learning good from bad

One area of research that incorporated the concept of motivated cognition already a long time ago is the area of learning research. In behaviorist tradition learning has been viewed as an associative process either promoting or inhibiting behaviors, due to their contingency with rewards or punishments respectively (reinforcement learning; Skinner, 1966). Classical conditioning on the other hand, physiological responses to rewards or punishments can be elicited by a neutral stimulus (conditioned stimulus: CS) that have been presented in contingency with these rewards or punishments (unconditioned stimulus: UCS) (Pavlov, 1927). In reinforcement learning behaviors that are contingent with a reward will increase in probability and behaviors that are contingent with a punishment or non-reward will decrease in probability. Learning models stipulate that during multiple encounters an expectation is developed of the probability and the magnitude of a reward (expected value) associated with a given behavioral response (Sutton & Barto, 1998). When faced with multiple options for behavior, the action with the highest expected value will have the highest probability of occurring. Reward prediction errors occur when an actual reward outcome deviates from the expected reward. These prediction errors are

thought to be instrumental in learning since they signal that a certain behavior is more or less advantageous than expected.

An important neural substrate underlying reinforcement learning is the midbrain dopamine system, as is demonstrated in both animal and human studies (See Figure 1). The midbrain dopamine system has been indicated as an important Single cell recordings from midbrain DA neurons in monkeys demonstrated that activity in these neurons provide a reflection of reward prediction errors (Schultz, 1998). A phasic increase in firing was found after a reward was provided. However when a reward was preceded by a predictive cue, after multiple pairings, DA neuron firing was no longer triggered by the reward delivery but by the onset of the predictive stimulus. This DA burst is therefore thought to back-propagate to the earliest predictive event. When an expected reward was not delivered however, a transient dip in firing rate could be observed. This indicates that the firing rate in the midbrain DA neurons tracks the reward expectation, and responds accordingly to violations of expectation. Human fMRI studies have shown that such reward prediction errors are also coded in the nucleus accumbens (NA) which receives its dopaminergic inputs from the VTA (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006).

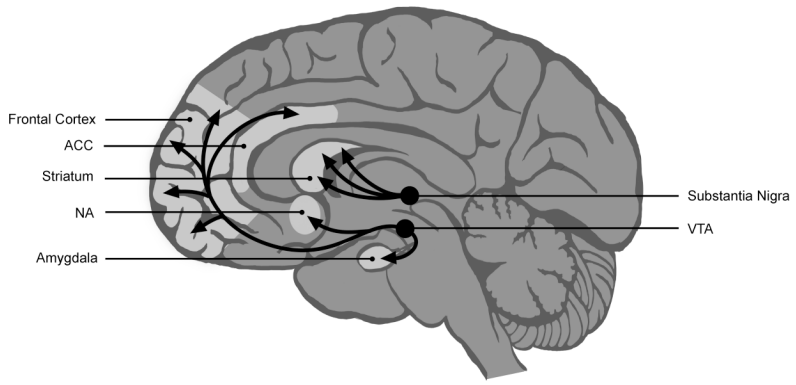

Figure 1. Midbrain Dopamine system wth projections from the Ventral Tegmental Area (VTA) to limbic regions, Amygdala, Nucleus Accumbens (NA), and to frontal and medial (Anterior Cingulate Cortex: ACC) cortical structures

Human electroencephalography (EEG; see Box 1) studies have identified a negative event-related potential (ERP) that similarly follows the reward prediction error of choice outcomes (See Figure 2; Gehring & Willoughby, 2002; Hajcak, Moser, Holroyd, &

Simons, 2007; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997). This component differentially occurs after delivery of rewards or losses (more negative after losses) and is found to be generated in the anterior cingulate cortex (ACC; Gehring & Willoughby, 2002; Miltner, et al., 1997; Segalowitz et al., 2010). Several different names have been used in the literature to refer to this component, medial frontal negativity (MFN), feedback error related negativity (fERN), and feedback related negativity (FRN). Throughout this thesis I will use the term feedback related negativity (FRN) to refer to this component. Similar to the responses of midbrain DA neurons, the FRN is strongest when an outcome is unexpected (large prediction error), and is therefore thought to be instrumental in reinforcement learning. The FRN has good test-retest reliability, and individual differences in FRN amplitude have been related to individual differences in reinforcement learning proficiency and risk taking (Santesso, Dillon, et al., 2008; Santesso & Segalowitz, 2009).

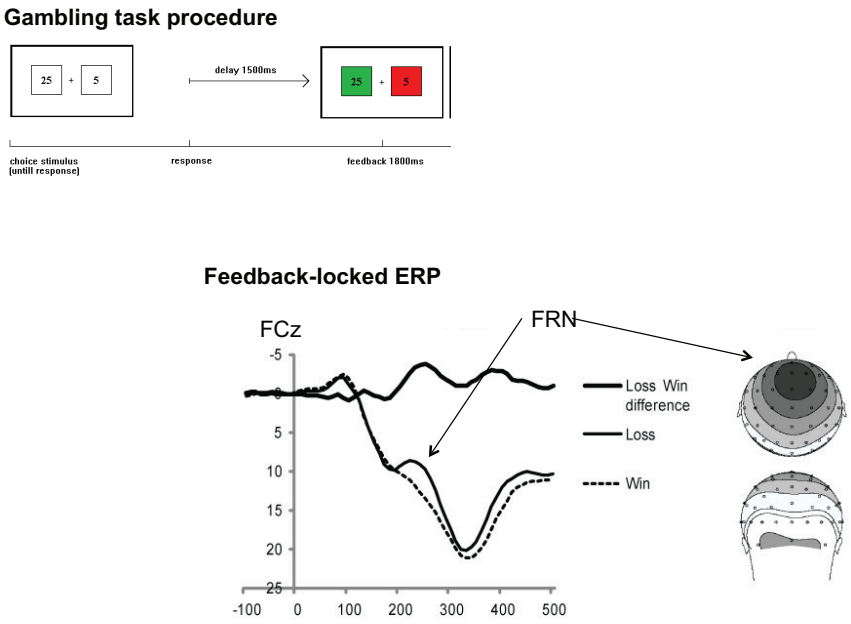

Figure 2. Example trial from a gambling task including loss and reward delivery (upper panel), and feedback related ERP responses (FRN; lower panel)

Interestingly, also oscillatory EEG activity during resting-state is found to be correlated to risk taking in a reinforcement learning task. Schutter and van Honk found that a relatively high contribution of slow frequency theta power compared to high frequency beta power (high theta/beta ratio) before task performance predicted poorer learning in a reinforcement learning task (Schutter & Van Honk, 2005).

BOX 1: resting-state EEG and event-related potentials

In this thesis brain activity has been measured using two different methods of electroencephalographic (EEG) recordings and analysis, resting-state EEG and event-related potentials (ERP). The basic priciple of EEG is that electrical activity from post-synaptic potentials in the neurons creates an electro-magnetic field which can be measured at the scalp. Since only synchronous activity in well aligned neurons will result in electro-magnetic field with suficient strength to be measured on the scalp surface, EEG mostly reflects brain activity in cortical areas.

Resting-state EEG refers to the ongoing EEG activity measured during a task-free period in which the participant is not involved in any specific cognitive activity.Resting-state EEG is characterized by oscillatory activity in different frequency bands originally termed delta (1-4 Hz), theta (4-7 Hz), alpha (7-13 Hz), beta (13-30 Hz) and gamma (30 Hz and above). The relative contributions of different frequency band activity during resting-state is found to be highly stable over time and may therefore display trait like individual differences in basal brain physiology (Corsi-Cabrera et al., 2007, Williams et al., 2005). Although not strictly separable, different neurophysiological systems are thought to underlie activity in the different frequency bands. This thesis will mainly focus on activity in the theta and beta frequency bands, and the theta/beta ratio. Theta activity is thought to originate from limbic brain structures, it has been argued to reflect emotional processing (Knyazev, 2007). High frequency beta activity is thought to be generated in widespread cortical areas, and has been related to cognitive control and inhibition of distracting stimuli (Engel & Fries, 2010). Theta/beta ratio is thought to reflect the extent to which subcortical motivational drives are inhibited by cortical cognitive control mechanisms (Schutter et al., 2004).
The event-related potential (ERP) technique more specifically examines EEG brain activity related to cognitive operations or to processing of stimuli. The brain responses to these events is usually much smaller in amplitude than the ongoing brain activity, and is therefore not identifiable in the ongoing EEG signal (low signal-to-noise ratio). By repeating the critical event many trials and averaging the EEG signal over these trials, time-locked to this event, it is possible to cancel out the uncorrelated ongoing EEG activity, and isolate the activity that is specifically related to the processing of the critical event. This technique provides a powerful tool to investigate how the brain responds differently to specific events compared to others (e.g. winning money versus losing money, or perceiving threatening stimuli versus safe stimuli). The low signal-to-noise ratio however imposes constraints on the minimum number of repetitions needed (usually 80-100 per event condition). Consequently, experimental ERP recordings take much longer time than resting-state EEG recordings. This makes it difficult to use ERPs in order to track fast changes in brain response, such as in many learning paradigms.

This finding is interesting because increased resting state theta/beta ratios are a common characteristic of patients suffering from Attention Hyper Activity Disorder (Clarke, Barry, McCarthy, & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002; di Michele, Prichep, John, & Chabot, 2005; Snyder et al., 2008), a pathology which clinical profile includes impulsivity and impaired reinforcement learning and risk taking (Drechsler, Rizzo, & Steinhausen, 2010; Ernst et al., 2003; Luman, Oosterlaan, Knol, & Sergeant, 2008; Luman, Tripp, & Scheres, 2010). From these observations, the possibility follows that resting-state EEG theta/beta ratio reflects activity in neurophysiological substrates that are involved in reinforcement learning.

The source of human scalp recorded EEG theta activity has been localized in the ACC (Scheeringa et al., 2008). Moreover it is thought to be a more indirect reflection of

rhythmic theta activity originating in the septo-hippocampal system (Gallinat et al., 2006; Mitchell, McNaughton, Flanagan, & Kirk, 2008). Beta activity is thought to be generated in cortico-cotical and cortico-thalamic loops (Pfurtscheller & Lopes da Silva, 1999), and to reflect cognitive control over subcortical motivational drives (Schutter, Leitner, Kenemans, & Van Honk, 2006). According to some researchers increased theta power in ADHD could be caused by insufficient dopaminergic inhibition of septo-hippocampal activity (di Michele, et al., 2005). In line with this idea, clinical studies have indicated that theta/beta ratio is specifically increased in a subgroup of ADHD patients that responds to stimulant medication (Clarke, Barry, McCarthy, & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, et al., 2002). Moreover, treatment with stimulant medication reliefs ADHD symptoms and normalizes theta/beta ratio in these patients (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003). In sum, it is reasonable to assume that resting-state theta/beta ratio reflects individual differences in reinforcement learning proficiency, and the functionality of the underlying neurophysiological mechanisms. In this thesis, two studies were conducted, investigating associations of theta and beta activity with reinforcement learning.

A second type of associative learning, classical conditioning, is often studied in aversive contexts. By pairing a neutral stimulus to an aversive stimulus (unconditioned stimulus, UCS), a defensive reaction can develop already upon presentation of the cue stimulus (conditioned stimulus, CS). This defensive reaction can be measured in different physiological systems, for example by heightened autonomic arousal (skin conductance response, SCR) or potentiation of the eye blink startle reflex (fear potentiated startle, FPS). It has been found that learning success dissociates high and low anxious participants (Grillon, 2002a). Therefore it has been proposed that the failure to learn the association between a CS+ and an aversive UCS (and thereby the failure to use the CS- as a cue for safety) may be at the basis of anxiety disorders due to the increased sense of unpredictability (Baas, van Ooijen, Goudriaan, & Kenemans, 2008; Grillon, 2002b). Importantly, several studies have found that participants who failed to condition showed markedly reduced sympathetic orienting responses (SCR) to the CS stimuli when these stimuli were presented before being paired to the aversive UCS (Baas, 2001; Fuhrer & Baer, 1965; Otto et al., 2007). The orienting response is a set of behavioral, physiological (autonomic an central nervous system) reactions that are thought to improve the perception of novel stimuli (Kenemans, Verbaten, Roelofs, & Slangen, 1989; Sokolov, 1983). Sufficient perception of neutral (but potentially relevant) cue stimuli may be a prerequisite

for the establishment of associative learning when this CS is coupled to a threatening UCS. The fourth chapter of this thesis discusses whether these electro-cortical reflections of the OR (in addition to SCR) can predict subsequent associative learning of a CS-UCS contingency. Investigation of OR EEG activity may be interesting because it directly reflects cortical stimulus processing, while SCR reflects autonomic responses to these stimuli.

1.2. Motivational drives in attention

The crossroad between emotion and cognition has been incorporated more recently in the area of attention. The interaction between emotion and attention was first studied in the context of anxiety. When using threat related stimuli in a behavioral attention task, anxious individuals were found to more strongly orient attention towards threatening stimuli than non-anxious individuals. This was evident as longer search times in a visual search task when threatening stimuli were used as distracters (Hodsoll, Viding, & Lavie, 2005). Also, including negative words in a Stroop paradigm causes interference with color naming in highly anxious people (MacLeod & Hagan, 1992). Other studies using modifications of the Stroop task, requiring color naming of facial pictures showing angry (threat) or neutral expressions, indicated that not anxiety but the motivational direction (approach, withdrawal) mostly determines whether people attend towards or away from threat (Van Honk, Tuiten, de Haan, van den Hout, & Stam, 2001). Attention towards threat is governed by approach related motivation, both in positive (e.g. reward seeking; Putman, Hermans, & Van Honk) and negative emotional dispositions (e.g. anger; Van Honk, et al., 2001). A great deal of research has been done showing that spatial attention is involuntarily drawn towards threat stimuli, when participants are sufficiently anxious (for reviews see Cisler & Koster, 2010; Mogg & Bradley, 1998). This effect is most often only evident for individuals that have high trait anxiety, or who suffer from phobia for the specific stimuli that are used (e.g. Fox, Russo, Bowles, & Dutton, 2001; Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Mogg, Holmes, Garner, & Bradley, 2008). The occurrence of such attentional bias is thought to contribute to the development and maintenance of anxiety disorders.

Williams et al. (1988) argued that high and low anxious individuals differ in the way they allocate their attention whenever a threat is located. After initial detection of a threat, high anxious individuals were argued to direct attention towards the source of threat. In contrast low anxious Individuals were thought to bias attention away from the threat.

Based on this model attentional retraining tasks have been developed as a therapeutic tool in the treatment of anxiety disorders. An alternative model ("cognitive-motivational" model) was proposed by Mogg and Bradley (1998). According to this model the threat value of a stimulus is assessed by a "valence evaluation system", which provides input to the "goal attainment system" where the appropriate allocation of cognitive resources and action is determined. Whenever a threat is detected, the "goal attainment system" will interrupt current goals, and attention will be oriented towards the source of the threat. This model postulates that all individuals will orient towards a threat when the threat is perceived as sufficiently strong. Anxious individuals differ from non-anxious individuals in the threshold that the valence evaluation system holds for threat detection, with high anxious individuals appraising a stimulus more easily as threat than high anxious individuals.

In this thesis an emotional modification of the exogenous spatial cuing task will be used to study the influence of threat on attention (see Box 2). In this task visual cue stimuli are coupled to a threat through association with an aversive physical stimulation (i.e. loud human scream), which is commonly experienced as highly aversive. In contrast with studies using verbal or pictorial signals of threat, in which attentional bias is mostly only induced in high anxious individuals (Fox, et al., 2001; Koster, et al., 2006; Mogg, et al., 2008; Yiend & Mathews, 2001), studies using variants of the task used in this thesis generally show attentional bias to threat in general samples, not selected for high anxiety (Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004, 2005; Van Damme, Crombez, Eccleston, & Koster, 2006; Van Damme, Crombez, & Lorenz, 2007; Van Damme et al., 2004). In this thesis cues signaling aversive physical stimulation are used to study individual differences in threat related attentional bias, and underlying neural mechanisms.

Box 2: emotional spatial cuing task

The influence of emotion on the deployment of spatial attention has been studied using a variety of tasks. In this thesis a specific variant of the exogenous spatial cuing task is used in several chapters (Ch5, 6, & 7). In the original exogenous spatial cuing task (Posner & Peterson, 1990) cue stimuli are presented at peripheral locations. Subsequently presented targets can appear in the same location as the cue (valid cuing) or in the opposite location (invalid cuing). When the stimulus onset asynchrony (SOA) between cue and target is short (up to 200ms), validly cued targets are normally responded to faster than invalidly cued targets (cuing facilitation). This reflects that attention is drawn towards the cued location. When the SOA is longer (>200ms), attention is thought to be moved away from the cued location and reaction times to valid targets become longer than those to invalid targets (inhibition of return).

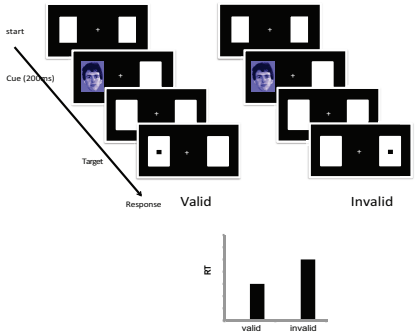

Figure 1. schematic trial sequence in the exogenous cuing task, and hypothetical reaction time data for valid and invalid trials

In this thesis a modification of this task was used in which two different cues could be presented. Cues were differentially associated with an aversive or non-aversive stimulation (loud noise or soft tone), thereby becoming predictive of threat (threat cue) or predictive of safety (neutral cue). Previous studies using this task demonstrated that the cue validity effect was increased after the threat cue compared to the neutral cue, indicating that spatial attention is drawn stronger towards threats cues than to neutral cues (Koster et al. 2004).

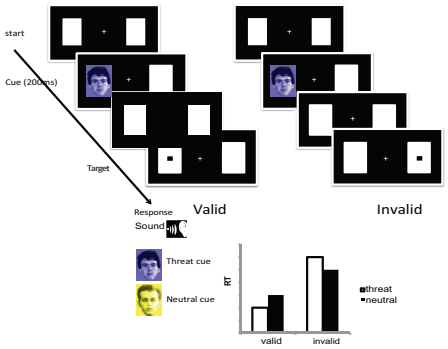

Figure 2. Emotional modulation of the exogenous cuing task, with threat cues and neutral cues, and hypothetical reaction time data

Neurocognitive studies have shown enhanced processing of visual targets when they are preceded by a threatening cue stimulus compared to targets preceded by a neutral cue. Event related EEG studies indicate that targets following threat cues are characterized by an enhanced occipital P1 component (Li, Li, & Luo, 2005; Pourtois, 2004; Santesso, Meuret, et al., 2008), which is indicative of enhanced extrastriate visual processing (Hillyard & Anllo-Vento, 1998). Moreover, processing of threat cues is found to elicit stronger early C1 component, which is thought to reflect early visual processing in V1 (Eldar, Yankelevitch, Lamy, & Bar-Haim, 2010; Pourtois, 2004). Also later contralateral parietal N2pc components have been found for threatening versus neutral cue stimuli, reflecting stimulus-driven, involuntary orienting (Fox, Derakshan, & Shoker, 2008). An fMRI study confirms that activity in the extrastriate visual cortex was enhanced for targets presented after threat cues (Armony & Dolan, 2002). Moreover activity and amygdala activity after presentation of threatening cue stimuli. Neuropsychological studies show that patients with amygdala damage do not show such increased extrastriate activity when seeing threatening cues (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004), suggesting that the amygdala is critically involved in the enhancement of visual processing in response to threat stimuli. In this thesis two studies are focused on the influence of threat on spatial attention. These studies employed both behavioral and electro-physiological measures to investigate how individual differences in anxiety and BIS affect emotional cuing and how threat related stimuli influence different stages of attentional processing (see Box 3).

Whereas the above discussed studies focus on threat as a motivationally salient stimulus feature, recently interest has grown into the influence of reward on attention allocation. Although the detection of threat is thought to be highly relevant for survival, reward detection may be equally motivationally relevant. Recent research shows that reward can influence attentional processing in various ways. Reinforcement of correct detection of a target stimulus with a high reward, increases attentional capture by this target, compared to when low rewards are provided (Kiss, Driver, & Eimer, 2009). Furthermore, when responses to targets have been highly rewarded on a given trial, inclusion of target features in distractor stimuli, causes interference in later trials (Hickey, Chelazzi, & Theeuwes, 2010a, 2010b; Libera & Chelazzi, 2006, 2009). The extent of this effect is found to be correlated to the reward related brain activity in the anterior cingulate cortex (Hickey, et al., 2010a). These findings have been interpreted in a reinforcement

learning framework, stating that an attentional bias is developed towards stimuli that predict good outcomes and away from stimuli that predict bad outcomes (Hickey, et al., 2010b). Given the findings on the influence of threat on attention discussed above, it does not seem likely that attention is actually directed away from signals that are associated with negative events (e.g. punishment or threat). The influence of reward and punishment is examined in Chapter 7 of this thesis.

Box 3: Self-report measures in neurocognitive research

Self-report questionnaires are often used to assess individual differences in personality traits related to neurocognitive functions. In this thesis several self-report questionnaires have been used that aim to measure trait anxiety and related constructs.

Trait anxiety is measured with the Spielberger State-Trait Anxiety Inventory (STAI), which consists of twenty questions pertaining to anxiety (e.g. I feel nervous and restless). Answers are given on a four-point Likert scale (total score ranging from 20 to 80).

The BIS/BAS scale was developed by Carver and White (1994) to measure the individual differences in the sensitivity of the aversive and appetitive motivational systems (behavioral inhibition system[BIS] and behavioral activation system[BAS], in accordance with Gray's reinforcement sensitivity theory). The BIS scale consists of seven item and can be scored on a four-point Likert scale (possible total scores from 7 to 28). The BAS scale consists of thirteen items and can be further divided in three subscales measuring, drive, fun seeking and reward responsiveness.

The Attentional Control Scale (ACS; Derryberry & Reed, 2002) aims to measure individual differences in attentional control capacity. It consists of twenty items that describe two subscales. The "focus" subscale measures the ability to focus attention in the face of distracting stimuli, while the "shift" subscale assesses the capacity to flexibly shift between different mental activities.
Using self-report measures in relation to neurophysiological mechanisms has several advantages and disadvantages. Self-report measures do not give a direct reflection of the related neurobiological system, even if the name of the scale may suggest so (specifically in the case of the BIS/BAS scale). Therefore it is important to find correlating neurocognitive markers in order to establish construct validity of the scales. On the other hand, the use of questionnaires has clear practical advantages. Using self-report measures, it is possible to assess large samples at relatively low costs, possibly over a distance (e-questionnaires). It should be noted that neurocognitive validation of the questionnaire strongly adds to the explanatory power of the questionnaires in such large samples.

A third issue in the emotion-attention interaction is the influence of anxiety on "cool" cognition. In the above discussed designs, the critical factor was always how attention can be drawn towards/held by stimuli that are associated with an emotionally/motivationally significant reinforcement. There is however accumulating evidence that anxiety can cause interference with "purely" cognitive processes. By "purely cognitive" I here mean using stimuli that do not have intrinsic emotional/motivational significance, or are not predictive of such motivationally salient stimuli. The "attentional control theory" proposes that anxiety-related intrusion (e.g., rumination) consumes cognitive processing capacity

(Eysenck, Derakshan, Santos, & Calvo, 2007). Consequently, anxious individuals are thought to have less cognitive control capacity available for task performance. This reduced capacity should be evident as a stronger influence of bottom-up (stimulus driven) attentional processes, at the expense of controlled (top-down) attentional control. In line with this idea, several studies have demonstrated poor attentional performance in highly anxious individuals. Furthermore, remarkably consistent inverse correlations have been found between measures of trait anxiety and scores on a self-report scale measuring attentional control capacity (Attentional Control Scale [ACS; see Box 3]; Derryberry & Reed). In this thesis correlations between trait anxiety scores and ACS scores are discussed in several chapters (Chapters 4, 5 and 8). Furthermore, despite the fact that the ACS scale is often used in anxiety research, it is not yet clear to how scores on the ACS relate to actual cognitive performance. Studies that have investigated the relation between task performance and ACS score have not found correlations (Bishop, Jenkins, & Lawrence, 2007; Reinholdt-Dunne, Mogg, & Bradley, 2009). In Chapter 8 the relation between ACS and anxiety with inhibitory control in the stop signal task is discussed. The stop signal task requires participants to respond quickly to imperative stimuli, but inhibit prepotent response tendencies, whenever stop signals are presented. This involves both attentional control and motor inhibition. Correlations between self-reported attentional control and anxiety scores and inhibitory performance may provide further insight into whether different aspects of cognitive performance are related to attentional control and to anxiety.

1.3. Costs of cognitive performance

Whereas the first two sections deal with the effects that emotion/motivation can have on cognitive functioning, the last section addresses the way in which cognitive performance can have an impact on motivation. Working long hours on cognitively effortful tasks can induce a state of mental fatigue, which is characterized by deterioration in mood, motivation and cognitive performance. At a cognitive level fatigue is found to have the most profound influence on higher cognitive control functions. Early cognitive psychology research has demonstrated that simple cognitive performance remains relatively intact with progressive time-on-task. In contrast, the coordination of more complex behavioral repertoires is found to be particularly compromised (Bartlett, 1943). These findings are supported by later findings in cognitive neuroscience (Boksem, Lorist, & Meijman, 2005;

Lorist et al., 2000; Van der Linden, Frese, & Meijman, 2003; Van der Linden, Frese, & Sonnentag, 2003).

Besides these cognitive effects, mental fatigue is also known to affect motivation. According to Meijman fatigue is characterized both by decrements in the ability to perform as well as decrements in the willingness to perform (Meijman, 1991). In many studies participants report an increasing aversion against further task performance as time-on-task progresses. In a recent review Boksem and Tops (2008) argue that the decision to invest effort into task performance is based on an unconscious cost-benefit analysis. If the potential rewards of an action outweigh the energetical costs, the action is worth performing. If the expected reward is smaller, less effort will be exerted to obtain it. This effect is known as effort discounting (Botvinick, Huffstetler, & McGuire, 2009). Animal studies show that effort discounting is strongly based on the midbrain DA system and the ACC (Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). According to Boksem and Topps (2008), the energetical costs of action get a higher weight when energetical resources are depleted. Therefore, during fatigue higher rewards should be obtained to maintain equal levels of performance.

The cognitive and motivational effects of fatigue are notoriously hard to disentangle. When motivation to perform drops during fatigue naturally task performance deteriorates. Similarly, task performance will decline due to impaired cognitive abilities. Therefore, performance decline during mental fatigue could reflect the loss of willingness to perform, or a loss of the capability to perform, or both (Meijman, 1991). In this thesis I describe two studies in which the effects of mental fatigue on cognition and motivation are examined separately. One way to circumvent these confounding factors is to examine the effects of fatigue using physiological read-out measures that can be elicited automatically, without effort for the participant, but do relate to cognitive or motivational processing (Van der Linden, Massar, Schellekens, Ellenbroek, & Verkes, 2006). For example, van der Linden et al. (2006) have measured the modulation of the eye-blink startle reflex before and after 90 minutes of fatigue inducing task performance. The startle response is a reflexive muscle contraction that can be elicited by high intensity stimuli (e.g. loud noise). Modulation of the startle reflex by a preceding stimulus (pre-pulse inhibition; PPI) is thought to reflect a mechanism that protects information processing from interfering stimuli (sensorimotor gating; Braff, Geyer, & Swerdlow, 2001). During fatigue PPI was found to be decreased, suggesting that this mechanism is no longer fully functional in a fatigued state. This method may be informative about the effectiveness of

neurophysiological mechanisms and the resulting cognitive deficits during fatigue, but, since PPI is a reflexive measure and does not require effortful processing by the participant, be minimally influenced by motivational decrease.

In the present thesis I present two studies that separately examine the cognitive and the motivational effects of mental fatigue. In Chapter 9 the effect of fatigue on involuntary attentional orienting towards novel stimuli is assessed. Specifically, it was examined whether fatigue effects are dependent on the specific nature of the cognitive activity that has led to fatigue. In daily live many types of work can lead to a state of fatigue. Also in controlled experiments many different cognitive tasks have been used to induce a state of mental fatigue. So far, it is not clear whether the detrimental effects of fatigue on cognition are dependent on the specific cognitive operations that are targeted in these tasks, or whether fatigue effects are more uniform across different fatigue inducing tasks. This question was addressed by contrasting the effects of fatigue, caused by 90 minutes of continuous performance on tasks involving different levels of working memory demands (0-Back versus 2-Back). The effects of fatigue were assessed by measuring involuntary ERP responses to novel stimuli (P3a). P3a generation is thought to be involuntary and non-effortful, but does depend on the available attention resources (Friedman, Kazmerski, & Cycowicz, 1998; Holdstock & Rugg, 1995; Zhang, Chen, Yuan, Zhang, & He, 2006). In Chapter 10 the motivational effect of mental fatigue is addressed in the context of reward and loss processing. As discussed in section 1.1, the delivery of rewards and losses is characterized by the FRN event-related potential. Since the FRN is thought to reflect a motivational response, promoting rewarded behavior and inhibiting punished behavior, it is possible that during states of low motivation (i.e. fatigue) an alteration in reward evaluation occurs. Fatigue is thought to shift the balance between the reward and effort expenditure in such a way that higher rewards are needed to motivate behavior and unrewarded (punished) behaviors are inhibited more strongly (Boksem & Tops, 2008).

1.4. Outline of this thesis

The interaction between cognition and motivational drives will be discussed in this thesis along the three themes described above. The first section focuses on the influence of motivational drives on learning. In chapters 2 and 3 resting state theta and beta activity will be examined as a biomarker for motivational disposition. In Chapter 2 we examined whether there is a relationship between rest EEG theta and beta measures and neural responses to gains and losses (FRN) in a gambling task. Chapter 3 will elaborate on how rest EEG theta and beta activity predicts reinforcement learning. Specifically, it was examined whether rest EEG differentially predicts learning to pursue rewards or learning to avoid losses. Chapter 4 describes how classical fear conditioning can be predicted from pre-task orienting responses (as measured with skin-conductance response and ERPs).

Section II focuses on the interaction between motivational drives and attention. The influence of threat related stimuli on spatial orienting is examined in Chapter 5 and 6. In Chapter 5 the influence of threat related stimuli on the reflexive engagement of attention and the disengagement of attention was examined. Specifically, it was investigated whether individual differences in trait anxiety were related to these aspects of spatial attention. Since the processes of reflexive attention rely on a relatively fast succession of cue and target stimuli, it is difficult to measure electrophysiological responses in this task, without causing overlap between cue and target related brain activity. For that reason longer cue target asynchronies (resulting behaviourally in inhibition of return) were used in Chapter 6 to study the influence of threat stimuli on attention. ERP responses to threat related and safe spatial cues were reported. In Chapter 7 we explored whether spatial attention is also affected by secondary reinforcements. By differentially associating monetary reward or loss to cue stimuli, the motivational salience of these stimuli was manipulated. The influence of these stimuli on spatial attention was examined using a cuing task similar to the one used in Chapter 5. In Chapter 8, the relation between trait anxiety and attentional control is examined in the context of "cool" cognition was investigated. Individual differences in inhibitory control were assessed using a stop signal task. Correlations between inhibitory performance and self-report measures are assessed.

Section III focuses on the after-effects of prolonged cognitive activity. The state of mental fatigue that is induced by long periods of effortful cognitive performance has detrimental effects on both cognitive functioning as well as on motivation. In Chapter 9 we aimed to dissociate effects of mental fatigue based on the nature of the specific cognitive activity that had led to fatigue. ERP brain responses were measured to novel stimuli in

rested and fatigued states. The effects of fatigued states caused by a long period of task performance involving high or low working memory demands were contrasted. In Chapter 10, the influence of mental fatigue on motivational drive was examined. ERP responses to gains and losses during gambling were recorded before and after a period of effortful (fatigue inducing) task performance. We were specifically interested in the effect of fatigue on FRN and P300 components.

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Section I: Learning good from bad: Motivational drives in reinforcement learning and classical conditioning

Chapter **2**

Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment?

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Submitted

Abstract

Increased theta (4-7 Hz)-beta (13-30 Hz) ratio in resting state EEG has been associated with risky disadvantageous decision making in the Iowa Gambling Task (IGT), and is suggested to reflect impaired reinforcement learning. From earlier findings it is unclear whether theta or beta oscillations have dissociable contributions to this relation. The first aim of the present study was therefore to examine whether resting-state EEG theta and beta were separately correlated to risky decision making in the IGT. Furthermore a second task was used to assess whether the expected relationship could be explained by differences in reward sensitivity or differences in punishment sensitivity. Results showed that resting state theta, but not beta activity, correlated negatively with reinforcement learning in the IGT. In addition, theta was found to correlate specifically with reward motivated learning in the second task, but not with punishment learning. In addition to replicating earlier findings, the present results provide novel insights into the relation between theta-beta ratios and decision making by showing that resting-state theta activity is correlated to reinforcement learning, and that this correlation may be driven by individual differences in reward sensitivity.

Introduction

The resting state electroencephalogram (EEG) provides an indirect measure of brain activity and contributions of EEG activity in specific frequency bands have been associated with affective and motivational dispositions (Coan & Allen, 2004; Putman, van Peer, Maimari, & van der Werff, 2010). Furthermore, resting-state power profiles show high test-retest reliability over time, and are thought to reflect stable, trait-like indices of brain function (Jausovec & Jausovec, 2007; Williams et al., 2005). It has recently been found that the ratio between low frequency 4-7 Hz theta waves and fast 13-30 Hz beta waves (theta/beta ratio) was predictive of learning performance in the Iowa gambling task (Schutter & Van Honk, 2005). In this task people need to learn to make choices based on the balance between reward and punishment outcomes. Advantageous choices are characterized by frequent low gains, and infrequent low losses, resulting in a net gain. Disadvantageous choices are associated with frequent high gains, but infrequent higher losses, leading to long term loss (Bechara, Damasio, Damasio, & Anderson, 1994). Individuals with high resting-state theta/beta ratio less strongly developed a preference for advantageous choices as compared to individuals with low theta/beta ratio (Schutter & van Honk, 2005). This finding indicates that resting-state theta/beta ratio can serve as a marker for risky decision making.

Decision making in the IGT, however, cannot be equivocally attributed to a single motivational process. Choices that lead to long term loss are associated with both high gains and high losses. Therefore, impaired learning in this task could be due to an excessive drive to obtain rewards, or alternatively to a decreased propensity to avoid punishment. It is possible that resting-state EEG in a particular frequency band specifically relates to either one of these tendencies. Investigating the specificity of this relation is of interest because reward processing and punishment processing are thought to be partially governed by different brain structures. While the midbrain dopamine system and the striatum are implicated in both reward processing and in punishment processing, the anterior insula seems to be additionally involved in punishment (Bresnahan, Anderson, & Barry, 1999; Matthews & Amelang, 1993). Furthermore, reward and punishment prediction errors, which are instrumental in reinforcement learning, are thought to be carried by midbrain dopamine (DA) serotonergic (5-HT) raphe nucleus signals respectively (Bechara, et al., 1994; Knyazev, 2007; Schultz, 1999). As such, impaired learning of risky decision making in high theta/beta individuals could be related to either of these systems. In order to examine whether resting-state EEG was specifically related to reward or

punishment sensitivity, we incorporated a second task that separately assesses these two motivational systems (Pessiglione et al., 2006). In this task stimuli are associated with either a chance to win money, or a chance to lose. Reward sensitivity would be expressed as the propensity to choose gain-related stimuli, while punishment sensitivity is reflected in the extent to which loss-related stimuli are avoided. Resting-state EEG was measured before participants performed the two gambling tasks. Correlations between resting-state EEG and IGT learning scores, and reward and punishment sensitivity were analyzed.

A further issue is whether theta and beta activity have dissociable contributions to the expected correlations. It has been argued that increased theta/beta ratio is mainly due to inter-individual variation in theta activity (di Michele, Prichep, John, & Chabot, 2005; Snyder & Hall, 2006). It may therefore be expected that correlations between theta/beta ratio and gambling performance are mostly related to theta power. In order to evaluate whether baseline theta and beta activity have separate contributions to risk learning in the gambling tasks, correlations between task performance and theta and beta activity were analyzed separately.

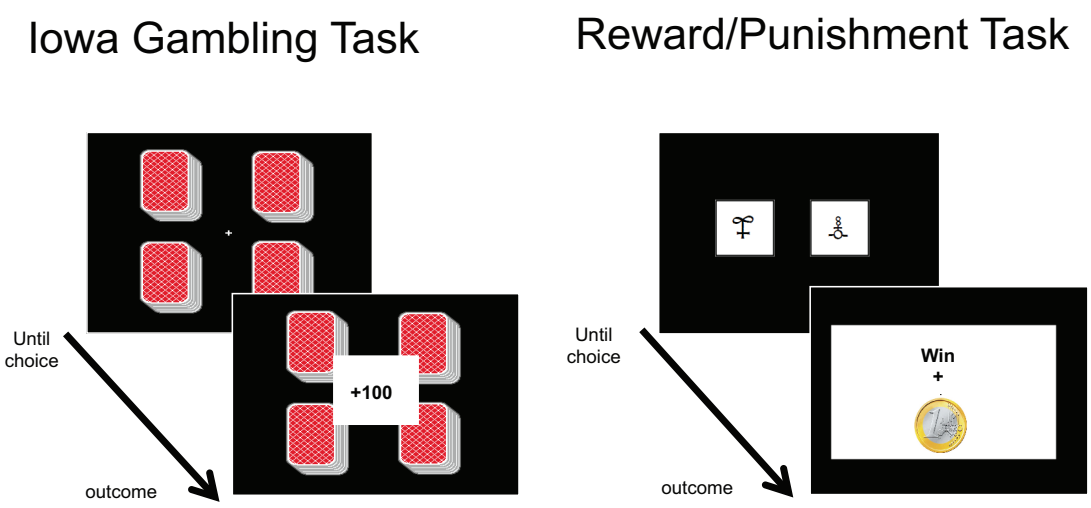

Figure 1. Trial procedures of the Iowa Gambling Task and the Reward/Punishment Task

Methods

Participants

Thirty-one healthy participants (8 males; mean age = 23.2, sd = 5.7) were recruited from Utrecht University campus. All participants had normal or corrected-to-normal vision. Four participants were left-handed, all others were right-handed. All participants signed informed consent before starting the experiment, in accordance with the declaration of Helsinki. Participants received payment or course credits for participation.

EEG recording

Resting state EEG was measured from 9 electrodes placed according to the international 10/20 system (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). Vertical and horizontal EOG was recorded with electrodes placed above and below the left eye, and at the outer canthi of each eye. EEG was recorded with BioSemi ActiveTwo Ag/AgCl active electrodes, using the CMS/DRL system as online reference. Four minutes of resting-state EEG were recorded (2 minutes eyes open, 2 minutes eyes closed). EEG analysis was done following methods described in earlier studies (Schutter & van Honk, 2005). Data were offline referenced (average reference), filtered (1 Hz high-pass, 30 Hz low-pass), and divided in to 4-second segments. Automatic eye movement correction was applied (Gratton, Coles, & Donchin, 1983), and segments containing muscle or other artifacts (activity exceeding ± 60 μV) were excluded from further analysis. Spectral power estimation was done with a Fast Fourier transformation (Hamming window: 10%). Power values in the theta band (4-7 Hz), and beta band (13-30 Hz), and theta/beta ratios were calculated.

Iowa Gambling Task

A computerized version of the Iowa Gambling Task was used (See Figure 1). Participants were instructed to choose from four decks of cards by clicking on one deck using a mouse. After choosing a card the amount that was lost or won was presented in the middle of the screen. Unbeknownst to the subjects, two decks provided frequent large rewards, but infrequent larger losses (disadvantageous decks), adding up to a net loss over trials. The other two decks (advantageous decks) were associated with lower gains. Infrequent losses, however, were also less high, creating a positive expected value. The task lasted for 100 trials, and participants were instructed to try to win as much money as possible. Performance was quantified as the percentage of advantageous choices per block of 20

trials. Learning score was calculated as the difference between the first block and the last block.

Reward-punishment sensitivity

The reward-punishment task was adapted from Pessiglione et al. (2006). Subjects had to learn to distinguish between symbols that were presented in pairs. For one pair, one symbol was associated with a high chance of winning money and a lower chance of winning nothing (80% win, 20% nothing). The other symbol was associated with the reversed reward probability (20% win, 80% nothing). For a second pair, one symbol was characterized by a high probability of losing (80% loss, 20% nothing), while the other symbol had a reversed loss probability. Outcome feedback was provided after every trial by presenting a picture of a euro coin together with the word 'win' or 'lose' for winning and losing trials respectively. On trial in which nothing was won or lost, only the word 'nothing' was presented (without showing a euro coin). A third (neutral) pair did not yield any rewards or losses. For one symbol in this neutral pair, a euro coin was presented accompanied by the word 'look', on 80% of the trials, and the word 'nothing' was presented on 20% of the trials. For the other symbol the outcome probability was reversed. Neither outcome feedback for this pair resulted in a loss or a gain. Participants were not aware of the reinforcement schedule when starting the task. They had to learn by trial-and-error, and were instructed to earn as much money as possible, while keeping losses to a minimum. On every trial one stimulus pair was presented. Participants could choose for the left or right symbol by pressing a corresponding button. The position of the symbols on the screen was randomized, and trials for each stimulus pair were randomly intermixed. A total of thirty trials per stimulus pair were completed. Performance was quantified as the average of correct choices per block of 10 trials, for the win and the loss pairs separately. Learning scores were calculated as the difference between the first block and the last block.

Statistical analysis

The relation between learning scores from the IGT and from the reward/punishment task with resting state theta/beta ratio's was determined at midline electrode sites (Fz, Cz, Pz). Because of non-normal distribution of resting-sate EEG parameters non-parametric Spearman's correlations (rho) were calculated. To analyze whether any correlations were specific to theta or beta power, separate Spearman correlations were calculated between

learning scores and theta and beta power separately. In addition, median-split divisions based on theta-beta ratio and theta power were calculated, and used in a Resting-state Group (high theta, low theta) x Block (1, 2, 3, 4, 5) ANOVA for the IGT, and a Resting-state Group (high theta, low theta) x Block (1, 2, 3) x Condition (gain, loss) ANOVA for the reward/punishment learning task.

Results

Iowa Gambling Task

In the IGT participants are presented with four decks of cards (see Figure 1). By trial and error they have to learn to distinguish between the advantageous decks (two good decks) and the disadvantageous decks (two bad decks). Performance is quantified as the percentage of advantageous choices within blocks of 20 trials. Learning scores were calculated as the difference between the last and the first block. Correlational analysis showed that IGT learning scores were significantly correlated with resting-state theta/beta ratio at Fz (rho = -.36, $p < .05$), but not a at Cz and Pz (p's > .1), indicating that individuals with higher frontal theta/beta ratio's showed poorer learning. In order to examine the contributions of theta and beta power to the observed relation, correlational analyses yielded a significant correlation between IGT learning score and theta power (rho = -.48, $p < .01$), but not beta power (rho = .18, p = .33).

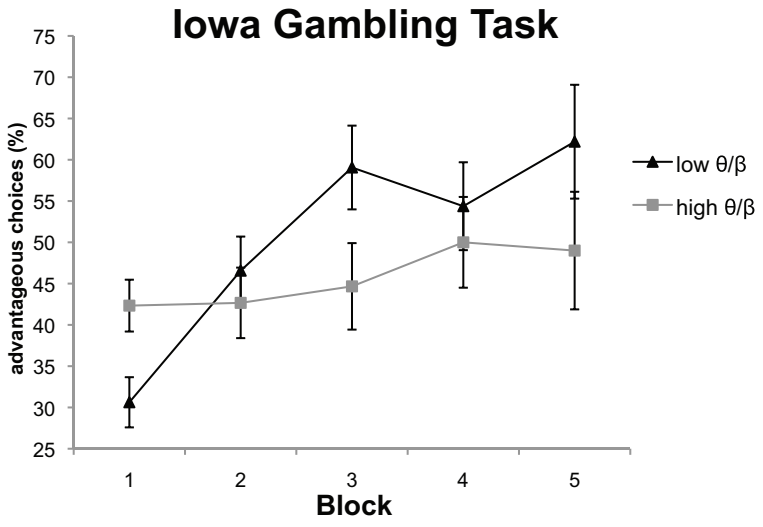

Figure 2. Percentage of advantageous choices in the Iowa Gambling Task for high and low theta/beta individuals. Error-bars represent ± 1 SEM.

Median-split comparison (See Figure 2) of individuals with high and low theta/beta ratio, yielded a significant interaction between IGT block and theta/beta group ($F(4,26) = 2.87$, $p < .05$, $\eta^2_p = .09$), Follow-up analyses for high and low theta/beta groups separately showed a significant Block effect for the low theta/beta group ($F(4,12) = 3.89$, $p < .05$, $\eta^2_p = .56$), but not for the high theta/beta group ($F < 1$). This effect of block indicated that individuals with low resting-state theta/beta ratio learned to avoid disadvantageous choices over time, while high theta/beta individuals did not show significant improvement.

Reward/Punishment task

Correlation analysis showed that learning scores for reward, punishment and neutral trials were not significantly correlated with resting-state theta/beta ratio (p's > .4). Resting-state theta power, however, was highly correlated with reward learning score (Fz: rho = .40, $p < .05$; Cz: rho = .42, $p < .05$; Pz: rho = .48, $p < .01$), but not with learning scores in punishment and neutral trials (p's > .4). Resting-state beta power again did not correlate with either reward, punishment or neutral learning score (p's > .1

Subsequently, a median-split analysis was performed to compare individuals with high and low resting-state theta power (Figure 3). A Block (1, 2, 3) x Condition (Gain, Loss, Neutral) x Group (high theta, low theta) yielded a significant Block x Condition x Group 3-way interaction ($F(4,116) = 3.43$, $p < .05$, $\eta^2_p = .11$). Follow-up analyses were performed for the Gain, Loss and Neutral conditions separately. Mirroring the correlational analysis a significant Block x Group interaction was found in the Gain condition only ($F(2,58) = 4.63$, $p < .05$, $\eta^2_p = .14$). Further disseminating the interaction in the gain condition showed that in block 2 and 3, the high theta group chose significant more often for the 'win' stimulus in win-trials (Block 2: $t(14) = 2.7$, $p < .05$; Block 3: $t(14) = 4.02$, $p < .001$). The low theta group did not score above chance level in any block in this condition (all p's > .3). Finally, the ANOVA for the Loss condition did not yield a similar interaction , but a significant main effect of block ($F(2,58) = 4.0$, $p < .05$, $\eta^2_p = .12$) was observed, indicating that both high and low theta groups learned to avoid losses. In the neutral condition no significant main effects or interactions were found (all p's > .1). These findings indicate that individuals with high resting-state theta power showed more reward-seeking behavior than low theta individuals. On the other hand, both groups showed equal punishment sensitivity.

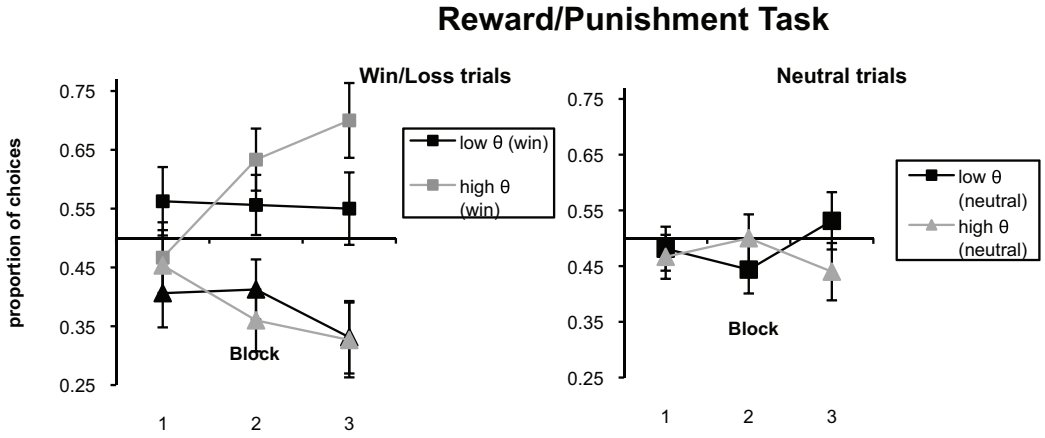

Figure 3. Performance in the Reward/Punishment Task for high and low theta individuals. The left panel shows mean proportion of high probability reward choices in gain trials and high probability punishment choices in loss trials. The right-hand panel shows choice patterns in neutral trials. Error-bars represent ± 1 SEM.

Discussion

The present results demonstrated a negative association between resting-state EEG theta/beta ratio and learning performance in the Iowa gambling task, replicating earlier findings (Schutter & van Honk, 2005). This association was primarily driven by a correlation between IGT performance and theta power, while no correlations between IGT learning and beta power were found. Moreover, in the second task, baseline theta power was primarily correlated to reward sensitivity, and not punishment sensitivity. Again, no correlations between performance measures and beta power were found. These data show that the association between resting-state theta/beta ratio and risk learning can be explained by individual differences in slow wave theta power. Slow wave theta EEG is thought to reflect the interaction between subcortical and cortical limbic structures, including the hippocampus and the cingulate cortex (Mitchell, McNaughton, Flanagan, & Kirk, 2008; Scheeringa et al., 2008). While event-related theta EEG has been found to be involved in error/punishment processing (Kamarajan et al., 2008), emotion processing (Aftanas, Pavlov, Reva, & Varlamov, 2003) and the resolution of conflict between response options (Cavanagh, Cohen, & Allen, 2009), increased theta activity during resting state conditions has been associated with impulsivity in patients with ADHD and healthy volunteers (Aftanas, et al., 2003; Bresnahan, et al., 1999). The present data therefore may suggest that resting-state theta reflects individual differences in motivational balance that

influence risk learning and reward processing. In line with this interpretation, recent findings from our lab showed an association between resting state theta/beta ratio, and risk taking and feedback related EEG activity during a gambling task. A subset of the sample showed a positive correlation between behavioral risk-taking and resting-state theta/beta ratio (Massar et al., in press). For this group, theta power was negatively correlated with feedback related ERP activity during reward/punishment processing (feedback related negativity: FRN). Taken together, these findings suggest that resting-state EEG theta activity reflects the propensity to seek rewards in reinforcement paradigms.

The finding that resting-state theta was related to reward sensitivity but not punishment sensitivity in the reward/punishment task, is of interest because in the study originally reporting this task, reward learning (but not punishment learning) was found to be affected by pharmacological manipulations of dopamine (Pessiglione et al. 2006). Since clinical ADHD studies showed that increased resting-state theta/beta ratio differentiates patients that respond well to dopaminergic medication from patients that do not respond (Clarke, Barry, McCarthy, & Selikowitz, 2002), it could be thought that resting-state theta activity may be a reflection of the functionality of the DA system. The direct involvement of DA in resting-state theta in healthy individuals will need to be verified in future studies. However, given the strong link between DA function and reward learning, finding a biomarker for DA function would be an interesting possibility.

In sum, the present study shows that high resting-state theta power is a useful biomarker associated with poor risk learning and increased reward sensitivity. Furthermore, resting state theta power seems to be the main determinant of correlations between risk learning and theta/beta ratio as found earlier (Schutter & van Honk, 2005).

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Chapter **3**

Resting-state EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking

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Abstract

Objective. Feedback-related negativity (FRN) is associated with reinforcement learning and punishment sensitivity. Furthermore, reinforcement learning proficiency can be predicted from pre-task resting-state EEG theta/beta ratio. In this study it was examined whether there was a relation between resting-state theta/beta ratio in rest and FRN amplitude during a gambling task, and if such a correlation would be related to theta activity or to beta activity.

Methods. Resting-state EEG and self-report measures of punishment sensitivity (BIS) were obtained from 52 healthy volunteers. FRN was recorded during a gambling task.

Results. FRN amplitude was negatively correlated with theta/beta ratio in high BIS individuals. Furthermore, source localization indicated that resting-state theta activity generated in the anterior cingulate cortex (ACC) accounted for this correlation. For low BIS individuals no correlation was found.

Conclusion. High resting-state theta/beta ratio is associated with low amplitude FRN and high risk-taking in individuals that are sufficiently sensitive to punishments. This relationship is carried by ACC resting-state theta activity.

Significance: This link between resting-state brain activity, self-report measures and feedback processing may contribute to further understanding the biological basis of conditions that are accompanied by abnormal theta/beta ratio and reward processing, such as attention deficit hyper activity disorder (ADHD).

Introduction

Background brain activity as measured in resting-state EEG shows individual differences in spectral power profiles. These differences are found to be highly stable over time and are therefore thought to reflect basic physiological properties of brain function (Corsi-Cabrera et al., 2007, Williams et al., 2005). As such, resting-state EEG profiles have been related to personality traits and affective styles (e.g. Coan and Allen, 2004, Hewig et al., 2006, Jausovec and Jausovec, 2007). Interestingly, the relative contribution of slow wave theta activity (4-7 Hz) compared to fast wave beta activity (13-30 Hz), quantified as theta/beta ratio, has been related to impulsive behavior such as faster responding (van Dongen-Boomsma et al., 2010), and lower response inhibition (Putman et al., 2010). Furthermore, high theta/beta ratio has been associated with increased risk taking in the Iowa Gambling Task (Schutter and Van Honk, 2005). These findings point towards a relation between resting-state theta/beta ratio and behavioral inhibition, such that people with high theta/beta ratios are more impulsive and tend to take higher risks. This idea is all the more interesting since increased theta/beta ratio and theta power are common features of attention-deficit/hyperactivity disorder (ADHD; Clarke et al., 2002b, di Michele et al., 2005, Snyder and Hall, 2006), a condition that is characterized by impulsivity and risk taking (Ernst et al., 2003, Masunami et al., 2009, Sonuga-Barke et al., 2008).

It has been suggested that high theta/beta ratio mainly reflects increased power in the theta band (di Michele, Prichep, et al. 2005; Snyder and Hall, 2006). Rodent studies show that theta EEG is generated for a large part in the septo-hippocampal system (Vertes and Kocsis, 1997). Efferent connections from the hippocampus transfer rhythmic theta activity to limbic cortical areas, including the cingulate cortex (Gray, 1982, Gray and McNaughton, 2000). Extended cortical areas have been associated with theta-frequency EEG activity during resting state in human EEG studies. A combined EEG and fMRI study found that resting state EEG theta power correlated with BOLD activity in a network including frontal, parietal and medial cortical areas, with a maximum in the medial prefrontal cortex (Scheeringa et al., 2008). Using a distributed dipole source reconstruction method (LORETA) Clemens et al. (2010) showed that resting state theta EEG was mainly localized in medial parts of the cortex including the anterior cingulate cortex (ACC), medial frontal gyrus, posterior cingulate and precuneus.

Specifically, the medial frontal sources of theta activity may be of interest, since the medial frontal cortex including the ACC has been implicated in reinforcement learning and

risk taking. During gambling tasks, negative voltage deflections have been observed after receiving performance feedback or reward/punishment information (Gehring and Willoughby, 2002, Miltner et al., 1997). Similar to resting-state theta activity, this feedback related negativity (FRN) has a frontal midline scalp distribution and is thought to originate in the ACC (Gehring and Willoughby, 2002). The FRN is thought to be instrumental in learning from feedback information (Cohen et al., 2007, Frank et al., 2005, Hajcak et al., 2007, Holroyd and Coles, 2002, Nieuwenhuis et al., 2004). Individual differences in FRN amplitude have been related to risk taking and reinforcement learning proficiency (Frank et al., 2005, Franket al., 2007, Santesso et al., 2008), and to personality traits such as punishment sensitivity (Balconi and Crivelli, 2010, De Pascalis et al., 2010). The reinforcement learning theory of the FRN proposes that dopaminergic (DA) projections from the midbrain ventral tegmental area (VTA) transfer reward or error information to the ACC, causing pyramidal cells in the ACC to fire whenever the outcome of an action is worse than expected (Holroyd and Coles, 2002). Interestingly, it has been argued that resting-state theta activity can also be modulated by dopaminergic inputs from the midbrain DA system into the septo-hippocampal system, at least in ADHD patients (di Michele, Prichep, 2005). Increased theta power in ADHD patients can be normalized by dopaminergic medication (along with a reduction of clinical symptoms) (Clarke et al., 2002a, Clarke, Barry, 2002b). Given these similarities, it is possible that both EEG theta and the FRN during gambling represent activity in the reward circuit. As such, increased risk taking behavior for people with high resting-state theta/beta ratio, as found by Schutter and van Honk (2005), may be mediated by sub-optimal error-feedback signaling.

The functional significance of resting-state beta activity is less well known. It has been hypothesized to reflect cognitive mechanisms originating from widespread cortical areas (Schutter and van Honk, 2005). Investigations into whether resting-state theta and resting-state beta activity have separate contributions have, as yet, not been undertaken. In order to examine this in the present study, resting-state theta and beta activity and theta/beta ratio were calculated from resting-state EEG, and correlated with feedback-related EEG activity and risk-taking behavior during a gambling task. We first examined whether resting-state theta/beta ratio was correlated to FRN amplitude and to risk-taking behavior. A negative correlation between theta/beta ratio and FRN amplitude, and a positive correlation between theta/beta ratio and risk-taking was expected. Secondly, in order to examine separate contributions of theta and beta activity to the expected

correlations, the correlational analyses were repeated for resting-state theta and beta power separately.

An additional point is that self-report measures of punishment sensitivity (Behavioral Inhibition System [BIS]; Carver and White, 1994) have been found to be related to FRN amplitude. Higher punishment sensitivity scores were associated with larger amplitude FRN (Amodio et al., 2008; De Pascalis, Varriale, 2010), and its response related counterpart, the error related negativity (ERN; Boksem et al., 2008, Boksem et al., 2006). The BIS was originally proposed by Gray as a neurophysiological system underlying aversive motivation, consisting of the septo-hippocampal system and its cortical projections (Gray, 1982; Gray and McNaughton, 2000). Activation in the BIS system in response to signals of punishment is thought to cause inhibition of ongoing, goal-directed actions. Individual differences in BIS reactivity are commonly measured by self-report scales and are related to anxiety and negative affectivity (Carver and White, 1994). Given the neurophysiological overlap and the demonstrated relationships between BIS, theta activity and FRN, it is possible that the relationship between theta activity and FRN is modulated by punishment sensitivity. Self-report scores of BIS were collected, to examine the possibility of such a modulatory effect.

Methods

Participants

Fifty two subjects were recruited (mean age = 21.9, s.d. = 3.14, 24 males, 28 females) through flyers distributed at the university campus. Subjects were screened by means of a short interview to ensure they met inclusion criteria. All participants, except for one, were university students. All participants were healthy volunteers, and reported no psychiatric or neurologic disorders, nor brain trauma. Furthermore participants declared not to use drugs or psychoactive medication, and to have normal or corrected-to-normal vision. Informed consent was obtained and participants received payment for taking part in the study. The protocol was approved by the medical ethical committee of the University Medical Center in Utrecht, in accordance with the standards set by the Declaration of Helsinki.

BIS / BAS questionnaire

Behavioral Inhibition and Behavioral activation scores were obtained using the BIS/BAS questionnaire (Carver and White, 1994, Dutch translation by Franken et al., 2005). The BIS/BAS questionnaire is a 20 item questionnaire consisting of two scales, behavioral inhibition (BIS) and behavioral activation (BAS). Data from the BIS scale will be presented here. The BIS scale consists of seven items thought to assess punishment sensitivity or the drive to avoid aversive events. The BIS scale has an inter-trial reliability of $\alpha = .74$ (Carver and White, 1994). Typical items of the BIS scale are: "I feel pretty worried or upset when I think or know somebody is angry at me", or "I worry about making mistakes". Items are answered on a four-point Likert scale, indicating to what extent the subject considers the statement in the given item to be true for him or herself. In this study, the BIS scale was used because it was previously found to be correlated to feedback-related and error-related electrophysiological activity (Balconi et al. 2010, Boksem et al., 2006, De Pascalis et al., 2010). A median-split procedure was used to classify participants as high BIS or low BIS.

Gambling Task

The gambling task as described by Gehring and Willoughby was applied (Gehring and Willoughby, 2002). Two squares, one containing the number 5 and the other the number 25, were presented to the left and the right, respectively, from a fixation cross. Participants had to choose one of the squares, in order to gamble for the corresponding amount (in Euro cents). After a 1-second delay the squares turned red or green, indicating loss or gain of the chosen amount. Feedback stayed on screen for 1 second. Participants were informed that the total amount that was gained in this task would be added to their compensation as a bonus. Outcome was determined in a random fashion to assure similar numbers of loss and win trials. The total number of trials was 160.

EEG recording

EEG signals were recorded with 64 Biosemi active electrodes (Biosemi, Amsterdam, the Netherlands), which were positioned according to the standard 10/10 EEG system. The outmost lateral positions were Fp1/Fp2, AF7/AF8, F7/F8, FT7/FT8, T7/T8, TP7/TP8, P9/P10, PO7/PO8, and O1/O2. Midline extended from Fpz to Iz. EOG electrodes were placed above and below the left eye and on the outer canthi of each eye. Reference

electrodes were placed on both mastoids, for offline re-referencing. The Biosemi active electrode system uses an active online referencing, through a Common Mode Sense and a Driven Right Leg electrode (MettingVanRijn et al., 1996). All data were recorded with a 512 Hz low-pass filter at a sampling rate of 2048 Hz, and data were stored for offline analysis.

Procedure

Upon entering the lab subjects signed informed consent, and received verbal instructions, after which the EEG electrodes were mounted. The recording session started with 4 minutes of resting-state EEG (2 minutes eyes open and 2 minutes eyes closed), after which the gambling task was performed. At the end of the experimental session personality questionnaires were filled out. EEG preparation and recording, and the gambling task, together performance lasted approximately one hour.

Data reduction and analysis

Behavioral performance. Choice preference in the gambling task was quantified per subject as the overall proportion of high (25 cents) choices. Risk taking after a loss was quantified as the proportion of high choices after a preceding high loss (-25 cents) trial, and risk taking after winning as the proportion of high choices after a high win (+25 cents).

Resting-state EEG. EEG data were analyzed using Brian Vision Analyzer software (Brain Products Gmbh, Germany). Resting-state analysis was based on a previous study from our lab (Schutter and van Honk, 2005). Spectral power calculations were obtained from the 4 minutes resting-state EEG (eyes open/eyes closed). Recorded data were offline re-referenced to the averaged signal of both mastoids, filtered with a 1 Hz high-pass filter and a slope of 24 dB/oct, and a 30 Hz low-pass filter with a slope of 24 dB/oct, and segmented in 4 second epochs. Ocular artefact was controlled using the Gratton and Coles algorithm (Gratton et al., 1983). Activity that exceeded 60 µV between two subsequent sample points, or exceeded an absolute voltage of 80 µV, was considered an artefact, as was low activity of a 0.3 µV difference or less in a 50 ms time window. Segments containing artefacts were omitted from further analysis. A Fast Fourier Transform was performed using a 10% Hamming window. All segments were averaged to obtain spectral power. Absolute theta (4-7 Hz) power, beta (13-30 Hz) power, and the theta/beta ratio were estimated as average values in a frontocentral electrode cluster (FCz and four surrounding electrodes Fz, Cz,

FC1, and FC2). To correct for non-normality EEG power values and ratio were log transformed (Putman et al., 2010). Separate analysis of eyes-open and eyes closed resting state theta and beta power in our sample demonstrated that eyes-open and eyes-closed power scores were highly correlated ($theta_{frontal\text{-}central}$: r = .895, p <001; $beta_{frontal\text{-}central}$: r = .913). Therefore we used an average score of eyes-open and eyes-closed power for further statistical analysis.

ERPs. ERP analysis was conducted following earlier studies from our lab (Massar et al., 2010). EEG data recorded during the gambling task were re-referenced offline to the averaged signal of both mastoids, and subsequently filtered with a 0.3 Hz high-pass filter and a slope of 24 dB/oct, a 30 Hz low-pass filter with a slope of 24 dB/oct and a 50 Hz notch filter. Data were segmented into 1600 ms windows with a 100 ms resting-state with respect to the feedback stimulus onset. Ocular artefact was controlled using the Gratton and Coles algorithm (Gratton et al., 1983), and segments containing artefacts were removed (difference criterion between two subsequent data points of 60μV; differences criterion within segment of 100 μV; absolute amplitude criterion of 80μV). Average ERPs for loss and win trials separately, as well as a loss-win difference potential, were derived for each subject. Calculation of the FRN was based on methods described by Gerhing and Willoughby (2002). FRN amplitude was quantified at midline electrodes (Fz, FCz, Cz and Pz) as the average amplitude of the difference wave in the 200-300 ms post-feedback-stimulus window. The use of a difference wave in FRN quantification is a common method. It must be noted that a disadvantage of using a difference wave is that resulting differences can be due to win-related activity or to loss-related activity. An advantage, on the other hand, is that it can accurately quantify the loss-win difference when no clear deflections are present in FRN latency window, as is often the case for win-locked ERPs.

Source localization. To evaluate whether neural sources of resting-state theta or beta activity were correlated with FRN amplitude standardized low resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) was used. sLORETA computes standardized current density in a cortical grey matter solution space, based on the Montreal Neurological Institute (MNI) brain template. sLORETA does not presuppose any specific number of sources, but computes the smoothest possible solution, assuming that scalp recorded EEG is resulting from simultaneous activation of neighboring neurons. Current density was calculated at the peak latency of the FRN difference wave (255 ms, DC=0).

Statistical analysis. The relation between resting-state theta/beta ratio and FRN amplitude was examined using analysis of covariance (ANCOVA) with Electrode (Fz, FCz, Cz, Pz) as within-subjects factor, BIS (low, high) as between-subjects factor, and theta/beta ratio and a BIS x theta/beta ratio interaction term as covariates. In case of significant interactions follow-up analyses were performed. All analyses were initially carried out with theta/beta ratio as predictor. To unravel the separate contributions of theta and beta power, analyses were repeated using either theta power or beta power as predictor. To examine the relation between resting-state EEG and BIS to task performance, similar ANCOVA's were performed with performance scores as dependent variables, and BIS and Resting-state EEG as predictors.

Statistical non-parametric mapping (SnPM; included in the sLORETA analysis package) was applied for all voxels to estimate the location of resting-state theta and beta activity that correlated with FRN amplitude. The statistical nonparametric mapping (SnPM) method operates under the null-hypothesis that the correlation coefficient in each voxel (i.e. correlation of resting-state EEG current density per voxel with FRN amplitude) is not different from zero. A probability distribution is constructed by running a large number of random permutations of the data (Nichols & Holmes, 2002). In this case a critical value can be determined for which the chance of occurring under the null-hypothesis is lower than a set alpha level. When the observed correlation coefficient in a voxel exceeds this critical value, the correlation for this voxel can be considered significant. Here, the number of random permutations was set to 2000 and alpha level was set at .05 (corrected for multiple comparisons). Correlations between FRN amplitude and resting-state EEG current density were assessed. Results therefore indicate which sources of resting-state EEG are significantly correlated with FRN amplitude. SnPM analyses were conducted for theta and beta activity separately.

Results

Scalp recorded EEG

Figure 1 shows the Feedback-related ERP waveforms (A), the scalp distribution of the FRN (B), and scalp distributions for theta, beta, and theta/beta (C). The FRN as well as theta/beta ratio and theta power featured a medial frontal distribution. In contrast, beta power was marked by discrete central and occipital maxima.

The ANCOVA for FRN revealed a significant BIS x theta/beta interaction effect ($F(1,48) = 7.46$, $p < .01$). Furthermore, there were significant main effects of electrode ($F(3,46) = 7.45$, $p < .01$), BIS ($F(1,48) = 5.9$, $p < .05$), and a marginally significant electrode x BIS interaction effect ($F(1,48) = 3.3$, $p = .057$). To further analyze the BIS x theta/beta interaction effect, Electrode x Theta/beta ANCOVA's were conducted for high and low BIS groups separately. In the low BIS group no main effect of theta/beta or interactions between electrode and theta/beta were found (F's < 1). In contrast, in the high BIS group theta/beta ratio was found to significantly predict FRN amplitude ($F(1,26) = 6.6$, $p < .05$). Correlations show that in the high BIS group high theta/beta ratio's were associated with low FRN amplitudes (r = .48, p < .05 at FCz; see Figure 2). The absence of an electrode x theta/beta interaction indicated that this correlation was not different across the four electrode locations.

Further examination of the electrode x BIS interaction showed that the high BIS group had a higher FRN amplitude than the low BIS group at Fz ($t(1,50) = 2.12$, $p < .05$), FCz ($t(1,50) = 2.11$, $p < .05$), and Cz ($t(1,50) = 2.4$, $p < .05$), but not at Pz ($p > .2$).

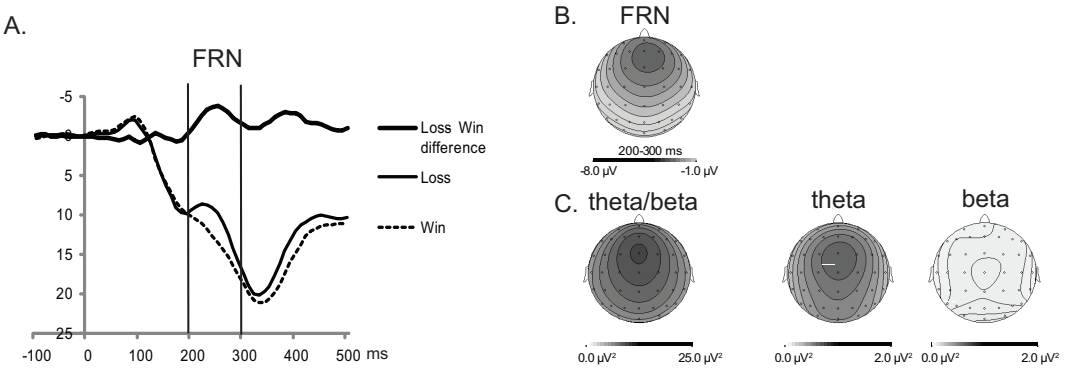

Figure 1. a) Feedback-locked waveforms at FCz. Time 0 indicates feedback onset, b) scalp distribution of FRN difference wave (200-300ms), c) scalp distributions for resting-state EEG theta/beta ratio, theta power and beta power.

To investigate the possibility that the relation between resting-state EEG theta/beta ratio and FRN amplitude in the high BIS group was due to either theta power alone or beta power alone, the above described ANCOVA was repeated for theta and beta power separately. Entering theta power as a covariate yielded results that were highly similar to the analysis with theta/beta ratio. A marginally significant BIS x theta interaction ($F(1,48) = 3.4$, $p = .07$) was found.

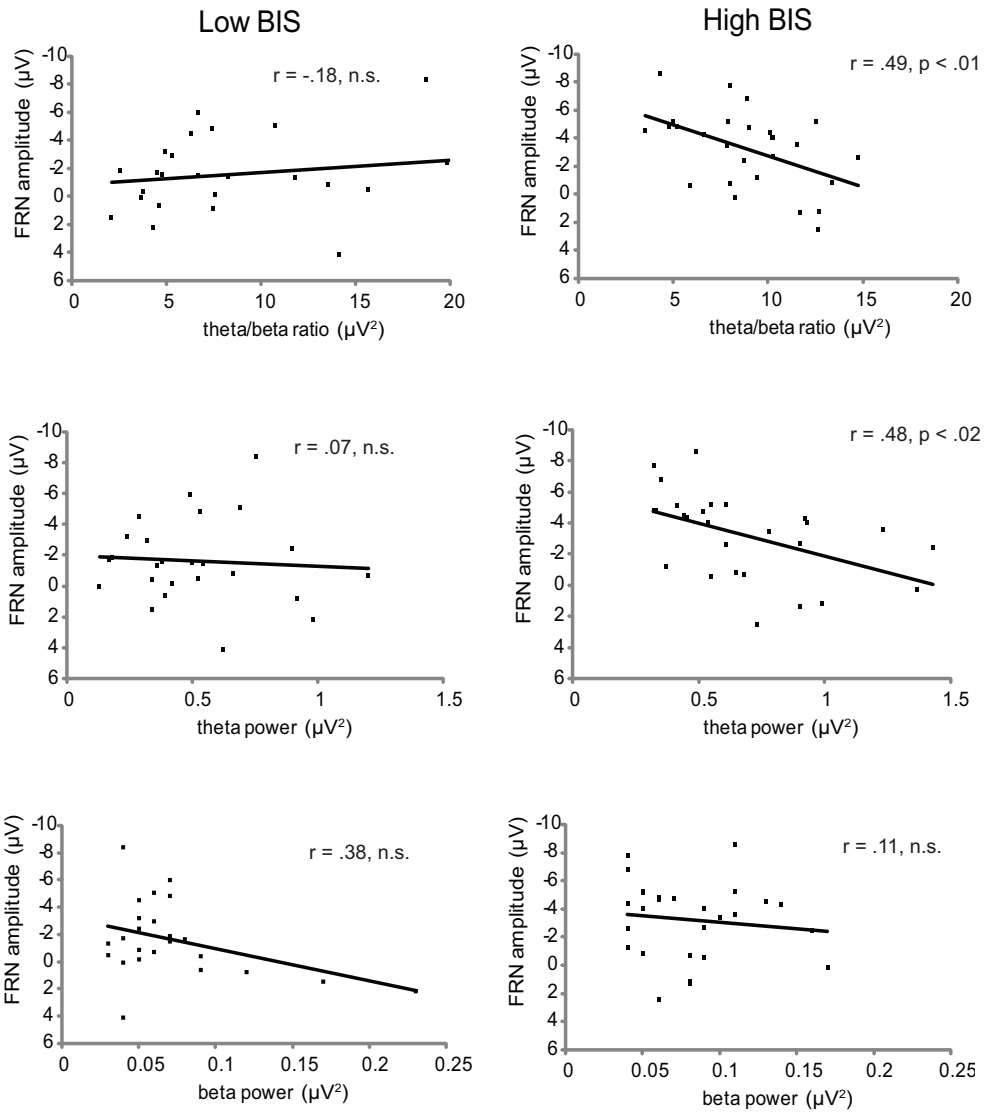

Figure 2. Correlations between FRN amplitude at FCz and baseline EEG theta/beta ratio and theta and beta power for high and low BIS participants separately.

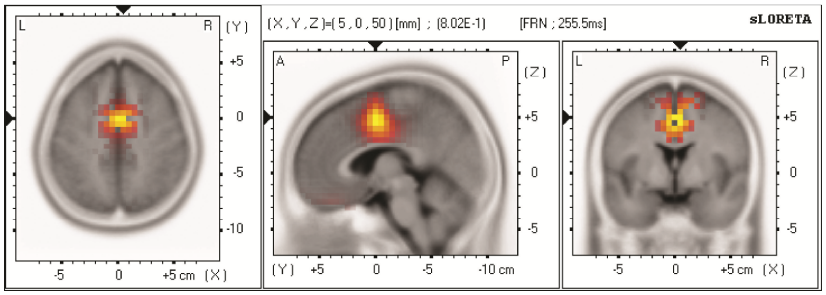

Figure 3. sLORETA source localization of the FRN loss-win difference wave at 255ms post-feedback

addition, again significant main effects of electrode ($F(3,48) = 5.64$, $p < .05$), BIS ($F(1,48) = 3.46$, $p < .01$), and a marginally significant electrode x BIS interaction ($F(3,48) = 3.33$, $p = .056$) were observed. Follow-up analysis for high and low BIS separately showed a significant effect of theta power in the high BIS group ($F(1,25) = 9.14$, $p < .01$; r = .49, p < .01; see Figure 2), but not in the low BIS group ($F < 1$; r = .07, n.s.). A similar analysis with beta power as covariate did not show any significant main or interaction effects including beta power (p's >.1).[1]

Source localization

Source localization of the FRN sLORETA source localization was performed at the same FRN latency. This analysis showed highest current density in a medial frontal cluster, peaking in the cingulate gyrus (see Figure 3; peak MNI coordinates: x = 5, y = 0, z = 50; BA 24).

[1] Analysis of theta and beta power was conducted at the fronto-central location corresponding to the peak distribution of theta/beta ratio. This was done to evaluate the separate contributions of theta and beta to the theta/beta-FRN correlation at the sites at which theta/beta ratio was maximal. As an anonymous reviewer noticed, resting-state beta power did not show the same fronto-central distribution, but rather a central and an occipital peak. However, repeating the ANCOVA analysis using beta power at central (Cz, C1, C2, FCz, CPz) or occipital electrode clusters (Oz, O1, O2, POz, PO3, PO4) also did not yield significant effects of beta power (all p values > .1).

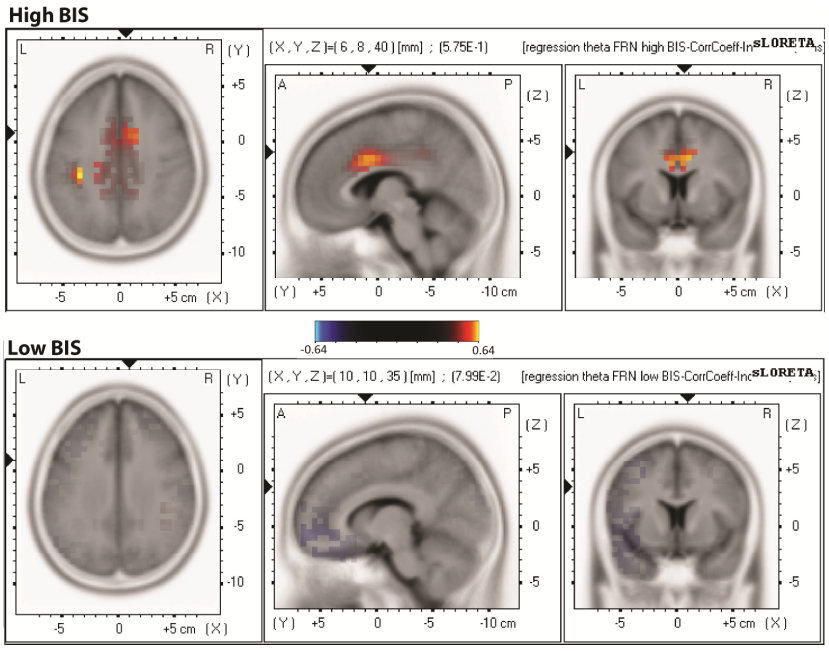

Figure 4. Clusters in the theta band that correlated with FRN amplitude for high BIS group (upper panel), and low BIS group (lower panel)

SnPM regression analyses were conducted in sLORETA to examine whether specific sources of resting-state theta and beta power were related to individual differences in FRN amplitude and BIS. This analysis showed that the current density for baseline theta was correlated with FRN amplitude in a cluster of voxels in the cingulate gyrus bilaterally (see Figure 4; right: five voxels peaking at MNI coordinates: x =10, y = 10, z =35; left: four voxels peaking at: x= -10, y = 15, z = 30) and in two voxels in the left post-central gyrus (MNI coordinates: x = -35, y = -30, z = 40; x = -35, y = -25, z = 40; respectively), for the high BIS group only. For the low BIS group, theta current density in none of the voxels was significantly correlated with FRN amplitude. A similar correlational analysis for resting-state beta activity yielded no significant correlations between beta sources and FRN amplitude, neither for high nor for low BIS groups.

Behavioral data

The overall average proportion of high choices was 0.56 (*sd* = .14). Participants more often chose high gambles after losing a high amount (p = .62) than after winning a high amount (p = .53; $t(51) = 3.05$, $p < .005$). To examine the relationship between BIS and resting-state EEG on the one hand and behavioral adjustment patterns on the other hand, proportions of high choices were entered into an analysis of covariance, with previous outcome (win, loss)

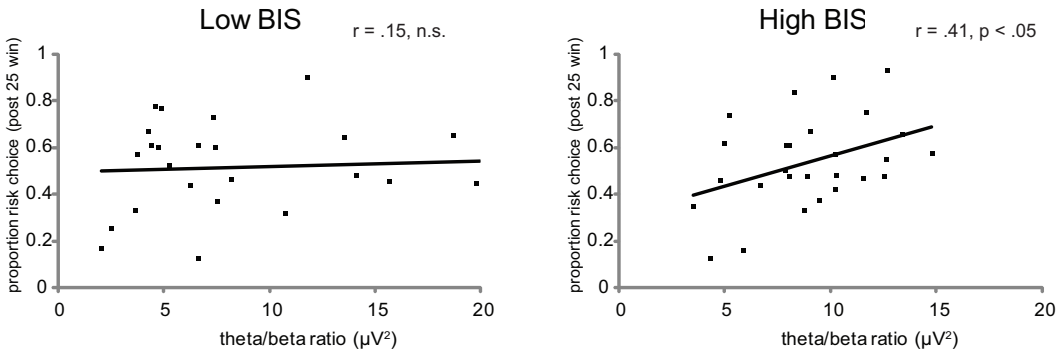

Figure 5. Correlations between theta/beta ratio and the proportion of high gambles directly following a high win trial for high and low BIS participants separately.

as a within-subjects factor, BIS (high, low) as a between-subjects factor, and theta/beta ratio as covariate. Furthermore a BIS x theta/beta ratio interaction term was entered. This analysis yielded a marginally significant three-way interaction between Previous outcome, BIS, and Theta/beta ratio ($F(1,48) = 3.47$, $p = .069$), and no further main or interaction effects. To examine this interaction further, follow-up ANCOVA's were carried out for BIS groups separately. Similar to the FRN analysis discussed above, in the low BIS group no significant effects of theta/beta ratio on behavior were noted (all F's < 1). In contrast, in the high BIS group a significant main effect of previous outcome was found ($F(1,25) = 7.44$, $p < .05$), as well as a significant interaction between previous outcome and theta/beta ($F(1,25) = 5.95$, $p < .05$). Correlation analysis in this group showed that theta/beta ratio predicted the proportion of high choices after high win trials ($r = -.41$, $p < .05$, see Figure 4), but not after high losses ($r = -.09$, n.s.). In the low BIS group no correlations were found between behavior and theta/beta ratio (all p's >.4).

Finally, the ANCOVAs for choice behavior with theta or beta power separately as covariates, did not reveal any significant main or interaction effects (all F's < 1). Also, no relation between the overall proportion of high choices and BIS and resting-state EEG was found (all F's < 1.5).

Discussion

In this study we found that resting-state EEG theta power and resting-state theta/beta ratio correlated with feedback related ERP activity and risk taking during a gambling task. This correlation was modulated by self-reported punishment sensitivity (BIS). High resting-state

theta power (and theta/beta ratio) was associated with reduced amplitude of the feedback-related negativity (FRN), and increased risk taking following high gains, in individuals with relatively high punishment sensitivity scores. For individuals with low punishment sensitivity no such correlations were present. In contrast to theta power, there were no correlations between resting-state beta power and FRN amplitude.

The behavioral inhibition system is theorized to reflect the sensitivity to punishments or non-rewards (Gray, 1982). In the most recent version of Gray's theory, BIS is thought to be specifically active in conflict situations (Gray and McNaughton, 2000). One instance of conflict is a situation in which positive and negative reinforcement are equally probable and there is no certainty as to whether an action will lead to reward or punishment (as was the case in the present study; Leue and Beauducel, 2008). The present findings suggest that sufficient sensitivity to punishments is necessary to reveal the relationship between feedback-related electrophysiological reactivity (FRN) and resting-state EEG theta activity.

High resting-state theta/beta ratio was not only related to FRN, but also to risk-taking during the gambling task. Behavioral choice scores mirrored the FRN findings, in that no correlations between resting-state EEG and choice tendencies was found in the low BIS group, whereas in the high BIS group there was in fact a positive correlation between theta/beta ratio and risk-taking. This relation was most pronounced for choices directly following high win trials. This might reflect that baseline theta/beta ratio reflects the propensity to perseverate after successful, rewarded actions. It is remarkable that behavioral risk-taking correlated with resting-state theta/beta ratio, but not with theta or beta separately. In contrast, the correlation between theta/beta ratio and FRN amplitude could be explained by an underlying direct correlation between theta power and FRN amplitude. The finding that FRN amplitude correlated particularly with theta power, but risk-taking was only correlated with theta/beta ratio may indicate more factors are involved in directing behavioral choice. Whereas the FRN and theta power are physiologically closely related to each other, the FRN activity might represent just one step involved in the decision making process. The FRN may be a fast motivational or affective reaction to the detection of the reward prediction error. The further decision process might be dependent on control mechanisms related to beta activity (Schutter and van Honk, 2005). The present data do provide support for the idea that theta activity and FRN generation are related to

each other. However, it is not possible to draw strong conclusions about physiological mechanisms and functional significance of resting-state beta power.

With respect to theta power the present study demonstrated that for high-BIS individuals the part of theta activity that correlated with FRN amplitude has its most likely generators in the ACC. This might indicate that synchronized oscillatory activity in the ACC at rest (as reflected in high amplitude theta power) restricts phasic firing of the ACC in reaction to feedback information. It should be noted that theta activity in the human resting-state EEG has also been reported to have generators in more widespread cortical areas (Clemens, et al., 2010; Scheeringa, et al., 2008). The current source localization however shows that specifically the contribution from the ACC to scalp-recorded theta is correlated with the feedback-related negativity. A possible mediating mechanism for the relationship between resting-state theta activity and FRN is the midbrain DA system. The dominant theory of the FRN states that the FRN results from dopaminergic error signals from the VTA to the ACC (Frank et al., 2006; Holroyd and Coles, 2002), although other neurotransmitters have been implicated in FRN generation as well (Jocham and Ullsperger, 2009). Furthermore, it has been argued that theta activity in the septo-hippocampal system can be modulated by inhibiting dopaminergic input from the midbrain DA system (di Micheleet al., 2005; Gasbarriet al., 1997). It is possible that inter-individual variance in resting-state theta power and FRN amplitude both reflect underlying individual differences in midbrain DA functioning. This idea however remains to be tested. It might be specifically interesting with respect to ADHD. Increased theta/beta ratio in ADHD patients has been reported to differentiate responders to dopaminergic medication from non-responders (Clarke, et al., 2002 b,c). Furthermore, treatment with DA medication normalizes excess theta in these patients (Clarke et al., 2002 a; Clarke, et al., 2003). In the current study only healthy participants were included and therefore the results do not speak directly to issues of pathology.

In the present study we have focused on the relationship between error-feedback processing and EEG theta activity in resting-state. Recently however, a considerably amount of research has investigated the link between dynamic, task-related theta activity and feedback and error processing. Event-related increases in theta power and theta phase synchrony after a response error (Luu, et al., 2004; Trujillo and Allen, 2007) or after feedback (Cavanagh, et al., 2010; Kamarajan, et al., 2008; Marco-Pallares, et al., 2008) have been repeatedly reported. Moreover, it has been proposed that FRN and ERN to a

large extent reflect average phase-locked theta responses (Cohen, et al., 2007; Luu, et al., 2004; Trujillo and Allen, 2007). It should be noted that the negative relationship between FRN amplitude and resting-state theta power (as presently found) cannot simply be an artifact of phase-locking of resting-state theta activity after feedback. Phase-locking of high power resting-state theta would result in high amplitude feedback-related ERPs. Instead, high theta power was associated with low amplitude FRNs. This implicates that an additional mechanism, besides phase locking, plays a role in FRN generation. Similar findings have been reported for the relation between resting-state theta power and short-latency visual evoked potentials (Klimesch et al., 2004).

In conclusion, the present study provides support for the idea that resting-state EEG can provide a biomarker for reward and loss processing. The hypothesized inverse correlation between resting-state EEG (theta power and resting-state theta/beta ratio) and feedback related ERP activity was found. This correlation was modulated by self-reported punishment sensitivity (BIS), since it was only present in the high BIS group, but not in the low BIS group. A negative correlation between theta/beta ratio and theta power with FRN amplitude was found, which was modulated by self-reported punishment sensitivity. This correlation specifically involves theta activity generated in the ACC. Furthermore, in line with earlier findings (Schutter and van Honk, 2005), high theta/beta ratio was associated with risk-taking. Again, this relation was only present in relatively high punishment sensitive participants.

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Chapter **4**

Electrodermal and electrocortical orienting responses but not trait anxiety predict fear conditioning

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Submitted

Abstract

The orienting response (OR) is a cluster of physiological reactions in response to novel or salient stimuli, and is thought to reflect the level of attention that is directed to this stimulus. Increased OR measured with skin conductance responses (SCR), prior to fear conditioning, can predict subsequent conditioning effectivity. The current study examined whether the predictive value of OR was also present in electrocortical (EEG) measures of orienting, and whether these measures were related to self-reported trait anxiety and attentional control. Results showed that participants who became aware of the CS-UCS contingency had differential SCR during conditioning, and had larger SCR and EEG orienting responses (P2, P3, late positive potential) to the to-be-CSs prior to conditioning. Conditioning and OR however, did not correlate with trait anxiety or self-reported attentional control. These findings suggest that the likelihood that associative learning will be effective is indicated by electrodermal and EEG orienting responses. However, OR might be more indicative of state than of trait factors.

Introduction

The orienting response (OR) is a cluster of physiological reactions to novel or salient stimuli that are thought to facilitate the perceptual processing an d identification of these (potentially relevant) stimuli (Sokolov, 1983). These reactions are manifest in measures of central nervous system activity (e.g. in event-related electroencephalographic potentials [ERPs]) as well as in peripheral measures (e.g. skin conductance responses [SCR]). The OR responses are strong during the first few presentation of a novel stimulus, but habituate rapidly after repeated presentation. Also stronger OR responses are found after stimuli that have behavioral relevance (Kenemans, et al. 1988; Verbaten, et al. 1986). As such, OR responses are viewed as an index for attentive processing and preparation for action (Bradley, 2009; Frith & Allen, 1983).

In 1965, Fuhrer and Baer reported a positive relation between skin conductance response OR and fear conditioning. Participants that successfully learned the association between auditory cue stimuli (CS) and an aversive shock (unconditioned stimulus, UCS) showed both differential SCR to the CS+ and CS- tones during conditioning, and larger SCRs to the auditory tones, prior to conditioning (Fuhrer & Baer, 1965). This suggests that stronger orienting of attention to the initially neutral stimuli used in conditioning experiments may facilitate learning associations between these stimuli and emotionally relevant events. Such a mechanism has been proposed in several learning theories (e.g. Mackintosh, 1975). In later years, other researchers have replicated the finding that the magnitude of OR SCR before the start of a conditioning procedure is predictive of the later awareness of the CS-UCS contingency, both in adults (Baas, 2001; Otto, et al., 2007), and in children (Gao, et al., 2010).

The skin conductance response is a peripheral measure of orienting. Therefore it does not provide detailed insight into the precise steps of information processing of the stimulus that may predict later learning. Using EEG a series of cortical orienting ERPs has been identified including an early negativity (N1), and later positive components (P2, P3, Late Positive Potential [LPP]), that are strongly related to the OR SCR. N1 and P2 have a frontal central scalp distribution and may reflect fast signaling from dopaminergic projections to the frontal cortex. P3 and LLP show a more parietal distribution and are thought to reflect norepenephrinergic projections from the locus coeruleus to parietal cortical areas (Nieuwenhuis, De Geus, & Aston-Jones, 2010). These OR ERPs show

similar patterns of fast habituation after repeated stimulus presentation and dishabituation with behavioral relevance (Kenemans, et al., 1992; Kenemans, et al., 1989; Nieuwenhuis, De Geus, & Aston-Jones, 2010; Rushby & Barry, 2007; Zimmer, 2006). Therefore the OR ERP components are also thought to reflect attentional processing of stimuli. Thus far, no studies have investigated whether the amplitude of OR ERPs can also be predictive for the effectiveness of a subsequent conditioning procedure

A further matter of interest is whether individual differences in OR responses reflect trait characteristics of attention and anxiety. Several studies have suggested that the failure to become aware of CS-UCS contingencies during fear conditioning procedures is associated to higher levels of anxiety (Baas, et al., 2008; Grillon, 2002). Furthermore it has consistently been found that trait anxiety is negatively correlated to scores on the Attentional Control Scale, a self-report measure of attentional control capacity (ACS: Derryberry & Reed, 2002; Healy & Kulig, 2006; Ólafsson et al., 2011). It could be that the magnitude of orienting responses reflects trait-like individual differences in attentional processing. If this is the case, OR response amplitude should be correlated with self-reported attentional control and trait anxiety.

In the present study SCR and ERP orienting responses were measured during the presentation of the two visual stimuli that would subsequently be used as CS+ and CS- in the fear conditioning procedure that directly followed these initial presentations. During the following conditioning procedure, one stimulus (CS+) was consistently associated with the occurrence or the absence of an aversive shock, while the other (CS-) was not. Directly after the conditioning procedure, contingency awareness was measured. Pre-conditioning OR responses from participants who correctly reported the CS-UCS contingency were compared to those from participants who remained unaware of the contingency. It was expected that both pre-conditioning OR reflected in SCR and ERP components would be stronger for participants who gained aware knowledge of the contingency as compared to pre-conditioning OR responses for unaware participants. The possible trait-like character of the OR was assessed by calculating correlations between self-reported trait anxiety and attentional control on the one hand and OR SCR and ERP amplitudes on the other hand. Additionally, SCR responses were also measured during the conditioning procedure to

verify whether post-task awareness properly reflected differential conditioning at the physiological level[2].

Methods

Participants

Fifty healthy volunteers participated (27 females, 23 males, mean (sd) age = 21.9 (3.1)). Participants reported no history of psychiatric or neurological pathology, and did not use psychoactive drugs or medication. Participants had normal or corrected-to-normal vision and no hearing problems. They were paid €10/hour for participation.

Personality questionnaires

Trait anxiety was measured with the Spielberger State and Trait Anxiety Inventory (STAI; Spielberger, Gorusch, & Lushene, 1970; van der Ploeg, Defares, & Spielberger, 1980). Attentional control was measured with the Attentional Control Scale (ACS; Derryberry & Reed, 2002, translated by Morren, unpublished).

Stimuli and apparatus

Visual cue stimuli (CS) were 8 seconds duration square-wave gratings (0.5 cycles/degree or 4.0 cycles/degree) presented on a computer screen. The unconditioned stimulus (UCS) was a train of electrocutaneous shocks (150 pulses, train duration = 750 ms) administered to the left wrist. Shock intensity was determined individually by a work-up procedure. Six shock stimuli were delivered to the participant. After each shock stimulus the participant rated the aversiveness of the shock. Shock intensity was adjusted incrementally based on this rating in order to reach subjective a rating of 'considerably aversive' for every participant. Auditory startle probes were delivered during inter-trial intervals, but not during CS presentation. Discussion of startle analysis will not be included in this report.

Procedure

According to the declaration of Helsinki, the complete procedure was approved by the local medical ethical committee and written informed consent was taken from each

[2] ERPs during the conditioning procedure were also recorded, but due to the fast changing nature of the learning task, resulting ERP averages across 8 trials were not applicable and single trial analysis lacked a sufficient signal-to-noise ratio.

participant before commencing the experiment. After verbal instructions, electrodes were applied. Subsequently, participants were placed in a dimly lit, sound attenuated room and the shock work-up was performed. Next, both visual cues were presented two times in the absence of a UCS (orienting phase). Orienting SCR and ERPs were measured. In the following conditioning phase, visual cues were presented eight times in a quasi- random order (maximally two sequential repetitions of the same CS). One CS (CS+) was accompanied by a UCS (starting 150ms before CS+ offset and co-terminating with the CS+). Inter-trial-interval (ITI) varied between 32 and 36 seconds. After the conditioning phase subjects were asked to describe any relation they had noticed between the visual cues and the shock. Participants who reported the correct association between CS+ and UCS were classified as 'Aware', while all others were classified as 'Unaware'. Subsequently, participants were shown the CS+ and CS- stimulus and indicated on visual analogue scales how much they had expected to receive a shock during presentations of this stimulus during the experiment, and how anxious they had felt after the corresponding stimulus. Differential expectancy and anxiety scores were calculated by subtracting the CS- score from the CS+ score.

Electrophysiological measurement and analysis

All physiological measurements were acquired through a Biosemi system. SCR was measured from the palmar surface of the right middle and index finger. SCR was scored in a 1-7 s window after stimulus onset as the largest peak relative to a 1 second pre-stimulus baseline. EEG was recorded from 9 locations (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) through active Ag/AgCl electrodes, and referenced offline to average mastoids. Analyses were done with brain Vision Analyzer (Brain Products GmbH, Gilching, Germany). Data was filtered (low pass 0.5 Hz, 12 dB/oct, high pass 40 Hz, 24 dB/oct). Epochs of -100 ms to 1000 ms around CS onset were selected. Ocular-artifacts were corrected (Gratton, Coles, & Donchin, 1983) and segments with amplitude artifacts (activity > 60 μV) were deleted. Data were averaged over the four orienting trials. The large amplitude of ERPs elicited by the first few presentations of novel stimuli provide ample signal-to-noise ratio to calculate ERPs using only a few trials (Kenemans, et al., 1989; Kenemans, et al., 1988; Zimmer, 2006). Four OR ERPs were identified (N1: average amplitude 80-120 ms post-stimulus; P2: 200-250ms; P3: 250-350ms; and late positive potential, LPP: 500-800 ms).

In the statistical analyses (SPSS 18.0 repeated measures ANOVA), orienting SCR and ERPs of the Aware subjects were compared to the unaware subjects. Orienting SCR amplitudes were analyzed with factors Awareness (aware, unaware) x CS (CS+, CS-) x trial (2). The ERPs components identified above were analyzed with factors Awareness (aware, unaware) x CS (CS+, CS-) x electrode position (9 positions). In the Conditioning phase, SCR conditionability was analyzed with factors Awareness x CS x trial (8). Follow-up analyses were performed for aware and unaware groups separately, if interactions including Awareness were significant.

Results

Awareness

Nineteen out of 50 participants could correctly verbalize the CS-UCS association, while 31 participants were unaware of the contingency. The unaware group contained relatively more females (N = 20; 67.7%) then the aware group (N=7; 36.8%). This difference approached significance ($\chi^2(1) = 3.6$, $p = .057$). Differential expectancy and differential anxiety scores were significantly higher for the aware participants compared to the unaware group (expectancy: aware = 74.2, unaware = 6.0, $t(48) = 7.7$, $p < .001$; anxiety: aware = 32.6, unaware = -1.4, $t(48) = 3.1$, $p < .005$).

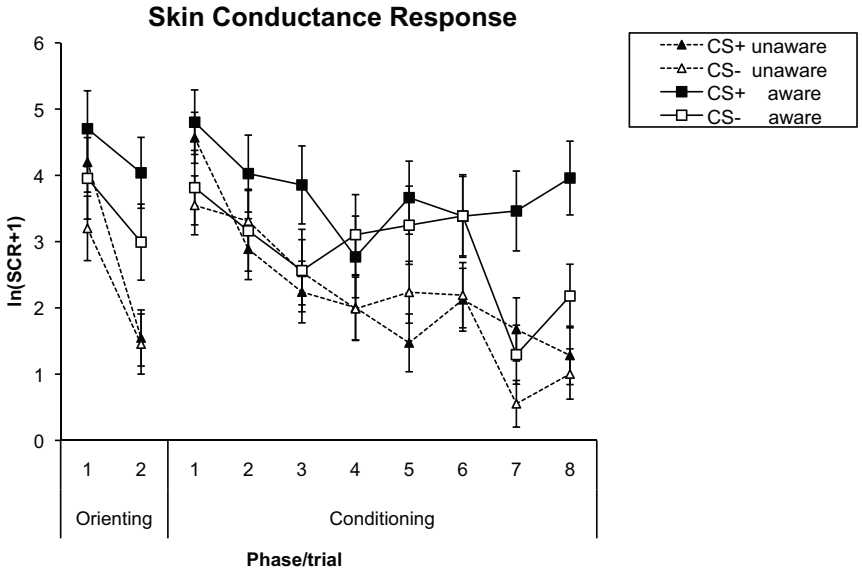

Figure 1. SCR response amplitude in Orienting phase and Conditioning phase plotted separately for the Aware group and the Unaware group

Orienting Responses

SCR. The aware group showed higher orienting responses as compared to the unaware group ($F(1,48) = 7.3$, $p < .01$, $\eta_p^2 = .13$; see Figure 1, left hand panel). A difference that was mainly present in the second orienting trial (Awareness x Trial interaction $F(1,48) = 6.6$, $p < .05$, $\eta_p^2 = .12$). No significant main effect for CS ($F(1,48) = 3.34$, $p = .072$) or interactions including CS were found (F's < 1.5).

ERPs. For orienting ERPs (See Figure 2) no difference was found for the aware versus the unaware group in the N1 latency range ($F < 1$). Higher amplitudes were found for the aware group compared to the unaware group at later latencies. This difference was marginally significant for the P2 ($F(1,48) = 3.6$, $p < .065$, $\eta_p^2 = .07$), and significant for the P3 ($F(1,48) = 4.3$, $p < .05$, $\eta_p^2 = .08$). For the LLP an Awareness x Electrode interaction was found ($F(1,48) = 3.1$, $p < .05$, $\eta_p^2 = .06$). Follow-up analyses indicated that amplitude was higher for the aware group at parietal electrodes (P3: $t(48) = 2.9$, $p < .01$; Pz: $t(48) = 2.82$, $p < .01$; P4: $t(48) = 2.2$, $p < .05$) and central electrodes (C3: $t(48) = 2.94$, $p < .01$; Cz: $t(48) = 2.5$, $p < .01$) but not at right-central electrode C4 ($t(48) = 1.92$, $p = .061$) and frontal electrodes (all p's > .15).

Conditioning

SCR. During the Conditioning phase (Figure 1, right hand panel) an Awareness x CS interaction ($F(1,48) = 6.4$, $p < .05$, $\eta_p^2 = .12$) indicated that the aware group showed potentiated SCR for CS+ compared to CS- ($F(1,18) = 8.6$, $p < .01$, $\eta_p^2 = .32$), while the unaware group showed no differential SCR response ($F(1,30) = 0.5$, $p = .49$). A significant Trial main effect ($F(7, 48) = 13.6$, $p < .001$, $\eta_p^2 = .69$) indicated that SCR amplitude decreased (habituated) in later trials. No significant Awareness x trial ($F(7, 48) = 1.48$, $p = .2$), or Awareness x CS x trial interactions ($F < 1$) were found.

Questionnaires

The aware group and unaware group did not differ in level of trait anxiety (Aware: mean (sd) = 35.4 (7.2), Unaware: mean (sd) = 35.1 (6.8); $t(48) = -.17$, $p = .86$) or attentional control (Aware: mean (sd) = 50.4 (6.6), Unaware: mean (sd) = 52.5 (8.8); $t(48) = -.9$, $p = .37$). Furthermore, no correlation was found between both self-report measures and any of the physiological orienting measures (SCR or ERP; all p's > .1). As found before, trait anxiety and attentional control were negatively correlated to each other ($r = -.51$, $p < .001$).

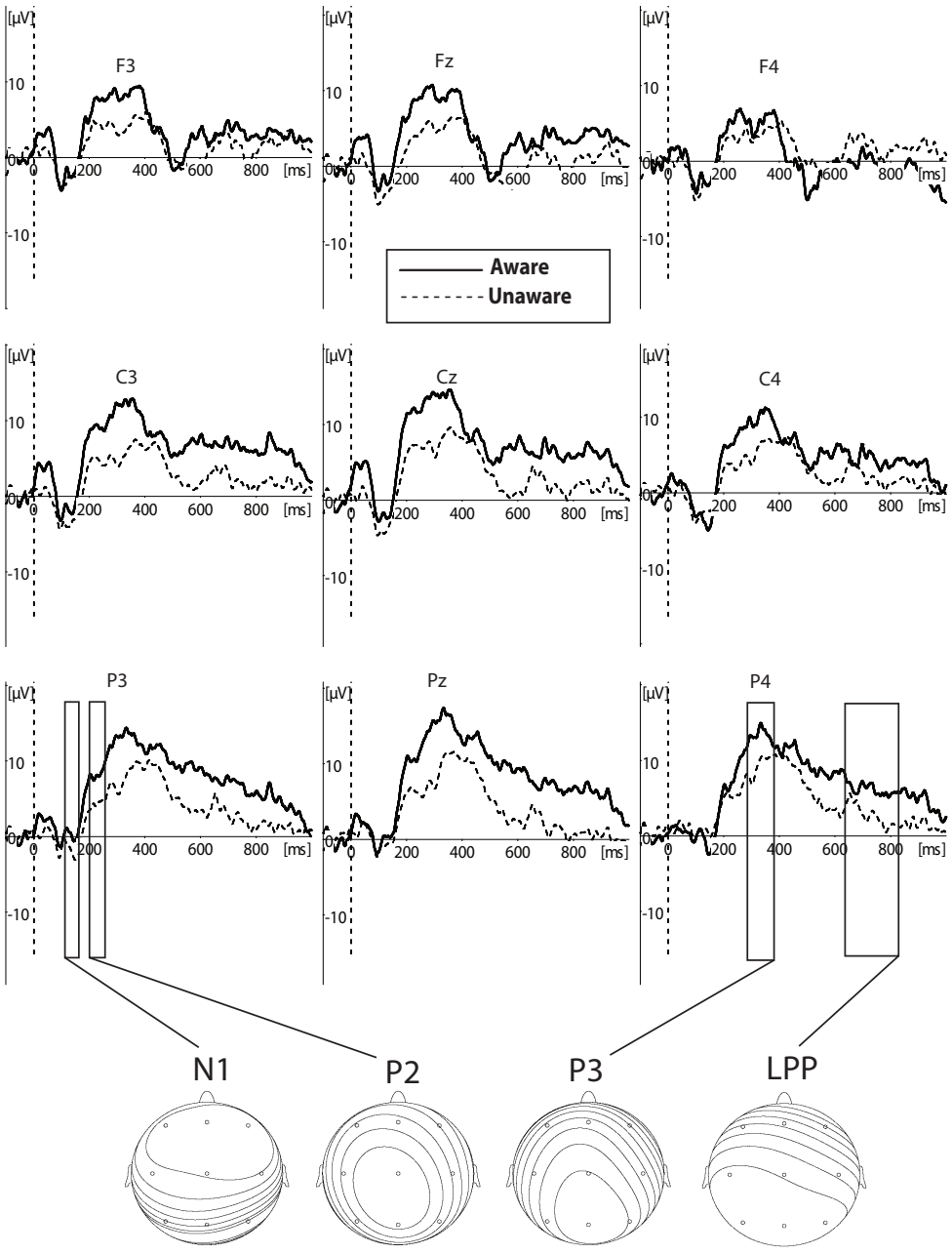

Figure 2. Orienting ERP's during Orienting phase plotted separately for the Aware group and the Unaware group.

Discussion

The present findings indicate that individuals who show successful differential fear conditioning in a threat-of-shock paradigm had stronger orienting responses to the CSs directly prior to conditioning. Both SCR and ERPs (P2, P3 and LLP) to initial presentation

of CS's were larger for participants that became aware of the CS-reinforcement contingency than for participants that did not become aware. These findings confirm and extend earlier studies that show a positive relation between skin conductance OR and later fear conditioning (Baas, 2001; Fuhrer & Baer, 1965; Gao, et al., 2010; Otto, et al., 2007).

Different accounts for the generation of the OR have been formulated (Sokolov, 1963; Maltzman, 1979; Barry, 2009). Originally Sokolov proposed that the OR was a whole body that was mainly sensitive to stimulus novelty. The amplitude of the OR thereby was based on the mismatch between physical stimulus properties and a "neural model" of the priorly presented stimuli. Other models, however, have postulated more specifically that the OR consists of a deviance detection component, which is based on thye mismatch between stimulus properties, and a relevance component, that is determined by the perceived stimulus significance (Maltzman, 1979; Barry, 2009). The present data would fit well with the latter conceptualization. It may be possible that those participants who perceived the visual cue stimulus as relevant, showed stronger orienting during OR phase. More elaborate stimulus processing by these participants, in turn, may have facilitated learning the relevant CS-UCS contingency in the subsequent conditioning phase.

The finding that OR ERPs had increased amplitude for the aware participants adds to the current knowledge. Parallels between orienting ERPs and skin conductance OR have been reported previously (Kenemans, et al., 1989; Rushby & Barry, 2007; Zimmer, 2006). Compared to SCR, ERPs are a more direct reflection of stimulus processing. Moreover, different ERP components may reflect different stages in stimulus processing. While the P2 and P3 have been related to attentional selection and stimulus evaluation (Potts, 2004), the LPP is thought to reflect attentional orienting after a stimulus has been identified as significant (Lang & Bradley, 2010). In addition, different physiological mechanisms may be involved.The posterior distribution of the P3 and late positivity have been argued to involve norepinephrinergically innervated posterior cortical regions (Nieuwenhuis, de Geus, & Aston-Jones, 2010), while in the earlier P2 component, additional dopaminergic inputs to frontal regions (related to stimulus novelty) may be involved (Polich, 2007).

A secondary finding of the present study was that OR and conditioning awareness were not related to self-reported trait anxiety and attentional control. We explored this possibility because highly consistent correlations between anxiety and attentional control have been reported (Derryberry & Reed, 2002; Healy & Kulig, 2006; Ólafsson et al., 2011). Failure to show differential UCS expectancy after conditioning has been tentatively

associated with higher levels of anxiety (Baas, et al., 2008; Grillon, 2002a). The expected correlation between self-reported trait anxiety and attentional control were again established in this study. However, no evidence was found that physiological OR measures were associated with these self-report trait measures. This may indicate that orienting responses probably reflect different attentional processes from those assessed with the Attentional Control Scale. OR responses may index more situational or state-related aspects of attention. In sum, the present study demonstrated that participants who gained contingency awareness during fear conditioning, had more pronounced orienting responses than participants that were unable to report the correct contingency. This enhanced OR was reflected both in cortical and electrodermal measures of orienting, thereby replicating and extending earlier findings.

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Section II: Motivational drives in attention: costs and benefits of motivational salience

Chapter **5**

Attentional bias in high and low anxious individuals: evidence for threat induced effects on engagement and disengagement

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Abstract

Attentional bias to threatening visual stimuli (words or pictures) is commonly present in anxious individuals, but not in non-anxious people. There is evidence to show that attentional bias to threat can be induced in all individuals when threat is imposed by threat not of symbolic nature, but by cues that predict aversive stimulation (loud noise or electric shock). However, it is not known whether attentional bias in such situations is still influenced by individual differences in anxiety. This question was addressed in two experiments using a spatial cuing task in which visual cues predicted the occurrence of an aversive event consisting of a loud human scream. Speeded attentional engagement to threat cues was positively correlated with trait anxiety in Experiment 1. Experiment 2 showed that speeded attentional engagement was present only in participants selected for high anxiety but not in low anxious participants. In both experiments, slower disengagement from threat cues was found in all participants, irrespective of their trait anxiety levels.

Introduction

Mechanisms of automatic attention enable us to orient reflexively towards relevant locations and events in our environment. Certain stimuli can automatically draw attention because of their physical salience or biological relevance. The reflexive detection of threat has obvious advantages for survival, hence phylogenetically old mechanisms are assumed to have evolved to bias attentional resource allocation towards stimuli associated with threat. The detection of threat is found to trigger an automatic fear response, through amygdala activation (LeDoux, 1995; Öhman, 2005), which in turn activates a large cortical network, involving extrastriate cortex (Surguladze *et al.*, 2003; Vuilleumier *et al.*, 2004), and parietal and frontal regions (Pourtois *et al.*, 2006).

The influence of threat on the allocation of attention has often been investigated using modifications of spatial cuing paradigms (Posner & Peterson, 1990). By briefly presenting a cue stimulus in a particular spatial location, attention is directed towards that location. Consequently, detection of a subsequent target stimulus is faster and more accurate when this target appears in the same location (valid cuing) compared to when it is presented in a different location (invalid cuing). When a cue represents a threat, this cue validity effect can be enhanced. Anxious people, for instance, show a larger cuing effects when spatial cues were threat-related words and angry faces (Fox *et al.*, 2001), or pictures of threatening scenes cues (Yiend & Mathews, 2001), as compared to neutral cue stimuli.

Threat-related attentional bias is more pronounced in individuals with a high anxious personality than in persons who are less anxious (Bar-Haim *et al.*, 2007; Matthews & Wells, 2000; Mogg & Bradley, 1998; Puliafico & Kendall, 2006). For instance, high anxious people were slower to react to invalid targets cued by threat words than those cued by neutral words, while non-anxious people did not show such a bias (Fox et al., 2001). In contrast, in certain experimental set-ups, low anxious individuals tend to show facilitated detection of targets in non-threat locations compared to threat locations, essentially avoiding the negative emotional material (MacLeod *et al.*, 1986). Furthermore, it is repeatedly found that this enhanced validity effect is mostly due to slowing of responses to invalid targets after presentation of a threat cue as compared to a neutral cue. In contrast responses to validly cued targets are usually not affected by the threat content of the cues (Fox et al., 2001; Fox *et al.*, 2002; Koster *et al.*, 2004b; Yiend & Mathews, 2001). This suggests that the presence of a threat leads to difficulties to disengage attention from its

location, rather than facilitating the initial engagement of attention to its location. Following these observations it has been argued that this compromised ability to direct attention away from threat, once it has been detected, differentiates anxious and non-anxious individuals. Moreover, this inability could be instrumental in maintaining and enhancing the experience of anxiety (Fox et al., 2001).

The specificity of these attentional bias effects, both in terms of anxiety level (high anxiety) and processing stage (disengagement), seem to be partly influenced by threat value. By comparing pictures that were rated as highly threatening to those rated as moderately threatening, attentional biases to threat were demonstrated in low anxious individuals and in unselected samples, but only in the high threat condition (Mogg *et al.*, 2000; Wilson & MacLeod, 2003). Furthermore, some studies find evidence for facilitated engagement by highly threatening pictures (Koster *et al.*, 2006; Koster *et al.*, 2007). However results are not always consistent, since not all studies confirm the findings that the effects of highly threatening cue stimuli on attention extend to early processing stages (facilitated engagement; Koster et al., 2004b), and to populations of low anxious people (Koster et al., 2006).

The studies discussed above all used verbal or pictorial threat stimuli. Although these stimuli are rated as aversive subjectively, the threat imposed by these stimuli is rather indirect. Recently a new paradigm has been introduced in which threat is imposed by impending direct aversive stimulation of the participant (i.e. a loud noise or electrical shock; Koster *et al.*, 2004a; Van Damme *et al.*, 2006). Attentional cuing is induced by intrinsically neutral visual stimuli that validly or invalidly cue the location of a subsequent target stimulus. Through association with an aversive stimulation, a cue is found to cause both facilitated engagement and delayed disengagement effects (Koster et al., 2004a; Van Damme et al., 2006). Moreover, these effects have been found in unselected samples of healthy participants (Koster et al., 2004a; Van Damme et al., 2006). An advantage of this paradigm is that it poses a direct threat that is likely to be evaluated as aversive by a wide range of people. In addition, it measures attentional engagement and disengagement from neutral cue stimuli, avoiding possible confounding stimulus differences that can influence attentional allocation (e.g. differences in luminance or complexity). A growing body of evidence confirms that threats of this type can cause attentional threat biases (engagement and disengagement) in a general population (Koster et al., 2004a, 2005; Van Damme et al., 2006; Van Damme *et al.*, 2007). It thus seems that these direct aversive stimulations stand

apart from more indirect verbal and pictorial threat stimuli, in that they cause more robust modulation of attentional cuing effects in a wider population. All studies so far using these aversive stimulations have been conducted in unselected samples and no indication of anxiety levels have been reported. It is therefore unclear whether the modulation effects caused by these aversive stimuli are uniformly present in high and low anxious individuals, or if the strength of these threat bias effects is influenced by individual differences in anxiety.

The current study was designed to investigate whether the engagement and disengagement components of attentional biases to threat are influenced by trait anxiety when threat is imposed by cues that directly predict aversive stimulation. Two experiments were carried out using a task based on the modified spatial cuing task described by Koster et al. (2004a). Experiment 1 studied a sample of unselected participants, allowing for correlational analysis of the relationship between trait anxiety and attentional bias, specifically separating the engagement and the disengagement components. In Experiment 2, participants were preselected for either low or high trait anxiety to compare these groups in attentional bias and to verify whether participants with particularly low trait anxiety would still display an attentional bias.

An additional topic was addressed that may be of importance, but which has received relatively little attention in the literature on attentional biases discussed above. Trait anxiety scores are repeatedly found to correlate with scores on the attentional control scale (ACS), a self-report measure of attentional control (Derryberry & Reed, 2002; Healy & Kulig, 2006). This could imply that low attentional control, rather than high anxiety per se, may underlie attentional bias effects in these individuals. It is therefore unclear whether individual differences in attentional bias can be predicted by differences in anxiety directly, or whether differences in attentional control may underlie this relationship. To test this possibility, the present study included correlational analyses between attentional bias scores, trait anxiety measures and a measure of attentional control (Derryberry & Reed, 2002).

Experiment 1

Methods

Participants

Fifty seven participants (23 males, 34 females; mean age (*SD*) = 21.1 (*2.4*)) were recruited by flyers posted at the Utrecht University campus. For participation participants received either €13,- or course credits.

Apparatus

Visual stimuli were presented on a CRT computer monitor (refresh rate: 75 Hz) using the E-prime 1.1 (SP3) software package (Psychological Software Tools). The monitor was placed at a distance of 60 cm from the participant's eyes. Sounds were presented through a pair of Sennheiser headphones. Responses were given by pressing the 'q' and 'p' buttons on a QWERTY computer keyboard.

Stimuli and Task

The task was adapted from Koster et al. (2004) in which a stimulus that is associated with an aversive event serves as a cue in an exogenous cuing task (See Figure 1). During the task, a white fixation cross (1 x 1° visual angle) was shown in the center of the screen on a black background. To the left and right of the fixation cross were two white boxes (height 6.5°, width 4.8°). The distance from the centers of the boxes to the fixation cross was 9.2°. Trials began with the presentation of one of two face cues in either the left or the right box for 200 ms. The cues were two pictures of male faces colored either blue or yellow. The cue was followed by a brief (13.3 ms) presentation of the initial screen, after which the target square appeared in either the left or the right box. The target stimulus was a black 1 x 1° square. In 75% of the trials, the target square appeared in the same box as the face (valid trials), and in 25% of the trials the target square appeared in the opposite box (invalid trials). The participant's task was to press 'q' if the dot appeared in the left box and a 'p' if it appeared in the right box. To make sure that the participant would not press the button in response to the cue, 5% of the trials were catch trials in which no target stimulus was presented. On these trials, participants had to withhold their response. In order to ensure that the participant's gaze would remain fixated on the centre of the screen,

on several trials the fixation cross was briefly (100 ms) replaced with a digit (0.5° in height), which the participant had to name aloud as fast as possible (digit trials). The practice phase and the test phase consisted of 72 valid trials, 24 invalid trials, 6 catch trials, and 6 digit trials. In the practice phase, both cues were still neutral and no reinforcements were presented. This phase was intended to acquaint the participants with the task. After that, the experimental phase began, in which one cue was coupled to an aversive sound (threat cue), and the other was coupled to a neutral sound (neutral cue). Participants received an explicit instruction about this contingency. The color of the threat and neutral cues was counterbalanced between subjects. Sounds were delivered 200 ms after response, in 25% of the trials. The aversive sound was a recording of a human scream adopted from previous work by Lissek et al. (2005), while the neutral sound was a low intensity 1000 Hz sine wave (300 ms; 70 dB(A)).

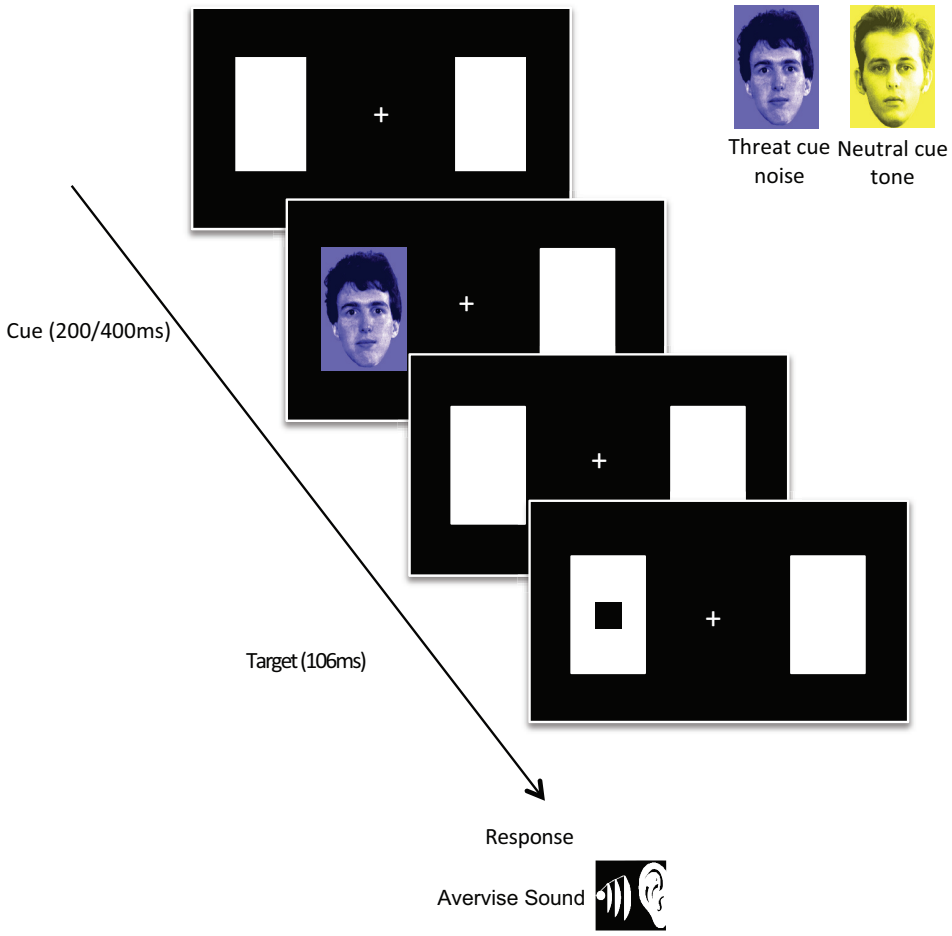

Figure 1. Trial schedule in the Emotional Spatial Cuing Task. Reinforcement was delivered on 25% of the trials

Procedure

Upon arrival at the laboratory, the participant first filled out the STAI-trait questionnaire (Spielberger *et al.*, 1970; van der Ploeg *et al.*, 1980). Subsequently, the emotional cuing task was performed. After completion of the task a manipulation check was performed to check subjective experience of the face cues and the aversive stimulation. Participants filled out 10-point Likert scales in which they indicated for each of the face cues how (un)comfortable they felt viewing it (0 = very comfortable, 9 = very uncomfortable), how aversive the scream was, and how strongly they expected each of the face cues to be followed by the scream (0 = certainly not, 9 = certainly). Furthermore they rated the aversiveness of the scream (0 = absolutely not aversive, 9 = highly aversive). Finally, participants completed the attentional control scale (Derryberry & Reed, 2002, translated in Dutch by Morren), the BIS/BAS questionnaire (Carver & White, 1984), and the Pleasure Seeking and Harm Avoidance subscales of the Cloninger's Temperament and Character Inventory (Cloninger *et al.*, 1993; Dutch translation by de la Rie *et al.*, 1988).

Data reduction and analysis

Only correct responses were included in the analysis of reaction times (RTs). Responses faster than 150ms, or slower than 1000 ms were marked as outliers and were also not included in the analysis (Koster et al., 2004a). To test effects of threat on attentional cuing, median reaction times were entered into a 2×2 (Validity: valid, invalid; Cue type: threat, safe) repeated measures ANOVA. A total threat cuing effect was calculated by subtracting the validity effect (invalid – valid) for the aversive cue from the validity effect for the neutral cue. Separate attentional engagement and disengagement effects were calculated as the RT(valid neutral cue) – RT(valid aversive cue) and RT(invalid aversive cue) – RT(invalid neutral cue) respectively. Note that these subtractions were made such that in all cases larger positive values indicate stronger modulation. Three participants were excluded from analysis because they had more than two responses on catch trials. Another two participants were considered outliers because of extreme engagement disengagement scores (more than three s.d. from average), and were also excluded.

Results

The resulting sample (N=52) had a mean age of 21.2 (*SD* = 3.4, 23 males, 29 females). Questionnaire mean scores were *M* = 35.8, (*SD* = 8.1) for STAI-trait, *M* = 19.1 (*SD* = 4.0) for the BIS scale, *M* = 40.6 (*SD* = 5.9) for the BAS scale, *M* = 20.6 (*SD* = 6.3) for the Pleasure Seeking subscale, *M* = 13.1 (*SD* = 5.2) for the Harm Avoidance scale, and *M* = 50.9 (*SD* = 6.0) for the ACS.

Subjective Ratings

The aversiveness of the noise was rated *M* = 7.5 (*SD* = 1.5) on a scale ranging from 0 to 9 (highly aversive). Expectancy of the aversive sound was higher after the threat cue than after the neutral cue (*M* = 6.5 ,*SD* = 1.7 vs. *M* = 2.5, *SD* = 2.1) on a 0-9 scale, $t(51) = -9.0$, $p < .001$), but ratings of discomfort did not differ between the threat cue and the neutral cue (*M* = 4.6, *SD* = 1.8) vs. *M* = 5.1, *SD* = 1.6) on a 0-9 scale, $t(54) = 1.3$, $p = .19$).

Reaction Time Data

Reaction time data are displayed in Figure 2. Average hit rates were > 95% in all conditions and were not analyzed in more detail. A 2×2 repeated measures ANOVA with Validity (valid, invalid) and Cue type (threat, neutral) as factors was conducted. Reaction time data showed a significant validity effect, $F(1, 51) = 114.3$, $p < .001$, $\eta_p^2 = .69$, indicating faster responses after valid cues than invalid cues. Also, there was a significant cue type effect, $F(1, 51) = 23.9$, $p < .001$, $\eta_p^2 = .32$, showing that on average responses after the threat cue were slower than after the neutral cue. Importantly, the crucial Validity × Cue type interaction was significant, $F(1, 51) = 45.3$, $p < .001$, $\eta_p^2 = .47$, demonstrating a stronger validity effect for the threat cue than for the neutral cue. Further analysis of these validity effects showed that reaction time after an invalid threat cue (*M* = 381.2 ms, *SD* = 55.2) was significantly longer compared to after a neutral cue (*M* = 356.5 ms, *SD* = 52.2), $t(51) = 7.8$, $p < .001$. In contrast, there were no significant differences in reaction times on valid trials between threat cues (*M* = 331.3, *SD* = 47.3) and neutral cues (*M* = 335.5, *SD* = 52.8), $t(51) = -1.5$, $p = .15$. Visual inspection of individual participants' data confirmed that while almost all individuals show an effect on disengagement, effects on engagement vary around zero (visible in correlation plots discussed below; Figure 3).

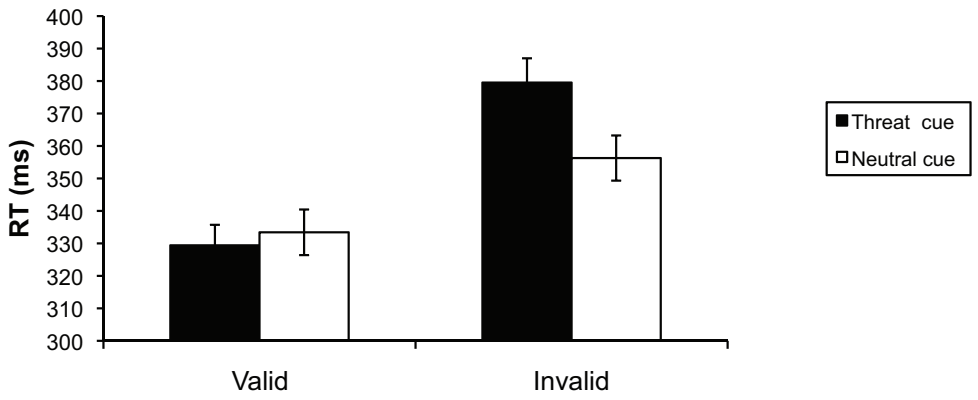

Figure 2. Reaction time data of unselected sample in Experiment 1. Bars and error bars represent mean RT and standard error of the mean.

Correlation Data

The effect of cue type on the validity effect (RT threat [invalid-valid) - RT neutral [invalid-valid]) showed a significant correlation with the STAI-trait (r = .31, p < .05) and a marginally significant correlation with BIS and Harm Avoidance (r = .24, p = .09; r = .27, p = .06 respectively), but not with the Pleasure Seeking subscale of the TCI , with BAS or with ACS (r = -.05, n.s., r = .04, n.s.; r = -.11, n.s., respectively). Inspection of the engagement and disengagement effects separately showed that STAI correlated only with the engagement effect (see Figure 3; engagement r = .36, p < .01; disengagement r = .10, n.s.), while BIS only correlated with emotional modulation on invalidly cued trials (engagement r = .01, n.s.; disengagement r = .31, p < .05). Harm Avoidance did not correlate with any of the emotional cuing components separately (valid trials r = .22, n.s.; invalid trials r = .17, n.s.). Furthermore, a marginally significant inverse correlation between ACS and the engagement effect (r = -.23, p < .10); with subscale shifting r = -.26, p = .06, not with subscale focus r = .04, n.s.. ACS and its subscales also correlated with STAI (r = -.50, p < .001; subscale focus r = -.48, p < .01, subscale shifting r = -.32, p < .01). Partial correlation between STAI and the engagement score, controlled for ACS-shifting was significant (r = .30, p < .05), while partial correlation between ACS-shifting and engagement, controlled for STAI was not significant (r = -.16, p = .25).

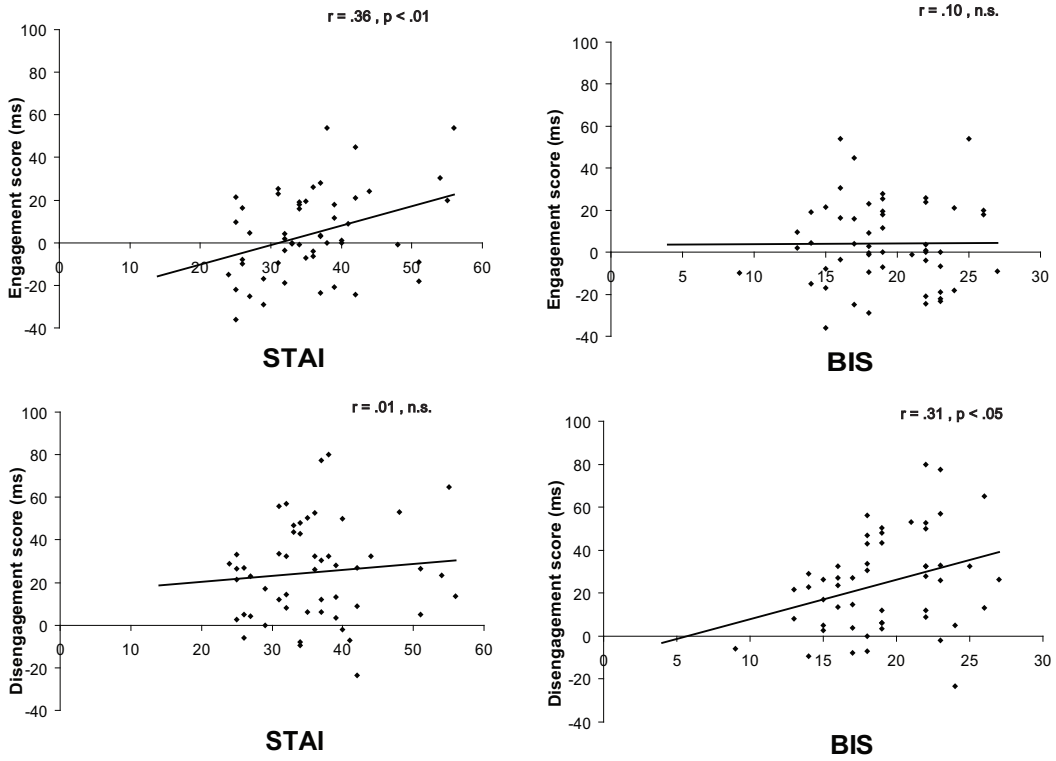

Figure 3. Correlations between personality trait scores trait anxiety (left) and behavioral inhibition (right), with the threat effects on engagement (upper panels), and disengagement components (lower panels) from Experiment 1

Discussion

The data from Experiment 1 partially replicate earlier findings that attentional bias to threat can be induced in a normal unselected sample when using cues that predict a highly aversive noise as a threatening event. In line with earlier studies (Koster, et al. 2004), attentional bias consisted mostly of slowed responding to invalid targets after a threat cue. In this sample nearly all participants showed this effect, indicating that with the current aversive stimulation attentional disengagement from threat is impaired in an unselected sample of participants irrespective of trait anxiety. Despite this generality, there was still considerable variability in the size of this effect, which was positively correlated with behavioral inhibition (BIS). Gray argues that BIS reflects the tendency of an organism to inhibit ongoing actions when one is faced with a threat (Gray, 1987). The effect of threat cues in the present study may therefore be related to inhibition of the reallocation of attention to targets that were not at the threat location (invalidly cued targets), especially in individuals with high BIS. On the other hand, the engagement was not significant, and

therefore we failed to replicate previous studies (e.g. Koster, 2004). Interestingly, the size of the engagement effect (although not significant on group level) was positively correlated to trait anxiety. A high anxiety score was associated with faster responses for validly cued targets after a threat cue. That this variance appears partly due to individual differences in anxiety may explain our inability to replicate findings of facilitated engagement on a group level. The sample contained relatively few high trait anxious participants, as can be seen in Figure 3. The distribution of anxiety scores was slightly positively skewed (skewness = .77). It is therefore possible that high anxious individuals were relatively underrepresented in this sample. Previous studies did not report trait anxiety levels. Therefore it is not possible to check whether effects on engagement found in these studies were related to the contribution of high anxious individuals (Koster et al., 2004a, 2005; Van Damme et al., 2006; Van Damme et al., 2007; Van Damme *et al.*, 2004b).

Experiment 2

In order to test whether the relation between the engagement effect and trait anxiety (and the absence of such a relation for the disengagement effect) were reliably present in a wider population, groups of high and low anxious people were selected in Experiment 2. The task, stimuli and procedure were the same as in Experiment 1. From the results of Experiment 1 it was hypothesized that differences between high and low anxious people would be mainly in the facilitating effects of direct aversive threat on subsequent valid target detection. The slowing of disengagement from threat cues, on the other hand, should not be influenced by anxiety.

Participants

Potential participants were selected from a database of 445 students who had filled out the STAI-trait questionnaire 1-1.5 year earlier. People whose scores on the STAI trait questionnaire were in the highest 30 % (STAI trait > 40) or the lowest 30% (STAI trait < 33) were invited to participate in the experiment and received €13,- or course credits. A total of 21 high anxious and 23 low anxious participants performed the experiment. During the experiment participants filled in the STAI-trait questionnaire for a second time, and

only participants who still scored within the predefined criteria for the anxiety group division at the time of testing were included in the analysis.

Statistical Analysis

Reaction times were entered into a 2×2×2 (Group × Validity × Cue Type) ANOVA, with Group as a between-subjects factor, and the others as within-subject factors.

Results

During time of testing four participants in the low-anxious group had STAI scores that exceeded the criterion (STAI > 33), and four participants from the high-anxious group scored below criterion (STAI < 40). These participants and were excluded from the analysis. The remaining groups of low anxious subjects (N = 19) and high anxious subjects (N = 17) did not differ in age ($t(34) = .12$, $p = .22$), and number of males and females included ($\chi^2(34) = .56$, $p = .46$). Personality questionnaire data are displayed in Table 1. The two groups differed on all three questionnaires pertaining to anxiety (STAI-trait, BIS, and Harm Avoidance ($t(34) > 2.6$, $p < .05$ for all comparisons) as well as on the ACS, but not on the BAS and Pleasure Seeking scales. Furthermore, none of the ratings on cue pleasantness and noise expectancy differed significantly between groups ($t < 1.9$, $p > .05$ for all ratings).

	Low-anxious		*High-anxious*		*Difference*	
	M	*SD*	*M*	*SD*	*t*	*p*
N (female/male)	19 (15/4)		17 (15/2)		(χ^2) 0.56	.46
Age	20.7	*1.4*	21.6	*2.8*	0.12	.22
Questionnaires						
STAI-trait	28	*2.5*	45.5	*6.7*	-10.7	.01
BIS	18.6	*3.1*	21.4	*3.2*	2.6	.05
BAS	41.2	*4.1*	42.1	*3.9*	0.6	.53
Pleasure Seeking	20.9	*6.5*	21.2	*6.2*	0.2	.87
Harm Avoidance	9.7	*4.9*	18.2	*6.4*	-4.5	.01
ACS	56.5	*6.1*	46.9	*6.6*	4.5	.01
Subjective Ratings						
Aversiveness of noise	7.3	*1.4*	7.5	*1.2*	-0.6	.55
Comfortable (threat cue)	3.6	*1.5*	4.4	*1.6*	-1.4	.17
Comfortable (neutral cue)	6.1	*1.3*	5.7	*1.5*	0.8	.46
Expectancy of noise (threat cue)	6.9	*1.4*	6.4	*2.4*	0.9	.39
Expectancy of noise (neutral cue)	1.8	*2*	3.2	*2.5*	-1.9	.07

Reaction Time data

Reaction times for both groups are presented in Figure 4. Average hit rates were > 95% in all conditions for both groups and were not analyzed in more detail. As in Experiment 1, validly cued targets were responded to faster than invalidly cued targets (main effect validity, $F(1,34) = 64.6$, $p < .001$, $\eta_p^2 = .71$), and as expected this effect was greater for threat cues than for neutral cues (Validity x Cue type, $F(1,34) = 31.6$, $p < .001$, $\eta_p^2 = .48$). This interaction was modulated by level of anxiety at trend level, reflected in a marginally significant interaction between Group x Validity x Cue type ($F(1,34) = 3.3$, $p = .079$, $\eta_p^2 = .09$). Since from Experiment 1 specific hypotheses were derived, predicting that low and high anxious people show a difference in the Validity x Cue type interaction only in valid trials, but not in invalid trials, we further examined this marginally significant interaction. The analysis was followed up by 2×2 (Validity x Cue type) repeated measures ANOVAs for both groups separately. In the low anxious group a validity main effect, $F(1,18) = 37.8$, $p < .001$, $\eta_p^2 = .68$, and a Validity x Cue type interaction were found, $F(1,18) = 8.3$, $p < .05$, $\eta_p^2 = 32$. This interaction indicated that the validity effect was stronger for the threat cue (46 ms) than for the neutral cue (25 ms). Analysis of the subcomponents of this threat modulation of the validity effect showed that in the low anxious group the effect of threat on attentional disengagement was significant, $t(18) = 2.9$, $p < .05$. This indicates slower reaction times in invalid trials after threat cues (M = 373.6 ms, SD = 53.9) than after neutral cues (M = 357.6 ms, SD = 44.8). In contrast the effect of threat on the engagement component was not significant, $t(18) = 1.3$, n.s., indicating that RT was not different for valid threat trials (M = 327.4 ms, SD = 34.0) compared to neutral trials (M = 332.2 ms, SD = 35.7). For the high anxious group, there was also a validity main effect, $F(1,16) = 27.9$, $p < .001$, $\eta_p^2 = .78$, and a Validity x Cue type interaction, $F(1,16) = 24.1$, $p < .001$, $\eta_p^2 = .60$, with stronger validity effects on threat trials (M = 51.9 ms, SD = 29.4) than neutral trials(M = 11.6 ms, SD = 18.2). Moreover, the threat modulation in this group was composed of both a significant effect on disengagement, $t(16) = 3.1$, $p < .01$, and on engagement $t(16) = 3.2$, $p < .01$. This indicates significantly slower RT in invalid trials for threat cues (M = 376.3 ms, SD = 43.4) than for neutral cues (M = 354.6 ms, SD = 33,5), and in valid trials, faster RT after threat cues (M = 328 ms, SD = 24.7) than after neutral cues (M = 346.7 ms, SD = 42.0).

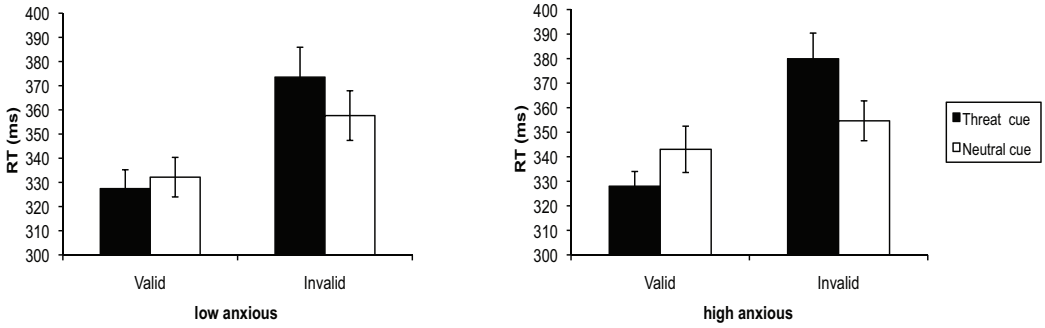

Figure 4. Reaction time data for high and low anxious participants in Experiment 2. Bars and error bars represent mean RT and standard error of the mean.

Finally, direct comparison of the low and high anxious groups showed that the engagement effect was stronger in the high anxious group than in the low anxious group ($t(34) = 2.1$, $p < .05$), while no significant differences in disengagement were found ($t(34) = .63$, $p = .53$).

Discussion

Results of Experiment 2 largely confirm the pattern that was found in Experiment 1. Both high and low anxious participants showed impaired disengagement from threat cues, and these groups did not significantly differ in size of this effect. Facilitated engagement was only found for high anxious participants, confirming the association between anxiety and attentional engagement found in Experiment 1.

General Discussion

The data of Experiments 1 and 2 show a clear and consistent picture of how attentional bias to stimuli that predict a direct aversive stimulation (loud sound) is related to trait anxiety. Studies using verbal or pictorial threat stimuli usually find that only anxious individuals have difficulties to disengage attention from threat stimuli (Fox et al., 2001; Mogg & Bradley, 1998; Yiend & Mathews, 2001). Even when pictures are used that are rated as highly threatening, prolonged disengagement time is not reliably found in low anxious people and in unselected samples (Koster et al., 2006; Koster et al., 2007). In contrast, the present study shows that using cues that invoke anticipation of aversive stimulation can cause prolonged disengagement effects in high anxious as well as in low

anxious people. Moreover, this effect was not found to be correlated with anxiety. It is possible that the anticipation of the loud auditory stimulation in this task poses an unambiguous threat that is perceived to be aversive by both high and low anxious people. Lissek et al. (2006) argued that in situations in which an unambiguous threat is presented, fear responses will be more or less homogeneous across individuals, and individual differences in anxiety will have a minimum impact. The data on disengagement seem to be in line with this idea. It is interesting to note, however, that despite the fact that disturbed disengagement was generally present in most participants, there was still considerable inter-individual variability in the strength of this effect (M = 36.7, SD = 30.5 for Experiment 1; M = 20.3, SD = 27.4 for Experiment 2. And although no relation between trait anxiety and the size of the disengagement effect was found, disengagement scores in Experiment 1 were positively correlated with BIS. This shows that even in relatively unambiguous threat situations there is room for individual differences in personality to determine reactions to threat.

In contrast to the disengagement effect, however, there was a clear relation between trait anxiety and the size of engagement effect. In Experiment 1 engagement was positively correlated with the trait anxiety score, and in Experiment 2 only the high trait anxious group (but not the low trait anxious group) showed a significant engagement effect. While the disengagement effect was in the same direction for the majority of the participants, a substantial portion of participants showed a reversed effect on engagement. In Experiment 1, half of the unselected participants had negative engagement scores, indicating slower responses after valid threat cues. Therefore this study did not replicate findings of facilitated engagement to cues predicting aversive stimulation reported in earlier studies (e.g. Koster et al., 2004b). In the present study the aversive auditory stimulation was consistently rated as highly aversive (Exp. 1: M = 7.5; and Exp 2: high anxious M = 7.5, low anxious M = 7.3; all scores on a scale from 0 to 9). These ratings are comparable to (or even higher than) ratings reported in other studies that do find engagement effects (ranging from M = 5.0 to M = 6.8; Koster et al., 2004a; ranging from M = 5.0 to M = 6.8; Koster et al., 2005; Van Damme *et al.*, 2004a; Van Damme et al., 2006; on scales from 0 to 10). Therefore differences in aversiveness cannot account for this discrepancy. An alternative explanation could be that the anxiety scores in Experiment 1 were relatively low. As discussed above, trait anxiety scores in Experiment 1 were slightly positively skewed, as 40 % of the participants had low anxiety scores with respect to the criterion for selection in

Experiment 2 (STAI-trait ≤ 33), while only 25 % percent scored within the high anxiety range (STAI-trait ≤ 40). Since we found a positive correlation between STAI-trait score and the engagement effect, it is possible that a relative overrepresentation of low anxious participants in this sample has obscured engagement effects on group level. Earlier studies using the current paradigm have not reported anxiety scores (e.g. Koster et al., 2004b), therefore it is not possible to compare psychometric distributions of the samples in these studies with the current study. An additional explanation could be found in a recent study by Mogg et al. (2008). They argued that the presentation of threat cues can cause a general slowing of responding to subsequent target stimuli, providing another possible explanation for the absence of an effect on engagement. Such a slowing would cancel any simultaneous speeding effect caused by a faster detection of threat signals, essentially obscuring the effects on attentional engagement. However, Mogg et al. (2008) found this general slowing effect to be larger in anxious people. In contrast, in the present study the anxious subjects responded relatively fast after valid threat cues. Furthermore, response slowing on invalid trials was not found to be related to anxiety. Therefore general response slowing does not seem to sufficiently explain the pattern of results in this study. In summary, the results of the current investigation are the first to show that the threat of direct aversive stimulation situations induces more uniform effects on the disengagement component across individuals while effects on engagement are positively correlated to anxiety.

It further should be noted that in this study an uneven validity ratio was used (75% valid / 25% invalid), which means that fewer trials were used to calculate average RT for invalid trials than for valid trials. As a consequence, RT scores for invalid trials may have a lower reliability than RT scores for valid trials. The absence of a relation between the disengagement effect and trait anxiety may have been due to a lower reliability of. However, this does not seem likely since disengagement scores were positively related to behavioral inhibition (BIS), and therefore seem sufficiently sensitive to individual differences. On a related note, the uneven validity ratio makes the cue partially predictive of the target location. Therefore response preparation may have been an additional factor causing validity effects. In this study it is not possible to examine the influence of threat on perception and response preparation separately. However, earlier research has shown that response preparation effects alone are not sufficient to explain threat disengagement effects (Fox et al., 2001).

A secondary aim of the present study was to explore the influence of attentional control capacity on attentional modulation by threat stimuli. It has been repeatedly found that trait anxiety is associated with less strong attentional control (Derryberry & Reed, 2002; Healy & Kulig, 2006). Several ideas have been postulated to explain this relationship. Eysenck's attentional control theory hypothesizes that "anxiety impairs attentional control by increasing the influence of the stimulus-driven attentional system" (Eysenck *et al.*, 2007). In contrast, Compton (2000) suggested that low attentional control (especially slowness to disengage attention) predicts negative affect. The results from the current study indeed show a significant negative correlation between self-reported attentional control and trait anxiety. However the correlation between anxiety and the engagement effect remains significant when controlled for attentional control. The relationship between trait anxiety and attentional bias to threat therefore cannot be ascribed to differences in attentional control, providing no support for Compton's view. The current data, however, are correlational and one should be cautious with drawing strong conclusions on the causality of this relationship.

In summary, Experiments 1 and 2 showed that stimuli that predict direct aversive stimulation can cause facilitated engagement effects. The size of these effects is correlated to the level of trait anxiety. Slowed disengagement from threat cues was found in virtually all participants. The size of this effect was related to behavioral inhibition, but not to anxiety. Furthermore, individual differences in attentional control capacity were not sufficient to explain these effects.

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Chapter **6**

Attentional bias to threat cues: Reduced inhibition of return and modulation of cue-elicited electrocortical potentials

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Abstract

Spatial attention can be modulated by stimuli that signal a threat. Although many studies use spatial cuing tasks, only few have examined the influence of threat on inhibition of return (IOR). IOR refers to slower orienting towards locations that have recently been attended. Reduced IOR after pictorial or verbal threat cues have been reported, but results are mixed. In this study threat was induced by associating peripheral cues with the occurrence of an aversive event (loud human scream). Furthermore, event-related potentials (ERPs) were recorded in order to track the potential influence of threat on stimulus processing. Participants performed an exogenous cuing task. Peripheral target stimuli were preceded by a cue stimulus which could be presented at the same (valid) or opposite location (invalid) as the target. After a pre-association baseline phase, subjects received the explicit instruction that cue stimuli were differentially predictive of an aversive scream (threat cue) or a soft beep tone (neutral cue). Behavioral results showed faster reaction times for invalid than for valid cues (IOR). This effect was similar for both cue types in the baseline phase. In the threat phase, IOR was reduced after threat cues compared to neutral cues. ERP data demonstrated that cue-locked brain activity was characterized by a medial frontal positivity (frontal P2) that was increased for threat cues as compared to neutral cues. These results suggest that threat cues evoke stronger attentional processing and reduce IOR on a behavioral level.

Introduction

Inhibition of return (IOR) refers to the phenomenon that attention is biased away from previously attended locations if no relevant stimuli are present in that location. Most often IOR is found using exogenous spatial cuing tasks (Posner & Peterson, 1990). The detection of a task-relevant peripheral target stimulus is influenced by the location of a preceding non-predictive spatial cue. If the stimulus onset asynchrony (SOA) is short (< 200 ms) target detection is facilitated if the target is presented in the same location as the cue (valid cuing), compared to when a target is presented in the opposite location from the cue (invalid cuing). However, when the SOA is longer, this effect reverses and detection of validly cued targets is slower than invalidly cued targets. The facilitated detection at short SOA's is thought to reflect that spatial attention is reflexively drawn towards the cued location (cuing facilitation). Inhibition of return is observed in impaired detection at longer SOA's, reflecting that attention is biased away from the cued location provided that sufficient time has passed without a relevant event occurring at the attended location. Theoretical accounts propose that IOR facilitates visual search of the environment by biasing attention towards novel locations thereby increasing the probability of detecting relevant stimuli (Klein, 2000).

Given the idea that attentional mechanisms including IOR are evolved to facilitate the detection of (biologically) relevant stimuli, it could be expected that the motivational properties of cue stimuli may modulate the occurrence of IOR. In fact a large literature exists that demonstrates that several aspects of spatial attention can be influenced by threatening cues (for reviews see; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Cisler & Koster, 2010; Pessoa, Kastner, & Ungerleider, 2003; Yiend, 2009). Using short SOA's stronger cuing facilitation after threat cues than after non-threat cues has been found repeatedly (Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo, & Dutton, 2002; Koster, Crombez, Verschuere, VanVolsem, & De Houwer, 2007; Koster, Verschuere, Crombez, & Van Damme, 2005; Massar, Mol, Kenemans, & Baas, 2010; Mogg et al., 2000; Wilson & MacLeod, 2003; Yiend & Mathews, 2001). Most consistently, performance costs for invalid threat cues are more pronounced than performance benefits for valid threat cues. This has been interpreted as reflecting increased difficulty disengaging attention from threatening cue stimuli, when attention needs to be redirected to invalidly cued targets.

Studies examining the influence of emotional cues on IOR are less numerous, and have yielded mixed results. Yiend and Matthews (2001) and Fox et al. (2002) found that the magnitude of IOR was decreased when pictures of aversive scenes or angry faces were used as cues. In line with studies on cuing facilitation, these findings are thought to indicate that attention takes longer to disengage from threat locations. Thereby the redirecting of attention to non-cued locations, as in IOR, is hindered. However, other studies have not found evidence for the modulation of IOR by threatening cues (Lange, Heuer, Reinecke, Becker, & Rinck, 2008; Stoyanova, Pratt, & Anderson, 2007), or found reduced IOR for threat only in subgroups of their samples (e.g. highly trait anxious individuals; Fox, et al., 2002; Verkuil, Brosschot, Putman, & Thayer, 2009; Waters, Nitz, Craske, & Johnson, 2007). The different results from these studies might be due to differences in the way threat has been induced in cues (e.g. angry v.s. fearful faces) or to different response modes used (target localization versus discrimination).

Whereas previous IOR studies used inherently affective pictures as cues, the present study used a different approach. Here, peripheral cues conveyed threat of direct physical annoyance administered on a subset of trials. Threat was induced by associating cues to the occurrence of an aversive event (loud noise). Visual cue stimuli with different colors were used (faces colored blue or yellow). Cues with one color could be followed by an aversive noise, while cues with the other color could be followed by a neutral (soft) tone. Using this procedure one cue became selectively predictive of a threat, while the other cue was predictive of non-threat. This procedure has been used in previous studies and has consistently induced attentional modulation in general populations (Koster, Crombez, Verschuere, & De Houwer, 2004; Massar, et al., 2010; Van Damme, Crombez, & Eccleston, 2004). As discussed above, especially disengagement of attention from threat cues was found to be impaired in both anxious and non-anxious individuals (Massar, et al., 2010). Given this slowing of attentional disengagement, it could be expected that IOR would be decreased in magnitude when target stimuli were preceded by threat cues compared to safe cues.

A further aim of this study was to investigate the electrophysiological processes by which threat stimuli may modulate IOR. Because we were especially interested in how the processing of threat stimuli influences attentional deployment, we focused on analysis of cue-related ERPs. So far only a few studies have focused on ERP activity following the cue to assess processes underlying the occurrence of IOR. Tian et al. (2011) identified

several different sensory and attentional components. They argued that while early visual components would be related to initial attentional capture by the cue, a later fronto-central positivity (starting 250 ms post cue) was specifically related to the initiation of IOR. On the other hand Wascher, Falkenstein and Wild-Wall (2011) reported a fronto-central negativity (N2) peaking at 350 ms post cue, which they argued to reflect the initiation of inhibition. Given the fact that the morphology of cue-locked ERP waveforms was markedly different between these two studies, we aimed to identify the presence and latency of these fronto-central positive and negative components by visual inspection. To study the influence of threat on these processes, ERPs after cues that were associated with an aversive noise were compared to ERPs after cues that were associated to a non-threatening auditory stimulus, focusing on the components thus identified.

Following our previous study (Massar et al., 2010) we had participants indicate the location of the target for a performance read-out measure in the first experiment. However, as this procedure potentially confounds selective attention and selective motor preparation (to the side of the cued location), a second experiment reported here utilized a feature-discrimination task with respect to the targets. This modification turned out to be quite inconsequential for the main results.

Methods

Participants

Twenty volunteers were recruited at the university campus (Experiment 1: 5 females; mean age = 21.9, sd = 4.0; 3 left-handed; Experiment 2: 6 females, mean age (sd) = 22.2 (3.9), all right-handed). All participants had normal or corrected-to-normal vision and were naïve to the purpose of the experiment. Subjects earned €13 or course credits by participating. Participants filled out written informed consent before starting the experiment.

Stimuli and Task

The stimuli and task used in this study were based on a paradigm used in a previous study that used instructed threat combined with a spatial cueing task (Massar et al, 2010). A schematic illustration of this task is provided in Figure 1. The basic task display consisted of two white boxes (height 6.5°, width 4.8° visual angle), presented laterally on left and right side of a central fixation cross (1°x1°). Distance between the fixation cross and the centre of the boxes was 9.2°. Exogenous spatial cues consisted of pictures of male faces

(neutral expression) in either blue or yellow color, which were presented in one of the two peripheral boxes. Cue duration was jittered around two intervals (short: jittered 50 ms around 187 ms; long jittered 50 ms around 387 ms), and followed by a 13 ms blank presentation of the peripheral boxes (in total constituting a 200 ms short SOA and a 400ms long SOA). The two SOA conditions were included as to induce cuing facilitation at short SOA's and IOR at long SOA's. Target stimuli (2.4° visual angle diameter grating patch) were presented for 106 ms in the center of one of the peripheral boxes. Target gratings were tilted 5° to the left or 5° to the right, and could be presented either in the same location as the cue (valid) or in the opposite location (invalid).

In experiment 1 participants had to respond based on target location. (press the <v> key on a keyboard for targets presented in the right box, press <m> for targets presented in the right box). In experiment 2 participants performed a discrimination task in which they had to respond to target orientation (press <v> for leftwards tilted targets, press <m> for rightwards tilted targets). Participants were instructed that cues were not predictive of target location and that they had to respond to targets as fast and as accurately as possible.

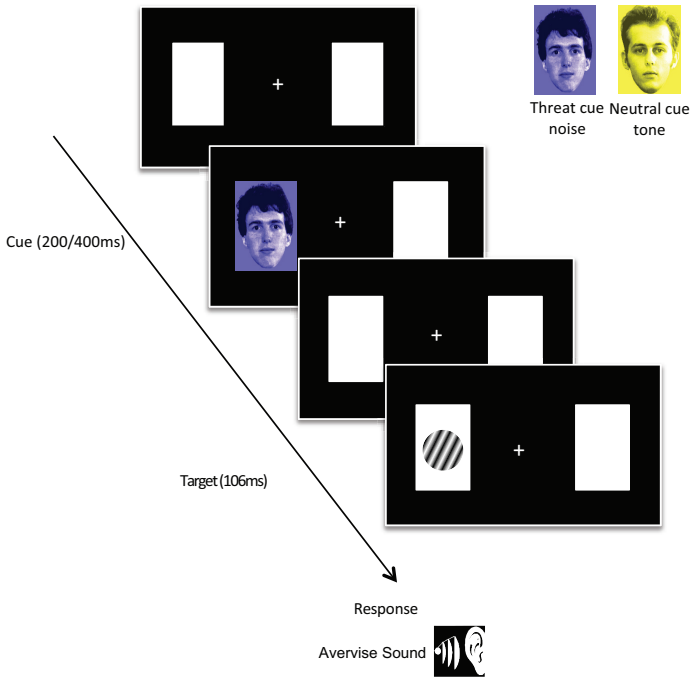

Figure 1: Trial Schedule in the Emotional Spatial Cueing Task. In the baseline phase no reinforcements were presented. In the threat phase reinforcements were delivered on 25% of the trials. The example illustrates a reinforced trial in the valid condition.

The tasks were each performed in two distinct phases. During the *baseline phase* no auditory stimuli were presented, therefore all cues were non-threatening. The crucial characteristic of threat phase was that cues were differentially associated with threat or with non-threat. Cues with one color (blue or yellow) could be followed by an aversive noise (100 dB human scream, 300 ms. duration), and the other cue with the other color was sometimes followed by a neutral auditory stimulus (1000 Hz pure tone, 300 ms., 70 dB). Consequently, one of the cues was predictive of an aversive stimulation (threat cue), while the other cue predicted the absence of threat (neutral cue). The cue color that was associated with threat or with non-threat was counter balanced between participants. Auditory stimuli were presented in 25 % of the trials and were always delivered at the end of the trial (200 ms post response). Participants received explicit instructions to keep their eyes fixated on the central fixation cross during the entire length of the experiment, and an additional task at fixationwas included to further stimulate subjects to maintain fixation. During a digit trial a number from 0 to 9 was presented for 100 ms at the location of the fixation cross and subjects were instructed to name the number aloud as quickly as possible. The task started with a short practice block of 34 trials (32 trials and 2 digit trials) to get acquainted with the task. Subsequently, participants performed the baseline and threat phases, both consisting of 5 blocks of 136 trials (64 trials per cue type and 8 digit trials) making up a total of 680 trials per phase.

Procedure

After entering the lab participants signed an informed consent form and EEG equipment was applied. Then they received verbal task instructions and performed a short practice block, during which no auditory stimuli were presented. After the practice block the aversive and neutral sound were presented once each for the participants to get acquainted with these stimuli. Subsequently, participants performed the baseline and threat phase of the cuing task. Before the threat phase began subjects received explicit instructions concerning which cue would be associated with the aversive and neutral sound. After completion of the task participants rated the subjective experiences of the cue stimuli (0 = very uncomfortable, 9 = very comfortable), the aversiveness of the auditory stimuli (0 = absolutely not aversive, 9 = highly aversive), and their expectancies about whether the

aversive stimulus would follow either cue stimuli (0 = absolutely unexpected, 9 = highly expected), on 10-point Likert scales.

Behavioral analysis

During the task manual reaction time (RT) and accuracy were monitored. For RT quantification incorrect responses, fast guesses (RT < 100 ms) and late responses (RT > 1000 ms) were excluded. Also responses exceeding three times SD from the individual mean RT were considered outlier responses and were discarded. For the resulting responses, mean RT was calculated for each phase (Baseline, Threat), SOA (Short, Long), Validity (Valid, Invalid), and Cue Type (Threat, Neutral). IOR scores were calculated by subtracting the mean RT in invalid trials from the mean RT in valid trials (positive scores indicate stronger IOR) in all experimental conditions separately. Individual mean reaction times were subjected to a Phase x SOA x Validity x Cue Type repeated-measures ANOVA. Follow-up ANOVAs were performed where significant interactions were found. Of specific interest were interaction terms that included Phase, Validity and Cue Type, since these may reflect that the IOR effect was modulated by Cue Type, depending on whether there was a differential threat association (threat phase) or not (baseline phase).

EEG recording and analysis

EEG was recorded from 64 Biosemi Active 2 electrodes positioned at standard 10/10 positions. The standard Biosemi reference includes CMS/DRL sensors embedded in the electrode cap (MettingVanRijn, Kuiper, Dankers, & Grimbergen, 1996). Electrodes for offline re-referencing were placed on the left and right mastoids. Vertical EOG was measured using 2 facial electrodes placed in the superior and inferior areas of the left orbit and horizontal EOG were recorded by 2 electrodes placed on the outer canthi of both eyes. All data were recorded with a 512 Hz low-pass filter at a sampling rate of 2048 Hz and stored for offline analysis.

Data were analysed using Brain Vision Analyzer (Brain Products GmbH, Germany). The EEG and EOG were digitally filtered with a 1-30 Hz bandpass filter. Data were segmented in -100 ms to 500 ms windows around cue or target onset periods. Segments containing EEG or EOG activity exceeding ±75 μV were considered artifacts and were removed from further analysis. ERPs were calculated only for long SOA trials to

minimize the possible overlap between cue-related ERPs and subsequent target processing. Cue-locked ERPs were calculated for all experimental conditions separately: Phase (baseline and threat), Location (left and right), and Cue Type (Threat and Neutral). By visual inspection of cue-locked waveforms two clear fronto-central components were identified that both peaked at fronto-central locations (FCz): a positive component between around 200 ms post-cue presentation which may correspond with the fronto-central positivity reported by Tian et al (2011). From here on this positivity will be termed P2. Following the P2, a negative component around 350 ms post- cue, which could reflect the fronto-central N2 as described by Wascher and Tipper (2011). The amplitude of these components was quantified as the average amplitude at electrode FCz in a window between 190-260 ms for the frontal P2 and 300-350 ms for the frontal N2. An earlier negative component was also observed around 100 to 200 ms after cue presentation (N1). Since this component has not been linked to IOR in previous studies we will concentrate on the later P2 and N2 components in this study. For statistical analysis ERP amplitudes were subjected to a Phase x Cue Location x Cue Type repeated-measures ANOVA. Follow-up ANOVAs were performed where significant interactions were found. We were specifically interested in the Phase x Cue Type interaction, since this term indicated whether cue-related ERPs were different between the threat cue and the neutral cue, depending on phase.

Results

Trait Scores and Subjective Ratings

Mean scores on trait questionnaires were: STAI (Mean = 30.3, SD = 4.74); BIS (Mean = 18.0, SD = 3.02); BAS (Mean = 39.5, SD = 4.30). The aversiveness scores of the noise and the neutral sound showed a significant difference, $t(9) = 10.3$, $p < .001$, with higher aversiveness scores for the noise, Mean = 7.6 (SD = .97), compared to the neutral sound, Mean = 0.9 (SD = .16). The expectancy of the aversive sound being presented after the threat cue was rated 7.2 (SD = 1.32), as opposed to 0.8 (SD = 1.39) for the neutral cue ($t(9) = 9.1$, $p < .001$). The difference in ratings of how comfortable participants felt watching either the threat and the neutral face cue was significant, $t(9) = 3.3$, $p < .01$, indicating lower comfort scores for the threat cue, (mean = 4.2 , SD = .92) compared to the neutral cue (mean = 6.4, SD = 1.43).

Accuracy Scores. Mean accuracy scores in all conditions were between 97 and 100% and were not analyzed in further detail.

Reaction times. Reaction time data are displayed in Figure 2a. A 2 x 2 x 2 x 2 repeated measures ANOVA with Phase (baseline, threat), SOA (short, long), Validity (valid, invalid) and Cue Type (Threat, Neutral) as factors was conducted. A significant SOA x Validity interaction was found $F(1, 9) = 52.05$, $p < .001$, $\eta p^2 = .853$, indicating a difference in validity effects between the short SOA (IOR scores: 33.7ms) and the long SOA condition (IOR = 16.1ms).

Central to this study was the question whether IOR effects were modulated by cue type (threat versus neutral). This contrast was reflected in a significant Phase x Validity x Cue Type interaction ($F(1, 9) = 11.26$, $p < .01$, $\eta p^2 = .556$), indicating different validity effects for the neutral and the threat cue between the baseline and threat phase. In order to interpret this interaction, separate 2 x 2 repeated measures ANOVA's with Validity and Cue Type as factors were conducted for the baseline and threat phase. Data were collapsed over short and long SOA's since no significant Phase x Validity x Cue Type x SOA 4-way interaction was found.

Baseline phase: A significant main effect for validity was observed in the baseline phase, $F(1, 9) = 47.84$, $p < .001$, $\eta p^2 = .84$. Planned paired t-tests indicated slower reaction times for valid compared to invalid targets, hence IOR. Importantly, No significant Cue Type x Validity effect was found in the baseline phase, $F(1, 9) = 1.39$, $p = .27$, $\eta p^2 = .134$, illustrating that IOR did not differ between the cues.

Threat phase: In the threat phase, a significant main effect for validity was also observed, $F(1, 9) = 34.53$, $p < .001$, $\eta p^2 = 793$, indicating the presence of IOR. Moreover, a significant Cue Type x Validity effect was found, $F(1, 9) = 9.78$, $p < .05$, $\eta p^2 = 521$. Follow-up paired t-tests showed that although the IOR effect was present in both cue type conditions, the amount of IOR was significantly reduced on trials with threat cues (20.7 ms) compared to the neutral cues (31.0 ms; $t(9) = 3.13$, $p < .05$).

ERP Measures

P2. The P2 waveform to the cue is displayed in Figure 2b. A 2 x 2 x 2 repeated measures ANOVA on the P2 amplitude at FCz with Phase (Baseline and Threat), Cue Type (threat

and neutral) and Cue Location (left and right) as factors was conducted. A significant Phase x Cue Type interaction $F(1, 9) = 17.86$, $p < .01$, $\eta p^2 = .67$, revealed different effects of the cues on the P2 amplitude between the baseline and threat phase. To further investigate this effect of Cue Type on the P2 amplitude, separate analyses for the baseline and threat phase were conducted. Because the Phase x Cue Type x Location interaction was not significant, data were collapsed over left and right cue locations. In the baseline phase, no significant main effect for Cue Type was found ($F(1, 9) = .47$, $p = .51$, $\eta p^2 = .05$). However, a significant effect of Cue Type was found in the threat phase, $F(1, 9) = 12.56$, $p < .01$, $\eta p^2 = .58$, showing larger P2 amplitudes for the Threat compared to the Neutral Cue.

N2. A Phase (baseline, threat) x Cue Type (threat, neutral) x Location (left, right) ANOVA did not yield any main effect or interaction including Cue Type or Location (all F's < 1). Only a marginally significant Phase main effect was found ($F(1,9) = 4.7$, $p = .058$, $\eta p^2 = .34$), indicating that N2 amplitude was more negative during the threat phase than during the baseline phase.

Results Experiment 2: Discrimination Task

Results

Trait Scores and Subjective Ratings

Mean scores on trait questionnaires were: STAI (Mean = 36.9, SD = 6.49); BIS (Mean = 18.5, SD = 2.99); BAS (Mean = 37.1, SD = 2.28). Post-task aversiveness ratings were higher for the aversive noise (Mean = 7.9, SD = .74) than for the neutral auditory stimulus (Mean = 1.1, SD = .88; $t(9) = 17.493$, $p < .001$). Aversive noise was more strongly expected after threat cues (rated 7.4, SD = 1.26) than neutral cues (1.8, SD = 2.29; $t(9) = 6.836$, $p < .001$). The difference in ratings of how comfortable participants felt watching either the threat and the neutral face cue was marginally significant, $t(9) = -2.17$, $p = .058$, indicating lower comfort scores for the threat cue, mean = 4.2 (SD = 1.99) compared to the neutral cue, mean = 5.4 (SD = 2.17).

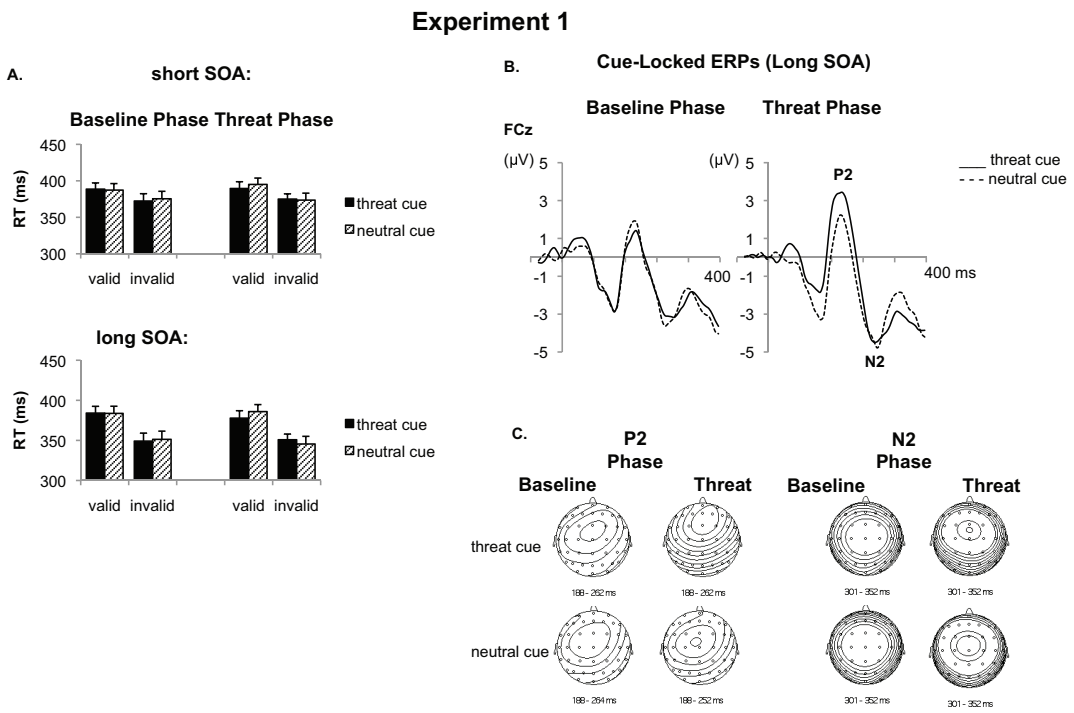

Figure 2: A) Mean RT and standard errors of the mean for targets following the Neutral and Threat cues in Valid and Invalid conditions after a short SOA (200 ms; upper panel) long SOA (400 ms; lower panel) for the baseline and threat phase. B) Cue-Locked ERPs for long SOA trials at FCz in the baseline and threat phase (collapsed over cue location). C) Scalp distributions of the P2 and N2 components for every cue type per phase.

Behavioral results

Accuracy. Mean accuracy scores in all conditions were between 89 and 93% and were not analyzed in further detail.

Reaction times. The reaction time data are displayed in Figure 3a. A 2 x 2 x 2 x 2 repeated measures ANOVA with Phase (baseline, threat), SOA (short, long), Validity (valid, invalid) and Cue Type (Threat, Neutral) as factors was conducted. A significant Phase x SOA x Validity x Cue Type interaction was found, $F(1, 9) = 6.67$, $p < .05$, $\eta p^2 = .425$. To further investigate this interaction separate Phase x Validity x Cue Type repeated measures ANOVAs were performed for short and long SOA separately. For short SOA trials only the Phase main effect approached significance ($F(1,9) = 3.96$, $p = .08$), indicating that on average participants responded faster in the threat phase (mean RT = 594.8 ms, SD = 20.7) than in the baseline phase (mean RT = 625.5 ms, SD = 22.0). All other effects were non-significant (all F's < 2). This indicated that for short SOA trial no IOR was present, and no modulation of RT by threat was found.

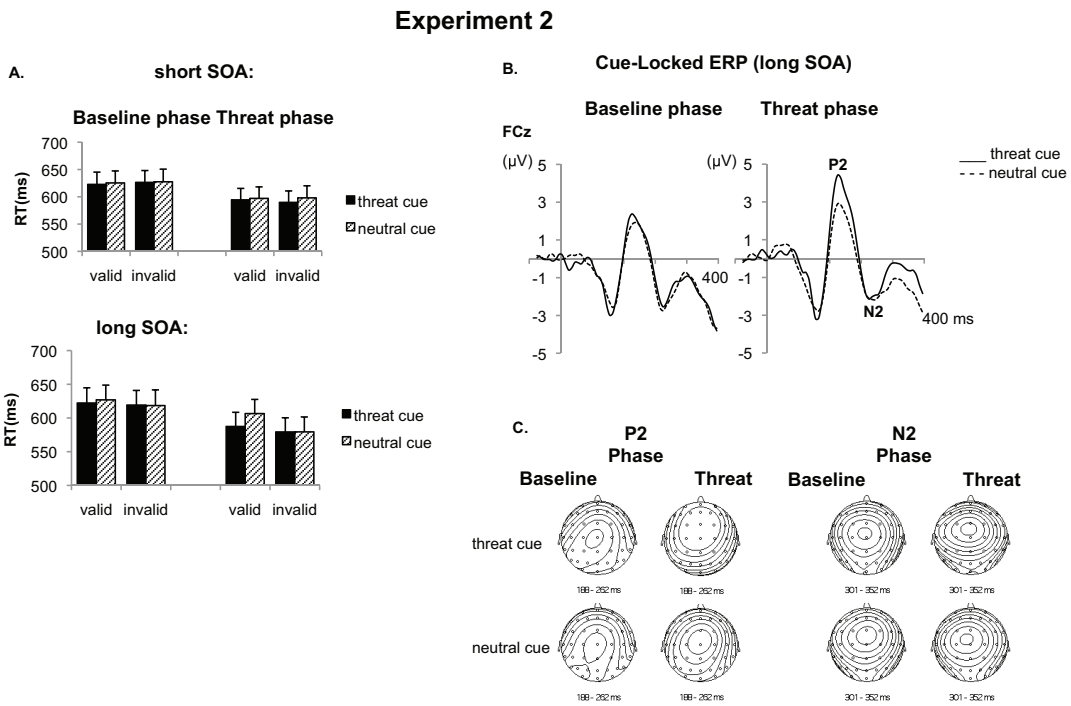

Figure 3:A) Mean RT and standard errors of the mean for targets following the neutral and threat cues in Valid and Invalid conditions after a short SOA (200 ms; upper panel) long SOA (400 ms; lower panel) for the baseline and threat phase. B) Cue-Locked ERPs for long SOA trials at FCz in the baseline and threat phase (collapsed over cue location). C) Scalp distributions of the P2 and N2 components for every cue type per phase.

For the long SOA trials a Phase x Validity x Cue Type repeated measures ANOVA yielded a significant 3-way interaction ($F(1,9) = 5.11$, $p < .05$, $\eta p^2 = .36$). This interaction was further dissected with separate Validity x Cue Type ANOVA's for baseline and threat phase. For the baseline phase no significant main effects or interactions were found (all F's < 1). This indicated that no IOR was present in the baseline phase for both cue types. Reaction times in the threat phase were characterized by a significant validity main effect ($F(1,9) = 14.07$, $p < .01$, $\eta p^2 = .610$), and critically for this study a Validity x Cue Type interaction ($F(1,9) = 6.45$, $p < .05$, $\eta p^2 = .418$). Paired-sample T-tests showed IOR scores were significantly higher for neutral trials (mean IOR = 27.1, SD = 23.8) than for threat trials (mean IOR = 8.1, SD = 12.5; $t(9) = 2.54$, $p < .05$).

ERP Measures

P2. Cue-Locked ERP waveforms are illustrated in Figure 3b. A 2 x 2 x 2 repeated measures ANOVA was conducted on P2 amplitude at FCz with Phase (Baseline and

Threat), Cue Type (Threat and Neutral) and Cue Location (Left and Right) as factors and a significant Phase x Cue Type interaction was observed ($F(1, 9) = 8.42$, $p < .05$, $\eta p^2 = .48$). Because this interaction did not differ between Cue Locations, the Cue Type effect was analyzed with separate ANOVA's for the baseline and threat phase collapsed over cue locations. No significant difference between the threat and the neutral cue was found in the baseline phase ($F(1, 9) = .52$, $p = .49$, $\eta p^2 = .05$) indicating that P2 amplitudes were not different between threat cues (mean amplitude = 1.63, SD = 0.39) and neutral cues (mean amplitude = 1.36, SD = 0.60). In contrast, during the threat phase P2 amplitudes after threat cues were significantly higher (mean amplitude = 3.26, SD = 0.48) than after neutral cues (mean amplitude = 2.06, SD = 0.79).

N2. A Phase x Cue Type x Location ANOVA yielded a significant three-way interaction ($F(1,9) = 5.77$, $p < .05$, $\eta p^2 = .391$). Follow-up ANOVAs however, demonstrated that this interaction was due to a Cue Type x Location interaction in the baseline phase ($F(1,9) = 9.09$, $p < .05$, $\eta p^2 = .503$), but not in the threat phase ($F(1,9) = .04$, $p = .84$). The interaction effect in the baseline phase was not of our primary interest, however to be complete, follow up t-tests were conducted. Paired T-tests showed that N2 amplitude during baseline was more negative for left side presented neutral cues (-2.8, SD = 1.7) than for right side neutral cues (-1.8, SD = 1.4; $t(9) = 2.8$, $p < .05$). N2 amplitudes for threat cues in baseline were not different across cue locations ($t(9) = -2.0$, n.s.).

Discussion

The present findings demonstrate clearly that IOR can be modulated by the threat value of an exogenous spatial cue stimulus. It was hypothesized that IOR would be reduced for cues that signal a threat. In the localization task (experiment 1) behavioral data showed robust IOR in both short and long SOA trials in baseline. Critically, when cues were differentially associated with threat or non-threat, IOR was reduced for trials in which a threat cue was used. In the discrimination task (experiment 2) no IOR was evident when the SOA was short. This was the case both during the baseline phase and the threat phase. Furthermore, no modulation of response times by threat was found in short SOA trials. In contrast, in long SOA trials threat value of the the cue did affect response time patterns. In the baseline phase IOR was not found to be significant, however in the subsequent threat phase an IOR pattern occurred after neutral cues, which was absent after threat cues. It therefore seems that in experiment 2 IOR was found only when cues were not motivationally relevant

(neutral cue), and only after longer SOA's. The fact that in the discrimination task no IOR was found in short SOA trials is in line with findings that in discrimination tasks IOR only occurs in with longer cue-target intervals (Lupiáñez, Milán, Tornay, Madrid, & Tudela, 1997). It is however not fully clear why IOR only developed in during the threat phase. It could be possible that longer practice in the task increases the ablility to direct attention away from the non task-relevant cue stimuli, hence introducing IOR only at a later stage during the task.

Together these data add to the earlier findings of reduced IOR for threat cues in anxious individuals (Fox, et al., 2002; Verkuil, et al., 2009; Waters, et al., 2007) and in non-anxious individuals (Fox, et al., 2002; Yiend & Mathews, 2001). IOR is thought to reflect a bias of attention away from a previously cued location when no relevant stimuli are detected in this location (Klein, 2000). Therefore the present findings suggest that attention is less easily biased away from threat locations. In line with this interpretation earlier studies have demonstrated that attention is less easily disengaged from threatening cues (Fox, et al., 2001; Fox, et al., 2002; Koster, et al., 2004; Massar, et al., 2010).

It must be noted that in contrast to our earlier study (Massar, et al, 2010), no cuing facilitation was found at short SOA (200ms) trials in the present study. In experiment 1 IOR was present for both short and long SOA's, while in experiment 2 no IOR or facilitation was present in short SOA trials. This difference could be explained by the fact that an uneven validity ratio containing 75% valid trials was used in our previous study, whereas presently 50% of the trials were valid. The use of an unequal number of valid and invalid trials renders the cue predictive of the target location, and probably introduces voluntary orienting towards cue locations. In conttrast, at 50% validity, no such expectancy of target location is possible. Therefore attention can more swiftly directed away from the cue stimulus once it is identified as not task-relevant.

In parallel with the behavioral data the cue-related ERPs were also modulated by threat stimuli. Whereas during baseline no differences between ERPs elicited by both cue types were evident, differential ERP responses were found during the threat phase, when one cue was associated with threat and the other was not. A positivity with fronto-central scalp distribution was found around 200 ms post-cue onset latency (P2). During the threat phase, the amplitude of this P2 was higher for threat cues compared to that for the neutral cues. This was both the case in the localization task aswell as in the discrimination task. This positivity may be equivalent to the frontal positivity reported by Tian et al. (2011),

which had a latency that was slightly longer (250-350ms) than that of the positivity found here. Wasscher et al. (2011) did not report analysis of this frontal positivity, but from their figure a similar positive component can be identified (in the young adult group). According to Tian and colleagues this positivity may reflect the initiation of the inhibitory process that leads to behavioral IOR. The finding that in the present study P2 amplitudes are highest in the condition in which IOR is smallest (following threat cues in the threat phase), however, des not very well fit this interpretation.

An alternative explanation could be that the frontal positivity as found presently is a variant of the frontal selection positivity (FSP). The FSP is a positive potential that reflects attentional selection of relevant stimulus features (Johanna M. P. Baas, Kenemans, & Mangun, 2002; Kenemans, Kok, & Smulders, 1993; Kenemans, Lijffijt, Camfferman, & Verbaten, 2002; Potts, 2004). The FSP shows a fronto-central distribution and peaks around 200 mslatency, similar to the P2 in the present study. Interestingly, Baas et al. (2002) demonstrated that the FSP is found not only when a stimulus was behaviorally relevant (as by task instructions), but also when stimuli gained significance because they were predictive of an aversive shock. This may implicate that attentional selection of threatening stimuli is stronger or more automatic than selection of neutral stimuli (i.e. attentional selection of threatening stimuli takes place even in the absence of behavioral relevance with respect to the current task). In support of this idea, studies that have used other attentional paradigms have also found increased frontal P2 amplitudes for social threat stimuli (e.g. fearful faces; Amodio, 2009; Ashley, Vuilleumier, & Swick, 2004).

Wascher and colleagues reported a fronto central negativity in stead of a positivity in cue-locked ERPs in an IOR task. They argued that this N2 reflected inhibitiory control. In the present study a clear N2 was present around 350 ms after cue presentation. Similar to the P2 the N2 peaked at a frontocentral scalp location. However N2 amplitude was not modulated by threat. Both cue types elicited equal N2 amplitudes both in the baseline phase and during the threat phase. It therefore seems unlikely that the N2 is related to the behavioral threat modulation of IOR.

The exact functional significance of different cue related ERP components in the context of the IOR remains to be resolved. The few studies that have reported cue-locked ERPs have shown largely different ERP morphologies (Tian, et al., 2011; Wascher, et al., 2011). The waveforms found in the present study also differ in some aspects from those previously reported.Here we show that part of the cue-related ERP is sensitive to the threat

manipulation in a manner that suggest enhanced attention to the threat cue. This effect was superposed on or preceded basic waveforms that may reflect attentional capture or inhibition of return independently of the affective modulation. Since cue-target intervals are relatively long for IOR paradigms (as compared to cuing facilitation), cue-related ERPs provide a valid means to examine how brain responses to cue stimuli give rise to spatial attention allocation, while minimizing component overlap from later target processing.

Importantly, the finding of comparable threat modulation of IOR across the two tasks strongly suggests that this threat modulation does not concern motor facilitation. Peripheral cues as presently used may induce motor preparation for the side of body congruent with the cue (the 'Simon' effect). If target localization is used as task, the Simon effects adds to or may even completely explain the validity effect. With feature discrimination, cue-induced motor preparation is completely orthogonal to the selection of the correct response (left or right) to the target. Hence, threat modulation of IOR in this task may very well reflect attentional processing at a more perceptual level. The effects of threat on both behavioral IOR and cue-locked ERP's were nevertheless highly comparable between both tasks. Therefore it can be thought that similar attentional mechanisms are underlying the reduction of IOR by threat, both during target localization and discrimination modes.

In conclusion, the present study adds to the knowledge about both IOR as well as attentional processing of emotionally valued stimuli. Both in the localization task as well as in the discrimination task, smaller IOR was found followinfg threat cues than following neutral cues. This modulation at behavioral level was accompanied by robust increases in attentional processing of threat-related stimuli.

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Chapter **7**

Stimuli that predict negative and positive feedback guide spatial attention

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Abstract

Recent studies have demonstrated that stimuli that are associated with monetary reinforcement can attract reflexive spatial attention. Previous results have been explained in a reinforcement learning framework, stating that due to monetary reinforcement an attentional bias develops towards stimuli that signal good outcomes and away from bad outcomes. Findings on effects of monetary rewards on spatial attention appear quite consistent. In contrast, the effects of monetary loss have not been well studied. In this study, cue stimuli that predicted monetary reward, punishment, or no reward/punishment (neutral) were presented as peripheral cues in an exogenous spatial cuing task. Results demonstrated that, compared to neutral cues, the cue validity effect was larger both for reward related cues and for punishment related cues. In conclusion, these findings show that in accordance with earlier studies, attention is biased towards cues that are associated with monetary reward. Extending the interpretation in earlier studies however, attention was similarly biased towards (rather than away from) monetary punishment cues.

Introduction

Recently, there is a growing interest into the influence of monetary reward on attention. Studies have demonstrated that reward related stimuli can modulate different aspects of attention. Stimuli that are associated with a high rewards more strongly draw spatial attention, as compared to stimuli that are associated with lower rewards (Kiss, Driver, & Eimer, 2009). Furthermore, when responses to target stimuli have been highly rewarded, inclusion of target features in distractor stimuli causes attentional interference (Hickey, Chelazzi, & Theeuwes, 2010a, 2010b; Libera & Chelazzi, 2006, 2009). This effect can be long lasting (Anderson, Laurent, & Yantis, 2011; Libera & Chelazzi, 2009). These findings indicate that attention can be biased to prioritize the processing of stimuli that are associated with monetary reward. This phenomenon has been explained in analogy with the reinforcement learning theory, which states that behaviors that lead to rewards will be promoted, while behavior that leads to non-reward or punishment will be inhibited. In parallel, it has been suggested that reward can modulate attention in such a way that attention is biased towards stimuli that are associated with good outcomes, biased away from stimuli that are associated with bad outcomes (Hickey, et al., 2010b).

Most studies up to date however have examined the influence of reward on attention only by comparing rewards of varying magnitude (see Rutherford, O'Brien, & Raymond, 2010 for an exception). In contrast, not much is known about how monetary punishment influences attention. From the reinforcement learning perspective as described above it would be predicted that, since punishment represents a bad outcome, attention would be biased away from stimuli that are associated with punishment. However, there is reason to think that attending away from cues that signal punishment is not viable. Similar to rewards, punishments are motivationally relevant signals, which can guide behavioral adaptation (Cools et al., 2009; Hester, Murphy, Brown, & Skilleter, 2010; Skinner & Campbell, 1947). It could be expected that attentional mechanisms are biased to increase detection and perception of stimuli that are motivationally relevant, be it positive or negative. In fact, a long tradition of research within the field of emotion has demonstrated that attention is reflexively drawn towards negative emotional stimuli (e.g. angry faces, aversive scenes, electric shocks), as well as stimuli that predict the occurrence of such negative stimuli (Fox, 1993; Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Mogg & Bradley, 1998; Öhman, Flykt, & Esteves, 2001; Van Damme, Crombez, & Eccleston, 2004; Yiend & Mathews, 2001). In that sense, it could be expected that stimuli

that predict monetary punishment may have a similar alerting effect, and actually automatically attract spatial attention. One study that has used cue stimuli that were associated with monetary punishment in exogenous spatial attention failed to find effects of punishment (Rutherford, et al., 2010). Value associations in that study however, were established by rewarding responses to one stimulus while punishing responses to other cues in a pre-task training procedure. Such a procedure can actually train participants to voluntary direct attention away from punishment related stimuli (Koster, Baert, Bockstaele, & De Raedt, 2010). In the present study we set out to examine the effects of reward and punishment related stimuli on involuntary deployment of spatial attention. We used an adapted version of the exogenous spatial cuing task, in which cues can be differentially predictive of reward or no reward, or of punishment or no punishment.

Methods

Participants

Fifty three participants were recruited from the university campus (28 males, 25 females; mean age [sd] = 23.6 [6.9]). Participants were randomly assigned to a reward or to the punishment condition of the spatial cuing task, resulting in a sample of N= 26 in the reward condition and N= 27 in the punishment condition. Participants signed informed consent before the start of the experiment, and received monetary compensation or course credits for their participation.

Task

In order to study whether reward related and punishment related stimuli both modulate spatial attention in the same direction, a modified version of Posner's exogenous spatial cuing task (Posner, 1980) was used in the current study (See Figure 1). This paradigm has previously been used, showing that stimuli that predict aversive stimulations such as loud noises or electric shocks draw spatial attention towards their location (Koster, et al., 2004; Massar, Mol, Kenemans, & Baas, 2010; Van Damme, et al., 2004).Peripheral cue stimuli were pictures of male faces (neutral expression) in either a blue or a yellow color (size: 6.5º x 4.8º visual angle). Cues were presented for 200 ms at either the left or right from a central fixation cross (9.2º distance from center). Thirteen ms after cue offset a target stimulus was presented in the same location as the cue in half of trials (valid cuing) or in the opposite location in the other half of trials (invalid cuing). Participants responded to the

location of the target by a left or right button press. The task was carried out in two phases. In the baseline phase correct responses were rewarded with 1 point. In order to maintain task engagement intermediate scores were presented after every block of 40 trials. Importantly, the same amount of points was awarded for correct responses, regardless of the color of the cue. In contrast, during the following acquisition phase, differential feedback was provided depending on the cue color. Participants were instructed that now points would be awarded for performance averaged over several trials. If average performance was good and fast enough, extra points could be gained. If average performance was bad, points could be lost. Unknown to the participants the presented feedback was not related to their actual performance but was determined by the color of the cue that was presented during that trial. In the reward condition trials in which cue of one color was presented could be followed by positive feedback ("good, +10 points"), while the other color cue could be followed by neutral feedback ("normal, +1 point"). In the punishment condition one cue color could be followed by negative feedback ("bad, -10 points"), versus neutral feedback following the other cue color. In this way, the only predictor of feedback valence was the cue color. Performance feedback was delivered after 25% of the trials, and the color of the cues that were associated with reward, punishment or neutral feedback were counterbalanced between subjects. Valid and invalid trials of both cues were present in a random order with the restriction that no more than three trials of the same type would be presented subsequently. A total of 24 trials per cue type in each phase were completed, with equal number of valid and invalid trials. In addition, six catch trials were presented per phase. In these trials only a cue was presented not followed by a target, and no response was required. Responses on catch trials could reflect that participants responded to the cue rather than target presentation. Participants who responded too often to catch trials (responses on more than two trials) were excluded from further analysis. Furthermore, on several trials the fixation cross was briefly (100 ms) replaced with a digit (digit trials, 6 per phase). Participants were instructed to name this digit aloud as fast possible. These trials were introduced to motivate the maintenance of central fixation.

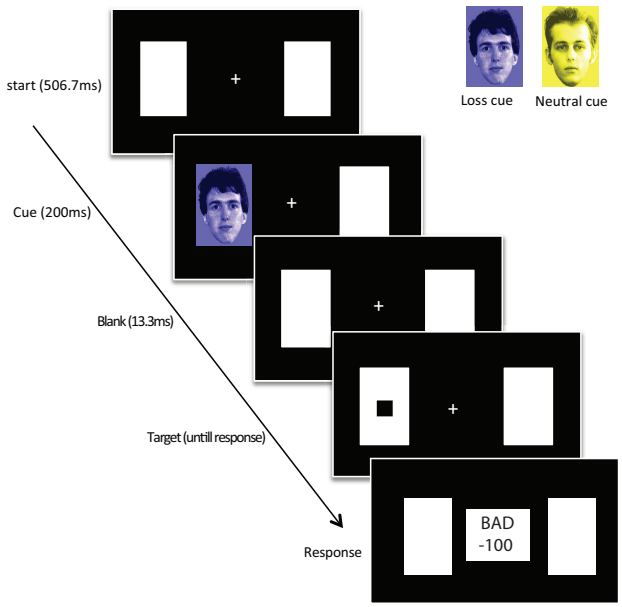

Figure 1.Trial procedure for trials in the punishment condition (acquisition phase). Negative cues were predictive of punishment, while neutral cues were predictive of no punishment. In the reward condition one cue was predictive of reward (positive cue) and the other for no reward (neutral cue).

Data analysis

Response accuracy and reaction times were recorded. For correct responses, RTs were filtered for extremely quick (< 200 ms) and extremely late responses (> 1000 ms) and outliers (± 3 times sd from average RT). Average RT was analyzed with a Phase (baseline, acquisition) x Validity (valid, invalid) x Cue type (negative, neutral) repeated measures ANOVA. Cue validity indices (*CVI)* were calculated as RT invalid – RT valid, for each phase and cue type separately. The reward and punishment condition were analyzed separately

Awareness check

After completion of the task contingency awareness and subjective experience of the cue stimuli were assessed. Participants filled out 10-point Likert scales in which they indicated for each of the face cues how strongly they expected each of the cues to be followed by loss (or gain) of extra points (0 = *certainly not*, 9 = *certainly*) and how pleasant they found the cue stimulus (0 = *very unpleasant*, 9 = *very pleasant*).

Table 1: Group characteristics for the reward condition group and the punishment condition group

	Reward condition		Punishment condition			
	Mean	sd	Mean	sd	t	p
age	23.48	7.83	24.18	6.92	.32	.75
STAI	37.35	9.67	37.95	9	.22	.82
BIS	16.22	4.47	14.41	3.69	1.45	.15
BAS	25.78	4.54	25.14	4.6	.47	.64

Results

Group characteristics

Three participants in the reward condition and five participants in the punishment condition had more than two responses on catch trials. For these participants it could not be guaranteed that they responded correctly to the onset of target stimuli and not to cue stimuli, and they were discarded from further analysis. The resulting samples (reward: N= 23, Punishment: N= 22) did not differ in age, trait anxiety or punishment/reward related personality scores (BIS/BAS; see table 1). Further behavioral analysis was performed for the reward and the punishment conditions separately.

Reward condition. Accuracy scores were between 97% and 100%. RT results are depicted in Figure 2. A Phase x Cue x Validity interaction was found ($F(1,22) = 8.1$, $p < .01$, $\eta^2 = .27$). Follow-up ANOVA's for the two phases separately showed that in the baseline phase no significant main effects or interaction between Cue and validity were found (p's > .3). Crucially, in the acquisition phase a significant Cue x Validity interaction was found ($F(1,22) = 16.5$, $p < .001$, $\eta^2 = .43$). This interaction was caused by a larger CVI for positive cues (18.9 ms) than for neutral cues (3.0ms; $t(22) = 4.1$, $p < .001$).

Punishment condition. Accuracy scores were between 96% and 100%. Resulting RT scores are depicted in Figure 2. Statistical analysis yielded a Phase x Cue x Validity interaction ($F(1,21) = 11.7$, $p < .01$, $\eta^2 = .36$). Follow-up ANOVA's for the two phases separately showed that in the baseline phase no significant main effects or interaction between Cue and validity were found (p's > .1). In the acquisition phase, again a strong Cue x Validity interaction was found ($F(1,21) = 13.5$, $p < .001$, $\eta^2 = .39$). Similar to the reward condition,

this interaction was caused by a larger CVI for negative cues (12.7 ms) than for neutral cues (-1.7ms ; $t(21) = 3.7$, $p < .001$).

Awareness check

Table 2 shows the post-task pleasantness and expectancy ratings. T-tests showed that participants did not have different expectations of loss/gain for different cue types (negative vs neutral: $t(21) = .94$, n.s.; positive vs neutral: $t(22) = .59$, n.s.). Nor did they evaluate either one of the cues as more pleasant than the other (negative vs neutral: $t(21) = -.40$, n.s.; positive vs neutral: $t(22) = -.69$, n.s.).

Discussion

The current data provide a confirmation of recent findings from investigations into the interaction of monetary reward and attention (Anderson, et al., 2011; Hickey, et al., 2010a, 2010b; Kiss, et al., 2009), showing that stimuli that are associated with rewards more strongly guide spatial attention than neutral stimuli.

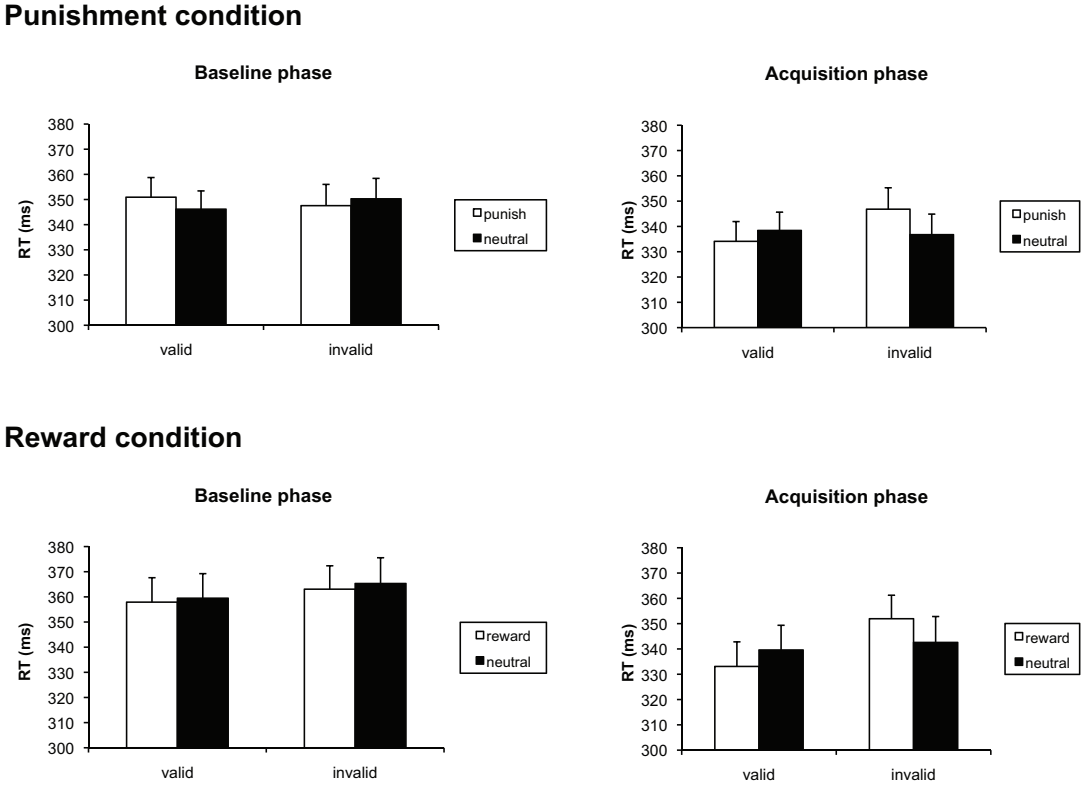

Figure 2. Mean reaction times for the negative and positive condition in the spatial cuing task (Error bars represent ±1 SEM).

Table 2. Post-task pleasantness and expectancy ratings per cue type.

	punishment cue		*neutral cue*	
punishment condition	Mean	*sd*	mean	*sd*
Expectancy	4.6	*1.7*	4.2	*1.8*
Pleasantness	5.0	*1.5*	5.1	*1.3*
reward condition	*reward cue*		*neutral cue*	
Expectancy	4.2	*2.2*	4.0	*1.9*
Pleasantness	4.2	*1.7*	4.4	*1.3*

. In addition, the present study extends earlier findings by demonstrating that this attentional modulation was not only present for reward related stimuli but was also present when cue stimuli were predictive of monetary punishment. In the reward condition cue stimuli that predicted the occurrence of monetary reinforcement (reward or punishment) led to an increase of the Cue Validity Index (CVI) compared to cue stimuli that predicted no reward (neutral cues), and in the punishment condition CVI was increased following stimuli that predicted monetary punishment compared to cues that predicted no punishment.In contrast to the idea that attention is biased towards stimuli that predict good outcome, but away from stimuli that predict bad outcomes (Hickey, et al., 2010b), the current data demonstrate that the spatial attention is drawn towards punishment related stimuli.

A difference with the earlier studies investigating the effect of monetary reinforcement on spatial attention (Anderson, et al., 2011; Hickey, et al., 2010a, 2010b; Kiss, et al., 2009; Rutherford, et al., 2010), is that in those studies the critical (reinforcement related) stimuli served both as target stimulus and as distracter stimulus. When attention towards a target was rewarded in one trial (or in a training phase), stimulus features of this target automatically attracted attention when used as distracter in later trials. In the present study, reinforcement related stimuli never served as target. In all conditions cues were task irrelevant and should be ignored in order to detect target stimuli. Despite their irrelevance for task performance, cues that were associated with monetary reinforcement attracted attention, causing a larger cue validity effect than cues that were associated with no reinforcement.

One limitation of this study is that the effect of reward and punishment associated stimuli on attention was assessed in a between-subjects fashion. It is therefore not well possible to compare whether reward and punishment related stimuli have a similarly strong effect on attention. For future studies it would be interesting to incorporate both reward and punishment stimuli in a within-subjects design. Also it would be of interest to ask whether individual differences in reward or punishment sensitivity mediate the strength of reward and punishment related attentional modulation. In conclusion, the present data provide support for the idea that attention is involuntary drawn towards stimuli that predict monetary gain. Moreover, the present findings for the first time demonstrate that a similar attentional bias can be induced by stimuli that predict monetary loss. These data suggest that not the outcome valence but rather the relevance for current goals (i.e., reaching a high score) is critical for the involuntary attraction of spatial attention. This interpretation is in line with a growing body of attention research in domains such as emotion, addiction and biological drives, showing that both aversive and appetitive stimuli can automatically attract attention if they are sufficiently arousing or relevant to the current goals of the subject (Ehrman et al., 2002; Tapper, Pothos, & Lawrence, 2010; Vogt, De Houwer, Koster, Van Damme, & Crombez, 2008).

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Chapter **8**

Motor inhibition and trait anxiety: An attentional control perspective

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Abstract

The capacity to inhibit predominant motor tendencies is an important aspect of cognitive control that has been associated with impulse control and psychopathologies such as attention deficit hyper activity disorder (ADHD). In this study the relationship between such motor inhibition and individual differences in trait anxiety was examined. Two opposing hypotheses were tested. On the one hand anxiety has been associated with increased activity of the behavioral inhibition system, predicting that anxious individuals would show good inhibitory performance. On the other hand, anxiety has been associated with impaired attentional control, predicting poor inhibitory performance for anxious individuals. In the present study motor inhibition was assessed using the stop-signal task. Stop signal reaction time (SSRT) was not correlated with trait anxiety, nor with self-reported behavioral inhibition (BIS), but a negative correlation between SSRT and self-reported attentional control was found. Mean go reaction times were associated with both ACS score (negatively) and trait anxiety (positively). Neither of these performance measures was significantly associated with BIS score**.** We conclude that motor-inhibition capacity is tightly associated with self-reported attentional control, but dissociated from self-reported train anxiety and behavioral inhibition. If anything, trait anxiety is associated with global reaction-time measures of attention.

Introduction

The ability to inhibit ongoing actions is thought of as an important aspect of cognitive control. In laboratory settings inhibitory control is often studied using the stop-signal task (Logan, 1994). In this task participants usually perform a speeded choice reaction time task in which they have to respond manually to a (visual) go-stimulus. Occasionally, with some delay after go-stimulus presentation, a stop-stimulus is presented which indicates that the participant has to withhold the intended response. Following the main theoretical model of response inhibition (the horse-race model, Logan, 1994), the probability of a successfully stopped response depends on the speed at which the go-process is completed compared to the speed of the inhibitory process. If the go-process is finished before the stop-process, the response cannot be inhibited. If the stop-process finishes before the go-process, horse-race model predicts that the response will successfully be inhibited. Although, by definition, no overt responses are made during successful inhibitions, the stop-signal paradigm allows determining the speed at which the stop-process is executed (stop-signal reaction time; SSRT). Deficits in inhibitory control in the stop-signal task have been related to different psychopathologies such as attention deficit hyper activity disorder (ADHD), obsessive compulsive disorder (OCD) and schizophrenia (for a meta-analysis see Lipszyc & Schachar, 2010).

Several researchers have argued that motor inhibition is intimately related to anxiety. Starting from Gray's Reinforcement Sensitivity Theory (Gray & McNaughton, 2003), anxiety is thought to be based on an inhibitory drive (behavioral inhibition system; BIS). In risky situations where a potential threat is present, the BIS system is thought to inhibit ongoing behavior and promote scanning of the environment. In anxious individuals an overactive BIS system is suspected to induce a stronger inhibitory drive. Partial support for this idea is provided by findings that individuals with high scores on self-report measures of trait anxiety (Neo, Thurlow, & McNaughton, 2011) and behavioral inhibition (Knyazev, Levin, & Savostyanov, 2008) show differences in electrocortical acitivty (EEG alpha power and de-synchronization) during stop-signal task performance as a function of either self-report. It should be noted that the relation between SSRT and self-report trait anxiety was not reported on in the first study, while the second study did not find a relation between BIS and SSRT.

Furthermore, most clinical studies find no difference in SSRT between anxiety disorder patients and healthy controls (Daugherty , Quay , & Ramos 1993; Epstein, Johnson, Varia, & Conners, 2001; Landrø, Ulleberg, Stiles, Jonassen, & Lyche, 2010; Lau, Christensen, Hawley, Gemar, & Segal, 2007; Manassis, Tannock, & Barbosa, 2000; Oosterlaan & Sergeant, 1996, 1998; Schachar & Logan, 1990). Only one study reported a longer SSRT for anxiety disorder patients (Korenblum, Chen, Manassis, & Schachar, 2007). An explanation for this could be that anxiety is not only related to an overactive BIS, but also to disturbed attentional control. The latter can be defined as the competence of strict focusing on relevant information on the one hand, combined with swift shifting of the focus when this is adaptive with changing environmental demands on the other. A number of studies have demonstrated that attentional performance is impaired in self-reported anxious individuals (e.g. Ansari, Derakshan, & Richards, 2008; Bishop, Jenkins, & Lawrence, 2007; Coombes, Higgins, Gamble, Cauraugh, & Janelle, 2009; Derakshan, Smyth, & Eysenck, 2009). Consistent with these findings is the observation that scores on a self-report scale of attentional control correlate inversely with self-reported trait anxiety (Attentional Control Scale [ACS]; Derryberry & Reed, 2002; Healy, 2010; Ólafsson et al., 2011). According to the attentional control theory formulated by Eysenck and colleagues, anxiety is associated with reduced cognitive processing efficiency, because anxiety-induced intrusions (e.g., rumination) take up central executive processing capacity (Eysenck, Derakshan, Santos, & Calvo, 2007). The attentional control theory predicts that anxiety specifically interferes with cognitive operations involving focused attention and attentional shifting.

Recent theoretical accounts of the stopping process, based on electro-cortical brain-potential evidence, have stressed the dual nature of the stop task (Kenemans & Kähkönen, 2011; Overtoom et al., 2009). On the one hand focused attentional control is needed to meet the demands of the continuous go task, as reflected in the go reaction time measure. On the other hand, an on-going preparedness to react appropriately to occasional stop signals (‘inhibitory control’) is instrumental in stopping performance. From the theoretical considerations outlined above, we expect that self-report trait anxiety is associated with either impaired attentional control (longer go RTs), or enhanced inhibitory control (shorter SSRTs). While the latter could also be characteristic of higher self-report behavioral inhibition, the former would be associated more with reduced self-report attentional control.

Additionally, it is possible that the shifting aspect of self-report attentional control translates into better inhibitory control (shorter SSRTs) as well.

Methods

Participants

Fifty two participants (average age [sd] = 21.9 [3.14], 24 males) were selected through bulletin board announcements at the university campus. Participants were screened through a telephone interview. Exclusion criteria were a history of psychiatric disorder and use of psychoactive medication. Furthermore, all participants indicated to have normal or corrected-to-normal visual ability and no hearing problems. Participants signed for informed consent upon entering the lab. All procedures were approved by the local medical ethical committee at the university medical center.

Stop signal task and procedure

Participants were seated in a sound-attenuated, dimly lit cabin approximately 60 cm away from a computer screen. Visual go-stimuli were presented on a black background in the center of the screen (blue circle or square; extending 1° visual angle). Participants were instructed to respond as fast as possible to go-stimuli with a left or right button press. On 40% of the trials the go-stimulus was followed by an auditory stop signal (a 83dB, 1000Hz pure tone, 400 ms). Upon hearing the stop-signal, participants had to withhold their response. The interval between go- and stop-stimulus was jittered in a range of 250 ms around a variable SOA. Average SOA was adjusted before each task block, based on a staircase procedure aimed at maintaining stopping accuracy around 50%. If responses in the stop-trials were correctly withheld on more than 50% of the times, SOA was increased with 50 ms. If less than 50% correct stops occurred, SOA was decreased with 50 ms. This procedure was included to maintain a stop rate around 50%. Test blocks were preceded by one go-practice block (40 go-only trials), in which the response mapping was trained (left response for square, right response for circle, or vice versa). This block consisted of 40 trials. Subsequently, a block containing go- and stop-trials (130 in total) was completed to practice the stop-procedure. Following the practice blocks participants performed four task blocks of 126 trials each. This complete procedure was repeated using the opposite response mapping. In that way all participants completed 520 trials (312 go-trials, 208 stop-trials) per response mapping. After finishing the stop signal task participants filled out

self-report questionnaires assessing trait anxiety (Spielberger state-trait anxiety inventory [STAI]; Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983), attentional control capacity (ASC; Derryberry & Reed, 2002), and behavioral inhibition (BIS; Carver and White, 1994). Participants received monetary compensation or course credits for participation.

Data reduction and statistical analysis

Mean RT and error rate were calculated for go-trials. Stop rate was calculated for stop-trials and corrected for omissions following Tannock et al. (Tannock, Schachar, Carr, Chajczyk, & Logan, 1989). From the combined stop rates and the go-reaction-time distribution, stop-signal reaction times (SSRTs) were derived, following Logan (1994). Correlations between self-report STAI-trait, ACS, and BIS scores on the one hand, and task-performance measures on the other, were calculated.

Table 1. Self-report personality scores and behavioral performance measures in the stop-signal task (percentage correct responses [pcor], percentage errors [Per], percentage omissions [Pom], mean reaction time [MRT], standard deviation of the reaction time [SDRT], stimulus onset asynchrony [SOA], stop rate [SR], and stop signal reaction time [SSRT]).

		Mean	SD
personality score			
	STAI	35.0	6.7
	ACS	51.7	8.0
	BIS	19.6	3.0
stop-signal task			
	Pcor	96.3	2.7
	Per	2.5	2.0
	Pom	1.3	1.4
	MRT	476.7	54.8
	SDRT	96.9	17.1
	SOA	263.6	43.1
	SR	52.8	10.8
	SSRT	197.3	35.6

Results

One participant had performance that was very poor compared to other participants. SSRT (334.2 ms), percentage of omissions (6.5%), and percentage of correct responses (86.6%) all fell more than 3 standard deviations from the group averages. This participant was considered an outlier, and was not included in the correlational analysis. Average psychometric scores and performance scores for the remaining sample are summarized in Table 1.

Correlational analysis confirmed the expected inverse correlation between STAI trait and ACS scores ($r = -.52$, $p < .001$), as well as the correlation between STAI and BIS ($r = .61$, $p < .001$. The correlation between ACS and BIS, although in the expected direction, was not significant ($p = .076$). STAI trait score was not correlated with SSRT (see Table 2), nor was BIS score. In contrast, ACS score was inversely correlated with SSRT (See Figure 1). Mean RT, standard deviation of RT and stimulus onset asynchrony were significantly correlated with STAI. Higher STAI score then was associated with reduced performance. ACS score, on the other hand, was inversely correlated with percentage omissions and mean RT, indicating that higher ACS score was associated with better performance. There were no correlations between performance measures and BIS score.

Table 2. Correlation coefficients between trait scores and stop-signal task performance measures percentage correct responses [Pcor], percentage errors [Per], percentage omissions [Pom], mean reaction time [MRT], standard deviation reaction time [SDRT], stimulus onset asynchrony [SOA], Stop rate [SR], and stop signal reaction time [SSRT]).

	Pcor	Per	Pom	MRT	SDRT	SOA	SR	SSRT
STAI	0.04	-0.21	0.22	0.31*	0.28*	0.30*	0.17	0.15
ACS	0.13	0.08	-0.37**	-0.29*	-0.27	-0.16	-0.13	-0.31*
BIS	0.11	-0.13	-0.03	0.13	-0.02	0.21	0.00	0.02

** $p < .05$*

*** $p < .01$*

Discussion

The present data demonstrate that stopping performance is positively related to self-reported attentional control capacity, but is not significantly associated with self-report trait anxiety. Two opposing hypotheses were formulated, based on different theoretical accounts of anxiety. The first hypothesis was based on the reinforcement sensitivity theory by Gray and McNaughton (2003). This theory states that anxiety is a reflection of activation in the behavioral inhibition system. This BIS system is thought to suppress ongoing behavior in situations of conflict. Since trait anxiety is thought to reflect hyperactivity of the BIS system, augmented stopping performance could be expected for anxious individuals. The second hypothesis was based on the attentional control theory. From this view poor performance on attentional tasks, among which the stop signal task, could be expected to be associated with heightened anxiety. The present data do not provide conclusive evidence for either hypothesis. While a clear linear relation between attentional control and stopping performance was found, the correlation between self-report anxiety and stopping performance was non-significant.

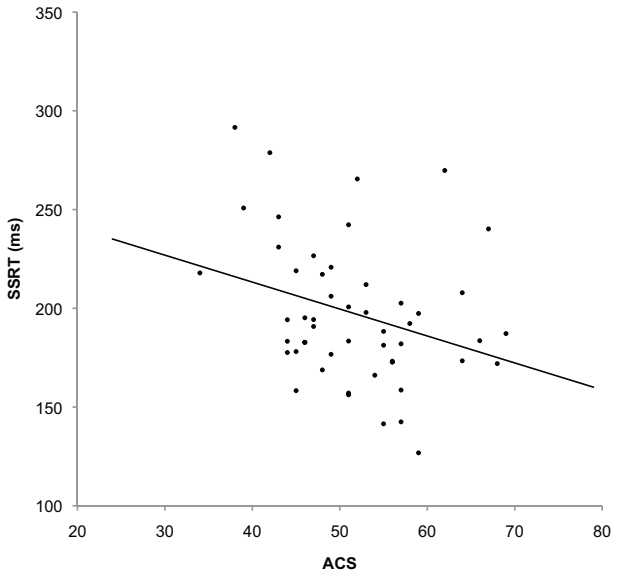

Figure 1. Scatter plot indicating the correlation between ACS scores and stop signal reaction time in the stop-signal task.

A possible explanation for this absence of a correlation between trait anxiety and stopping performance is that the hyperactive BIS account and the attentional control account are both valid. However, this would still predict a significant positive association between stopping performance and self-report BIS (to the extent that the latter reflects the activation of a 'true' underlying behavioral-inhibition system), and such a correlation was not found either. A related possibility is that low attentional control (reflected in self report) results in high STAI scores. A high STAI score in itself may be associated with enhanced stopping (because of the underlying behavioral-inhibition tendency), but this association is masked by the fact that high STAI scores go with low attentional control and therefore also with reduced stopping performance. In addition, as presently demonstrated, low attentional control and high trait anxiety both go with reduced task-directed focusing of attention as reflected in longer (go-) reaction times.

Another perspective comes from electrophysiological studies that have revealed that attentional and inhibitory processes are initiated in sequence in the stop signal task (Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005). Early perceptual processing of the stop signal, as evident in auditory N1, is thought to be dependent on attentional focus in the task. In normal populations N1 amplitude is enhanced for successful as compared to failed stops. In patients suffering from ADHD this N1 enhancement for successful inhibitions is diminished (Bekker, Overtoom, Kenemans, et al., 2005; Bekker, Overtoom, Kooij, et al., 2005). If the N1 effect reflects attentional control, it may be expected that this N1 effect is reduced in anxious participants. On the other hand, a later frontocentral P3 also shows higher amplitude for successful stop trials compared to failed ones (Bekker, Kenemans, et al., 2005; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004), and this P3 effect is also reduced in ADHD patients (Bekker, Overtoom, Kenemans, et al., 2005; Bekker, Overtoom, Kooij, et al., 2005; Johnstone, Barry, & Clarke, 2007; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). This P3 effect reflects a separate inhibitory mechanism which could be related more specifically to BIS activity.

The presently demonstrated significant relation between self-reported attentional control and stopping performance deserves further consideration. Previous studies failed to find significant correlations between ACS scores with visual search (high versus low perceptual load, Bishop et al., 2007) or with measures derived from the attentional network task (flanker interference, orienting, alerting; Reinholdt-Dunne, Mogg, & Bradley, 2009). The objective measures of attentional control as assessed in these studies may have

reflected too much either one of the major aspects of attentional control as probed in the ACS: Focusing (flanker interference, orienting) and flexibility (visual search, alerting). In contrast, stopping performance may reflect a delicate interplay between focusing and flexibility, and therefore we actually expected in advance to find a relation between ACS and stopping performance. Specifically, the preparedness to react appropriately to occasional stop signals ('inhibitory control'), as mentioned in the introduction, has been hypothesized as being implemented by means of a top-down-controlled potentiation of an inhibitory connection between the auditory cortex and the motor system (Kenemans & Kähkönen, 2011; Overtoom *et al.*, 2009). In effect, this scenario implies a top-down controlled anticipatory focus on occasional requirements to shift attention to a different stimulus class so as to activate the appropriate associated response, in this case an inhibitory signal to the motor system. This in turn matches the dual nature of attentional control as embodied in the ACS: top-down controlled focusing and shifting of attention.

In conclusion, the present study demonstrates a clear correlation between self-reported attentional control and individual differences in inhibitory control. In contrast, the relation between self-reported trait anxiety and inhibitory control remains elusive, and further research is needed to disentangle the possible contributions of reduced attentional control and possibly enhanced inhibitory drive.

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Section III: Costs of cognitive performance: mental fatigue effects in cognitive and motivational domains

Chapter **9**

Manipulation specific effects of mental fatigue: evidence from novelty processing and simulated driving

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Abstract

Mental fatigue has a wide range of effects on cognitive, behavioral and motivational measures. It can be expected that specific effects in which fatigue becomes manifest is dependent on the nature of fatigue inducing activity (e.g. level of control and working memory demands). Presently, it was studied how fatigue caused by tasks that differ on the level of working memory demands (0-Back, 2-Back) affects brain function (novelty processing, P3a) and performance (driving). Results showed that fatigue did not affect driving performance. Fatigue did reduce P3a amplitude, but only after 2-Back. P3a was also reduced during driving. The effects of fatigue and driving on P3a were additive. In summary, both driving and fatigue reduced P3a amplitude. Driving effects were always present. Fatigue effects on novelty processing were dependent on the cognitive demands of the fatigue inducing task.

Introduction

Mental fatigue is a multi-component phenomenon that involves changes in mood, motivation, attention and cognition. The state of mental fatigue can derive from a variety of causes. Sleep loss, prolonged working hours and biorhythmical fluctuations can all result in the combined state of inattention, distractibility, loss of goal-directedness and loss of willingness to exert further effort, that is well known as '*being tired*'. Changes in performance and cognition that accompany fatigue have often been related to the occurrence of errors and accidents, with obvious risks when happening in the context of industry and transportation (Baker *et al.*, 1994; Brown, 1994; Petridou & Moustaki, 2000; Swaen *et al.*, 2003).

In general, mental fatigue is found to cause slower responding and higher error rates in reaction time tasks. More specifically, people show less efficient preparation (Lorist *et al.*, 2000) and more perseveration in switch tasks (Van der Linden *et al.*, 2003a), less flexibility and a loss of systematic exploration strategies in learning tasks (Van der Linden *et al.*, 2003b), and higher intrusion of irrelevant information into cognitive processing (Boksem *et al.*, 2005; Van der Linden & Eling, 2006). These performance decrements suggest that mental fatigue causes a depletion of top-down control capacity, leading to declined integrity of goal-directed behavior (Duncan *et al.*, 1996; Fuster, 1989; Miyake *et al.*, 2000). Consistently, fatigue leads to problems in planning and coordination of action sequences, disrupting performance mostly in novel or complex tasks (Bartlett, 1943; Hockey, 1993).

Mental fatigue can be caused by prolonged engagement in many different cognitive activities. People, for instance, report fatigue after tasks that put constant demands on working memory and updating of information (e.g. scheduling task: Van der Linden et al., 2003b), but also after performing stimulus-response tasks that involve alertness and selective attention, but minimal working memory load (e.g. flanker task: Boksem *et al.*, 2006). Research thus far has employed a wide variety of tasks to induce mental fatigue. However, a direct test of how fatigue effects depend on varying task demands is still lacking. Since fatigue is viewed as a depletion of cognitive resources, it seems unlikely that tasks that recruit different levels of cognitive processing will lead to uniform fatigue effects. The current study addresses this question by comparing the effects of fatigue, systematically varying the level of demands that were put on working memory

and top-down control. By doing so, we expected to cause different levels of cognitive depletion. Electro-cortical and behavioral fatigue effects were measured as novelty P3a ERP activity (novelty processing) and simulated driving respectively.

Novelty Processing and Mental Fatigue

Novelty processing refers to the detection of and orienting towards novel stimuli in the environment. When novel stimuli are presented, an automatic shift of attention towards those stimuli can take place. In EEG recordings, brain reactions to such novel stimuli are typically characterised by a frontocentral positivity (P3a) that peaks around 300 ms (Friedman *et al.*, 2001). P3a generation is triggered by bottom-up deviance detection (Debener *et al.*, 2002). Consequently, P3a is elicited irrespective of whether novelty is presented in or outside the focus of attention (Friedman *et al.*, 1998), even if attention is highly focussed on a primary task in a different modality (Muller-Gass *et al.*, 2007). Despite its bottom-up origin the amplitude of the P3a has been found sensitive to the amount of attentional resources that are available. P3a was reported to increase when attention is focused on the modality in which the novel stimuli are presented (Combs & Polich, 2006; Muller-Gass & Schröger, 2007), and to decrease when attention is diverted away (Friedman *et al.*, 1998; Holdstock & Rugg, 1995; Zhang *et al.*, 2006). For example, when attentional control and working memory are focused on an unrelated visual task (SanMiguel *et al.*, 2008), or to response categorization (Berti & Schröger, 2003) P3a amplitude is decreased. On the other hand, P3a is increased when processing of the novel stimulus is included in the focus of working memory (Muller-Gass & Schröger, 2007). It therefore seems that while P3a is triggered by automatic bottom-up processing, its generation can be hindered when top-down attentional resources are less available to evaluate the stimulus. During fatigue such control resources are especially compromised. Consequently, it can be expected that P3a amplitude is attenuated during a state of mental fatigue, particularly when caused by a task that puts high demands on these control resources. Partial support for this hypothesis is provided by findings that P3a amplitude is reduced after sleep deprivation (closely associated with mental fatigue, Gosselin *et al.*, 2005), and in patients with sleep related problems (Gosselin *et al.*, 2006; but see Salmi *et al.*, 2005). The present study explicitly tested the question whether prolonged performance

on tasks that involves different levels of control and working memory, causes different levels of fatigue related P3a reduction.

The present study

In order to examine this question, novelty processing and driving performance were measured before and after performance of a fatiguing task. Fatigue was induced by 90 minutes of N-Back task performance. In two separate sessions two versions of the N-Back task were executed (0-Back and 2-Back), thereby systematically varying the demands that were put on working memory and attentional control. It was expected that putting continuous demands on control processes in the 2-Back task (in contrast to 0-Back) would lead to a depletion of cognitive control resources. Consequently, fatigue related P3a and behavioral decrements were expected to be more pronounced after 2-Back performance than after 0-Back performance, even when subjectively experienced fatigue would not differ between the two conditions. P3a is typically analyzed as the difference wave comparing novel stimulus ERP to a standard stimulus. In the present study however, it cannot be excluded that in addition to influencing novelty processing, fatigue also influences the processing of standard stimuli (Muller-Gass & Schröger, 2007). In order to control for this possibility additional analysis has been conducted on separate novel and standard ERPs.

Methods

Participants

12 volunteers (9 males, 3 females; mean age = 22.2, range (19-28)) were recruited from a student population. All were screened to have no hearing problems, normal or corrected-to-normal vision, no sleep or fatigue-related problems, and not to work night shifts. In addition, participants did not take prescription medicine, did not use drugs, had to restrain from drinking alcohol on the night before the experimental sessions, and any caffeinated drinks on the day of the experiment. As a reward for their effort participants received either course credits or 54 Euros. All participants signed written informed consent before starting the experiments.

Procedure

Fatigue was induced by 90 minutes of either 0-Back or 2-Back task performance. By increasing the number of memory elements that need to be remembered and updated the different levels of the N-Back task recruit different levels of working memory and control, and could thereby be expected to induce different states of fatigue. Participants were tested in both fatigue-manipulation conditions (0-Back, 2-Back), which took place in two separate sessions, before and after which driving ability and novelty processing were assessed (see schedule in Figure 1). Upon entering the lab participants filled out informed consent and the EEG equipment was applied. Participants performed a simulated driving task during which novel auditory stimuli (unrelated to the driving task) were presented. Secondly, the novel stimuli were also presented when the participants did not perform the driving task. Subsequently, participants performed 90 minutes of N-Back task in order to induce mental fatigue. After finishing the manipulation task, post-manipulation measurement of driving ability and the novelty processing was done. A questionnaire assessing subjective fatigue was filled out three times during the experiment, before starting the fatigue manipulation task, after finishing the manipulation, and in a follow up measurement 40 minutes after the manipulation task. The order in which the 0-Back and the 2-Back sessions were presented, as well as the order of driving versus no-driving oddball presentation within-sessions, were counterbalanced between subjects.

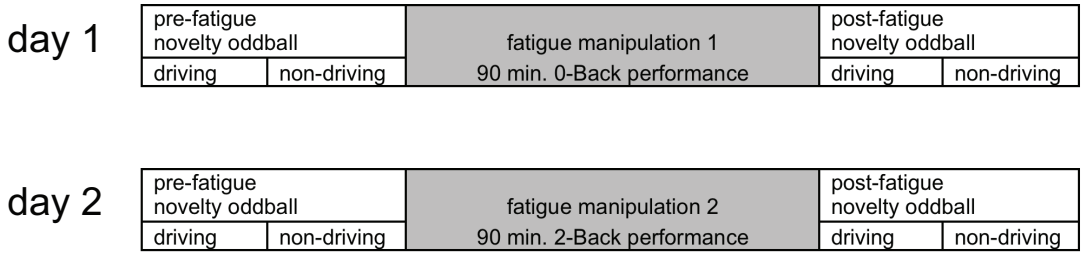

Figure 1. Schedules of the test procedure. On test day one, participants were subjected to a novelty oddball paradigm, both during driving and non-driving, followed by a 90 minutes fatigue inducing N-Back task (either 0-Back or 2-Back). Subsequently, a post fatigue novelty oddball was presented. On test day two, participants were subjected to the same procedure, with the only difference that the other N-Back task was used as fatigue induction.

Techniques and Materials

Subjective Fatigue Assessment

Subjective fatigue was measured using the Rating Scale Mental Effort (RSME, Zijlstra, 1993). This scale consists of seven items that index different aspects of fatigue, such as required effort for attention focussing and visual perception, tiredness and boredom. All items were scored on an analogue scale, and load on one factor, mental fatigue.

Fatigue Manipulations

Fatigue was induced by 90 minutes of N-Back performance (0-Back, 2-Back). White letters were presented for 500 ms (with 2500 ms ITI) in the middle of a black screen using the Experimental Run Time System (ERTS, Berisoft, Germany). On presentation of a target stimulus participants were required to respond by a right button press and with a left button press on non-target presentation. In the 2-Back condition, targets were defined as any letter that is the same as the letter that was presented two trials prior to the current trial (with non-targets defined as being not the same as two trials earlier). In the 0-Back condition, participants were instructed to react to the letter 'X' as a target, and to any other letter as a non-target. Stimuli could be all letters in the alphabet. In both conditions a total of 1800 stimuli were presented and target probability was 30%.

Passive Oddball Paradigm

Auditory stimuli were presented through Victory ms-28 portable loudspeakers attached to the back of the head. In each condition, a total of 520 stimuli were presented, with an ISI of 2.2 s, and an intensity of 75 dB at ear level. 1000 Hz standard tones (80% of the stimuli) were intermixed with deviant tones (1100 Hz, 10% of the stimuli) and novel environmental sounds (10% of the stimuli). The latter stimuli were selected from a database (Fabiani & Friedman, 1995) and had a duration between 161 ms and 403 ms. The duration of standard and deviant tones was 338 ms, which equals the mean duration of the novel stimuli. In total, two sets of novel stimuli were used, such that different stimuli were presented in pre- and post-manipulation measurement. However, within the pre- and post-manipulation measurement the same set was used for driving and non-driving condition. Also, the sets and the order of presentation were kept constant for the two separate test sessions. Participants were instructed to ignore the sounds. In order to examine effects of attention

allocation, two oddball sessions were presented during both pre- and post-manipulation. In one session a simulated driving task was performed as a background task, and in the other session no behavioural task was performed. Duration of oddball presentation was 20 minutes per session.

Simulated Driving

The simulated driving environment was presented using the Divided Attention Steering Simulator (DASS, Stowood instruments, UK). The DASS is a fixed-base steering simulator in which the outlines of a car and a road are presented on a black computer screen. Participants were required to keep the car on the middle of a winding road using a Thrustmaster steering wheel, while the car moves forward at a constant speed. The primary outcome measure is the steering error from the middle of the road (standard deviation of lateral position, SDLP).

EEG recording

EEG data were recorded from 32 Biosemi active electrodes (Biosemi, Amsterdam, the Netherlands), which were positioned according to standard 10/10 EEG positions. Electrodes were placed in nine lines with outmost lateral positions Fp1/Fp2, AF3/AF4, F7/F8, FC5/FC6, T7/T8, CP5/CP6, P7/P8, PO3/PO4, and O1/O2. Midline electrodes stretched from Fz to Oz. EOG electrodes were placed above and below the left eye and on the outer canthi of each eye. Reference electrodes were placed on both mastoids, for offline re-referencing. Biosemi active electrode system uses an active online referencing, through a Common Mode Sense and a Driven Right Leg electrode (CMS/DRL, MettingVanRijn *et al.*, 1990). All data were recorded with a 512 Hz low-pass filter at a sample rate of 2048 Hz, and stored for offline analysis.

Data reduction and analysis

Performance. Driving performance was measured by calculating the standard deviation of the lateral position (SDLP) during the 20 minutes driving task. Data were statistically analyzed with a 2x2 (time x manipulation type) repeated measures ANOVA

*ERPs***.** EEG data were analyzed using Brian Vision Analyzer software (Brain products). Data were re-referenced offline to the averaged signal of both mastoids, and subsequently

filtered with a 0.16 Hz high-pass filter and a slope of 24 dB/oct, a 30 Hz low-pass filter with a slope of 24 dB/oct and a 50 Hz notch filter. Artefacts were removed semi automatically and eye movements were corrected using the Gratton & Coles algorithm (Gratton *et al.*, 1983). Average waveforms for novel and standard stimuli and a novel-standard difference wave were calculated per oddball condition (driving, non-driving), time (pre-, post-manipulation), manipulation condition (0-Back, 2-Back), and site (Fz, Cz, Pz). P3a was quantified as the average amplitude at Fz, Cz and Pz, in a time area of 50 ms around the peak in the Grand Average difference wave (300-350 ms after stimulus presentation). Amplitudes were statistically analysed using repeated measures ANOVA'. Greenhouse-Geiser corrected F values are reported where appropriate. To assess effects on novel processing independently of effects on standard processing all analyses were repeated on the novel and standard raw waveforms (Muller-Gass & Schröger, 2007).

Results

Fatigue Manipulation Check

Self-reported fatigue was increased directly after the fatigue manipulations, and decreased during follow-up. These effects were present independent of the type of fatigue manipulation. A manipulation-type (0-Back, 2-Back) × time-of-measurement (pre-fatigue, post-fatigue, follow-up) repeated measures ANOVA of the RSME data revealed a significant main effect of time-of-measurement $F(2,10) = 17.07$, $p < .005$. Post-hoc contrasts showed that fatigue was significantly increased after the manipulation (mean pre-fatigue = 45.4, mean post-fatigue = 71.9; $F(1,11) = 37.53$, $p < .001$). In the 40 minutes follow up measurement RSME score was again decreased (mean follow-up = 52.1; $F(1,11) = 14.08$, $p < .005$) The absence of a manipulation-type main effect and a time × manipulation interaction ($p > .5$) indicated that the increase in subjective fatigue was the same after 0-Back and after 2-Back performance.

Driving Performance

Driving performance was not affected by fatigue in either manipulation condition. A manipulation-type (0-Back, 2-Back) × time-of-measurement (pre-fatigue, post-fatigue) repeated measures ANOVA for SDLP did not show any significant interactions or main effects ($F_{time}(1,11) = .02$, $p = .88$; $F_{manipulation}(1,11) = .12$, $p = .74$; $F_{time \times manipulation}(1,11) = 1.02$, $p = .33$).

P3a

Difference waves

The P3a (novel-standard) difference waves (depicted in Figure 2) show two important effects. First, there was a reduction in P3a amplitude in the post-manipulation measurement (fatigued) which was more pronounced after the 2-Back manipulation than after the 0-Back manipulation. Secondly, P3a amplitude was decreased during driving. The effects of fatigue and driving were additive, such that the reduction of P3a by driving was present both before and after the fatigue manipulation. To statistically analyze these effects P3a amplitudes were entered into a 2×2×2×3 repeated measures ANOVA with manipulation-type (0-Back, 2-Back), time (pre-, post-manipulation), driving (driving, non-driving) and site (Fz, Cz, Pz) as factors.

Fatigue. The effect of fatigue was reflected in a time × manipulation-type interaction ($F(1,11) = 6.01$, $p < .05$). To further analyze this interaction post hoc ANOVA's with data collapsed over driving condition and site were conducted for both manipulation conditions separately. These analyses showed that a reduction in P3a was highly significant after the 2-Back manipulation ($F(1,11) = 24.77$, $p < .001$), but there was no significant time effect in the 0-Back manipulation condition ($F(1,11) = 0.16$, $p = .70$). Furthermore, in the omnibus analysis a significant time × site interaction was found ($F(1,11) = 6.34$, $p < .05$). Post hoc analyses, with data collapsed over manipulation-load and driving condition, revealed a significant amplitude decrease post-manipulation relative to pre-manipulation at Cz ($F(1,11) = 8.88$, $p < .05$) and Pz ($F(1,11) = 13.37$, $p < .005$), but not at Fz ($F(1,11) = 0.07$, $p = .80$).

Driving. The driving effect was reflected in a driving × site interaction ($F(2,10) = 9.13$, $p < .05$). Follow-up ANOVA's on separate electrode sites (data collapsed over time and manipulation-type) showed that compared to the non-driving condition P3a amplitude in the driving condition was marginally significantly reduced at Fz ($F(1,11) = 4.27$, $p = .063$), and significantly reduced at Cz and Pz ($F(1,11) = 35.68$, $p < .001$; $F(1,11) = 93.18$, $p < .001$). The absence of 4-way and 3-way interactions including driving and time or driving and manipulation-type, indicated that this P3a reduction during driving was present independent of fatigue (after both 0-Back and 2-Back manipulations).

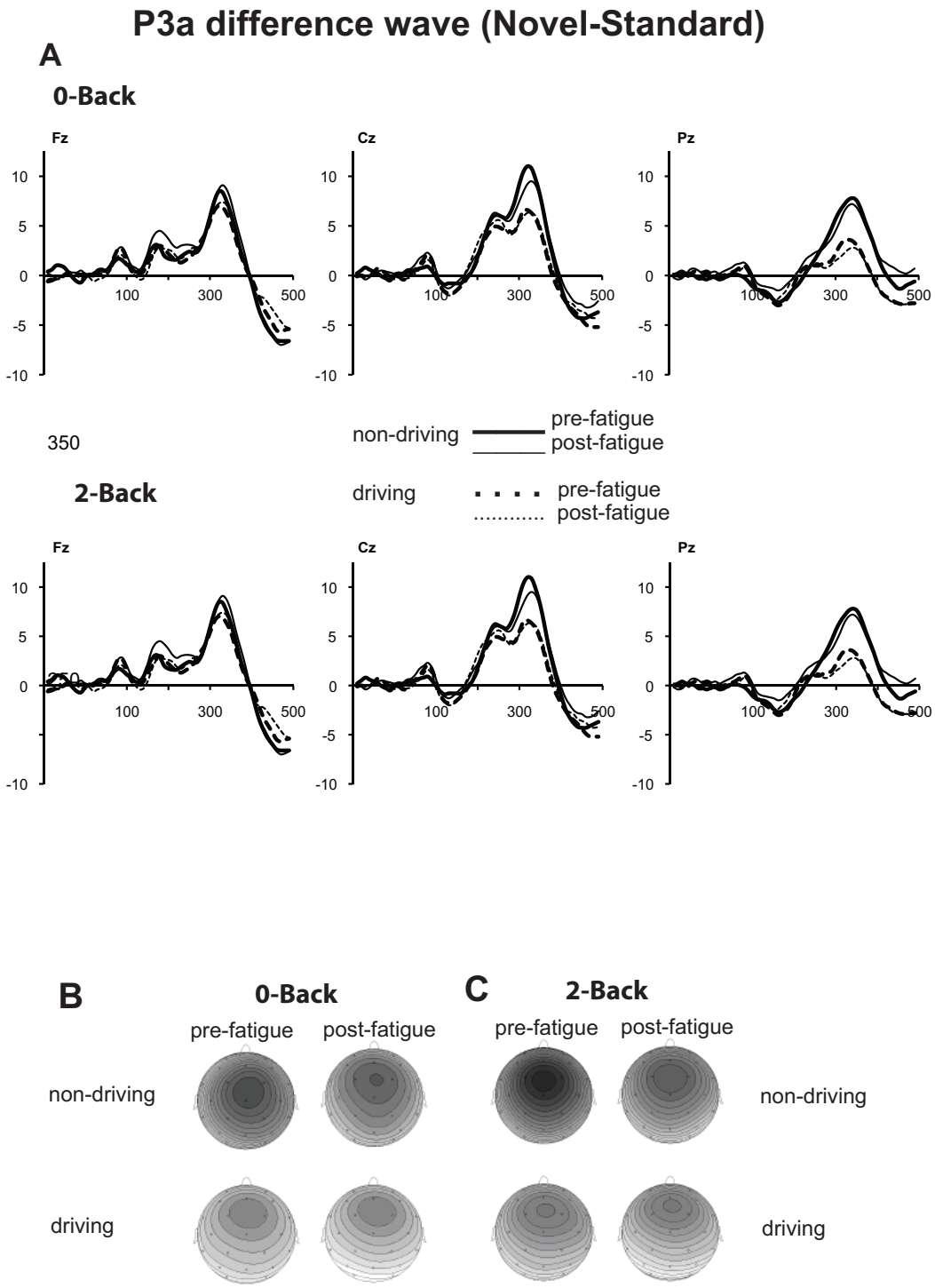

Figure 2. Difference waves calculated as novel ERP – standard ERP. a) Difference waves at Fz, Cz, Pz for pre-fatigue (bold lines) and post-fatigue (thin lines) measurement, during non-driving (continuous lines) and driving (dashed lines). b) scalp distributions plots in the 0-Back session. c) scalp distribution plots in the 2-Back session.

To assure that the above described effects on P3a difference wave were indeed due to differences in processing of the novel stimuli, statistical analyses were reconducted over the raw ERP waves for novel stimuli separately from standard stimuli.

Novel stimuli. A similar pattern of effects as found in the P3a difference waves can be seen in the novel ERPs (see Figure 3). Amplitudes were reduced during driving, and an additive reduction after the fatigue manipulation was visible after 2-Back but not after 0-Back performance. Statistical analysis on novel ERPs was conducted in the same way as the difference waves (manipulation-type × time × driving condition × site repeated measures ANOVA). Similar to the difference waves, novel wave analysis showed the presence of the time × manipulation-type interaction ($F(1, 11) = 6.16$, $p < .05$), and the driving × site interaction ($F(2,10) = 11.86$, $p < .005$).

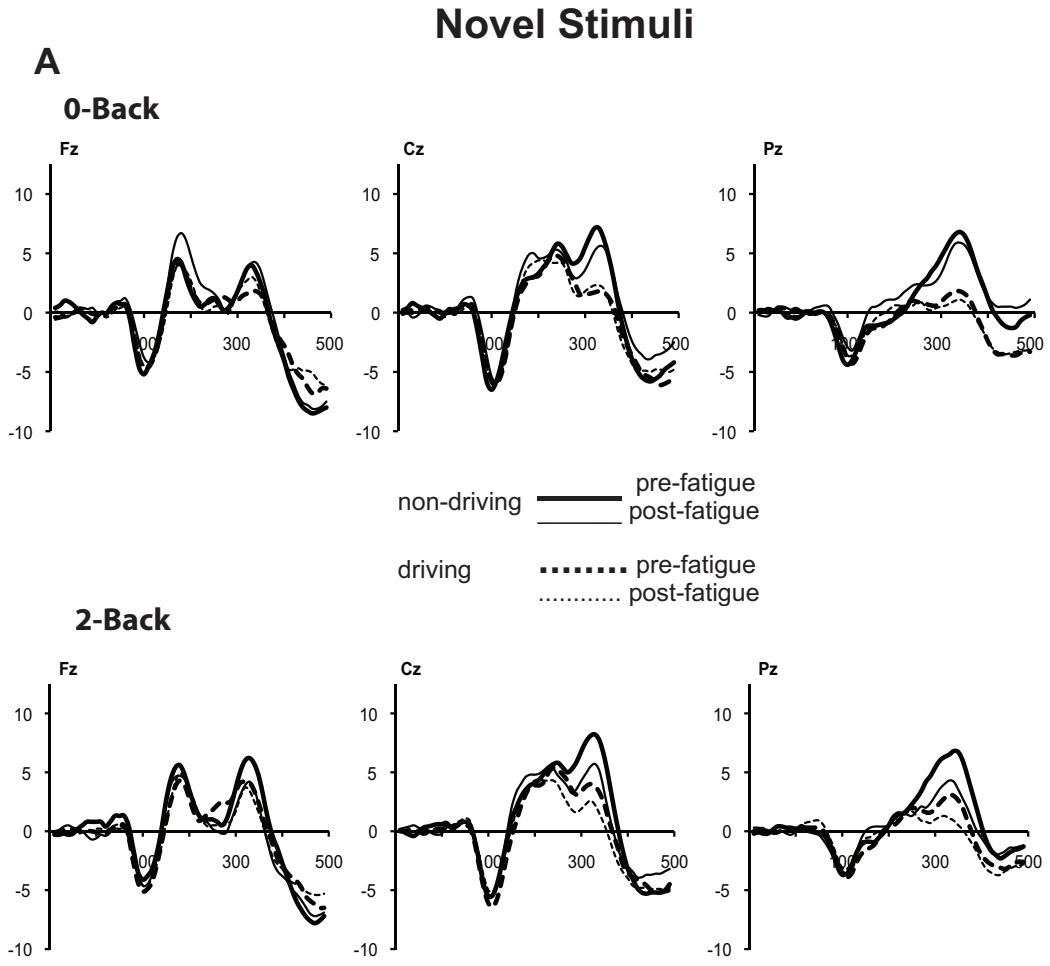

Figure 3. Novel stimulus locked ERPs in the 0-back manipulation session (upper panel), and 2-Back session (lower panel) at Fz, Cz and Pz. Waveforms are displayed separately for pre-fatigue (bold lines) and post-fatigue (thin lines) measurement, during non-driving (continuous lines) and driving (dashed lines).

However, the time × site interaction that was found in the difference waves was not significant in the novel ERPs. This indicated that the effects of fatigue were present at all electrodes. Follow-up ANOVAs for the time effect (collapsed over driving and site), confirmed that a post-manipulation reduction of P3a amplitude was present in the 2-Back condition ($F(1,11) = 48.78$, $p < .001$), but not in the 0-Back condition (all p's > .1). Follow-up analysis of the driving effect with separate repeated measures ANOVA's for driving and non-driving amplitudes (collapsed over time and manipulation) showed a marginally significant site effect in the non-driving ($F(2,10) = 3.52$, $p = .074$; simple contrasts: Fz < Cz, $F(2,10) = 10.77$, $p < .01$, and Cz = Pz, $F < 1$). During the driving task P3a amplitudes were attenuated such that no difference between sites was present ($F < 1$).

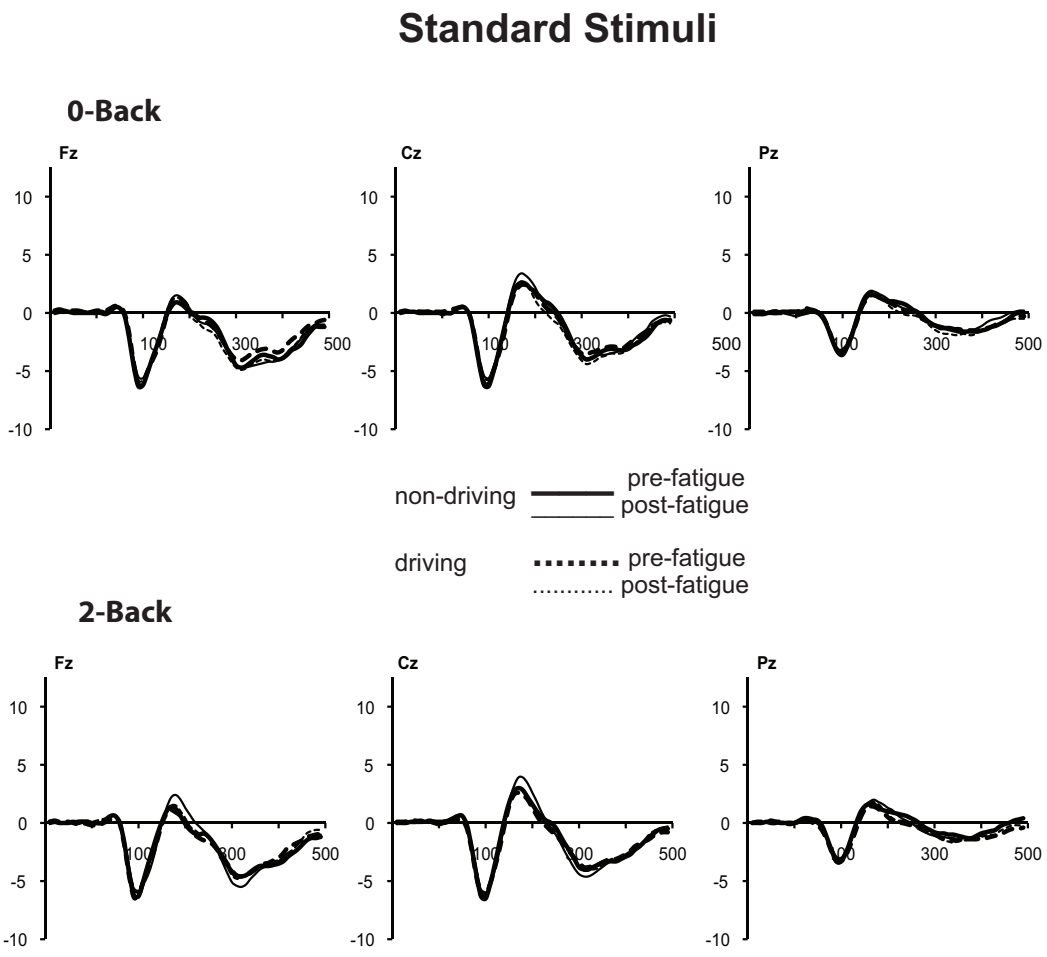

Figure 4. Standard stimulus locked ERPs in the 0-back manipulation session (upper panel), and 2-Back session (lower panel) at Fz, Cz and Pz. Waveforms are displayed separately for pre-fatigue (bold lines) and post-fatigue (thin lines) measurement, during non-driving (continuous lines) and driving (dashed lines).

These results confirm that the effects of driving and fatigue were reflected in the P3a difference wave were present in a similar manner for the novel ERPs. The scalp distribution of the novel ERPs was more posterior however, than the distribution of the difference waves.

*Standard stimuli. S*tandard stimuli evoked a different ERP pattern than novel stimuli (see Figure 4). In the P3a time window (300-350 ms post stimulus) no positive peak was present. Rather a negativity occurred that peaked at Fz (site main effect $F(2,10) = 118.58$, $p < .001$; simple contrasts Fz > Cz > Pz; $F(1,11) = 9.00$, $p < .05$; $F(1,11) = 93.27$, $p < .001$). But effects of fatigue (time × manipulation-type interaction) and driving (driving × site interaction) were not found in the standard ERP. The frontal distribution and the polarity of this standard ERP explain the slight difference in distribution between the novel ERP and the novel-standard difference wave. Crucially, the effects of driving and fatigue that were found in P3a difference waves were not due to changes in the standard ERP.

Discussion

In the current study it was investigated whether effects of mental fatigue on novelty processing and driving performance depended on working memory load of the fatigue-inducing task. The main hypothesis was that depletion of attentional control and working memory resources after performance of the high load 2-Back task, would cause more pronounced fatigue effects. Novelty processing, measured as P3a amplitude, was indeed attenuated after 90 minutes of performance of the 2-Back task. This reduction was not significant after an equally long period of 0-Back performance. Importantly, this attenuation of P3a amplitude after 2-Back performance was specifically due to effects on ERPs following novel stimuli. ERPs locked to standard stimuli did not show these same effects. It can therefore be argued that novelty processing was diminished after a long period of continuous 2-Back execution. These findings have several implications.

First, in line with our expectation, novelty processing can be compromised during a state of mental fatigue, specifically when caused by prolonged recruitment of attentional control and working memory. Depletion of these resources may obstruct processing of unexpected novel stimuli. In accordance with findings of attenuated P3a during dual task paradigms (Berti & Schröger, 2003; Friedman et al., 1998; Zhang et al., 2006), this finding

supports the notion that novelty processing, although it is bottom-up triggered, is dependent on the availability of attentional control resources. Since mental fatigue is thought to often go along with depletion of attentional control (Lorist *et al.*, 2003; Van der Linden et al., 2003a), and since we specifically targeted this aspect (by comparing 0-Back and 2-Back related fatigue effects), it seems reasonable to argue that in our study this indeed was the mechanism through which novelty processing was decreased.

Different views on the functional significance of the P3a have been formulated. On the one hand P3a can be interpreted as index of bottom-up distraction. P3a amplitude and novelty induced performance decrements on a primary task are found to be positively related (e.g. Berti & Schröger, 2003; Escera et al., 2003; SanMiguel et al., 2008). Some recent accounts, however, emphasize a possible role in higher cognitive functions, such as the overriding or inhibition of context (i.e. active task rules) (Luu & Tucker, 2002; Polich, 2007), possibly activating a control network that facilitates switching of action programmes (Barcelo *et al.*, 2006). The relation between depleted attentional control and attenuated P3a amplitude in the present study seems to be more in line with the latter interpretations. However, the main aim of this study was not to precisely unravel the functional significance of the P3a, but rather to examine whether effects of mental fatigue were dependent on attentional control load of the fatigue inducing task.

The present study clearly shows that the manifestation of mental fatigue effects are task related. Novelty processing decrements were significant only when fatigue was caused by the 2-Back task, and not by the 0-Back task. As argued above, it can be thought that depletion of control capacity and working memory was more pronounced after the 2-Back, consequently compromising P3a generation. It must be noted that the subjective appraisal of the level of mental fatigue was similar after both tasks.

Therefore differential effects cannot easily be explained as reflecting factors relating to subjective fatigue. It therefore can be concluded that the nature of mental activity influences effects of the resulting fatigue on brain processes. An important direction for future research should be to systematically investigate the impact of different types of mental activity on cognitive, behavioural and emotional performance. By doing so it may increase understanding about the cognitive and biological mechanisms underlying different fatigue aspects, and may identify risk factors that are specific to certain types of activity (for instance the manifestations of fatigue that are typical to transportation, or air traffic control jobs).

Considering the effects of fatigue on behavioural performance it is remarkable that no decline in simulated driving was found. Even though subjects felt substantially more tired, both after 0-Back and 2-Back performance, steering error (SDLP) did not increase. A reason for this could be that the driving task was relatively easy. The purpose of the task was to steer the car along a curved road, without the presence of other traffic or unexpected events. Generally, the effects of fatigue show mostly in complex or novel tasks (Broadbent, 1979; Hockey, 1993), which makes it plausible that fatigue effects are not (yet) showing in this task. In order to get a better understanding of the effects of fatigue (and in particular the effects of different forms of mental activity) on behaviour and performance, future studies should include more complex tasks.

A further limitation of this study is that no direct assessment of attentional control has been conducted. Although it is plausible that a depletion of attentional control and working memory was more pronounced after prolonged 2-Back performance than after 0-Back performance, no formal comparison of attentional control capacity was included in the current design. The outcome variable rather was an automatically triggered process that was not related to performance on a task. Using such automatic measures in fatigue research has an important advantage over task related performance or physiological measures. Since fatigue inherently goes along with decreased motivation (Meijman, 2000), performance related measures are always vulnerable to the loss of motivation or strategic changes in task execution. Using measures of automatic, non effortful processing therefore can provide insight into the cognitive effects of fatigue that are separate from task disengagement (Van der Linden et al., 2006). On the on the hand, to confirm that 2-Back performance indeed causes a depletion of attentional control resources, future studies should include direct measurements of cognitive control.

Furthermore no non-fatigued control condition was included in this study. Therefore effects of habituation of P3a cannot be ruled out (Friedman & Simpson, 1994; Kazmerski & Friedman, 1995). However, it is not very likely that it was the primary cause of P3a reduction after the fatigue manipulation. The set of novel stimuli that was used post-manipulation was different from the stimuli in the pre-manipulation measurement. Therefore any differences between pre-and post-manipulation P3a amplitude cannot be explained by habituation due to repetition of stimuli. Furthermore, there is no reason to suspect that habituation would be different after different fatigue manipulations. The

finding that P3a attenuation is most prominent after 2-Back performance, thus, cannot be accounted for by habituation.

In summary, fatigue effects on novelty processing are dependent on the cognitive demands of the fatigue inducing mental activity. Strong depletion of attentional control and working memory capacity after 2-Back task performance, was associated with a marked reduction of P3a. 0-Back task performance, did not show such effects. Furthermore, depletion related decrease of P3a was present both when attention was focussed on a driving task, and when no simultaneous task was performed, while driving performance was not affected by fatigue.

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Chapter **10**

Brain potentials reveal enhanced loss-gain processing during mental fatigue

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Abstract

In everyday life a state of mental fatigue is often experienced after periods of prolonged cognitive effort. Besides declining cognitive performance mental fatigue is characterized by a loss of motivation to exert further effort, reflecting a shift in cost-benefit balance. It has been found that increasing monetary incentives can restore behavioral performance levels. The evaluation of reward and loss outcomes is central to such a cost-benefit balance, and could therefore be expected to be altered during mental fatigue. In this study the neural correlates of reward/loss evaluation during mental fatigue were examined. Outcome related EEG potentials during a gambling task (FRN, P3) were measured during a well-rested state and after 1-hour performance of a cognitively effortful (fatigue inducing) task. Increased FRN amplitude was found during fatigue as compared to a rested state. P3 amplitude was not affected by mental fatigue. A control group, that did not perform a cognitively effortful task, did not show similar change in FRN amplitude. Results indicated that outcome evaluation can be altered during a state of mental fatigue.

Introduction

Prolonged working on effortful cognitive tasks can bring about a state of mental fatigue. Mental fatigue associated with a variety of changes in biochemical balance and brain function (Mizuno et al., 2011; Nozaki et al., 2009; Tajima et al., 2010). On a behavioral level mental fatigue is found to strongly impair performance. Early studies on mental fatigue have found declined psychomotor vigilance (Grant, 1971), and impaired coordination of complex behavioral repertoires (Bartlett, 1943). In later years studies on mental fatigue demonstrated that specifically the higher cognitive functions (executive control) were disrupted. This becomes evident in deterioration in different domains such as selective attention (Boksem, Meijman, & Lorist, 2005; van der Linden & Eling, 2006), motor planning and preparation (Lorist, 2008; Lorist et al., 2000; van der Linden, Frese, & Meijman, 2003), and error monitoring (Boksem, Meijman, & Lorist, 2006; Kato, Endo, & Kizuka, 2009; Lorist, Boksem, & Ridderinkhof, 2005).

Besides these cognitive impairments, motivational decline is also thought to be an intrinsic aspect of mental fatigue. From everyday experience and formal research it is clear that, when working on demanding tasks for a long time, the aversion to exert further effort is growing (Hockey, 1993; Meijman, 2000). Such reluctance can often be dealt with by disengaging from maintaining performance levels or even stop task performance completely. By reducing the effort invested in performing a task, energy can be preserved, but also performance levels will drop (Sarter, Gehring, & Kozak, 2006). Such disengagement is thought to be an adaptive reaction to declining energy levels and resource depletion. Some researchers argue that the experience of fatigue serves as a bio-alarm, warning against excessive energy expenditure (Tajima, et al., 2010). Overriding this warning signal may lead to long term imbalances which may result in chronic fatigue or burn-out (Tops et al., 2007).

According to Boksem and Tops (2008), a subconscious cost-benefit analysis is performed in order to regulate energy expenditure. A given action is worth performing if it results in rewards,, but when the (energetical) costs of behavior outweigh the expected rewards this behavior is not favorable and may therefore be abandoned more easily. During fatigue this cost-benefit balance is thought to be shifted, in such a way that higher rewards are needed to maintain effortful performance. This idea is supported by findings that the decline in performance after a long period of task performance can be partially alleviated if extra monetary rewards are made available (Boksem, et al., 2006).

Because the evaluation of rewards and losses is a central factor in such a subconscious cost-benefit analysis, it could be expected that the neural mechanisms of reward/loss processing are modulated by mental fatigue. In electrophysiological event-related potential (ERP) studies the difference between reward and loss processing is characterized by a fronto-central negativity around 200 to 300 ms after outcome presentation (Gehring, 2002; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997; Nieuwenhuis, Holroyd, Mol, & Coles, 2004). This ERP component is termed feedback related negativity (FRN). The FRN is commonly investigated using gambling tasks in which the outcome of a bet can be either a gain or a loss of money. FRN amplitude is more negative after loss outcomes than after gain outcomes and is therefore thought to represent a prediction-error signal. Reward/loss information is coded by midbrain dopamine (DA) neurons, from where it is transferred to frontal cortical areas among which the anterior cingulate cortex (ACC). The ACC activity, in turn, is thought to be send to motor areas where it serves as a training signal, promoting actions that lead to gains and suppressing actions that lead to losses (Holroyd & Coles, 2002). Commonly, the FRN is followed by a parietal positivity starting around 300 ms post outcome (P3). P3 amplitude is found to be sensitive to reward magnitude (Yeung & Sanfey, 2004), and sometimes also to outcome valence (Hajcak, Moser, Holroyd, & Simons, 2007; Holroyd, Hajcak, & Larsen, 2006; Wu & Zhou, 2009).

In this study we exploratively investigated whether outcome related ERP components could be altered in a state of mental fatigue. Participants performed a gambling task before and after a one-hour fatigue inducing cognitive task. Electro-encephalographic (EEG) recordings were taken during the gambling tasks in order to examine changes in outcome related ERPs (FRN and P3).

Methods

Participants

Twenty eight participants were recruited (17 females; mean age (s.d.) = 21.4 (2.0)) were recruited through the Peking University intranet message board. Participants had normal or corrected-to-normal vision, and indicated not to work night shifts, and not to have sleep or fatigue related problems. Participants received 75 Chinese Yuan (approximately 12 US$) for participation, and were instructed that the money won during the gambling tasks would be added to the compensation as bonus. All participants signed informed consent before commencing the experiment. Half of the participants were assigned to an experimental

(fatigue) group (8 females; mean age (SD) = 21.9 (2.7)). The other half of the participants were assigned to a control group (9 females; mean age (SD) = 20.9 (1.5)).

Procedure

Upon entering the lab, informed consent was signed and participants received instructions. EEG equipment was applied and participants were seated in a sound attenuated, dimly lit room. The experimental session started with the pre-manipulation session of a gambling task. Subsequently participants in the experimental group performed a fatigue inducing effort task for one hour non-stop. Participants in the control group were instructed that they could relax and watched a self-selected video documentary for one hour. After this manipulation all participants performed the gambling task for a second time. Directly before the first and second measurements of the gambling tasks subjective state (boredom, energetic state, mental fatigue and physical fatigue) was assessed on five point Likert scales (1 = not at all; 5 = extremely).

Gambling task

The gambling task used in this study to measure the FRN was developed by Yu and Zhou (2009). On each trials the stakes for which could be gambled (20 or 150 cents) were presented in a white box in the center of a computer screen, accompanied by the question "bet or don't bet" in Chinese. Participants indicated whether they would like to bet in this trial by pressing a left or right button on a joystick (response mapping was counterbalanced between subjects). They were instructed that they could win or lose the stakes when they decided to bet, but that no money would be lost or gained if they did not bet on a given trial. 1500ms after a choice was made the gambling outcome was presented in the center of the screen. Wins were indicated as (+150) or (+20) in green color, losses were presented in red color (-150) or (-20). On "no bet" trials outcomes the hypothetical outcome was presented in white (-150,-20, +150 or +150). Before starting the formal test participants received verbal instructions and performed 20 practice trials. The formal test consisted of six blocks of 40 trials.

Fatigue induction

Experimental procedure. In the experimental group fatigue was induced through one hour performance of an effortful switch task (Botvinick, Huffstetler, & McGuire, 2009). Colored numbers were presented in the center of the computer screen. Participants had to respond to either the scale (lower or higher than 5) or the parity of the number (odd or even), based on the color in which the target number was presented (blue or yellow). The two target colors were presented in an intermixed fashion, introducing frequent switches between critical target features (color changed on 50% of the trials). This procedure requires participants to frequently change and update stimulus-response mappings. This task is found to involve effortful attention and to be aversive, in that it is avoided when participants are given the opportunity to do so (Botvinick, et al., 2009; Botvinick & Rosen, 2008; Kool, McGuire, Rosen, & Botvinick, 2010). In total, the fatigue inducing task was performed for six blocks of 244 trials, and lasted 60 minutes.

Control procedure. After the first measurement of the gambling task participants were instructed that they would have a resting break. They were told that the aim of the break was for them to relax, and they watched a self-selected video for one hour, after which the gambling task was resumed. In order to keep all other factors comparable to the experimental condition, participants were instructed to stay seated in the experimental room and light and temperature were kept constant.

EEG recording and analysis

EEG was recorded using 64 tin electrodes mounted in an elastic cap (Brain Products, Munich, Germany). Electrodes were positioned according to the international 10–20 system. Electrodes were placed supra-orbital from the right eye to record vertical electro-oculogram (VEOGs) and at the outer canthus of the left eye for horizontal EOG (HEOG). All signals were referenced online to a nose-tip electrode. Electrode impedance was kept below 10 kΩ for EOG channels and below 5 kΩ for all other electrodes. The online recording was done using a (0.016-100 Hz) band pass filter and 500 Hz sampling frequency.

Data were offline re-referenced to the mean of the left and right mastoids and filtered with a 1 Hz high-pass filter (24 dB/oct) and a 20 Hz low-pass filter (24 dB/oct). Data were segmented in -200 ms to 1000 ms time windows locked to gambling outcome presentation. Ocular artefacts were corrected using an automatic algorithm (Gratton, Coles,

& Donchin, 1983), and segments containing other artefacts (activity exceeding ±60 μV) were discarded from further analysis. Segments were averaged for win and loss outcomes separately, and a loss-win difference wave was calculated. Visual inspection of the waveforms demonstrated that an identifiable FRN deflection was present in the 'bet' trials, but not in the 'no bet' trials. ERPS were therefore further analysed only for the 'bet' outcomes. The FRN was defined as the average amplitude between 200 and 300 ms at electrode FCz. P3 was calculated at electrode Pz as the average amplitude in between 300 and 410 ms in the loss-win difference wave. Resulting ERPs were statistically analysed by means of Outcome (win, loss) x Time (pre-manipulation, post-manipulation) x Group (fatigue, control) mixed-model ANOVA.

Results

Subjective State Ratings

Analysis of subjective state rating was conducted by mixed-model measures ANOVAs for physical fatigue, boredom, energetical state, and mental fatigue. These analyses yielded significant main effects of Time for physical fatigue ($F(1,26) = 6.45$, $p < .05$) and boredom ($F(1,26) = 7.61$, $p < .05$). This indicated that participants felt more physically fatigued and bored during the post-manipulation measurement compared to the pre-manipulation measurement. The absence of interactions or main effects for Group indicated that this increase was not different across the fatigue and the control groups. On the other hand, repeated measures ANOVAs yielded significant Time x Group interactions for mental fatigue ($F(1,26) = 4.35$, $p < .05$) and energetical state ($F(1,26) = 5.61$, $p < .05$). Follow-up analyses showed that for the fatigue group energetical state decreased (energetic: pre-manipulation (s.d.) = 3.57 (.76), post-manipulation (s.d.) = 2.64 (.84); $t(13) = -3.79$, $p < .01$). For the control group no changes in energetical state were found (pre-manipulation (s.d.) = 3.14 (.77), post-manipulation (s.d.) = 3.07 (.73); $t(13) = -3.8$, $p < .01$). Mental fatigue ratings increased for both groups but more so for the fatigue group (pre-manipulation (s.d.) = 1.71 (.82), post-manipulation (s.d.) = 3.07 (1.07); $t(13) = -.27$, n.s.) than for the control group (pre-manipulation (s.d.) = 2.0 (.39), post-manipulation (s.d.) = 2.5 (.65); $t(13) = -2.46$, $p < .05$).

Gambling Task

Behavior. Participants in the fatigue group chose to bet in 60% of the trials during the pre-manipulation gambling task, and in 58% of the trials in the post-manipulation task. In the control group, participants betted in 55% of the trials pre-manipulation, and in 58% post manipulation. A Time (pre-manipulation, post-manipulation) x Group (fatigue, control) ANOVA indicated that these percentages were not different across groups or time of measurement (all F's < 1.7).

ERPs.

Outcome-locked waveforms are illustrated in Figure 1. For FRN amplitude a Time (pre-manipulation, post-manipulation) x Outcome (Win, Loss) x Group (fatigue, control) yielded a strong main effect of Outcome ($F(1,26) = 25.61$, $p < .001$). Furthermore, a significant Time x Outcome ($F(1, 26) = 4.93$, $p < .05$) and a Time x Outcome x Group interaction ($F(1, 26) = 7.62$, $p < .01$) were found. Overall FRN amplitudes were more negative-going for loss trials (5.91 μV) than for win trials (7.96 μV). The three-way interaction was further examined with Outcome x Time ANOVAs for the fatigue group and the control group separately. For the fatigue group a significant Outcome x Time interaction ($F(1,13) = 9.53$, $p < .01$) indicated that the loss-win difference was larger after the fatigue manipulation (-2.92 μV) than before the manipulation (-.98 μV) . For the control group an outcome main effect was found ($F(1,13) = 32.11$, $p < .001$), but the Outcome x Time interaction was not significant ($F(1,13) < 1$). This indicated that the loss-win difference during the pre-manipulation (2.26 μV) was not different from post-manipulation (2.05 μV).

For P3 amplitude the Time (pre-manipulation, post-manipulation) x Outcome (Win, Loss) x Group (fatigue, control) yielded a main effect of Outcome ($F(1,26) = 18.28$, $p < .001$), indicating that overall P3 was more positive for win trials (10.68 μV) than for loss trials (9.05 μV). No significant main effects or interactions including Group or Time were found (all F's < 2.1), which implies that P3 amplitude was not influenced by the fatigue and control manipulations.

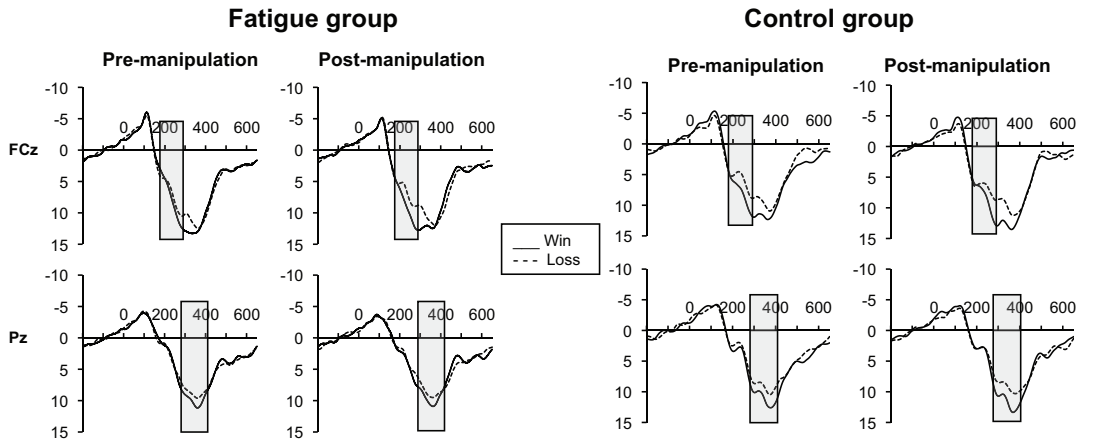

Figure 1. Outcome-locked ERPs for pre and post-manipulation measurement in the fatigue group (left panels) and control group (right panels). Marked windows in the upper panels (electrode FCz) indicate the FRN, and in the lower panels (electrode Pz) indicate the P3.

Discussion

The present data demonstrate that reward/loss evaluation can be altered during a state of mental fatigue. Although behaviorally the tendency to bet was not changed, changes were found in the electrophysiological responses to gambling outcome delivery. After one hour of effortful task performance an increase in feedback related negativity was found. This change was not found in a control group that also performed the gambling task before and after manipulation, but did not perform an effortful task during the one hour interval. Following the FRN the P3 amplitude was more positive for wins outcomes than for loss outcomes. This P3 effect however was not affected by fatigue.

Several theories have proposed a central role of motivation decline and reward-expenditure imbalance in fatigue (Boksem & Tops, 2008; Hockey, 1993; Meijman, 2000). Whereas motivation decline is a common finding, much of the evidence is based on behavioral performance and self-report measures. To our knowledge, this is the first human study that directly examines the effect of mental fatigue on neural correlates of reward processing in a gambling task. The increase in FRN amplitude, as found presently, may reflect that action outcome is monitored more extensively during mental fatigue. This interpretation would be in accordance with ideas about the functionality of fatigue. Since fatigue represents a state of energetical depletion, resource preservation is thought to be an important implicit goal. The experience of mental fatigue is therefore thought to serve as a bio-alarm (Tajima, et al., 2010), signaling a cost-benefit imbalance (Boksem & Tops, 2008). The FRN is viewed as a training signal that drives behavioral changes (Holroyd &

Coles, 2002). An increase in FRN during mental fatigue may reflect a stronger signal to inhibit behavior that has led to unfavorable outcomes.

It should be noted that in the present findings among the four Time x Group conditions, the Fatigue Pre-manipulation deviated most from the other three conditions. In contrast, the Fatigue post-manipulation was not much different from the pre and post-manipulation measurement in the control group. It might therefore be thought that a pre-manipulation difference in the mental states of both groups underlies the present findings, rather than a difference in mental state due to the manipulation. However, due to the between-subjects nature of the present design it is possible that individual differences in baseline FRN were present. Individual differences in FRN amplitude are found quite commonly (see also Chapter 2). Moreover, repeated measurements of the FRN yield rather stable amplitudes when tested in the same participant, under the same circumstances (Segalowitz et al., 2010). Therefore we hold it more plausible that the within-subject changes in FRN amplitude, as found presently in the fatigue group, may be attributed to the active manipulation (i.e. fatigue induction). These findings however, do deserve replication using a full within-subjects design.

Another issue that is deserves mention is that the current findings of increased FRN amplitude during fatigue may seem at odds with findings in other studies on fatigue that response-locked ACC activity during error-monitoring (ERN) is decreased during mental fatigue (Boksem, et al., 2006; Kato, et al., 2009; Lorist, et al., 2005). The ERN is often viewed as reflecting the same error monitoring system as the FRN, signaling when behavior is erroneous (and therefore unfavorable). It could be expected that FRN and ERN amplitude would change in the same direction during fatigue. In the above mentioned studies however the ERN was measured during the course of a fatigue inducing task. It is possible that the ERN decrease reflects a disengagement of effortful processing with time-on-task. Response-locked ERN amplitude is found to be positively correlated with task engagement (Tops & Boksem, 2010). Therefore during fatigue, the withdrawal of energetical resources from task performance may result in less vigorous monitoring of performance in that task. As argued above, it is possible throughout that the withdrawal from task performance results from altered reward/loss evaluation as found presently. This idea is partially supported by findings that ERN amplitude (and performance) can be restored during fatigue if increased monetary incentives are offered (Boksem, et al., 2006).

In this study reward and loss evaluation were assessed during a gambling task. This gambling task was clearly distinct from the fatigue inducing task. Moreover, the reward delivery in the gambling task did not depend on effortful task performance, but rather on the simple (non-effortful) choice to bet or not. An advantage of this procedure is that reward/loss processing can be investigated rather isolated from the confounding influence of performance decline and increasing error rates that commonly accompany a state of fatigue. A limitation, on the other hand, is that the FRN and P3 findings do not reflect a direct assessment of the cost-benefit balance of energy expenditure. The alteration in reward/loss processing as found here should be viewed as a carry-over effect, showing that prolonged effortful performance in one task can affect reward evaluation in a later, unrelated task. It would be interesting for future research to more directly examine the relation between effort expenditure and reward delivery during a state of mental fatigue (Botvinick, et al., 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009).

In addition to the fronto-central FRN, the later parietal P3 was also influenced by gambling outcome (more positive for win outcomes than for loss outcomes). It has been argued that P3 should not be sensitive to outcome valence (Yeung & Sanfey, 2004). Other studies however have found similar outcome valence effects on P3 amplitude (Hajcak, et al., 2007; Holroyd, et al., 2006; Wu & Zhou, 2009). It therefore seems that valence evaluation is not necessary confined to the earlier fronto-central FRN, but can spread to later posterior components. The functional significance of this outcome valence effect on P3 amplitude is not well understood yet. Hajcak and colleagues (2007) argued that it could reflect a difference in expectation of win and loss outcomes. Wu and Zhou (2009) suggested that it might reflect a more elaborate attentional evaluation of the outcome stimuli. A related possibility is that tasks such as the one used presently feature true monetary wins (bonus) but only virtual losses (that is, a net loss is never subtracted from the nominal participant's fee). Thus, wins have more affective relevance than losses and P300 may respond to this. For this study however the critical finding was that this P3 effect was not influenced by fatigue manipulation. In an earlier study we have found decreased P300 amplitude in a different task (novelty oddball task) during a state of fatigue (Massar, Wester, Volkerts, & Kenemans, 2010). This difference with the current study could be due to the fact that stimuli during the novelty oddball novel are not signaling relevant events, but should actually be ignored. The finding that overall P300 amplitude did not change due

to fatigue or repeated presentation, may indicate that outcome stimuli remained relevant to the observers, irrespective if they were fatigued or not.

In conclusion, the present study demonstrates that the neural correlates of reward/loss evaluation can be altered during a state of mental fatigue. After prolonged performance of an effortful cognitive task, FRN amplitude was increased compared to baseline. P3 was not affected by fatigue.

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Chapter **11**

General Discussion

Chapter 11: General Discussion

The studies presented in this thesis addressed the interactions between motivation, emotion, and cognition. The starting point for the research in this thesis was the question how inter-individual neurophysiological differences can be related to reward- and threat-related learning processes. Central to this question was the idea that individual differences in resting-state electrophysiological activity reflect motivational reward and punishment drives, and would therefore be predictive for acquiring associations in n reinforcement learning and fear conditioning tasks. The first part of the thesis focused on resting-state EEG theta/beta ratio in relation to reinforcement learning, and on EEG orienting responses in fear conditioning. In the second section of this thesis the focus was shifted to the interaction between threat, reward and attention. I presented studies on how stimuli that are predictive of negative (aversive noise, monetary loss) and positive events (monetary gain) exert an influence on spatial attention. Furthermore, I have examined the contributions of trait anxiety on attentional control and motor inhibition. The third section was concerned with the influence of mental fatigue as a result of prolonged periods of cognitive performance on cognitive processing and motivational responses to reward and loss. In this chapter, the key findings of these studies will be discussed. The relation between our findings and their theoretical contexts as well as some open questions that would be interesting to tackle in future research will be included into the discussion.

11.1 Reinforcement learning

The findings reported in Chapter 2 and 3 both indicate that resting-state EEG theta activity and theta/beta ratio are predictive of reward-related learning and decision making. In Chapter 2 resting-state theta power was correlated with learning performance in two separate gambling tasks. Higher theta power was associated with more risky decisions in the Iowa gambling task (IGT), and with stronger reward motivated learning in the reward/punishment task. In Chapter 3 high resting-state theta power was associated with lower FRN amplitude during gambling outcome presentation, but only in a group of high punishment sensitive (high self-reported BIS) participants. These data suggest that resting-state EEG activity is a reflection of activity which originates from a neuronal circuit underlying reward related decision making.

The findings from both Chapters 2 and 3 indicated that the correlation between theta/beta ratio, and reward processing and decision making, could be explained by individual differences in theta activity, and not as much in beta activity. In Chapter 2 risk taking in the IGT and reward motivated learning were significantly associated with theta power, but not to beta power, and in Chapter 3 FRN amplitude in high BIS individuals was correlated with theta but not beta power. Together these findings suggest that the circuits underlying resting-state theta activity is devoted to the processing of reward. It is thought that rhythmic theta activity originates in the septo-hippocampal system from where it is transferred to cortical areas, most notably midline structures among which the Anterior Cingulate Cortex (ACC; di Michele, Prichep, John, & Chabot, 2005; Gallinat et al., 2006). Human scalp recorded EEG theta activity in resting-state has been demonstrated to mainly reflect activity in the in the ACC. EEG beta activity is thought to originate from widespread cortical areas, and to reflect activation in cortico-cortical and cortico-thalamic loops (Engel & Fries, 2010). While the theta rhythm has been mostly related to motivational drives, beta is proposed to be related to top-down processing and involved in cognitive processes

The finding that resting-state theta is mainly related to reward but not punishment sensitivity is of interest because partly different brain circuits have been implicated in reward and punishment processing. The original study reporting the reward/punishment task that was currently used found that pharmacological manipulation of DA exclusively affected reward seeking (approach) behavior (and not punishment avoidance), and reward related activity in the ventral striatum (Pessiglione et al. 2006). Reward seeking was increased after DA agonist intake, and decreased after DA antagonist administration. Interestingly, clinical ADHD studies suggest that there is also a link between DA and resting-state theta. Increased theta/beta ratio is found to be an electrophysiological characteristic of a subgroup of patients that respond well to dopaminergic medication (Clarke, Barry, McCarthy, et al., 2002). Furthermore, the theta/beta ratio is found to normalize after effective treatment of these patients with methylphenidate (Clarke, Barry, Bond, et al., 2002; Clarke, et al., 2007). Taken together, these findings suggest a direct relation between theta activity and dopaminergic functioning. However, the directionality of such a relationship remains unclear. The positive correlation between theta power and reward seeking as found in Chapter 2 suggests that high resting-state theta reflects increased DA activity, whereas ADHD medication studies in patients implicate that

increased theta power is a result of DA deficiency in this population. Direct investigation of dopaminergic functioning in future studies is necessary to clarify these issues and to confirm the hypothetical existence of a relationship between resting-state theta and DA. Furthermore, an interpretation that different anatomical and neurochemical substrates underlie reward and punishment processing should be accepted with caution, since many studies show that DA functioning also influence punishment related learning (Frank & O'Reilly, 2006; Robinson, et al., 2010).

11.2 Fear conditioning

In Chapter 4 classical conditioning of fear responses was examined. Visual cue stimuli were either coupled (CS+) to the occurrence of an aversive shock (UCS) or not coupled to such an aversive stimulation (CS-). After eight paired CS+/UCS and eight CS- presentations, only part of the sample of participants reached conscious awareness concerning the CS-UCS contingency. In line with earlier studies, the group of participants that could correctly report the contingency, showed stronger sympathetic orienting responses (SCR) to CS stimuli that were presented before the conditioning procedure started (Baas, 2001; Fuhrer & Baer, 1965; Gao, Raine, Venable, Dawson, & Mednick, 2010; Otto et al., 2007). Moreover, larger P3-like electro-cortical responses to these pre-CS stimuli were also observed for aware subjects. Such P3-like responses are generally associated with allocation of attention ('orienting') to the stimulus and updating of memory contents based on new information (Duncan-Johnson & Donchin, 1982). The findings in this chapter suggest that the occurrence of sufficient orienting responses may be instrumental in learning associations between the "oriented to" stimuli and relevant events (i.e. electric shocks) that accompany these stimuli. The use of ERPs to measure orienting responses in addition to SCR can be informative because ERPs index the cortical substrate of attentive stimulus processing, while the SCR reflects sympathetic activation (Bradley, 2009; Kenemans & Ramsey, in press)

Contrary to our expectations, contingency awareness was not related to individual differences in anxiety. From earlier studies it was expected that the failure to learn to distinguish stimuli that signal a potential threat and stimuli that signal safety, would contribute to the perceived unpredictability of threat. This in turn would result in sustained feelings of anxiety (Baas, van Ooijen, Goudriaan, & Kenemans, 2008; Christian Grillon,

2002; C. Grillon, 2002). There were also no correlations between pre-conditioning responsivity on the one hand, and anxiety and attention questionnaire scores on the other. This makes it difficult to determine what factors contribute to increased orienting and eventually learning.

From a different point of view, P3 and LPP are often reported during enhanced emotional/attentional processing (e.g. emotional picture viewing; Hajcak, Moser, & Simons, 2006; Schupp et al., 2000), and are thought to reflect norepinephrinergic (NE) projections to the parietal and occipital cortical areas (Nieuwenhuis, De Geus, & Aston-Jones, 2010). Therefore, individual variations in learning performance and OR ERPs could be related to differences in norepinehrinergic function or even genetic make-up. Such NE-driven responses to initially novel stimuli that are instrumental in explicit learning about these stimuli ('awareness') can be easily related to the well-known sensitivity of explicit, and especially emotional, memory to noradrenergic manipulation (Cahill, Prins, Weber, & McGaugh, 1994; Strange & Dolan, 2004; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). This idea should be further tested in future studies.

It is also worth mentioning here that one of the theoretical starting points of my project was that there would be a positive relation between risky decision making, theta/ beta ratio, and small FRNs on the one hand, and threat learning (fear CS+/CS- conditionability) on the other. For example, a clear positive relation has been reported between self-reported negative affect and strength of the ERN (Hajcak, McDonald, & Simons, 2004; Luu, Collins, & Tucker, 2000) . Such associations were actually explicitly tested in the sample described in chapters 3 and 4, but could not be confirmed at all.

11.3 Spatial attention

In Chapter 4 it was shown that stimuli predictive of an aversive event can elicit physiological fear responses (at least measurable in fear potentiated SCR). In Chapter 5 and 6 we have further investigated how such threat associated stimuli can exert an influence on attentional processing, specifically in the context of spatial attention. The main findings from Chapter 5 indicate that cue stimuli that predicted a threat (aversive human scream) increased the cue validity effect compared to neutral cues. Furthermore, in combination Chapter 5 and 6 demonstrated that threat can modulate spatial attention at various stages of attentional processing. In Chapter 5 participants responded faster to

validly cued targets when the targets were associated with a threatening noise than when they were associated with a neutral tone. This effect indicates that initial orienting towards threat cues is faster than orienting towards neutral cues. On the other hand, participants responded more slowly to invalidly cued targets following threat cues than following neutral cues, indicating that disengagement of spatial attention from threat cues is more difficult than from neutral cues. In Chapter 6 a longer interval between cue onset and target onset was used allowing attention to be directed away from the cued location. This mechanism, inhibition of return (IOR), is thought to reflect an active bias away from the cued location when no relevant stimulus is present, and results in slower responses to validly than invalidly cued targets. Results from Chapter 6 showed that for threat related cues this IOR effect was smaller (or even non-present) compared to neutral cues. This may suggest attention is less easily biased away from stimuli that predict a threat.

Interestingly, the effects of threat on the disengagement, and IOR components of spatial attention were found in groups of participants that were not restricted to highly anxious individuals. Slowed disengagement in Chapter 5 was found both in an unselected sample of individuals as well as in preselected high and low trait anxious participants. In Chapter 6 both groups of participants showed moderate trait anxiety scores. Studies using verbal or pictorial threat stimuli (e.g. negative words, angry faces, aversive scenes) to study attentional bias most often find that only high anxious individuals show slowed disengagement (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Mathews & Mackintosh, 1998; Mogg & Bradley, 1998; Puliafico & Kendall, 2006), and reduced IOR following threat cues (Fox, Russo, & Dutton, 2002; Verkuil, Brosschot, Putman, & Thayer, 2009; Waters, Nitz, Craske, & Johnson, 2007). In contrast, studies using cues that convey threat of direct physical annoyance (similar to the procedure that was used in this thesis) do consistently find attentional modulation by threat stimuli in general populations (not specifically selected for high anxiety; Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Van Damme, Crombez, & Eccleston, 2004; Van Damme, Crombez, Hermans, Koster, & Eccleston, 2006). An explanation for this discrepancy could be that the appraisal of pictorial threat stimuli is dependent on individual differences in anxiety (Mogg & Bradley, 1998). Anxious people, for example, may find a picture of an angry face highly threatening, while non-anxious individual may experience such a stimulus as only mildly threatening. In contrast, the aversive stimulations that were used in the studies

in this thesis (loud noises, electric shocks) were commonly experienced as aversive by high and low anxious individuals. Supporting this notion is the finding that mean aversiveness ratings ranged from 7.3 to 7.9 (on a scale from 0 to 9), and did not differ between high and low anxious samples (Chapter 5). Such consistently high aversiveness ratings could indicate that the noise sound induced a highly threatening or "strong" situation. Fear responses in such a "strong" situation are thought to be more uniform across individuals (Lissek, Pine, & Grillon, 2006). This interpretation would be in line with the "cognitive-motivational" model proposed by Mogg and Bradley (1998), which postulates that whenever a stimulus is identified as a threat, the attentional system interrupts any current goals and orients towards the source of this threat (see also van Honk et al., 2004). In contrast, other models have proposed that anxious and non-anxious individuals differ mostly in the way the attentional system is employed whenever a threat is detected (Williams, Watts, MacLeod, & Mathews, 1997). While high anxious individuals are argued to orient attention towards the source of threat, low anxious individuals are thought to direct attention away from the threat (attentional avoidance). The findings presented in this thesis clearly favor the former model over the latter, in that attention towards threat related stimuli is found in both high and low anxious participants (Chapter 5), and directing attention from threat stimuli was found to be more difficult than directing it from neutral stimuli (Chapter 5 and 6). However, Chapter 5 does show that the magnitude of attentional modulation by threat is not insensitive to individual differences in anxiety related personality traits. Facilitated initial engagement of attention to threat stimuli was found to be positively correlated with trait anxiety (STAI-trait), and disengagement of attention form threat cues was related to self-reported BIS score. The groups included in Chapter 6 were not large enough (N=10 per experiment) to reliably calculate correlations between effects and personality traits.

In Chapter 6 the electrophysiological processes by which threat affects attention were examined. Different from most EEG studies on attentional modulation by threat, the focus of this chapter was on attention related neural responses to cue stimuli. Results demonstrated that a frontal central positive component peaking around 200 ms post-cue (P2) was specifically potentiated after threat stimuli. An earlier EEG study on cue related brain activity during IOR has reported a similar fronto-central component (Tian, Klein, Satel, Xu, & Yao, 2011). This component was interpreted as reflecting the initiation of the attentional inhibition process, directing attention away from the cued location. However,

given the fact that in our study threat cues were accompanied by larger P2 amplitudes but reduced IOR, it does not seem likely that this component reflects the inhibitory aspect of IOR. We have alternatively proposed that the cue-locked P2 could be equivalent to the frontal selection positivity (FSP) that is found in selective attention studies (Baas, Kenemans, & Mangun, 2002; Kenemans, Kok, & Smulders, 1993; Kenemans, Lijffijt, Camfferman, & Verbaten, 2002; Potts, 2004). The FSP reflects attentional selection of relevant stimulus features and is found to be sensitive to the threat value of stimuli (Baas, Kenemans, Bocker, & Verbaten, 2002). In this view the increased P2 amplitude may reflect that attentional processing of threat stimuli is more elaborate than non-threatening stimuli. It is conceivable that due to such increased processing the attentional redirection (disengagement) from a threat stimulus that must precede IOR is thwarted, thereby resulting in reduced IOR on a behavioral level. Given the present data I propose that the study of cue-locked ERPs in IOR is a promising avenue for further research. Since IOR occurs at relatively long cue target onset asynchronies, it provides a good possibility to study how exogenous cues influence attention, while minimizing the overlap between cue and target related EEG activity.

A further question is whether a similar attentional mechanism (more elaborate processing of threat stimulus reflected in increased P2 amplitude after threat cues) underlies the slower disengagement of attention from threat cues in short SOA exogenous cuing tasks (as in Chapter 5). Originally the aim of Chapter 6 was to examine both IOR and cuing facilitation. For that reason, short SOA trials were included in the cuing tasks. However, no cuing facilitation, but IOR or no cuing effect was found for short SOA trials. Rather, faster RT on invalid trials than valid trials (IOR) was found on short SOA trials in experiment 1, and no cuing effect was found in experiment 2. This unexpected result could be due to different task parameters used in chapter 5 and chapter 6 (e.g. validity ratio, number of trials, response mode). It would be interesting for future studies to further examine the time-course of attentional modulation by threat and P2 potentiation under varying SOAs. Furthermore individual differences in trait anxiety in threat-modulated IOR could be studied by including larger samples or extreme groups.

11.4 Secondary reinforcers and spatial attention

The results from Chapter 7 indicate that not only stimuli that are associated with threat can attract spatial attention, but also stimuli that predict secondary reinforcement (monetary

reward or punishment). In line with recent findings the data presented in Chapter 7 show that cue validity effects in the exogenous spatial cuing task are increased if cues are associated with monetary reward, indicating that spatial attention is attracted to these stimuli stronger than to neutral stimuli. This finding is in line with several recent studies finding involuntary attentional orienting towards reward related stimuli (Anderson, Laurent, & Yantis, 2011; Hickey, Chelazzi, & Theeuwes, 2010a, 2010b; Kiss, Driver, & Eimer, 2009).

Although the detection of threat is thought to be prioritized in attentional processing because of its survival value (Öhman & Mineka, 2001), recent studies have found that appetitive stimuli (e.g. food stimuli, or addiction related stimuli) can also attract attention involuntarily depending on the current goals (Ehrman et al., 2002; Tapper, Pothos, & Lawrence, 2010; Vogt, De Houwer, Koster, Van Damme, & Crombez, 2008). As discussed in the introduction, originally the amygdala was implicated as the primary structure in threat detection (LeDoux, 1995, 1996). Consistently, amygdala activity was found to be related to attentional modulation by threat related stimuli (Armony & Dolan, 2002; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004), involving modulation of the sensitivity of sensory areas, and the initiation of a bias of attention towards threat locations, either directly or through engaging the attentional system (Vuilleumier, 2005). Recently however, studies have shown that the amygdala is not only reactive to threat stimuli, but also to positive affective stimuli, depending on the active goals and individual predisposition (Cunningham, Raye, & Johnson, 2005; Cunningham, Van Bavel, & Johnsen, 2008). In this view the amygdala is a salience/relevance detector that instigates a bias of attention towards those stimuli that are most relevant to the current goal.

Of importance for the study presented in Chapter 7 are also recent reconsiderations of the function of the midbrain dopamine (DA) system. It has been argued that stimuli that are associated with a greater transient response of the DA system attain salience, and therefore have a stronger impact on attention (Hickey, et al., 2010a). The dominant idea about the midbrain DA system has been that DA activity phasically increases when a reward is presented (or predicted), and in contrast, decreases when non-reward or punishment is encountered (Schultz, 1998). More recently, distinct subsets of DA neurons have been found to activate after aversive stimulation (Brischoux, Chakraborty, Brierley, & Ungless, 2009; Schultz, 2007). Following these observations, it has been proposed that specific neuronal populations are concerned with the encoding of value (reward or punishment), while other neurons code for motivational salience (relevance), promoting attentional orienting (Bromberg-Martin,

Matsumoto, & Hikosaka, 2010). Taken together, current knowledge suggests that flexible attentional mechanisms exist that bias perception towards a more rapid and extensive processing of those stimuli that signal relevant events, both aversive and appetitive. This provides an explanation for why both threatening stimuli (e.g. angry faces or electric shocks; Fox, et al., 2002; Van Damme, et al., 2004) and rewarding stimuli (e.g. food and money; Kiss, et al., 2009; Tapper, et al., 2010) can act as potent attentional cues. The data from Chapter 7 fit well with such a motivational salience account of attention.

11.5 Anxiety and attentional control

A consistent finding across the studies of this thesis is that self-report scores of trait anxiety are inversely correlated with self-report scores of attentional control (Chapters 4, 5, 8), as shown in two independent samples of participants (Chapters 4 and 8 were based on largely the same sample; Chapter 5 concerns a separate sample). A negative correlation between trait anxiety and ACS scores has also consistently been reported in other studies (Derryberry & Reed, 2002; Healy, 2010; Ólafsson et al., 2011). In contrast, a differentiation was found concerning specific cognitive performance measures that correlated with both self-report measures. The findings from Chapter 5 demonstrated that STAI-trait and BIS scores were correlated with attentional performance in a spatial threat cuing task. Faster attentional engagement to and slower disengagement from cues that predicted a threatening stimulation were associated with high STAI and BIS scores respectively. No correlations with ACS were found with task-performance parameters. In contrast, motor inhibition in a stop-signal task was inversely correlated with self-reported attentional control, but not with STAI-trait or BIS scores. The finding of a behavioral performance measure that correlates with ACS score is in itself interesting, because even though this scale is developed to assess attentional control capacity, other studies have not found correlations between ACS score and attentional performance (Bishop, Jenkins, & Lawrence, 2007; Reinholdt-Dunne, Mogg, & Bradley, 2009). The finding that inhibitory control in the stop signal task (SSRT) correlated with ACS score therefore provides support for the construct validity of this scale.

The fact that ACS scores and anxiety scores correlated with behavioral performance in different tasks could indicate that ACS is related to attentional performance in neutral (non-threatening) situations, while trait anxiety is more indicative of performance under threat. In Chapter 4 attention was drawn by cues that predicted a highly aversive stimulation, whereas in Chapter 8 attentional performance was assessed in a stop

task in which the stimuli carried no specific threat value. This explanation however is not consistent with findings that anxiety is associated with poor attentional performance in other tasks in which no specific threat is introduced, such as antisaccade tasks (Ansari, Derakshan, & Richards, 2008; Derakshan, Smyth, & Eysenck, 2009), and dual task performance (Eysenck, Payne, & Derakshan, 2005). Another possibility could be that anxiety interferes with attentional control by prioritizing stimulus-driven attention over top-down controlled attentional focus (Eysenck, Derakshan, Santos, & Calvo, 2007). It is possible that anxiety is a stronger predictor of performance in tasks which predominantly tax stimulus driven attention (such as the exogenous spatial cuing task), while ACS is more related to performance in tasks in which focused, top-down attentional control is the main determinant of performance.

A way to test the first possible explanation would be to assess the correlation between ACS, STAI and inhibitory performance in the stop task, using stimuli that vary in the level of threat. Much like the way in which threat is introduced in the exogenous spatial cuing task in Chapters 5 and 6, threat related stimuli can be used as stop or go-stimuli in the stop signal task (Pessoa, Padmala, Kenzer, & Bauer, 2011). Correlations between SSRT and STAI (and BIS) could be expected to arise when stop stimuli carry a threat value. The second possibility could be examined using tasks that are more dependent on top-down attentional control such as the endogenous spatial cuing task, or selective attention tasks. Correlations with task performance would be expected to be mainly present with ACS and not with STAI (if no threatening stimuli are used). In both cases, the examination of neural correlates can provide further insights, because different components are thought to be related to top-down attention and bottom-up attention (e.g. cue locked ERPs and target locked ERPs in the endogenous cuing task respectively; Mangun & Hillyard, 1991; Van der Lubbe, Neggers, Verleger, & Kenemans, 2006).

11.6 Mental Fatigue

The third and final section of this thesis addressed the effects of mental fatigue on cognition and motivation. In Chapters 9 and 10 mental fatigue was induced by long periods of effortful cognitive activity. Participants worked on cognitive tasks for one hour or longer continuously. Under such a regimen usually performance declines gradually with progressing time-on-task. This could both be due to decreasing cognitive processing capacity, or to a loss of motivation to perform (Hockey, 1993; Meijman, 2000). Chapter 9

has focused on the cognitive aspect of fatigue. By contrasting the effects of prolonged performance on two tasks with different working memory demands, we aimed to test whether the effects of fatigue on cognition are general or task specific. ERP responses to novel auditory stimuli were recorded before and after 90-minutes of cognitive task performance. Specifically, these ERPs feature a late positive deflection as a prototypical response to infrequent, unexpected, and unknown stimuli that bear no obvious relation to the context task ('novelty P3' or 'P3a'). Findings indicated that participants reached a state of fatigue, after performance of both tasks. Novelty P3 however, was found to be reduced only after the high working memory load task, and not after the low working memory load task. These findings demonstrate that the neurocognitive effects of mental fatigue are not uniform, but depend on the specific nature of the cognitive activity that has induced fatigue. Importantly, the P3a is thought to reflect involuntary attentional orienting towards novelty (Friedman, Cycowicz, & Gaeta, 2001). Since this is supposed to be an automatic process which does not require effortful attention, reduced novelty processing more likely reflects cognitive deterioration. Although the P3a was originally thought to represent distraction (failed attentional control), more recent accounts however, suggest that the P3a has a more important role in information updating and flexible cognitive control (Barcelo, Escera, Corral, & Perianez, 2006; Barcelo, Perianez, & Knight, 2002), or functions as a generic prefrontal behavioral interrupt signal (Kenemans & Kähkönen, 2011)

As to motivation, it is known that fatigue is accompanied by a reduced willingness to exert further effort. Boksem and Tops (2008) have argued that an unconscious cost-benefit analysis is performed for the evaluation of energetical investments. When the expected reward is disproportionally small, relative to the amount of energy that needs to be invested for a certain action, this action is less worth performing. During fatigue the balance between the energetical costs of an action and the potential rewards is shifted. As a consequence, less effort is invested into task performance ('conservation withdrawal'), or higher rewards are needed to maintain sufficient levels of performance (Boksem, Meijman, & Lorist, 2006). The finding that FRN amplitude is enhanced during fatigue (Chapter 10) may be a reflection of such a shift in cost-benefit balance. The increase in FRN amplitude, as found presently, may reflect that action outcome is monitored more extensively during mental fatigue. Furthermore, an increase in FRN during mental fatigue may reflect a stronger signal to inhibit behavior that has led to unfavorable outcomes.

It must be noted that in the experimental design used in Chapter 10, neurophysiological responses to rewards and punishments were recorded during a gambling task. This task did not involve effortful processing, and therefore the FRN recorded in this chapter, is only an indirect reflection of any shift in effort-reward balance. It would be interesting for future studies to assess this mechanism more directly by varying the magnitude of effort and reward orthogonally (Botvinick, Huffstetler, & McGuire, 2009; Botvinick & Rosen, 2008).

11.7 Future directions

The work in this thesis provides a basis for further research in various directions. Several open questions have been discussed in the separate sections above. Here I aim to provide an integrative view of some further open questions.

As outlined above the responsiveness to reward and loss has been evaluated in different chapters. Firstly it was demonstrated that there is a network with resting-state activity in the theta mode that is related to processing of reward/loss feedback and reinforcement learning. This network was mostly related to individual differences in reward sensitivity

Secondly, spatial attention is found to be automatically guided by threat related stimuli but also by stimuli related to monetary reward and monetary loss. An open question is whether the extent to which spatial attention is drawn towards cues predicting monetary reinforcement is also related to anxiety and reward and punishment sensitivity. A study by Hickey et al. (Hickey, Chelazzi, & Theeuwes, 2010), shows that orienting spatial attention towards reward signals is proportionate to self-reported behavioral activation (BAS), which is a measure of reward sensitivity. It remains to be tested whether resting-state theta power relates to attentional bias towards reward, in the same way that self-reported reward sensitivity does.

Furthermore, reward/loss processing was found to be increased during mental fatigue. It would be interesting to examine whether this enhanced reaction to reward/loss outcome would also result in enhanced reward or punishment related learning during fatigue. Given the interpretation that increased FRN during fatigue could signal stronger inhibition of punished actions, it could be expected that fatigue would enhance punishment motivated learning, more than it would reward related learning. This question could be

answered by examining performance on the reward-punishment task in a state of fatigue, compared to a rested state. For now, this remains to be tested.

Another recurring theme in this thesis is the interrelation between attention and anxiety. Although self-reported attentional control and anxiety were consistently correlated, and BIS and anxiety were correlated, BIS and attentional control were not directly correlated. Moreover no behavioral or neural measures were found that correlated with all of these self-report scales. This could mean that the trait-anxiety scale conveys two separate aspects, one that pertains to attentional distractibility during normal, non-threatening situations (which might be related to ACS), and one that specifically relates to anxious responding when a threat is present (which might relate to BIS).

Besides the possibilities already discussed in section 11.5 (varying threat levels during a stop task, or varying top-down versus bottom-up demands in "cool" cognitive tasks) another possibility to further disentangle separate contributions of attentional control and BIS to trait anxiety, would be to evaluate factor structure of the trait anxiety scale. It would be of interest to identify items that are specifically related to either ACS or to BIS, but not both.

A further important question concerns the biochemical mechanisms underlying this relation. An obvious lead is dopamine (Braver & Cohen, 1999; Redgrave & Gurney, 2006). Does dopaminergic manipulation modulate feedback processing like it does to error processing (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004; de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006; Zirnheld et al., 2004)? And does it do so consistently with theta power, as does for example methylphenidate in ADHD (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002)?

Another finding in thesis was the relation between attentional orienting (as reflected in electrocortical and sympathetic responses) and subsequent fear learning. Here, the noradrenergic system could be implicated, as detailed in section 11.2. Future research should further elucidate the relation between NE-driven orienting, fear learning, awareness of contingencies, and explicit (emotional) memory. Norepinephrine has also been implicated in the parietal control of spatial attention (Coull, Nobre, & Frith, 2001). This thesis demonstrated that co-localization of threat and cued spatial attention promoted the engagement of spatial attention and thwarted its disengagement. Whereas the former may

indeed be primarily noradrenergically mediated, the disengagement mechanism may well rest on other mechanisms such as the cholinergic system (Meinke, Thiel, & Fink, 2006).

Finally, measures of 'cool' motor inhibition turned to have only an indirect relation with measures of 'hot' affect, only evident in selective correlations with self-report measures. On the other hand, ADHD patients are typically impaired in such motor inhibition, and this impairment is remedied by methylphenidate methylphenidate (Lijffijt et al., 2006; Overtoom et al., 2009), which promotes dopaminergic and noradrenergic transmission. These patients also show enhanced theta and methylphenidate reduces theta. Given the relation between theta and risky decision making or weak reinforcement learning, a further analysis of the relation between theta, reinforcement learning, and dopamine and norepinephrine seems an obvious way to go.

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Appendix **A**

Nederlandse samenvatting

Samenvatting

Een belangrijk thema in de studie naar het menselijk (en dierlijk) gedrag is de vraag hoe gedrag gevormd wordt door beloning en straf. Beloning, in de breedste zin van het woord, kan gezien worden als elke verandering in de situatie die als prettig ervaren wordt, of bevorderlijk is voor het welzijn van een organisme in een gegeven toestand (bijvoorbeeld het consumeren van voedsel, pijn verlichting, sex, het verkrijgen van geld). Straf, in tegenstelling, kan gedefinieerd worden als elke verandering die als onprettig ervaren wordt, of een bedreiging vormt voor het welzijn (bijvoorbeeld pijn, het verlies van geld, of het uitblijven van een verwachtte beloning). De overlevingskans van een organisme is sterk afhankelijk van het succesvol verkrijgen van beloningen en het vermijden van bedreigingen (straffen). Verschillende theorieën beschrijven dat gedrag ten behoeve van het nastreven van beloningen (appetetieve motivationele drive) en het vermijden van straffen (aversieve motivationele drive) aangestuurd wordt door specifieke, evolutionair oude hersensystemen (onder andere het mesencephalisch dopamine systeem voor de appetitieve drive, en de amygdala en het septo-hipocampaal systeem voor de aversieve drive). De onderzoeken in dit preofschrift zijn met name gericht op de invloed deze motivationele drives een invloed hebben op cognitie (en andersom). De onderzoeken zijn gestructureerd aan de hand van drie thema's.

Deel 1: motivationele drives en het leren van beloningen en straffen

Een startpunt van het onderzoek in dit proefschrift was het idee dat individuele verschillen fysiologische activiteit in de bovenbeschreven motivationele hersencircuits een weergave kunnen geven van individuele balans in appetetieve en aversieve motivationele drives. Uit eerder onderzoek bleek dat motivationeel gedreven gedrag in laboratorium taken gecorreleerd was met neurofysiologische activiteit gemeten met elektro-encefalografie (EEG) tijdens rust (wanneer de participant geen specifieke taak uitvoert). Een direct aanknopingspunt voor het huidige onderzoek was de bevinding dat de relatieve bijdrage van langzame golf activiteit (theta, 4-7 Hz) ten opzichte van snellere beta activiteit (13-30 Hz) in het rust EEG voorspellend was voor de leerprestatie in een laboratorium goktaak (Iowa Gambling Taak, IGT). In de IGT moeten participanten kiezen om kaarten te trekken uit verschillende decks. Na elke keuze wordt er feedback geleverd over de (geldelijke)

opbrengst of het verlies die keuze te weeg heeft gebracht. Op basis van deze feedback leren participanten dat de snelheid van leren gerelateerd is aan de verhouding tussen theta en beta activiteit in het rust EEG (theta/beta ratio). Participanten met een hoge theta/beta ratio leerden slechter deze gaande weg kaarten te kiezen die meer winst opleveren dan verlies. Er is echter gevonden taak uit te voeren dan participanten met een lage theta/beta ratio (Schutter & van Honk, 2005).

Het experiment beschreven in **hoofdstuk 2** bouwt direct voort op deze bevindingen. Een nieuwe groep participanten voerde de IGT uit nadat het rust EEG gemeten was. Een vergelijkbare correlatie tussen theta/beta ratio en IGT leerprestatie werd gevonden in deze groep, wat een beter inzicht geeft in de betrouwbaarheid van de eerdere bevindingen. Bovendien werd gevonden dat deze correlatie met name gebaseerd was op een samenhang tussen IGT prestatie en theta activiteit, maar niet met beta activiteit. Leerprestatie in de IGT hangt af van zowel de drive om winsten te behalen als de drive om verliezen te vermijden. Het echter niet mogelijk om op basis van IGT prestatie na te gaan of één van beide drives meer van belang is voor de gevonden correlatie met EEG theta activiteit. Om dit te onderzoeken hebben we de participanten een tweede goktaak laten uitvoeren, waarbij het leren van beloningen en het leren van straffen onafhankelijk van elkaar zijn geïmplementeerd. De resultaten van deze taak wezen uit dat EEG theta activiteit significant gecorreleerd was met leerprestatie op basis van beloningen, maar niet met leren op basis van straffen.

In **hoofdstuk 3** is onderzocht of ook de hersenresponsen die betrokken zijn bij de verwerking van beloningen en straffen gecorreleerd zijn aan rust EEG theta/bet ratio (en theta activiteit). In het EEG is een hersenpotentiaal waar te nemen rond 250 ms nadat winst of verlies feedback wordt geleverd. Deze potentiaal wordt *Feedback Related Negativity* (FRN) genoemd en is meer negatief na verliezen dan na winsten. De FRN heeft een fronto centrale schedel verdeling en bronlokalisaties wijzen uit dat deze mogelijk gegenereerd wordt in de Anterieure Cingulate Cortex (ACC). De FRN lijkt een rol te spelen in het aanpassen van gedrag op basis van de verkregen feedback (Holroyd & Coles, 2002). In dit hoofdstuk hebben we onderzocht of de amplitude van de FRN samenhangt met individuele verschillen in rust EEG theta/beta ratio. Deze correlatie bleek inderdaad aanwezig te zijn, echter, alleen voor een subgroep van de participanten die gekenmerkt was door een hoge score op de *Behavioral Inhibition Scale* (BIS) vragenlijst. Wederom was de correlatie

afhankelijk van de samenhang tussen FRN amplitude en theta activiteit, maar niet beta activiteit. Bronlokalisatie wees uit dat ook theta mogelijk in de ACC gegenereerd wordt.

In **hoofdstuk 4** zijn individuele verschillen in een ander vorm van leren, namelijk klassieke conditionering, bestudeerd. Bij klassieke conditionering worden associaties tussen verschillende stimuli geleerd (in plaats van de associatie tussen een actie en een uitkomst zoals in hoofdstuk 2 en 3). Wanneer een neutrale stimulus herhaaldelijk tegelijkertijd wordt aangeboden met een belonings- of strafstimulus, dan wordt deze neutrale stimulus voorspellend voor de bekrachtigingstimulus. Hierdoor kan de neutrale stimulus (*conditioned stimulus*+, CS+) op zichzelf vergelijkbare fysiologische reacties opwekken als de bekrachtigingstimulus. De snelheid waarmee deze stimulus-stimulus associatie geleerd wordt in klassieke conditionering is ook aan individuele verschillen onderhevig. In hoofdstuk 4 hebben we specifiek gekeken naar de conditionering van een neutrale visuele stimuli aan een aversieve stimulatie (elektrische schok). Het bleek dat na een aantal gepaarde aanbiedingen van de visuele CS+ en de elektrische schok, maar een deel van de proefpersonen deze associatie bewust kon rapporteren. Deze proefpersonen vertoonden ook hogere fysiologische opwinding bij het zien van de CS+ (gemeten door middel van de huidgeleidingsrespons), terwijl de proefpersonen die zich niet bewust werden van de associatie niet een dergelijke verhoging vertoonden. Een andere bevinding in hoofdstuk 4 was dat de proefpersonen die zich bewust werden van de associatie, al vóór de gekoppelde aanbieding van de CS en de schok sterkere huidgeleidingsreacties vertoonden bij het zien van de visuele stimuli. Deze fysiologische responsen bij de aanbieding van nieuwe of saillante stimuli wordt *orienting responses* genoemd, en worden in verband gebracht met de mate van aandacht die gericht wordt op de gericht wordt op de verwerking van de stimulus. Ook in het EEG werden verhoogde *orienting responses* gevonden voor deze groep. Dit alles wijst erop dat fysiologische opwinding die gepaard gaat met de waarneming van nieuwe stimuli mede beinvloedt hoe goed het conditioneringsproces verloopt wanneer deze stimulus later aan een aversieve stimulatie gekoppeld wordt. De mate van leren en de sterkte van de *orienting responses* was echter niet gerelateerd aan individuele verschillen in angstigheid of aan vragenlijstscores van aandachtscontrole.

Deel 2: de voordelen en kosten van motivatie in aandacht

In **hoofdstuk 5** is onderzocht of stimuli die geassocieerd zijn met een aversieve stimulatie (vergelijkbaar met de CS+ stimuli in hoofdstuk 4), ook sterker de aandacht trekken waaneer zij in de visuele omgeving gepresenteerd worden. Hiertoe werden stimuli die voorspellend waren een aversieve stimulatie (een harde schreeuw) op een locatie in het visuele veld gepresenteerd. Na een korte tijd (213 ms) werd er een tweede stimulus aangeboden, ofwel op dezelfde plaats als de voorafgaande 'cue' stimulus, ofwel op een andere plaats, de participanten in dit experiment moeten aangeven waar ze de tweede stimulus zien. Uit de resultaten blijkt dat er sneller gereageerd wordt op stimuli die voorafgegaan worden door een cue op de zelfde plaats, dan wanneer deze voorafgegaan worden door een cue op een andere plaats in het visuele veld. dit effect wordt het cue validiteiteffect genoemd. Bovendien werd gevonden dat wanneer een cue voorspellend was voor een hard geluid dit cue validiteiteffect groter was dan wanneer een cue gebruikt werd die niet geassocieerd was aan een hard geluid. Dit geeft aan dat de focus van aandacht in de visuele ruimte sterker wordt gestuurd door stimuli die geassocieerd zijn aan dreiging dan door neutrale stimuli. Dit effect was groter voor mensen die hoog scoorden op angst- en strafgevoeligheidsvragenlijsten .

Wanneer de tijd tussen de cue en de daaropvolgende stimulus (*stimulus onset asynchrony*, SOA) langer wordt (200-300 ms of langer) wordt gevonden dat reactietijden langzamer worden voor stimuli die voorafgegaan zijn door een cue op de zelfde plaats, dan voor stimuli die op een andere plaats worden aangeboden. Dit geeft aan dat de ruimtelijk aandacht, nadat deze naar een cue locatie is getrokken, niet lang op deze locatie blijft, maar snel wordt verplaatst naar andere locaties in het visuele veld. Dit fenomeen heet *Inhibition of Return* (IOR).

In **hoofdstuk 6** zijn de hersenprocessen onderzocht die ten grondslag liggen aan IOR, en is onderzocht of IOR ook beïnvloed wordt door de dreigingswaarde van cue stimuli. hiertoe werd een vergelijkbare experimentele taak gebruikt als in hoofdstuk 6 (met langere SOA's van circa 400 ms).Hersenactiviteit werd gemeten doormiddel van EEG. In de reactietijd patronen bleek dat IOR minder groot was wanneer cue stimulus dreiging voorspelde dan waaneer een niet dreigende cue aangeboden werd. Dit geeft aan dat aandacht minder snel wordt wegbewogen van de locatie van dreiging. Bovendien werd er in het EEG signaal gevonden dat cues stimuli die een dreiging voorspellen een sterkere

hersenpotentiaal opwekken dan stimuli die niet voorspellend zijn voor een dreiging. Deze hersenpotentiaal was maximaal over fontaal centrale schedellocaties (rond 200 ms na de aanbieding van de cue stimulus). deze potentiaal komt sterk overeen met hersenpotentialen die in eerder onderzoek gerelateerd zijn aan selectieve aandachtsselectie voor relevante stimulus eigenschappen (*Frontal Selection Positivity*, FSP). Het lijkt daarom aannemelijk voor dreigingstimuli een vergelijkbare aandachtsselectie plaatsvindt.

In **hoofdstuk 7** is onderzocht of aandacht ook getrokken kond worden door stimuli die voorspellend zijn voor secundaire bekrachtiging (geld). Het zelfde experimentele paradigma als in hoofdstuk 5 werd gebruikt met als verschil dat cue stimuli niet geassocieerd waren met een hard geluid, maar met het winnen of verliezen van geld. Net als cue stimuli die een aversieve stimulatie voorspelden in hoofdstuk 5, werd in dit hoofdstuk gevonden dat cue stimuli die voorspellend waren voor secundaire bekrachtiging het cue validiteiteffect vergrootten. Dit effect was zowel aanwezig voor stimuli die winst voorspelden als stimuli die verlies voorspelden. Deze bevinding geeft aan dat de aandachtsverdeling in de visuele ruimte niet alleen door de dreigingswaarde van een stimulus bepaald wordt, maar dat ook stimuli die geassocieerd zijn met andere motivationeel relevante gebeurtenissen en soortgelijke aandachtstrekkende werking krijgen.

Hoofdstuk 8 gaat in op de samenhang tussen angstigheid en motor inhibitie (d.w.z. het onderdrukken van sterke motor responsen). Motor inhibitie, gemeten met de *stop-signal* taak, is afhankelijk van een goede inhibitoire controle en van een goede aandachtscontrole. Een interessant gegeven is dat uit vragenlijst onderzoek blijkt dat angstigheid positief samenhangt met inhibitie, maar negatief met aandachtscontrole. Daardoor zou angstigheid op twee tegenovergestelde manieren motor inhibitie kunnen beïnvloeden. De resultaten van dit hoofdstuk laten geen correlatie zien tussen motor inhibitie en angstigheid, of inhibitievragenlijst score. Wel is er een samenhang tussen motor inhibitie prestatie op de taak en aandachtscontrole score.

Deel 3: mentale vermoeidheid en de kosten van cognitie

Het laatste deel van dit proefschrift is gericht op neurocognitieve en motivationele effecten van mentale vermoeidheid. Mentale vermoeidheid is een toestand die kan optreden na lange periodes van intensieve cognitieve activiteit, en heeft negatief effecten op cognitieve prestatie en op de motivatie om verder te werken.

In **hoofdstuk 9** is onderzocht of de effecten van vermoeidheid hetzelfde zijn wanneer vermoeidheid is veroorzaakt door verschillende vormen van cognitieve activiteit. Om vermoeidheid te veroorzaken voerden participanten 90 minuten lang een cognitieve taak uit zonder rust. Deze taak kon ofwel een hoge mate van werkgeheugen belasting vereisen ofwel een lage mate van belasting. Hoewel na afloop participanten aangaven na beide taken even moe te zijn, en hun prestatie op een latere rijsimulator taak niet verschilde na de hoge dan wel de lage belastingsvariant van de vermoeidheidstaak, werd er een duidelijk verschil gevonden in hersenresponsen. Na het uitvoeren van de hoge belastingstaak gedurende 90 minuten, was de EEG hersenpotentiaal in reactie op omgevingsgeluiden (P3a) minder sterk dan vóór het uitvoeren van de taak, wanneer men nog goed uitgerust was. De P3a potentiaal wordt gezien als een reflectie van een automatische verschuiving van de aandacht naar onverwachte of saillante stimuli in de omgeving. Deze bevindingen geven aan dat in sommige gevallen de hersenen minder sterk reageren op omgevingsstimuli wanneer men vermoeid is. Belangrijk is dat het optreden van dit effect afhangt van de aard van de cognitieve activiteit die tot vermoeidheid geleid heeft. Wanneer het werkgeheugen lange tijd belast is geweest kan een dergelijke verzwakte reactiviteit optreden, maar wanneer het werkgeheugen nauwelijks belast is (maar men wel vermoeid is) werd dit effect niet gevonden.

Een belangrijke kwestie in vermoeidheidsonderzoek is de vraag of een verminderde cognitieve prestatie onder vermoeidheid aangeeft of men niet goed meer kán presteren, of dat men niet de motivatie niet heeft om nog goed te wíllen presteren (motivatie). De resultaten van hoofdstuk 9 duiden op een verminderde capaciteit. De P3a potentiaal geeft namelijk een automatische verwerking van omgevingsstimuli weer, waarvoor geen bewuste moeite gedaan moet worden. De bevinding dat deze potentiaal minder sterk is in een vermoeide staat (na langdurige werkgeheugenbelasting) is om die reden waarschijnlijk niet erg beïnvloed door een verminderde motivatie. Toch is een afgenomen motivatie om te presteren een centraal kenmerk van mentale vermoeidheid. Het is mogelijk dat tijdens vermoeidheid de kosten van het volhouden van een goede prestatie (investering van energie) en de opbrengsten hiervan niet meer goed in balans zijn. Hierdoor kan er eerder voor gekozen worden om minder moeite te investeren in de taakuitvoer wanneer de opbrengst niet als niet voldoende ervaren wordt.

In **hoofdstuk 10** heb ik onderzocht of er een effect is van vermoeidheid op de verwerking van straffen en beloningen. Participanten voerden een 60 minuten lange

cognitieve taak uit, waarna in een goktaak de FRN gemeten werd. Participanten die de vermoeidheidstaak hadden uitgevoerd lieten een sterkere FRN zien tijdens vermoeidheid dan vóór het uitvoeren van de vermoeidheidstaak. Voor participanten die geen vermoeidheidstaak hadden uitgevoerd was dit niet duidelijk het geval. Dit zou kunnen betekenen dat een sterkere afweging van kosten en opbrengsten in de hersenen plaatsvindt tijdens vermoeidheid. Deze interpretatie van deze bevindingen is echter niet zonder meer te maken. Het zal interessant zijn om in vervolgonderzoek na te gaan of de keuzes om energie te investeren in taakuitvoer ook sterker afhangen van verwachtte beloningen en straffen tijdens vermoeidheid dan in een uitgeruste toestand.

Appendix **B**

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Appendix **C**

Publication List

Publication list

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (In press). Resting-state EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clinical Neurophysiology.* http://dx.doi.org/10.1016/j.clinph.2012.03.005.

Massar, S. A. A., Mol, N. M., Kenemans, J. L., & Baas, J. M. P. (2010). Attentional bias in high- and low-anxious individuals: Evidence for threat-induced effects on engagement and disengagement. *Cognition & Emotion, 25*(5), 805-817.

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Van der Linden, D., **Massar**, S. A. A., Schellekens, A. F., Ellenbroek, B. A., & Verkes, R. J. (2006). Disrupted sensorimotor gating due to mental fatigue: preliminary evidence. *International Journal of Psychophysiology, 62*(1), 168-174.

Submitted

Massar, S.A.A., Kenemans, J. L., & Schutter, D. J. L. G. (submitted). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment?

Massar, S.A.A., Kenemans, J. L., Baas, J. M. P. (submitted). Electrodermal and electrocortical orienting responses but not trait anxiety predict fear conditioning.

Heitland, I., Oosting, R. S., Baas, J. M. P., **Massar**, S. A. A., Kenemans, J. L., & Böcker, K. B. E. (in revision). Genetic polymorphisms of the dopamine and serotonin system modulate neurophysiological response to feedback and risk taking in healthy humans.

Invited presentations

Massar, S.A.A. (2011). Emotional and motivational modulation of attention. Ghent University, Belgium

Massar, S.A.A. (2009). Individual differences in reinforcement learning: ACC reactivity and baseline EEG. International Symposium on the Neural Basis of Decision Making: Decisions and Emotions. Groesbeek, the Netherlands

CV

Stijn Massar was born on 3 August 1979 in Jakarta, Indonesia, and grew up in Breda, the Netherlands. In 1997 he graduated from Nassau Scholengemeenschap (Gymnasium) in Breda, the Netherlands. He started an undergraduate program in Applied Mathematics at University Twente, but switched to psychology at Radboud University Nijmegen, the Netherlands where he received his doctoraal (drs/MA) in Work and Organizational Psychology in 2005. In 2007 he received an MSc in Neuroscience and Cognition from Utrecht University, the Netherlands, after which he started a PhD at the department of Experimental Psychology at Utrecht University, under supervision of Leon Kenemans. As of Februari 2012 he works as a post-doctoral researcher in the Cognitive Neuroscience Laboratory led by Michael Chee at Duke-NUS graduate medical school, Singapore.