Stressing reward: Does sex matter?

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TABLE OF CONTENTS

CHAPTER 1

General introduction

Introduction

Biological sex matters to brain function. A striking quantity and diversity of sex influences on the human brain and related brain functioning have been reported in numerous studies (Cahill, 2006; Ingalhalikar et al., 2014). Although it is realized more and more that sex does matter, differences between men and women are still largely ignored in experimental studies examining neural mechanisms underlying cognitive, affective and behavioral functioning (Beery & Zucker, 2011; Cahill, 2006). For example, brain researchers prefer to include only male participants, in order to exclude menstrual cycle-related variability in females, precluding the possibility of investigating sex differences. Nevertheless, many findings on men are generalized to women, without any justification. This male bias in neuroscience is especially large in animal studies, but also present in human studies (Beery & Zucker, 2011). This situation retards progress in understanding the brains of men and women, and why they show different vulnerabilities to developing certain disorders. Ultimately, this affects the development of appropriate sex-specific treatments, especially those which are relevant for women.

An important class of disorders in which sex influences are apparent, are stress-related disorders (e.g., post-traumatic stress disorder, depression, cardiovascular diseases), as evidenced by their sex-specific prevalence rates (Kajantie & Phillips, 2006; Wang et al., 2007). Stress-related disorders form a major public health concern, affecting a high percentage of the community. For example, the Global Burden of Disease 2010 studies reported a global point prevalence of 4.4% for major depressive disorder, equivalent to 298 million cases worldwide, and a prevalence of 1.6% for dysthymia, equivalent to 106 million cases (Ferrari et al., 2013). It has been proposed that the physiological reactions in response to stress exposure play an important role in the development of stress-related disorders, which suggests that the sex-specific prevalence rates of these disorders may be related to sex-specific stress responses (Kajantie & Phillips, 2006). In addition, gonadal hormone fluctuations have been put forward as an important factor in the pathogenesis of certain (stress-related) disorders in women (Deecher, Andree, Sloan, & Schechter, 2008; Steiner, Dunn, & Born, 2003a). Premenstrual dysphoric disorder, for example, is characterized by affective lability, irritability, depressed mood, and/or anxiety. These symptoms occur during the late luteal or premenstrual phase of the menstrual cycle, which is marked by a steep

decline in hormone levels, and remit around menses onset (American Psychiatric Association, 2013).

Importantly, the neural underpinnings of these biological sex influences on the development of stress-related disorders remain largely unknown. This thesis was explicitly aimed at investigating effects of acute stress exposure on brain function, through a series of studies combining behavioral measures with high-temporal-resolution electroencephalography (EEG) measures. In our studies, we focused on the effects of acute stress on the neural processing of reward prospect and action outcomes or feedback[1], as these functions have been proposed to be central in the development of certain stress-related disorders (Russo & Nestler, 2013). In more detail, we examined whether acute stress effects differed between men and women, and we investigated the role of fluctuations in gonadal hormone levels across the menstrual cycle in women.

Are men and women similar or different?

Men and women show differences in brain and behavior. Whether these differences are the product of nature and/or nurture has been the topic of much debate, during the past century. Furthermore, whereas some researchers stress the importance of investigating brain and behavioral differences between men and women (Cahill, 2006, 2014; Halpern, 2012), other researchers warn against overinflating these differences (Fine, 2014; Hyde, 2005, 2014). In this regard, political motives never seem far away. This is nicely illustrated by the "gender similarities hypothesis", which was formulated by Hyde (2005, p. 581): "males and females are similar on most, but not all, psychological variables". She based this hypothesis on a meta-analysis of 46 meta-analyses of psychological so-called gender differences research. The meta-analysis included the categories cognitive performance, personality and social behaviors, and psychological well-being. Of the 124 effect sizes (Cohen's *d*), 30% were close to zero (≤ 0.10), indicating that the difference between men and women was negligible, 48% were small (0.11–0.35), 15% were moderate (0.36–0.65) and only

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[1] In this thesis, we use the terms "action outcomes" and "feedback" interchangeably. Note that these terms include positive and negative outcomes. They encompass monetary gains and losses following choices in a simple gambling task (studies 1 and 2) and feedback combining information on performance and eventual reward delivery following both reactions in a monetary incentive delay task (study 3). The term "reward prospect" is relevant for the third study, in which we examine the stage of reward anticipation preceding behavior, in addition to the stage of feedback following behavior.

8% of the studies showed large effect sizes (≥ 0.66; percentages add up to 101% due to rounding), indicating highly relevant differences between men and women. While these results indeed mean that 78% of the investigated differences were small or close to zero, they also indicate that on 70% of the variables differences existed, ranging in effect size from small to large, and that on 23% of the variables the effect size was at least moderate. Therefore, the conclusion based on this meta-analysis could have gone either way, depending on the focus or political agenda of the researcher: men and women are indeed similar, or men and women do differ. Instead, it is probably more realistic and fruitful to conclude that males and females show both similarities and differences in behavior.

Sex differences versus gender differences

Both the terms "sex differences" and "gender differences" are used to describe differences between men and women. Generally, "sex" is used to specify the biological characteristics that define males and females, while "gender" is used to refer to the socially constructed roles, behaviors and attributes, which a given society regards appropriate for men and women (World Health Organization, 2015). An example of a sex difference is that females can give birth to children, whereas males cannot. An example of a gender difference is that in Saudi Arabia men drive cars while women do not; not because woman cannot drive, but because only men are allowed to. With regard to many differences, however, it is not that simple to discriminate between the contributions of nature and nurture. Often, the two are entangled. In this thesis, we will use the term "sex differences" to refer to differences between men and women, although we recognize that an individual's behavior and brain function in a particular context and at a certain point in time is the product of a complex developmental process, involving interactions between genes, hormones, the brain, social experience and cultural context (Rippon, Jordan-Young, Kaiser, & Fine, 2014).

Sex differences in the brain

Biological sex has a widespread influence on brain anatomy, chemistry and function (Becker et al., 2008; Cahill, 2006). Sex differences that exist in the brain range from effects on the level of single neurons to the level of structural and functional connectivity patterns, indicating how the different parts of the brain are connected and interacting. Concerning anatomy, men have greater overall brain volumes relative to women. However, when controlling for total volume, men have a higher percentage of white matter, which mainly consists of myelinated axons, while women have a higher percentage of gray matter, which mainly contains neuronal cell bodies (see for review, Cosgrove, Mazure, & Staley, 2007). The volumes of several brain structures have also been reported to differ between the sexes. For example, relative to total volume, men have a larger orbitofrontal cortex, amygdala and hypothalamus, whereas women have a larger anterior cingulate cortex, dorsolateral prefrontal cortex, nucleus accumbens and hippocampus (Goldstein et al., 2001). Notably, all brain areas mentioned in the previous sentence are part of neural networks involved in stress regulation and/or reward/feedback processing (Dedovic, D'Aguiar, & Pruessner, 2009; Starcke & Brand, 2012).

Anatomical differences between the brains of men and women also exist on the level of connectivity patterns, that is of patterns of neuroanatomical links in the brain. A recent structural connectivity study by Ingalhalikar et al. (2014) investigated the patterns of white matter in a sample of 949 youths (aged 8–22 years). Male brains exhibited greater within-hemispheric connectivity, along with enhanced modularity and transitivity. According to the researchers, "modularity describes how well a complex neural system can be delineated into coherent building blocks (subnetworks)", while "transitivity characterizes the connectivity of a given region to its neighbors" (p. 924). Female brains revealed greater between-hemispheric connectivity and cross-module participation. On the basis of these findings, the authors proposed that male brains are wired to facilitate communication between perception and action, while female brains are structured to facilitate connectivity between left-hemisphere – analytical and sequential – and right-hemisphere – spatial and intuitive – processing modes.

Besides sex differences in anatomy, differences exist in brain chemistry. For example, sex differences have been reported in serotonin, dopamine and gamma-aminobutyric acid (GABA) systems (Cosgrove et al., 2007). In general, neurotransmission within these systems is enhanced in females compared to males.

Disturbances in these systems have been linked to the development of a wide array of disorders, such as mood disorders, addiction disorders and schizophrenia (Cosgrove et al., 2007). Moreover, there is evidence that neurotransmitter levels in women vary across the menstrual cycle. For example, cortical GABA levels in healthy women decline between the follicular and luteal phases, whereas the opposite pattern is present in women with premenstrual dysphoric disorder (Epperson et al., 2002).

In addition to sex differences in neurotransmitter systems, a major difference in brain chemistry can be found in circulating gonadal hormone levels (Andreano & Cahill, 2009). These hormones are not only important for sexual differentiation of the brain during early development and for reproductive behavior, but also modulate other functions, such as cognition, motivation and stress regulation (Becker, 2009; McEwen, 2002). For example, testosterone levels in men have been related to spatial ability (Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005).

Relevant for this thesis is that especially fluctuations in the female hormone levels of estradiol and progesterone across the menstrual cycle have been associated with fluctuations in stress-sensitivity and reward-related behaviors. The menstrual cycle with a median length of 29.5 days (Becker et al., 2005) consists of the follicular phase, the period from menses until ovulation, and the luteal phase, the period between ovulation and menses onset (Chabbert Buffet, Djakoure, Christin Maitre, & Bouchard, 1998; see Fig. 1). In the early follicular phase, levels of estradiol and progesterone are very low. From the midfollicular phase, estradiol levels increase to peak during the late follicular phase, while progesterone remains low. During the luteal phase, estradiol levels decrease to a moderate level, while progesterone levels increases to peak at the midluteal phase. The late luteal phase is characterized by a drop of both hormone levels (Chabbert Buffet et al., 1998). Animal studies have yielded ample evidence that estradiol and progesterone interact with neural networks involved in stress regulation and motivational behaviors (Becker, 2009; McEwen, 2002; Shansky et al., 2004). However, knowledge about the neural mechanisms in humans is scarce (Dreher et al., 2007).

In addition to the anatomical and chemical differences, men and women show differences in brain function. For example, studies have consistently shown enhanced global cerebral blood flow in females relative to males, both during rest and cognitive activity, along with a higher cerebral metabolic rate of glucose utilization (Cosgrove et al., 2007). Sex differences have also been reported in studies examining functional connectivity, that is, connectivity between brain regions that share functional properties. For example, men showed greater focal intrahemispheric activation during
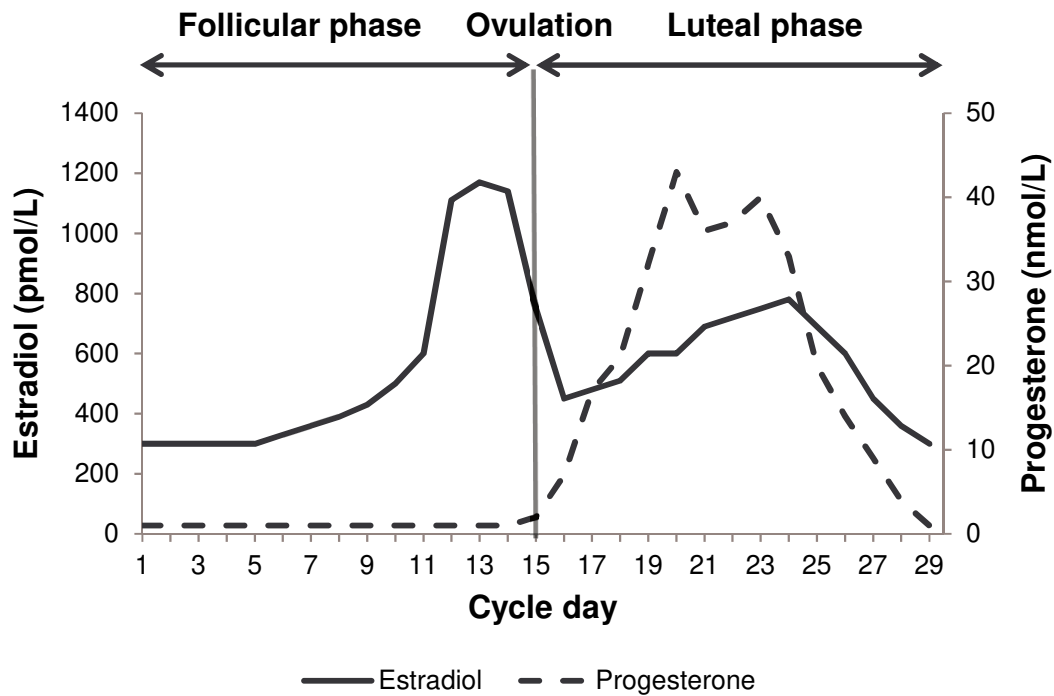
Figure 1. Plasma concentrations of estradiol and progesterone across a menstrual cycle (length 29 days). Note that actual levels of these hormones vary across individuals. Cycle length and timing of ovulation vary with the length of the follicular phase. The luteal phase has a relatively fixed length of 13–15 days.

performance of a spatial task, in which they outperformed women (Gur et al., 2000), whereas women showed greater interhemispheric activation on a language task, in which they outperformed men (Shaywitz et al., 1995).

Sex differences in behavior

Whether sex differences in the brain extend to the behavioral level has been the subject of an ongoing discussion. Although the abovementioned meta-analysis by Hyde (2005) showed many behavioral similarities in men and women, differences of moderate or large effect sizes are evident as well. For instance, males outperform females on three-dimensional mental rotation tasks, whereas females show an advantage on verbal fluency tasks (Hyde, 2014). In addition, men reach higher scores than women at tasks involving spatial memory, while women perform better at tasks involving verbal memory (Andreano & Cahill, 2009). Furthermore, males score higher on the psychological dimensions sensation seeking and physical aggression, whereas

females score higher on the dimensions agreeableness/tender-mindedness and interests in things versus people (Hyde, 2014).

Importantly, sex differences in the brain are not necessarily associated with differences in behavior (Cahill, 2006). As proposed by De Vries (2004), neural sex differences might serve at least two functions. First, they may indeed generate differences in behavior and overt functions, such as differences in reproductive behavior and cognitive functions. Second, they may do the opposite as well, that is, they may avert differences in behavior and functions by compensating for other physiological sex differences, such as gonadal hormone levels. This explains findings of numerous studies reporting sex differences in neural activity in the absence of behavioral differences (e.g., Grabowski, Damasio, Eichhorn, & Tranel, 2003; Piefke, Wess, Markowitsch, & Fink, 2005).

Sex-specific prevalence rates of stress-related disorders may be related to sex differences in physiological stress responsiveness

A striking illustration of the importance of sex influences on brain and behavior are the sex-specific prevalence rates of stress-related disorders. For example, men are more susceptible to substance abuse and hypertension, whereas women have higher rates of depression disorders, autoimmune diseases, and chronic pain (see for reviews, Kajantie & Phillips, 2006; Wang et al., 2007). Notably, some of these sex differences are only present during women's reproductive years, indicating that the observed sex-specific disease pattern may be partly due to effects of ovarian hormone fluctuations (Deecher et al., 2008). For example, unipolar depression is approximately twice as prevalent in females relative to males. This sex difference emerges in early adolescence, when girls start menstruating, and disappears after the menopausal transition (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993).

The annotation "stress-related" refers to the notion that chronic exposure to stress constitutes an important factor in the development of stress-related disorders. For example, stressful life events, such as unemployment or the loss of a partner, have been causally related to the onset of major depression (Kendler, Karkowski, & Prescott, 1999). A "stressor" can be described as any potential or actual disturbance of an individual's environment. Individuals differ in the way they respond to stressors. Therefore, "stress" is defined as the subjective state of sensing potentially adverse

changes in the environment. When a stressor is perceived as stressful, it causes the activation of various physiological pathways including the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), which constitute the physiological stress response (Joëls & Baram, 2009; Kajantie & Phillips, 2006). This stress response facilitates behavioral adjustments to threatening events, and is supported by adaptations of neural functioning at various levels of the central nervous system (Joëls & Baram, 2009). Importantly, the functioning of both the HPA axis and the ANS have been linked to the development of various disorders, such as coronary heart disease and depression (see for review, Kajantie & Phillips, 2006). In addition, individual differences in the physiological stress response have been related to differing health risks. Accordingly, the sex-specific prevalence rates of stress-related disorders might be related to sex-specific stress responsiveness (Kajantie & Phillips, 2006).

Both the HPA axis and the ANS show sex differences in stress responsiveness and gonadal hormones appear to modulate these responses to stress (see for reviews, Kajantie & Phillips, 2006; Kudielka, Hellhammer, & Wüst, 2009). During their reproductive years, women show lower HPA axis and ANS responsiveness to stress relative to men of the same age. Importantly, women in the luteal phase of their menstrual cycle show salivary cortisol responses which are similar to those of men, whereas women in the follicular phase show smaller cortisol responses. After menopause, both HPA axis and ANS axis responsiveness increase (Kajantie & Phillips, 2006; Otte et al., 2005). These sex differences have been linked to the need for protection of the developing foetus in the womb, from excessive exposure to stress hormones (Kajantie & Phillips, 2006). A challenging question is whether in the long run, as a consequence of *chronic* stress exposure, these sex differences in physiological stress responsiveness may lead to different vulnerabilities to the pathogenesis of certain stress-related disorders.

Focus on neural processing of reward prospect and action outcomes: Modulations by acute stress, biological sex and/or menstrual cycle phase?

Healthy people are able to adapt their behavior on the basis of expectations about future results and feedback on previous actions. Accordingly, external cues predicting the possibility of rewards – during the stage of reward anticipation –, and

positive or negative outcomes following certain choices – during the stage of feedback – have a strong influence on subsequent behaviors. Increasing evidence suggests that certain stress-related disorders, such as substance abuse, depression, and obsessive compulsive disorder, are related to disrupted neural processing during the stages of reward anticipation and/or feedback (Charney & Nestler, 2009; Russo & Nestler, 2013). As a consequence, in these people, the influence of reward cues and action outcomes seems disturbed, resulting in less efficient behavior. For example, addicted people suffer from increased craving for certain substances and a loss of control over intake, depressed individuals no longer experience pleasure from rewards, whereas persons with obsessive compulsive disorder derive reward from maladaptive habitual behaviors (Charney & Nestler, 2009). Given the putative role of reward-prospect- and feedback-related neural processing in the pathogenesis of certain stress-related disorders, we chose to focus on these mechanisms, in order to gain a better understanding of the sex-specific pathways to stress-related disorders.

In light of the evidence for disturbed neural processing during reward anticipation and/or outcome evaluation and sex differences in physiological stress responsiveness, an important question is whether the sex-specific prevalence rates in stress-related disorders might be related to sex-specific disturbances of reward-prospect- and/or feedback-related processing under stress. Indeed, brain regions concerned with reward-prospect- and feedback-related processing have been shown to be affected by stress exposure (Dedovic et al., 2009; Starcke & Brand, 2012), supporting the notion that stress may affect brain activity during reward anticipation and outcome evaluation. Furthermore, exposure to acute stress has been shown to influence behaviors associated with these stages. For example, stress exposure stimulates the consumption of alcohol (Koob, 2008; Uhart & Wand, 2009) and food (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009). In addition, stress exposure has been reported to impair learning from feedback (Bogdan & Pizzagalli, 2006; Petzold, Plessow, Goschke, & Kirschbaum, 2010). More specifically, a few studies have reported sex-specific effects of acute stress on decision-making behavior, with stress-related increases in risk taking in women as opposed to decreases in risk taking in men (Lighthall, Mather, & Gorlick, 2009; Van den Bos, Harteveld, & Stoop, 2009). It is unclear, however, how these differential stress effects on decision making might be related to differential stress effects on feedback processing.

Moreover, sex differences in acute stress effects during reward anticipation and/or outcome evaluation may be dependent on the female menstrual cycle. For

example, the luteal phase has been associated with increased stress-related cardiovascular reactivity and cortisol levels relative to the follicular phase (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Lustyk, Olson, Gerrish, Holder, & Widman, 2010; Lustyk, Douglas, Shilling, & Woods, 2012; Tersman, Collins, & Eneroth, 1991). Furthermore, the follicular phase has been associated with intensified subjective responses to stimulant drugs relative to the luteal phase (Terner & De Wit, 2006). In contrast, the *late* luteal has been related to a higher appreciation of alcohol compared to the *mid*follicular phase (Evans & Levin, 2011). Note that many studies employ broad definitions of the menstrual phases under investigation. Given the high variability in hormone levels across the menstrual cycle, this is undesirable.

In sum, a better understanding of the *neural* underpinnings of stress effects on reward-prospect- and feedback-related *behaviors* in men and women is crucial to understanding sex differences in health and disease. Therefore, the aim of the present thesis was to investigate 1) the effects of acute stress on brain activity during reward anticipation and feedback stages, 2) whether effects on feedback-related processing differed between men and women, and 3) whether effects on reward-prospect- and feedback-related processing were modulated by menstrual cycle phase. Given the current lack of knowledge about these phenomena in the healthy population, and given our goal to investigate possible pathways to stress-related disorders, we decided to investigate these effects in healthy participants. In addition, although stress-related disorders are generally caused by *chronic* exposure to stress (Kendler, Karkowski, & Prescott, 1999) and the impact of *acute* relative to *chronic* stress may differ in both quality and intensity (Pizzagalli, 2014), we chose to examine the effects of *acute* stress, because acute stress is omnipresent in everyday life for both healthy and diseased individuals and can be manipulated in a laboratory setting.

Methods to study effects of acute stress on the neural processing of reward prospect and action outcomes

Stress induction procedures

In order to examine effects of acute stress, we used two different stressors: white noise and aversive movie fragments. In the first two experiments documented in chapters 2 and 3, we used loud white noise as a stressor. Since the Industrial

Revolution, characterized by the transition from hand production methods to the use of machinery, exposure to noise has become an important stressor in everyday life. Noise is pervasive in urban settings, ranging from low-intensity office noise to high-intensity aircraft noise, and is potentially detrimental to both auditory and non-auditory health (see for review, Basner et al., 2014). For example, noise exposure has been related to annoyance, cardiovascular disease, sleep disturbance and decreased cognitive performance in children (Basner et al., 2014).

Stress is thought to play a major role in the underlying mechanisms relating noise exposure to health problems. Acute noise exposure has been shown to activate the HPA axis and the sympathetic nervous system, leading to increases of stress hormones including epinephrine, norepinephrine and cortisol (Babisch, 2003). Moreover, acute noise exposure has been reported to affect performance on tasks relying on higher-order cognitive functions (Arnsten & Goldman-Rakic, 1998; Szalma & Hancock, 2011).

The employment of a noise stressor had two advantages relative to other stressor types, such as performing in front of a jury. First, a noise stressor is easily applicable in the laboratory. One only needs a noise generator or compact disk player and two loudspeakers. Second, we wanted to use a stressor which would be equally stressful to women and men, in order to investigate the influence of equal stress levels on behavior and brain activity in both sexes. There is evidence that sex differences depend on the nature of the stressor. Stroud, Salovey and Epel (2002), for example, investigated sex differences in HPA axis responses to achievement and social rejection stressors in young females (not using hormonal contraceptives) and males (all subjects between 17 and 23 years), neglecting possible modulations by menstrual cycle phase. Whereas women showed larger cortisol responses to the social rejection challenges, men showed larger cortisol responses to the achievement challenges. The authors link their findings to literature on sex differences in personality, stating that women generally have a stronger interpersonal orientation, whereas men have a stronger instrumental orientation (see for review, Stroud et al., 2002). As far as we know, there is no literature on sex-specific effects of acute noise stressors. Exposure to an acute noise stressor, which is neither an achievement nor a social rejection stressor but a physical stressor, may pose a similar threat to the well-being of both females and males leading to similar stress levels.

The magnitude of sound is commonly measured in decibels (dB). The dB scale represents a logarithmic scale to measure sound pressure level, which reflects the effective pressure of a sound relative to a fixed reference value (i.e., the human

hearing threshold for a sound with a frequency of 1000 Hz). As an illustration, a doubling of sound energy (e.g., two fighter jets instead of one) is equivalent to an increase in sound pressure level by 3 dB, while a ten-fold increase in sound energy is equivalent to an increase in sound pressure level by 10 dB (Basner et al., 2014). Importantly, the human ear is not equally sensitive to stimuli of different frequencies. The apparent subjective loudness of low-frequency sounds is smaller than that of high-frequency sounds (Fletcher & Munson, 1933). Modern instruments for measuring sound levels take into account both the measured sound pressure level in dB and the frequency of the sound, resulting in A-weighted decibel levels, denoted as dB(A). This unit is most commonly used in the noise stress literature and is also used in this thesis.

In the first experiment, we exposed participants to either a predictable or unpredictable noise stressor, during task performance in the stress condition. The predictable noise stressor consisted of continuous white noise (85 dB(A)), while the unpredictable noise stressor consisted of discontinuous white noise (75 to 95 dB(A)), containing both noise and silence intervals. In the second experiment, we only applied the unpredictable noise stressor. In both studies, the stress condition lasted approximately 25 minutes. In both experiments, the employed sound levels were harmless, in the sense that no overstimulation was expected. For comparison, the threshold of pain lies around 120 dB(A); sounds above this level can cause acute mechanical damage to the ear. In addition, household devices produce sounds around 60 dB(A), traffic causes noise around 80 dB(A), while rock concerts can show sound levels of 120 dB(A) or even higher. Furthermore, exposure limits of occupational organizations are set at approximately 80 to 90 dB(A) for a duration of 8 hours (Basner et al., 2014).

In the third experiment, we used highly aversive movie clips containing scenes with extreme violence, along with a self-referencing instruction (i.e., participants were prompted to watch the fragments attentively, imagining being an eyewitness), as a stressor. We chose to use this stressor instead of the noise stressor we used in the previous studies, as this study included only women, who have been reported to be especially sensitive to interpersonal stress (Stroud et al., 2002). The clips were taken from a commercially available movie [Irréversible (2002), Gaspar Noé] and have been successfully used in previous studies to elicit physiological and psychological stress responses (Henckens, Hermans, Pu, Joëls, & Fernández, 2009; Ossewaarde et al., 2010; Qin, Hermans, Van Marle, Luo, & Fernández, 2009; Van Marle, Hermans, Qin, & Fernández, 2009). To validate the stress induction procedure using the movie clips, we measured heart rate, heart rate variability, and subjective emotions, during

watching of these movie clips; and we measured salivary cortisol and subjective negative affect, prior to and after the task blocks. Both subjective and physiological stress measures confirmed that the procedure yielded mild to moderate stress responses in the participants.

Brain activity measures

For the purpose of investigating effects on brain activity during reward anticipation and feedback stages, we used electroencephalography (EEG). EEG is the recording of electrical activity of the brain through electrodes attached to the scalp. EEG measures voltage fluctuations at the scalp, resulting from the synchronous activity of large assemblies of parallel-oriented neurons, producing extracellular field potentials. These potentials can only be recorded from the scalp if they are strong enough and have the right orientation (radially oriented with respect to the scalp). Therefore, EEG mostly reflects activity in cortical areas. An important advantage of EEG is the high temporal resolution, that is, fluctuations in potentials can be measured at the millisecond scale.

The EEG signal is the summation of three categories of brain activity (Tallon-Baudry & Bertrand, 1999). Firstly, *background* activity is activity that is always present, but is not related to experimental stimuli. Secondly, *evoked* activity is activity that is elicited by experimental stimuli, and is strictly phase-locked to stimulus onset. Thirdly, *induced* activity is activity that is elicited by experimental stimuli, but is not phase-locked to stimulus onset.

For many years, EEG studies have concentrated on evoked activity. Because an evoked response appears at the same latency and phase in each trial, it can be detected by averaging multiple single-trial responses relative to stimulus onset. The resulting averaged signal is called an event-related potential (ERP). An ERP waveform consists of a series of positive and negative voltage deflections. These observable peaks are traditionally related to specific stages of information processing or specific functions. However, they reflect the summation of several underlying or latent components, which add up to a specific waveform. Thus, visual deflections and latent components are not equivalent. Although we would like to measure the latent components directly, we can only draw assumptions about them from the observed ERP waveforms (Luck, 2014).

In this thesis, we applied different measures of the feedback-related negativity (FRN). The FRN is a negative ERP component which is evoked by external feedback

and is larger in amplitude following negative relative to positive outcomes (e.g., Gehring & Willoughby, 2002). The measurement of this – like any – component is complex, given the possible overlap between the FRN and surrounding components, which presumably reflect partly different, latent neural processes. The literature on the FRN shows different ways to measure the FRN, which deal or not deal with this problem. In this thesis, FRN amplitude was measured in three ways, either neglecting or correcting for overlap with surrounding components, enabling the comparison of different measurement methods.

In addition to ERP analysis, recent years have witnessed the emergence of oscillatory analysis in EEG studies. Stimulus-related oscillatory activity includes both evoked (i.e., phase-locked to stimulus onset) and induced (i.e., non-phase-locked) activity. Large-scale brain networks underlying cognition have been proposed to interact through synchronized, neuronal oscillations (Fries, 2005; Siegel, Donner, Engel, 2012; Varela, Lachaux, Rodriguez, Martinerie, 2001). These rhythmic fluctuations of neuronal assemblies are reflected in the EEG. Accordingly, it has been proposed that the analysis of the spatiotemporal oscillatory dynamics of the EEG yields results that are more directly related to the underlying neurophysiological phenomena, compared to the analysis of ERP components (Cohen, Wilmes, Van de Vijver, 2011). A method which is commonly used to analyze stimulus-related oscillatory dynamics of the EEG, is time-frequency analysis. One can use this method to determine which frequencies show the largest changes in power at specific points in time and location, and how their phase angles synchronize across time and location (Roach & Mathalon, 2008). In chapters 3 and 4, we used time-frequency analysis to examine stimulus-related changes in oscillatory power.

Outline of the thesis

Aim of this thesis was to gain more insight into the effects of acute stress on neural mechanisms underlying reward anticipation and outcome evaluation. Of special interest were possible modulations of acute stress effects on feedback-related processing by biological sex. Furthermore, we examined whether acute stress effects on reward-prospect- and feedback-related processing in women are influenced by gonadal hormone levels.

Table 1 gives an overview of the experiments in this thesis. Purpose of the ERP study described in chapter 2 (study 1) was to examine the impact of exposure to an

acute noise stressor on feedback processing, and whether this effect depended on stressor predictability. Male participants performed a gambling task, in both control and stress conditions, the latter with either predictable or unpredictable noise. On every trial, they received feedback indicating whether their choice had resulted in a monetary gain (positive feedback) or loss (negative feedback). Feedback processing was operationalized by the FRN, which was measured in three ways, either neglecting or correcting for overlap with surrounding components. The results demonstrated that acute noise stress impairs feedback processing. Stressor predictability did not modulate this effect significantly. Importantly, FRN results differed between FRN measures, highlighting the influence of ERP-component measuring methods on results found.

Given the stress-related impairment of feedback processing in men as described in chapter 2, the EEG study documented in chapter 3 (study 2) aimed at investigating sex influences on acute stress effects on feedback processing. In this second study, we employed the same gambling task as in the first study along with the unpredictable noise stressor, including both sexes. In order to minimize the influence of hormonal fluctuations across the menstrual cycle on feedback processing (Ossewaarde et al., 2011b) and stress responsiveness (Kirschbaum et al., 1999; Kudielka et al., 2009; Ossewaarde et al., 2010), females participated during the midluteal phase of their menstrual cycle. We analyzed brain activity using both ERP and time-frequency analyses. The results showed that acute noise stress impairs performance monitoring in both sexes, as reflected in FRN amplitudes and feedback-related theta power. In addition, we found a sex difference in feedback-related beta-band power which was limited to the stress condition. This finding suggests that sex-specific stress effects on neural feedback processing may constitute a factor underlying sex-specific stress responses.

Objective of the EEG study documented in chapter 4 (study 3) was to examine the combined effects of menstrual cycle phase and acute stress on brain activity during reward anticipation and outcome evaluation. Female participants were tested once during both late follicular and late luteal phases, performing in both control and stress conditions. Stress was induced by showing participants highly aversive movie fragments in combination with a self-referencing instruction. This procedure was validated by measurements of heart rate, heart rate variability and subjective emotions, during the movie clips, and measurements of salivary cortisol and subjective negative affect, prior to and after the task blocks. Participants performed a monetary incentive delay task, enabling the investigation of both reward anticipation and feedback stages.

Brain activity was analyzed using both ERP and time-frequency measures. The results demonstrated independent as well as interaction effects of menstrual phase and stress induction on reward-prospect- and feedback-related brain activity. Phase modulated the sensitivity to the valence of feedback, with a stronger signaling of negative performance outcomes in the late follicular relative to the late luteal phase. In contrast, in the control condition, the late luteal versus late follicular phase was associated with a heightened sensitivity to reward condition, with enhanced performance monitoring following feedback in potential-reward versus no-reward trials. Stress affected attentional preparation during reward anticipation, but enhanced the influence of reward condition on the processing of positive performance outcomes. In contrast with our expectations, we found no evidence for an increased sensitivity to stress during the late luteal compared to the late follicular phase.

In chapter 5, the different findings of the current work are integrated. In addition, some critical considerations are presented along with possible directions for future research.

Table 1

Overview of studies in this thesis.

Experiment (Chapter)	Sex	Menstrual cycle phase	Stressor	Task	Reward anticipation following cue	Behavior	Outcome evaluation
1 (2)	Male	n.a.	Acute noise stressor (predictable or unpredictable)	Gambling task	n.a.	Choice	- Monetary gain - Monetary loss
2 (3)	- Male - Female	- n.a. - Midluteal	Unpredictable acute noise stressor	Gambling task	n.a.	Choice	- Monetary gain - Monetary loss
3 (4)	Female	- Late follicular - Late luteal	Highly aversive movie clips with a self-referencing instruction	Monetary Incentive Delay task	- Potentially rewarding trials - Nonrewarding trials	Target detection	- Hit, rewarded - Hit, nonrewarded - Miss, nonrewarded

CHAPTER 2

Acute noise stress impairs feedback processing

Abstract

We examined the impact of acute noise stress on the feedback-related negativity (FRN) and whether this effect depended on stressor predictability. Participants performed a gambling task in a silence and a noise condition with either predictable or unpredictable noise. FRN amplitude was measured in three ways, either neglecting (mean amplitude) or correcting for overlap with other components (base-to-peak; mean amplitude minus average mean amplitude of surrounding peaks). Notably, results differed between measures. Valence and magnitude both affected the FRN. These effects were additive on the mean amplitude and base-to-peak measures, but interactive on the mean amplitude corrected for both peaks measure. Acute noise stress specifically modulated valence and magnitude effects on the FRN, although evidence differed between measures as to whether valence and/or magnitude were processed differently. These findings indicate that acute stress impairs cognitive control by the anterior cingulate cortex. Stressor predictability added little to the explanation of effects.

Introduction

Effects of stress exposure on cognitive control

Exposure to acute stress modulates neural functioning at various levels of the central nervous system (Joëls & Baram, 2009). In general, the brain seems to switch from thoughtful, regulated behavior to reflexive behavior, in stressful situations (Arnsten, 2009; Arnsten & Goldman-Rakic, 1998). Consequently, stress generally improves performance on well-rehearsed and simple tasks, which rely mainly on lower level automatic processing, while stress impairs performance on novel and complex tasks, which require top-down control (Arnsten & Goldman-Rakic, 1998).

Adequate control of behavior requires the continuous evaluation of action outcomes with regard to internal goals. Humans use feedback information from their internal and external environment to evaluate and adjust ongoing behavior. Studies using electroencephalographic (EEG) recordings from human participants have identified an event-related brain potential (ERP) component that is elicited in response to external feedback: the feedback-related negativity (FRN). The FRN is a negative ERP component with a fronto-central scalp distribution, that peaks between 250 and 300 ms after feedback delivery. It is larger in amplitude in response to negative outcomes, such as monetary losses, than in response to positive outcomes, such as monetary gains (e.g., Gehring & Willoughby, 2002; Miltner, Braun, & Coles, 1997). The neural generator of the FRN has been located in the dorsal anterior cingulate cortex (ACC; Ridderinkhof et al., 2004), a brain structure which plays a critical role in cognitive control (Botvinick et al., 2001).

An important question in the present study is whether acute stress exposure affects ACC activation during feedback processing, as reflected in the FRN. Empirical studies have repeatedly emphasized the link between stress-related disorders and abnormal feedback processing. Depressive illness, for example, is associated with a blunted behavioral and neural response to feedback information (Steele et al., 2007). Nevertheless, up till now, little is known about the effects of acute stress exposure on the FRN.

We used loud white noise as a stressor. Noise is a common stressor in everyday life, which has been shown to activate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to increases of stress hormones including

epinephrine, norepinephrine and cortisol (Babisch, 2003). Moreover, acute noise exposure impairs higher-order cognitive functioning (Arnsten & Goldman-Rakic, 1998).

Two important psychological determinants of the stressfulness of a situation are lack of control and unpredictability (Lupien et al., 2007). Breier et al. (1987) exposed participants to loud, pure, discontinuous – and thus unpredictable – noise under both controllable and uncontrollable conditions. They found enhanced stress responses after the uncontrollable relative to the controllable stress condition, reflected in higher self-ratings of feeling stressed and higher levels of stress hormones after uncontrollable stress. The role of unpredictability in determining the stressfulness of noise exposure is less clear. In the present study, our second aim was to investigate this role, by manipulating the predictability of the noise stressor. Participants were exposed to either continuous or discontinuous white noise. In both conditions, participants had no control over the noise they were exposed to. However, as discontinuous noise is less predictable than continuous noise, we hypothesized that the impact of noise exposure on feedback processing would be more salient in the discontinuous noise condition.

Interpretation of the FRN

According to the reinforcement learning (RL) theory of the FRN, its amplitude reflects the impact of midbrain dopamine signals on the ACC (Holroyd & Coles, 2002; Holroyd et al., 2004; Nieuwenhuis et al., 2004). Events that are worse than expected (leading to phasic decreases in dopamine activity) are associated with large FRNs, whereas events that are better than expected (leading to phasic increases in dopamine activity) result in small FRNs. Moreover, the RL theory claims that the amplitude of the FRN is sensitive to the size of the reward prediction error, that is the difference between the actual and expected outcome of a certain action.

Two prominent aspects of feedback are valence and magnitude. Feedback valence indicates whether the outcome of an action is positive or negative, whereas feedback magnitude reflects the degree of positivity or negativity. Previous research has yielded inconclusive results as to which aspects of feedback are reflected in the FRN. Some studies have reported a valence effect in the absence of a magnitude effect (Hajcak et al., 2006; Holroyd et al., 2006; Sato et al., 2005; Yeung & Sanfey, 2004), whereas other studies have reported main effects of both valence and magnitude (Goyer et al., 2008; Wu & Zhou, 2009) or a main effect of trial type combining valence and magnitude, with an effect of magnitude on gain trials only (Marco-

Pallarés et al., 2008). The abovementioned studies used different experimental tasks, which may partly explain the variation in results. For example, information about the magnitude of the outcome in the upcoming trial was given beforehand, or not; feedback was clearly depicted during feedback presentation, or not; alternative outcomes were shown, or not.

The third aim of our study was to examine once more the combined effects of feedback valence and magnitude on the FRN. Participants performed a simplified version of the gambling task devised by Gehring and Willoughby (2002). They chose between two white cards, without being given information about the magnitude of the outcome in the upcoming trial. After every choice, they received feedback indicating both the valence and magnitude of the outcome of their choice. Feedback was clearly depicted in numbers, while valence was emphasized by card color; no alternative outcomes were shown. Thus, participants received all feedback information clearly presented at one point in time, during feedback presentation. As a result, reactions to feedback valence and magnitude were not confounded with prior knowledge of magnitudes, nor with concerns about alternative outcomes. During task performance, we recorded brain activity. Moreover, we measured reaction times and choices, in order to examine whether the valence and magnitude of previous outcomes influenced current choice behavior.

From the perspective of the RL theory of the FRN, the size of the reward prediction error determines the amplitude of the FRN. Although we did not manipulate reward expectation explicitly, one could claim that the expected value in our trials was zero, as all four possible outcomes had equal weights. Consequently, one would expect a larger FRN for 1) losses relative to gains, as losses are worse and gains are better than expected; 2) small relative to large gains, as a large gain is better than a small gain; 3) large relative to small losses, as a large loss is worse than a small loss. With regard to the impact of acute noise stress, we expected that the effects of feedback valence and magnitude on the FRN would be smaller in the noise relative to the silence condition. In addition, we expected that the discontinuous noise type would be more deleterious than the continuous noise type.

Measurement of the FRN

The measurement of the FRN is complex due to possible overlap between the FRN and other ERP components, most notably the P300. Although one would like to isolate the latent neural process(es) causing the FRN from other processes, it is

impossible to determine precisely which latent neural processes add up to any specific ERP waveform (Luck, 2005). In the literature, different ways to measure the FRN are reported. Several studies determine the FRN as the mean amplitude value in a pre-defined time window (e.g., 200-300 ms) following feedback onset, and thus do not correct for possible overlap (e.g., Luque et al., 2012; Wu et al., 2011). Another common practice is to calculate the loss-minus-gain difference per condition and use either the mean amplitude value or the peak value in a pre-specified time window of the difference wave (e.g., Van der Helden et al., 2010; Ma et al., 2011). The latter method implies a partial correction for overlap. However, a disadvantage of this method is that the resulting difference wave includes neural activity on both gain and loss trials, precluding separate examinations of gain- and loss-related activity. A third way of measuring the FRN is base-to-peak, defining the FRN as the voltage difference between the lowest point in a time window and either the preceding peak or the average of both the preceding and following peaks (e.g., Holroyd et al., 2003; Yeung & Sanfey, 2004). This method corrects for overlap with the preceding or both preceding and following peaks, but has two disadvantages. First, underlying neural processes in the FRN window are confounded with processes in the other time windows, anyhow. However, by correcting for the latter, both uncommon processes (i.e., unrelated to the FRN) and common processes (i.e., related to the FRN) are eliminated, which is adequate or inadequate, respectively. More specific, processes causing the FRN might already start in the time window of the preceding peak. By correcting for this peak, common variance is eliminated resulting in an underestimation of the FRN. Second, the base-to-peak approach is biased against detection of positive shifts in the ERP within the FRN window, as it determines the lowest point in this window. Positive feedback might elicit a positive ERP response, which might be underestimated, using this approach.

In the present study, we chose to measure the FRN in three different ways, in order to directly compare findings among these measures. From the abovementioned methods, we used the first and third method: measuring the FRN as a mean amplitude value, and measuring the FRN via the regular base-to-peak approach, correcting for the preceding peak only. In addition, we measured the FRN as a mean amplitude value corrected for the average of the mean amplitude values of the preceding and following peaks. We added this measure for two reasons. First, the use of mean amplitude measures is preferable over peak amplitude measures, because the former are less sensitive to noise in the data compared to the latter (see Luck, 2005). Second, overlap may exist from activity in both the preceding and following time windows. If one

wants to correct for overlap, it seems logic to correct for both peaks.

In sum, the aim of the present study was threefold. First, we examined whether acute noise stress modulates the cognitive control functioning of the ACC, as reflected in the FRN. Second, we investigated whether this effect depends on the predictability of the noise stressor. Third, we replicated research on the combined effects of feedback valence and magnitude on the FRN. To address these aims, we recorded ERPs from participants as they performed a simple gambling task in a silence condition and in a noise condition with either predictable or unpredictable noise. The FRN was measured in three different ways. Findings were compared among these three measures.

Methods

Participants

Thirty-two healthy, male undergraduates from the University of Groningen (mean age = 21.7 years, range 18–28 years) participated in the experiment. Candidates were included after a telephone screening if they reported: no evidence of current or past psychiatric disorders, neurological disorders, or head injuries; absence of CNS-active medication; absence of smoking; right-handedness; normal or corrected-to-normal vision; and normal hearing. Participants received student credits for their participation. In addition, they received a small monetary bonus depending on the outcomes of the gambling task, as described below. All participants gave written informed consent. The experimental protocol was approved by the Ethical Committee Psychology of the Psychology Department of the University of Groningen.

Procedure

Participants were instructed to abstain from alcohol and from caffeine-containing substances 12 h before the experiment. They arrived at the laboratory at 9.00 a.m. Participants were seated in front of a computer screen, in a dimly lit, sound-attenuated, electrically shielded cabin. A serial response box was placed under their hands. They completed a gambling task in two conditions, a noise condition and a silence condition. The order of conditions was counterbalanced across subjects. There was one practice block of 1-minute duration (excluding instructions) before the experimental trials. In each condition, the gambling task consisted of 5 trial blocks of

5-minute duration. Both conditions were separated by a 15-minute break in which subjects remained seated in the cabin. Participants were informed about the order of conditions, number of blocks per condition, and break between conditions, before the practice block.

Task

Each trial (see Fig. 1) started with the presentation of a fixation cross, which remained on the screen during the whole trial. After 500 ms, two white cards appeared on either side of the fixation cross. These cards remained on the screen until the participant selected one of them by pressing a button with either her/his left or right index finger, corresponding to the location of the chosen card. After the response, the chosen card was highlighted with a thick yellow border, for a randomly varying interval of 800–1200 ms. Then, the card turned into one of two colors, either cyan or magenta, emphasizing the valence of the outcome (gain or loss). At the same time, a number (5 or 25, either positive or negative; representing euro cents) appeared on the selected card, indicating how much money was won or lost at the trial. The assignment of the two colors to gain or loss was counterbalanced across participants. This feedback display remained present for 1000 ms, after which the next trial started. At the end of each block, participants received additional feedback indicating the amount of money earned during the previous block.
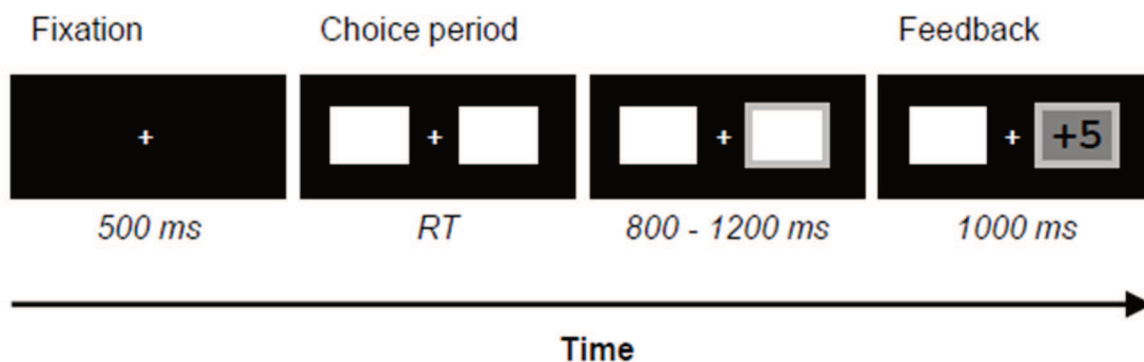

Figure 1. Sequence of events during a single trial of the gambling task. Each trial started with the presentation of two cards, one of which the participant selected with a left- or right-hand button-press. After a variable interval, feedback was presented, indicating the amount of money won or lost.

All stimuli were presented against a black background on a computer screen, placed at a distance of ~1 m from the participant. The fixation cross was presented in a white 22-point bold Courier New font. The two cards on either side of the fixation cross were white rectangles each covering 9.6 cm x 7.1 cm. The distance between the fixation cross and the centers of the rectangles was 5.9 cm. The yellow border that was displayed around the chosen card had a border width of 0.2 cm. The numbers in the feedback display were presented in a black 64-point bold Courier New font.

The outcome of each trial was determined randomly by the computer program, with equal weights for of all four possible outcomes and with replacement. The participants were not informed about this. Before the practice block, they were instructed about the meaning of the colors and the numbers in the feedback display. They were informed that they started the experiment with €5, and that the value of each chosen outcome would be added or subtracted. In addition, they were told that they would receive feedback indicating the amount of money earned during the previous block, after each block. Furthermore, they were told that their end score would be added to or subtracted from the €5 starting money, at the end of the task, and that they would keep the resulting amount of money. Finally, participants were instructed that their goal was to earn as much money as possible, and that they were free in choosing their strategies. To increase the motivational properties of the monetary incentives, our cash box was kept on the table at which the participant was seated. During the break between two conditions, participants were informed about their total score in the first condition. In addition, it was repeated that they were free in choosing their strategies. After completion of the task, most participants reported that they had attempted to find a systematic pattern or patterns in the feedback sequences.

Participants performed equal numbers of trials in the silence condition and the noise condition. They earned as much money in the silence condition as in the noise condition. Participants reached an average end score of 52 euro cents ($SD = 701$), that was added to the €5 starting money and paid to them, at the end of the experimental session. Participants with an end score of minus €5 or less received no bonus money.

Noise stressor

During the noise condition, participants were exposed to either continuous or discontinuous white noise. The continuous white noise type (85 dB(A), 0–10 kHz) was generated by a digital noise generator. The discontinuous white noise type (75–95

dB(A), 0–10 kHz) was played from a compact disc, produced at our department.[1] This noise type consisted of both noise intervals and inter-noise (silence) intervals. The duration of each noise interval varied from 2 to 7 seconds, during which the intensity of noise varied between 75 and 95 dB(A). The duration of inter-noise intervals also varied from 2 to 7 seconds. Half of the noise intervals were followed by an inter-noise interval, whereas the other half were followed by another noise interval. An inter-noise interval was never followed by another inter-noise interval. The duration and intensity of noise intervals and the duration of inter-noise intervals were randomly determined. Both noise types were delivered by two loudspeakers in stereo mode placed on either side of the computer screen.

Electrophysiological recordings and data reduction

EEG was measured using 28 Sn electrodes attached to an electrocap (ElectroCap International Inc., Eaton, Ohio, USA), positioned according to the 10-10 system. Recordings were taken from channels FP1, FP2, AFz, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, PO7, O1, Oz, O2 and PO8. They were referenced to the computed average of both mastoids. Horizontal electro-oculogram (EOG) was recorded bipolarly using two electrodes placed at the outer canthi of both eyes. Vertical EOG was measured using two electrodes placed above and below the left eye. All electrode impedances were kept below 5 kΩ. EEG and EOG signals were amplified with a 1 second time constant (0.16 Hz high-pass) and a 200 Hz low-pass filter, and sampled at 2000 Hz.

EEG and EOG data were off-line filtered, using a 30 Hz low-pass filter with a slope of 48 dB/oct., and down-sampled to 256 Hz. Data were segmented in 1000-ms epochs, starting 100 ms before feedback onset. Epochs with too high activity (maximal allowed voltage step ±60 μV) were rejected. After removal of these artifacts, EEG was corrected for eye movements and blinks using the regression procedure of Gratton et al. (1983). Then, epochs which contained EEG voltage differences exceeding 200 μV, or EEG amplitudes exceeding +/- 100 μV, were eliminated. After these ocular correction and artifact rejection procedures, EEG was averaged relative to a 100 ms

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[1] In a pilot experiment, we examined the subjective effects of exposure to the discontinuous white noise. Immediately before and after task performance, participants filled in the shortened Dutch version of the Profile of Mood States (Wald & Mellenbergh, 1990). Participants in the noise group (*n* = 17) compared to those in the silence group (*n* = 19) showed a significantly larger decrease in vigour. In addition, they reported an increase in tension, while the silence group reported a decrease in tension. These results confirm that exposure to (discontinuous) noise elicits stress in participants.

pre-feedback baseline. Separate averages were calculated for each combination of valence (gain vs. loss), magnitude (large vs. small), and noise (silence vs. noise), resulting in eight average waveforms for each electrode and participant.

Data analysis

Behavioral measures

To investigate the influence of previous outcomes on the behavior on current trials, mean reaction times and stay/switch percentages were computed as a function of the outcome on the previous trial (+/- 5/25 euro cents). On stay trials, participants selected the card on the same side as on the previous trial, whereas on switch trials, they chose the card on the other side. Behavioral data were analyzed using repeated measures analysis of variance (ANOVA) with the within-subjects factors valence (gain vs. loss), magnitude (large vs. small), and noise (silence vs. noise), and the between-subjects factors noise type (continuous vs. discontinuous) and condition order (silence–noise vs. noise–silence). Moreover, we examined whether choice behavior differed between the first and second half of the experiment. Therefore, we computed mean reaction times and stay percentages for both halves of the experiment, as a function of valence and magnitude. Then, we performed repeated measures analyses on mean reaction times and stay percentages, respectively, with the within-subjects factors time on task (first half vs. second half), valence and magnitude, and the between-subjects factors noise type and condition order. Note that in these analyses, time on task is confounded with noise, but that condition order reveals which half of the experiment is performed in the silence condition and which half is performed in the noise condition.

ERPs

As discussed in the introduction, the FRN was measured in three different ways. First, we quantified the FRN as the mean amplitude in the 230–300 ms post-feedback interval. Second, we measured the FRN as the difference in voltage between the 230–300 ms mean amplitude and the average of the mean amplitudes of the preceding (180–225 ms window) and following (320–390 ms window) peaks. Third, we measured the FRN base-to-peak. Firstly, we identified the most positive value within the 150–230 ms post-feedback window. Then, we identified the most negative value within a window extending from this maximum to 330 ms post-feedback. The base-to-peak FRN was defined as the difference between these most positive and most

negative values. FRN data were extracted from FCz, where the effect of valence was found to be maximal. Latency windows of the FRN and its preceding and following peaks were based on visual inspection of the grand average ERP waveforms.

The three FRN measures were each subjected to repeated measures ANOVAs with the within-subjects factors valence (gain vs. loss), magnitude (large vs. small), and noise (silence vs. noise), and the between-subjects factor noise type (continuous vs. discontinuous). Whenever necessary, additional analyses were conducted to elucidate significant interactions. Adjustment for multiple comparisons was applied using the Bonferroni method.

Finally, to gain more insight into the possible role of overlapping components, we performed repeated measures ANOVAs on the peaks preceding and following the FRN, at FCz. The P200 was measured as the mean amplitude value in the 180–225 ms post-feedback window. The P300 was measured as the mean amplitude value in the 320–390 ms post-feedback window.

Results

Behavioral results

On every trial, participants could win or lose either 5 or 25 euro cents. Unbeknownst to the participants, there was no strategy they could learn to maximize their gains or minimize losses. Feedback was presented in a random order and thus not related to the choices they made. However, their behavior indicated that they were sensitive to the outcomes of their choices. Table 1 shows mean reaction times and mean stay percentages as a function of condition order, time on task, valence and magnitude. Participants showed longer reaction times if the magnitude of the outcome on the previous trial was large than if the magnitude was small ($F(1, 28) = 13.22$, $p = .001$). This magnitude effect appeared to be more salient after gain trials than after loss trials, but the magnitude by valence interaction failed to reach significance ($F(1, 28) = 3.78$, $p = .062$).

Following gains as well as losses, participants stayed with the same option on the majority of trials (gains: $M = 66\%$, $SD = 21$; losses: $M = 55\%$, $SD = 15$). In general, participants were more likely to select the card on the same side as they chose on the previous trial, if they had just won money than if they had just lost money (valence: $F(1, 28) = 7.12$, $p = .012$), and if they started in the silence condition relative

Table 1

Mean reaction times (ms) and mean stay percentages as a function of condition order, time on task, valence and magnitude (standard deviations in parentheses). Numbers in regular font refer to the silence condition, numbers in bold font refer to the noise condition.

Time on task	First half		Second half	
Condition order	Mean RT	Mean Stay perc.	Mean RT	Mean Stay perc.
Silence–noise				
Large gain	674 (539)	77 (19)	**482 (199)**	**79 (16)**
Small gain	583 (360)	73 (20)	**436 (184)**	**75 (21)**
Large loss	576 (402)	54 (20)	**469 (232)**	**49 (26)**
Small loss	569 (419)	62 (20)	**449 (193)**	**63 (24)**
Noise–silence				
Large gain	**496 (199)**	**56 (18)**	431 *(208)*	58 *(27)*
Small gain	**481 (185)**	**57 (18)**	402 *(178)*	56 *(28)*
Large loss	**475 (171)**	**54 (18)**	419 *(197)*	54 *(17)*
Small loss	**452 (171)**	**51 (17)**	425 *(199)*	55 *(21)*

to the noise condition (condition order: $F(1, 28) = 6.47$, $p = .017$). However, valence and condition order interacted on stay percentages (valence by magnitude by condition order interaction: $F(1, 28) = 4.67$, $p = .039$). The valence effect was only present in participants who started in the silence condition, not in those who started in the noise condition (silence–noise: $F(1, 14) = 8.76$, $p = 0.010$; noise–silence $F(1, 14) < 1$). The condition order effect only applied to gains, not to losses (gains: $F(1, 28) = 7.80$, $p = .009$; losses: $F(1, 28) < 1$). Noise as such did not modulate these behavioral effects.

Mean reaction times seemed to be longer in the first relative to the second half of the experiment, but the effect of time on task did not reach significance ($F(1, 28) = 3.51$, $p = 0.071$). Stay percentages were equal in both halves of the experiment ($F(1, 28) < 1$).

To summarize, participants showed longer reaction times after large compared to small outcomes. In addition, participants were more likely to stay on the same side after gains than after losses, but only if they started in the silence condition. Choice behavior did not change over time. These findings indicate that both valence and magnitude of previous outcomes, as well as condition order affected choice behavior.

Table 2

Summary of effects on three different FRN measures. Effects are only included when significant for at least one measure. The *F*- and *p*-values are reported.[a]

FRN measure Effect	Mean amplitude		Mean amplitude minus average mean amplitudes preceding and following peaks		Base-to-peak	
	F	*p*	*F*	*p*	*F*	*p*
Valence	67.31	<.001	54.14	<.001	24.09	<.001
Magnitude	51.83	<.001	41.31	<.001	38.86	<.001
Valence by magnitude	1.46	.237	6.20	.019		
Valence by noise	5.94	.021	3.01	.093		
Magnitude by noise	2.16	.153			4.71	.038
Magnitude by noise by noise type			8.25	.007		

[a] Degrees of freedom $F(1,30)$. Entries with an *F*-value less than 1 are omitted.

Table 3

Summary of effects on the P200 and the P300 at FCz. Effects are only included when significant for at least one measure including the FRN measures. The *F*- and *p*-values are reported.[a]

Effect	*F*	*p*	*F*	*p*
Valence	14.86	.001	3.91	.057
Magnitude	13.45	.001	9.14	.005
Valence by magnitude	4.24	.048	13.21	.001
Valence by noise	4.88	.037		
Magnitude by noise			1.65	.208
Magnitude by noise by noise type	5.15	.031	12.98	.001

[a] Degrees of freedom $F(1,30)$. Entries with an *F*-value less than 1 are omitted.

ERP results

Table 2 summarizes the main results of the repeated measures ANOVAs on the three FRN measures. Figure 2 shows the grand-average ERPs at FCz as a function of valence and magnitude. In general, the FRN was more negative in response to losses relative to gains. In addition, the FRN was more negative for small relative to large outcomes. These effects were significant for all three FRN measures, but largest for the mean amplitude measure. A valence by magnitude interaction was observed only

on the mean amplitude corrected for both peaks measure. The effect of valence was larger for small relative to large outcomes, but present for both magnitudes (small: $F(1, 30) = 75.82$, $p < .001$; large: $F(1, 30) = 33.15$, $p < .001$). The effect of magnitude was larger for losses than for gains, but present for both types of feedback (losses: $F(1, 30) = 57.06$, $p < .001$; gains: $F(1, 30) = 15.06$, $p = .001$).

Considering preceding and following peaks, valence and magnitude had (nearly) significant main effects and a significant interaction effect on the P200 and P300 (see Table 3). In general, the P200 was more negative in response to losses compared to gains, and in response to small compared to large outcomes. The valence effect was present for both magnitudes, but larger for large relative to small outcomes (large: $F(1, 30) = 16.23$, $p < .001$; small: $F(1, 30) = 9.68$, $p = .004$). The magnitude effect was only significant for gains, not for losses (gains: $F(1, 30) = 16.71$, $p < .001$; losses: $F(1, 30) = 3.23$, $p = .082$). The P300 was more negative for small gains relative to losses and large gains. Post hoc comparisons between all outcomes corroborated that small gains generated less positivity than large gains ($p = .001$, Bonferroni corrected), small losses ($p = .007$) and large losses ($p = .008$). Thus, the valence effect was only present for small outcomes, while the magnitude effect only applied to gains. Measuring the FRN while correcting for both P200 and P300 resulted in a larger valence effect for small relative to large outcomes, and a larger magnitude effect for losses relative to gains.
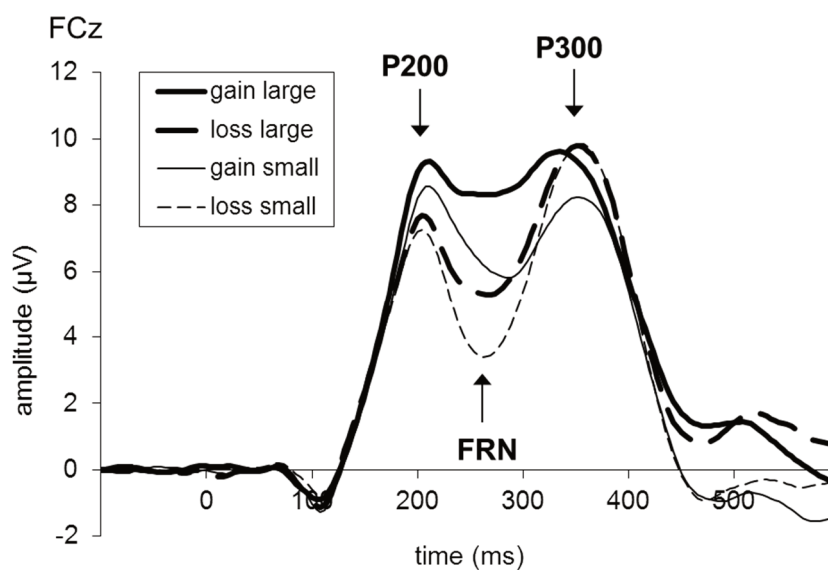

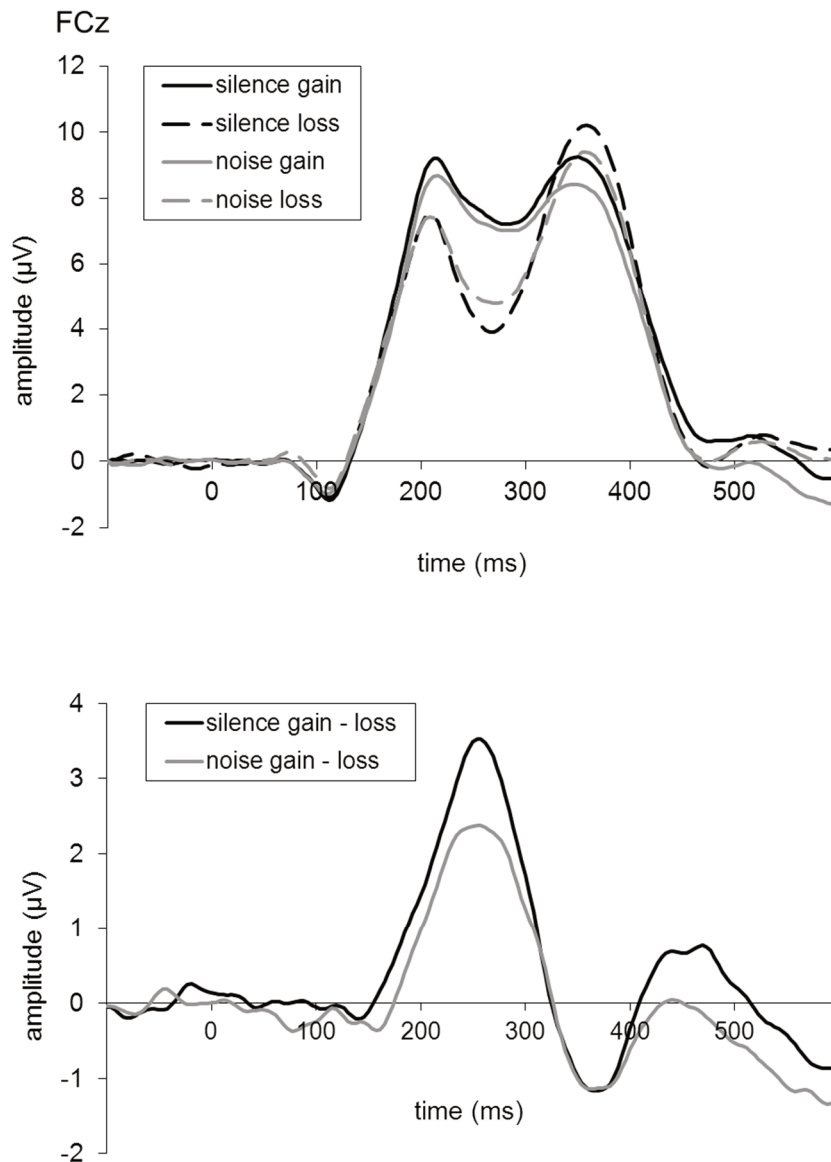**Figure 2.** ERPs from FCz as a function of valence and magnitude.

Figure 3. ERPs from FCz as a function of valence and noise, collapsed over noise types (top), and the gain-loss difference waves for both conditions (bottom).

Figure 3 depicts the ERPs as a function of valence and noise, collapsed over noise types, and the gain-loss difference waves for both conditions. The valence effect seems to be smaller in the noise relative to the silence condition, but present in both conditions. This was confirmed by the repeated measures ANOVA on the mean amplitude measure, revealing a significant valence by noise interaction, and by additional analyses for both conditions separately (valence effect in silence: $F(1, 30) = 59.88$, $p < .001$; noise: $F(1, 30) = 42.74$, $p < .001$). Separate analyses for gains and losses showed a significant effect of noise only for loss trials ($F(1, 30) = 5.95$, $p = $

.021), suggesting that especially loss processing is affected by noise exposure. The repeated measures ANOVA on the mean amplitude corrected for both peaks measure yielded a valence by noise interaction approaching significance. However, the repeated measures ANOVA on the base-to-peak measure yielded a non-significant valence by noise interaction.

With regard to preceding and following peaks, valence and noise had a significant interaction effect on the P200, but not on the P300 (see Table 3). Measuring the FRN while correcting for the P200 reduced the valence by noise interaction on the FRN, as most clearly reflected in the base-to-peak measure.

Figure 4 compares the ERPs as a function of valence and noise, for both noise types separately. Visual inspection of this figure suggests that the impact of noise exposure on the effect of valence was more pronounced for discontinuous noise than for continuous noise. However, interactions involving valence, noise and noise type did not reach the level of significance.

Figure 5 shows the ERPs as a function of magnitude and noise, collapsed over noise types, and the large-small difference waves for both conditions. It shows that the magnitude effect might be smaller in the noise compared to the silence condition, but present in both conditions. This was confirmed by the repeated measures ANOVA on the base-to-peak measure, yielding a significant magnitude by noise interaction, and by additional analyses for both conditions (magnitude effect in silence: $F(1, 30) = 37.08$, $p < .001$; noise: $F(1, 30) = 19.96$, $p < .001$). In addition, the repeated measures ANOVA on the mean amplitude corrected for both peaks measure yielded a significant magnitude by noise by noise type interaction (see Fig. 6). Additional analyses showed a nearly significant magnitude by noise interaction for discontinuous noise ($F(1, 15) = 5.72$, $p = .030$), but not for continuous noise ($p = .124$). However, the repeated measures ANOVA on the mean amplitude measure did not yield a significant interaction involving magnitude and noise.

Considering preceding and following peaks, the effect of magnitude on the P200 and P300 depended on the combination of noise and noise type, as confirmed by significant magnitude by noise by noise type interactions (see Table 3). However, additional analyses on the P200 showed no significant magnitude by noise interaction, for neither of the noise types (continuous: $p = .081$, discontinuous: $p = .212$). Additional analyses on the P300 yielded a significant magnitude by noise interaction for continuous noise ($F(1, 15) = 9.65$, $p = .007$), but not for discontinuous noise ($p = .080$). The effect of magnitude was only significant in the silence condition of the continuous noise group $F(1, 15) = 16.35$, $p = .001$), not in the noise condition.
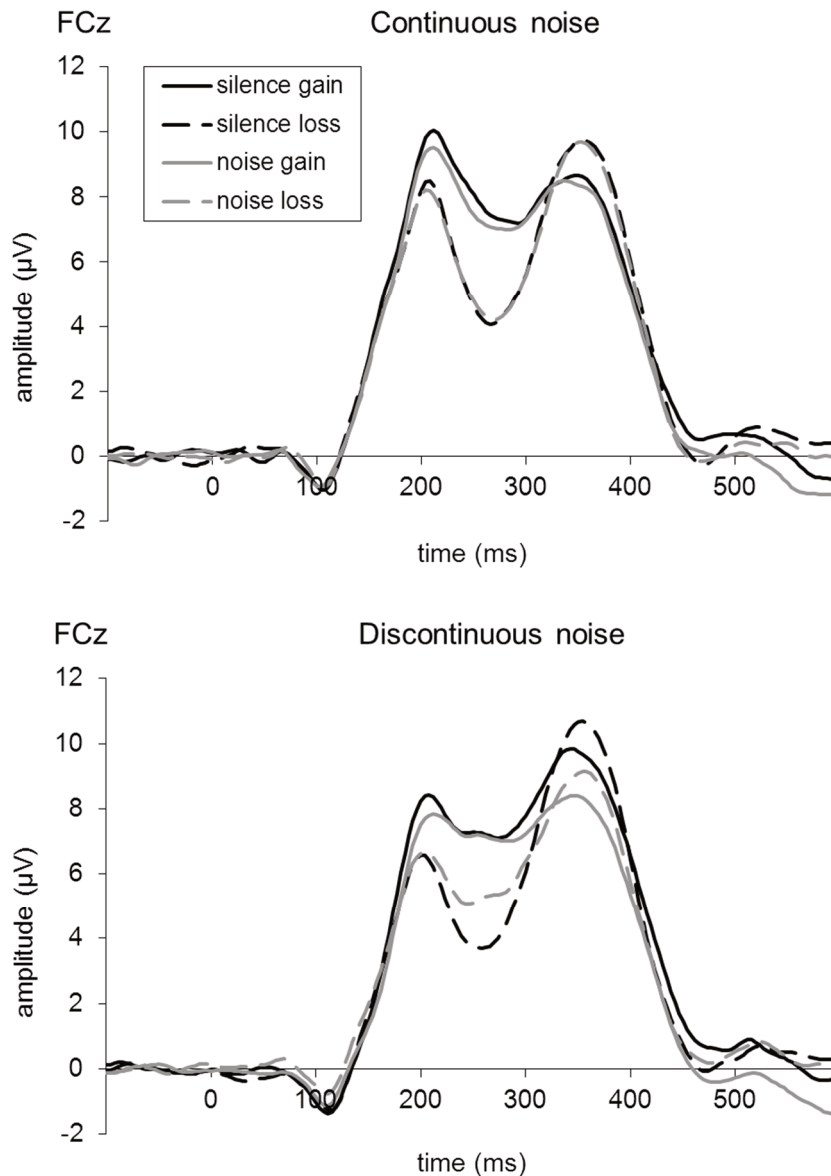
Figure 4. ERPs from FCz as a function of valence and noise, for continuous noise (top) and discontinuous noise (bottom).

Nevertheless, measuring the FRN while correcting for the P200 or for both P200 and P300 lead to significant interactions involving magnitude and noise.

Summarizing, results differed between the different FRN measures used. Feedback valence and magnitude both affected the FRN. These effects were additive on the mean amplitude measure and the base-to-peak measure, but interactive on the mean amplitude corrected for both peaks measure. Evidence for modulation of the valence effect on the FRN by noise exposure was found on two FRN measures (mean amplitude, mean amplitude corrected for both peaks), with a smaller valence effect in
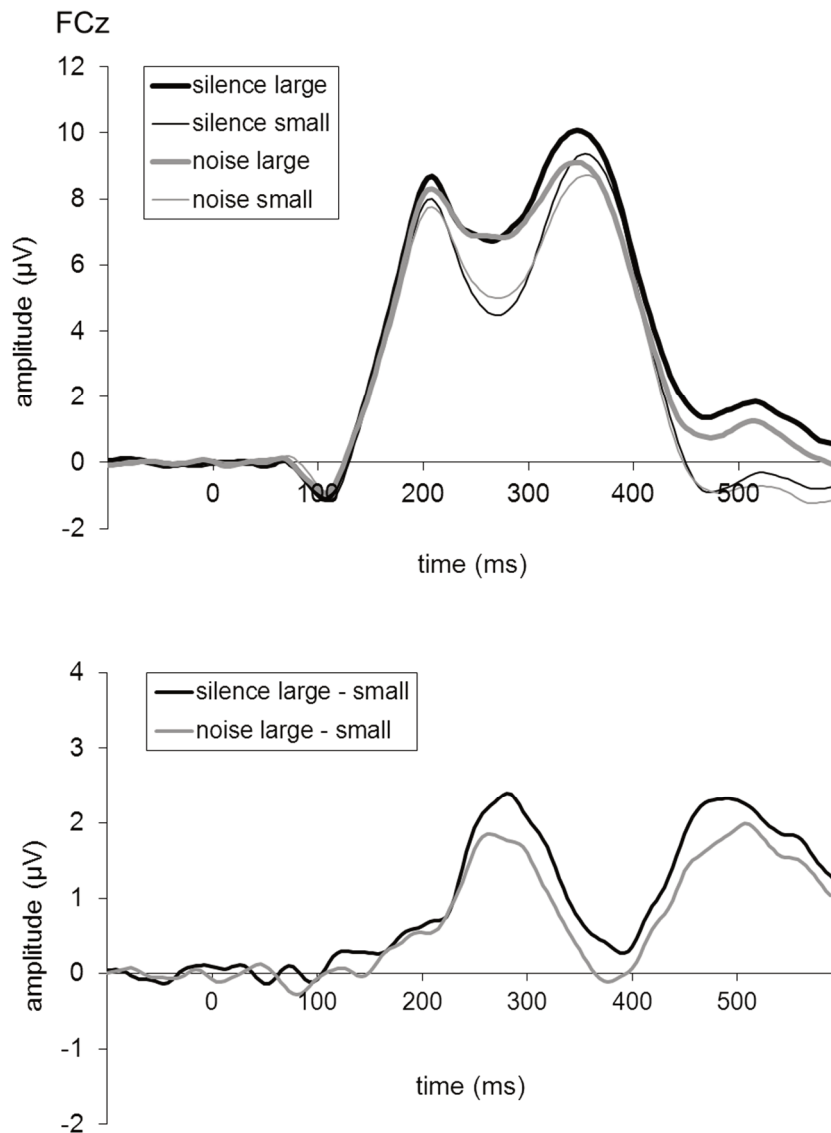
Figure 5. ERPs from FCz as a function of magnitude and noise, collapsed over noise types (top), and the large-small difference waves for both conditions (bottom).

the noise relative to the silence condition. Measuring the FRN while correcting for the P200 reduced the valence by noise interaction on the FRN. Noise type did not have an additional effect. In addition, some evidence for modulation of the magnitude effect by noise exposure was found on two FRN measures (base-to-peak, mean amplitude corrected for both peaks), with generally a smaller magnitude effect in the noise compared to the silence condition. However, this magnitude by noise interaction only had an effect on the mean amplitude corrected for both peaks measure, when participants were exposed to discontinuous noise, not to continuous noise. Measuring

the FRN while correcting for either the P200 or for both P200 and P300 lead to significant interactions involving magnitude and noise, while these were not present on the mean amplitude measure.

Discussion

Aim of this study was to examine whether acute noise stress modulates the cognitive control functioning of the ACC, as reflected in the FRN. In addition, we investigated whether this effect depends on the predictability of the noise stressor. Moreover, we re-examined the combined effects of feedback valence and magnitude on the FRN. We used three FRN measures in order to directly compare findings among these measures. Notably, results differed between FRN measures. Feedback valence and magnitude both affected the FRN. These effects were additive on the mean amplitude measure and base-to-peak measure, but interactive on the mean amplitude corrected for both peaks measure. Acute noise stress had no general effect on the processing of feedback, but specifically modulated the effects of valence and magnitude. Evidence differed between FRN measures as to which aspect(s) of feedback was (were) processed differently under stress. The predictability of the noise stressor did not add much to the explanation of these effects.

Participants performed a simple gamble task. After every choice, they received feedback indicating the amount of money won or lost on that particular trial. Because feedback information was unrelated to actual choices made, there was no strategy participants could use to maximize their gains. Nevertheless, behavior was modulated by the outcomes of previous choices. This is consistent with the idea that, when subjects are faced with uncertainty, they try to gather information to improve future choices (Platt & Huettel, 2008). Participants took more time to make a choice in trials following large compared to small gains or losses, suggesting that the previous outcome is taken into account, especially if that outcome is large. Moreover, we found that participants who started in the silence condition were more likely to repeat the previous choice, if that choice had resulted in a gain than if that choice had resulted in a loss. This effect was independent of the magnitude of the outcome. It indicates that winning reinforces the behavior that has shown to be successful. This valence effect on stay percentages was not present in participants who started in the noise condition. Possibly, starting in the noise condition affects participants' strategies relative to starting in the silence condition. The present set-up, however, does not allow for

detailed analysis of this condition order effect. Remarkably, following losses as well, participants were likely to stay with the same option, although only on a small majority of the trials. This might be explained by what is called the 'explore-exploit' dilemma: "the tension between seeking new information and choosing the best option, given what is already known" (Platt & Huettel, 2008, p. 401). Two earlier studies reported stay percentages around 45% after losses (San Martín et al., 2010; Wu & Zhou, 2009).

In line with previous studies, we found a larger FRN for losses compared to gains, and a larger FRN for small relative to large outcomes (Goyer et al. 2008; Marco-Pallarés et al., 2008; Wu & Zhou, 2009). Traditionally, the FRN has been related to the valence but not to the magnitude of outcomes (Hajcak et al., 2006; Holroyd et al., 2006; Sato et al., 2005; Yeung & Sanfey, 2004). Remarkable is, that in those studies reporting an effect of magnitude, the magnitude of outcomes was clearly depicted in numbers during feedback presentation, as in our study. Studies presenting magnitude information only at the beginning of the trial and using abstract signs to indicate valence only at feedback presentation (Holroyd et al., 2006; Sato et al., 2005), and a study using abstract signs to indicate both valence and magnitude at feedback presentation (Hajcak et al., 2006) failed to find an effect of magnitude. This less salient representation of outcome magnitude during feedback presentation might have resulted in less efficient encoding of this information, as reflected in the FRN.

Our findings with regard to the combined effects of feedback valence and magnitude on the FRN are partly inconsistent with the RL theory of the FRN. This theory claims that FRN amplitude is sensitive to the size of the reward prediction error, that is the difference between the actual and expected outcome of behavior (Holroyd & Coles, 2002; Holroyd et al., 2004; Nieuwenhuis et al., 2004). Indeed, we found a larger FRN for losses relative to gains, and for small relative to large gains. However, we also found a larger FRN for small relative to large losses, although the latter are a worse outcome than the former, and deviate more strongly from the expected value, i.e., zero. How can this finding be explained?

Over the past several years, research on the function of the ACC, the generator of the FRN, has been largely guided by two perspectives (Botvinick, 2007; Yeung & Nieuwenhuis, 2009). According to one perspective, of which the RL theory is a prominent representative, the ACC evaluates action outcomes and guides decision making (Holroyd & Coles, 2002; Holroyd et al., 2004; Nieuwenhuis et al., 2004). According to another perspective, the ACC serves to monitor for response conflict, the simultaneous activation of competing responses. This conflict-related activity leads to

compensatory adjustments in control (Botvinick, 2007). From the perspective of the conflict monitoring theory of the ACC, the level of response conflict determines the amplitude of the FRN. This might explain why small losses elicit larger FRNs than large losses. Small losses may cause more behavioral uncertainty than large losses. Whereas large losses are the worst outcomes and clearly point to the need for behavioral adjustments, small losses are less easy to interpret with respect to badness and necessary adjustments, and may therefore cause more response conflict than large losses. The conflict monitoring theory also accounts for a larger FRN for (1) losses relative to gains, as losses cause more behavioral uncertainty than gains; and (2) small relative to large gains, as small gains are positive but not optimal outcomes.

As stress influences activity in brain structures involved in feedback evaluation (Arnsten, 2009; Joëls & Baram, 2009; Ossewaarde et al., 2011a), we expected acute noise stress to modulate the processing of feedback information regarding gains and losses. Exposure to loud white noise indeed affected feedback processing relative to the silence condition. Unpredictability of the noise stressor added little to this difference: the impact of noise exposure on feedback processing was similar for discontinuous and continuous noise.

Acute noise stress specifically modulated the effects of valence and magnitude on the FRN. However, evidence differed between FRN measures as to whether feedback valence and/or magnitude were processed differently under stress. On the one hand, noise exposure modulated the valence effect on the mean amplitude measure of the FRN, although this effect was reduced if the mean amplitude was corrected for both peaks surrounding the FRN. The effect of valence was smaller in the noise relative to the silence condition. This modulation was mainly due to the differential processing of losses, as opposed to gains, in the noise relative to the silence condition. As described earlier, the negativity elicited by negative outcomes signals the need for adjustments and learning from feedback (Botvinick, 2007; Holroyd & Coles, 2002). Our findings implicate that this corrective signal is less strong under conditions of acute noise stress, possibly resulting in less adaptive behavior. Differences between FRN measures resulted from a significant valence by noise interaction on the P200. Note, however, that ERP differences between gain and loss trials were maximal around the FRN peak.

On the other hand, noise exposure modulated the magnitude effect on the base-to-peak measure and on the mean amplitude corrected for both peaks measure, but the latter only applied to the discontinuous noise group. The effect of magnitude was smaller in the noise compared to the silence condition. This suggests that participants

were less able to discriminate between large and small outcomes, when they were exposed to noise, indicating that subjects make less use of feedback information to optimize subsequent behavior, under stressful conditions. Evidence for modulation of the magnitude effect by noise exposure differed between FRN measures, as a consequence of significant magnitude by noise interactions on previous and following peaks. Note that ERP differences between large and small trials were maximal during the FRN time window.

Our findings are consistent with studies showing that acute noise stress affects higher-order cognitive control functions (e.g., Arnsten & Goldman-Rakic, 1998; Hartley & Adams, 1974; Hillier et al., 2006; Hockey, 1970; Szalma & Hancock, 2011). In addition, our findings are in line with previous studies showing modulated feedback processing under conditions of stress. More specifically, studies have reported that stress reduces the ability to modulate behavior as a function of past positive feedback (Bogdan & Pizzagalli, 2006); reduces the use of negative feedback during learning, but not the use of positive feedback (Petzold et al., 2010); slows learning in a feedback-based gambling task (Preston et al., 2007); and reduces responses to positive feedback in the medial PFC (Ossewaarde et al., 2011a). With regard to the FRN, Foti and Hajcak (2009) have shown that the enhancement of the feedback negativity to negative versus positive feedback is inversely related to self-reported stress reactivity.

Measuring the FRN is complex due to possible overlap between the FRN and other components. In the literature, several ways to measure the FRN are reported. In the present study, we used three different FRN measures in order to directly compare findings among measures. Importantly, we found that results differed between measures. Correcting for either the preceding peak or both peaks yielded smaller main effects of valence and magnitude, and smaller or different interaction effects, compared to the results for the uncorrected mean amplitude measure. As the results of the repeated measures ANOVAs on the P200 and P300 showed, effects of valence and magnitude and modulations of these effects by acute noise stress also occurred during the time windows of these peaks. In addition, these effects differed between the P200 and P300. As a result, choosing only the preceding peak or both peaks to correct for overlap has important consequences for the results found.

In conclusion, we found that feedback valence and magnitude both affect the FRN. Acute noise stress modulates these effects, independent of the predictability of the noise stressor. When subjects are exposed to noise, the cognitive control functioning of the ACC seems to be impaired. Although these findings globally

applied to all three FRN measures, the exact outline was different for each measure.

Acknowledgments

CHAPTER 3

Acute stress modulates feedback processing in men and women: Differential effects on the feedback-related negativity and theta and beta power

Banis, S., Geerligs, L., & Lorist, M. M. (2014).
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Abstract

Sex-specific prevalence rates in mental and physical disorders may be partly explained by sex differences in physiological stress responses. Neural networks that might be involved are those underlying feedback processing. Aim of the present EEG study was to investigate whether acute stress alters feedback processing, and whether stress effects differ between men and women. Male and female participants performed a gambling task, in a control and a stress condition. Stress was induced by exposing participants to a noise stressor. Brain activity was analyzed using both event-related potential and time-frequency analyses, measuring the feedback-related negativity (FRN) and feedback-related changes in theta and beta oscillatory power, respectively. While the FRN and feedback-related theta power were similarly affected by stress induction in both sexes, feedback-related beta power depended on the combination of stress induction condition and sex. FRN amplitude and theta power increases were smaller in the stress relative to the control condition in both sexes, demonstrating that acute noise stress impairs performance monitoring irrespective of sex. However, in the stress but not in the control condition, early lower beta-band power increases were larger for men than women, indicating that stress effects on feedback processing are partly sex-dependent. Our findings suggest that sex-specific effects on feedback processing may comprise a factor underlying sex-specific stress responses.

Introduction

Several mental and physical disorders show sex-specific prevalence rates. For example, men have higher rates of addiction disorders and cardiovascular diseases, whereas women are more susceptible to depression and anxiety disorders and autoimmune diseases (see for reviews, Kajantie & Phillips, 2006; Wang et al., 2007). Physiological responses to stress have been proposed to play an important role in the pathogenesis of these disorders. This raises the possibility that sex-specific prevalence rates are at least partly due to sex-specific stress responses (Kajantie & Phillips, 2006). Nevertheless, the neural mechanisms underlying these effects are largely unknown. Increasing evidence suggests that particular stress-related disorders, such as mood disorders and drug addiction, are associated with abnormal feedback processing (Forbes, Shaw, & Dahl, 2007; Russo & Nestler, 2013). In the present study, we therefore focused on feedback-related neural activity in men and women.

Recent research has revealed that exposure to acute stress alters decision-making behavior by modulating risk-taking behavior (Lighthall, Mather, & Gorlick, 2009; Porcelli & Delgado, 2009; Preston, Buchanan, Stansfield, & Bechara, 2007; Starcke, Wolf, Markowitsch, & Brand, 2008; Van den Bos, Harteveld, & Stoop, 2009), and by affecting learning from feedback. A number of studies, for example, have found that stress impairs learning from positive feedback (Bogdan & Pizzagalli, 2006) or negative feedback (Petzold, Plessow, Goschke, & Kirschbaum, 2010). However, a recent study found that the effects of stress on reward learning (learning from seeking reward) or punishment learning (learning from avoiding punishment) depend on the punishment sensitivity and stress reactivity of the participant (Cavanagh, Frank, & Allen, 2011). This indicates that stress effects on feedback learning are not necessarily negative and depend on individual characteristics.

Feedback processing and feedback learning are of crucial importance to adaptive decision making. Although there is some knowledge about the behavioral effects of stress on feedback learning, knowledge about the neural underpinnings of these stress effects is scarce. Brain regions that are associated with feedback processing and learning (e.g., the ventral striatum, medial frontal cortex (MFC), orbitofrontal cortex (OFC), and lateral prefrontal cortex (PFC) have been shown to be sensitive to stress-induced changes (see for reviews, Dedovic, D'Aguiar, & Pruessner, 2009; Starcke & Brand, 2012), supporting the notion that stress influences feedback

processing and learning. In addition, recent fMRI studies have reported reduced responses of these brain areas to monetary outcomes under stress (Ossewaarde et al., 2011a; Porcelli, Lewis, & Delgado, 2012). In the current study, our first aim was to gain more insight into the impact of acute stress on feedback processing in men and women on a neural level, applying electroencephalography (EEG).

Studies using EEG have identified an ERP component that is elicited in response to external feedback: the feedback-related negativity (FRN). The FRN is a negative ERP component, which peaks between 250 and 300 ms after feedback delivery, is maximal over frontocentral scalp sites, and is larger in amplitude following negative compared to positive feedback (Gehring & Willoughby, 2002; Miltner, Braun, & Coles (1997). The major contributors to the FRN are probably located in the MFC (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The specific function of the MFC in feedback processing has been debated: evaluating decision outcomes to guide reward-seeking behavior (Holroyd & Coles, 2002; Nieuwenhuis, Holroyd, Mol, & Coles, 2004); or monitoring for response conflict (the simultaneous activation of competing responses), with conflict detection leading to compensatory adjustments in control (Botvinick, Cohen, & Carter, 2004). Botvinick (2007) has tried to reconcile these two perspectives, proposing that these different functions may be part of a general learning system biasing behavioral decision making toward cognitively efficient strategies. Emerging evidence points at functional interactions between the MFC and other prefrontal cortical regions (Cohen, Wilmes, & Van de Vijver, 2011; Ridderinkhof et al., 2004; Van de Vijver, Ridderinkhof, & Cohen, 2011). Monitoring-related activity in the MFC appears to serve as a signal that engages regulatory processes in the lateral PFC to implement behavioral adjustments.

In a previous study (Banis & Lorist, 2012), we investigated the impact of acute noise stress on the FRN in men, and whether effects depended on stressor predictability. Participants performed a gambling task in a control and a stress condition with either a predictable or unpredictable noise stressor. FRN amplitude was measured in different ways, either neglecting or correcting for overlap with other components. We found that acute noise stress specifically modulated valence and magnitude effects on the FRN, with smaller effects in the stress relative to the control condition, although evidence differed between measures as to whether valence and/or magnitude were processed differently. We interpreted these findings as a stress-induced impairment of feedback processing. Stressor predictability added little to the explanation of effects. In the current study, we further examined the impact of acute noise stress on feedback processing, using the same gambling task in combination with

the unpredictable noise stressor, but now in both sexes.

Until recently, most EEG studies on feedback processing have focused on the FRN, which only reflects oscillations that are phase-locked to the feedback. Nevertheless, recent research has demonstrated that the analysis of oscillatory activity, which includes both phase-locked and non-phase-locked oscillations, can provide complementary insights into feedback processing (Cohen et al., 2011; Cohen, Elger, & Ranganath, 2007). Theta power increases over frontocentral scalp sites have been shown to be larger after negative feedback or losses compared to positive feedback or gains (Cavanagh, Frank, Klein, & Allen, 2010; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Cohen et al., 2007; Cohen, Elger, & Fell, 2009; Di Bernardi Luft, Nolte, & Bhattacharya, 2013; Marco-Pallarés et al., 2008; Van de Vijver et al., 2011). Theta-band oscillations in the frontal network have been proposed to play an important role in signaling unfavorable outcomes and implementing adjustments (Van de Vijver et al., 2011). Findings with regard to beta power are less equivalent. Positive outcomes have been shown to induce increased upper beta-band power over frontocentral sites relative to negative outcomes (Cohen et al., 2007; Marco-Pallarés et al., 2008; Van de Vijver et al., 2011). However, another study found larger increases for losses relative to gains, in both lower and upper beta-bands (Cohen et al., 2009). The functional role of beta-band activity in feedback processing is largely unknown. Beta-band oscillations in general have been proposed to signal the tendency to maintain the status quo of the current sensorimotor or cognitive state (Engel & Fries, 2010). In the present study, we used both the FRN and feedback-related changes in theta and beta oscillatory power to investigate feedback processing.

Importantly, a number of studies have found that effects of acute stress on decision-making behavior are sex-dependent. Two studies found increased risk taking in men and decreased risk taking in women, during stress (Lighthall et al., 2009; Van den Bos et al., 2009). A later fMRI study by Lighthall et al. (2012) could not replicate this sex-dependent stress effect on risk taking, but did find greater reward collection and faster decision speed in males and less reward collection and slower decision speed in females, under stress. In addition, the latter study found that the behavioral sex differences were accompanied by different neural activation patterns; with stress, activation in the dorsal striatum and anterior insula was increased in males but decreased in females (Lighthall et al., 2012). Thus, current knowledge suggests that stress affects decision-making behavior, that these effects are sex-dependent, and that these sex-dependent stress effects on decision-making behavior are associated with sex-dependent brain activity. However, it is not clear whether these differential stress

effects on decision making may be linked to differential stress effects on feedback processing. Therefore, the second aim of our study was to examine whether acute stress effects on feedback processing differ between men and women.

In sum, the aim of the present study was twofold. First, we examined whether acute stress alters decision making by affecting feedback processing, as reflected in the FRN and feedback-related changes in theta and beta oscillatory power. Second, we investigated whether stress effects are sex-dependent. Participants performed a gambling task, in a control and a stress condition, while their EEG was recorded. Stress was induced by exposing participants to a noise stressor. Based on the studies described above and our previous study (Banis & Lorist, 2012), we expected a decreased sensitivity to monetary outcomes under stress, with regard to the FRN. Based on the idea that the FRN and theta-band activity partly reflect similar processes (Cavanagh et al., 2012; Cohen et al., 2007), we expected a similar stress effect on theta power. With regard to beta-band activity and to sex differences, we did not formulate hypotheses beforehand.

Methods

Participants

Sixty-one healthy, right-handed undergraduate students from the University of Groningen (37 females, mean age = 21.1 years, range 18–40 years; 24 males, mean age = 21.9 years, range 18–28 years) participated in the experiment. Data from 16 male participants were also used in a previous study (Banis & Lorist, 2012). In this previous study, we examined the impact of acute noise stress on the FRN and whether effects depended on stressor predictability, in men only. During the stress condition, participants were either exposed to a predictable ($n = 16$) or unpredictable noise stressor ($n = 16$). For the current study, we used the unpredictable noise stressor to investigate the impact of acute noise stress in both men and women. We included the 16 male participants from the unpredictable noise stressor group, from our previous study. Subsequently, we measured eight additional male and 37 female participants. Participants reported no evidence of current or past psychiatric disorders, neurological disorders, or head injuries, and were free of CNS-active medication. They were non-smokers, and had normal or corrected-to-normal vision and normal hearing. In addition, female participants had not used hormonal contraceptives within the previous

four months. They were not pregnant and had regular menstrual cycling with normal mean cycle length (24–35 days).

To minimize the influence of hormonal fluctuations across the menstrual cycle on feedback processing (Ossewaarde et al., 2011b) and stress responsiveness (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka, Hellhammer, & Wüst, 2009; Ossewaarde et al., 2010), females participated during the putative midluteal phase of their cycle, between day 10 and day 5 prior to menses (Hampson & Young, 2008). Moreover, it has been shown that during this phase, the hypothalamic-pituitary-adrenal (HPA) stress response to laboratory stressors is relatively comparable to the response in men (Kirschbaum et al., 1999).

Measurement days were scheduled on the basis of self-reported menstrual cycle durations and date of onset of the current cycle. Females with a typical cycle length of 29 days were scheduled on day 20–25 from the first day of menses (day 1). Females with shorter or longer cycles were planned accordingly. Retrospectively, the menstrual cycle phase was verified by tracking backward from the date of onset of the next menses that was reported by the participant. As a result, 13 females were excluded from data analysis. In addition, one female withdrew from participation after five minutes in the stress condition, because she could not endure the noise stressor. Consequently, 23 females completed the experiment, during their midluteal phase (mean age = 20.4 years, range 18–31 years).

Participants received either course credits or €20 for participation. In addition, they received a monetary bonus depending on their gambling scores, as described below. The study was approved by the Ethical Committee Psychology of the Psychology Department of the University of Groningen, and all participants gave written informed consent.

Procedure

Participants were instructed to abstain from alcohol and caffeine-containing substances 12 h before the experiment. They arrived at the laboratory at 9.00 a.m. and filled out a questionnaire before application of the electrocap. Participants were seated in front of a computer screen, in a dimly lit, sound-attenuated, electrically shielded cabin. A serial response box was placed under their hands. They completed a gambling task in a stress condition and in a control condition, the order of which was counterbalanced across subjects. Both conditions were separated by a break of 15 minutes, in which subjects remained seated in the cabin.

Gambling task

Participants performed a simplified version of the gambling task devised by Gehring and Willoughby (2002; see for technical details, Banis & Lorist, 2012). Each trial started with the presentation of two white cards, one of which the participant selected with a left- or right-hand button-press, according to the location of the chosen card. After the response, the chosen card was highlighted with a thick yellow border, for a randomly varying interval. Then, the card turned into either cyan or magenta, emphasizing the valence of the outcome (gain or loss). Simultaneously, a number (+/- 5 or 25; representing euro cents) appeared on the selected card, indicating how much money was won or lost at the trial. The assignment of the two colors to gains or losses was counterbalanced across participants. This feedback display remained at the screen for 1000 ms, after which the next trial started. At the end of each trial block, participants received additional feedback indicating the amount of money earned during that block. The gambling task consisted of 5 trial blocks of 5-minute duration each, in each experimental condition. Before the experimental trials, there was one practice block of 1-minute duration (excluding instructions).

Each trial outcome was determined randomly by the computer program, with equal weights for all four possible outcomes and with replacement. Participants were not informed about this. Before the practice block, they were instructed about the meaning of the feedback display. They were told that they started the experiment with €5, and that the value of each selected outcome would be added or subtracted, and that they would keep the resulting sum of money. In addition, they were told that they would receive feedback indicating the amount of money earned during the block, at the end of each block. Finally, participants were instructed that their goal was to earn as much money as possible, and that they were free to choose any strategy to achieve this. Our cash box was kept on the table at which participants were seated, to increase the motivational properties of the monetary incentives. During the break between both conditions, participants were informed about their total score in the first condition. In addition, it was repeated that they were free to choose any strategy. After task completion, most participants reported that they had made an effort to find a systematic pattern in the feedback sequences.

Participants performed equal numbers of trials in the control condition ($M = 495$ trials, $SD = 37$) and the stress condition ($M = 490$ trials, $SD = 38$; paired $t(46) = 1.07$, n.s.). The amount of money participants earned was comparable in the control (total score $M = 45$ euro cents, $SD = 430$) and the stress condition (total score $M = 16$ euro cents, $SD = 402$; paired $t(46) = .35$, n.s.). Participants reached an average end

score of 61 euro cents (SD = 614), which was added to the €5 starting money and paid to them, at the end of the experimental session. Participants with an end score of minus €5 or less received no bonus money. Trial numbers, total scores and end scores were similar for both sexes.

Stress induction

In order to induce a stressful state, participants were exposed to a noise stressor. This stressor consisted of discontinuous white noise of varying intensity (75–95 dB(A), 0–10 kHz), produced at our department. It included both noise intervals and inter-noise (silence) intervals. The length of each noise interval varied from 2 to 7 seconds, during which the intensity of noise varied between 75 and 95 dB(A). The length of inter-noise intervals also varied from 2 to 7 seconds. Half of the noise intervals were followed by an inter-noise interval, whereas the other half were followed by another noise interval. An inter-noise interval was never followed by another inter-noise interval. The length and intensity of noise intervals and the length of inter-noise intervals were randomly determined. The noise was played from a compact disc, and delivered by two loudspeakers in stereo mode placed on either side of the computer screen. Acute noise exposure is a common stressor, which activates the HPA axis and the sympathetic nervous system, leading to increases of stress hormones including epinephrine, norepinephrine and cortisol (Babisch, 2003). Moreover, acute noise exposure has been shown to impair cognitive functioning on novel and complex tasks (Arnsten & Goldman-Rakic, 1998; Szalma & Hancock, 2011).

The subjective effects of exposure to the noise stressor were investigated in a pilot experiment. Participants were randomly assigned to either a silence condition (n = 19) or a noise condition (n = 17). Immediately before and after task performance, participants filled in the shortened Dutch version of the Profile of Mood States (Wald & Mellenbergh, 1990). Participants in the noise group showed a significantly larger decrease in vigor (M = -3.4, SD = 3.4) relative to those in the silence group (M = -0.8, SD = 3.7; $t(34)$ = -2.17, p = .019, one-tailed). In addition, they reported an increase in tension (M = +0.6, SD = 1.5), while the silence group reported a decrease in tension (M = -0.4, SD = 2.0; $t(34)$ = 1.69, p = .050, one-tailed). These results confirm that exposure to the discontinuous white noise of varying intensity elicits stress in participants.

Electrophysiological recording and data reduction

EEG was measured using 28 Sn electrodes attached to an electrocap (ElectroCap International Inc., Eaton, Ohio, USA), positioned according to the 10-10 system. Recordings were taken from channels FP1, FP2, AFz, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, PO7, O1, Oz, O2 and PO8, and referenced to the computed average of both mastoids. Horizontal electro-oculogram (EOG) was recorded bipolarly using two electrodes placed at the outer canthi of both eyes. Vertical EOG was measured using two electrodes placed above and below the left eye. All electrode impedances were kept below 5 kΩ. EEG and EOG signals were recorded with a 2000-Hz sample rate, a 0.16-Hz high-pass filter and a 200-Hz low-pass filter.

Off-line, EEG and EOG data were down-sampled to 256 Hz, after additional filtering with a low-pass filter of 30 Hz and a slope 48 dB/oct, for the ERP analysis only. For the ERP analysis, data were segmented in 1000-ms epochs, starting 100 ms before feedback onset. For the time-frequency analysis, segments covered 3000 ms, starting 1000 ms before feedback onset. Epochs with too rapidly changing activity (maximal allowed voltage step ±60 µV) were rejected. After removal of these artifacts, EEG was corrected for eye movements and blinks using the regression procedure of Gratton, Coles and Donchin (1983). Then, epochs which contained EEG voltage differences exceeding 200 µV, or EEG amplitudes exceeding +/- 100 µV, were eliminated. After these ocular correction and artifact rejection procedures, EEG was averaged relative to a 100 ms pre-feedback baseline. For the ERP analysis, separate averages were calculated for each combination of valence (gain vs. loss), magnitude (large vs. small), and stress induction (stress vs. control), resulting in eight average waveforms for each electrode and participant. For exploratory intersite phase synchronization analyses, preprocessed EEG data were converted to current source density (CSD) using the methods of Kayser and Tenke (2006). CSD estimates are based on the second spatial derivative of voltage between nearby electrode sites, acting as a reference-free, spatially enhanced signal representation. This CSD transformation accentuates local electrical activities at the expense of diminishing the representation of distal activities (Cavanagh, Cohen, & Allen, 2009). Thus, applying a CSD filter increases spatial selectivity and minimizes volume conduction effects.

Time-frequency analyses were performed with the Matlab-based FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). To study the oscillatory dynamics of the EEG, single-trial feedback-locked data were convolved with a family of complex Morlet wavelets. These wavelets contained a fixed number of cycles of

sinusoidal oscillations for each frequency band (4–7 Hz, 5 cycles; 8–12Hz, 6 cycles; 13–20 Hz, 7 cycles; 21–30 Hz, 7 cycles). This analysis produced raw power estimates for each time point between 400 ms pre-feedback and 1000 ms post-feedback (in 10-ms steps) at frequencies of 4–30 Hz (in 0.5-Hz steps). Subsequently, a single-trial relative baseline correction was applied, in which each power value was divided by the average power of the pertaining frequency in the -400–-200 ms pre-feedback interval (Grandchamp & Delorme, 2011). Then, we calculated the average power in each of the three frequency bands, for each combination of valence, magnitude and stress induction, for each participant. This single-trial approach to baseline correction has two advantages. First, it is less sensitive to the presence of noisy trials relative to classical baseline correction methods (Grandchamp & Delorme, 2011). Second, it allows one to focus on phasic effects. Any tonic differences in signal between the stress induction conditions or between the sexes would also influence the baselines. By dividing by the single-trial baseline power values we corrected for tonic differences and were able to focus on phasic differences in the feedback-related interval. To evaluate tonic differences in power, we checked whether baseline power values differed between stress induction conditions and sexes. Therefore, we calculated the average absolute power in the baseline interval (-400–-200 ms pre-feedback), for each of the three frequency bands, for each stress induction condition, for each participant.

Intersite phase synchrony (ISPS) represents the extent to which phase angle differences between electrodes are consistent over trials at each time-frequency point (Lachaux, Rodriguez, Martinerie, & Varela, 1999). To confirm the importance of theta-band activity in communicating the need for increased cognitive control between the MFC and the lateral PFC, we explored ISPS between FCz and F3/F4. Therefore, we ran time frequency analyses producing estimates of phase angles for each time point between 400 ms pre-feedback and 1000 ms post-feedback (in 10-ms steps) at frequencies of 4–7 Hz (in 0.5-Hz steps). Subsequently, we ran connectivity analyses for channel combinations FCz and F3, and FCz and F4. Then, a condition-specific baseline correction was applied: from each ISPS value in the feedback-related interval the average ISPS value of the pertaining frequency in the -400–-200 ms pre-feedback interval was subtracted, for each participant and condition.

Data analysis

Behavioral measures

To investigate the influence of previous outcomes on current behavior, mean reaction times (RTs) and stay/switch percentages were computed as a function of the outcome on the previous trial (+/- 5 or 25 euro cents). On stay trials, participants selected the card on the same side as on the previous trial, whereas on switch trials, they chose the card on the other side. Behavioral data were analyzed using repeated measures analysis of variance (ANOVA) with the within-subjects factors valence (gain vs. loss), magnitude (large vs. small), and stress induction (stress vs. control), and the between-subjects factor sex (male vs. female). Whenever necessary, additional analyses were conducted to elucidate significant interactions. For post-hoc tests, adjustment for multiple comparisons was applied using the Bonferroni method.

ERPs

For the feedback-related ERP analyses and oscillatory analyses, we focused on data from channel FCz, which is consistent with previous studies using frontocentral electrodes for these analyses (see Cohen et al., 2009; Fig. 1). In our previous study, the FRN was measured in three different ways (Banis & Lorist, 2012). In order to be able to compare current FRN results with the previous results, we used the same FRN measures. First, the FRN was quantified as the mean amplitude in the 230–300 ms post-feedback interval, which is in line with previous studies (e.g., Di Bernardi Luft et al., 2013; Gehring & Willoughby, 2002; Luque, López, Marco-Pallarés, Càmara, & Rodríguez-Fornells, 2012). Second, the FRN was measured base-to-peak, which is also common practice (e.g., Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003; Yeung & Sanfey, 2004). For this purpose, we identified the most positive value within the 150–230 ms post-feedback window and, subsequently, the most negative value within a window extending from this maximum to 330 ms post-feedback. The base-to-peak FRN was quantified as the difference between these most positive and most negative values. Third, the FRN was measured as the difference in voltage between the 230–300 ms mean amplitude and the average of the mean amplitudes of the preceding (180–225 ms window) and following (320–390 ms window) peaks. Subsequently, these three FRN measures were each subjected to repeated measures ANOVAs with the within-subjects factors valence, magnitude and stress induction, and the between-subjects factor sex. Post-hoc, we ran repeated measures ANOVAs for both sexes separately, in order to elucidate divergent findings with regard to stress induction effects between the current study and our previous study (Banis & Lorist, 2012).
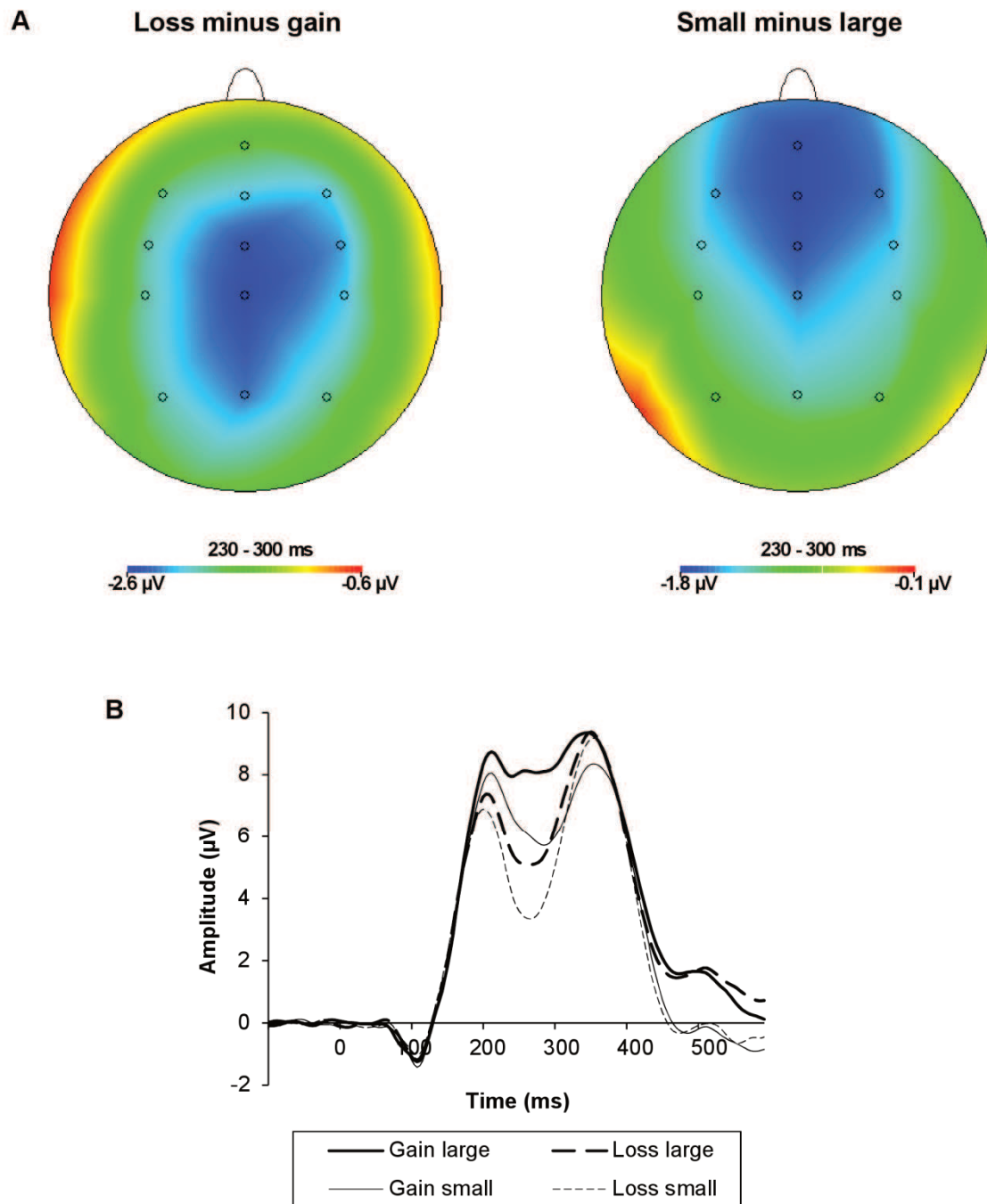
Figure 1. Topographical voltage maps and ERPs from FCz as a function of feedback valence and magnitude. (A) Topographical voltage maps (230–300 ms post-feedback) of the difference between loss and gain trials (left) and the difference between small and large outcome trials (right). (B) ERPs: The solid lines represent gain trials; the dashed lines represent loss trials. Thick lines represent large outcome trials; thin lines represent small outcome trials. The FRN was more negative in response to losses compared to gains, and in response to small relative to large outcomes.
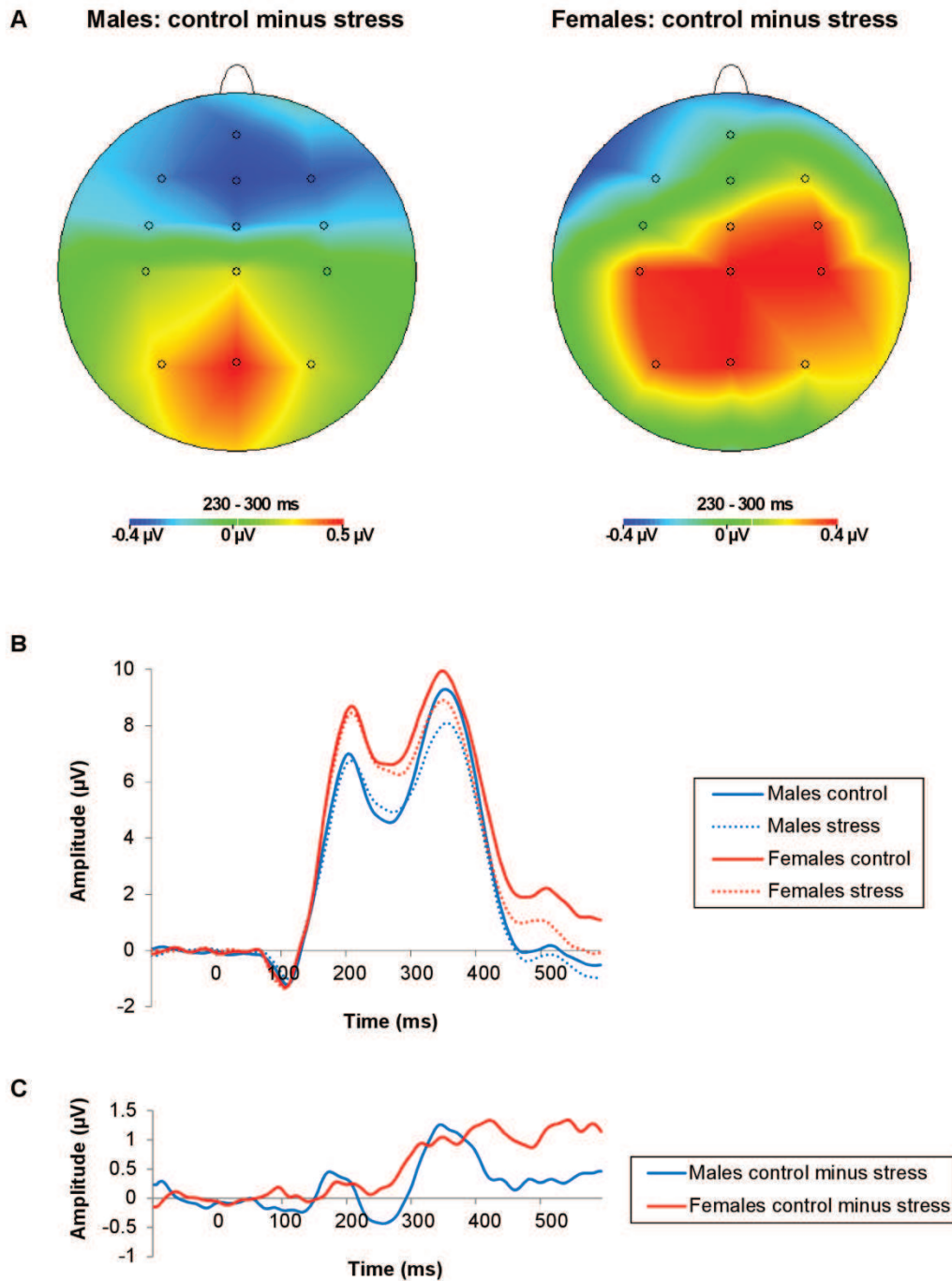
Figure 2. Topographical voltage maps and ERPs from FCz as a function of stress induction and sex. (A) Topographical voltage maps (230–300 ms post-feedback) of the difference between control condition and stress condition trials, for males (left) and females (right), separately. (B) ERPs: The solid lines represent control condition trials; the dotted lines represent stress condition trials. The blue lines represent males; the red lines represent females. (C) ERP difference waves of control minus stress condition trials, for males (blue line) and females (red line). The FRN amplitude was smaller in the stress relative to the control condition, but only as quantified by the mean amplitude (230–300 ms post-feedback) corrected for both preceding (180–225 ms) and following (320–390 ms) components. Sex did not modulate the FRN significantly.

Furthermore, visual inspection of the ERPs (Fig. 2) indicated that the P300 was affected by stress induction as well. As P300 amplitude might influence findings with regard to the FRN as quantified by the mean amplitude relative to preceding and following peaks, we ran post-hoc repeated measures ANOVAs on the P300. The posterior P300 was quantified as the mean amplitude at Pz, in the 300–400 ms post-feedback interval, which is in accordance with previous studies (Polich, 2007). In addition, as effects on the peak following the FRN (320–390 ms post-feedback, at FCz) diverged from effects on the posterior P300, we also analyzed this fronto-central P300.

Oscillatory power

Time windows of frequency bands were selected on the basis of average power plots across all eight conditions and across all participants, at FCz (Fig. 3). Theta (4–7 Hz) was quantified as the mean activity in a 200–500 ms post-feedback window; while both lower beta (13–20 Hz) and upper beta (21–30 Hz) were measured in an early (0–300 ms) as well as a late (300–600 ms) post-feedback window, which is in line with previous studies (e.g., Van de Vijver et al., 2011). The resulting power values were analyzed using repeated measures ANOVA with the within-subjects factors valence, magnitude and stress induction, and the between-subjects factor sex. In addition, we examined whether power values differed in the baseline, between stress induction conditions and sexes. Average absolute baseline power values were subjected to repeated measures ANOVAs with the within-subjects factor stress induction, and the between-subjects factor sex. Finally, we performed post-hoc analyses to investigate whether significant valence and magnitude effects on feedback-related changes in oscillatory power were associated with significant valence and magnitude effects on behavioral measures, respectively. Therefore, we calculated Pearson correlation coefficients between the pertaining effects.

Exploratory analyses: Theta-band intersite phase synchrony. Theta-band ISPS was quantified as the mean ISPS value in a 200–500 ms post-feedback window. Theta-band ISPS was explored between medial frontal (FCz) and lateral prefrontal (F3, F4) sites. The ISPS values were analyzed using repeated measures ANOVA with the within-subjects factors valence, magnitude and stress induction, and the between-subjects factor sex.
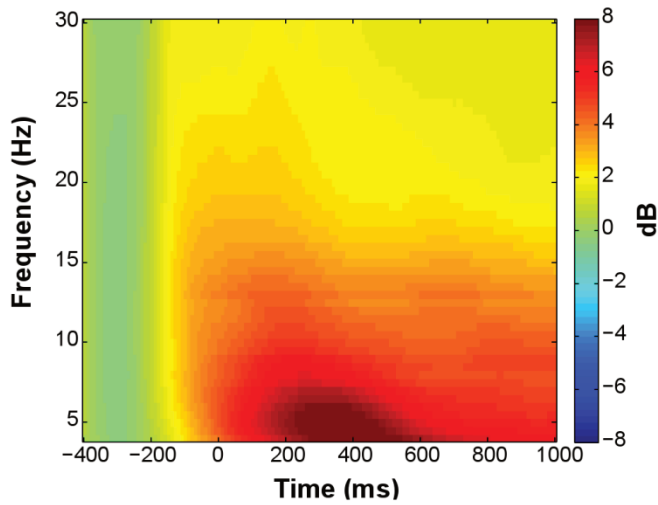
A   Relative power at FCz averaged over all conditions

B   Relative power at FCz in three frequency bands
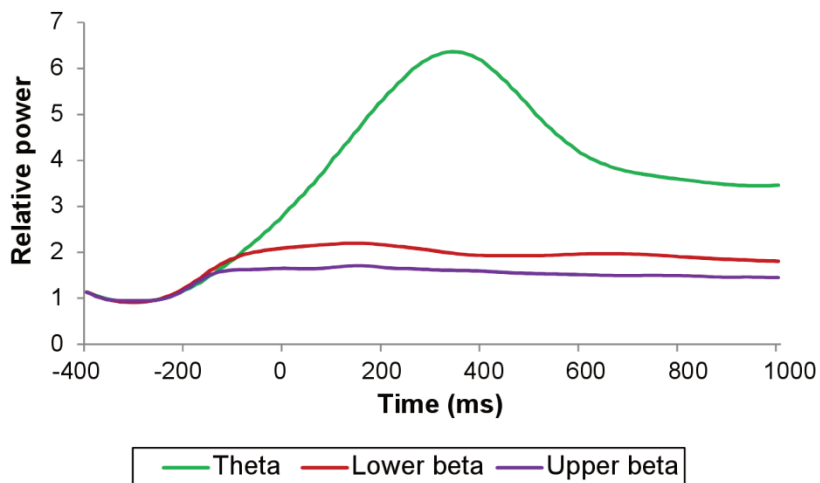
Figure 3. Time-frequency plot and line plots of relative power in different frequency bands, averaged over all conditions. (A) Time-frequency representation of relative power at FCz averaged over all conditions. Only for time-frequency plots, relative power averages were converted to a decibel (dB) scale, enabling comparison between different frequencies. (B) Line plots of relative power at FCz in the theta-band (4–7 Hz), lower beta-band (13–20 Hz), and upper beta-band (21–30 Hz), averaged over all conditions.

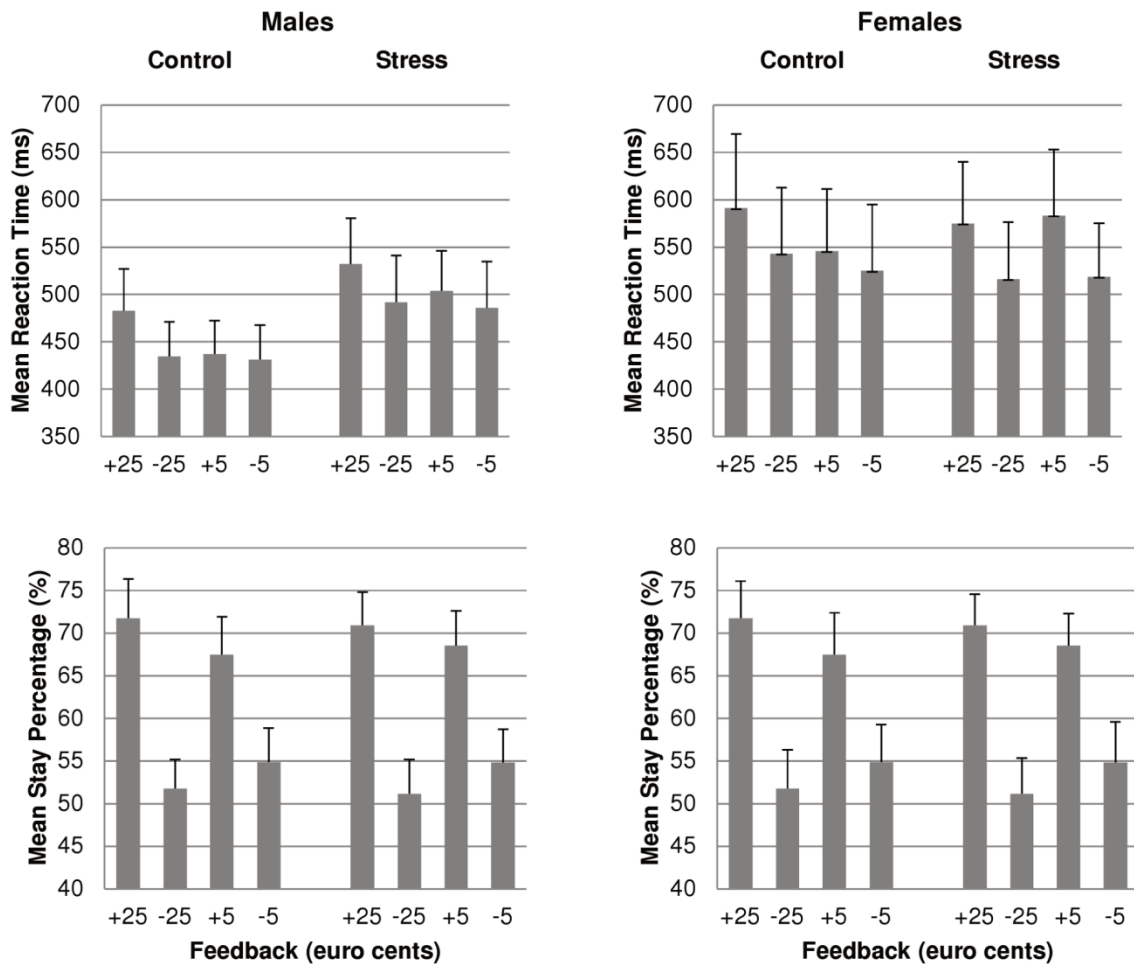**Figure 4. Behavior as a function of feedback type and stress induction, for males and females, separately.** Mean reaction times and mean stay percentages as a function of feedback valence and magnitude, and stress induction, for males (left) and females (right), separately. Error bars represent standard errors. Participants showed longer RTs after gain than after loss trials, and after large magnitude compared to small magnitude trials. In addition, participants were more likely to repeat their card choice of the previous trial, after gains than after losses, especially after large outcomes. Neither stress induction nor sex affected behavior significantly.

Results

Behavioral results

Participants could win or lose either 5 or 25 euro cents, on each trial. Unbeknownst to the participants, there was no strategy they could learn to maximize their gains and minimize their losses. Despite feedback being presented in random order and thus not related to choices made, participants' behavior indicated that they

were sensitive to the outcomes of their choices (Fig. 4). Participants showed longer RTs after gain trials than after loss trials ($F(1, 45) = 20.73$, $p < .001$), and after large magnitude compared to small magnitude trials ($F(1, 45) = 4.58$, $p = .038$). In addition, participants were more likely to repeat their card choice of the previous trial, after gains than after losses ($F(1, 45) = 42.67$, $p < .001$; Fig. 4), especially after large outcomes (valence by magnitude: $F(1, 45) = 4.84$, $p < .033$; large: $F(1, 45) = 35.69$, $p < .001$; small: $F(1, 45) = 35.09$, $p < .001$). Neither stress induction nor sex affected RTs or stay percentages significantly.

ERP results

FRN

Table 1 summarizes the results of the repeated measures ANOVAs on the three FRN measures. The FRN was more negative in response to losses compared to gains, and in response to small relative to large outcomes (Fig. 1). These valence and magnitude effects were significant for all three FRN measures. Stress induction had a significant effect on the FRN, but only as quantified by the mean amplitude corrected for both surrounding peaks measure (Fig. 2). The FRN was smaller in the stress relative to the control condition. Sex did not modulate the FRN significantly.

Figure 5 shows the grand average ERPs per magnitude, as a function of valence and stress induction, for males (left) and females (right). Visual inspection suggests that valence had a smaller effect on the FRN in the stress relative to the control condition, for both large and small outcomes, in males, and for large but not small

Table 1

Summary of effects on three different FRN measures. The $F(1, 45)$- and p-values are reported.

FRN measure	Mean amplitude (MA)		MA corrected for both peaks[1]		Base-to-peak	
Effect	*F*	*p*	*F*	*p*	*F*	*p*
Valence	75.70	<.001	65.71	<.001	30.59	<.001
Magnitude	66.30	<.001	50.07	<.001	44.43	<.001
Stress induction	<1	n.s.	6.57	.014	<1	n.s.
Sex	3.27	n.s.	<1	n.s.	<1	n.s.
Stress induction by sex	1.23	n.s.	1.46	n.s.	1.68	n.s.

[1] Mean amplitude 230–300 ms post-feedback minus average of mean amplitudes preceding and following peaks.
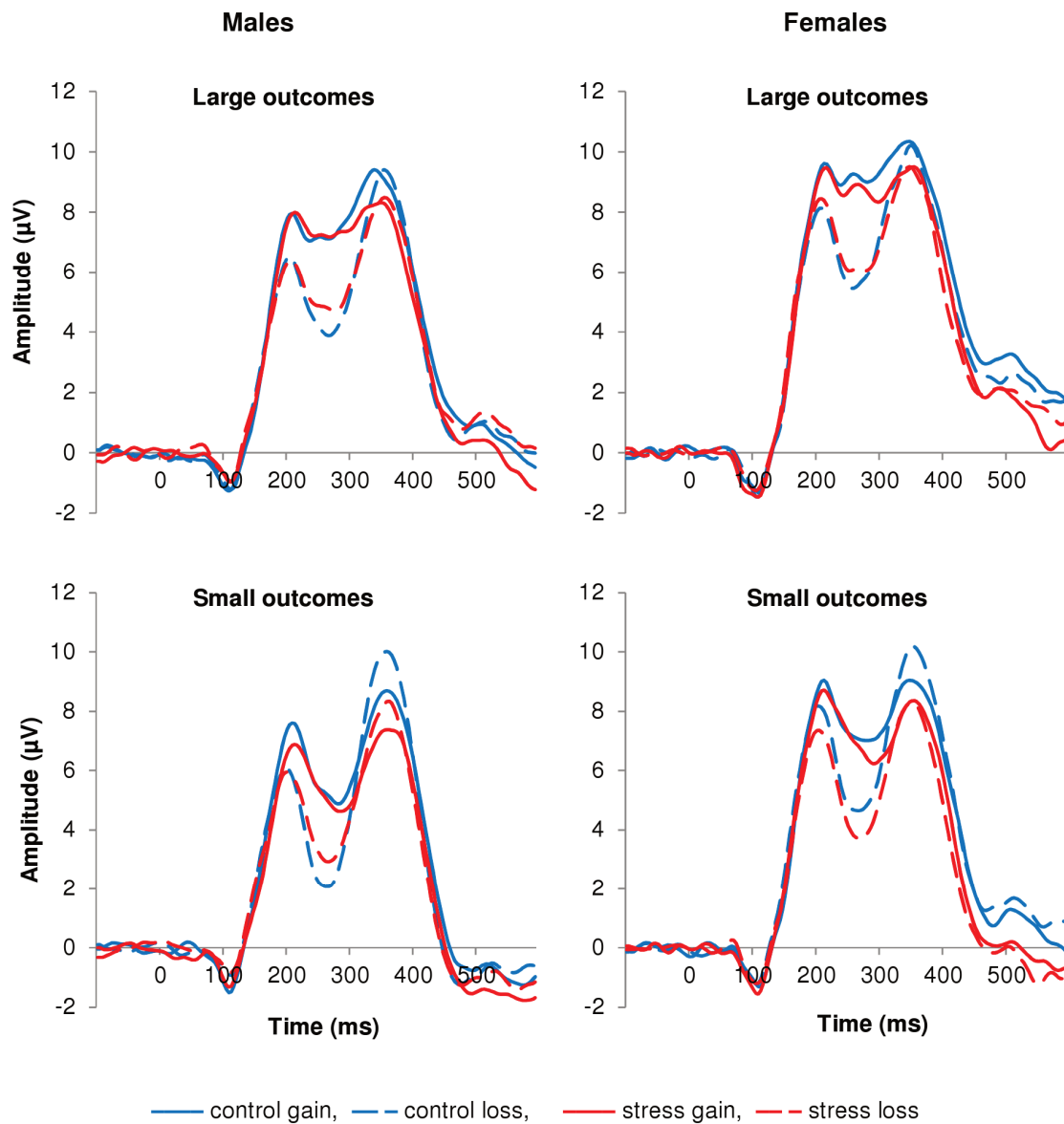
Figure 5. ERPs from FCz per magnitude, as a function of feedback valence and stress induction, for males and females, separately. ERPs from FCz per magnitude, as a function of feedback valence and stress induction, for males (left) and females (right), separately. The solid lines represent gain trials; the broken lines represent loss trials. The blue lines represent the control condition; the red lines represent the stress condition. The FRN amplitude was smaller in the stress relative to the control condition, but only as quantified by the mean amplitude (230–300 ms post-feedback) corrected for both preceding (180–225 ms) and following (320–390 ms) peaks. Interactions involving valence, magnitude, stress induction and sex did not reach significance.

outcomes, in females. However, interactions involving valence, magnitude, stress induction and sex did not reach significance (for all three FRN measures and for all comparisons: $F(1, 45) \leq 2.63$, n.s).

In our previous study (Banis & Lorist, 2012), where only male participants were included, we found a significant valence by stress induction interaction on the mean amplitude measure, and a significant magnitude by stress induction interaction on the base-to-peak measure, which we did not find in the current study. In order to clarify these divergent findings with regard to stress induction effects, we performed repeated measures ANOVAs on the pertaining measures, for both sexes separately. Neither of the two mentioned interactions were significant, although the analyses did reveal a few trends. The repeated measures ANOVAs on the mean amplitude measure showed a nonsignificant valence by stress induction interaction in males ($F(1, 23) = 3.09$, $p = .092$) and a nonsignificant valence by magnitude by stress induction interaction in females ($F(1, 22) = 3.80$, $p = .064$). The repeated measures ANOVAs on the base-to-peak measure showed nonsignificant magnitude by stress induction interactions in both sexes (both males and females: $F < 1$, n.s.).

P300

Table 2 summarizes the results of the repeated measures ANOVAs on the posterior P300 and the fronto-central P300, respectively. The posterior P300 was more positive in response to gains relative to losses, and in response to large compared to small outcomes. The magnitude effect on the posterior P300 was present for both gains ($F(1, 45) = 39.05$, $p < .001$) and losses ($F(1, 45) = 8.52$, $p = .005$), but more pronounced for gain trials. In addition, the posterior P300 amplitude was smaller in the

Table 2

Summary of effects on the posterior P300 (Pz) and the fronto-central P300 (FCz). The $F(1, 45)$- and p-values are reported.

P300 measure	Posterior P300		Fronto-central P300	
Effect	*F*	*p*	*F*	*p*
Valence	25.22	< .001	< 1	n.s.
Magnitude	33.60	< .001	13.30	.001
Valence by magnitude	7.97	.007	9.73	.003
Stress induction	4.53	.039	3.42	.071
Magnitude by stress induction	12.10	.001	5.77	.020

stress relative to control condition, but this effect was only significant for small outcomes ($F(1, 45) = 7.19$, $p = .010$), not for large outcomes ($F(1, 45) = 2.34$, $p = .134$).

The fronto-central P300 was more positive in response to large relative to small outcomes, but only for gains ($F(1, 45) = 21.70$, $p < .001$) not for losses ($F(1, 45) = 1.35$, $p = .251$). In addition, the fronto-central P300 was smaller in the stress relative to the control condition, but this effect was only significant for small outcomes ($F(1, 45) = 5.41$, $p = .025$), not for large outcomes ($F(1, 45) = 1.66$, n.s.).

Oscillatory power results

Theta power and both early (0–300 ms post-feedback) as well as late (300–600 ms) lower and upper beta-band power increased after all feedback types, in both stress induction conditions, relative to a pre-feedback baseline interval (Fig. 3). The observed theta power increase was larger for losses than gains, and for small relative to large outcomes (valence: $F(1, 45) = 15.37$, $p < .001$; magnitude: $F(1, 45) = 19.70$, $p < .001$; Fig. 6, Fig. 7). In addition, the increase was more pronounced in the control compared to the stress condition ($F(1, 45) = 7.26$, $p = .010$; Fig. 7, Fig. 8). Sex did not modulate theta power.

Early lower beta power was more pronounced for large relative to small outcomes ($F(1, 45) = 4.57$, $p = .038$; Fig. 6, Fig. 9). In addition, early lower beta power depended on the combination of stress induction condition and sex (stress induction by sex: $F(1, 45) = 6.22$, $p = .016$: Fig. 8, Fig. 9). Both sexes showed similar power increases in the control condition, while in the stress condition, males showed larger power increases than females (sex effect in stress condition: $F(1, 45) = 6.68$, $p = .013$). Separate analyses for both sexes revealed an effect of stress induction, in males only, with larger power increases in the stress relative to the control condition, approaching significance (stress induction effect in males: $F(1, 23) = 4.18$, $p = .053$). Late lower beta power was larger for losses relative to gains ($F(1, 45) = 4.29$, $p = .044$; Fig. 6, Fig. 9). In this late interval, males showed larger increases in lower beta power compared to females, in both stress induction conditions (sex: $F(1, 45) = 6.99$, $p = .011$; stress induction by sex: $F(1, 45) = 3.24$, n.s.; Fig. 8, Fig. 9).
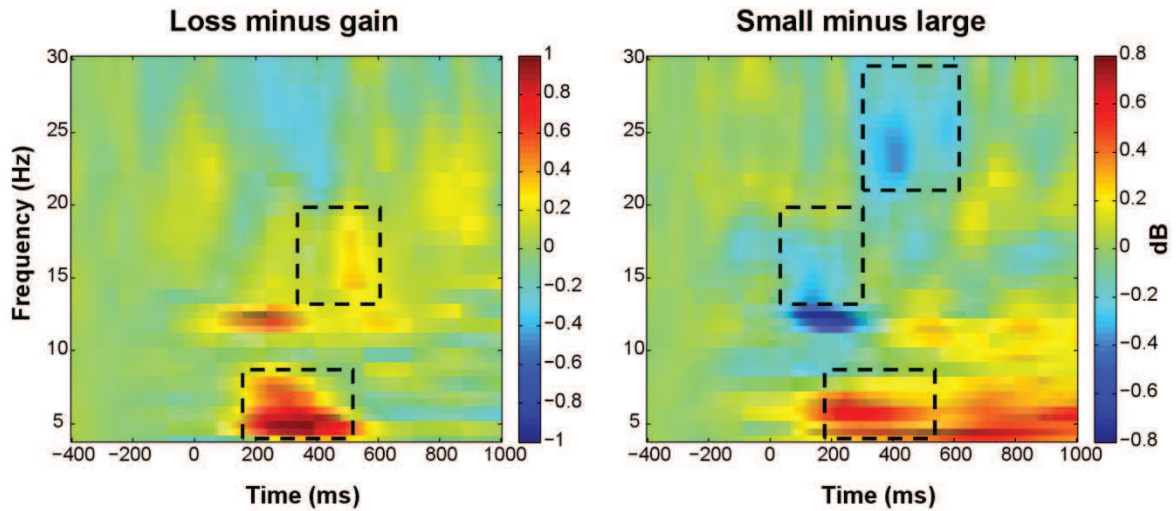
Figure 6. Time-frequency plots showing effects of feedback valence and magnitude. Time-frequency representations of the difference between loss and gain trials (left), and of the difference between small and large outcome trials (right). The plots show relative power (dB) at FCz. Only for time-frequency plots, relative power averages were converted to a decibel (dB) scale, enabling comparison between different frequencies. Line boxes highlight larger increases in theta and late lower beta-band power for losses relative to gains (left); larger increases in theta power and smaller increases in early lower beta-band and late upper beta-band power for small compared to large outcomes (right).
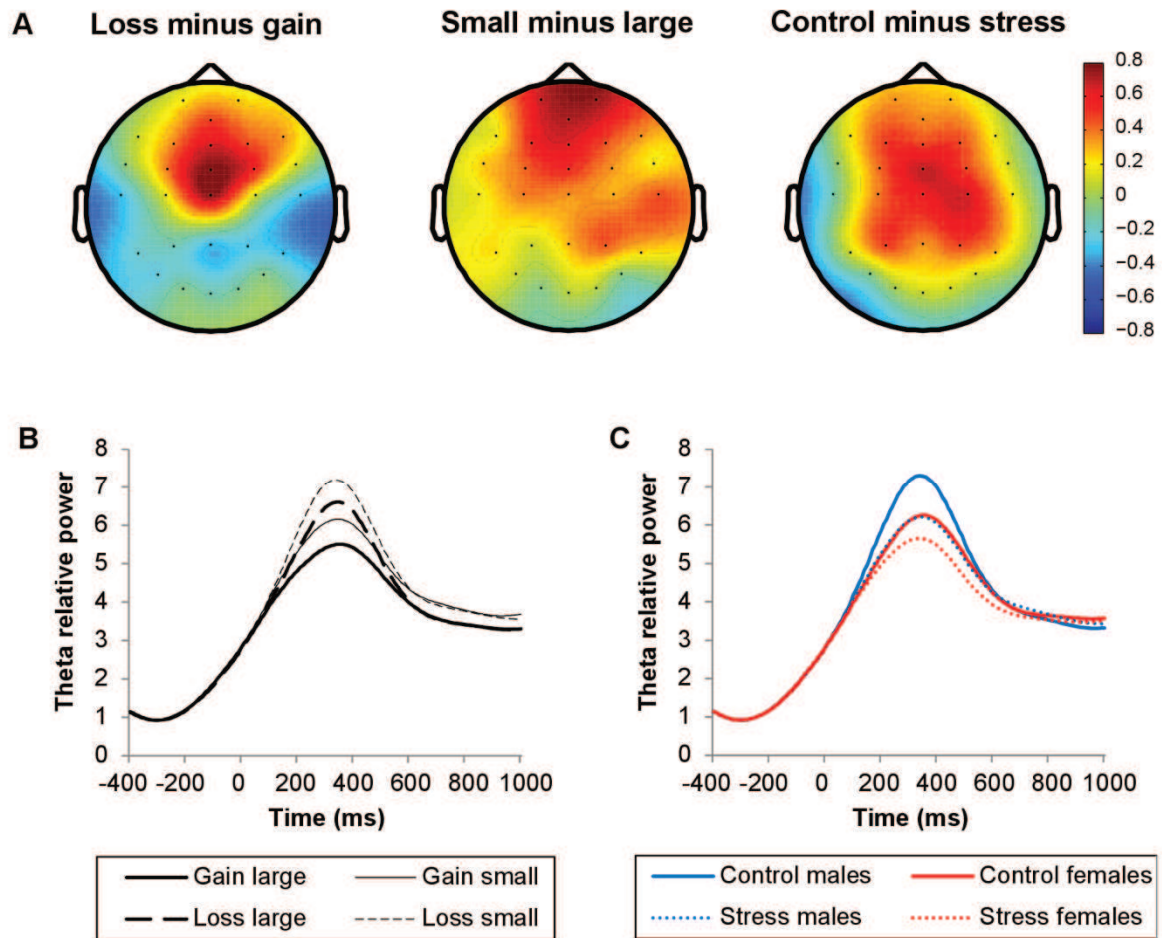
Figure 7. Topographical maps and line plots of theta relative power. Plots of theta relative power (4–7 Hz, 200–500 ms post-feedback). (A) Topographical maps of the difference between loss and gain trials, the difference between small and large outcome trials, and the difference between control condition and stress condition trials. (B) Line plots of theta relative power at FCz as a function of valence and magnitude. (C) Line plots of theta relative power at FCz as a function of stress induction and sex. Theta power increases were larger following losses versus gains, small versus large outcomes, and in the control versus stress condition. Sex did not modulate theta power significantly.
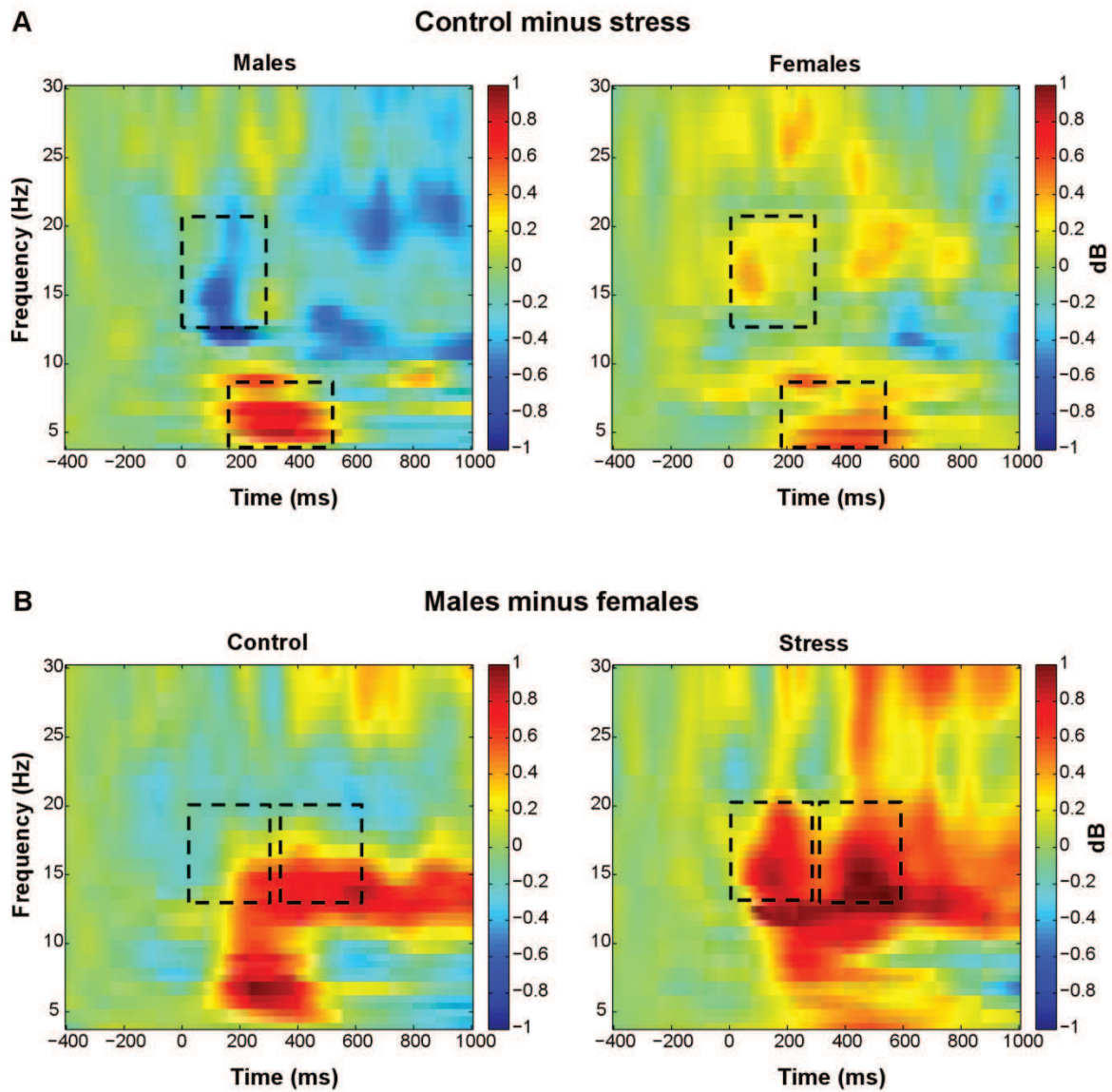
Figure 8. Time-frequency plots showing stress induction by sex interaction. (A) Time-frequency plots for the difference between control and stress trials, for males (left) and females (right). (B) Time-frequency plots for the difference between males and females, in control trials (left) and stress trials (right). The plots show relative power (dB) at FCz. Only for the time-frequency plots, relative power averages were converted to a decibel (dB) scale, enabling comparison between different frequencies. Line boxes highlight larger theta power increases in the control relative to the stress condition in both sexes. Males only showed an effect of stress induction on early lower beta-band power, approaching significance ($p = .053$), with larger increases in the stress relative to the control condition. More pronounced increases in lower beta power were observed in males than in females. In the early interval, this sex difference was restricted to the stress condition, whereas in the late interval, this difference was observed for both conditions.

Figure 9. Topographical maps and line plots of lower beta-band relative power. Plots of lower beta-band relative power (13–20 Hz). (A) Topographical maps of the difference between loss and gain trials (300–600 ms post-feedback), the difference between large and small outcome trials (0–300 ms), and the difference between males and females (0–600 ms). (B) Line plots of lower beta-band relative power at FCz as a function of valence and magnitude. (C) Line plots of lower beta-band relative power at FCz as a function of stress induction and sex. Lower beta-band power increases were larger following losses than gains (300–600 ms), and larger for large relative to small outcomes (0–300 ms). More pronounced increases in lower beta power were observed in males than in females. In the early interval, this sex difference was restricted to the stress condition, whereas in the late interval, this difference was observed for both conditions.
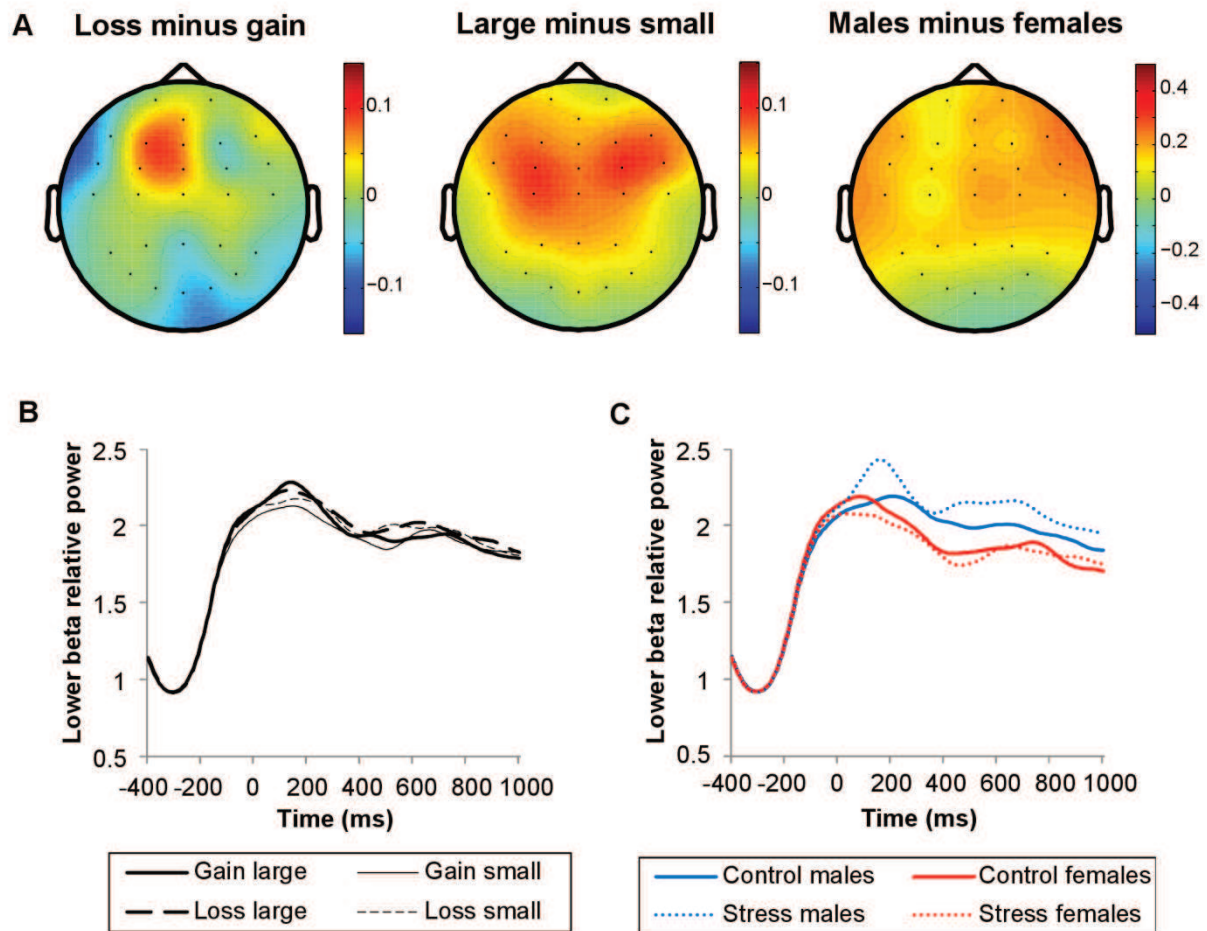
A   **Large minus small**

B
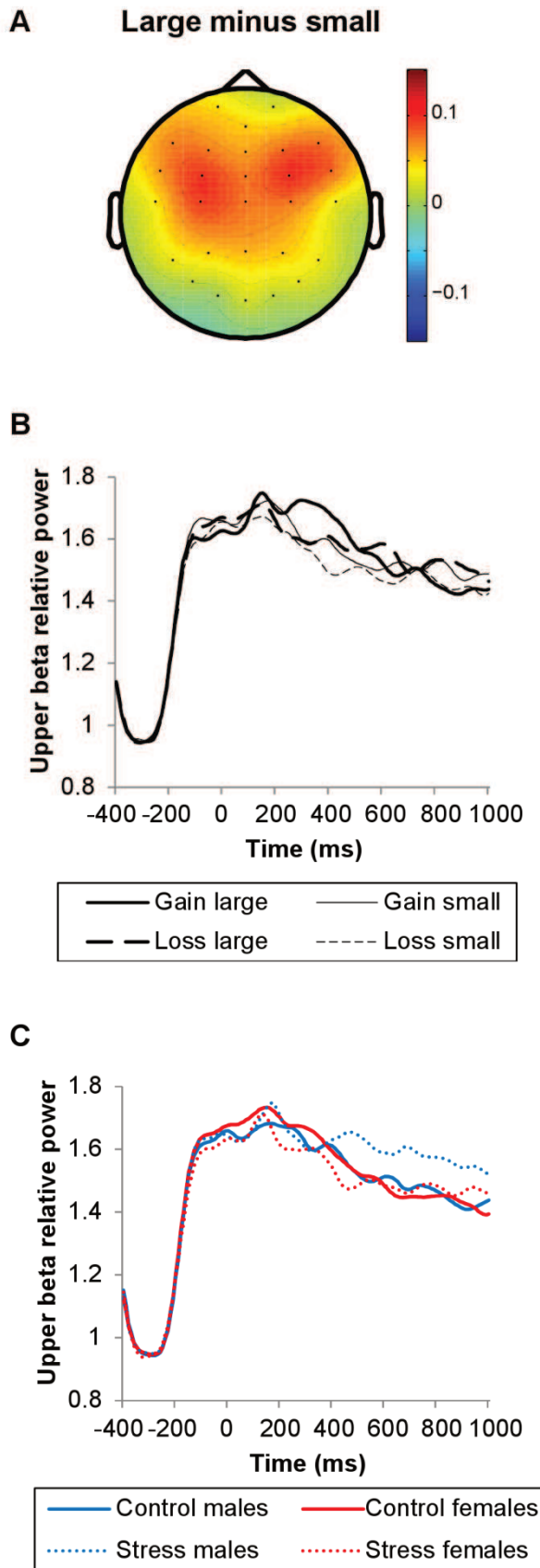
Figure 10. Topographical maps and line plots of upper beta-band relative power. Plots of upper beta-band relative power (21–30 Hz). (A) Topographical map of the difference between large and small outcome trials (300–600 ms post-feedback). (B) Line plots of upper beta-band relative power at FCz as a function of valence and magnitude. (C) Line plots of upper beta-band relative power at FCz as a function of stress induction and sex. Upper beta-band power increases were larger for large relative to small outcomes (300–600 ms). Neither stress induction nor sex modulated upper beta-band power significantly.

C

Whereas lower beta power was modulated by feedback magnitude in the early interval, upper beta power was modulated by feedback magnitude in the late interval. Similar to early lower beta power, late upper beta power was more pronounced for large relative to small outcomes ($F(1, 45) = 5.63$, $p = .022$; Fig. 6, Fig. 10). Neither stress induction nor sex influenced upper beta power (Fig. 8, Fig. 10).

Furthermore, we examined whether absolute power values differed in the baseline interval (-400–-200 ms pre-feedback), between stress induction conditions and sexes. Neither stress induction nor sex modulated theta baseline power. However, sex modulated lower beta baseline power, with larger power values for females relative to males ($F(1, 45) = 5.21$, $p = .027$), in both stress induction conditions. Note that in the feedback-related interval, men showed larger increases in lower beta power than women, relative to the baseline interval. In the early interval, this sex difference was present only in the stress condition, while in the late interval, this sex difference was present in both control and stress conditions. Furthermore, stress induction affected upper beta baseline power, with larger power values for the stress relative to the control condition ($F(1, 45) = 6.78$, $p = .012$), for both sexes.

Finally, we performed post-hoc analyses to investigate whether significant valence and magnitude effects on feedback-related changes in oscillatory power were associated with, significant valence and magnitude effects on behavioral measures, respectively. Effects of valence and magnitude on feedback-related theta and beta power were not significantly correlated with effects of valence and magnitude on mean RTs and mean stay percentages (Table 3).

In short, theta power was larger following losses than gains, small compared to large outcomes, and in the control relative to the stress condition. Theta power did not depend on sex. Late lower beta-band power was larger following losses than gains. Both early lower beta and late upper beta power were larger for large relative to small outcomes. More pronounced increases in lower beta power were observed in males than in females. In the early interval, this sex difference was restricted to the stress condition, whereas in the late interval, this difference was observed for both conditions. Whereas neither stress induction nor sex affected theta baseline power, these factors differentially modulated lower and upper beta baseline power. Effects of valence and magnitude on feedback-related oscillatory power were not significantly correlated with effects on behavior.

Exploratory results: Theta-band intersite phase synchrony. Theta-band ISPS was significantly higher after loss trials compared to gain trials between FCz and F3 ($F(1, 45) = 33.84$, $p < .001$), and between FCz and F4 ($F(1, 45) = 51.30$, $p < .001$).

Table 3

Correlations between effects on behavior and oscillatory power. Pearson's *r*(47)-values are reported (all nonsignificant).

Effect on behavior	Valence effect on reaction times	Valence effect on stay percentages	Magnitude effect on reaction times
Effect on oscillatory power	r	r	r
Valence effect on theta power	.174	.171	n/a[1]
Valence effect on late lower beta-band power	-.052	.152	n/a
Magnitude effect on theta power	n/a	n/a	.080
Magnitude effect on early lower beta-band power	n/a	n/a	.016
Magnitude effect on late upper beta-band power	n/a	n/a	.100

Correlations between significant valence and magnitude effects on feedback-related changes in oscillatory power and significant valence and magnitude effects on behavioral measures, respectively.

[1] Not applicable.

Neither stress induction nor sex affected theta-band ISPS between these sites.

Discussion

Aim of the present study was to investigate whether acute stress alters decision making by modulating feedback processing, and whether stress effects differ between men and women. In order to do so, we examined effects of feedback valence and magnitude on the feedback-related EEG response, in a control and a stress condition, in men and women. We used both ERP and time-frequency analyses, measuring the FRN and changes in theta and beta oscillatory power, respectively. During the stress condition, participants were exposed to a noise stressor. While the FRN and feedback-related theta power were similarly affected by stress induction in both sexes, feedback-related beta power depended on the combination of stress induction condition and sex. Behavior was not modulated by stress induction or sex.

Participants completed a simple gambling task, in which each choice was followed by feedback indicating the amount of money won or lost on that trial. They

were instructed to earn as much money as possible, but as gains and losses were assigned randomly, there was no strategy they could learn to optimize their monetary results. Nevertheless, participants' choice behavior indicated that they actually were sensitive to the valence and magnitude of previous outcomes. They were, for example, more likely to repeat their previous choice, if that choice had resulted in a gain than if that choice had resulted in a loss, indicating that they took previous outcomes into account, in their decisions. This is in line with the idea that decision makers, when faced with uncertainty, actively search for information to improve future choices (Platt & Huettel, 2008).

Effects of feedback valence and magnitude

The effects of feedback valence and magnitude on the FRN and feedback-related theta power showed a consistent pattern. Both the FRN and theta power were larger for losses compared to gains, and for small relative to large outcomes, which is in line with previous studies investigating the effects of valence and/or magnitude on these measures (FRN, both valence and magnitude: Goyer, Woldorff, & Huettel, 2008; Marco-Pallarés et al., 2008; Wu & Zhou, 2009; theta power, valence: Cohen et al., 2007; Cohen et al., 2009; Marco-Pallarés et al., 2008; theta power, magnitude: HajiHosseini, Rodríguez-Fornells, & Marco-Pallarés, 2012). According to the conflict monitoring theory, MFC activity – as reflected in the FRN amplitude and theta power increase – is especially high in situations of high behavioral uncertainty (Botvinick, 2007; Cavanagh et al., 2012). This increased MFC activity is thought to communicate a need for increased cognitive control to the lateral PFC, which performs regulatory processes to implement adjustments (Cohen et al., 2011; Ridderinkhof et al., 2004; Van de Vijver et al., 2011). Losses are more likely to cause a higher level of behavioral uncertainty relative to gains: decisions preceding losses were apparently wrong and require adjustments of behavior; whereas decisions preceding gains were apparently right, indicating that choice behavior was efficient. In addition, small outcomes probably generate more uncertainty than large outcomes, as their meaning is less equivalent: a small gain is a gain, but still not optimal; and while a large loss clearly points to a need for adjustments, it is less clear what to do after a small loss (Banis & Lorist, 2012). Our findings fit well with the uncertainty account of MFC activity, as we did observe an increase in FRN and theta power in response to losses and small outcomes relative to gains and large outcomes, respectively.

Our exploratory analyses of theta-band ISPS between the MFC and lateral PFC

revealed increased ISPS after loss relative to gain trials, which is in accordance with earlier studies (Cavanagh et al., 2009; Van de Vijver et al., 2011). It confirms the importance of theta oscillations in signaling a need for increased cognitive control between the MFC and the lateral PFC. Nevertheless, ISPS between these sites was not affected by magnitude, while theta power was, suggesting that connectivity and power in the theta-band can be differentially modulated by feedback properties.

The effects of valence and magnitude on feedback-related beta power differed between frequency bands and across time windows. In general, beta-band activity has been linked to the maintenance of a sensorimotor or cognitive state (Engel & Fries, 2010). From this perspective, it might be expected that beta power increases are larger when the maintenance of the status quo is likely intended (e.g., after gains) than when a change is intended (e.g., after losses). Previous studies have indeed shown increased upper beta-band power over frontocentral sites in response to positive versus negative feedback or gains versus losses (Cohen et al., 2007; HajiHosseini et al., 2012; Marco-Pallarés et al., 2008; Van de Vijver et al., 2011). In the present study, however, we could not replicate this valence effect on upper beta-band power. Moreover, for late lower beta-band activity we even found the opposite effect, that is larger power for losses than gains, indicating that this functional interpretation of beta-band activity neither holds for *lower* beta-band activity in feedback processing.

A somewhat different interpretation of the functional role of beta-band activity has been postulated by Baker (2007). With regard to motor control, he proposed that beta-band activity "may hold overt motor output constant in order to render the interpretation of the proprioceptive state more effective". The processing of proprioceptive feedback is necessary for monitoring the status quo and recalibrating the sensorimotor system. In addition, this monitoring of the peripheral state may enable the maintenance of a constant motor output through rapid feedback corrections (Baker, 2007). If beta-band activity has a similar function in cognitive processing, our findings suggest that losses relative to gains are followed by a more effective monitoring of feedback information.

In addition to feedback valence, beta-band activity was influenced by feedback magnitude. Increases in early lower beta-band power as well as late upper beta-band power were larger after large relative to small outcomes. Only a few studies, using gambling tasks, investigated the effects of feedback magnitude on beta-band activity. Marco-Pallarés et al. (2008) found enhanced upper beta power (20–30 Hz, 250–400 ms post-feedback) for maximum relative to minimum gains but not for losses. In a more recent study by HajiHosseini et al. (2012), no effect of magnitude on beta-

gamma activity (25–35 Hz, 200–400 ms) was found. Following the interpretation of Baker (2007), our findings suggest that large relative to small outcomes, similar to losses versus gains, are followed by a more effective processing of feedback information. With regard to behavior, large relative to small outcomes were indeed followed by slightly slower RTs. Nevertheless, the respective magnitude effects on mean RTs and beta-band activity did not correlate.

It should be noted that effects of feedback valence and magnitude on beta-band activity were present but not maximal at FCz (see Fig. 9, Fig. 10), the electrode we chose on the basis of previous feedback processing literature (Cohen et al., 2007; HajiHosseini et al., 2012; Marco-Pallarés et al., 2008; Van de Vijver et al., 2011). Further research is needed to clarify the functional role of beta-band activity in feedback processing, and to determine which brain areas communicate through beta oscillations during feedback processing.

Effects of acute noise stress and sex

Stress has been shown to affect brain regions underlying feedback processing and feedback learning (see for reviews, Dedovic et al., 2009; Starcke & Brand, 2012). Therefore, we expected acute noise stress to modulate feedback-related brain activity in the present study. Indeed, we found that the increase in theta power in response to feedback was smaller in the stress relative to the control condition. Importantly, this stress effect on theta power was not yet present in the pre-feedback baseline interval, but specifically occurred in response to feedback. Increases in theta power are thought to signal a need for increased cognitive control in uncertain conditions (Botvinick, 2007; Van de Vijver et al., 2011). Therefore, the smaller increase in the stress relative to the control condition indicates that acute stress affects performance monitoring and, as a possible consequence, adjustments in cognitive control. Furthermore, stress-related theta modulations were similar for males and females, suggesting that the impact of acute stress on performance monitoring in this task does not differ between men and women in the midluteal phase of their menstrual cycle.

Based on previous studies, we expected the FRN to be affected by acute noise stress as well (Banis & Lorist, 2012; Foti & Hajcak, 2009). Indeed, we found a smaller FRN in the stress relative to the control condition. However, this stress effect on the FRN was only present for the mean amplitude corrected for both peaks measure. Although the effects of valence and magnitude on the FRN were largely similar in the present study and in our previous study (Banis & Lorist, 2012), the effects of stress

induction showed dissimilarities between the two studies. In the current study, we found a significant main effect of stress induction on the mean amplitude corrected for both peaks measure, which was absent in the previous study. Visual inspection of the ERPs in our previous study did suggest an effect of stress induction on this FRN measure which seemed more pronounced for the unpredictable relative to the predictable noise stressor (see Fig. 3-6, in Banis & Lorist, 2012). This stress induction by stressor type interaction suggests that the divergent findings between the current study and the previous study may be partly due to the fact that in the current study, all participants ($n = 47$) were exposed to the unpredictable noise stressor, whereas in the previous study, only half of the participants ($n = 16$) were exposed to this stressor, while the other half were exposed to the predictable stressor. However, note that this interaction did not reach significance in the previous study and was therefore not reported. In our previous article (Banis & Lorist, 2012), we did not report the following statistics for the mean amplitude corrected for both peaks measure, as they were nonsignificant. The FRN was nonsignificantly smaller in the stress relative to the control condition (stress induction: $F(1, 30) = 3.55$, $p = .069$). This stress induction effect was nonsignificantly more pronounced for the unpredictable relative to the predictable noise stressor (stress induction by stressor type: $F(1, 30) = 3.37$, $p = .077$).

In addition, in the previous study, we found a significant valence by stress induction interaction on the mean amplitude measure, which we did not find in the current study. Visual inspection of ERPs in the present study suggested differential stress induction effects between men and women, on this measure (see Fig. 5). However, pertaining interaction effects did not reach significance. Post-hoc analyses for both sexes separately also did not yield significant interaction effects, although the valence by stress induction interaction in males approached significance. The divergent findings may be partly explained by the fact that the previous study had 32 male participants, whereas the current study had only 24 male participants, implicating reduced power in the present study.

Finally, in the previous study, we found a significant magnitude by stress induction interaction on the base-to-peak measure, which we did not find in the current study. We cannot explain this divergent finding, as the post-hoc analyses for both sexes separately showed nonsignificant interactions in both males and females. In conclusion, part of the divergent findings between the present and previous study may be explained by differences in experimental set-up (i.e., number and sex of participants, and noise stressor type). Although the findings of both studies together suggest that stress induction indeed affects the FRN, more research with larger sample

sizes is evidently needed before well-founded conclusions on this matter can be drawn.

As in our previous study, we found that FRN results were dependent on the method of measuring FRN amplitude (Banis & Lorist, 2012). More specifically, we found that stress induction only had a significant effect on the FRN if the amplitude was computed relative to both surrounding peaks. Post-hoc analysis of the fronto-central P300 showed that the amplitude was smaller in the stress relative to the control condition, for small outcomes. Correcting for the amplitude of this fronto-central P300 yielded a main effect of stress induction on the FRN, compared to the results for the FRN measures that did not correct for this component (mean amplitude measure, base-to-peak measure). Due to possible overlap between the FRN and other ERP components, the measurement of the FRN is complex. One would like to isolate the latent neural processes underlying the FRN, but it is impossible to determine precisely which latent processes add up to any specific ERP component (Luck, 2005). By correcting for the P300, one aims to eliminate neural processes that are unrelated to the FRN. Nevertheless, it remains inconclusive which correction procedure is most appropriate, as it is not clear when and where overlap between components starts and ends.

As we stated earlier, our findings with regard to the effects of feedback valence and magnitude were largely comparable across FRN and theta measures, suggesting that these measures reflect similar neural processes. Accordingly, it has been proposed that the FRN partially reflects a theta-band oscillatory process (Cavanagh et al., 2012; Cohen et al., 2007). Importantly, while the present stress effects were similar for the mean amplitude corrected for both peaks FRN measure and theta power, the other two FRN measures did not show stress effects. These discrepant findings between FRN measures might suggest that measuring the FRN while correcting for overlap with both surrounding components, relative to measuring the FRN while neglecting overlap with other components (mean amplitude) or correcting for the preceding component only (base-to-peak), results in a measure that better captures theta-band activity. Feedback processing and learning likely rely on large-scale brain networks which communicate through synchronized electrophysiological oscillations. As Cohen et al. (2011) have discussed, conceptualizing the feedback-related EEG response as a temporal-spatial-frequency landscape of oscillatory dynamics – instead of an ERP component with one peak – enables research results to be directly related to neurophysiological phenomena, such as population-level neuronal activity.

Up till now, little is known about the effects of acute stress on oscillatory power in response to action outcomes. Nevertheless, our findings with regard to theta power

– smaller feedback-related increases in the stress relative to the control condition – are in accordance with previous studies showing that acute noise stress has a deleterious effect on higher-order cognitive control functions (e.g., Arnsten & Goldman-Rakic, 1998; Szalma & Hancock, 2011). Moreover, we found additional evidence for stress-induced modulations of feedback processing. Stress seems to impair the ability to modulate behavior as a function of past positive or negative feedback (Bogdan & Pizzagalli, 2006; Petzold et al., 2010). In addition, stress reduces reward-related activation in the MFC (Ossewaarde et al., 2011a), and in the dorsal striatum and OFC (Porcelli et al., 2012). The same brain regions have been linked to the generation of feedback-related oscillations: the MFC is implicated in the generation of feedback-related theta oscillations (see Cohen et al., 2011), while the OFC is a likely source of feedback-related beta oscillations (Marco-Pallarés et al., 2008).

While stress-related theta modulations were similar for both sexes, stress-related lower beta-band modulations were sex-dependent. In the stress condition, men showed larger feedback-related increases in early lower beta power than women. Men and women also showed tonic differences in lower beta-band power as revealed by the larger baseline power values for females than males, in both stress induction conditions. The stress by sex interaction only became significant after feedback presentation, indicating that stress had an additional impact on sex differences, in the feedback-related interval. These differential stress effects on feedback processing may be related to sex-specific stress effects on decision-making behavior, that have been reported in recent studies (Lighthall et al., 2009; Lighthall et al., 2012; Van den Bos et al., 2009). As feedback processing and learning are crucial to adaptive decision making, their modification will likely affect decision making. Note, however, that in the present study, these effects were not reflected in behavioral changes, possibly due to the fact that participants could not learn a strategy to improve their performance.

Abnormal feedback processing is regarded as a causal factor in the pathogenesis of particular stress-related disorders (Forbes et al., 2007; Russo & Nestler, 2013). Depression, for example, is characterized by negative mood and anhedonia, that is loss of the ability to experience pleasure from normally rewarding stimuli. Neurophysiological studies have reported enhanced (Tucker, Luu, Frishkoff, Quiring, & Poulsen, 2003) as well as blunted (Steele, Kumar, & Ebmeier, 2007) responses to feedback in depressive patients, these opposite findings being ascribed to differences in illness severity. Considering the sex-specificity of the stress effects on feedback processing we observed, one might argue that differences between men and women may indeed explain (at least partly) the sex-specific prevalence rates of these

stress-related disorders.

In the early interval, men showed larger increases in lower beta power than women, only in the stress condition. In the late interval, this sex difference was present in both control and stress conditions, indicating that the neural underpinnings of feedback processing in general are at least partly sex-dependent. Sex differences in feedback processing may be related to sex differences in decision-making behavior. Van den Bos et al. (2009) conducted a review on sex differences in performance on the Iowa Gambling Task, a decision-making task in which subjects have to learn through exploration to differentiate between long-term advantageous and long-term disadvantageous card decks. Both men and women solve this task, but women need more trials before they consistently prefer the long-term advantageous decks. On the basis of their review, the authors proposed that men focus on long-term pay off of decks, while women focus on both long-term pay off and on win-loss frequencies. They suggested that women may be more sensitive than men to occasional losses. In the present study, however, we did not find evidence for the latter.

In conclusion, we have found that acute stress impairs performance monitoring in both sexes, as reflected in changes in FRN amplitude and frontocentral theta-band power. In addition, our findings with regard to early lower beta-band power suggest that men and women show sex-dependent stress effects on feedback processing, as well. The latter effects may be related to sex-specific prevalence rates in stress-related disorders.

CHAPTER 4

The combined effects of menstrual cycle phase and acute stress on reward-related processing

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Abstract

We investigated the combined effects of menstrual cycle phase and acute stress on reward-related processing, employing a monetary incentive delay task in combination with EEG. Females participated during late follicular and late luteal phases, performing in both control and stress conditions. We found evidence for both independent and interaction effects of phase and stress on reward-related brain activity. Phase modulated the sensitivity to feedback valence, with a stronger signaling of negative performance outcomes in the late follicular versus late luteal phase. In contrast, in the control condition, the late luteal versus late follicular phase was associated with a heightened sensitivity to reward condition, with enhanced performance monitoring in potential-reward versus no-reward trials. Stress decreased attentional preparation during reward anticipation, but increased the influence of reward condition on the processing of positive performance outcomes. We found no evidence for an increased sensitivity to stress during the late luteal versus late follicular phase.

Introduction

Fluctuations in gonadal hormone levels are thought to play an important role in the development of certain psychiatric disorders in women (Deecher, Andree, Sloan, & Schechter, 2008; Steiner, Dunn, & Born, 2003a). For example, the increased vulnerability to depression in women relative to men appears to be most pronounced during the late luteal (i.e. premenstrual) phase, the postpartum period, and the perimenopausal period, all stages in which hormonal fluctuations are steep (Deecher et al., 2008). This association between fluctuating hormones and disorders with sex differences in prevalence rates may be partly based on hormonal modulations of the brain's reward and stress circuitries (Kajantie & Phillips, 2006; Russo & Nestler, 2013). Moreover, activity within reward systems has been shown to be influenced by stress exposure (Dedovic, D'Aguiar, & Pruessner, 2009; Starcke & Brand, 2012). However, only little is known about how hormonal modulations of reward-related processing and stress regulation interact. In the present study, we aimed at examining the combined effects of menstrual cycle phase and acute stress on reward-related processing, using the menstrual cycle as a natural paradigm to examine the effects of changing hormone levels.

The menstrual cycle has a median length of 29.5 days (Becker et al., 2005), which can be divided into the follicular phase, the period from menstruation until ovulation, and the luteal phase, the period between ovulation and menses onset (Chabbert Buffet, Djakoure, Christin Maitre, & Bouchard, 1998). In the early follicular phase, levels of the gonadal hormones estradiol and progesterone are very low. Estradiol levels start rising from the midfollicular phase and peak during the late follicular phase, while progesterone remains low. During the luteal phase, estradiol levels decrease to a moderate level, while progesterone increases, peaking at the midluteal phase. The late luteal phase is marked by a steep decline of both estradiol and progesterone levels (Chabbert Buffet et al., 1998). Animal studies have shown widespread neurophysiological effects of these hormones (Becker, 2009; McEwen, 2002), but their influence on the brain's reward and stress circuitries in women has remained elusive (Dreher et al., 2007).

Preclinical research has yielded substantial evidence that estradiol and progesterone interact with mesolimbic and mesocortical dopamine (DA) systems, which play an important role in reward-related behaviors (Becker, 2009; McEwen).

Especially, estradiol appears to potentiate DA activity, whereas progesterone has been hypothesized to oppose this effect (Jackson, Robinson, & Becker, 2006). In humans, subjective responses in women to stimulant drugs have been reported to be increased during the follicular compared to the luteal phase (see for review, Terner & De Wit, 2006). Findings from fMRI studies have supported the stimulating influence of estradiol on the brain's reward system. For example, Dreher et al. (2007) found that brain reward areas showed increased activity in the midfollicular relative to the midluteal phase. In addition, Thomas, Météreau, Déchaud, Pugeat, and Dreher (2014), investigating the impact of hormonal treatment (HT) during the menopause transition, scanning women immediately after estradiol therapy and before progesterone administration, found that HT increased responsiveness of reward areas. Furthermore, estradiol and progesterone may interact on the reward system, resulting in decreased reward-related neural activity, as evidenced by Bayer, Bandurski, and Sommer (2013), who found a reduced sensitivity to the magnitude of gains and losses, in the midluteal compared to the early follicular phase.

Importantly, given the high variability of hormone levels across the cycle, differences between the follicular and luteal phases in reward-related processing might well depend on the specific subphases examined. More specifically, it has been hypothesized that the sudden drop in hormone levels during the late luteal phase causes a decline in endogenous DA activity, mimicking a withdrawal state, which in turn may cause enhanced DA release in response to reward cues (see for review, Ossewaarde et al., 2011b). This could, for example, explain the more frequent cravings of women for foods in combination with increases in energy intake in the (late) luteal relative to the follicular phase (Davidsen, Vistisen, & Astrup, 2007; Dye & Blundell, 1997), and the higher liking of alcohol consumption in the late luteal compared to the midfollicular phase (Evans & Levin, 2011). Findings from fMRI studies on this topic have yielded equivocal results. Ossewaarde et al. (2011b) found enhanced ventral striatal responses to reward anticipation during the late luteal as compared to the late follicular phase. In contrast, Macoveanu et al. (2016), employing a sex-steroid hormone manipulation which reduced estradiol and testosterone levels, found *reduced* amygdala responsivity to the magnitude of rewards in the manipulation compared to the placebo condition in the mid- to late follicular phase. In sum, the evidence is mixed with regard to the influence of dropping hormone levels on reward-related brain activity.

Besides changes in reward-related processing, the menstrual cycle has been associated with changes in stress-sensitivity. Stress-related cardiovascular reactivity

and cortisol levels have been shown to increase in the luteal relative to the follicular phase (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Lustyk, Olson, Gerrish, Holder, & Widman, 2010; Tersman, Collins, & Eneroth, 1991). In addition, neuroimaging studies have shown that neural responses in the stress response circuitry to emotional stimuli vary across the cycle (Goldstein, Jerram, Abbs, Whitfield-Gabrieli, & Makris, 2010; Ossewaarde et al., 2010; Protopopescu et al., 2005). Given that the brain's stress circuit is densely populated with estradiol receptors, and elevated estradiol levels during the late follicular phase have been associated with an attenuation of stress-related brain activity (Jacobs et al., 2015), these cycle-related fluctuations in stress-sensitivity may be related to gonadal hormone fluctuations, as well.

In addition to the menstrual cycle-related variability in reward-related processing and stress-sensitivity, both effects might be interrelated, as exposure to stress has been shown to modulate reward-related behaviors. For example, acute stress enhances eating in the absence of hunger (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009), and stress stimulates the transition to and maintenance of alcohol and drug dependence (Koob, 2008; Uhart & Wand, 2009). Neuroimaging studies have shown that stress may reduce potential-reward-related activity in the medial prefrontal cortex during reward anticipation (Ossewaarde et al., 2011a) and decrease sensitivity to the valence of monetary outcomes in the dorsal striatum and orbitofrontal cortex (Porcelli, Lewis, & Delgado, 2012). Furthermore, in two previous electroencephalography (EEG) studies (Banis, Geerligs, & Lorist, 2014; Banis & Lorist, 2012), we found evidence for impaired processing of monetary outcomes, under acute stress.

Aim of the present study was to investigate the combined effects of menstrual cycle phase and acute stress on reward-related processing. We compared the late luteal phase, characterized by a steep decline in hormone levels, and the late follicular phase, marked by high estradiol and low progesterone levels. Stress was induced by exposing participants to highly aversive (versus neutral) movie fragments in combination with a self-referencing instruction, immediately before the task blocks (e.g., Henckens, Hermans, Pu, Joëls, & Fernández, 2009). To validate the procedure, we measured heart rate, heart rate variability, and subjective emotions, during the movie clips; and salivary cortisol and subjective negative affect, prior to and after the task blocks.

To examine reward-related processing, we used a modified version of the monetary incentive delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000). The task consists of potentially rewarding and nonrewarding trials, indicated by a cue.

Following this cue, participants are presented with a target upon which they have to react as quickly as possible, by pressing a button. Feedback informs them whether they have reacted within the presentation time of the target and whether they have won money in that trial. During task performance, we applied EEG. Employment of the MID task in combination with the high temporal resolution of the EEG recordings enables the examination of successive stages of reward-related brain activity, related to reward anticipation and feedback (Broyd et al., 2012).

So far, EEG studies of reward-related processing have mainly focused on the processing of feedback, whereas the stage of reward anticipation has received less attention. Recent research suggests that the prospect of reward may enhance attentional preparation to upcoming stimuli (Van den Berg, Krebs, Lorist, & Woldorff, 2014). In the EEG time domain, cues signaling the impending presentation of a stimulus requiring a response, elicit the contingent negative variation (CNV; Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The CNV has been shown to reflect the orienting to and anticipation of the imperative stimulus, and response preparation (Grent-'t-Jong & Woldorff, 2007; Van Boxtel & Böcker, 2004). In the frequency domain, attentional preparation to upcoming stimuli has been associated with cue-related alpha power reductions over occipital regions representing the attended location, which are thought to reflect an increase in cortical excitability facilitating the processing of upcoming stimuli (Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Worden, Foxe, Wang, & Simpson, 2000). Top-down control signals from the fronto-parietal attentional network are thought to be the source of these attention-related modulations (Capotosto, Babiloni, Romani, & Corbetta, 2009). As reward prospect may amplify attentional preparation (Van den Berg et al., 2014), we expected potential-reward-related enhancements of the CNV and reductions in alpha power, in the current study.

With regard to the processing of feedback, the feedback-related negativity (FRN) is a well-known ERP component, which is elicited in response to external feedback and is larger in amplitude following negative compared to positive outcomes (e.g., Gehring & Willoughby, 2002). In the frequency domain, increases in theta power over frontocentral scalp sites have been shown to be larger after negative relative to positive outcomes (e.g., Cohen, Elger, & Ranganath, 2007). Both the FRN and feedback-related theta oscillations are thought to reflect the signaling of unfavorable outcomes (Cohen, Wilmes, & Van de Vijver, 2011; Van de Vijver, Ridderinkhof, & Cohen, 2011). Based on these findings, we expected larger FRN amplitudes and larger increases in theta power following misses compared to hits, in the present study.

In sum, we investigated the combined effects of menstrual cycle phase and acute stress on reward-related brain activity, as reflected in cue-related and feedback-related EEG measures. Based on the literature described above, we expected changes in sensitivity to reward prospect and feedback information across the menstrual cycle, as reflected in phase modulations of cue-related and feedback-related EEG measures. In addition, we expected acute stress to impair reward-related neural processing, as reflected in stress modulations of these measures. Finally, we expected an increased sensitivity to stress during the late luteal relative to the late follicular phase, as reflected in enhanced subjective and physiological stress responses, and in enhanced impairments of reward-related neural processing.

Method

Participants

Due to the novelty of the current design, we could not predict effect sizes in advance. Given the extensive design of the study and the application of strict inclusion and exclusion criteria, we aimed at including as many participants as possible. Our final sample ($n = 17$) permitted the detection of large effects.

Eighteen healthy, non-pregnant, right-handed females (mean age = 20.7 years, range 19–26 years) completed both experimental sessions. None of the women had used hormonal contraceptives within the six months previous to these sessions, and all had regular menstrual cycling with normal mean cycle length (mean = 29 days, range 26–34 days). They had no history of psychiatric disorders including Premenstrual Dysphoric Disorder (PMDD), as determined with the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) and the Premenstrual Symptoms Screening Tool (PSST; Steiner, Macdougall, & Brown, 2003b). None of the participants had experienced severe physical or emotional trauma. Furthermore, participants reported no evidence of neurological or endocrine disease; no current use of psychoactive medication or drugs or corticosteroids; no habit of watching violent movies or playing violent video games; and normal or corrected-to-normal vision. Participants did not consume more than three alcoholic beverages per day on average, and did not smoke. In addition, participants were asked not to consume alcohol 24h prior to the experiment. Participants received either course credits or money for their participation. In addition, they received a monetary bonus depending on their task

scores, as described below. The study was approved by the Ethical Committee Psychology of the Psychology Department of the University of Groningen, and all participants gave written informed consent.

Design and procedure

Participants were tested in a crossover design with the counterbalanced factors menstrual cycle phase (late follicular versus late luteal) and stress induction (stress versus control). Each woman was tested once during the late follicular phase and once during the late luteal phase, performing in both stress induction conditions during each session. During a screening session prior to the actual experiment, candidates completed the PSST (Steiner et al., 2003b) and the M.I.N.I. (Sheehan et al., 1998). In addition, all participants received instructions for the ovulation predictor test (see below).

Timing of experimental sessions was determined as follows. Late follicular phase sessions were scheduled between days 8 and 12 with respect to the first day of the menstrual cycle (day 1 = menses onset; mean time point of session: day 10.7, SD = 1.2). All late follicular sessions took place in menstrual cycles of normal length (M = 28.6, SD = 2.5, range 24–33 days). Late luteal phase sessions were planned following the luteinizing hormone (LH) surge, as determined using commercially available ovulation predictor tests (Dutch Diagnostics, Zutphen, The Netherlands). Sessions were scheduled between days 10 and 14 after the surge (day 0 = LH surge; mean time point of session: 3.3 days before menstruation started, SD = 1.6). For menstrual cycle phase verification, we measured salivary progesterone levels on both session days. In addition, all participants were asked to report the date of onset of their next menses. These verification measures also allowed us to confirm that no participant was pregnant during the experiment.

On the days of the experimental sessions, participants arrived at the laboratory at 11.30 a.m. After the application of the electrocap and the electrocardiogram (ECG) electrodes, participants practiced the MID task. Then, they provided salivary samples for progesterone determination, after which they had a resting period of 5 min.

All experimental testing took place between 13.00 and 17.00 p.m. to ensure relatively stable and low levels of endogenous cortisol. Participants completed two task blocks (12 min each) of the MID task, in both stress induction conditions (Fig. S1). Immediately before the task blocks, participants were shown highly aversive versus neutral control movie fragments (2:20 or 1:30 min). In addition, halfway

through the task blocks (after 6 min), part of the preceding fragment (0:45 min) was shown again. The order of stress induction conditions was counterbalanced across subjects. Both conditions were separated by a break of 75 min. Participants completed the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) and provided salivary samples for cortisol determination, at three time points, in both stress induction conditions: before the first task block (t1), after the first task block (t2) and after the second task block (t3). In addition, participants rated their emotions while watching the movie clips, after the second task block of both conditions.

Stress induction

To induce a stressful state, highly aversive movie fragments were shown to the participants immediately before the task blocks. In addition, halfway through the task blocks, part of the preceding fragment (0:45 min) was shown again. The four movie clips were selected from a distressing movie [Irréversible (2002), Gaspar Noé] and contained scenes with maximally aggressive behavior and violence against men and women. Occasionally, people in the video shouted and cried out in anger, pain, or distress. The effectiveness of these movie clips in inducing stress has been confirmed in previous studies (Henckens et al., 2009; Ossewaarde et al., 2010). For the control condition, neutral fragments from another movie [Comment j'ai tué mon père (2001), Anne Fontaine] were shown. Stressful and neutral movie clips were comparable in amount of speech, human presence, luminance, and language. Participants were instructed to view the movie clips (2:20, 1:30, 1:30, 1:30 min, respectively) attentively, imagining being an eyewitness of the events. Additionally, they were asked to watch constantly, not to look away from the screen.

Monetary incentive delay task

The task was a modified version of the MID task as developed by Knutson et al. (2000). Each task block consisted of 80 potentially rewarding trials and 80 nonrewarding trials. Participants completed two task blocks per stress induction condition, resulting in 160 potentially rewarding trials and 160 nonrewarding trials per condition.

Each trial (Fig. S2) started with the presentation of a fixation cross, for a randomly varying interval of 800–1200 ms. Then, a cue was presented for 250 ms signaling potential reward (a plus sign within a circle) or no reward (a times sign

within a circle), starting the anticipation phase. Following a second presentation of a fixation cross (800–1200 ms), a brief target (a white square) appeared on the screen with a start duration of 200 ms. Participants were instructed to push a button as fast as possible upon detection of the target, irrespective of the cue type. Following a third presentation of a fixation cross (800–1200 ms), there was an outcome phase in which feedback was presented for 1000 ms. Feedback informed participants whether they had pushed the button within the presentation time of the target ("hit!" or "miss!"), and whether they had won money in that trial ("+€10" or "+€0"). In potentially rewarding trials only, hits were rewarded with €10. At the end of each task block, participants received additional feedback indicating the amount of money earned during the previous block. They were told that they would earn a percentage of their cumulative total win, after both experimental sessions, but were not told the exact percentage. To equalize total gain across conditions and participants, the presentation time of the target was adapted on a trial by trial basis per reward condition. Target duration was shortened by 20 ms when the previous target was hit; it was lengthened by 10 ms when the previous target was missed (Ossewaarde et al., 2011b). In addition, target duration was set to never exceed 100–1000 ms boundaries.

Progesterone sampling and analysis

To measure progesterone levels, single saliva samples (3 ml) were collected during both experimental sessions, using saliva tubes (Greiner Bio One, Alphen aan de Rijn, Netherlands). Participants were requested not to brush or floss their teeth, and to abstain from eating and drinking anything but water, for 3 h prior to saliva sampling. All samples were stored at a maximum temperature of -20°C until analysis. Thawed samples were prepared for biochemical analysis by centrifuging them for 10 min at 2000 g. Progesterone concentrations were determined in duplicate samples employing an in house radioimmunoassay, with a sensitivity of 37 pmol/L (Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands).

After progesterone determination, one participant was excluded from further analysis, because her salivary progesterone level in the follicular phase (371.0 pmol/L) deviated more than three standard deviations from the group mean ($M = 79.1$ pmol/L, $SD = 74.9$). Salivary progesterone levels from 17 participants were analyzed using a paired t-test.

Measurements of stress and data reduction

Subjective measurements of stress

Mood was assessed using the PANAS (Watson et al., 1988), at three time points in each stress induction condition: before the first task block (t1), after the first task block (t2), and after the second task block (t3; Fig. S1). In addition, after the second task block of each stress induction condition, participants rated their emotions while watching the movie clips, on a 10-point scale (1 = not at all, 10 = very much so). Those emotions included anger, fear, sadness, happiness, disgust, and surprise.

Physiological measurements of stress

To measure the hypothalamic-pituitary-adrenal (HPA) axis stress response as reflected in cortisol levels, saliva samples (2 ml) were collected using saliva tubes, at three time points in each stress induction condition: before the first task block (t1), after the first task block (t2), and after the second task block (t3; Fig. S1). All samples were stored at a maximum temperature of -20°C until analysis. Thawed samples were prepared for biochemical analysis by centrifuging them for 10 min at 2000 g. Cortisol concentrations were determined in duplicate samples using an in house radioimmunoassay, with a sensitivity of 0.30 nmol/L (Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands). Baseline-corrected cortisol levels were determined by subtracting baseline cortisol levels at t1 from cortisol levels at t2 and t3 in each stress induction condition. This baseline correction was applied to account for the typical decline in cortisol levels over the course of the day (Edwards, Clow, Evans, & Hucklebridge, 2001).

To measure the sympathetic nervous system stress response as reflected in heart rate (HR) and heart rate variability (HRV), we recorded the ECG during the movie clips. The ECG was registered using three Sn electrodes, which were placed on the sternum (common electrode) and on the left and right sides of the body, between the two lower ribs. R-peaks in the ECG signal were detected online, with an accuracy of 2 ms, using Portilab (Twente Medical Systems International). These R-peaks were used to create inter-beat interval (IBI) time series. IBI's were visually inspected and manually corrected, upon which mean HR and mean power of HRV in the mid-frequency band (0.07–0.14 Hz) were calculated, using the CARSPAN spectral analysis program (Mulder, 1992). Heart rate variability, especially variability in the 0.10 Hz band, is suppressed during mental effort (e.g., Mulder, De Waard, & Brookhuis, 2005). Power spectral data were Ln-transformed to reduce inter-individual differences in range and to normalize the data (Van Roon, 1998).

Electrophysiological recordings and data reduction

EEG was measured using 28 Sn electrodes attached to an electrocap (ElectroCap International Inc., Eaton, Ohio, USA), positioned according to the 10-10 system. Recordings were taken from channels FP1, FP2, AFz, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, PO7, O1, Oz, O2 and PO8. Horizontal electro-oculogram (EOG) was recorded bipolarly using two electrodes placed at the outer canthi of both eyes. Vertical EOG was measured using two electrodes placed above and below the left eye. All electrode impedances were kept below 10 kΩ, besides the two reference electrodes on both mastoids which were kept below 5 kΩ. EEG and EOG signals were filtered with a 0.16-Hz high-pass filter and a 200-Hz low-pass filter, and recorded with a 500-Hz sample rate.

Off-line, EEG and EOG data were re-referenced to the computed average of both mastoids. Data were down-sampled to 256 Hz, after additional filtering: for the ERP analysis, with a low-pas filter of 30 Hz and a slope of 48 dB/oct; for the TFR analysis, with a low pass filter of 55 Hz and a slope of 48 dB/oct.

For the ERP analyses of cue-related and feedback-related segments, data were segmented in 1150-ms epochs, starting 100 ms before cue or feedback onset, respectively. For the TFR analysis, segments covered 3000 ms, starting 1000 ms before cue/feedback onset. Epochs with too rapidly changing activity (maximal allowed voltage step ±60 μV and ±75 μV for the ERP and TFR analyses, respectively) were rejected. After removal of these artifacts, EEG was corrected for eye movements and blinks using the regression procedure of Gratton, Coles, and Donchin (1983). Then, for the ERP analyses only, epochs which contained EEG voltage differences exceeding 200 μV, or EEG amplitudes exceeding +/- 100 μV, were eliminated. Furthermore, ERP/TFR segments were visually inspected for edge artifacts and other remaining artifacts. After these ocular correction and artifact rejection procedures, EEG was averaged relative to a 100 ms pre-cue/feedback baseline. For the ERP analysis of cue segments, separate averages were calculated for each combination of phase (late follicular versus late luteal), stress induction (stress versus control), and reward condition (potential-reward versus no-reward), resulting in eight average waveforms for each electrode and participant. For the ERP analysis of feedback segments, separate averages were calculated for each combination of phase, stress induction, feedback valence (hit versus miss), and reward condition, resulting in sixteen average waveforms for each electrode and participant.

Time-frequency analyses were performed with the Matlab-based FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). To study the oscillatory

dynamics of the EEG, single-trial cue/feedback-locked data were convolved with a family of complex Morlet wavelets. These wavelets contained a fixed number of cycles of sinusoidal oscillations for each frequency band (4–7 Hz, 5 cycles; 8–12Hz, 6 cycles; 13–20 Hz, 7 cycles; 21–30 Hz, 7 cycles). This analysis produced raw power estimates for each time point between 400 ms pre-cue/feedback and 1050/1000 ms post-cue/feedback (in 10-ms steps) at frequencies of 4–30 Hz (in 0.5-Hz steps). Subsequently, a condition-specific, relative baseline correction was applied. First, we calculated average spectral power across trials per condition per participant. Then, we divided the average power at each time point by the average power of the pertaining frequency in the -400–-200 ms pre-cue/feedback interval.
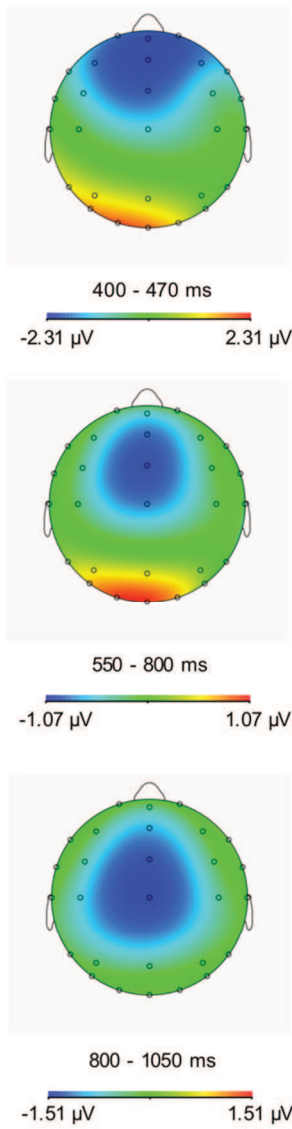
Data analysis

Measurements of stress

Negative affect ratings and baseline-corrected cortisol levels were subjected to repeated measures analyses of variance (rANOVAs) with the within-subjects (WS) factors phase, stress induction and time (negative affect: t1, t2, t3; cortisol: t2, t3). Emotion ratings were subjected to rANOVAs with the WS factors phase, stress induction and emotion (six emotions). HR and HRV values were subjected to rANOVAs with the WS factors phase, stress induction and clip (clip 1, clip 2).

Treatment of missing data. One cortisol sample from one participant was missed due to researcher error (forgetting to sample), and two HR as well as HRV measurements from another participant were missed due to technical problems during the experiment. Excluding participants because of missing data possibly affects the representativeness of findings and reduces statistical power (Graham, 2009). Therefore, we used the multiple imputation method (Multiple Imputation module of SPSS Version 21.0: imputation method automatic, linear regression) to predict the values of these missing data, as described by Van Buuren (2007).

Behavioral measures

Reaction time data of responses during the MID task were first filtered by removing values below 100 ms (Hsu, 2005; Ulrich & Miller, 1994). Subsequently, outliers relative to participants' condition-specific (phase by stress induction by reward condition) means were eliminated, using the outlier removal algorithm outlined by Van Selst and Jolicoeur (1994). The resulting mean reaction times were subjected to rANOVAs with the WS factors phase, stress induction and reward condition.

A Potential reward minus no reward

400 - 470 ms

-2.31 µV   2.31 µV

550 - 800 ms

-1.07 µV   1.07 µV

800 - 1050 ms

-1.51 µV   1.51 µV

B

Fz

Follicular no reward — Follicular potential reward
Luteal no reward — Luteal potential reward

FCz

Cz

Time (ms)

C Control minus stress

400 - 470 ms

-0.94 µV   0.94 µV

D

Fz

Time (ms)

Follicular control ···· Follicular stress
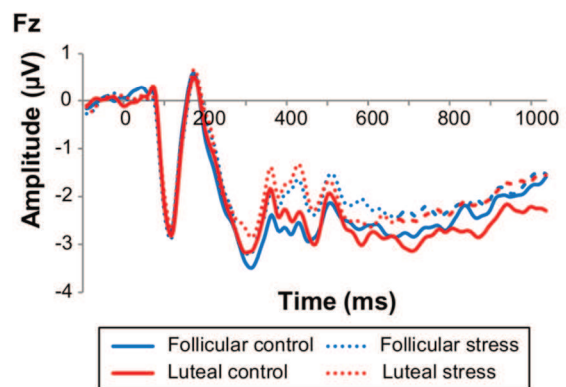Luteal control ···· Luteal stress
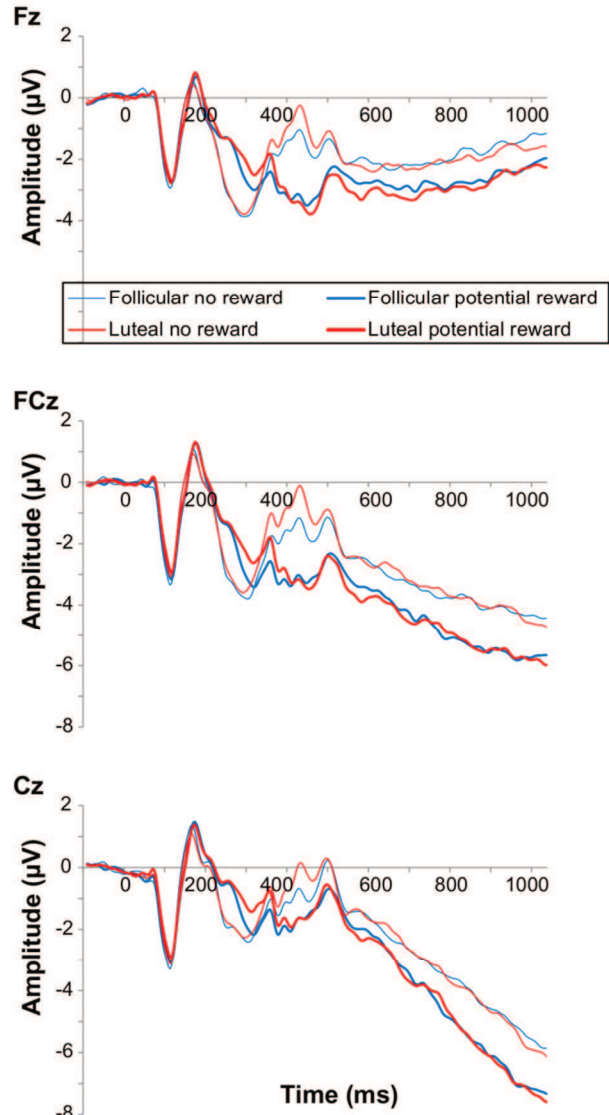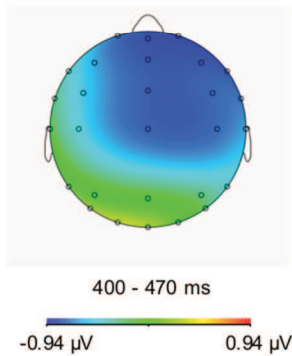
Figure 1. Cue-related topographical voltage maps and ERPs. (A) Topographical voltage maps (400–470 ms, 550–800 ms, 800–1050 ms post-cue) of the difference between potential-reward and no-reward trials, showing the shift from frontal to more posterior sites. (B) ERPs from Fz, FCz and Cz:

thick lines represent potential-reward trials; thin lines represent no-reward trials; blue lines represent the late follicular phase; red lines represent the late luteal phase. The CNV was more negative following potential-reward relative to no-reward cues. The reward condition effect did not significantly differ between late luteal and late follicular phases. (C) Topographical voltage map (400–470 ms) of the difference between control condition and stress condition trials. (D) ERPs from Fz: solid lines represent the control condition; dotted lines represent the stress condition; blue lines represent the late follicular phase; red lines represent the late luteal phase. The CNV was smaller in the stress relative to the control condition, during the early interval (400–470 ms), independent of phase.

ERPs

For the ERP analyses, electrodes and time windows were selected on the basis of previous studies and visual inspection of ERP waveforms and topographic maps collapsed across conditions and participants.

Cue-related ERPs. In line with previous findings, we found that the CNV was already detectable around 400 ms post-cue, and that its topography shifted from anterior to posterior sites (Fig. 1; Grent-'t-Jong & Woldorff, 2007; Van den Berg et al., 2014).[1] We quantified the CNV as the mean amplitude in three consecutive windows, at three different electrodes: between 400 and 470 ms at Fz, between 550 and 800 ms at FCz, and between 800 and 1050 ms at Cz. The resulting CNV measures were analyzed using rANOVAs with the WS factors phase, stress induction and reward condition.

Feedback-related ERPs. In our previous studies, we found that FRN results were dependent on the method of measuring FRN amplitude (Banis et al., 2014; Banis & Lorist, 2012). Therefore, the FRN was measured in two ways. First, the FRN was quantified as the mean amplitude (MA) between 250 and 325 ms post-feedback at FCz (see Fig. 2; Di Bernardi Luft, Nolte, & Bhattacharya, 2013; Gehring & Willoughby,

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[1] In the present study, participants were instructed to react as quickly as possible upon detection of the target, and were thus stimulated to prepare instantly following cue-onset. Cue-target intervals were very short, ranging from 1050 to 1450 ms. This experimental set-up is similar to the set-ups by Van den Berg et al. (2014) and Grent-'t-Jong and Woldorff (2007), who employed short cue-target intervals as well (700 or 1300 ms, and 900 or 1900 ms, respectively). These short cue-target intervals appear to stimulate fast attentional orientation, as reflected in the early onset of a sustained negative polarity, around 400 ms after cue-onset, in the latter two and the present studies. According to Grent-'t-Jong and Woldorff (2007) attentional orienting is initiated by the medial frontal cortex, which then engages medial parietal areas. Furthermore, from around 400 ms, our ERPs show activity overlapping with the supposedly early CNV. We presume that this activity reflects sensory-evoked activity caused by the visual offset of our cue, at 250 ms (Luck, 2014). A similar pattern is visible in the ERPs reported by Van den Berg et al. (2014) employing a cue duration of 400 ms, somewhat later in the cue-related interval.
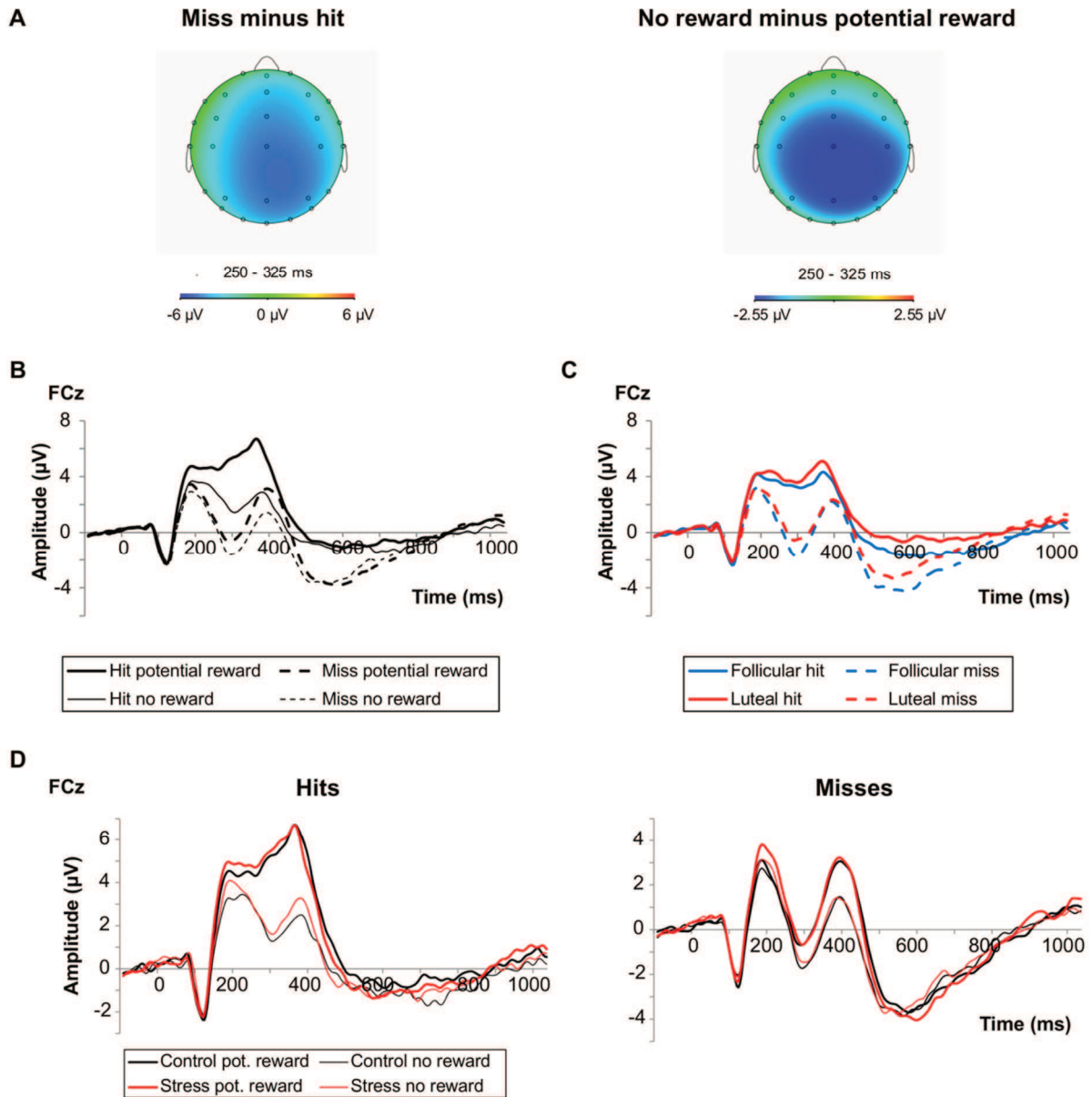
Figure 2. Feedback-related topographical voltage maps and ERPs. (A) Topographical voltage maps (250–325 ms post-feedback) of the difference between miss and hit trials (left) and between no-reward and potential-reward trials (right). (B) ERPs from FCz as a function of feedback valence and reward condition: solid lines represent hit trials; dashed lines represent miss trials; thick lines represent potential-reward trials; thin lines represent no-reward trials. The FRN was larger in response to misses relative to hits, and in no-reward compared to potential-reward trials. The feedback valence effect on the FRN was most pronounced in potential-reward trials. (C) ERPs from FCz as a function of feedback valence and menstrual cycle phase: solid lines represent hit trials; dashed lines represent miss trials; blue lines represent the late follicular phase; red lines represent the late luteal phase. The effect of feedback valence on the FRN (as quantified by the MAC) was more pronounced in the late follicular relative to the late luteal phase. (D) ERPs from FCz as a function of reward condition and stress induction, for hits and misses separately. Thick lines represent potential-reward trials; thin lines

represent no-reward trials; black lines represent the control condition; red lines represent the stress condition. The effect of reward condition on the processing of feedback valence was more pronounced in the stress relative to the control condition, especially due to differential processing of hits. This result only applied to the FRN as quantified by the MAC.

2002). Second, the FRN was measured as the difference in voltage at FCz between the 250–325 ms mean amplitude and the average of the mean amplitudes of the preceding (P200: 160–220 ms window) and following (P300: 350–410 ms window) peaks (MAC = mean amplitude corrected for surrounding peaks; Banis & Lorist, 2012; Yeung & Sanfey, 2004). The resulting FRN measures were analyzed using rANOVAs with the WS factors phase, stress induction, feedback valence and reward condition.

We added the MAC measure to account for possible overlap between the FRN and other ERP components, most notably the P300. In our most recent study including oscillatory power analyses (Banis et al., 2014), we found that the results of the MAC measure best matched the results of feedback-related theta power, a measure which is more directly related to neurophysiological phenomena. Recent studies have further supported the idea that correction for surrounding peaks approaches may yield more reliable results than the mean amplitudes approach, and that studies should include several measuring methods to demonstrate the reliability of reported findings (Mushtaq, Stoet, Bland, & Schaefer, 2013; Pfabigan, Sailer, Lamm, 2015). In order to gain more insight into the possible role of overlapping components in the present study, we performed rANOVAs on the peaks surrounding the FRN, as well.

Oscillatory power

For the time-frequency analyses, electrodes and time windows were selected on the basis of previous studies, and visual inspection of average topographical plots and average power plots across conditions and participants (see Fig. 3, Fig. 4; Cohen, 2014).

Cue-related power. Cue-related alpha (8–12 Hz) was quantified as the mean activity between 400 and 1050 ms post-cue, at Oz (Capotosto et al., 2009; Thut et al., 2006; Worden et al., 2000). For exploratory purposes, cue-related theta (4–7 Hz) was quantified as the mean activity at Fz, between 200 and 500 ms post-cue. The resulting power values were analyzed using rANOVAs with the WS factors phase, stress induction and reward condition.

Feedback-related power. Feedback-related theta power (4–7 Hz) was

A   Cue-related relative power averaged over all conditions, at Oz
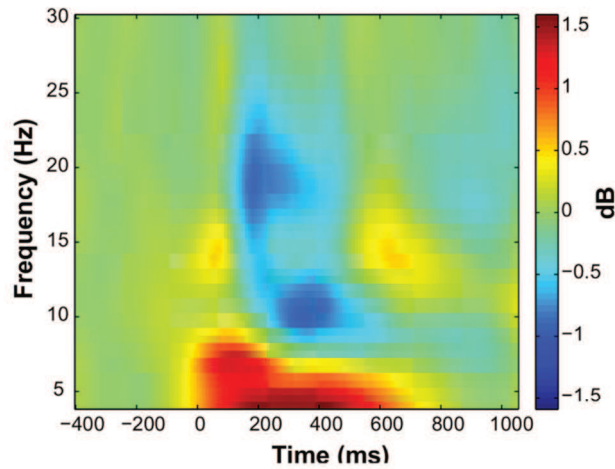
B   Cue-related relative alpha power averaged over all conditions, at Oz

Figure 3. Time-frequency and line plots of cue-related relative power, averaged over all conditions. (A) Time-frequency representation of cue-related relative power at Oz, averaged over all conditions. Only for time-frequency plots, relative power averages were converted to a decibel (dB) scale, enabling comparison between different frequencies. (B) Line plot of cue-related relative alpha (8–12 Hz) power at Oz, averaged over all conditions.

quantified as the mean activity at Fz, between 300 and 600 ms post-feedback. The resulting power values were analyzed using rANOVAs with the WS factors phase, stress induction, feedback valence and reward condition.

Specifications statistical analyses

For all rANOVAs in this study, the univariate results are reported, with Greenhouse-Geisser corrected p-values for non-sphericity being reported when appropriate. Reported p-values are two-tailed unless specified as one-tailed. Effect

A Feedback-related relative power averaged over all conditions, at Fz

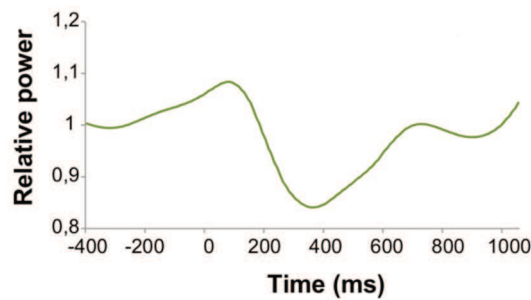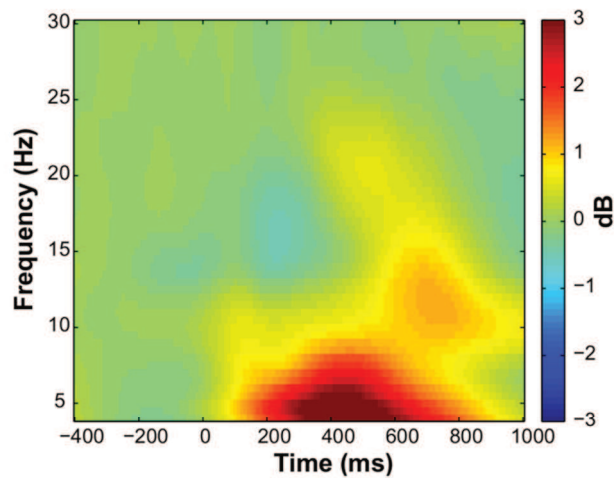## B Feedback-related relative theta power averaged over all conditions, at Fz
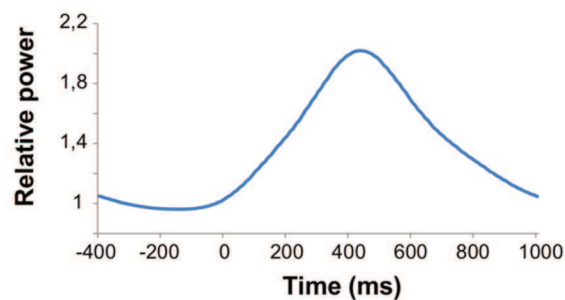
Figure 4. Time-frequency and line plots of feedback-related relative power, averaged over all conditions. (A) Time-frequency representation of feedback-related relative power at Fz, averaged over all conditions. Only for time-frequency plots, relative power averages were converted to a decibel (dB) scale. (B) Line plot of feedback-related relative theta (4–7 Hz) power at Fz, averaged over all conditions.

sizes are reported using partial eta-squared (η_p^2), which is the proportion of variance explained by a given variable of the variance remaining after excluding variance explained by other variables (Richardson, 2011). Values of .01, .06, and .14 are considered to reflect small, medium, and large effects, respectively (Cohen, 1969, as cited in Richardson, 2011). As power was limited in this study due to the small sample size, we also reported effects showing p-values approaching significance (between .05 and .10). These effects should be interpreted with caution. For analyses following up on significant interactions, we applied the Bonferroni method in order to adjust for multiple comparisons.

Results

Progesterone levels

Salivary progesterone levels were higher in the late luteal phase (M = 197.2 pmol/L, SD = 128.0) than in the late follicular phase (M = 61.9 pmol/L, SD = 18.0, $t(16)$ = 4.47, p < .001), confirming that participants were on average tested during the intended menstrual cycle phase. Late luteal progesterone levels varied from < 37 pmol/L (level not measurable by assay) to 491.0 pmol/L. Fifteen participants showed the highest levels during the late luteal phase. One participant showed a slightly lower level during the late luteal (47.4 pmol/L) compared to the late follicular phase (60.7 pmol/L), while another participant showed similar levels during both phases (< 37 pmol/L). The latter two participants had their menses onset shortly after their luteal sessions, that is on the same date.

Measurements of stress

Subjective measurements of stress

Participants reported having experienced more anger, fear, sadness, disgust and surprise, and less happiness, while watching the aversive relative to the neutral movie clips (stress induction: $F(1, 16)$ = 67.96, p < .001, η_p^2 = .81; stress induction by emotion: $F(5, 80)$ = 62.97, p < .001, η_p^2 = .80; Table 1). In addition, the effect of stress induction depended on the combination of emotion and phase ($F(5, 80)$ = 2.55, p = .034, η_p^2 = .14). Especially, the stress-related increase in disgust seemed to be more pronounced in the late follicular relative to the late luteal phase, but the stress induction by phase interaction did not reach significance ($F(1, 16)$ = 5.92, p = .027, η_p^2 = .27).

In addition, participants reported higher negative affect in the stress relative to the control condition (stress induction: $F(1, 16)$ = 6.34, p = .023, η_p^2 = .28; Fig. 5). This stress induction effect was modulated by time (stress induction by time: $F(1.50, 23.95)$ = 4.35, p = .034, η_p^2 = .21). At baseline, there was no significant difference in negative affect between both stress induction conditions ($F(1, 16)$ = 1.40, n.s., η_p^2 = .08), while at t2 and t3 participants did report higher negative affect in the stress compared to the control condition (t2: $F(1, 16)$ = 5.21, p = .036, η_p^2 = .25; t3: $F(1, 16)$ = 7.27, p = .016, η_p^2 = .31). Importantly, phase did not affect negative affect (F < 1, n.s.).

Table 1

Mean ratings of emotions experienced during movie clips, as a function of menstrual cycle phase and stress induction (standard deviations in parentheses).

Phase	Follicular		Luteal	
Emotion	**Stress**	**Control**	**Stress**	**Control**
Anger	5.9 (1.9)	1.4 (0.9)	5.8 (2.5)	1.7 (1.2)
Fear	5.7 (1.7)	1,9 (1.1)	5.8 (1.8)	2.7 (2.0)
Sadness	4.0 (1.8)	2.2 (1.2)	4.5 (2.2)	2.0 (0.9)
Disgust	8.0 (1.0)	1.2 (0.6)	7.4 (1.8)	1.5 (1.2)
Surprise	6.1 (1.7)	3.5 (2.1)	5.0 (2.3)	3.8 (1.8)
Happiness	1.4 (0.9)	4.3 (1.8)	1.4 (0.7)	3.7 (2.0)

Physiological measurements of stress

HR was higher during the aversive movie clips than during the neutral movie clips (stress induction: $F(1, 16) = 3.36$, $p = .043$, one-tailed, $\eta_p^2 = .17$; Fig. 5). Notably, overall HR during the movie clips was higher during the late luteal phase ($M = 66.3$, $SD = 10.9$) than during the late follicular phase ($M = 61.4$, $SD = 8.6$; phase: $F(1, 16) = 5.22$, $p = .036$, $\eta_p^2 = .25$). In addition, HRV was lower during the aversive relative to the neutral movie clips ($F(1, 16) = 8.94$, $p = .009$, $\eta_p^2 = .36$; Fig. 5). Phase did not affect HRV significantly.

Furthermore, baseline-corrected cortisol levels were higher in the stress relative to the control condition (stress: $M = +0.53$ nmol/L, $SD = 1.57$, control: $M = -0.29$ nmol/L, $SD = 0.51$; stress induction: $F(1, 16) = 3.56$, $p = .039$, one-tailed, $\eta_p^2 = .18$; Fig. 5). The observed pattern suggests that the effect of stress increased with time, but the stress induction by time interaction did not reach significance ($F(1, 16) = 4.19$, $p = .057$, $\eta_p^2 = .21$),. Phase did not affect these baseline-corrected cortisol levels. Notably, phase did affect cortisol levels at baseline, that is immediately before the first task block in both stress induction conditions, with higher levels during the late follicular ($M = 3.48$, $SD = 1.73$) relative to the late luteal phase ($M = 2.85$, $SD = 1.53$; phase: $F(1, 16) = 8.53$, $p = .010$, $\eta_p^2 = .35$).

In summary, the results from both subjective and physiological stress measurements confirmed that our stress induction procedure yielded mild to moderate stress responses. These stress responses were not significantly modulated by phase. Furthermore, phase affected physiological measures independent of stress induction. Baseline cortisol levels were higher in the late follicular relative to the late luteal
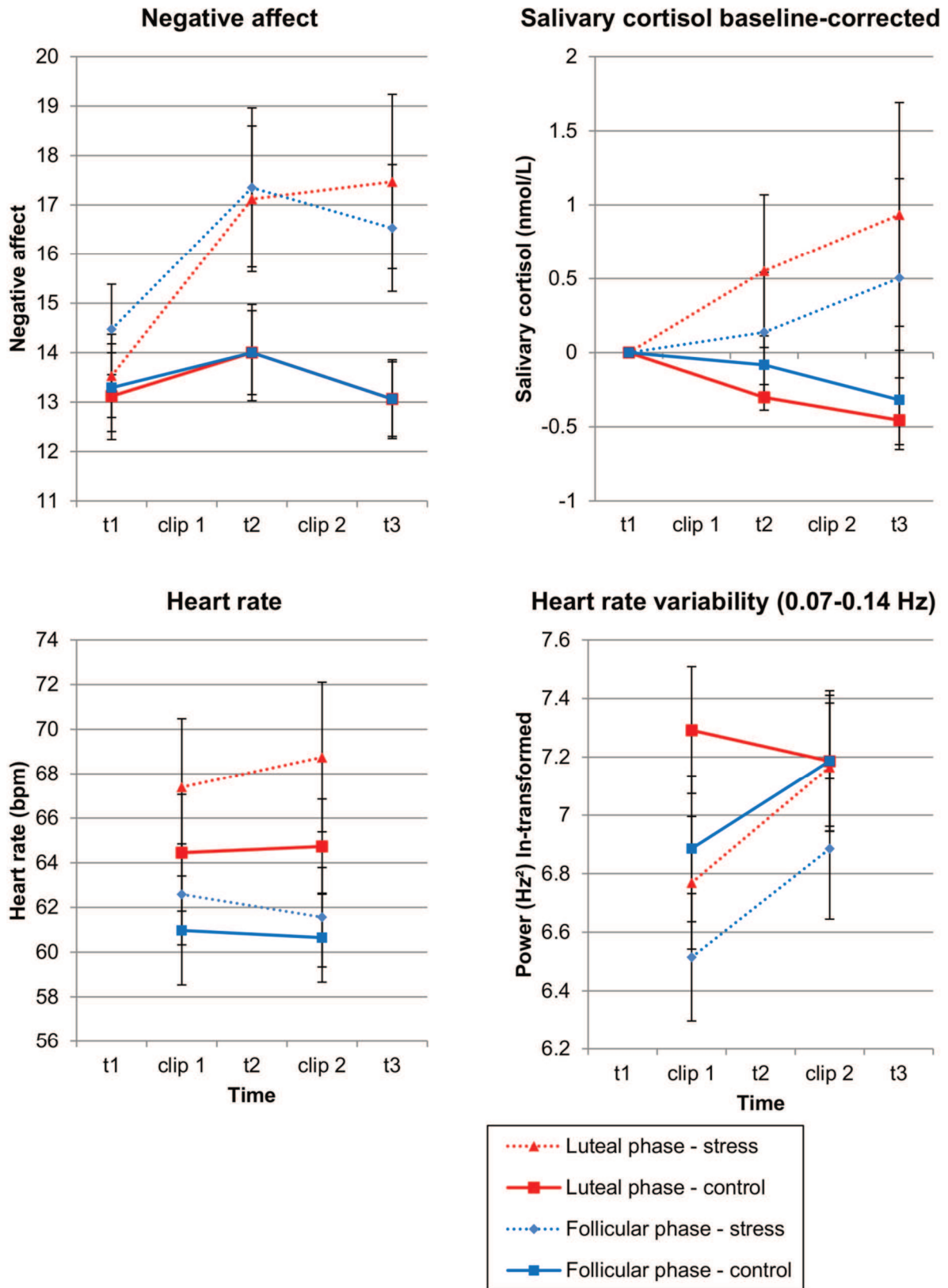
Figure 5. Effects of stress induction on subjective and physiological stress measures. Mean negative affect, baseline-corrected salivary cortisol, heart rate and heart rate variability (0.07–0.14 Hz) as a function of time, stress induction and menstrual cycle phase. Error bars represent standard

errors. Solid lines represent the control condition; dotted lines represent the stress condition; blue lines represent the late follicular phase; red lines represent the late luteal phase. Participants reported higher negative affect in the stress relative to the control condition, at t2 and t3 (top left). Heart rate was higher and heart rate variability was lower during the aversive compared to the neutral movie clips (bottom). Baseline-corrected cortisol levels were higher in the stress relative to the control condition (top right). Furthermore, phase affected physiological measures independent of stress induction: baseline cortisol levels were higher in the late follicular relative to the late luteal phase, whereas overall HR during the movie clips was higher during the late luteal versus late follicular phase.

phase, whereas overall HR during the movie clips was higher during the late luteal versus late follicular phase.

Behavioral results

Responses to targets were faster during potential-reward trials ($M = 158$ ms, $SD = 9$) than during no-reward trials ($M = 163$ ms, $SD = 9$; reward condition: $F(1, 16) = 29.52$, $p < .001$, $\eta_p^2 = .65$). Neither phase nor stress induction modulated RTs. The observed mean percentage of hits was slightly higher for potential-reward trials ($M = 37.9\%$, $SD = 1.4$) than for no-reward trials ($M = 37.1\%$, $SD = 1.3$; $t(16) = 2.89$, $p = .011$). All participants won approximately the same amount of money ($M = 24.12$ euros, $SD = 0.82$).

ERP results

Cue-related activity

The CNV was quantified in three successive post-cue time windows at Fz, FCz and Cz, respectively. During all three intervals, the CNV was larger, that is more negative, following potential-reward compared to no-reward cues (Fig. 1; Table 2). In the early interval (400–470 ms), the CNV was affected by stress, with smaller amplitudes in the stress relative to the control condition. Phase did not influence this stress induction effect on the CNV (stress induction by phase: $F < 1$, n.s.).

Feedback-related activity

In general, the FRN was larger, that is more negative, in response to misses relative to hits, and in no-reward compared to potential-reward trials (Table 3; Fig. 2). These feedback valence and reward condition effects were significant for both FRN measures. Feedback valence effects were dependent on reward condition. For both

Table 2. Summary of effects on cue-related EEG measures. The values of $F(1, 16)$, p and η_p^2 are reported.[a]

EEG measure	CNV – Fz 400–470 ms			CNV – FCz 550–800 ms			CNV – Cz 800–1050 ms			Alpha – Oz 8–12 Hz 400–1050 ms		
Effect	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Reward condition	17.57	.001	.52	11.56	.004	.42	18.23	.001	.53	7.17	.017	.31
Reward condition by phase	3.85	.067	.19									
Stress induction	4.72	.045	.23									

[a] Effects are only included if p-value < .10 for at least one measure. Entries with an F-value < 1 are omitted.

Table 3. Summary of effects on feedback-related EEG measures. The values of $F(1, 16)$, p and η_p^2 are reported.[a]

EEG measure	FRN – FCz Mean amplitude (MA) 250–325 ms			FRN – FCz MA corrected for surrounding peaks[1]			Theta – Fz 4–7 Hz 300–600 ms		
Effect	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Feedback valence	85.50	< .001	.84	42.64	< .001	.73	2.26	.153	.12
Reward condition	31.25	< .001	.66	8.36	.011	.34	9.05	.008	.36
Feedback valence by reward condition	33.40	< .001	.68	15.71	.001	.50	2.90	.108	.15
Feedback valence by reward condition by stress induction				9.51	.007	.37			
Feedback valence by phase	1.40	.253	.08	6.62	.020	.29	1.50	.238	.09
Feedback valence by stress induction by phase	1.55	.230	.09				3.74	.071	.19
Reward condition by stress induction by phase							6.55	.021	.29

[a] Effects are only included if p-value < .10 for at least one measure. Entries with an F-value < 1 are omitted.

[1] Mean amplitude 250–325 ms post-feedback minus average of mean amplitudes preceding (160–220 ms window) and following (350–410 ms window) peaks (MAC).

FRN measures, the effect of feedback valence was more pronounced in potential-reward (MA: $F(1, 16) = 99.52$, $p < .001$, $\eta_p^2 = .86$; MAC: $F(1, 16) = 46.96$, $p < .001$, $\eta_p^2 = .75$) than in no-reward trials (MA: $F(1, 16) = 45.94$, $p < .001$, $\eta_p^2 = .74$; MAC: $F(1, 16) = 28.15$, $p < .001$, $\eta_p^2 = .64$). In addition, separate analyses per feedback valence showed that the effect of reward condition was stronger in hit (MA: $F(1, 16) = 39.84$, $p < .001$, $\eta_p^2 = .71$; MAC: $F(1, 16) = 21.65$, $p < .001$, $\eta_p^2 = .58$) compared to miss trials (MA: $F(1, 16) = 7.91$, $p = .013$, $\eta_p^2 = .33$; MAC: $F(1, 16) = 2.38$, n.s., $\eta_p^2 = .13$).

The effects of feedback valence and reward condition on peaks surrounding the FRN, that is the P200 and P300, were similar to their effects on the FRN (Table 4). In general, the P200 and P300 were larger in response to hits relative to misses, and in potential-reward versus no-reward trials (Fig. 2). For both the P200 and P300, the effect of feedback valence was larger in potential-reward (P200: $F(1, 16) = 26.68$, $p < .001$, $\eta_p^2 = .63$; P300: $F(1, 16) = 30.07$, $p < .001$, $\eta_p^2 = .65$) relative to no-reward trials (P200: $F(1, 16) = 16.33$, $p = .001$, $\eta_p^2 = .51$; P300: $F(1, 16) = 11.06$, $p = .004$, $\eta_p^2 = .41$). Additionally, the effect of reward condition was larger in hit (P200: $F(1, 16) = 8.54$, $p = .010$, $\eta_p^2 = .35$; P300: $F(1, 16) = 41.25$, $p < .001$, $\eta_p^2 = .72$) relative to miss trials (P200: $F(1, 16) = 3.31$, $p = .088$, $\eta_p^2 = .17$; P300: $F(1, 16) = 10.52$, $p = .005$, $\eta_p^2 = .40$). Measuring the FRN while correcting for overlap with these surrounding peaks (MAC) resulted in smaller, but still large, main and interaction effects of feedback valence and reward condition, relative to the MA measure.

Table 4. Summary of effects on feedback-related P200 and P300 at FCz. The values of $F(1, 16)$, p and η_p^2 are reported.[a]

EEG measure	P200 160–220 ms			P300 350–410 ms		
Effect	F	p	η_p^2	F	p	η_p^2
Feedback valence	32.89	< .001	.67	23.42	< .001	.59
Reward condition	7.41	.015	.32	28.15	< .001	.64
Feedback valence by reward condition	5.89	.027	.27	17.18	.001	.52
Stress induction	3.41	.083	.18			
Reward condition by stress induction				4.54	.049	.22
Feedback valence by reward condition by stress induction				6.22	.024	.28

[a] Effects are only included if p-value < .10 for at least one measure including the FRN measures. Entries with an F-value < 1 are omitted.

Stress induction modulated the feedback valence by reward condition interaction on the FRN, but only as quantified by the MAC (Table 3). The effect of reward condition on the processing of feedback valence was more pronounced in the *stress* ($F(1, 16) = 17.85$, $p = .001$, $\eta_p^2 = .53$) relative to the *control* condition ($F(1, 16) = 5.50$, $p = .032$, $\eta_p^2 = .26$; Fig. 2). Separate analyses per feedback valence (see above) showed that the significant effect of reward condition on the processing of hits was stronger in the stress relative to the control condition (reward condition by stress induction: $F(1, 16) = 6.61$, $p = .021$, $\eta_p^2 = .29$), whereas the nonsignificant effect of reward condition on the processing of misses was not modulated by stress induction (reward condition by stress induction: $F < 1$, n.s.; Fig. 2).

With regard to FRN-surrounding peaks, stress induction modulated the feedback valence by reward condition interaction on the P300, not on the P200 (Table 4). Reward condition only had a significant effect on the processing of feedback valence in the *control* condition ($F(1, 16) = 33.02$, $p < .001$, $\eta_p^2 = .67$), not in the *stress* condition ($F(1, 16) = 4.31$, $p = .054$, $\eta_p^2 = .21$; Fig. 2). Furthermore, separate analyses per feedback valence condition showed, opposite to the effects on the MAC measure of the FRN, that the effect of reward condition on the processing of hits was stronger in the control relative to the stress condition (reward condition by stress induction: $F(1, 16) = 7.64$, $p = .014$, $\eta_p^2 = .32$), whereas stress induction did not modulate the effect of reward condition on the processing of misses (reward condition by stress induction: $F < 1$, n.s.; Fig. 2).

Furthermore, phase modulated the effect of feedback valence on the FRN as quantified by the MAC (Table 3). Feedback valence had a significant effect in both phases, but more pronounced in the late follicular ($F(1, 16) = 37.38$, $p < .001$, $\eta_p^2 = .70$) relative to the late luteal phase ($F(1, 16) = 34.98$, $p < .001$, $\eta_p^2 = .69$; Fig. 2). Separate analyses per feedback valence suggested that this phase effect especially concerned the processing of misses ($F(1, 16) = 4.85$, $p = .043$, $\eta_p^2 = .23$), with a larger FRN in the late follicular compared to the late luteal phase, and not of hits ($F < 1$, n.s.), although the former effect as such was not significant after correction for multiple comparisons. Phase had no significant effect on the FRN-surrounding peaks (i.e., P200 or P300).

Oscillatory power results

Cue-related power

Alpha power reductions were larger following potential-reward compared to

A Potential reward minus no reward
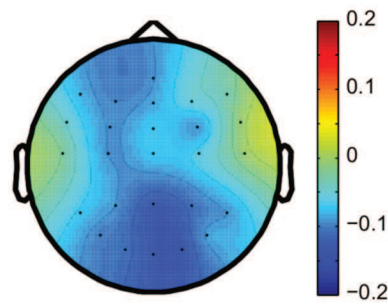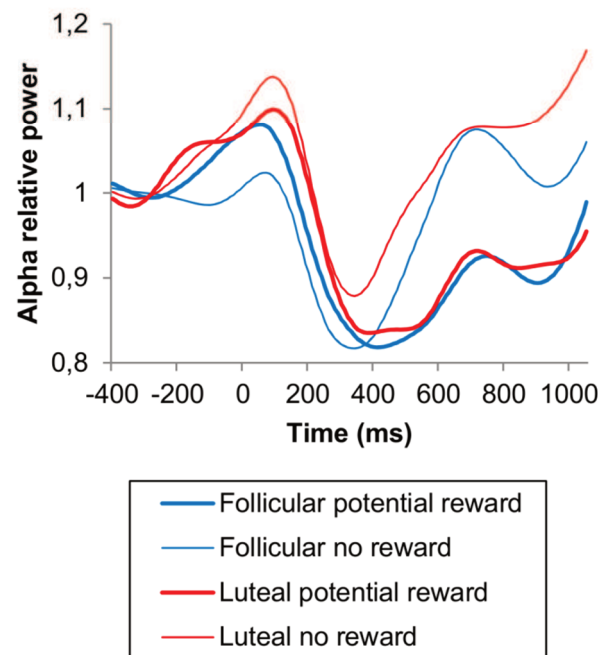
Figure 6. Cue-related topographical map and line plot of alpha relative power (8–12 Hz). (A) Topographical map of the difference between potential-reward and no-reward trials (400–1050 ms post-cue). (B) Line plot of alpha relative power at Oz as a function of reward condition and phase. Thick lines represent potential-reward trials; thin lines represent no-reward trials; blue lines represent the late follicular phase; red lines represent the late luteal phase. Alpha power reductions were larger following potential-reward relative to no-reward cues, independent of phase.

no-reward cues (Table 2, Fig. 6; Fig. S3). Phase did not modulate this reward condition effect on alpha power. In addition, stress induction did not affect alpha power.

Exploratory analysis. Cue-related theta power increases were larger following no-reward relative to potential-reward cues ($F(1, 16) = 13.95$, $p = .002$, $\eta_p^2 = .47$), in contrast with feedback-related theta power increases (see below).

Feedback-related power

Visual inspection of Figure 7 suggests the presence of a feedback valence effect in the late follicular phase on theta power, at least during the control condition, and the absence of a feedback valence effect in the late luteal phase, but the pertaining feedback valence by stress induction by phase interaction did not reach significance (Table 3).

In contrast with feedback valence, reward condition did have a significant effect on theta power, with larger increases in potential-reward versus no-reward trials (Table 3, Fig. 7; Fig. S4). However, this reward condition effect depended on the combination of phase and stress induction. In the late follicular phase (reward condition: $F(1, 16) = 4.85$, $p = .043$, $\eta_p^2 = .23$; reward condition by stress: $F(1, 16) = 6.23$, $p = .024$, $\eta_p^2 = .28$), reward condition had a significant effect during the stress ($F(1, 16) = 9.28$, $p = .008$, $\eta_p^2 = .37$), but not during the control condition ($F < 1$, n.s.). In the late luteal phase, reward condition had an effect in both stress induction conditions (reward condition: $F(1, 16) = 9.08$, $p = .008$, $\eta_p^2 = .36$; reward condition by stress induction: $F < 1$, n.s.).

Discussion

Aim of the present study was to investigate the combined effects of menstrual cycle phase and acute stress on reward-related processing. Participants were tested during the late follicular and late luteal phases, as verified by salivary progesterone determination, and performed in both control and stress conditions. The stress induction procedure yielded mild to moderate stress responses, which did not significantly differ between menstrual cycle phases. During the MID task, participants responded faster to targets in potential-reward relative to no-reward trials, confirming that the task was successful in eliciting motivated behavior. We found evidence for both independent and interaction effects of menstrual cycle phase and stress induction on reward-related brain activity. In this section, we will first discuss our findings with regard to phase effects during reward anticipation and feedback. Then, we will discuss our findings concerning acute stress effects in late follicular and late luteal phases. Finally, we will discuss limitations of the present study.
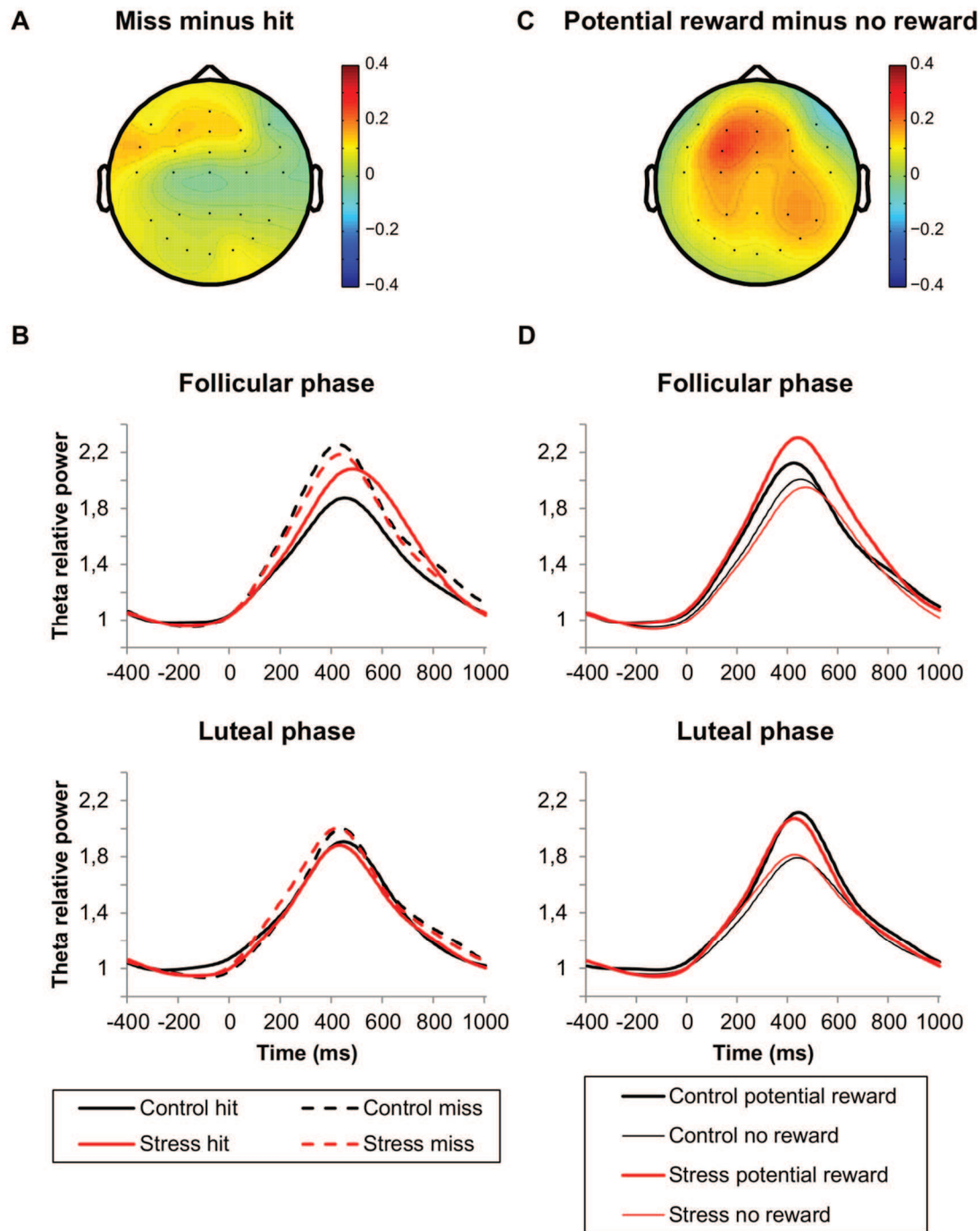
Figure 7. Feedback-related topographical maps and line plots of theta relative power (4–7Hz).
(A) Topographical map of the difference between miss and hit trials (300–600 ms post-feedback). (B) Line plot of theta relative power at Fz as a function of feedback valence and stress induction, for the late follicular (top) and late luteal phases (bottom). Solid lines represent hit trials; dashed lines represent miss trials; black lines represent the control condition; red lines represent the stress condition. Theta power increases were not significantly larger following misses compared to hits. The feedback valence by stress induction by phase interaction did not reach significance. (C) Topographical map of the difference between potential-reward and no-reward trials (300–600 ms post-feedback). (D) Line plots of theta relative power at Fz as a function of reward condition and stress

induction, for the late follicular (top) and late luteal phases (bottom). Thick lines represent potential-reward trials; thin lines represent no-reward trials; black lines represent the control condition; red lines represent the stress condition. In general, theta power increases were larger in potential-reward relative to no-reward trials, but this effect depended on the combination of phase and stress induction condition. In the late follicular phase, reward condition had a significant effect in the stress condition only, whereas in the late luteal phase, reward condition had a significant effect in both stress and control conditions.

Effects of phase during reward anticipation and feedback

Late follicular phase: Heightened sensitivity to valence of feedback

Phase modulated brain activity during the stage of feedback. More specifically, the effect of feedback valence on the FRN as quantified by the MAC was more pronounced in the late follicular relative to the late luteal phase. The FRN is thought to reflect the signaling of unfavorable outcomes and a need for increased cognitive control (Cohen et al., 2011; Van de Vijver et al., 2011). In accordance with this notion, we found larger FRN amplitudes following misses relative to hits. The additional finding that this valence effect was more pronounced in the late follicular relative to the late luteal phase, suggests that the signaling of unfavorable (versus favorable) outcomes was stronger in the late follicular phase.

Our findings with regard to the processing of feedback valence are in accordance with fMRI studies supporting a potentiating influence of estradiol on the brain's reward system in the presence of low progesterone levels, during reward delivery (Dreher et al., 2007; Thomas et al., 2014). In addition, our findings are in line with findings from a study employing a hormone manipulation reducing estradiol levels in women, to some extent mimicking the late luteal phase, resulting in a decreased responsivity to the magnitude of rewards (Macoveanu et al., 2016).

Late luteal phase: Heightened sensitivity to reward prospect

In contrast with the larger sensitivity to the valence of feedback in the late follicular compared to the luteal phase, we found that the late luteal relative to the late follicular phase is associated with an increased sensitivity to reward prospect, although not under stress. Theta oscillations in the frontal network are thought to play an important role in signaling negative outcomes and implementing behavioral adaptations (Van de Vijver et al., 2011), and previous studies have indeed reported larger feedback-related theta power increases after negative relative to positive

outcomes (e.g., Banis et al., 2014; Cohen et al., 2007). In the present study employing the MID task, we did not find a significant effect of feedback valence. We did find larger theta power increases in potential-reward compared to no-reward trials, suggesting that the level of communication in the frontal network following the reception of feedback is increased when a reward is at stake. These findings indicate that reward condition had a greater influence on feedback-related theta power than feedback valence, in the present study.

This reward condition effect on feedback-related theta power depended on the combination of phase and stress induction condition. Potential-reward-related increases in performance monitoring during the late luteal phase were present in both stress induction conditions. In the late follicular phase, this effect was limited to the stress condition. These findings indicate that the late luteal relative to the late follicular phase is associated with a heightened sensitivity to reward condition, under control conditions. Similarly, Ossewaarde et al. (2011b) reported enhanced ventral striatal responses in the late luteal compared to the late follicular phase, during reward anticipation. These authors proposed that the enhanced sensitivity to reward prospect might be related to the late luteal drop in hormone levels, decreasing endogenous DA activity, causing increased DA release following reward cues. However, our findings are in contrast with the earlier mentioned studies supporting a potentiating influence of estradiol on the brain's reward system, during reward anticipation as well (Dreher et al., 2007; Thomas et al., 2014).

Conclusion

Our findings provide evidence that female gonadal hormone levels influence reward-related processing, and that these effects may differ between specific psychological components of reward-related processing. Whereas the late follicular phase seems to be associated with an increased sensitivity to the valence of feedback, the late luteal phase appears to be related to a heightened sensitivity to the prospect of reward. As Berridge, Robinson, and Aldridge (2009) pointed out, reward-related processing can be dissected into anticipatory ("wanting"), consummatory ("liking"), and learning components, which are associated with distinct neurobiological substrates. The factor reward condition in the current study might be linked to the "wanting" component; the factor feedback valence might be related to the "liking" component; and both factors might be related to the learning component. The neurobiological substrates underlying these different components may be differentially

affected by gonadal hormone levels. Consequently, the steeply declining estradiol levels in the late luteal phase might cause an increase in wanting, whereas the high estradiol combined with low progesterone levels in the late follicular phase might cause an increase in liking. The reported increase in depression risk in women, during stages of steep decline in hormonal levels (Deecher et al., 2008), may be related to a loss of distinction between positive and negative stimuli. Consequently, this might result in a lower appreciation of normally rewarding stimuli, that is anhedonia, which is a core symptom of depression (Russo & Nestler, 2013).

Effects of acute stress in late luteal and late follicular phases

Subjective and physiological stress responses: No support for an increased stress sensitivity in the late luteal phase

In contrast with our hypothesis, we did not find significant differences in subjective and physiological stress responses between the late luteal and late follicular phases. Therefore, we cannot confirm that the high estradiol levels in the late follicular phase attenuate stress reactivity relative to the dropping levels in the late luteal phase. Previous studies did report increased *psychophysiological* reactivity to laboratory stressors in the luteal relative to the follicular phase (Kirschbaum et al., 1999; Lustyk et al., 2010; Tersman et al., 1991). Notably, the latter studies compared approximately *mid*luteal and *mid*follicular phases, while we compared *late* luteal and *late* follicular phases. Given the evidence that progesterone may stimulate HPA axis activity (Roca et al., 2003), the enhanced stress response in the midluteal phase might be explained by the peaking levels of progesterone, during this phase. These differential findings indicate that stress-sensitivity may fluctuate across the menstrual cycle, but that phases of heightened sensitivity are confined to specific subphases, characterized by specific hormonal conditions.

An enhanced stress sensitivity in the late luteal phase might be limited to women with PMDD (Epperson et al., 2007). This is in line with a recent review concluding that clear evidence for a specific premenstrual mood syndrome in *healthy* women is lacking (Romans et al., 2012).

Acute stress affects attentional preparation during reward anticipation

We found that stress affected brain activity during reward anticipation, which is in line with previous studies (Dedovic et al., 2009; Ossewaarde et al., 2011a; Starcke & Brand, 2012). However, in contrast with our expectations of an increased sensitivity

to stress during the late luteal compared to the late follicular phase (e.g., Kirschbaum et al., 1999; Lustyk et al., 2010), the results indicated no significant phase differences in the way stress affected attentional preparation to upcoming targets, as reflected in the CNV.

Stress decreased CNV amplitudes in this early interval, indicating impaired attentional orienting to subsequent targets under stress (Grent-'t-Jong & Woldorff, 2007). This is in accordance with the notion that stress especially impairs higher-order functions, such as top-down attentional control (Arnsten & Goldman-Rakic, 1998). However, stress did not affect RTs, whereas reward condition did, which is possibly related to the difference in the respective effect sizes on the CNV ($\eta_p^2 = .23$ versus $\eta_p^2 = .52$).

Acute stress increases impact of reward condition on feedback processing

In addition to the effect of acute stress on attentional preparation during reward anticipation, acute stress modulated brain activity during the processing of feedback information. FRN amplitudes following hits were larger in no-reward trials than in potential-reward trials, especially in the stress compared to the control condition. Notably, this finding only applied to the FRN as quantified by the MAC measure, taking into account surrounding peaks, and not to the MA measure. Unfortunately, it is impossible to precisely discriminate between overlapping components using the EEG technique (Luck, 2014), and processes underlying the FRN might already start and continue in earlier and later time windows, respectively. In the present study, the MAC measure showed a result pattern which was opposite to that of the frontocentral P300, the latter showing a larger effect of reward condition on the processing of hits in the *control* relative to the stress condition. One cannot be sure whether the observed interactions on the MAC were caused by FRN-related activity or by P300-related activity. However, the P300 was maximal at parietal electrodes, indicating that the FRN and P300 reflect different processes.

Although acute stress impaired attentional preparation during reward anticipation, it seemed to enhance the impact of reward condition on the processing of hits. Nevertheless, stress did not influence *performance* monitoring per se, that is, monitoring whether targets were hit or not. Participants seemed to be more sensitive to the actual delivery of reward following hits rather than being more focused on hitting versus missing targets, when exposed to stress. This interpretation seems to be in accordance with behavioral evidence showing increased consumption of rewarding

substances under stressful circumstances (e.g., Koob, 2008; Rutters et al., 2009; Uhart & Wand, 2009).

As proposed by Maier, Makwana, and Hare (2015), exposure to acute stress may impair self-controlled decisions in favor of actions leading to immediate reward, by increasing the influence of immediately rewarding attributes and decreasing the potency of regions promoting goal-directed behaviors. The stress-related increase in sensitivity to reward prospect during the processing of hits, in the present study, is in line with this theory. Nevertheless, we did not find evidence for stress-related impairments of performance monitoring.

Previous neuroimaging/EEG studies, however, have found a decreased sensitivity to feedback information in stress versus control conditions (Banis et al., 2014; Banis & Lorist, 2012; Porcelli et al., 2012). In two preceding studies, we examined the impact of acute noise stress on feedback-related EEG measures, employing a simple gambling task (Banis et al., 2014; Banis & Lorist, 2012). In both studies, we found evidence for modulation of the FRN by acute stress exposure, either by decreasing feedback valence and magnitude effects on the FRN (Banis & Lorist, 2012) or by a general decrease in FRN amplitude (Banis et al., 2014). In the latter study, we also investigated feedback-related theta power and found smaller increases in the stress relative to the control condition. These stress-related modulations of the FRN and feedback-related theta power were not replicated in the present study. This discrepancy might be explained by the employment of different tasks, which provided different contexts in which feedback was processed. The presence of the factor reward condition and/or the absence of loss trials in the MID task seem to have had a strong influence on brain activity, both during reward anticipation and feedback stages, as reflected in effects of reward condition on both cue-related and feedback-related theta power, and the absence of a significant effect of feedback valence on feedback-related theta power. These findings suggest that during the MID task, evaluation in terms of positive or negative prospects already takes place during the stage of reward anticipation. However, our exploratory analysis of cue-related theta power did not show stress-related modulations either, which indicates that stress did not impair evaluation of prospects.

Limitations

An important limitation of the present study was the small number of participants, which was sufficient to detect large effect sizes only and limits the

reliability of our findings. Therefore, our conclusions should be interpreted with care and require replication. Two other limitations concern the measurement of hormone levels, for menstrual cycle phase verification. First, in order to measure progesterone levels, we collected *single* saliva samples during both experimental sessions, while it is preferable to sample more often, as salivary hormone levels undergo strong fluctuations. Second, we did not measure estradiol levels, which is needed for a more precise estimation of the timing of sessions within the menstrual cycle. Finally, although our stress induction procedure was successful in eliciting stress, it did not result in the high levels of stress as induced by motivated performance tasks combining uncontrollability and social evaluative threat (Dickerson & Kemeny, 2004). The employment of stronger stressors might reveal phase-specific stress effects.

Conclusion

To summarize, we found evidence for both independent and interaction effects of menstrual cycle phase and stress induction on reward-related brain activity. Phase modulated the sensitivity to feedback valence, with a stronger signaling of unfavorable performance outcomes in the late follicular relative to the late luteal phase. In contrast, the late luteal relative to the late follicular phase was associated with an increased sensitivity to reward condition, with enhanced performance monitoring in potential-reward relative to no-reward trials, in the control condition. Stress impaired attentional preparation during reward anticipation, but increased the influence of reward condition on the processing of favorable performance outcomes. We found no evidence for an increased sensitivity to stress during the late luteal relative to the late follicular phase.

Acknowledgments

Supplementary figures
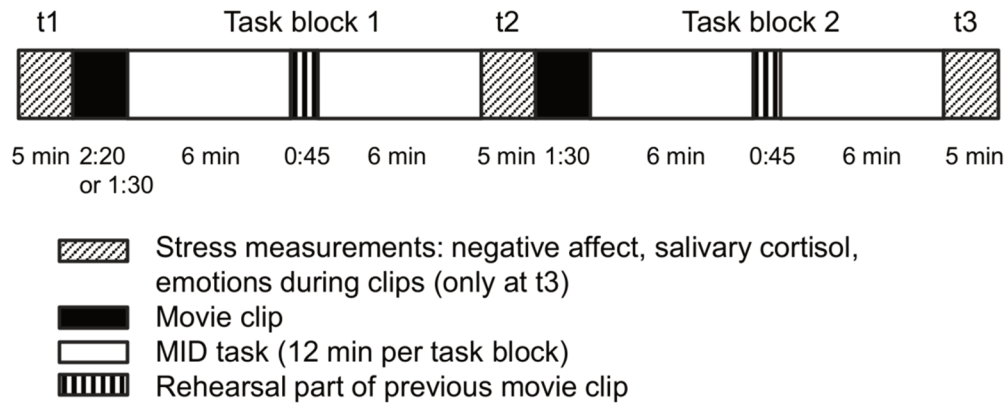
Figure S1. Experimental procedure for each stress induction condition. Participants completed two task blocks of the monetary incentive delay (MID) task, in both stress induction conditions. Immediately before the task blocks, participants were shown highly aversive versus neutral control movie clips. Halfway through the task blocks, part of the preceding fragment was shown again. Participants completed the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and provided salivary samples for cortisol determination, at three time points: before the first task block (t1), after the first task block (t2) and after the second task block (t3). In addition, participants rated their emotions during the movie clips, after the second task block. Both stress induction conditions were separated by a break of 75 min.
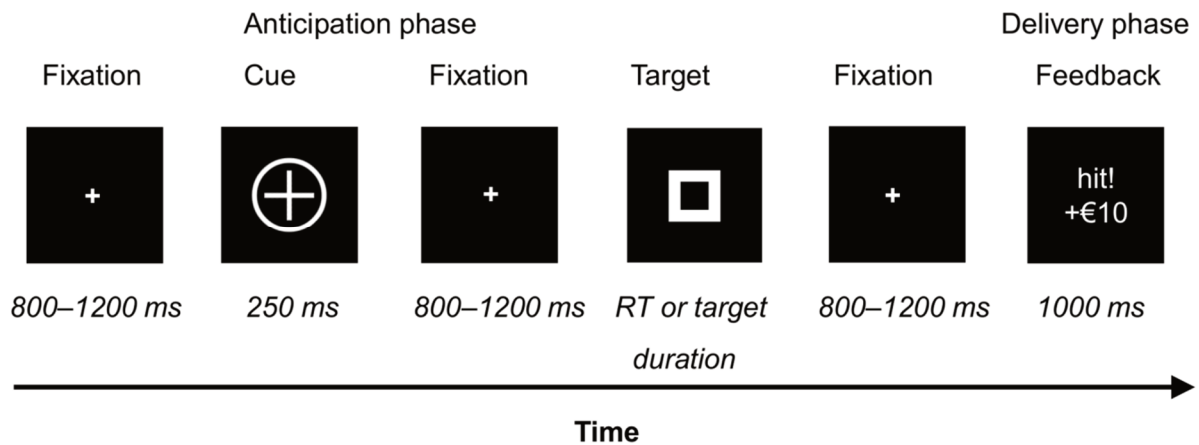
Figure S2. A single trial of the monetary incentive delay (MID) task. Each trial started with the presentation of a fixation cross, for a randomly varying interval of 800 to 1200 ms. Then, a cue was presented for 250 ms signaling potential reward (a plus sign within a circle) or no reward (a times sign within a circle), starting the anticipation phase. Following a second presentation of a fixation cross, a brief target (a white square) appeared on the screen with a start duration of 200 ms. Participants were instructed to push a button as fast as possible upon detection of the target, irrespective of the cue type. Following a third presentation of a fixation cross, there was an outcome phase in which feedback was presented for 1000 ms. Feedback informed participants whether they had pushed the button within the presentation time of the target, and whether they had won money in that trial. In potentially rewarding trials only, hits were rewarded with €10.

Potential reward minus no reward

Control minus stress

Follicular minus luteal

Figure S3. Cue-related time-frequency plots showing main effects of reward condition, stress induction and menstrual cycle phase. Time-frequency representations of the difference between potential-reward and no-reward trials (top), between control and stress condition trials (middle), and between late follicular and late luteal phases (bottom). The plots show relative power (dB) at Oz. Only for time-frequency plots, relative power averages were converted to a (decibel) dB scale. Line boxes highlight larger alpha power following no-reward relative to potential-reward cues. Neither stress induction nor phase had significant main effects on alpha power.
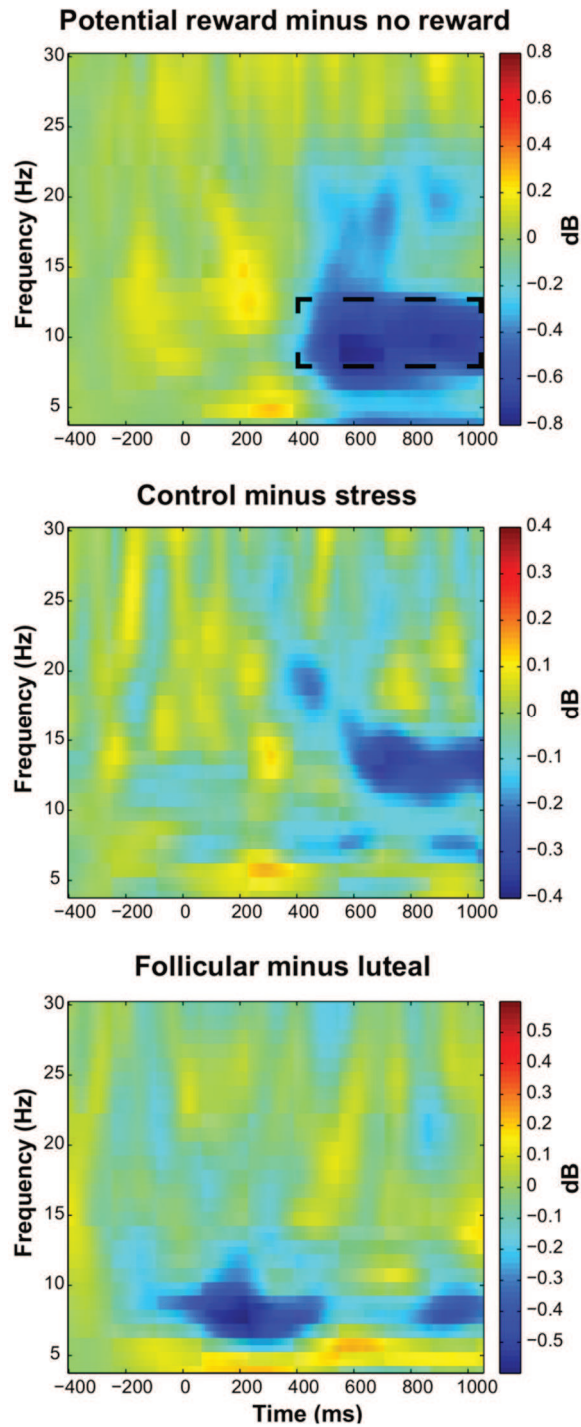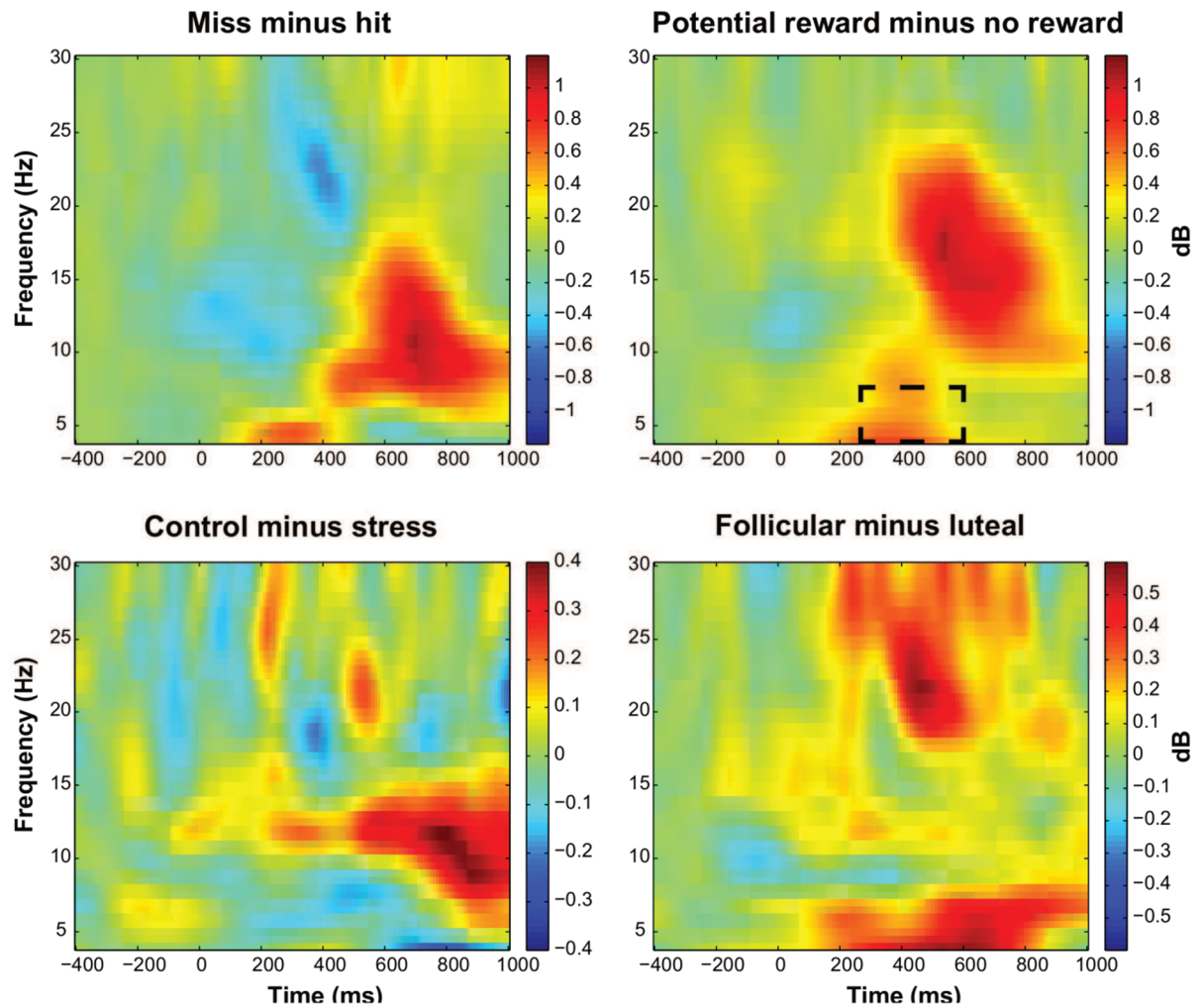
Figure S4. Feedback-related time-frequency plots showing main effects of feedback valence, reward condition, stress induction and menstrual cycle phase. Time-frequency representations of the difference between miss and hit trials (top left), potential-reward and no-reward trials (top right), control and stress condition trials (bottom left), and between late follicular and late luteal phases (bottom right). The plots show relative power (dB) at Fz. Only for time-frequency plots, relative power averages were converted to a decibel (dB) scale. The line box highlights larger theta power increases in potential-reward compared to no-reward trials. Neither feedback valence nor stress induction nor phase had significant main effects on theta power.

CHAPTER 5

General discussion

Introduction

The present thesis aimed at gaining knowledge on the impact of acute stress on the neural processing of reward prospect and action outcomes, in men and women, and across the female menstrual cycle. This research was instigated by the sex-specific prevalence rates of stress-related disorders, such as depression and cardiovascular diseases (Kajantie & Phillips, 2006; Wang et al., 2007), which comprise a major public health concern (Vos et al., 2012). These sex-specific prevalence rates have been linked to differences in the physiological responses of men and women to stress (Kajantie & Phillips, 2006). In women, moreover, fluctuations in gonadal hormones are considered a causal factor in the pathogenesis of certain stress-related disorders (Deecher, Andree, Sloan, & Schechter, 2008; Steiner, Dunn, & Born, 2003a).

Although sex influences are evident in the development of stress-related disorders, little is known about the neural mechanisms underlying these influences. The current research was explicitly aimed at investigating effects of acute stress on brain activity and modulations of these effects by sex and menstrual cycle phase, employing high temporal resolution electroencephalography (EEG). We focused on the neural processing of reward prospect and action outcomes, because these functions have been shown to be involved in the pathogenesis of stress-related disorders (Russo & Nestler, 2013). Considering the present paucity of knowledge on these phenomena in the healthy population and the large variety in manifestations in the population with stress-related disorders, we included only healthy men and women in our studies. In the first experiment, we examined the impact of acute stress on the processing of feedback, in males. In the second experiment, we investigated sex influences on acute stress effects on feedback processing. In the third experiment, we focused on menstrual cycle phase-related variability in effects of acute stress on reward-prospect- and feedback-related processing. In this chapter, the main findings of all experiments are summarized and integrated, and some critical issues are discussed along with ideas for future research.

Effects of acute stress on the neural processing of reward prospect and action outcomes

Exposure to acute stress has been shown to modulate decision-making behavior (e.g., Lighthall, Mather, & Gorlick, 2009; Starcke, Wolf, Markowitsch, & Brand, 2008). Adequate decision making depends on the ability to predict and to evaluate action outcomes with regard to internal goals, and adjust ongoing behavior accordingly. For this purpose, humans use information from their environment, such as reward cues (during reward anticipation) preceding certain choices, and positive or negative outcome information (during feedback) following certain choices. Exposure to acute stress appears to modulate behaviors associated with the processing of reward prospect and action outcomes, suggesting that their influence might be altered under stress. For example, studies have reported that acute stress enhances the consumption of rewarding substances (e.g., Koob, 2008; Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009; Uhart & Wand, 2009) and impairs learning as a function of past reward (Bogdan & Pizzagalli, 2006). Partly in contrast with the latter findings, a later study found that acute stress reduced learning from negative feedback, but not from positive feedback (Petzold, Plessow, Goschke, & Kirschbaum, 2010). So far, most research has been limited to examining stress-related modulations of reward-prospect- and feedback-related *behavior*. In the current set of studies, our first aim was to increase knowledge on the impact of acute stress on a *neural* level, applying EEG. Although we found some differences with regard to specific effects of stress on brain activity between our experiments, the overall picture that emerged was that acute stress modulated, mostly impaired, reward-prospect- and feedback-related processing.

The first two experiments (chapters 2 and 3) investigated the impact of exposure to an acute noise stressor on the processing of gains and losses. These studies utilized a simple monetary gambling task. After every choice, participants received feedback indicating the amount of money won or lost on that specific trial. The first study included male participants only, whereas the second study included both males and females in their midluteal phases. In both studies, we found evidence for impaired feedback processing under stress. In the first experiment, acute stress decreased feedback valence and magnitude effects on the feedback-related negativity (FRN). In the second experiment, acute stress led to general decreases in FRN amplitudes and feedback-related theta power.

The third experiment (chapter 4) investigated the influence of exposure to

highly aversive movie fragments in combination with a self-referencing instruction, on reward-prospect- and feedback-related processing, in female participants in their late follicular and late luteal (or premenstrual) phases. This study employed a monetary incentive delay (MID) task, consisting of potentially rewarding and nonrewarding trials, as indicated by a cue. Following this cue, participants had to react as quickly as possible upon presentation of a target. Finally, they received feedback on whether they had reacted within the presentation time of the target and whether they had won money in that trial.

Two important differences existed between the MID task employed in the third experiment and the simple gambling task used in our first two experiments. First, the MID task contained both reward anticipation and feedback stages, whereas in the simple gambling task only feedback was provided. During the anticipation stage, participants were informed about the possibility of winning money on the trial, that is they received information about reward prospect. During the feedback stage, they could actually receive a monetary reward, but only if their performance had been fast enough and if there was money at stake. Second, the MID task did not include trials in which participants could lose money, although it did include neutral trials in which no money was gained.

In the third experiment, we found evidence for stress-induced modulations of processing during both reward anticipation and feedback stages. During reward anticipation, stress reduced attentional preparation to upcoming targets, as reflected in smaller cue-related contingent negative variation (CNV) amplitudes, irrespective of reward condition. In contrast, during feedback, stress enhanced the influence of reward condition on the processing of positive performance outcomes. FRN amplitudes following hits were larger (more negative) in nonrewarding relative to potentially rewarding trials, especially under stress. As reward condition determined whether hits were accompanied with reward delivery or not, our findings suggest that actually winning money after good performance was of special relevance to stressed participants. Note that the stress-related modulations of the FRN and feedback-related theta power as found in the first two experiments were not replicated in the third study. We will return to this discrepancy later in this section.

In sum, all three experiments demonstrated stress-related modulations of brain activity during the stages of reward anticipation (chapter 4) and/or feedback (chapters 2, 3 and 4), although the findings differed along with employed study designs. Amplifications of the CNV have been linked to attentional preparation to upcoming targets (Falkenstein, Hoormann, Hohnsbein, & Kleinsorge, 2003; Grent-'t-Jong &

Woldorff, 2007), while amplifications of both the FRN and feedback-related theta power are thought to reflect the signaling of unfavorable outcomes and a need for increased cognitive control, in order to adapt subsequent behavior (Cohen, Wilmes, & Van de Vijver, 2011; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Van de Vijver, Ridderinkhof, & Cohen, 2011). Based on our findings with regard to the CNV, the FRN and feedback-related theta power, we can conclude that attentional preparation during reward anticipation (study 3) and feedback processing (studies 1 and 2) are impaired under stress. This is in line with previous research on acute stress showing negative effects on higher-order cognitive functions (e.g., Arnsten & Goldman-Rakic, 1998; Szalma & Hancock, 2011).

Higher-order cognitive functions, such as attentional preparation and feedback processing, are largely dependent on intact functioning of prefrontal networks, and it has been argued that acute stress effects on these functions might be related to the rapid chemical changes in these networks under stress (see for review, Arnsten, 2015). Porcelli, Lewis, and Delgado (2012), for example, using a simple guessing task in combination with a cold pressor stressor, found that stress led to a decreased sensitivity to the valence of monetary outcomes in the orbitofrontal cortex and dorsal striatum. These findings are in accordance with those of our first experiment, where we found a stress-related decrease in sensitivity to the valence of feedback, and with those of our second experiment, where we found a more general decrease in feedback-related brain activity under stress. In addition, Ossewaarde et al. (2011a), employing a similar MID task and stressor as we did in our third experiment, found that acute stress resulted in a reduction in potential-reward-related activity in the medial prefrontal cortex (mPFC), during reward anticipation. These findings are in line with those of our third study, where we found a stress-related decrease in attentional preparation following cues.

In contrast with the notion that acute stress impairs higher order cognitive functions (e.g., Arnsten & Goldman-Rakic, 1998), the third experiment revealed a higher sensitivity to reward condition during the processing of hits, in the stress compared to the control condition. Nevertheless, stress did not influence performance monitoring per se, that is, tracking whether targets were hit or missed. These findings indicate that participants were more sensitive to the actual delivery of reward following hits (rather than being more concentrated on hitting versus missing the target), under stress. This explanation appears to be in line with behavioral evidence showing that stress exposure stimulates the consumption of rewarding substances (e.g., Koob, 2008; Rutters et al., 2009; Uhart & Wand, 2009).

Exposure to acute stress may hinder self-controlled decisions in favor of actions leading to instantaneous reward, as recently hypothesized by Maier, Makwana, and Hare (2015). To test their hypothesis, they used a self-control task involving choices between primary foods varying on the features of taste and healthiness, in combination with socially evaluated cold pressor test. Notable, the researchers included only male participants ($n = 51$). They found that stress reduced self-control and increased the influence of immediately rewarding taste attributes on choice behavior. This behavior was accompanied by reduced functional connectivity between the ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal regions related to control; and increased connectivity between the vmPFC and the amygdala and striatal regions encoding tastiness. According to the authors, these findings indicate that acute stress may affect self-control decisions by both increasing the influence of immediately rewarding attributes and decreasing the potency of brain regions promoting goal-directed behaviors (Maier et al., 2015). The stress-related increase in sensitivity to reward condition during the processing of hits, which we found in the third study, is in line with this theory. However, the third study did not yield evidence for stress-related impairments of performance monitoring.

The stress-related modulations of the FRN and feedback-related theta power, reflecting impaired feedback processing, which we found in our first two studies, were not replicated in the third study. This discrepancy might be explained by different factors. First, the three studies employed different tasks. As we described above, the first two studies used a simple monetary gambling task, whereas the third study employed a MID task. These different tasks provided different contexts in which feedback stimuli were processed. The presence of the factor reward condition and/or the absence of loss trials in the MID task seem to have had a strong influence on brain activity, both during reward anticipation and feedback stages, as reflected in effects of reward condition on both cue-related theta power (larger increases following no-reward versus potential-reward cues) and feedback-related theta power (larger increases in potential-reward versus no-reward trials), and the absence of a significant effect of feedback valence on feedback-related theta power. These findings suggest that during the MID task, evaluation in terms of positive or negative prospects already takes place during the stage of reward anticipation. However, our exploratory analysis of cue-related theta power did not show stress-related modulations either, which indicates that stress did not impair the evaluation of prospects.

A second factor which might have caused differential stress effects on feedback-related brain activity in the three studies is the use of different stressors. The

first two experiments made use of a noise stressor, whereas the third experiment utilized highly aversive movie fragments. Although we could confirm the successfulness of the stress induction procedure in the third experiment, there is a possibility that exposure to the aversive movie clips was less stressful than exposure to the noise stressor. Unfortunately, we cannot compare the effectiveness of both stress induction procedures, as we did not directly validate the stressfulness of the acute noise stressor in the first two experiments.

A third factor which might explain the discrepancies in stress-related modulations of feedback-related brain activity between the three studies consists of sample-related differences in biological sex and menstrual cycle phase of female participants. Whereas the first study included males and the second study included males and females in their midluteal phases, the third study included females in their late follicular and late luteal phases. In general, reproductive women show lower physiological stress responsiveness than men (Kajantie & Phillips, 2006; Kudielka, Hellhammer, & Wüst, 2009). In the luteal phase, however, they show similar stress-related cortisol increases as men. Consequently, the average stress response in the third study may have been lower than the average stress responses in the first and second studies. We will elaborate on the roles of biological sex and menstrual cycle phase in the next sections.

Effects of acute stress on the neural processing of action outcomes in men and midluteal women

In the first study (chapter 2), we found evidence for the idea that acute stress impairs feedback processing on a neural level. Disturbances in feedback processing are regarded as causal factors in the development of certain stress-related disorders (Forbes, Shaw, & Dahl, 2007; Russo & Nestler, 2013). Therefore, the sex-specific prevalence rates of these disorders might be related to sex-specific effects of stress on feedback processing. Previous behavioral studies have found evidence for differences in stress effects on decision making, between men and women. These studies, for example, reported increased risk taking in men and decreased risk taking in women, under acute stress (Lighthall et al., 2009; Van den Bos, Harteveld, & Stoop, 2009). Furthermore, Lighthall et al. (2012) found that stress exposure increased decision speed in males, but decreased decision speed in females. Crucial to adaptive decision

making is adequate feedback processing. The question whether sex-specific stress effects on decision making are related to sex-specific stress effects on feedback processing was addressed in our second experiment.

In the second study (chapter 3), we investigated whether effects of acute stress on feedback processing differed between males and females. As we described above, this experiment employed an acute noise stressor in combination with a simple monetary gambling task. The sample included males and females during the midluteal phase. Our findings with regard to the FRN and feedback-related theta power, reflecting performance monitoring, revealed similar stress effects for men and women: acute stress decreased FRN amplitudes and feedback-related theta power in both sexes. Evidence for a sex-specific stress effect on feedback processing was limited to changes in lower beta-band power: under stress, both in an early (0–300 ms post-feedback) and later time window (300–600 ms), lower beta-band power increases were larger for men than women. In the early time window, no sex difference was observed in the control condition. In the later time window, the larger increases in men were observed in both control and stress conditions. Although the role of beta-band activity in feedback processing has not been clarified yet, it has been suggested that with regard to motor control, beta-band activity might enable proprioceptive feedback processing (Baker, 2007). Similarly, with regard to cognitive control, it might facilitate the processing of feedback information. Thus, although stress effects were largely similar for both sexes in the present study, the larger increases in early, lower beta-band power in men relative to women in the stress condition might reflect a stronger facilitation of early feedback processing in men under stress. This finding supports the idea that effects of acute stress on feedback processing are at least partly sex-specific.

Taken together, although we did find some evidence for sex-specific stress effects on feedback processing, stress effects were largely similar for both sexes. How should we interpret this? First, the detection of differences in stress effects on feedback processing between men and women might be limited due to the small size of the effects, similar to many sex differences on psychological variables (Hyde, 2005). The final sample of our second study included 47 participants (23 females), which is sufficient to detect stress induction by sex interactions of medium effect size, but insufficient to detect smaller effects. For example, the effect of acute stress on feedback-related theta power appeared to be stronger in males compared to female (see chapter 3, Fig. 7C), but the stress induction by sex interaction did not reach significance due to the small effect size ($\eta_p^2 = .01$). The inclusion of a larger number of participants would enable the detection of small sex differences as well.

Second, the high degree of similarity between effects of stress on feedback-related processing in men and women could be related to the fact that we included females in their midluteal phases. In general, reproductive women show lower levels of HPA axis and ANS reactivity to stress relative to men of the same age (Kajantie & Phillips, 2006; Kudielka et al., 2009). However, responses to stress appear to be modulated by gonadal hormone levels. More specifically, females in the luteal phase show stress-related cortisol responses which are comparable to those of males (Kajantie & Phillips, 2006; Otte et al., 2005). Therefore, in line with these findings, the response to the stressor may have been similar between the sexes in our second study with midluteal women. Unfortunately, we did not include physiological or subjective stress measures to evaluate stress reactivity in this experiment, which precludes a firm conclusion on this issue. Nevertheless, a similar stress response in men and women might explain the absence of differential stress effects on feedback processing.

Third, the similar stress effects on feedback-related brain activity in males and females could be linked to similar reactivity to an acute noise stressor in both sexes. As we discussed in the general introduction, one of the reasons why we chose to employ a noise stressor was that we assumed this stressor to be equally stressful for men and women. In contrast with the evidence that women are more sensitive than men to interpersonal stressors and men are more sensitive than women to achievement stressors (Stroud, Salovey, & Epel, 2002), there is no such evidence with regard to noise stressors. As we mentioned above, we cannot draw conclusions on the responsiveness to the noise stressor in male and female participants, as we did not use subjective and physiological stress measures. However, our findings with regard to brain activity support the idea that our noise stressor was equally stressful to men and women, and that the similar stress responses led to similar modulations of brain activity.

In conclusion, our findings point at largely similar stress effect on feedback processing for men and women measured during the midluteal phase of their menstrual cycle. These findings do not seem to be in line with the fact that women are *more* sensitive to depressive disorders than men during their reproductive years. How should this discrepancy be explained? As we pointed out above, the type of stressor and the menstrual cycle phase under investigation could be relevant. In addition, a broader perspective may give directions for future research on sex-specific stress effects over short and long terms. Recently, Ordaz and Luna (2012) wrote a review on the emergence of sex differences in physiological reactivity to acute psychosocial stressors, in adolescence. Two key points can be derived from their review. First, the

authors differentiate between three instead of two physiological response systems: in addition to two peripheral systems, the HPA axis and the ANS system, they distinguish a corticolimbic system. On the basis of their review, they conclude that, whereas males show greater HPA axis and ANS stress reactivity, females show greater corticolimbic stress reactivity. Second, the authors state that women respond with more intense negative affect to acute stressors than men, starting from adolescence, despite their lower peripheral stress responses. They hypothesize that, although negative affect has been shown to correlate with physiological stress reactivity, this association may be stronger in females than males. Furthermore, they propose that peripheral physiological responses may be less important to subjective awareness than corticolimbic systems. The increased subjective reactiveness in women may arise from an enhanced reactivity in brain areas translating stress responses into subjective awareness (Ordaz & Luna, 2012). In turn, the larger stress-related increase in negative affect in women relative to men could make them more vulnerable to depressive disorders.

Effects of acute stress on the neural processing of reward prospect and action outcomes during late luteal and late follicular phases

An important chemical difference between male and female brains lies in circulating levels of gonadal hormones. The menstrual cycle in women is characterized by variability in levels of estradiol and progesterone (Chabbert Buffet, Djakoure, Christin Maitre, & Bouchard, 1998). The early follicular phase is marked by very low levels of both hormones. From the midfollicular phase, estradiol levels start rising to peak in the late follicular phase, while progesterone levels remain low. In the luteal phase, estradiol levels decrease to a moderate level, while progesterone increases to peak in the midluteal phase. The late luteal phase is characterized by a steep decline of both hormone levels (Chabbert Buffet et al., 1998).

Animal studies have demonstrated that estradiol and progesterone are not only crucial for reproductive behavior, but influence many other functions, including motivation, cognition and stress regulation (Becker, 2009; McEwen, 2002). More specifically, preclinical research has yielded substantial evidence for neuroregulatory effects of estradiol and progesterone on mesolimbic and mesocortical dopamine (DA) systems, which play an important role in reward-prospect- and feedback-related

behaviors (Becker, 2009; McEwen). In humans, behavioral studies have shown that menstrual cycle phase is indeed related to variability in reward-related behaviors, such as food cravings and energy intake (Davidsen, Vistisen, & Astrup, 2007; Dye & Blundell, 1997), and in subjective responses to stimulant drugs (Terner & De Wit, 2006). In addition, the menstrual cycle has been associated with changes in stress sensitivity (e.g., Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Ossewaarde et al., 2010). These changes may be related to changes in hormonal levels as well. For example, the high levels of estradiol in the late follicular phase have been linked to a temperance of stress-related brain activity in women (Jacobs et al., 2015). Moreover, activity within brain reward systems has been shown to be affected by stress exposure (Dedovic, D'Aguiar, & Pruessner, 2009; Starcke & Brand, 2012), indicating that hormonal influences on reward-related processing and stress regulation may interact.

Given the abovementioned evidence for menstrual cycle-related variability in reward-prospect- and feedback-related behaviors and in stress sensitivity, the aim of the third study (chapter 4) was to investigate the combined effects of menstrual cycle phase and acute stress on the neural processing of reward prospect and action outcomes. Females participated in two experimental sessions, once during the late follicular phase and once during the late luteal phase, performing in both control and stress conditions in each session. As we described earlier, acute stress was induced by exposing participants to highly aversive movie clips in the third study, while the employment of the MID task in this study allowed the investigation of both reward anticipation and feedback stages. In line with our first hypothesis, we found phase-related changes in the sensitivity to the valence of feedback and in the sensitivity to reward condition. In line with our second hypothesis, we found that stress impaired attentional preparation during reward anticipation. However, we also found that stress increased the impact of reward condition on the processing of positive action outcomes. In contrast with our third hypothesis, we found no proof for an increased sensitivity to stress in the late luteal relative to the late follicular phase. In the following, we will first discuss our findings with regard to phase effects on brain activity during reward anticipation and feedback stages. Then, we will consider the effects of stress on reward-prospect- and feedback-related processing in both late follicular and late luteal phases.

Effects of menstrual cycle phase on the neural processing of reward prospect and action outcomes

Menstrual cycle phase especially modulated brain activity during the processing of action outcomes. With regard to the factor feedback valence, our findings indicate an enhanced sensitivity in the late follicular relative to the late luteal phase, with a stronger signaling of negative (vs. positive) action outcomes, as reflected in a larger valence effect on the FRN in the late follicular phase. The present findings are in line with the findings of an fMRI study reporting enhanced activation of brain reward areas following actual-reward versus no-reward delivery, in the midfollicular compared to the midluteal phase (Dreher et al., 2007). Animal research has yielded evidence that estradiol boosts DA activity in brain reward systems, whereas progesterone may oppose this effect (Jackson, Robinson, & Becker, 2006). Similarly, in humans, the increased activation of brain reward systems in the mid- or late follicular phase may be related to the presence of high estradiol, boosting DA activity, in combination with low progesterone levels (Dreher et al., 2007).

In contrast, our findings suggest an increased sensitivity to reward condition in the late luteal compared to the late follicular phase. The processing of feedback information was found to be influenced by whether or not participants could earn a reward or not in a particular trial. In case a reward was at stake, performance monitoring seemed to be enhanced, as reflected in increases in feedback-related theta power, compared to the no-reward condition. Importantly, this effect of reward condition during feedback processing depended on the combination of stress induction condition and menstrual cycle phase. In the stress condition, this effect was present during both late luteal and late follicular phases. In the control condition, however, only late luteal women showed increased feedback-related performance monitoring in potential-reward relative to no-reward trials. This increased performance monitoring was sustained by a nonsignificant trend during the stage of reward anticipation, suggesting an increased potential-reward-related amplification of attentional preparation in the late luteal relative to the late follicular phase. This enhanced sensitivity to reward condition during the late luteal phase may be related to the steep decline in hormonal levels, reducing endogenous DA activity, which has been proposed to lead to increased DA release following reward cues (see for review, Ossewaarde et al., 2011b).

The phase-specific influence of reward condition on feedback processing in the present study seem at odds with the phase-specific impact of feedback valence. However, it can be argued that the effects of menstrual cycle phase on feedback-

related brain activity may differ between specific psychological components of feedback or reward. As Berridge, Robinson, and Aldridge (2009) indicated, reward can be dissected into anticipatory ("wanting"), consummatory ("liking") and learning components, which are thought to be subserved by distinct neurobiological substrates. The factor reward condition in the present study might be related to "wanting", the factor feedback valence might be linked to "liking", while both factors might be associated with learning. The influence of gonadal hormone levels on these components may differ, because their neurobiological substrates differ. Accordingly, the drop in estradiol levels in the late luteal phase might lead to increased wanting, whereas the high estradiol in combination with low progesterone levels in the late follicular phase might cause enhanced liking. In addition, the current findings underscore the importance of clearly defining which subphases are to be examined. Distinguishing between merely follicular and luteal phases is insufficient, given the high variability in (changes in) levels of estradiol and progesterone in the course of the menstrual cycle.

Effects of acute stress in late follicular and late luteal phases

Exposure to the highly aversive movie clips induced largely similar stress responses during late follicular and late luteal phases, as reflected in both subjective and physiological stress measures as well as stress-related modulations of brain activity. In contrast with our expectations, we did not find an enhanced sensitivity to stress in the late luteal relative to the late follicular phase. This result could be interpreted in different ways. First, increased stress sensitivity in the late luteal phase might be confined to women with Premenstrual Dysphoric Disorder (PMDD). PMDD is characterized by symptoms of depressed mood, emotional instability, anxiety and/or irritability, which occur during the late luteal phase and disappear around the onset of menstruation (American Psychiatric Association, 2013). These symptoms have been argued to be related to a heightened sensitivity to stress during the late luteal phase, in women with PMDD relative to healthy women (Bannbers, Kask, Wikström, Risbrough, & Sundström Poromaa, 2011; Epperson et al., 2007).

Second, the absence of significant phase modulations of acute stress effects may be partly due to the small sample size (final $n = 17$) of our study. Visual inspection of Figure 5 in chapter 4, for example, suggests larger stress-related increases in heart rate and cortisol levels in the late luteal compared to the late follicular phase. However these effects did not reach significance. In addition, we

found a trend suggesting a larger stress-related increase in disgust in the late follicular relative to the late luteal phase. Disgust sensitivity in the sexual domain, defined as "the ease with which disgust is elicited by aberrant sexual behaviors", has been reported to be most pronounced during the late follicular phase, which was proposed to be related to conception risk (Fessler & Navarette, 2003). The present enhanced increase in disgust in the late follicular versus the late luteal phase is in line with this idea, considering the fact that three out of four aversive clips in the present study comprised sexual attacks or threats. These nonsignificant findings are in line with our expectations with regard to phase modulations of acute stress effects, suggesting that power might have been an issue in our third study.

Third, our stress induction procedure – showing participants highly aversive movie clips preceded by a self-referencing instruction – yielded mild to moderate stress responses in the participants. For example, heart rate during the movie clips increased from 62.7 bpm in the control condition to 65.1 bpm in the stress condition (4% increase). In addition, cortisol levels at the end of the condition, that is approximately 35 minutes after the first movie clip, increased from 2.8 nmol/L in the control condition to 3.9 nmol/L in the stress condition (39% increase). Cortisol responses peak between 21 and 40 minutes from stressor onset (Dickerson & Kemeny, 2004). For comparison, the Trier Social Stress Test (TSST) has been associated with a two to threefold rise in salivary cortisol levels in about 75% of all tested subjects and a mean heart rate increase of approximately 20 bpm (Kudielka, Hellhammer, & Kirschbaum, 2007). The TSST is a motivated performance task including a short preparation period and a test period in which the participant has to give a free speech (5 min) and perform mental arithmetic (5 min) in front of an audience. Importantly, the TSST-induced salivary cortisol response is significantly larger in men (200% to 400% increase) than in women (50% to 150% change; Kudielka et al., 2007). Given the fact that our stress induction procedure did not result in stress levels of this extent, we cannot conclude anything about the impact of stronger stressors in the late follicular versus late luteal phases. However, we can conclude that our stressor was a relatively mild stressor, which did not show phase-specific stress effects in the present sample.

Measurement and interpretation of the FRN

In our studies we examined the FRN, which is an ERP component reflecting the processing of outcome information. The measurement of the FRN is complicated due

to overlap with surrounding components, of which the P300 is most notable, which probably reflect different, neural processes. However, there is no consensus in the literature on how to deal with this problem. Most previous studies only report one way to measure the FRN, either neglecting or aiming to correct for overlap with other components (Sambrook & Goslin, 2014). In all three experiments, we used different ways to quantify the FRN: mean amplitude (MA), mean amplitude corrected for surrounding peaks (MAC), and base-to-peak.

Importantly, we found that results depended on the FRN measuring method. Correcting for either preceding and following peaks or only the preceding peak yielded smaller main effects of valence (all three experiments), magnitude (first two experiments), and reward condition (third experiment), and smaller or different interaction effects (all three experiments), relative to the results for the uncorrected mean amplitude measure. Based on the dependence of the effects on the measuring method, one might argue that the observed effects of these factors on FRN amplitude are not limited to the FRN. The question is whether underlying neural processes active in the FRN window are indeed unrelated to the processes in the preceding and following time windows. Only if they are, one would like to correct for them, not if they are related.

One way to avoid the problem with overlapping components in ERP waveforms is to use time-frequency analysis to analyze stimulus-related oscillatory activity. Cohen et al. (2011) have advocated the use of time-frequency measures instead of one-peaked ERP components to study the feedback-related EEG response. Using time-frequency measures would enable research results to be more directly related to neurophysiological processes, including neuronal activity at population level. The FRN has been proposed to reflect theta-band oscillatory processes (Cavanagh, Zambrano-Vazquez, & Allen 2012; Cohen, Elger, & Ranganath, 2007). Theta oscillations are thought to play an important role in signaling the need for increased cognitive control from the MFC to the lateral PFC (Cavanagh, Cohen, & Allen, 2009; Van de Vijver et al., 2011). For these reasons, we included the measurement of feedback-related theta power in the second and third experiment.

Is the use of feedback-related theta power preferable over the use of the FRN? In the second experiment, we could compare the results from all three FRN measures with the results from theta power. We found that the results from the MAC measure most closely resembled the theta results, with comparable effects of valence, magnitude and stress induction. However, we also found that the effect sizes of the valence and magnitude effects were larger for the MAC measure (valence: $\eta_p^2 = .59$,

magnitude: $\eta_P^2 = .53$) than for theta ($\eta_P^2 = .26$ and $\eta_P^2 = .30$, respectively), indicating that this FRN measure is somehow more sensitive to these factors than theta power. In the third experiment, we compared the results of two FRN measures (MA and MAC) and theta power. In this study, the picture was less clear as to which FRN measure showed the highest resemblance in results with theta power. Similar to the second experiment, we found that the effect sizes of valence were larger for the FRN measures (MA: $\eta_P^2 = .84$, MAC: $\eta_P^2 = .73$) compared to theta power ($\eta_P^2 = .12$). Furthermore, we found that feedback-related theta power was larger in potential-reward versus no-reward trials, whereas FRN amplitudes showed the opposite pattern, indicating that theta power and FRN measures are differentially influenced by reward condition. Thus, although feedback-related theta power could possibly be more directly related to underlying communication between neuronal populations, FRN measures show an enhanced sensitivity to the valence of feedback, which is considered the most important factor in feedback processing, and differential modulations by reward condition.

There has been an ongoing debate about the interpretation of the FRN. One dominant theory is that the FRN reflects the size of a reward prediction error (RPE), which is defined as the difference between the actual and expected outcome of behavior (Holroyd & Coles, 2002; Holroyd, Larsen, & Cohen, 2004; Nieuwenhuis, Holroyd, Mol, & Coles, 2004). In the first two experiments, we indeed found that losses generated larger FRN amplitudes compared to gains. However, we also found larger FRN amplitudes for small compared to large outcomes, for both gains and losses. Thus, small losses were followed by larger FRN amplitudes relative to large losses, whereas the latter event reflected a larger prediction error. Furthermore, in the third experiment, we found larger FRN amplitudes following misses relative to hits, especially in potential-reward trials, which is in line with the RPE theory. However, in contrast to what one would expect on the basis of this theory, we also found that the effect of reward condition was more important in hit trials than in miss trials. One would expect that the FRN amplitude would be especially large on miss trials were a reward was at stake. However, the effect of reward condition was relatively small in miss trials. Instead, we found that the effect of reward condition was more pronounced in hit trials: FRN amplitudes were larger following hits in no-reward versus potential-reward trails, although the fact that no reward was at stake was already communicated to the participant before feedback presentation, so that there was no prediction error with regard to the reward.

Altogether, our findings are in contrast with the RPE theory of the FRN. Our

results might be better explained by the conflict-monitoring theory of Botvinick (2007). According to this theory, FRN amplitudes are determined by the level of behavioral uncertainty following certain events. Higher response conflict, as reflected in the simultaneous activation of competing responses, is associated with larger FRN amplitudes. This would explain why small losses elicited larger FRN amplitudes than large losses, as small losses are less easy to interpret as to whether behavior should be adjusted or not. In addition, this would explain why FRN amplitudes in miss trials were less dependent on reward condition than amplitudes in hit trials, although both types of trials showed a similar pattern with larger amplitudes in no-reward compared to potential-reward trials. Misses are clearly unfavorable in both reward conditions, whereas hits in no-reward trials might yield more uncertainty than hits in potential-reward trials in terms of what one could do to achieve the pursued outcome.

Critical considerations and ideas for future research

The investigation of acute stress effects on reward-prospect- and feedback-related brain activity in healthy men and women during specific menstrual cycle phases is a challenging enterprise. A large number of factors need to be taken into account, while setting-up experiments and interpreting results. In the following, a selection of these factors will be discussed along with ideas for future research.

Representativeness of samples

In the studies described in this thesis, we examined effects of acute stress in healthy men and women. In line with previous research, we applied many inclusion and exclusion criteria to candidates for participation. Candidates were included if they were physically and mentally healthy and reported no evidence of current or past psychiatric disorders, neurological disorders, or head injuries. Other criteria were that they did not use CNS-active medication or drugs or smoked cigarettes, were right-handed and had (corrected-to) normal vision and hearing. In addition, female candidates had to have regular menstrual cycling with normal mean cycle length, were not pregnant, and had not used hormonal contraceptives within the previous four or six months. We have to take into account that this strict procedure might have affected the representativeness of our sample for the general population.

Volunteers indicated their interest in participating in our studies through signing

up via an electronic registration system used for recruitment of participants or via e-mail. They did this only after reading the in- and exclusion criteria. After registration, candidates were assessed during telephone screenings (studies 1 and 2) or separate screening sessions (study 3). If a candidate did not fulfill the criteria, we excluded him or her from participation. We noticed that the active screening of candidates instead of screening by self-report led to a drop in the number of suitable candidates. A considerable percentage of candidates, who initially stated to be healthy, appeared to have a history of disorders, after careful screening. Although one might question how one should define the healthy population, the application of the current selection criteria led to a very healthy sample, representative of a very healthy category within the general population.

Furthermore, since we are working in an academic environment, most of our participants were undergraduate students. This convenience sampling as such is a well-known threat to representativeness, as the average student is relatively young and intelligent compared to the general population. In addition, a large percentage of female students is or has recently been on hormonal contraceptives. Although we did not systematically investigate this, one could imagine that the selected women who had not been on hormonal contraceptives for the previous four or six months differed from the women who were on hormonal contraceptives, in other respects as well, which might be relevant to our studies. The careful selection of participants might pose limitations on the generalization of our findings.

Acute stressor types

For the purpose of investigating effects of acute stress, we used two different stressor types: loud white noise and highly aversive movie clips coupled with a self-referencing instruction. Previous research has shown that acute noise exposure activates the HPA axis and the ANS system, causing the release of stress hormones (Babisch, 2003). In addition, in a pilot study on the subjective effects of exposure to the discontinuous noise stressor, we could confirm its effectiveness. We validated the effectiveness of exposure to the movie fragments during the third experiment. This stress induction procedure was successful, as confirmed by subjective and physiological stress measures. This is in accordance with previous research employing this procedure (e.g., Henckens, Hermans, Pu, Joëls, & Fernández, 2009).

Although the stressors employed in the current work appeared to be successful in eliciting stress, they did not result in the *high* stress levels as induced, for example,

by the abovementioned TSST (see section: Effects of acute stress in late follicular and late luteal phases). Dickerson and Kemeny (2004) performed a meta-analysis of 208 studies on cortisol responses to acute psychological stressors. They hypothesized that especially uncontrollable threats to the social self would trigger cortisol elevations. The social self reflects one's social value, status and esteem and is formed through social assessments (De Waal, 1989; Gilbert, 1997; both as cited in Dickerson & Kemeny, 2004). On the basis of their meta-analysis, the authors concluded that not all stressors are equivalent, that the experience of distress might not be sufficient to elicit cortisol responses, and that only certain stressor types are associated with cortisol elevations. They found that verbal interaction tasks, cognitive tasks, and combinations of public speaking and cognitive tasks evoked significant cortisol responses. Emotion induction tasks (16 studies in meta-analysis; e.g., movie clips) and noise exposure (6 studies) were not associated with significant cortisol elevations. In accordance with their hypothesis, they found that motivated performance tasks characterized by uncontrollability and/or social evaluative threat elicited significant cortisol increases. The largest elevations were found for tasks containing both elements. A good example of the latter is the earlier mentioned TSST, which combines the elements of a motivated performance task, uncontrollability and social evaluative threat (Dickerson & Kemeny, 2004). Unfortunately, the meta-analysis did not consider sex differences in stress responses.

The conclusions of Dickerson and Kemeny (2004) indicate that the acute stressors employed in the current studies were of relatively mild quality. However, in the third study we did find significant modulations of cortisol levels following exposure to the highly aversive movie clips, indicating substantial stress levels. Furthermore, we did find alterations in reward-prospect- and feedback-related brain activity induced by exposure to the stressors. Our findings point out that even mild stress affects brain activity.

Effects of acute versus chronic stress

In the current set of experiments, we investigated the impact of *acute* stress on reward-prospect- and feedback-related activity. This research was motivated by the desire to increase our knowledge on the neural basis of the sex-specific prevalence rates of stress-related disorders. Importantly, stress-related disorders are triggered by *chronic* exposure to stress (Kendler, Karkowski, & Prescott, 1999). The effects of acute and chronic stress on certain motivation-related behaviors and associated brain

activity may differ, as discussed below.

Pizzagalli (2014) compared the role of acute and chronic stress in a review of the literature on the role of anhedonia, dopamine and stress in depression. Anhedonia is defined as the lack of reactivity to normally rewarding stimuli, reflected in a loss of pleasure. Pizzagalli concluded that acute and chronic stress exposure lead to reduced pleasure in humans. However, animal research has shown that only prolonged exposure to uncontrollable stressors leads to long-term neurobiological effects, such as a down-regulation of mesolimbic DA pathways and an increased sensitivity to novel stressors. Although preclinical findings cannot be directly translated to humans, similar changes might affect humans under chronic stress exposure (Pizzagalli, 2014). Further research should investigate the impact of these long-term neurobiological stress effects on reward-prospect- and feedback-related related brain activity in humans.

Menstrual cycle phase verification

The scheduling of the experimental sessions according to specific menstrual cycle phases is complicated due to both inter-individual differences and intra-individual differences in the length of the cycle (Hampson & Young, 2008). The first problem we encountered was that we had to exclude some of the female candidates, because their menstrual cycles had not stabilized yet. Full reproductive maturity, which is associated with a very high percentage of ovulatory cycles, is not reached in many women until their mid-20's (Hampson & Young, 2008). Metcalf and Mackenzie (1980, as cited in Hampson & Young, 2008) investigated ovulation over three months in 254 women. They found that 62% of the women aged between 20 and 24 years ovulated in every cycle, while this percentage rose to 88% of women between 25 and 29 years, and 91% of women over 30 years.

Normal menstrual cycles range from 24 to 35 days in reproductively healthy women. While the length of the luteal phase is relatively fixed between 13 to 15 days, the length of the follicular phase varies. The follicle takes at least 12 days to develop, meaning that cycles shorter than 24 days are mostly anovulatory. The length of the average cycle varies between women. In addition, the length of the cycle varies from one cycle to another cycle by two to four days, within women. This variability in cycle length between and within women hinders accurate prediction of the occurrence of specific phases in upcoming menstrual cycles.

Prospective targeting in order to include women in a study at particular days of

the cycle is unlikely to be completely successful. This is due to the limited accuracy of women's reports and, as mentioned above, the variability in cycle length within women. In our experiment, we had participants actively track their dates of menses onset, which has been shown to be more accurate than reports based on memory (Presser, 1974, as cited in Hampson & Young, 2008). Retrospectively, one can determine the menstrual cycle phase by counting backward from the date of onset of the next menstruation (Hampson & Young, 2008). We applied this method in the second experiment, where women participated during their midluteal phases, between days 10 and 5 prior to menses onset. Using this method, we had to exclude 13 from the initial 37 females (that is 35%) from our second experiment.

An alternative and perhaps more reliable method for menstrual cycle phase verification is the direct quantification of hormones (Hampson & Young, 2008). In the third experiment, we used ovulation predictor tests, which signal the luteinizing hormone (LH) surge preceding ovulation, to schedule the late luteal sessions. These sessions were planned between days 10 and 14 after the LH surge (= day 0). Late follicular sessions were scheduled between days 8 and 12 relative to menses onset (= day 1). Furthermore, we measured salivary *progesterone* levels on both late follicular and late luteal sessions, in order to check whether these levels were in accordance with targeted phases. The measurement of hormones via salivary samples is preferable above blood samples, because it is less invasive and stressful to participants. Ideally, one would measure both estradiol and progesterone on measurement days, to acquire a more precise estimation of the specific menstrual cycle phase, as specific progesterone levels can occur in multiple subphases of the menstrual cycle. Unfortunately, saliva *estradiol* assays are not widely available yet.

In many studies, menstrual cycle phases are defined broadly and/or not verified by measuring estradiol and/or progesterone. We observed that prospective targeting on the basis of self-report, as we applied in the second study, is an inaccurate and inefficient procedure, which requires exclusion of a large percentage of participants after participation. Future studies should investigate more circumscribed subphases, characterized by specific hormonal features. In addition, they should verify menstrual cycle phases as precisely as possibly, by measuring ideally both progesterone and estradiol, and by having participants actively record their menses onsets.

Conclusions

In this thesis, we investigated the impact of acute stress on brain activity during reward anticipation and outcome evaluation, in men and women, and across the female menstrual cycle. We found that acute stress modulated, mostly in a negative way, reward-prospect- and feedback-related processing. Effects of acute stress on feedback processing were largely similar for men and women. However, we also found evidence for sex-specific feedback-related brain activity under stress exposure, indicating a stronger facilitation of early feedback processing in men relative to women. The latter finding supports the idea that the influence of stress on feedback processing is partly dependent on sex. Finally, we found that effects of acute stress on reward-prospect- and feedback-related processing did not significantly differ between late follicular and late luteal phases. Nevertheless, we did find phase-related modulations of feedback-related processing, showing an enhanced sensitivity to the valence of feedback in the late follicular phase, and an increased reactivity to the prospect of reward in the late luteal phase. These findings provide evidence that menstrual cycle phase modulates feedback-related brain activity and that effects of phase may differ between specific psychological components of feedback. In this general discussion, we have tried to interpret and integrate the findings from our experiments, to provide alternative explanations, and to discuss limitations of our studies. Although sex differences research is increasing and the general picture is getting more clear, many details still have to be clarified. A better understanding of the brains of males and females under conditions of stress is crucial for the future development of appropriate interventions for stress-related disorders for both men and women.

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SAMENVATTING

Vrouwen verschillen van mannen in zowel hun gedrag als onderliggende hersenmechanismen. Of deze verschillen het product zijn van aanleg of opvoeding was en is nog steeds onderwerp van veel discussie. Hoewel sommige onderzoekers het belang benadrukken van onderzoek naar sekseverschillen in het brein en in gedrag, waarschuwen andere voor het overdrijven van deze verschillen. We zijn echter in een stadium beland, waarin wetenschappelijk gezien niet langer valt te ontkennen dat sekse van invloed is op ons gedrag en op de werking van onze hersenen.

In de afgelopen decennia is een groot aantal studies verschenen waarin gerapporteerd wordt over een diversiteit aan sekse-invloeden op het brein. Echter in experimenteel onderzoek naar de hersenmechanismen die ten grondslag liggen aan cognitie, emoties en gedrag worden verschillen tussen mannen en vrouwen vaak genegeerd. Er zijn talloze voorbeelden van hersenonderzoekers die bij voorkeur alleen mannelijke deelnemers includeerden, zodat ze geen rekening hoefden te houden met de invloed van de menstruele cyclus, en de daarmee gepaard gaande hormonale schommelingen, bij vrouwen. De bevindingen uit deze onderzoeken bij mannen werden vervolgens eenvoudigweg gegeneraliseerd naar vrouwen. Deze situatie is onwenselijk en vormt een serieuze belemmering voor de vooruitgang in het begrijpen van de verschillen en overeenkomsten tussen mannen en vrouwen. Studies naar deze sekseverschillen zijn bijvoorbeeld belangrijk om inzicht te verschaffen in waarom bepaalde mentale stoornissen bij de ene sekse meer voorkomen dan bij de andere sekse. Bovendien zijn deze studies cruciaal voor de ontwikkeling van effectieve behandelmethoden voor mensen met een mentale stoornis, met name voor die behandelingen die effectief zouden kunnen zijn voor vrouwen.

Een belangrijke categorie van stoornissen waarin de invloed van sekse evident is, zijn de stressgerelateerde stoornissen die gekenmerkt worden door sekseverschillen in prevalentie. Mannen leiden bijvoorbeeld vaker aan een verslaving of hoge bloeddruk, terwijl vrouwen vaker leiden aan een auto-immuunziekte of een depressie. Stressgerelateerde stoornissen komen veel voor en vormen daarom een belangrijke bron van zorg voor onze samenleving. In 2010 bijvoorbeeld leed 4.4% van de wereldbevolking aan een ernstige depressieve stoornis, wat overeenkomt met 298 miljoen personen, en werd bij 1.6%, equivalent aan 106 miljoen personen, een dysthyme stoornis gediagnosticeerd (Ferrari et al., 2013). Uit eerder onderzoek zijn

aanwijzingen naar voren gekomen dat in de ontwikkeling van stressgerelateerde stoornissen een belangrijke rol is weggelegd voor de fysiologische reactie van iemand op stress. We kunnen ons daarom afvragen of de sekseverschillen in prevalentie van deze stoornissen voor een deel worden veroorzaakt door verschillen tussen mannen en vrouwen in deze lichamelijke stressreactie. Daarnaast zijn er aanwijzingen gevonden dat bij vrouwen fluctuaties in geslachtshormonen een belangrijke rol kunnen spelen in de pathogenese van bepaalde stressgerelateerde stoornissen. Bekende voorbeelden hiervan zijn de postnatale depressie en de premenstruele dysfore stoornis (PMDD). Maar ook het feit dat vrouwen alleen gedurende hun vruchtbare periode, dat wil zeggen vanaf het moment dat ze beginnen te menstrueren tot na de overgang, vergeleken met mannen een verhoogde gevoeligheid hebben voor het ontwikkelen van een depressieve stoornis, is een duidelijke aanwijzing voor de belangrijke rol van fluctuerende geslachtshormonen bij vrouwen.

Hoewel er dus duidelijke aanwijzingen zijn voor invloeden van sekse op de ontwikkeling van stressgerelateerde stoornissen, is er nog maar weinig bekend over de neurale mechanismen die hieraan ten grondslag liggen. In dit proefschrift worden een drietal studies beschreven, die uitgevoerd zijn om te onderzoeken welk effect acute stress heeft op het functioneren van mannen en vrouwen en welke invloed de menstruele cyclus hierop heeft bij vrouwen. Door middel van deze onderzoeken, waarin zowel gedrag als hersenactiviteit werd gemeten, hebben we de relatie tussen stress, gedrag en onderliggende hersenmechanismen onderzocht. Hersenactiviteit werd gemeten aan de hand van elektro-encefalografie (EEG), waarbij de elektrische activiteit van de hersenen met behulp van elektroden op het hoofd van de deelnemer wordt gemeten. Dankzij de hoge temporele resolutie van deze methode, waarbij hersenactiviteit op milliseconde-niveau wordt gemeten, kan zeer nauwkeurig worden bepaald wanneer wat in onze hersenen gebeurt en hoe deze activiteit beïnvloed wordt door factoren zoals stress. In onze onderzoeken richtten we ons op de effecten van acute stress op de verwerking van beloningsprikkels[1] door onze hersenen en op de verwerking van uitkomsten van ofwel feedback op gedrag. Uit eerder onderzoek zijn namelijk aanwijzingen naar voren gekomen dat de manier waarop we juist deze informatie verwerken een centrale rol kan spelen in de ontwikkeling van stressgerelateerde stoornissen. We hebben met name onderzocht of de effecten van

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[1] De in dit proefschrift gebruikte Engelse term "reward" vertalen we in de Nederlandse samenvatting als beloning. In de wetenschappelijke literatuur wordt "reward" gedefinieerd als een positieve emotionele stimulus, die het gedrag bekrachtigt dat heeft geleid tot de beloning (Russo & Nestler, 2013).

acute stress verschillen tussen mannen en vrouwen en of de effecten van acute stress bij vrouwen afhankelijk zijn van de menstruele fase en de daaraan gekoppelde hormonale invloeden.

Sekse, de menstruele cyclus en het brein

De sekse van een persoon heeft een grote invloed op zowel de anatomie als de chemie als het functioneren van het brein. Sekseverschillen in het brein variëren van effecten op het niveau van zenuwcellen tot het niveau van structurele en functionele netwerken. Een belangrijk verschil in neurochemie tussen mannen en vrouwen wordt gevormd door niveaus van de in het brein circulerende geslachtshormonen. Deze hormonen zijn niet alleen belangrijk voor de seksuele differentiatie van het brein tijdens de vroege ontwikkeling en voor de voortplanting, maar deze hormonen hebben ook een belangrijke invloed op cognitieve functies, motivatie en stressregulatie. Relevant voor ons onderzoek is dat met name fluctuaties in de niveaus van de vrouwelijke hormonen estradiol en progesteron over de menstruele cyclus in verband zijn gebracht met fluctuaties in stressgevoeligheid en gemotiveerd gedrag, dat wil zeggen gedrag dat erop gericht is bepaalde beloningen te verkrijgen.

De menstruele cyclus duurt ongeveer 29.5 dagen en bestaat uit de folliculaire fase, de periode vanaf het begin van de menstruatie tot de ovulatie, en de luteale fase, de periode tussen ovulatie en het begin van de volgende menstruatie. In de vroege folliculaire fase zijn de niveaus van de geslachtshormonen estradiol en progesteron erg laag (zie Fig. 1 in Chapter 1). Het estradiolniveau stijgt vanaf de midfolliculaire fase en piekt tijdens de laatfolliculaire fase, terwijl het progesteronniveau laag blijft. Tijdens de luteale fase daalt het estradiolniveau tot een gematigd niveau, terwijl het progesteronniveau stijgt en piekt tijdens de midluteale fase. De laatluteale of premenstruele fase wordt gekenmerkt door een sterke daling in de niveaus van zowel estradiol als progesteron. Onderzoek bij dieren heeft sterk bewijs opgeleverd dat beide hormonen betrokken zijn bij stressregulatie en gemotiveerd gedrag. Over de precieze werking van deze hormonen bij mensen is echter nog veel onduidelijkheid.

Effecten van acute stress op de verwerking van beloningsprikkels en feedback in de hersenen

In de eerste twee onderzoeken (hoofdstukken 2 en 3) onderzochten we de invloed van blootstelling aan geluid op het verwerken van positieve (winst) en negatieve feedback (verlies). Geluid is een stressor waarvan we weten dat die bij mannen en vrouwen een stressreactie oproept. In onze experimenten maakten we gebruik van een eenvoudige goktaak, waarbij deelnemers moesten kiezen tussen twee witte kaarten. Ze deden deze taak in de stressconditie, dat is terwijl ze bloot werden gesteld aan het geluid, en in een controleconditie zonder geluid. Na iedere keuze ontvingen de deelnemers feedback die aangaf hoeveel geld er op die trial was gewonnen of verloren. Aan het eerste onderzoek namen alleen mannen deel, terwijl aan het tweede onderzoek zowel mannen mededen als vrouwen in de midluteale fase. In beide onderzoeken vonden we ondersteuning voor een negatieve invloed van acute stress op het verwerken van feedback in de hersenen. Met name vonden we negatieve effecten op de EEG-maten die het bewaken van prestaties ("performance monitoring") reflecteren. In het eerste experiment vonden we een verminderde gevoeligheid voor de valentie van feedback (winst versus verlies) en voor de grootte van de bedragen (± 5 of ± 25 eurocent) in de stressconditie vergeleken met de controleconditie. In het tweede experiment vonden we bij zowel mannen als vrouwen een verminderde gevoeligheid voor feedback als gevolg van stress opgewekt door het geluid. Dit effect was in tegenstelling tot het eerste experiment niet afhankelijk van winst of verlies of de grootte van het bedrag.

In het derde onderzoek (hoofdstuk 4) hebben we in plaats van geluid een andere stressor gebruikt. We hebben de invloed van blootstelling aan zeer aversieve filmfragmenten op het verwerken van beloningsprikkels en feedback onderzocht. Dit deden we bij vrouwen in de laatfolliculaire fase en in de laatluteale fase. In dit experiment maakten we gebruik van een "monetary incentive delay (MID)" taak ofwel een taak met geldelijke beloningsprikkels. Deze taak bestond uit trials waarbij een mogelijke beloning in het vooruitzicht werd gesteld en trials waarbij geen geld op het spel stond. Aan het begin van elke trial werd door middel van een cue (teken) aangegeven welke beloningsconditie op die trial van toepassing was. Met het verschijnen van de cue startte het anticipatiestadium. Na de cue volgde namelijk een target (doelwit) waarop de deelnemer zo snel mogelijk op een knop moesten drukken. Daarna ontving de deelnemer feedback, die aangaf of hij/zij snel genoeg had

gereageerd op het target (treffer versus misser) en al dan niet geld had gewonnen (afhankelijk van de beloningsconditie en het gedrag). Met het verschijnen van de feedback begon het feedbackstadium.

De hierboven beschreven MID-taak verschilde in twee belangrijke opzichten van de simpele goktaak die we gebruikten in de eerste twee experimenten. Ten eerste bevatte de MID-taak zowel een anticipatiestadium als een feedbackstadium, terwijl de simpele goktaak alleen het feedbackstadium bevatte. De MID-taak gaf ons daarmee de mogelijkheid niet alleen de verwerking van feedback, maar ook het effect van een beloningsprikkel tijdens het anticiperen op een target te onderzoeken. Ten tweede bevatte de MID-taak, in tegenstelling tot de simpele goktaak, geen trials waarin deelnemers geld konden verliezen, hoewel de taak wel neutrale trials bevatte waarin geen geld kon worden gewonnen.

In het derde experiment vonden we aanwijzingen voor effecten van acute stress tijdens zowel het anticipatie- als het feedbackstadium. Tijdens het anticipatiestadium had stress een negatieve invloed op de vroege oriëntatie van de aandacht op aankomende targets. De vrouwen leken meer moeite te hebben met het richten van de aandacht op relevante informatie in de stressconditie in vergelijking met de controleconditie. Dit effect was onafhankelijk van het al dan niet aanwezig zijn van een beloningsprikkel op de trial. Tijdens het feedbackstadium had stress echter een versterkend effect op de invloed van de beloningsconditie op het verwerken van treffers: het effect van het al dan niet ontvangen van een beloning was sterker in de stressconditie. Opvallend was dat we de negatieve effecten van stress tijdens het feedbackstadium die we vonden in de eerste twee experimenten (i.e. verminderde gevoeligheid voor feedbackinformatie), niet konden repliceren in het derde experiment.

Kortom, alle drie experimenten demonstreerden effecten van acute stress op hersenactiviteit, zowel tijdens het anticipatiestadium (hoofdstuk 4) alswel het feedbackstadium (hoofdstukken 2, 3 en 4). We kunnen concluderen dat acute stress een negatieve invloed heeft op de vroege oriëntatie van de aandacht op aankomende targets (onderzoek 3) en de verwerking van feedback (onderzoeken 1 en 2). Dit is in overeenstemming met eerder onderzoek waarin is aangetoond dat acute stress met name negatieve effecten heeft op hogere-orde cognitieve functies in tegenstelling tot functies die meer automatisch worden uitgevoerd. Naast de negatieve effecten van stress liet het derde experiment een positief effect zien. Deelnemers vertoonden in de stressconditie, in vergelijking met de controleconditie, een verhoogde gevoeligheid voor de beloningsconditie tijdens de verwerking van treffers. De beloningsconditie

bepaalde of een treffer werd gevolgd door een beloning of niet. Stress had echter geen invloed op de prestatiebewaking ("performance monitoring") op zich, dat wil zeggen het controleren of targets waren geraakt of niet. Onze bevindingen suggereren dat deelnemers vooral in de stressconditie gevoelig waren voor de daadwerkelijke ontvangst van een beloning na een goede prestatie. Deze verklaring zou in overeenstemming zijn met bevindingen van studies naar de effecten van stress op gedrag, waarin is aangetoond dat stressvolle omstandigheden de consumptie van belonende substanties, zoals calorierijk eten en alcohol, stimuleren.

Blootstelling aan acute stress heeft mogelijk een negatieve invloed op gecontroleerd gedrag ten faveure van acties die leiden tot een onmiddellijke beloning, zoals recent is voorgesteld door Maier, Makwana en Hare (2015). Deze onderzoekers testten hun hypothese door middel van een zelfcontrole-taak, waarin deelnemers keuzes moesten maken tussen verschillende soorten voedsel. Deze voedselsoorten varieerden in smaak en gezondheid. Als stressor gebruikten de onderzoekers een fysieke stressor, waarbij proefpersonen hun hand gedurende voor hen onbekende tijd (3 min.) in ijskoud water moesten steken, terwijl er opnames van hen werden gemaakt en de experimentleider hen in de gaten hield. De onderzoekers vonden ondersteuning voor hun hypothese. Blootstelling aan acute stress was van invloed op zowel de keuzes van de deelnemers als de functionele connectiviteit binnen hersennetwerken die een belangrijke rol spelen in respectievelijk de controle van gedrag en smaak. Volgens de auteurs tonen deze bevindingen aan dat de negatieve invloed van stress op het maken van gecontroleerde beslissingen twee oorzaken heeft: een sterkere invloed van eigenschappen die onmiddellijk belonend zijn (iets wordt gekozen omdat het lekker is), en een zwakkere invloed van hersengebieden die belangrijk zijn voor doelgericht gedrag (iemand kiest weloverwogen voor iets omdat het gezond is). De vergrote gevoeligheid voor de beloningsconditie tijdens het verwerken van treffers in de stressconditie, die we vonden in onze derde studie, is in overeenstemming met deze theorie. Wij vonden in deze studie (in tegenstelling tot onze eerste twee studies) echter geen ondersteuning voor het idee dat stress een negatieve invloed heeft op de prestatiebewaking.

Effecten van acute stress op de verwerking van feedback in de hersenen van mannen en vrouwen in de midluteale fase

In het tweede onderzoek (hoofdstuk 3) onderzochten we of de effecten van acute stress op de verwerking van feedback verschillen tussen mannen en vrouwen. Zoals we hierboven beschreven, maakten we in dit experiment gebruik van een geluidsstressor en een eenvoudige goktaak. Deelnemers aan het onderzoek waren mannen en vrouwen in de midluteale fase van hun menstruele cyclus. We vonden dat acute stress een negatieve invloed had op de prestatiebewaking, maar dat deze effecten niet significant van elkaar verschilden tussen beide seksen. Wel vonden we een sekseverschil tijdens de *vroege* verwerking van feedback (0–300 ms) in de stressconditie. Bij mannen leek sprake te zijn van een sterkere facilitatie van de verwerking van feedback dan bij vrouwen, tijdens blootstelling aan stress.

Kortom, onze bevindingen gaven slechts een beperkte ondersteuning voor het idee dat effecten van acute stress verschillen tussen mannen en vrouwen. Hiervoor kunnen we een drietal verklaringen geven. In de eerste plaats was onze steekproef (47 deelnemers, 23 vrouwen) voldoende groot voor het detecteren van interactie-effecten met een middelgrote effectgrootte. Kleinere effecten, die gangbaar zijn in onderzoek naar sekseverschillen, kunnen alleen worden gedetecteerd met een grotere steekproef. Het aantal proefpersonen in ons experiment zou dus te klein kunnen zijn geweest om subtiele effecten zichtbaar te maken. In de tweede plaats lieten we vrouwen deelnemen tijdens de midluteale fase van hun menstruele cyclus. Uit eerder onderzoek zijn aanwijzingen naar voren gekomen dat vrouwen tijdens de luteale fase een fysiologische stressrespons vertonen die vergelijkbaar is met de stressrespons in mannen. Het zou zo kunnen zijn dat een vergelijkbare fysiologische stressrespons in beide seksen heeft geleid tot een overeenkomstig effect van acute stress op de verwerking van feedback in de hersenen van mannen en vrouwen. In de derde plaats hebben we gebruik gemaakt van een acute geluidsstressor, omdat we veronderstelden dat deze even stressvol zou zijn voor mannen als voor vrouwen. In dit onderzoek hebben we geen subjectieve (bijv. stemming) of fysiologische (bijv. hartslag) metingen gedaan om het effect van de stressor te evalueren. Daardoor kunnen we in ons onderzoek niet valideren dat de mate van stress die de geluidsstressor opriep in mannen en vrouwen gelijk was. Onze resultaten met betrekking tot de effecten van stress op de hersenactiviteit vormen echter een ondersteuning voor het idee dat de acute geluidsstressor inderdaad even stressvol was voor beide seksen.

Effecten van acute stress op de neurale verwerking van beloningsprikkels en feedback tijdens de laatluteale en laatfolliculaire fase van de menstruele cyclus

Het doel van het derde onderzoek (hoofdstuk 4) was kennis te vergaren over de gecombineerde effecten van menstruele fase en acute stress op de verwerking van beloningsprikkels en feedback in de hersenen. Het onderzoek bestond uit twee experimentele sessies, één keer tijdens de laatfolliculaire fase en één keer tijdens de laatluteale of premenstruele fase. Beide sessies bevatten zowel de controleconditie als de stressconditie, gescheiden door een pauze van 75 minuten. Stress werd geïnduceerd door middel van blootstelling aan zeer aversieve filmfragmenten, terwijl het gebruik van de eerdergenoemde MID-taak onderzoek van zowel het anticipatie- als het feedbackstadium mogelijk maakte. We vonden dat de menstruele fase waarin een vrouw zich bevond tijdens deelname aan het onderzoek van invloed was op de hersenactiviteit gemeten tijdens het feedbackstadium. We vonden echter geen ondersteuning voor de hypothese dat vrouwen in de laatluteale fase gevoeliger zouden zijn voor stress dan in de laatfolliculaire fase.

De menstruele fase was van invloed op de hersenactiviteit tijdens de verwerking van feedback. In de eerste plaats vonden we dat vrouwen tijdens de laatfolliculaire fase, in vergelijking met de laatluteale fase, gevoeliger waren voor de valentie van feedback (missers versus treffers). Deze bevinding is in overeenstemming met enige recente fMRI-studies bij vrouwen, waarin werd gevonden dat het beloningssysteem sterker werd geactiveerd in omstandigheden waarin sprake was van een hoog niveau van estradiol in combinatie met een laag niveau van progesteron, zoals in de laatfolliculaire fase het geval is. Uit dieronderzoek was al eerder bekend dat estradiol een stimulerende werking heeft op het beloningssysteem, maar dat de aanwezigheid van progesteron dit effect mogelijk tegengaat. In de tweede plaats vonden we dat vrouwen juist tijdens de laatluteale fase, ten opzichte van de laatfolliculaire fase, in de controleconditie sterker reageerden op de beloningsconditie (of er al dan niet een beloning op het spel stond). Eerder is gesuggereerd dat deze verhoogde gevoeligheid zou kunnen samenhangen met de steile daling in het niveau van geslachtshormonen tijdens de laatluteale fase. Deze steile daling zou, via een reductie van de endogene activiteit van de in het beloningssysteem cruciale neurotransmitter dopamine, kunnen leiden tot een verhoogde afgifte van dopamine in reactie op beloningsprikkels. Dit is vergelijkbaar met een situatie van onthouding

(bijv. stoppen met roken), waarin iemand sterk verlangt naar een bepaalde stof (bijv. nicotine).

De effecten van de menstruele fase op feedbackgerelateerde hersenactiviteit die wij in ons onderzoek vonden, lijken met elkaar in tegenspraak. Een mogelijk verklaring ligt in het gegeven dat de valentie van feedback en beloningsconditie twee verschillende factoren zijn. Uit eerder onderzoek is gebleken dat verschillende aspecten van feedback en beloning worden verwerkt in overlappende, maar deels verschillende netwerken in de hersenen. De effecten van acute stress op de respectievelijke hersennetwerken kunnen van elkaar verschillen. Daarmee kunnen ook de effecten van stress op de functies die deze netwerken vervullen, van elkaar verschillen.

In tegenstelling tot onze verwachtingen vonden we geen significante verschillen in de effecten van acute stress tussen de laatluteale en laatfolliculaire fase. De effecten van stress op de subjectieve en fysiologische stressmaten en op de hersenactiviteit verschilden niet significant van elkaar tussen beide fasen. We vonden daarmee geen bevestiging van het idee dat het hoge estradiolniveau in de laatfolliculaire fase de stressreactiviteit zou verminderen in vergelijking met het sterk dalende estradiolniveau in de laatluteale fase. Deze bevindingen zijn voor meerdere interpretaties vatbaar. In de eerste plaats kan het zo zijn dat de vaak genoemde verhoogde stressgevoeligheid van vrouwen in de laatluteale fase alleen voorkomt bij vrouwen met PMDD. Deze stoornis wordt gekenmerkt door een sombere stemming, emotionele instabiliteit, angst en/of prikkelbaarheid, symptomen die verschijnen tijdens de laatluteale fase en verdwijnen rond het begin van de menstruatie (American Psychiatric Association, 2013). Deze symptomen zijn door eerdere onderzoekers toegeschreven aan een verhoogde gevoeligheid voor stress tijdens de laatluteale fase, bij vrouwen met een PMDD in vergelijking met gezonde vrouwen.

In de tweede plaats zou de afwezigheid van significante effecten van de menstruele fase op de acute stresseffecten kunnen samenhangen met de kleine steekproefgrootte (uiteindelijk $n = 17$) van het onderzoek. Visuele inspectie van Figuur 5 (hoofdstuk 4) bijvoorbeeld suggereert dat de stressgerelateerde stijgingen in hartslag en cortisol in de laatluteale fase groter waren dan in de laatfolliculaire fase. Deze effecten waren echter niet significant, wat zou kunnen wijzen op een gebrek aan power om dergelijke kleine effecten te kunnen meten.

In de derde plaats leidde de blootstelling aan onze stressor – deelnemers moesten aandachtig kijken naar zeer aversieve filmfragmenten, waarbij zij zich moesten inbeelden ooggetuige te zijn – tot milde tot gematigde fysiologische

stressreacties. De gemiddelde hartslag bijvoorbeeld steeg van 62,7 slagen per minuut in de controleconditie tot 65,1 slagen per minuut in de stressconditie (4% stijging). Het gemiddelde cortisolniveau aan het eind van de conditie steeg van 2,8 nmol/L in de controleconditie tot 3,9 nmol/L in de stressconditie (39% stijging). Ter vergelijking, de Trier Social Stress Test, die bekend staat als de gouden standaard onder stressoren, leidt tot cortisolstijgingen met 100% tot 200% in ongeveer 75% van alle deelnemers en een stijging van de gemiddelde hartslag met ongeveer 20 slagen per minuut (Kudielka, Hellhammer & Kirschbaum, 2007). Wel moet bij de interpretatie van deze effecten worden aangetekend dat de stijging in cortisol bij mannen gemiddeld genomen veel groter is (200% tot 400% stijging) dan bij vrouwen (50% tot 150% stijging; Kudielka et al., 2007). Onze stressor leidde niet tot dergelijke sterke fysiologische reacties, en was in fysiologisch opzicht dus relatief mild, maar had desondanks invloed op de hersenactiviteit in reactie op beloningsprikkels en feedback. Deze effecten waren echter niet significant afhankelijk van de fase waarin een vrouw zich tijdens deelname bevond.

Conclusies

In dit proefschrift onderzochten we de invloed van acute stress op de hersenactiviteit tijdens het stadium waarin iemand anticipeert op het verschijnen van een target en al dan niet een beloning in het vooruitzicht is gesteld, en tijdens het stadium waarin hij/zij feedback krijgt over het resultaat van zijn/haar gedrag. Daarbij onderzochten we of de effecten van acute stress verschilden tussen mannen en vrouwen, en tussen de laatfolliculaire en laatluteale fase. We hebben laten zien dat acute stress van invloed is, meestal in negatieve zin, op de verwerking van beloningsprikkels en feedback. Bovendien hebben we laten zien dat de effecten van acute stress op de verwerking van feedback grotendeels gelijk zijn voor beide seksen. We vonden echter ook enige aanwijzingen voor verschillen in hersenactiviteit tussen mannen en vrouwen tijdens het verwerken van feedback in omstandigheden van stress. Bij mannen leek in vergelijking met vrouwen sprake te zijn van een sterkere facilitatie van de vroegste verwerking van feedback, tijdens blootstelling aan stress. Deze bevinding ondersteunt het idee dat de invloed van stress op de verwerking van feedback gedeeltelijk afhankelijk is van iemands sekse. Tenslotte vonden we geen ondersteuning voor de hypothese dat de effecten van acute stress op de verwerking van beloningsprikkels en feedback groter zouden zijn in de laatluteale fase dan in de

laatfolliculaire fase. Wel vonden we aanwijzingen dat de manier waarop feedback wordt verwerkt afhankelijk is van de menstruele fase waarin een vrouw zich bevindt. Terwijl vrouwen gevoeliger waren voor de valentie van feedback in de laatfolliculaire fase dan in de laatluteale fase, reageerden vrouwen sterker op het vooruitzicht van een beloning in de laatluteale fase dan in de laatfolliculare fase. Deze bevindingen laten zien dat de menstruele fase van invloed is op hersenactiviteit tijdens de verwerking van feedback, en dat deze invloed mogelijk afhangt van de specifieke psychologische component die wordt verwerkt (valentie van feedback versus beloningsconditie).

Hoewel er een toename is in het onderzoek naar sekseverschillen in gedrag en hersenmechanismen en het algemene plaatje steeds duidelijker wordt, zijn er op meer gedetailleerd niveau nog grote hiaten in onze kennis. Een beter begrip van het functioneren van de hersenen van mannen en vrouwen onder normale en stressvolle omstandigheden is cruciaal voor de toekomstige ontwikkeling van geschikte behandelmethodes voor stressgerelateerde stoornissen voor zowel mannen als vrouwen.

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CURRICULUM VITAE

Hendrika Maria Banis (roepnaam Stella) werd geboren op 21 februari 1971 te Rijssen. Zij volgde het VWO op het Pius X College in Almelo. In 1990 vertrok ze uit Twente om Pedagogische Wetenschappen te gaan studeren aan de Rijksuniversiteit Groningen, waar zij in 1997 afstudeerde in de richting Orthopedagogiek. Daarna werkte zij als schoolbegeleider bij het Advies- en Begeleidingscentrum voor het Onderwijs in Groningen. In 2005 ging Stella terug naar de RuG om Psychologie te studeren. Zij studeerde in 2007 cum laude af in de richting Hersenen en Gedrag, bij de afdeling Experimentele Psychologie. Bij deze afdeling startte zij in 2008 haar promotietraject onder supervisie van prof. dr. M.M. Lorist, waarvan dit proefschrift de weerslag is. Vanaf 2015 is zij werkzaam als docent en coördinator bij de Onderwijseenheid Psychologie aan de RuG.

Stella woont samen met Mark Spruit en hun kinderen Mats (8 jaar), Mira en Julie (6 jaar).