Dissertation

The Influence of Emotional States on Memory-related Information Processing:

An Investigation of underlying Neural Oscillations

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English Summary

The overall goal of this dissertation project was to investigate the role of neural oscillations in emotion-cognition interaction. The project focused on memory-related information processing, since memory processes are profoundly modulated by emotion and a strong link between memory and neural oscillations has been established. In three studies, emotional states were induced in healthy subjects using emotional film clips. Subjects had to carry out specific memory-related cognitive tasks under the influence of the respective induced emotional state. Emotional state induction procedures were chosen to achieve a relatively high level of ecological validity, and to take steps towards a translational research approach that holds the possibility to translate the findings into the context of affective disorders that are often accompanied by cognitive deficits. In the first study, an episodic memory task was carried out in different mood states, and in the second and third study, a working memory and a mental arithmetic task were carried in a stressful emotional state, compared to neutral control condition. All three studies showed that memory-related neural oscillations were modulated by the emotional state. Correlations between emotional state-dependent modulations of neural oscillations and behavioral performance suggest that oscillatory neural activity plays a meaningful role in the interaction between emotion and memory-related processes. In the outlook section, clinical implications and the possibility to externally modulate oscillations by different stimulation techniques are discussed. In summary, this work suggests that studying the role of neural oscillations in emotion-cognition interaction is an area of research that holds promising possibilities for both, basic and clinical research.

Deutsche Zusammenfassung

Das übergeordnete Ziel dieser Dissertation bestand darin, die Rolle neuronaler Oszillationen in Prozessen der Emotions-Kognitions-Interaktion zu untersuchen. Der Fokus lag hierbei auf Gedächtnisprozessen, da zahlreiche Studien belegen, dass diese stark durch Emotionen beeinflussbar sind und ein bedeutsamer Zusammenhang zwischen Gedächtnis und neuronalen Oszillationen nachgewiesen wurde. In drei Studien wurden emotionale Zustände bei gesunden Probanden durch emotionale Filmausschnitte induziert. Die Aufgabe der Probanden bestand darin, die gedächtnisbezogenen Aufgaben unter dem Einfluss des induzierten emotionalen Zustands durchzuführen. Das Verfahren der emotionalen Zustandsinduktion wurde gewählt, um eine möglichst hohe ökologische Validität zu erreichen und um erste Schritte in Richtung eines translationalen Forschungsansatzes zu unternehmen, der die Möglichkeit bietet, die gewonnenen Erkenntnisse in den Kontext von affektiven Störungen zu übersetzen, welche oft mit kognitiven Defiziten einhergehen. In der ersten Studie wurde der Einfluss von verschiedenen Stimmungszuständen auf das episodische Gedächtnis untersucht. In Studie zwei und drei wurde der Einfluss von emotionalem Stress auf Arbeitsgedächtnis und mentale Arithmetik untersucht. Alle drei Studien zeigten, dass gedächtnisbezogene neuronale Oszillationen durch den emotionalen Zustand moduliert werden. Korrelative Zusammenhänge zwischen der emotionsabhängigen Modulation neuronaler Oszillationen und der Verhaltensleistung legen nahe, dass oszillatorische neuronale Aktivität eine bedeutende Rolle in der Interaktion zwischen Emotionen und gedächtnisbezogenen Prozessen spielt. Im Ausblick dieser Arbeit werden klinische Implikationen diskutiert, sowie die Möglichkeit, oszillatorische Aktivität durch elektrische Stimulation extern zu modulieren. Zusammenfassend legt diese Arbeit nahe, dass die Untersuchung der Rolle neuronaler Oszillationen in der Emotions-Kognitions-Interaktion einen vielversprechenden Forschungsbereich darstellt, der sowohl in der Grundlagen-, als auch in der klinischen Forschung zu neuen Erkenntnissen und Behandlungsmöglichkeiten führen kann.

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List of Abbreviations

ACC – anterior cingulate cortex

ANOVA – analysis of variance

BOLD – blood-oxygen-level dependent

Ca – catecholamine

DMN – default mode network

DSM-IV – Diagnostic and Statistic Manual of Mental Disorders

EEG – electroencephalography / electroencephalogram

ERD – event-related desynchronization

ERN – error-related negativity

ERP – event-related potential

ERS – event-related synchronization

FDR – false discovery rate

FFT – fast Fourier transform

fMRI – functional magnetic resonance imaging

FMT – frontal midline theta

FT – frontal theta

FWHM – full width at half maximum

Gc – glucocorticoid

HPA – hypothalamic–pituitary–adrenal axis

IAPS – International Affective Picture System

ICA – independent component analysis

IFG – inferior frontal gyrus

ISI – inter-stimulus interval

LF – later forgotten

LR – later remembered

MDD – major depressive disorder

mPFC – medial prefrontal cortex

MWT-A – Mehrfach-Wortschatz-Intelligenz-Test A

PANAS – Positive and Negative Affect Schedule

PFC – prefrontal cortex

PSD – power spectral density

SCID – Structured Clinical Interview for DSM-IV

SME – subsequent memory effect

SNS – sympathetic nervous system

WM – working memory

1. Introduction

Over the last two decades, the interplay between cognition and emotion has become a major research interest in the field of cognitive neuroscience (Ledoux 1996; Dolan 2002; Pessoa 2008). Historically, emotion and cognition have been viewed as largely separate domains, but converging evidence suggests that these two domains are fundamentally integrated in the brain and jointly contribute to behavior. In a similar vein, psychiatric research is beginning to acknowledge the fact that most psychiatric disorders are not only characterized by changes in emotional processing, but are also accompanied by cognitive dysfunctions (Millan et al. 2012). A precise understanding of the mechanisms that underlie cognition-emotion interactions in the brain is a crucial step to move forward in the treatment of cognitive deficits that accompany many psychiatric disorders.

In his influential review on the relationship between emotion and cognition, Pessoa (2008) provides three reasons why the view of separate emotional and cognitive brain regions is untenable. First, it has been shown that brain regions that were classified as emotional are involved in cognitive processing (e.g. the amygdala - Holland and Gallagher 1999). Second, regions that were previously classified as cognitive are involved in emotional processing (e.g. the lateral prefrontal cortex - Gray et al. 2002), and third, structural and functional connectivity suggests that emotion and cognition are fundamentally integrated in the brain. To date, most evidence for emotion-cognition interaction comes from brain imaging studies. However, especially the third of Pessoa's arguments gives rise to the assumption that macroscopic neural oscillations provoked by synchronized activity of large neural cell assemblies (see also section 1.2) might play a role in emotion-cognition interaction. Neural oscillations have been implicated in large-scale integration mechanisms, by which information from different brain regions is integrated (Varela et al. 2001; Buzsaki and Draguhn 2004). Such integration mechanisms are thought to play a fundamental role in emotion-cognition integration in the brain.

The main goal of this dissertation project was to investigate to which extent neural oscillations are involved in emotion-cognition interaction. The studies conducted within this project focus on memory-related information processing for the following reasons:

First, a large body of research suggests that memory-related processes are strongly influenced by emotion, and second, neural oscillations have been largely implicated in memory-related information processing. In fact, these interrelations further support the notion that neural oscillations might play a key role in the mechanisms of emotion-cognition interaction. However, surprisingly little research has been conducted in this field.

1.1 Emotional states

When studying emotion-cognition interaction in the laboratory, a crucial challenge is to induce specific emotions in the subjects in a controlled and repeatable fashion. A common method is to use emotional stimuli, e.g. emotionally valenced words, to study how the stimulus valence affects memory performance and memory-related cognitive processes in the brain (e.g. Grimm et al. 2012). This method has the advantages that the induced emotions are rather specific and that well-validated stimuli such as word lists (e.g. Vo et al. 2009), or pictures (e.g. Bradley and Lang 2007) are applied. Usually, brain responses within seconds after stimulus presentation are measured, and responses from emotionally valenced material are compared to responses from neutral control material. A supposed disadvantage of this method is that the ecological validity of such an experimental design is rather low, as in many situations in everyday life, the cognitive task at hand is not inherently emotional. Furthermore, the applied emotional material is often static, and valence changes occur frequently and artificially abrupt. Indeed, in everyday life it is more likely the case that the cognitive task itself is rather neutral, but cognitive processing is influenced by the emotional state of the subject. The same applies to cognitive deficits in psychiatric disorders. Cognitive deficits in such disorders are likely related to perturbations of the emotional state and not to the content of the cognitive task.

In the laboratory, several methods exist to induce such longer-lasting emotional states. In a common setting an emotional state is induced using strong emotional stimuli such as music (Koelsch 2005), or film clips (Qin et al. 2009), and the cognitive task is being carried out under the influence of the induced emotion. This can be done either during, or after the emotional state induction. The advantage of such a procedure is that it allows to measure effects that are independent from the content of the stimulus material and solely depend on the emotional state (state-dependence). Using emotional state induction also holds the possibility to investigate interaction effects between the emotional state and the valence of the stimulus material. Such effects have been termed ‘mood congruence’ (Blaney 1986), and are often investigated in memory paradigms (e.g. Lewis et al. 2005). A supposed disadvantage of emotional state induction procedures is that induced emotional states can be rather diffuse, and are more prone to inter-subject variability. It is rather likely, for instance, that listening to heavy metal music might induce different states in different subjects. In addition, the duration and the intensity of the induced emotional state are crucial factors to consider. Secondary measures that control for the effectiveness of the induction procedure are of importance here. Because of the rather diffuse nature of induced emotional states, simple dimensional models of emotion, such as the core affect model (Russell 2003), pose an appropriate way to describe the induced states. Many studies using emotional state induction focus on the valence dimension. Emotional state induction in this field is often label ‘mood induction’, and a good or elevated mood state is compared against a bad or depressed mood state (Clore and Huntsinger 2007). Another clinically relevant emotional state that is often induced in experimental settings is the state of psychological stress. (Dickerson and Kemeny 2004). In terms of the core affect model a high arousal and negative valence[1] state is usually compared against a low arousal and neutral valence state.

To date, most studies that investigated the mechanisms of emotion-cognition interaction used static emotional stimulus material in highly artificial experimental paradigms. Although these paradigms have afforded several critical insights, their real-world significance remains poorly understood (Okon-Singer et al. 2015). One step towards higher ecological validity is to induce longer-lasting emotional states combined with neutral stimuli instead of using static emotional stimulus material that includes many abrupt changes in stimulus valence. Furthermore, emotional state induction holds the advantage to study the effects of emotion on cognition independent from the content of the cognitive task. For these reasons, emotional state induction is suitable to translate

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[1] It has to be noted that stress is not inherently of negative valence, and not all studies focus on valence dimension of stress. However, most studies that applied psychological stress induction procedures induce stress that is perceived as negative, and the stress induction procedure applied in this work induces stress that clearly induces a negative valence / high arousal state. Therefore, stress that is perceived as positive is not further elaborated in this thesis.

findings from healthy subjects to clinical populations. The studies conducted in this dissertation project all used emotional state induction procedures via film clips. The goal was to induce states that are comparable to emotional state perturbations present in affective disorders, such as depressed mood or psychological stress. Cognitive tasks were presented after induction, and the stimulus material was neutral to investigate state-dependence effects.

1.2 Neural oscillations

Neural oscillations in the central nervous system arise from rhythmic neural activity that can be observed in individual neurons and in large neural cell assemblies. At the level of individual neurons, oscillatory activity is caused by rhythmic firing patterns of action potentials (Kandel et al. 2000). At the level of neural cell assemblies, synchronized activity of large neuronal populations gives rise to macroscopic oscillations that originate from postsynaptic dendritic currents. Such oscillations can be measured non-invasively using e.g. an electroencephalogram (EEG, Nunez and Srinivasan 2005). The frequency range of these macroscopic neural oscillations[2] in most cases lies between 0.5 and 100 Hz, and is conventionally divided into different frequency bands: delta (0.5 – 3.5 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (15 – 25 Hz), and gamma (>30 Hz). However, the boundaries of these classical frequency bands have been repeatedly scrutinized, and are susceptible to inter- and intra-individual changes (e.g. Klimesch 1999).

Despite the fact that the first discovery of neural oscillations dates back more than 85 years (Berger 1929), their functional significance is still under debate. However, several lines of evidence suggest that neural oscillations play a meaningful functional role in cognitive processing (Varela et al. 2001; Buzsaki and Draguhn 2004). Probably the most prominent function of neural synchrony is described in the binding-by-synchrony hypothesis, put forward by Singer and colleagues (Singer 1999). It provides a solution to the binding-problem (Treisman 1996) by assuming that separate features of a perceived object that are processed in distributed brain regions, bind through the process

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[2] In the following, for reasons of simplicity the term “neural oscillation” will be used to refer to macroscopic neural oscillations that can be measured at the scalp surface.

of neural synchronization. Going further, Engel and colleagues argue that neural synchronization does not only play a role in bottom-up stimulus processing, but also in the integration of information in many top-down processes such as action planning, working memory and selective attention (Engel et al. 2001).

Oscillatory activity, as measured by EEG recordings can be categorized as ongoing, evoked and induced oscillations (David et al. 2006). Ongoing oscillations wax and wane spontaneously during resting conditions, whereas evoked and induced oscillations are related to external stimulation. Evoked and induced oscillations differ in their phase-relationships to the stimulus. Evoked oscillations are phase-locked to the stimulus, whereas induced oscillations are not. A common conception is that evoked oscillations reflect a stimulus-locked event-related response, and that induced oscillations are generated by distinct higher-order top-down processes. Time-frequency analysis is the most frequently used analysis tool to measure event-related changes in neural oscillations. Usually, the event-related changes are compared to a pre-stimulus baseline period to measure effects of event-related synchronization (ERS), and event-related desynchronzation (ERD) of neural activity (Pfurtscheller and Aranibar 1977).

The focus of this dissertation project was to investigate induced neural oscillations in higher-order memory-related processes. Several EEG studies investigated encoding mechanisms during memory formation (e.g. Osipova 2006; Hanslmayr et al. 2009). A common conception is that successful encoding is related to ERS in the theta and gamma frequency ranges and to ERD in alpha and beta frequency ranges. It has been proposed that neural synchronization in the theta and gamma range allows for the transient interaction between cortical structures and the hippocampus (Nyhus and Curran 2010) and is involved in shaping synaptic plasticity (Axmacher et al. 2006; Fell and Axmacher 2011). On the contrary, processes of neural desynchronization have been linked to the activation of single highly specific brain regions involved in semantic stimulus encoding (Hanslmayr et al. 2011).

In recent years, neural oscillations in the theta frequency range located over the frontal cortex have received much attention. Many studies have shown that frontal theta (FT) oscillations are involved in various high-level cognitive processes, such as cognitive control (Cavanagh and Frank 2014) and working memory (Hsieh and Ranganath 2014). Due to their involvement in many higher cognitive processes and their clear frontal localization, FT oscillations have been proposed as a general communication mechanism of the prefrontal cortex (Cavanagh et al. 2012). Interestingly, FT oscillations have also been linked to blissful states during meditation (Aftanas and Golocheikine 2001), and break-down of the temporal structure of FT during rest has been observed in depressive patients (Linkenkaer-Hansen et al. 2005). These and several other studies indicate that FT is a good candidate to be involved in emotion-cognition interaction. However, direct evidence is still lacking.

1.3 Goals of the dissertation project

The main goal of this dissertation project was to investigate the role of neural oscillations in emotion-cognition interactions. Despite the fact that synchronized neural activity has been related to processes of information integration from distant brain regions, little research has been conducted in this field. The studies conducted in this project focused on memory-related information processing because memory processes are modulated by emotion, and have been linked to neural oscillations.

In the first study, effects of mood on episodic encoding and encoding-related EEG oscillations were investigated. The rationale for this study was abundant behavioral data of mood-effects on encoding strategies during episodic encoding. Furthermore, event-related EEG oscillations during encoding have been linked to subsequent recall. Therefore, we hypothesized mood-dependent modulations of encoding-related EEG oscillations during a subsequent memory paradigm (Paller and Wagner 2002). In the second and the third study, effects of acute psychological stress on working memory-related FT oscillations were investigated. The rationale for these two studies was that FT has been repeatedly linked to working memory, which is known to be impaired under stress. Thus, we hypothesized attenuated working memory-related FT oscillations under stress. The second study focused on different levels of task difficulty, and the third studies on the time course of FT in single trials during the natural and complex task of mental arithmetic.

An additional goal of this dissertation project was to conduct studies with relatively high ecological validity that can be translated to psychiatric conditions. Longer-lasting emotional states were induced that relate to mental states that are altered in affective disorders (mood and stress induction). A further reason to investigate emotional state effects on neural oscillations was that recent research has shown that neural oscillations can be modulated through external stimulation (Thut et al. 2011; Battleday et al. 2014). Thus, the results of this project might be applied to guide stimulation protocols in the treatment of cognitive deficits that accompany psychiatric disorders. Such possibilities are being discussed in the outlook section of the general discussion.

2. Encoding-related EEG oscillations during memory formation are modulated by mood state[3]

2.1 Abstract

Mood states have a strong impact on how we process incoming information. It has been proposed that positive mood facilitates elaborative, relational encoding, whereas negative mood promotes a more careful, stimulus-driven encoding style. Previous electrophysiological studies have linked successful information encoding to power increases in slow (<8 Hz) delta/theta and fast (>30 Hz) gamma oscillations, as well as to power decreases in midrange (8-30 Hz) alpha/beta oscillations. Whether different mood states modulate encoding related oscillations has not been investigated yet. In order to address this question, we used an experimental mood induction procedure and recorded EEGs from 20 healthy participants while they performed a free recall memory task after positive and negative mood induction. We found distinct oscillatory patterns in positive and negative mood, respectively. Successful encoding in positive mood was accompanied by widespread power increases in the delta band, whereas encoding success in negative mood was specifically accompanied by frontal power decreases in the beta band. On the behavioral level, memory performance was enhanced in positive mood. Our findings show that mood differentially modulates the neural correlates of successful information encoding and thus contribute to an understanding of how mood shapes different processing styles.

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[3] This chapter was published as Gärtner, M. and Bajbouj, M. (2014). Encoding-related EEG oscillations are modulated by mood state. Social, Cognitive and Affective Neuroscience, 9(12), 1934-41. Accessible online: http://dx.doi.org/10.1093/scan/nst184

3. Working memory-related frontal theta activity is decreased under acute stress[4]

3.1 Abstract

Acute stress impairs prefrontal cortex (PFC) function and has detrimental effects on working memory (WM) performance. Converging evidence from electrophysiological studies suggests a close link between WM processes and frontal theta (FT) activity (4-8 Hz). However, the effect of stress on WM-related FT activity has not been investigated yet. To shed light on this topic we acquired EEG data from 31 healthy male subjects who underwent a stressful and a neutral control condition. In both conditions, they performed an n-back WM task at two different difficulty levels. Our results showed that WM-related FT activity was decreased under stress. Behaviorally, we found performance impairments under stress in the difficult task condition that were related to FT decreases. Increased cortisol levels indicated a successful moderate stress induction. These findings indicate that FT is a potential neurobiological marker for intact PFC functioning during WM and further supports the recently made assumption that FT acts in the PFC to optimize performance.

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[4] This chapter was published as Gaertner, M., Rohde-Liebenau, L., Grimm, S. and Bajbouj, M. (2014). Working memory-related frontal theta activity is decreased under acute stress. Psychoneuroendocrinology, 43, 105-113. Accessible online: http://dx.doi.org/10.1016/j.psyneuen.2014.02.009

4. Frontal midline theta oscillations during mental arithmetic: effects of stress[5]

4.1 Abstract

Complex cognitive tasks such as mental arithmetic heavily rely on intact, well-coordinated prefrontal cortex (PFC) function. Converging evidence suggests that frontal midline theta (FMT) oscillations play an important role during the execution of such PFC-dependent tasks. Additionally, it is well-established that acute stress impairs PFC function, and recent evidence suggests that FMT is decreased under stress. In this EEG study, we investigated FMT oscillations during a mental arithmetic task that was carried out in a stressful and a neutral control condition. Our results show late-onset, sustained FMT increases during mental arithmetic. In the neutral condition FMT started to increase earlier than in the stress condition. Direct comparison of the conditions quantified this difference by showing stronger FMT increases in the neutral condition in an early time window. Between-subject correlation analysis showed that attenuated FMT under stress was related to slowed reaction times. Our results suggest that FMT is associated with stimulus independent mental processes during the natural and complex PFC-dependent task of mental arithmetic, and is a possible marker for intact PFC function that is disrupted under stress.

4.2 Introduction

The execution of complex cognitive tasks strongly depends on prefrontal cortex (PFC) function, and its network connections to other brain regions (Miller and Cohen 2001). PFC function during high-level cognition include the maintenance and manipulation of information in the absence of external stimulation, the protection of these fragile representations from external and internal distractions, and the top-down control of

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other brain regions (Goldman-Rakic 1995; Arnsten 2009). Converging evidence suggests a close relationship between PFC-dependent cognitive tasks and frontal midline theta (FMT, 4 – 8 Hz) oscillations (for reviews see Mitchell et al. 2008; Cavanagh and Frank 2014; Hsieh and Ranganath 2014). High-level cognitive processes that are coincided by FMT oscillations include working memory (Jensen and Tesche 2002; Onton et al. 2005; Itthipuripat et al. 2013; Zakrzewska and Brzezicka 2014), episodic encoding (Klimesch et al. 1997; Nyhus and Curran 2010; White et al. 2013) and retrieval (Klimesch et al. 2001; Osipova et al. 2006), mental arithmetic (De Smedt et al. 2009; Ishii et al. 2010; Ishii et al. 2014), error processing (Luu et al. 2004; Cohen 2011) and action monitoring (Cavanagh et al. 2012).

The broad range of cognitive phenomena that FMT oscillations have been related to make it challenging to interpret their functional role. Furthermore, it is questionable whether FMT fulfills the same function in all of the observed phenomena. Indeed, functional interpretations tend to focus on subsets of the described phenomena, such as cognitive control processes (Cavanagh and Frank 2014), or processes related to memory function (Hsieh and Ranganath 2014). One reason for different functional roles of FMT during cognitive control and memory processes is that the nature of these oscillations differs in various aspects. During cognitive control processes, it has been suggested that FMT oscillations might provide a mechanism by which the need for cognitive control is first realized, and then communicated to other brain regions (Cavanagh and Frank 2014). This type of FMT is usually phase-locked to the presented stimulus (evoked oscillations), and of transient nature. It has been observed in a broad range of cognitive tasks that require the allocation of attentional resources, and close relationship between event-related potentials (ERP), such as the error-related negativity (ERN) and evoked FMT oscillations has been reported (Trujillo and Allen 2007; van Driel et al. 2012). During working memory (WM), it has been suggested that FMT might be particularly relevant to maintain and manipulate information in the absence of external stimulation (Hsieh et al. 2011; Roux and Uhlhaas 2014). Reports of a negative relationship between FMT and default mode network (DMN; Raichle et al. 2001) activation, have put forward the assumption that FMT might also be relevant to focus attention on task demands, and inhibit task irrelevant information (Scheeringa et al. 2009). FMT during WM has been found to increase with memory demands (Gevins et al. 1997; Jensen and Tesche 2002), is not phase-locked to presented stimuli (induced oscillations), and usually of sustained nature. A few studies directly compared evoked and the induced FMT responses and found that only the induced response is modulated by increased WM demands (Missonnier et al. 2006; Deiber et al. 2007). In these studies, the evoked response was equally present in all task conditions that required focused attention, and was absent only in a passive viewing condition.

Because of the different cognitive phenomena that FMT oscillations have been involved in, is has been suggested that FMT might provide a general mechanism the PFC uses to establish network connections to other brain regions (Anderson et al. 2010; Cohen 2011). It is well-established that the neurochemical changes that occur during acute stress disrupt PFC network connections (Arnsten 2009; McEwen and Morrison 2013). Therefore, it can be assumed that FMT oscillations are affected by stress. In a recent study, first evidence has been provided that FMT oscillations during a WM task are decreased under stress (Gaertner et al. 2014). However, in the mentioned study a continuous WM paradigm (n-back task) was applied. In this task, information has to be maintained and updated continuously, which makes it difficult to clearly separate distinct mental processes in the time course of FMT oscillations.

Here, we applied a mental arithmetic task and a stress induction procedure to investigate FMT oscillations during a natural, complex cognitive task. Mental arithmetic induces workload, and naturally combines the three components (i.e. central executive, phonological loop, and visuo-spatial sketchpad) of the WM model proposed by Baddeley (Baddeley 2003; Imbo et al. 2007). Our task consisted of moderately difficult addition equations that had to be solved one after another and were preceded by a pre stimulus baseline period. The rather long trial durations (3 - 10 s) allowed for a detailed time course analysis. We hypothesized FMT increases during the mental arithmetic phase compared to a pre-stimulus baseline, and decreases of performance and FMT during stress.

4.3 Methods

Subjects and Procedure 31 healthy male subjects (age range: 20 – 50 years, mean = 31.90, SD = 8.31) participated in the study. They were recruited from a large database available to our research group (for details see Fuge et al. 2014). All subjects in the database were screened for psychiatric disorders, using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID). Subjects showing any type of psychiatric symptoms were not included in the database. The study was carried out in accordance with the declaration of Helsinki and approved by the local ethical review board. Information regarding the violent content of the film clips was provided before the study. All subjects signed a written consent after the experiment had been explained to them.

All subjects arrived between 1 and 3 p.m. in the EEG laboratory. Upon arrival they were seated in front of a computer screen where the preparation of the EEG cap and the completion of the experimental tasks took place. During the preparation phase, subjects practiced the experimental tasks to reduce order effects. They underwent a stress- and a neutral condition that were separated by a 20 minute break and counterbalanced across subjects. In each condition, subjects completed a mental arithmetic task that consisted of adding three digit numbers. The task lasted about 10 minutes and was preceded by a short film clip with either stressful or neutral content. Before the film clip and after the task salivary cortisol and subjective affect ratings (PANAS, Krohne et al. 1996) were assessed to control for the effectiveness of the stress induction. The mental arithmetic task was followed by two other tasks, one of which is reported in Gaertner et al. (2014).

Task The mental arithmetic task consisted of 50 trials in both conditions. Each trial started with the presentation of a fixation cross that was displayed for 2 seconds. It was followed by the presentation of a moderately difficult addition equation in which two 3-digit numbers had to be added. Equations were presented together with a result and subjects had to judge whether the presented result was correct or not. Subjects indicated their response with a mouse click on a “yes” or “no” button. After the button press the trial terminated, and if no response was received within 10 seconds, the experiment continued automatically with the next trial. Subjects were asked to respond as quickly and as accurately as possible, and they received no feedback whether their response was correct or not.

Stress induction Acute stress was induced through film clips with strongly aversive content, showing extreme violence against humans. For the neutral control condition, a set of matched neutral clips was used. The negative film clips were taken from the commercially available French movie “Irréversible” by Gaspard Noé, and the neutral scenes were taken from the movie "Comment j´ai tué mon père" by Anne Fontaine. This stress induction procedure has been shown to effectively induce stress in several published studies (e.g. Qin et al. 2009; Ossewaarde et al. 2010; Hermans et al. 2011). To involve subjects as much as possible in the film scenes and thereby increase the stress inducing effect, a self-referencing instruction was presented before the film clips. Neutral scenes were selected to be equal in luminance and similar in speech and human face presence.

Physiological and subjective measurements To control for the effectiveness of the stress manipulation, salivary cortisol and subjective ratings were assessed at baseline and after the task in both conditions. Saliva was sampled with salivette collection devices and samples were stored at −20 degree Celsius until analysis. The analysis was carried out at the department of biopsychology in Dresden, where samples were prepared for analysis by centrifuging at 1500×g for 5 min. Salivary-free cortisol concentrations were determined with a chemiluminescence assay with high sensitivity of 0.16ng/mL (IBL). For details of the procedure see Dressendorfer et al. (1992). The subjective mood state was assessed by obtaining positive and negative affect ratings, using the German version of the Positive and Negative Affect Schedule (PANAS; Krohne et al. 1996). All subjective ratings were obtained during saliva sampling.

EEG recording EEG data was recorded from 31 Ag/AgCl scalp electrodes (BrainCap32, Easycap, Herrsching-Breitbrunn, Germany), arranged according to the extended 10-20 system. Vertical eye movements and blinks were additionally recorded from an electrode placed below the right eye. An electrode placed on the nose tip served as common reference for all channels. Signals were amplified using an analogue 10 second time constant as highpass filter and then digitized with a sampling rate of 1000 Hz (BrainAmpMR plus, Brain Products, Gilching, Germany).

EEG preprocessing EEG data analysis was carried out in MATLAB (Version R2010b, The MathWorks, Inc., Massachsetts, USA), using custom scripts as well as the EEGLAB (Version 9.0.4, Delorme and Makeig 2004) and the Fieldtrip (Build 20140303, Oostenveld et al. 2011) toolboxes. In the first preprocessing step the EEG data of the mental arithmetic task from both conditions was merged, re-referenced to a common average reference, resampled to 200 Hz, and 1 Hz highpass filtered. Next, an infomax ICA (Bell and Sejnowski 1995) was applied, and eye movement related components were identified by visual inspection and removed from the data. A surface Laplacian filter was applied to reduce the effect of volume conduction (Hjorth 1975). In the next step, the EEG data was segmented into stimulus-locked epochs (-2 to 4 s relative to stimulus onset), and response-locked epochs (-3 to 1 s relative to response).Trials were flagged as bad and discarded from further analyses if one or more of the following criteria applied: 1. A trial duration < 3 seconds (indicating a random response) 2. A trial duration of 10 seconds (no response was given) 3. Occurrence of EEG data exceeding a range of ± 100 μV (artifactual data). Appliance of these criteria led to an average rejection rate of 17.2 % (SD = 14.3 %).

Time-frequency analysis Time-frequency representations for each subject, condition and electrode were calculated using zero-padded, hanning tapered Morlet wavelet decomposition, as implemented in EEGLAB newtimef() function. We calculated power for 99 linear-spaced frequencies ranging from 1 to 50 Hz, and 200 (167) linearly spaced time bins (advanced in 30 ms steps) across the stimulus-locked and response-locked epochs. To account for the trade-off between frequency and temporal resolution, the wavelets were modified, such that one cycle was used at the lowest frequency (1 Hz), increasing linearly to 25 cycles at the highest frequency (50 Hz). Time-frequency representations were convolved with a Gaussian kernel (1 Hz × 500 ms, FWHM), and stimulus-evoked (phase-locked) responses were removed from the data by subtracting for each condition the average waveform from the waveform of each individual trial before applying the time-frequency transform. Finally, the mean logpower of a baseline period (-1000 to 0 s relative stimulus onset) was subtracted at each frequency. To investigate possible effects of ERPs on the theta frequency range, control analyses without the removal of stimulus-evoked responses was conducted.

Statistical analysis Statistical analysis on the time-frequency data for all electrodes and conditions was performed using a cluster-based permutation approach (Maris and Oostenveld 2007). Three-dimensional statistical parametric maps (t-test, alpha = 0.05) were calculated in the electrode–time–frequency space (for details of the procedure see e.g. Kilner et al. 2005). A cluster was defined as the sum of t-values in adjacent electrode–time–frequency bins. Adjacency in the electrode space was taken as a given if at least two neighboring electrodes belonged to a cluster. The alpha level for the cluster analysis was set to 0.05 (corrected) and the number of random permutations was set to

1000. For this analysis, time-frequency data was restricted to a frequency range from 1 to 8 Hz, and to time bins from 0 to 3000 ms for the stimulus-locked epochs, and -2500 to -500 ms for the response-locked epochs. Exploratory analysis was performed on a higher frequency range (8 – 50 Hz). In the first step, conditions were compared against baseline, and in the second step the neutral condition was compared against the stress condition.

4.4 Results

Behavior and peripheral physiology On average, subjects had an error rate of 11.1 % during the experiment (SD = 9.3 %), and thus performed significantly better than chance level (50 %, T(30) = -23.26, p<0.001). The average reaction time was 4.87 s (SD = 0.94 s). Reaction times under stress were slower than in the neutral condition (T(30) = -2.23, p = 0.033), and the number of errors did not differ between conditions (T(30) = -1.05, p = 0.3, see Figure 4.4.1 A & B). Cortisol samples were analyzable for 27 out of 31 subjects. Increased cortisol levels under stress indicated a successful moderate stress induction (T(26) = -2.7, p = 0.012). Furthermore, negative affect ratings were higher in the stress condition (T(30) = -5.69, p < 0.001), while positive affect ratings did not differ significantly (T(30) = 1.5, p = 0.15, see Figure 4.4.1 C & D).

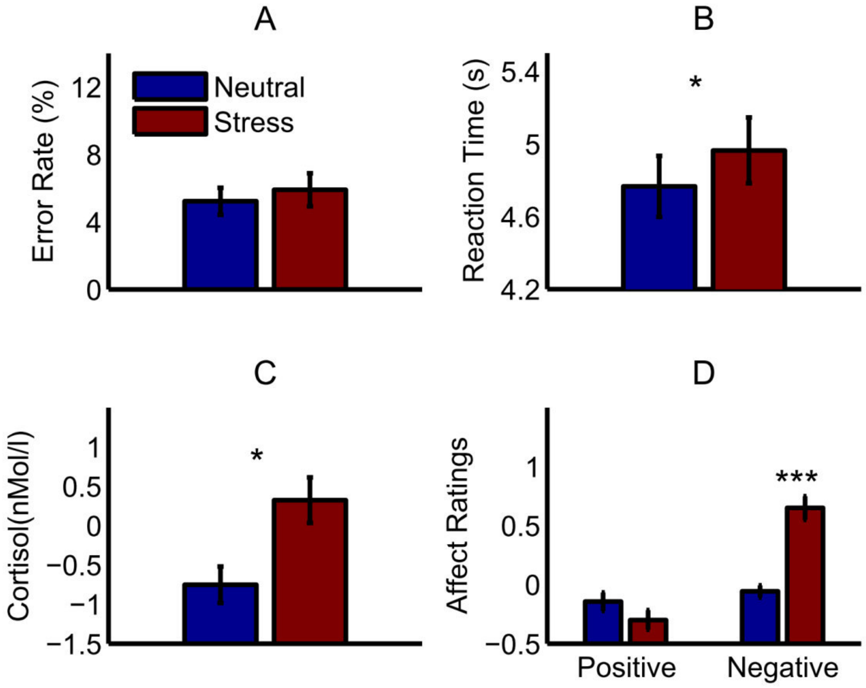

Figure 4.4.1: *Behavioral results and peripheral physiology.* (A) Error rates in the mental arithmetic task (B) Reaction times in the mental arithmetic task (C) Cortisol increases after the mental arithmetic task relative to a baseline measurement (D) Affect ratings after the mental arithmetic task relative to baseline ratings. Significant differences between conditions are marked: * $p < 0.05$; *** $p < 0.001$.

EEG Cluster analysis revealed significant power increases from baseline in both, the stimulus-locked and the response-locked time window. In the neutral condition and stimulus-locked time window one significant cluster (p = 0.002, cluster statistic, Figure 4.4.2) was observed. Cluster dimensions ranged from 3 to 7.5 Hz in the frequency domain, and from 740 to 3000 ms in the time domain. In the neutral condition and response-locked window one significant cluster (p = 0.001, cluster statistic, Figure 4.4.3) that ranged from 2 to 8 Hz in the frequency domain, and from -2500 to -500 ms in the time domain, was observed. In the stress condition and stimulus-locked time window one cluster reached significance (p = 0.016, cluster statistic, Figure 4.4.2). It ranged from 3.5 to 6.5 Hz in the frequency domain, and from 2015 to 3000 ms in the time domain. In the stress condition and response-locked window the observed significant cluster (p = 0.003, cluster statistic, Figure 4.4.3) incorporated frequencies from 3 to 7 Hz, and time bins from -2500 to -500 ms. In the electrode space all clusters were located over a frontal midline region centered around Fz. All cluster statistics and dimensions are summarized in Table 4.4.1.

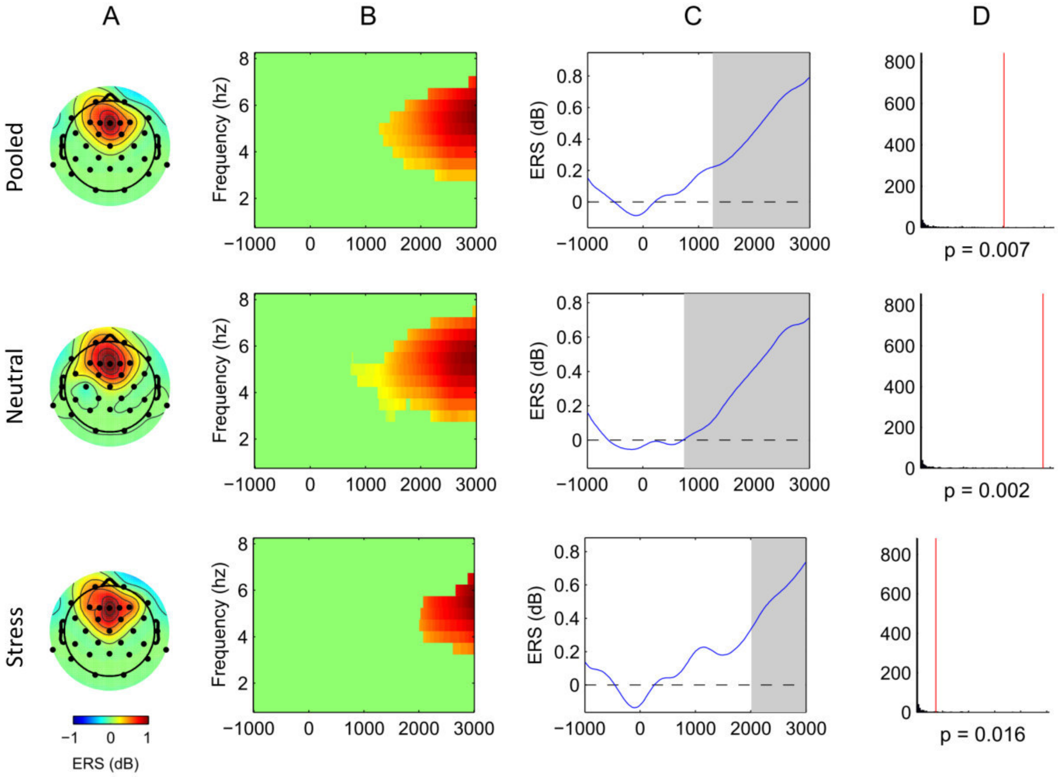

Figure 4.4.2: *Frontal midline theta increases during mental arithmetic in the stimulus-locked time window.*Cluster dimensions in the electrode-time-frequency space for pooled, neutral and stress conditions. Panel A – C show event-related synchronization (ERS) compared to a pre-stimulus baseline period (-1000 to 0 ms) in dB. Panel A shows the cluster dimensions in the electrode space. Panel B shows the cluster dimensions in the time-frequency space. Panel C shows the time course of the ERS. Panel D shows the distribution of random clusters in the cluster-based permutation test. The red line marks the position of the observed cluster.

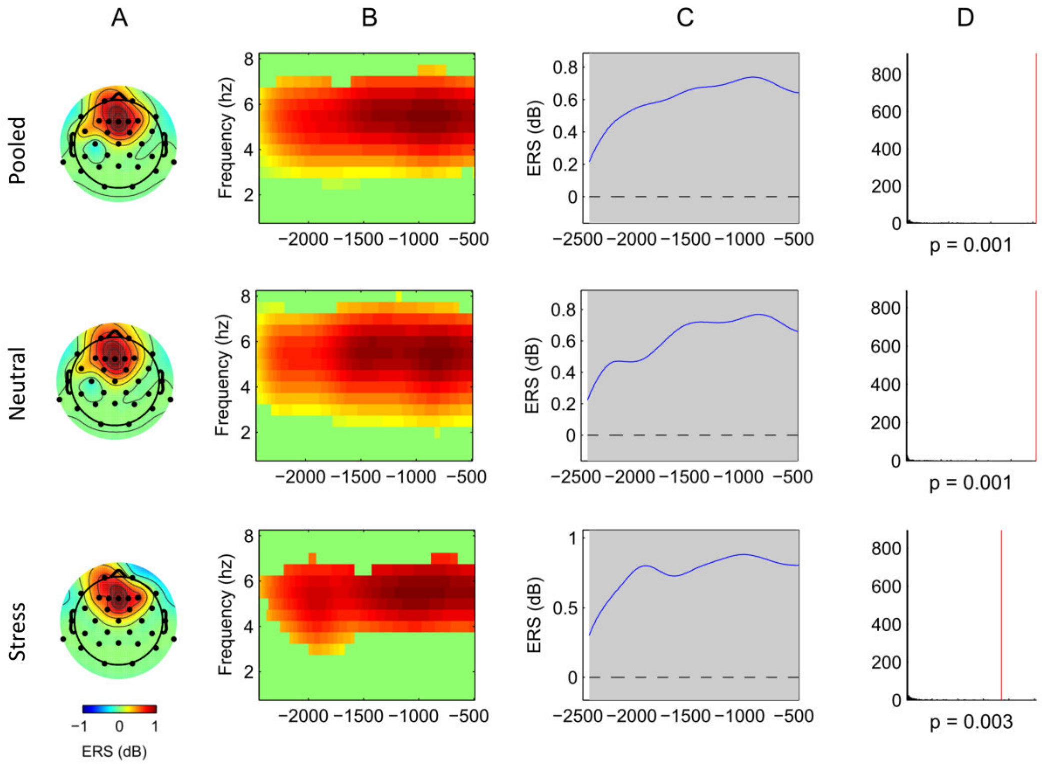

Figure 4.4.3: *Frontal midline theta increases during mental arithmetic in the response-locked time window.*Cluster dimensions in the electrode-time-frequency space for pooled, neutral and stress conditions. Panel A – C show event-related synchronization (ERS) compared to a pre-stimulus baseline period (-1000 to 0 ms) in dB. Panel A shows the cluster dimensions in the electrode space. Panel B shows the cluster dimensions in the time-frequency space. Panel C shows the time course of the ERS. Panel D shows the distribution of random clusters in the cluster-based permutation test. The red line marks the position of the observed cluster.

Control time-frequency analyses without ERP removal showed an additional cluster in the theta frequency range. It ranged from 1.5 to 7 Hz in the frequency range, and from 0 to 615 ms in the time domain. It was located over the complete posterior half of the cortex, centered at bilateral parieto-occipital electrodes (see supplementary Figure I.3). Exploratory time-frequency analyses for higher frequencies (8 – 50 Hz) revealed strong decreases in the frequency range from 8 to 48 Hz, which was strongest in the alpha (8 – 13 Hz), and beta (15 – 25 Hz) band. The decrease started in the stimulus-locked time window at stimulus onset, and remained decreased until the end of the response-locked time window. It was located over the entire posterior half of the cortex, and strongest at occipital electrode sites (see supplementary Figure I.4).

Condition	**Window**	**Clustersize (T-sum)**	**P-value**	**Frequency range (Hz)**	**Time window (ms)**	**Location**
Pooled	Stimulus	10118	0.007**	3 – 7	1255 – 3000	FM
Neutral	Stimulus	14154	0.002**	3 – 7.5	740 – 3000	FM
Stress	Stimulus	3722	0.016*	3.5 – 6.5	2015 – 3000	FM
Neutral vs. Stress	Stimulus	707	0.022*	5.5 – 7.5	1670 – 2160	LF, FM
Pooled	Response	30815	0.001***	2.5 – 7.5	-2500 – -500	FM
Neutral	Response	37159	0.001***	2 – 8	-2500 – -500	FM
Stress	Response	18543	0.003**	3 – 7	-2500 – -500	FM
Neutral vs. Stress	Response	-	-	-	-	-

Table 4.4.1: *Cluster statistics and dimensions.*Clustersize values are based on the sum of all t-values in the observed clusters. P-values are determined by the number of random permutation clusters that showed a larger clustersizes than the observed clusters. Location abbreviations used: LF = left-frontal, FM = frontal-midline. Significant p-values are marked: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Comparison of the neutral and the stress condition revealed one significant cluster that showed stronger power increases in the neutral condition ($p = 0.022$, cluster statistic, Figure 4.4.4). Cluster dimensions ranged from 5.5 to 7.5 Hz in the frequency domain, and from 1670 to 2160 ms in the time domain. In the electrode space the cluster was located over a frontal midline region (Fz) with a slight tendency towards the left hemisphere (F1 and F3).

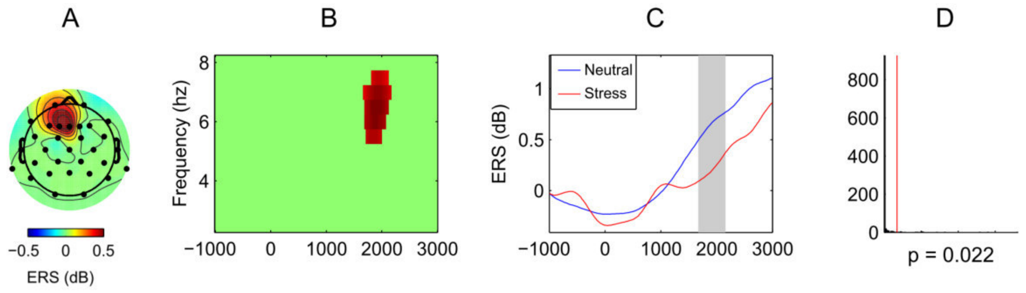

Figure 4.4.4: *Effects of stress on frontal midline theta during mental arithmetic (stimulus-locked time window).* Cluster dimensions in the electrode-time-frequency space for neutral vs. stress condition. Panel A – C show differences in event-related synchronization (ERS) between the neutral and the stress condition in dB. Panel A shows the cluster dimensions in the electrode space. Panel B shows the cluster dimensions in the time-frequency space. Panel C shows the time course of the ERS. Panel D shows the distribution of random clusters in the cluster-based permutation test. The red line marks the position of the observed cluster.

To test whether this difference in FMT activity was related to differences in behavioral performance, we conducted a between-subject correlation analysis (Pearson's correlation coefficient). For each subject the mean difference between conditions (neutral - stress) was calculated for FMT activity and reaction times. For FMT activity, the mean cluster value was calculated. Results showed that decreased FMT activity under stress was related to slower reaction times under stress. Applied to all 31 subjects the correlation was marginally significant (r = -0.31, p = 0.088). The correlation reached significance (r = -0.47, p = 0.013, Figure 4.4.5) if four subjects that did not show FMT increases (compared to baseline) were excluded.

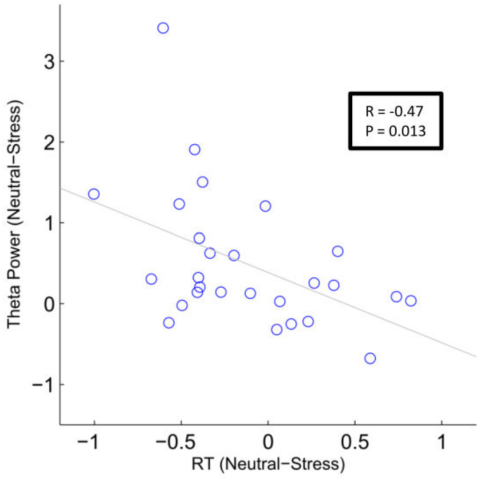

Figure 4.4.5: *Correlation analysis of stress effects during mental arithmetic.*Differences in frontal midline theta activity as a function of differences in reactions times. The blue circles depict single subject values (N = 27). The grey line depicts the least squares regression line.

4.5 Discussion

In this study, we investigated FMT oscillations during a mental arithmetic task that was carried out in a stressful and a neutral control condition. We found late-onset, sustained FMT increases during mental arithmetic compared to a pre-stimulus baseline period. In the stress condition, the onset of the FMT response was delayed. This difference was quantified by stronger FMT increases in the neutral condition in an early time window.

The increase in the theta band (3 – 8 Hz) we observed during mental arithmetic was characterized by a late onset (>700 ms), and a long duration (>2000 ms). It was not phase-locked to the presented stimuli (induced oscillations), and clearly located over the frontal midline region (centered around Fz). A large number of studies have reported such frontal midline theta (FMT) increases during different cognitive tasks. Several studies have used source localization techniques to identify possible generators of FMT (Gevins et al. 1997; Asada et al. 1999; Onton et al. 2005). These studies suggest that FMT could be generated in the anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC). Despite the differences between cognitive tasks that elicit FMT, it has been proposed that sustained, internally-directed cognition that is independent from external stimuli or responses could pose a potential common denominator (Hsieh and Ranganath 2014). During the mental arithmetic task we applied, this could represent the process of maintaining and manipulating single digits while adding up two 3-digit numbers. The late onset of the FMT response we report is in favor of this interpretation. It can be expected that encoding of the stimuli is completed prior to the onset of the observed FMT increase.

The maintenance and manipulation of digits during mental arithmetic is closely related to processes involved in WM (Imbo et al. 2007). During WM, it has been shown that FMT increases with workload (Gevins et al. 1997; Jensen and Tesche 2002). This is in line with the continuous increase of FMT we observed. During the process of adding up two 3-digit numbers, an increasing number of digits has to be kept in mind, which leads to increasing workload across the time course of the task. Although the relationship between FMT and WM processes is well-established, a functional interpretation is still lacking. For example, it remains an open question whether FMT plays a particular role in the maintenance of information, such as maintaining temporal sequence information in multi-item working memory paradigms (Hsieh et al. 2011), or whether it rather provides a general framework in which task-irrelevant information is inhibited to optimize performance (Scheeringa et al. 2009).

We found a decreased FMT response under stress. This finding is consistent with the results of a recently published study that observed stress-related FMT decreases during a working memory task (Gaertner et al. 2014). In contrast to this study, a detailed time course analysis of the FMT response was conducted here. The effect of stress on FMT was present in a time window ranging from 1670 to 2160 ms. It can be assumed that FMT in this time window is related to internally-directed mental operations, independent from stimulus- or response processing. Differences between conditions in FMT activity were only observed in the stimulus-locked time window, and not in the response-locked window. Furthermore, FMT started to increase much earlier in neutral condition (740 ms after stimulus presentation) than in the stress condition (2015 ms after stimulus presentation), and slowed reaction times under stress were associated with stress-related FMT decreases. A possible explanation could be that under stress subjects experienced difficulties to reach a state of focused attention and suppress task-irrelevant information. This assumption receives support from a study by Qin et al.

(2009) who found impaired DMN suppression in a WM task that was carried out under stress. Given the inverse relationship between DMN activity and FMT, this finding supports the view that FMT oscillation during demanding cognitive tasks might provide a mechanism by which fragile temporally stored information is protected from internal and external distractions.

Additional oscillatory signatures that were observed during mental arithmetic, such as the transient, stimulus-evoked increase in the theta frequency range, and decreases in higher frequency ranges, did not show differences between the neutral and the stress condition. A possible explanation could be that these EEG signatures are related to basic visual processing. The early onset of these responses, and their location over posterior electrode sites support this assumption. It is well-established that the PFC is the brain region most vulnerable to the detrimental effects of stress (Arnsten 2009). Since there is some evidence suggesting that FMT is generated in the PFC, our results support this line of evidence.

Our study had some limitations that have to be addressed in upcoming studies. The number of electrodes was rather small (31 electrodes). To further investigate precise topographic differences between the different types of FMT, high-density electrode arrays that allow for a more precise localization (and source localization) should be applied. Furthermore, we only recruited male subjects to control for effects of the hormonal cycle on the stress induction. Upcoming studies should investigate whether the observed effects can be generalized to both genders.

In conclusion, our results show late-onset, sustained FMT increases during mental arithmetic, and suggest that these increases are related to stimulus-independent mental processes. Externally induced stress reduced FMT during mental arithmetic, possibly indicating difficulties to focus attention and to suppress task-irrelevant information. As such, FMT poses a potential marker for intact PFC function that could prove useful in the treatment of stress-related diseases.

4.6 Acknowledgement

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5. General Discussion

The main objective of this dissertation project was to investigate the role of neural oscillations in emotion-cognition interaction. In the conducted studies, the influence of emotional states on memory-related information processing was investigated. The results of all three studies showed emotion-related changes in memory-related neural oscillations. Thus, it can be assumed that neural oscillatory activity plays a role in emotion-cognition interaction. The proposed involvement of neural oscillations in inter-regional communication processes could indicate that different emotional states lead to altered connectivity between distinct brain regions. In fact, emotion-related connectivity changes during memory tasks have been reported in several imaging studies in healthy subjects (e.g. Fastenrath et al. 2014). Furthermore, altered brain connectivity has been observed in psychiatric disorders (e.g. in depression - Carballedo et al. 2011). Some studies have investigated the relationship between interareal BOLD correlations and neural oscillations. It has been reported that especially slow oscillations contribute to interareal BOLD signals (Wang et al. 2012), and similarities between resting-state functional connectivity and source-based oscillatory neural activity have been observed (Brookes et al. 2011). However, more research is needed to clarify the exact relationship between functional connectivity in the BOLD signal, and neural oscillations.

The results of the first study (see chapter 0) showed that distinct oscillatory signatures accompanied successful encoding of information in different emotional states. The main difference was that synchronization processes in a slow frequency range accompanied successful encoding in a positive mood state, whereas processes of neural desynchronization predominantly in the beta frequency range characterized encoding success in a negative mood state. This finding is interesting for several reasons: It has been proposed that large-scale neural synchronization provides a mechanism for communication processes between distant brain areas (Varela et al. 2001), and especially slow neural oscillations have been related to interareal BOLD correlations (Brookes et al. 2011). Furthermore, there is evidence from simultaneous EEG-fMRI studies showing that neuronal synchronization in slower frequency ranges is associated with reduced BOLD activity (Scheeringa et al. 2011). On the contrary, it has been shown that neural desynchronization, especially in the beta band, is associated with increased BOLD activity in specific single brain areas. From several behavioral psychological experiments (for review see Clore and Huntsinger 2007), we know that a positive mood state promotes elaborative information encoding, focusing on linking incoming information to existing knowledge structures, whereas negative mood states promote more careful information encoding focusing on avoiding mistakes and encoding incoming information in a stimulus-driven bottom-up manner. Bringing together the proposed mechanisms for neural synchronization processes, and the behavioral effects of mood-dependent encoding, it can be assumed that encoding-related neural synchronization in positive mood is associated with elaborative information processing that possibly provides a mechanism to integrate information from multiple neural sources. In this context, it is worth noting that from a physical standpoint oscillation-based synchrony is the most energy-efficient mechanism for temporal coordination (Buzsaki and Draguhn 2004). This is in line with the above-mentioned link between neural synchrony and reduced BOLD activity, and it might also relate to the behavioral finding that positive mood promotes effortless encoding. Encoding-related neural desynchronization during negative mood, however, could be associated with the detailed analysis of the incoming information in a bottom-up manner. This assumption receives support from an EEG-fMRI study (Hanslmayr et al. 2011), in which it was shown that encoding-related beta band desynchronization is associated with increased activity in the inferior frontal gyrus (IFG), an area which is associated with semantic information processing. If the general pattern of enhanced neural synchronization in positive mood and enhanced neural desynchronization in negative mood prove robust in replication studies, it would have far-reaching implications that enhance our understanding on how different emotional states affect human information processing.

In line with several other studies, the results of the second and third study (see chapter 3 & 4) showed that working memory processes were associated with increased frontal theta (FT) activity. In both studies, it was shown that an emotional state of stress reduced working memory-related FT oscillations. The stress-related FT reductions were related to decreases in working memory performance. In the second study, a continuous working memory task with two different difficulty levels (moderate and difficult) was applied. Stress effects were observed only in the difficult task condition. A possible explanation for this interaction is that additional task-induced stress was perceived in the difficult task condition, and that a certain stress threshold must be exceeded to affect performance and FT. Since a continuous working memory task was applied, no time course analysis was possible in this study. To overcome this shortcoming, a further study was conducted in which the everyday task of mental arithmetic was investigated. It was shown that FT started to increase about one second after task presentation. This makes it very likely that FT increases regardless of the stimulus presentation and is directly associated with stimulus-independent top-down cognitive processing, presumably associated with working memory-related processes. Furthermore, detailed time course analysis showed that the reduced FT increase in the stress condition was due to a delayed onset.

Until today, the exact functional role of FT oscillations during working memory remains unclear. Therefore, effects of stress on FT can only be discussed in a speculative manner. An open question is whether FT is directly associated with the temporal storage of information contents, or if FT is rather related to mechanisms of focused and sustained attention that accompany the execution of working memory tasks. A possible role of FT oscillations during attention could be the protection of fragile temporary stored mental representations from task irrelevant distractions. A putative mechanism by which this protective function could be realized is that the oscillatory phase of rhythmic neural activity produces excitability fluctuations that determine temporal windows for communication (Fries 2005). An interesting finding with respect to this assumption is the inverse relationship between FT and default mode network (DMN, Raichle et al. 2001) activation. The DMN is often associated with task-independent thought, and is suppressed during the execution of cognitive tasks (Hampson et al. 2006). Cognitive deficits in affective disorders were also associated with difficulties to suppress DMN activity (Broyd et al. 2009). These results suggest that stress-effects on FT activity could be related to difficulties in the suppression of task-irrelevant thoughts.

In summary, the results of all three studies consistently showed that neural oscillations involved in memory-related information processing are modulated by emotional states. Successful episodic memory formation was accompanied by slow (delta / theta) synchronized oscillatory activity in positive mood, and by desynchronization in the beta frequency range in negative mood. Stimulus-independent top-down processing during working memory and mental arithmetic was accompanied by FT oscillations that were attenuated under stress. All three studies have in common that negative emotional states led to reductions of neural synchrony in a slow frequency range. However, from the studies conducted here, it would be too early to suggest a generalized impact of negative emotional states on slow oscillatory activity during memory-related information processing. Neural synchrony during episodic encoding and working memory is presumably associated with different functions. Nevertheless, it could be argued that negative emotional states are related to neurochemical changes that impede the process of neural synchronization independent from its functional significance. Upcoming research in this field will show whether such an assumption is tenable.

An additional goal of this dissertation project was to take steps towards a translational research approach by applying experimental designs that allow the translation from findings in healthy subjects to clinical populations. Therefore, we applied emotional state induction procedures that induce longer-lasting emotional states that can be linked to states that are present in affective disorders (e.g. negative mood or stress). The investigation of emotional state effects on cognitive processing in healthy subjects might yield insights about the mechanisms that lead to cognitive dysfunction in affective disorders. The induction of emotional states also holds the advantage that the cognitive task is independent from the emotional state, as is the case in clinical conditions. Regarding the temporal dimension, emotional state induction can also be considered as an intermediate level between the investigation of emotion-cognition interaction using emotional stimulus material on the one hand, and clinical investigations of cognitive dysfunction in affective disorders on the other. Experimental paradigms using emotional material investigate effects within seconds after stimulus presentation, whereas cognitive dysfunction in affective disorders might result from emotional state perturbations that are present for many years. Emotional states induced in the laboratory are intended to last several minutes up to a few hours. Emotional state induction via film clips can be compared to the experience from everyday life when walking out of the movie theater after watching an intense emotional movie. Indeed, the duration of the movie is longer than the film clips used in the laboratory, but these are limited to the most intense emotional scenes from the movies.

As mentioned earlier, the work presented here focused on memory processes because they are affected by emotion, and are strongly related to oscillatory EEG activity. An additional reason was that memory processes are particularly affected in affective disorders such as major depressive disorder (MDD, Millan et al. 2012). The results of the research conducted here suggest that cognitive deficits in such disorders could be related to altered memory-related oscillatory activity. In a negative mood state we found impaired episodic memory performance. This finding is in line with impaired performance in episodic memory tasks in depressive patients (e.g. Gorwood et al. 2008). Our EEG results provide a possible mechanism that could explain the performance impairments in negative mood. The task we applied required elaborative encoding, which we believe is associated with long-range neural synchronization processes in a slow frequency range. The absence of such synchronization processes in negative mood might provide an explanation for the decreased performance. Translating this explanation to MDD that is characterized by a persistent negative mood state, it can be assumed that memory-related long-range neural synchronization in slow frequencies is reduced in patients compared to healthy subjects. Similarly, the results of the second and third study can be linked to affective disorders. It is well-established that the neurochemical changes associated with stress can lead to stress-related affective disorders such as MDD (Mazure and Maciejewski 2003). The two conducted stress studies showed that stress-related performance decreases during working memory and mental arithmetic were associated with decreased FT oscillations. Translation of these results to clinical populations would suggest that working-memory related FT is decreased in patients with stress-related disorders when compared to healthy controls. Beside our results, several lines of evidence support the assumption that working memory-related FT is decreased in MDD, but to our knowledge direct evidence is still missing: There are studies showing altered FT oscillations in depressed patients in the resting state (Linkenkaer-Hansen et al. 2005), but not with respect to working memory. Furthermore, a negative relationship between FT and DMN activity has been established during working memory, and impaired DMN suppression during working memory has been found in depressive patients (Bartova et al. 2015).

FT has been previously proposed as a biomarker for anxiety and depressive disorders (Suetsugi et al. 2000; Gold et al. 2013). However, these authors suggest resting state measurements of FT. We believe that a promising alternative to establish FT (and maybe other EEG signatures) as a biomarker for depression, is to measure its occurrence during working memory or related tasks. A first step towards such cognition-related EEG biomarkers is to investigate the above-mentioned assumptions in clinical populations. In other words, to test the hypotheses that: 1. Depressive patients show less slow-frequency long-range neural synchronization than healthy controls during elaborative episodic encoding. 2. Depressive patients show attenuated FT increases during working memory - and related tasks compared to healthy controls.

Once these relationships have been established, resting state EEG measurements that are already part of everyday clinical practice can be augmented with experimental paradigms that measure episodic encoding or working memory processes. Especially working memory paradigms are very easy to implement and only require short duration (~10 minutes). The EEG results of these paradigms can then be used to further guide diagnosis and treatment. However, more basic research needs to be conducted before such cognition-related oscillatory biomarkers can be established in clinical practice. To this end, it is crucial to identify sources of between-subject variability in cognition-related neural oscillations that are not linked to performance. In our working memory study, we found clear working memory-related FT increases in 60-70 % of the healthy subjects. A few subjects that did not show FT increases, still showed good working memory performance. It needs to be investigated whether this is due to detection issues (e.g. scalp thickness or orientation of nerve cells might prevent FT from reaching the scalp surface), or whether these subjects make use of different cognitive strategies that do not require FT.

Establishing oscillatory biomarkers in clinical practice holds the additional advantage that neural oscillations can be externally modulated by electrical stimulation (Thut et al. 2011; Battleday et al. 2014), or by neurofeedback (Gruzelier 2014). This holds the possibility to directly treat cognitive deficits that are linked to altered oscillatory activity. Recent technical developments put forward equipment that allows to measure EEG activity and stimulate using the same electrode set-up, and in healthy subjects it has been shown that such electrical stimulation significantly improves performance (Snowball et al. 2013). A promising approach to treat cognitive deficits that accompany affective disorders is to directly stimulate at frequency ranges that show alterations from normal cognition-related oscillatory activity. The oscillatory signatures that have been identified in this dissertation project are promising candidates to treat memory-related deficits present in affective disorders such as MDD. Since they have been shown to be involved in emotion-cognition interaction, it will be an interesting question to investigate whether stimulation protocols targeting these signatures will lead to both, cognitive improvements and normalization of altered emotional states.

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Appendix

I. Supplementary Figures

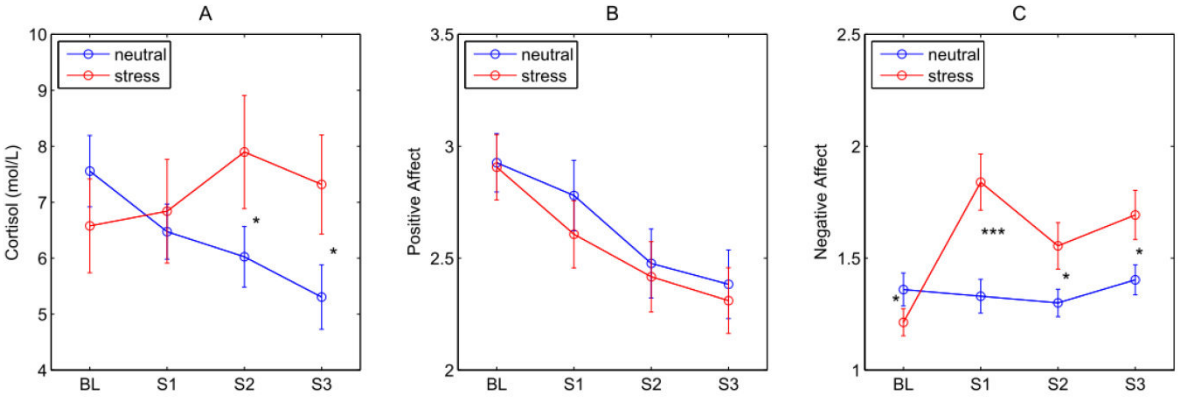

Figure I.1: *Raw cortisol data and subjective ratings.* (A) shows the raw cortisol data for all four measurement time points. (B) and (C) show the raw data of the positive and the negative affect scores obained by the PANAS. The blue line depicts data collected during the neutral condition. The red line depicts data collected during the stress condition. Paired t-ttests were conducted for all measurement time points between the neutral and the stress condition. Stars depict significant differences between conditions. One star depicts a p-value below 0.05, two stars depict a p-value below 0.01, and three stars depict a p-value below 0.001. On the x-axes BL depicts the baseline measurement, and S1-S3 depict the measurements after each of the three cognitive tasks. S2 depicts the measurement after the n-back task.

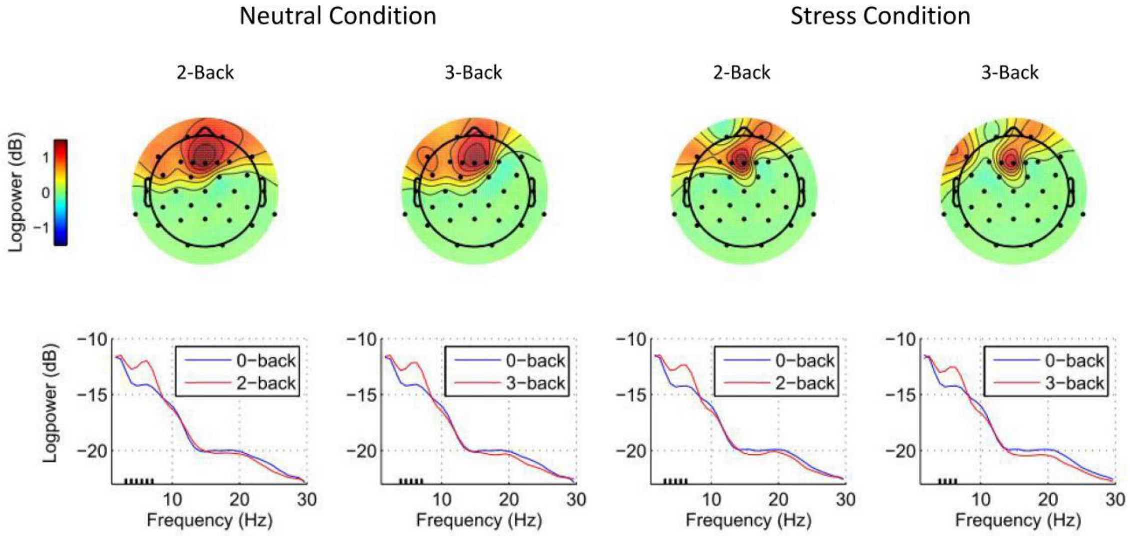

Figure I.2: *Topographic distribution and spectral power for the different experimental conditions.* The upper row shows the topographic distribution of theta band power (4-8 Hz) for the four experimental conditions relativ to baseline power (0-back) in the late time window (1000 – 1800 ms). Paired t-tests were calculated for each electrode and electrodes with unsignificant power increases (alpha = 0.01, FDR corrected) were masked. The lower row shows the spectral power distribution (1 - 30 Hz) for the four experimental conditions in the late time window (1000 – 1800 ms). Paired t-tests were calculated for each frequency bin. Black bars on top of the x-axis depict significant increases (alpha = 0.01, FDR corrected) from baseline.

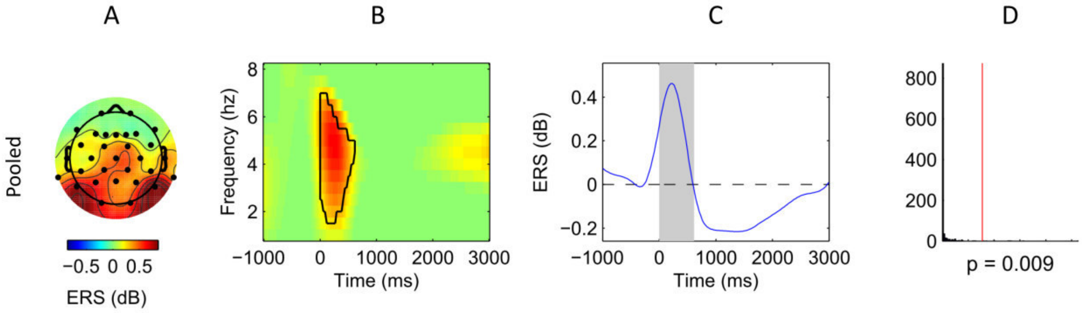

Figure I.3: *Phase-locked increases in the 1 to 8 Hz frequency range during mental arithmetic in the stimulus-locked time window.*Cluster dimensions in the electrode-time-frequency space for pooled conditions. Panel A – C show event-related synchronization (ERS) compared to a pre-stimulus baseline period (-1000 to 0 ms) in dB. Panel A shows the cluster dimensions in the electrode space. Panel B shows the cluster dimensions in the time-frequency space. Panel C shows the time course of the ERS. Panel D shows the distribution of random clusters in the cluster-based permutation test. The red line marks the position of the observed cluster.

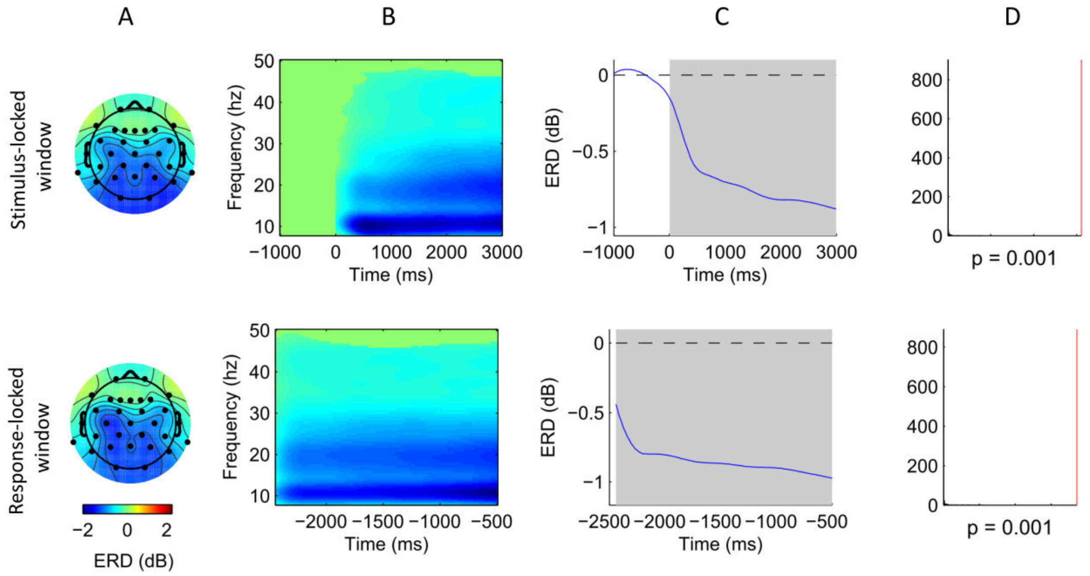

Figure I.4: *Event-related desynchronization (ERD) during mental arithmetic in the frequency range from 8 to 50 Hz.*Cluster dimensions in the electrode-time-frequency space for the stimulus-locked and response-locked time window. Panel A – C show event-related desynchronization (ERD) compared to a pre-stimulus baseline period (-1000 to 0 ms) in dB. Panel A shows the cluster dimensions in the electrode space. Panel B shows the cluster dimensions in the time-frequency space. Panel C shows the time course of the ERD. Panel D shows the distribution of random clusters in the cluster-based permutation test. The red line marks the position of the observed cluster.

II. Supplementary Tables

Analysis	**Effect**	**N**	**F**	**p**
Main ANOVA (2x2x3)	Time window	30	58.37	<0.0001 ***
	Emotional State	30	3.04	0.092
	Task difficulty	30	17.15	<0.0001 ***
	Time window X Emotional State	30	8.25	0.008 **
	Time window X Task difficulty	30	12.76	<0.0001 ***
	Emotional state X Task difficulty	30	0.40	0.656
	Time window X Emotional state X Task difficulty	30	0.99	0.370
Subsequent ANOVA 1 - early time window (2x3)	Emotional state	30	0.26	0.611
	Task difficulty	30	9.75	0.003 **
	Emotional state X Task difficulty	30	0.40	0.670
Subsequent ANOVA 2 - late time window (2x3)	Emotional state	30	7.08	0.013 *
	Task difficulty	30	16.34	<0.0001 ***
	Emotional state X Task difficulty	30	0.94	0.39

Table II.1: *Results of the ANOVAs for FT activity*

III. Curriculum Vitae[6]

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[6] Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.

IV. Selbständigkeitserklärung

Die Studien dieser Dissertationsschrift wurden in marginal modifizierten Versionen in internationalen Fachzeitschriften veröffentlicht. Die im jeweiligen Kapitel benannten Ko-Autoren können bestätigen, dass ich für die Entstehung der Arbeiten hauptverantwortlich war. Zudem versichere ich hiermit, dass ich die vorgelegte Arbeit selbständig verfasst habe. Andere als die angegebenen Hilfsmittel habe ich nicht verwendet. Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Berlin, 21.04.2015 Matti Gärtner