Emotion processing and working memory deficits in Bipolar Disorder: interactions and changes from acute to remitted state.

Emotionsverarbeitung und Arbeitsgedächtnisdefizite in der bipolaren Störung: Interaktionen und Veränderungen im Verlauf der Erkrankung.

Doctoral thesis for a doctoral degree

at the Graduate School of Life Sciences,

Julius-Maximilians-Universität Würzburg,

Section Philosophy II

submitted by

Juliane Kopf

From Dresden

Würzburg, 2014

Submitted on: ……..……..

Office stamp

Members of the *promotion committee*:

Chairperson: Prof. Dr. Peter Jakob

Primary Supervisor: Prof. Dr. Andreas Reif

Supervisor (Second): Prof. Dr. Paul Pauli

Supervisor (Third): Dr. Martin Herrmann

Date of Public Defence: ……..……

Date of Receipt of Certificates: …….

This thesis is dedicated to my daughter, Pipilotta.

You would have taken the world in a storm. You will always be with me.

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0. Abstract

BD is a severe and highly prevalent psychiatric illness characterized by oscillating mood episodes, where patients express either depressed mood, anhedonia, decreased activation along with concentration difficulties and sleep disturbances, or elevated mood with hyperactivity and loss of inhibitions. Between mood episodes, patients return to a relatively normal state of functioning without mood symptoms. Previous research on underlying neuronal mechanisms has led to a model of neuronal dysfunction in BD which states that BD arises from disruption in early development within brain networks that modulate emotional behavior. These abnormalities in the structure and function of key emotional control networks then lead to decreased connectivity among ventral prefrontal networks and limbic brain regions. This in turn creates a loss of emotional homeostasis, putting bipolar patients at risk for developing extreme mood states and switching among mood states. Two core components for BD have been identified, a *hyperactive* emotion processing system and a *hypoactive* cognitive functions system. It is controversial whether these deficits are still detectable in euthymia, so it is unclear if hyper- and hypoactivations represent state or trait-like characteristics. The aim of this study was to research both core components of BD with a paradigm eliciting differential activations in both cognitive and emotion processing networks. For this, an emotional word working memory paradigm was constructed to test for differences between manic, depressive, and remitted patients as well as a healthy control group. Differences were assessed in behavior, brain activation (as a correlate for the hypoactive cognitive functions system), measured with near-infrared spectroscopy (fNIRS), and electrophysiological changes in the late positive potential (as a correlate for the hyperactive emotion processing system), an event-related potential (ERP) measured with electroencephalography. 47 patients in the acutely ill phase and 45 healthy controls were measured. Of the 47 patients, 18 returned to the clinic for a second testing while in remission for at least 3 months. Acutely ill patients were classified into 4 groups according to their disorder status: a mildly depressed group, a depressed group, a manic group, and a mixed group along DSM-IV criteria. Analyses were calculated for 3 load conditions (1-back, 2-back and 3-back) and 3 valence conditions (negative, neutral, positive) for behavioral measures reaction time and omission errors, for brain activation and event related potential changes.

Results indicate that ill patients differed from controls in their behavioral performance, but the difference in performance was modulated by the mood state they were in. Depressed patients showed the most severe differences in all behavioral measures, while manic and mixed

patients differed from controls only upon different valence conditions. Brain activation changes were most pronounced in mildly depressed and manic patients, depressed patients and mixed patients did not differ as much from controls. ERP changes showed a significant difference only between mixed patients and controls, where mixed patients had an overall much higher ERP amplitude. When remitted patients were compared to controls, no differences in behavior, brain activation or ERP amplitude could be found. However, the same was true for differences in patients between acutely ill and remitted state. When looking at the overall data, the following conclusion can be drawn: assuming that the brain activation seen in the prefrontal cortex is part of the dorsal cognitive system, then this is the predominantly disturbed system in depressed patients who show only small changes in the ERP. In contrast, the predominantly disturbed system in manic and mixed patients is the ventral emotion processing system, which can be seen in a hyper-activation of ERP related neural correlates in mixed and hypo-activated neural correlates of the LPP in manic patients. When patients are remitted, the cognitive system regains temporary stability, and can be compared to that of healthy controls, while the emotion processing system remains dysfunctional and underlies still detectable performance deficits.

Zusammenfassung

Die bipolare Störung ist eine schwere und hochprävalente psychiatrische Erkrankung, welche gekennzeichnet ist durch oszillierende Stimmungsepisoden, in denen Patienten entweder unter Anhedonie leiden, über Aktivitätsverlust und Konzentrationsstörungen klagen und Schlafstörungen haben, oder in deutlich aufgehellter Stimmung sind, hyperaktiv werden und soziale Hemmungen verlieren. Zwischen diesen Stimmungs-extremen durchlaufen die Patienten Phasen mit Stimmungsnormalisierung, oft ohne weitere schwere kognitive Defizite. Bisherige Studien über die zugrundeliegenden neuronalen Mechanismen haben ein Model hervorgebracht, welches von einer Störung der frühen Entwicklung in Hirnregionen, die emotionales Verhalten regulieren, ausgeht. Diese Anomalitäten in Struktur und Funktion von Kernkomponenten der Emotionskontrolle führen dann zu einem Verlust der Konnektivität in ventralen präfrontalen und limbischen Netzwerken. Dieser Verlust wiederum verursacht einen Verlust an emotionaler Homöostase, welches die Patienten dem Risiko aussetzt, extreme Stimmungsschwankungen zu erfahren. Zwei Kernkomponenten der bipolaren Störung wurden aufgrund dieses Modells definiert: ein hyperaktives Emotionsverarbeitungssystem, und ein hypoaktives kognitives Funktionssystem. Es ist bis jetzt nicht klar, in welcher Art und Weise diese emotionalen und kognitiven Dysfunktionen auch im euthymen Zustand weiterbestehen.

Das Ziel dieser Studie war es, die beiden Kernkomponenten der Dysfunktion in der bipolaren Störung mit einem Paradigma zu untersuchen, welche beide Komponenten erfasst. Es wurde dazu ein emotionales Arbeitsgedächtnis Paradigma entwickelt, um Unterschiede zwischen akut kranken Patienten, gesunden Kontrollen und denselben Patienten im remittierten Zustand zu erfassen. Die Unterschiede sollten als Unterschiede der Reaktionszeit und Auslassungsfehler im Verhalten erfasst werden, ebenso als Unterschiede der Hirnaktivierung, gemessen mit funktionaler Nah-Infrarot Spektroskopie, und als Unterschiede in einem neurophysiologischen Korrelat, des „Late Positive Potential“ (LPP) betrachtet werden. 47 Patienten wurden rekrutiert, und eingeteilt nach dem Pol ihrer aktuellen Stimmungsepisode in schwer depressive Patienten, Patienten mit einer mittleren Depression, manische Patienten und Patienten im Mischzustand. Von den 47 akut kranken Patienten konnten 18 im remittierten Zustand wiederum gemessen werden. Anschließend wurden Gruppenunterschiede in 3 kognitiven Variablen (1-back, 2-back und 3-back) und 3 emotionalen Variablen (positiv, neutral, negativ) für Verhalten, Hirnaktivierung und Amplitudenänderung in der LPP berechnet.

Die Ergebnisse zeigen dass akut kranke Patienten sich in ihrem Verhalten von Kontrollen unterscheiden, jedoch wurden diese Unterschiede von der Art der aktuellen Stimmungsepisode moduliert. Schwer depressive Patienten zeigten die deutlichsten Unterschiede, während manische Patienten und Patienten im Mischzustand nur in den emotionalen Variablen Unterschiede zeigten. Die Hirnaktivierungsunterschiede waren am deutlichsten zwischen Patienten mit einer mittelschweren Depression und manischen Patienten, bei schwer depressiven Patienten und Patienten im Mischzustand waren diese Unterschiede deutlich schwächer ausgeprägt. Die LPP Analysen zeigten deutliche Unterschiede nur zwischen Patienten mit Mischbild und Kontrollen, die Patienten hatten hierbei eine deutlich erhöhte LPP Amplitude. Die Untersuchung der Unterschiede zwischen remittierten Patienten und Kontrollen ergab keine signifikanten Ergebnisse, ebenso die Analysen der Unterschiede zwischen akut kranken und remittierten Patienten. Alle Ergebnisse zusammengenommen, ergibt sich folgendes Bild: Wenn die Hirnaktivierung als Korrelat eines gestörten kognitiven Systems gesehen werden kann, und die LPP als Korrelat eines gestörten Emotionsverarbeitungssystems, dann könnte für Patienten mit einer mittleren oder schweren Depression das kognitive System das Hauptproblem darstellen, während für manische Patienten und Patienten im Mischzustand das Emotionsverarbeitungssystem das dominante Problem darstellt. Wenn die Patienten dann remittieren, erhält das kognitive System eine vorübergehende Stabilität zurück, das Emotionsverarbeitungssystem jedoch bleibt dysfunktional, und ist verantwortlich für die bestehenden emotionalen und kognitiven Defizite.

1. Introduction

1.1. Bipolar Disorder

Bipolar Disorder (BD) is a severe and, with a lifetime prevalence of 2.4% (Merikangas et al., 2007), a widely distributed psychiatric disorder. It affects the patient's mood, thoughts and activation levels, resulting either in a depressive episode, or ending in hypomania or mania. Both of these mood oscillations have to occur at least once and have to fulfill the diagnostic criteria of the International Classification of Diseases (ICD-10) (WHO, 1992) or the Diagnostic and Statistical Manual (DSM-IV) (APA, 2000), for a full account please see the appendix. In a depressive episode, the main symptoms include, among others, depressed mood, blunted activation, negative thoughts, concentration difficulties. It can even lead to suicidal ideation and has to be present for at least 2 weeks to justify the diagnosis. A manic episode is marked by elevated mood independent of the current situation, heightened confidence, pressured speech, hyperactivity, can be as bad as involving psychotic symptoms, and has to last at least a week. A hypomanic episode is characterized the same way, but is not severe enough to compromise work or social functioning. Symptoms can also occur simultaneously, patients in a so called mixed episode report for example thought racing and hyperactivity as well as a depressed mood and even suicidal ideation. It is characteristic that patients with mixed episodes have a heightened suicide risk (McElroy et al., 1992; Swann et al., 2007).

A number of other psychiatric disorders share symptoms with BD, making a clear distinction between these disorders sometimes difficult (Bromet et al., 2011; Laursen, Agerbo, & Pedersen, 2009; Tsuang, Woolson, Winokur, & Crowe, 1981). For example, attention deficit hyperactivity disorder (ADHD) also includes mood variability, recklessness, impulsivity and of course, hyperactivity as core symptoms, and can therefore be hard to be distinguished from hypomania. Disorders from the schizophrenic spectrum (such as schizophrenia, schizoaffective disorder or single psychotic episodes) also include cognitive deficits, psychotic symptoms, reduced activation levels, or thought racing as symptoms and can be mistaken for symptoms of a bipolar episode. Finally, major depressive disorder (MDD) is practically indistinguishable from BD during a depressive episode, resulting in incorrectly diagnosed patients. However, the correct diagnosis of a psychiatric disorder is crucial to the treatment effectiveness. It might be therefore necessary to define BD in more than just the symptomatic way.

In between phases, patients arguably recover completely from their mood and somatic symptoms, as well as from their cognitive dysfunctions. The evidence covering the recovery of patients is controversial. Some research shows remaining cognitive deficits during remission (Malhi et al., 2007; Mann-Wrobel, Carreno, & Dickinson, 2011; Martinez-Aran et al., 2004), while other research hints at complete recovery and suspects incorrect classification of patients as the underlying mechanism driving evidence for cognitive deficits in BD (Iverson, Brooks, Langenecker, & Young, 2011; Strakowski et al., 2012) . Indeed there are considerations arguing that patients who do not fully recover from their mood and cognitive pathology might be a different group of patients altogether and should not be mixed up with bipolar patients, whose core feature then would be the complete recovery between episodes (Altshuler et al., 2004; Aminoff et al., 2013; Bora, Yucel, & Pantelis, 2010; Bourne et al., 2013; Iverson, et al., 2011; Martino et al., 2008).

1.2. Pathophysiology

The origins of BD, like in many other psychiatric disorders, remain essentially unknown. Several hypotheses have been stated, claiming to explain the underlying molecular mechanisms of BD. BD therefore likely arises from the complex interaction of multiple susceptibility genes and environmental factors, which result in changes in intracellular signaling cascades, leading to modifications of synaptic number and strength, modeling of axonal and dendritic architecture and variations in neurotransmitter release. These changes then add up to form the phenotype. Which signaling cascades, neurotransmitters, and neuronal architecture changes are involved, can be studied with several different tools, such as genetic studies, research in neuroanatomy changes, neuroimaging methods, and research on neurotransmitter systems and neural networks (Strakowski, et al., 2012).

1.2.1. Genetic risk factors

Among psychiatric disorders, BD has one of the highest heritability rates of up to 75% (Cross-Disorder Group of the Psychiatric Genomics, 2013). Over the years, many studies have been published with assumed associations of BD with genetic polymorphisms. According to Seifuddin et. al (2012), 362 genes were tested in 487 studies, 50 of which were researched by at least three studies. The most widely studied gene was the serotonin transporter gene (*SLC6A4*), followed by the gene coding for the serotonin transporter 2A (*HTR2A*). However, results remain inconclusive (Seifuddin, et al., 2012). Only four of those genes, *BDNF*, *DRD4*, *DAOA*, and *TPH1*, were found to be nominally significant, however

none survived the correction for multiple testing. On the other hand, genome-wide studies using microarrays provided the first hits still significant at the genome-wide level, including variants in genes involved in calcium signaling such as *CACNA1C*. However, many of the investigated polymorphisms are intronic or intergenic, and the functionality of these is, at most, speculative. The solution to this problem is again discussed controversially. While some groups argue for more atheoretical genome-wide approaches (Cross-Disorder Group of the Psychiatric Genomics, 2013; Seifuddin, et al., 2012), it could also be argued that we need better theories about the neuronal mechanisms underlying the disorder, to establish molecular pathways involved, to find the common genetic linkages between bipolar patients.

1.2.2. Immunology and neuroendocrinology

A review by Langdan and McDonald (2009) has highlighted persisting neurobiological trait abnormalities in BD patients. The first system reviewed involves cytokines and related secretory products, which modulate immune function. Cytokines regulate growth, differentiation and function of many cells. They can be classified as pro-inflammatory or anti-inflammatory. In BD, the pro-inflammatory cytokine production seems to be increased across all phases of illness, even though pro-inflammatory processes are especially heightened during acute worsening of the disorder (Langan & McDonald, 2009). The hypothalamic-pituitary-adrenal axis (HPA) also seems to be involved in BD in an analogous fashion as it is the case in MDD. The glucocorticoid resistance coupled to that HPA axis dysfunction may be caused by known susceptibility genes for the illness (Langan & McDonald, 2009).

1.2.3. Molecular biology

Changes on the molecular level in BD involve signal transduction pathways and coordination of the cellular responses. Components of these pathways that have been researched are multifold. Cyclic adenosine monophosphate (cAMP) regulates many cellular functions, including metabolism and gene transcription through the activation of protein kinase A (PKA). Activated PKA phosphorylates other protein substrates, including cAMP-response element-binding protein (CREB). CREB is a transcription factor that provides a critical link between signal transduction and the expression of potentially relevant target genes, including the neuroprotective brain-derived neurotrophic factor (BDNF). The review paper shows evidence that PKA levels are increased permanently in BD. BDNF levels vary with the changing episodes and with the treatment, but studies could not show that BDNF levels are reduced as a trait feature of BD. G-Proteins, which are also involved in the cAMP signal pathway, provide the link between neurotransmitter binding and subsequent signaling

cascades. Studies researching G-proteins are controversial, while some suggest increased levels in all phases of the disorder, while others find a normalization of receptor-G-protein coupling with Lithium or valproic acid treatment. (Langan & McDonald, 2009; Schloesser, Huang, Klein, & Manji, 2007). Another signaling cascade involves the activation of the phosphoinositide second messenger system. Studies report state related abnormalities in phosphatidylinositol 4,5-bisphosphate levels and phospholipase C activity in BD.

Calcium ions are also involved in the mediation of synaptic plasticity, cell survival, exocytosis and cell death. Intracellular calcium signaling and homeostasis are regulated in a complex manner that includes extracellular entry, release from intracellular stores, specific uptake into organelles and binding to proteins. Calcium homeostasis seems altered across all mood states in BD (Langan & McDonald, 2009; Schloesser, et al., 2007).

1.2.4. Dopamine system

The dopamine system has been implicated in BD for many years (Anand et al., 2011; Andreazza & Young, 2013; Cousins, Butts, & Young, 2009). Four major pathways of dopamine neurotransmission have been identified in the human brain. The tuberoinfundibular pathway is restricted to the hypothalamus and regulates some functions of the anterior pituitary gland. The nigrostriatal pathway originates in the substantia nigra and projects to the dorsal striatum, with an established role in the motor system (Volkmann, Daniels, & Witt, 2010). The mesolimbic pathway stems from the ventral tegmental area (VTA) and terminates in the ventral striatum, hippocampus, and septum. The mesocortical pathway also originates in the VTA but projects more widely to the frontal and temporal cortices. These pathways modulate domains such as impulsivity and attention, reward seeking, emotional processing, working memory, and executive functions (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chudasama & Robbins, 2006). Considering that all of these functions are impaired in BD, and that a main class of medication for BD (i.e., antipsychotics) affects the dopamine system, a connection between BD and the dopamine system can well be assumed.

However, studies researching the connection between monoamine neurotransmitters and BD have been declining in the last years. The main reason for this again might be the heterogeneity of research methods, leading to contradicting evidence. The fact that antidepressant and antipsychotic medication are effective only after days to weeks of application, suggests that, while dysfunctions in the monoaminergic neurotransmitter systems are likely to play an important role in mediating some symptoms of BD, it might represent downstream effects of other, more primary abnormalities in signaling pathways. Another

reason for the loss of interest in dopaminergic research might be that this transmitter system is affected in many other psychiatric disorders and might therefore represent a common pathway at the end of a multitude of causes leading to a psychiatric disease.

1.2.5. Neuroanatomy

Post mortem studies in BD find a decrease in the density of neurons in several brain regions, for example in the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the hippocampus, the hypothalamus, and the amygdala (Benes, Todtenkopf, & Kostoulakos, 2001; Benes, Vincent, & Todtenkopf, 2001; Bezchlibnyk et al., 2007; Manaye et al., 2005; Rajkowska, Halaris, & Selemon, 2001). Other studies described a low glial cell number and size in the dorsolateral PFC in BD (Ongur, Drevets, & Price, 1998). One study even found that mood stabilizers might protect glia cells from the adverse effects of BD in the amygdala (Bowley, Drevets, Ongur, & Price, 2002). Taken together, this suggests that BD might be associated with neuronal and glial cell impairment (Andreazza & Young, 2013; Gigante et al., 2011).

Structural imaging studies are more controversial. In an extensive review, Savitz and Drevets (Savitz & Drevets, 2009) discuss neuroimaging findings in BD. Computed tomography and magnetic resonance imaging have revealed structural abnormalities in the brains of patients with BD. While overall gray matter volumes did not differ between BD patients and healthy controls (Brambilla et al., 2001), the literature hints at region specific reductions. The most consistent finding in that regard is possibly that of increased amygdalar volume in patients with BD (Savitz & Drevets, 2009). Findings in other areas are more diverse. Hippocampal volume is found to be reduced in some studies, others find no differences in volume between controls and BD patients. The same is true for caudate and putamen volumes, even if post mortem studies have shown volumetric differences (Savitz & Drevets, 2009). However, the striatum has been found to be enlarged in BD patients. To make matters more complicated, the striatal volume seems to decrease over time and with an increasing disease load. Evidence for ventricular enlargement is again mixed.

White matter hyperintensities (WMH) have been reported in BD, as well as grey matter volume reductions in the PFC, which have been consistently found in patients with BD. However, none of the findings mentioned above are entirely consistent, with findings contradicting each other in each region mentioned.

The same is even more so true for functional imaging studies. These studies are mostly functional MRI (fMRI) studies, and either report resting state measurements or measurements during cognitive and emotional tasks. Many studies have reviewed the massive amount of data produced over the years (Cerullo, Adler, Delbello, & Strakowski, 2009; C. H. Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Houenou et al., 2011; Keener & Phillips, 2007; Kempton, Geddes, Ettinger, Williams, & Grasby, 2008; Phillips & Vieta, 2007; Savitz & Drevets, 2009; Strakowski, et al., 2012; Strakowski, Delbello, & Adler, 2005). These reviews show that mainly 2 dimensions of BD are being studied in BD: emotion dysregulation, and with it the regions that are involved in emotion processing and regulation; and cognitive deficits occurring in BD. Studies demonstrated increases in activation in several different areas associated with emotion processing, such as the amygdala, orbitofrontal cortex, and a ventral limbic pathway involving the ventral striatum and the thalamus. On the other hand, studies on cognition report decreased activation in areas such as the dorsolateral and ventrolateral PFC, and the dorsal ACC. These areas are mainly associated with cognitive control and executive functioning, and reflect the neuropsychological symptoms that patients describe.

This has led to a model of dysfunction in emotion processing and cognitive deficits underlying BD, which is characterized by a hyperactive emotional regulation system and a hypoactive cognitive functions system. It is controversial whether these deficits are still detectable in euthymia, so it is unclear if hyper- and hypoactivations represent state or trait-like characteristics. The only consistent finding is that of a hypoactive PFC in all phases of the disorder. The current consensus model therefore is one that arises from disruption in early development within brain networks that modulate emotional behavior. These abnormalities in the structure and function of key emotional control networks then lead to decreased connectivity among ventral prefrontal networks and limbic brain regions. This in turn creates a loss of emotional homeostasis, putting bipolar patients at risk for developing extreme mood states and switching among mood states (Strakowski, et al., 2012).

1.3. Executive dysfunctions and emotion processing in BD

1.3.1. Emotions and emotional dysfunction in BD

Emotional dysfunction is one of the core symptoms of BD. Patients experience mood swings ranging from an elevated mood in mania, to irritation, to a depressed mood in a depressive phase. To understand how these mood swings arise, one has to first understand how emotions arise in healthy humans.

1.3.2. Emotions

Emotions can be defined in many ways. Here, the two most common definitions will be described (Gazzaniga, Ivry, Mangun, & Steven, 1998). One way is to list basic emotions, which are limited by the way they are expressed universally in a human face (Ekman & Friesen, 1971). Ekman and Friesen distinguished 6 basic human expressions translating to 6 basic emotions: anger, fear, disgust, happiness, sadness and surprise. Emotions can also be classified into dimensions of emotion. Emotions are not discrete states of being, but rather defined as reactions to stimuli and events. These reactions can be characterized by two factors: valence (pleasant-unpleasant) and arousal (low intensity-high intensity). Emotions then exist within a continuum of reactions (Osgood, 1957). Alternatively, emotions are classified based on the goals they motivate (Davidson, Ekman, Saron, Senulis, & Friesen, 1990). These goals can either motivate us to approach in situations or withdraw from situations and therefore define, within a continuum, the emotions we feel.

Current models of emotions state that "…emotions are valenced responses to external stimuli and/or internal mental representations that involve changes across multiple response systems, are distinct from moods in that they often have identifiable objects or triggers, can be either unlearned responses to stimuli with intrinsic affective properties, or learned responses to stimuli with acquired emotional value and can involve multiple types of appraisal processes that assess the significance of stimuli to current goals that depend upon different neural systems.", taken from Ochsner & Gross, (2005) (Cacioppo, Berntson, Larsen, Poehlmann, & Ito, 2000; Davidson, 2000; Kevin N Ochsner & Feldman Barrett, 2001; K. N. Ochsner & Gross, 2005; Phillips et al., 2003a; Scherer, Schorr, & Johnstone, 2001).

1.3.3. Emotion processing

As early as 1937, researchers have been proposing theories considering how emotions are processed in the brain, when James Papez introduced his theory about a circuit in the brain responsible for emotional reactions. He included the hypothalamus, the anterior thalamus, the

cingulate gyrus, and the hippocampus in this circuit, later called the "Papez Circuit", which later also contained the amygdala and the orbitofrontal cortex and was called the limbic system. Today, the amygdala and the orbitofrontal cortex are the main focus of emotion processing research (Adolphs, 2002).

The amygdala is possibly the most often implicated brain structure when it comes to emotion processing. The amygdala is stated to receive input relevant for emotion processing via two mechanisms: a subcortical route via the superior colliculus and the pulvinar thalamus, and a cortical route via the visual cortex (Adolphs, 2002; LeDoux, 1996). The subcortical, "low road", is activated as a fast response to emotionally relevant stimuli, and is activated even when the emotional stimulus is presented only subliminally (Morris, Ohman, & Dolan, 1999; Ohman, Lundqvist, & Esteves, 2001), whereas the cortical "high road" is activated later and represents the conscious processing of emotional stimuli. This activation of the amygdala is hypothesized to be modulated by the orbitofrontal cortex (Etkin, Egner, & Kalisch, 2011) and dysfunctions within these pathways underlie the psychopathology of emotional processing (Ohman & Mineka, 2001).

The orbitofrontal cortex is hypothesized to have multiple functions, but all relate to emotion, such as recognition of emotion, social and emotional decision making, control of the amygdala responses, and emotional learning (Adolphs, 2002; Gazzaniga, et al., 1998; Phan, Wager, Taylor, & Liberzon, 2002).

However, new research suggests that the picture is not as clear. Luiz Pessoa and Ralph Adolphs (Pessoa & Adolphs, 2010) suggest that the amygdala is not a processing organ, but rather fulfills a modulatory role in a wide array of networks all processing emotional information. It serves to allocate processing resources to emotionally relevant stimuli. They also state that the cortex is well capable of fast processing of stimuli and therefore a low road is not needed.

Accordingly, Phillips et al. (Phillips, et al., 2003a) synthesize animal and human studies on emotion regulation and suggest the following model: There are two neural systems processing emotion: a ventral and a dorsal system. The ventral system includes the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and PFC. It is important for the identification of the emotional significance of environmental stimuli and the production of affective states, as well as automatic regulation and mediation of autonomic responses to emotional stimuli. The dorsal system consists of the hippocampus, dorsal regions

of the anterior cingulate gyrus, and the PFC. Here, cognitive processes are integrated with and can be biased by emotional input. This in turn is important for the performance of executive functions, including selective attention, planning, and effortful rather than automatic regulation of affective states. These two systems interact with one another and dysfunctions in either system may underlie psychiatric disorders expressing emotional dysfunction.

Another model of emotion processing has been postulated by Jaak Panksepp, who states emotional feelings are organized within primitive subcortical regions of the brain. These networks can be distinguished in an anxiety network and a seeking network. In bipolar disorder, these postulated networks are dysfunctional, meaning that while in mania, the seeking network is overactive, in depression, the anxiety network is overactivated. The seeking network in Panksepp's model corresponds to the medial forebrain bundle and a major dopamine-driven, self-stimulation reward circuitry, which projects from the ventral midbrain to the nucleus accumbens to the medial frontal cortex (Panksepp, 1998, 2010).

1.3.4. Emotional dysfunction in BD

The literature on emotional dysfunction in BD is vast and extensive, this chapter will therefore not be comprehensive. Phillips et al. (2003b) developed a model for understanding the neurobiology of emotion perception in BD based on their model of emotion perception in healthy humans (for details, see Figure 1). They conclude that a predominantly ventral system is important for the identification of the emotional significance of a stimulus, and the production of an affective state. A predominantly dorsal system is important for the effortful regulation of the resulting states.

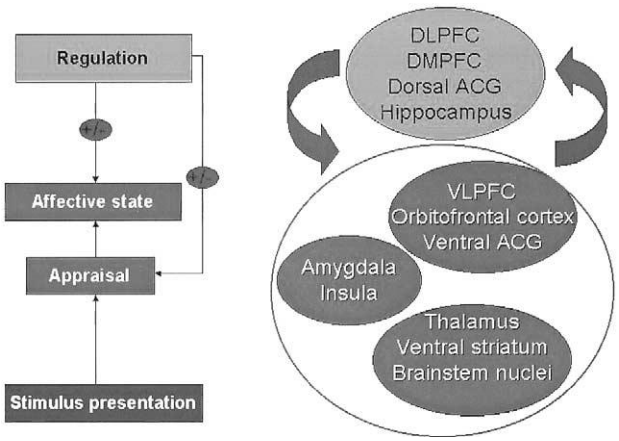

Figure 1. Schematic diagram depicting neural structures important for emotion perception (Phillips, et al., 2003b)

The interplay between these two systems is disrupted in BD, as can be seen in Figure 2. Enlarged rather than decreased amygdalar volumes and enhanced rather than reduced activity within the ventral system suggest a dysfunctional increase in the sensitivity of this system to identify emotional significance and produce affective states. Impaired effortful regulation of subsequent emotional behaviors might result from decreases in prefrontal cortical volumes and activity within the dorsal system.

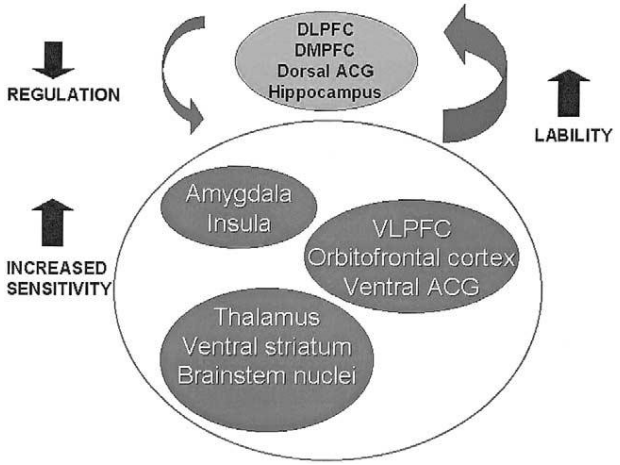

Figure 2. Schematic model for the neural basis of the observed deficits in emotion perception and behavior, and the relationship between these and the symptoms of BD (Phillips, et al., 2003b)

Interestingly, later reviews conclude the same dysfunctionality. Green et al. (2007) conclude that a growing body of research implicates an inhibitory role of PFC and cingulate brain areas that exert cognitive control upon sub-cortical and cortical emotion generation systems. This inhibitory role, however, fails in patients with BD. Townsend and Altshuler (2012) understate this model in their review by stating that the reviewed studies reveal that amygdala activation varies as a function of mood state, while the PFC remains persistently hypoactivated across mood states. They imply that emotional dysregulation and lability in mania and depression may reflect disruption of a frontal-limbic functional neuroanatomical network. Wessa and Linke (2009) introduce a model of emotion processing and then give evidence for a disruption of each module of this model, concluding that many studies have given evidence for the overactivation of a ventral system and the underactivation of a dorsal system leading to a dysfunctional emotion processing and eventually to symptoms of BD. However, they also point out that very little attention has been paid to the last part of the emotion processing: emotion regulation as a function of the dorsolateral prefrontal cortex (dlPFC). This has also been pointed out in an extensive review by Banich et al. (2009), who state that the two lines of research outlined in BD research, namely the one on cognitive dysfunctions and the one on

emotional processing, have been researched in healthy controls as well, and seemingly are independent from each other. However, in recent years it has become clear that the two lines of research should be investigated together in order to fully understand the implications of dysfunctions in either one.

Also, it has to be stated that no studies have been done researching the possible changes in emotion processing over the course of the disorder.

1.3.5. Working memory

A basic definition of working memory describes it as online maintenance and manipulation of information. This information may not be directly available in the current environment, but may also have been retrieved from long term memory. Working memory therefore refers to a broader class of memory phenomena which involve the maintenance and manipulation of active representations, without respect to their source.

Alan Baddeley and Graham Hitch have been considered the founders of working memory theory. In 1974, they hypothesized a working memory model which consists of three operating systems, two specialized subsystems devoted to the presentation of information of a particular type, meaning the visuo-spatial sketchpad for visual info and the phonological loop for any kind of verbal information. Those two subsystems are independent from each other. They are also called “slave systems”, and are controlled by a central executive system, which would coordinate the two subsystems. However, all three systems have limited capacity, which means only a finite amount of information is directly available for processing in memory. Information coming into the working memory systems is first analysed by perceptual modules and then transferred into specialized storage buffers. These buffers have no other role but to temporarily hold pre-processed units of information. The pieces of information that reside in such buffers are subject to passive, time-based decay as well as interference by items stored in the same specialized buffer (A. D. Baddeley & Hitch, 1974). To prevent that, Baddeley introduced an articulatory control process (A. Baddeley & Salame, 1986) in which the material can be rehearsed and so kept in the working memory storage. The same is claimed to be true for the visuospatial sketchpad. It is therefore necessary to distinguish two different processes, elicited by two different kinds of task. Maintenance tasks refer to the process of keeping information in mind in the absence of an external stimulus, which would correspond to the use of the slave systems in the working memory model. Manipulation on the other hand refers to the reorganization of the information being maintained, and corresponds to the central executive in the working memory model.

Maintenance tasks correspond to so-called “domain specific” theories, where the main difference between activated brain regions lays in the type of material being processed. According to the domain specific theory, the frontal cortex is the primary site of working memory processes and different regions within the frontal cortex process different types of information. The vlPFC is believed to be responsible for the maintenance of stimulus form (object information) whereas the dlPFC is responsible for the maintenance of stimulus location (spatial information) (Goldman-Rakic, 1998). The theory is based on electrophysiological recordings and is an extension of the object-spatial (“what” versus “where”) visual processing streams found in posterior regions (Mishkin, Ungerleider, & Macko, 1983).

The process specific theory focuses on the different processes performed within working memory (Petrides, 1995) and corresponds to manipulation tasks. Here, the difference between vlPFC and dlPFC lies not in the type of material being maintained but in the type of processes operating on that material. The vlPFC supports processes that transfer, maintain and match information in working memory. The dlPFC supports more complex processes operating on information that is currently maintained in working memory, such as monitoring and higher level planning.

This dissociation between process and stimulus domain could explain controversial findings about the constitution of working memory. The more processes are involved in a certain working memory task, the more brain regions are involved and the harder it is to extract information about the domains in activation patterns during neuroimaging methods (Fletcher & Henson, 2001; Gruber & von Cramon, 2003).

1.3.6. The N-back paradigm

The N-back task is a paradigm often used to research working memory processes. It combines both maintenance and manipulation processes. It requires the monitoring of a continuous sequence of stimuli, and is answered correctly when the current stimulus matches the stimulus n positions backwards in the sequence. For n>0, this task requires both maintenance of the last n stimuli in order and updating of these stimuli each time a new stimulus occurs. The value n is often viewed as proportional to the working memory load, the total demand placed on the maintenance and/or manipulation processes.

Different types of information can be used in n-back tasks, which can be differentiated into verbal stimuli, such as letters and words, and into nonverbal stimuli, such as shapes, faces,

and pictures. A second division concerns the type of monitoring that is required during the n-back task. This can be either the identity of the stimulus that has to be monitored (e.g., is this the same letter as the one presented n-back) or the location of the stimulus (e.g., is this letter in the same location as the one presented n-back) (Owen, McMillan, Laird, & Bullmore, 2005). Different brain structures are hypothesized to parallel these distinctions.

1.3.7. Working memory deficits in BD

Cognitive deficits in BD are widely studied, and there are some studies studying working memory in BD. All studies reported here have healthy control groups. Adler et al. (2004) gave 15 euthymic bipolar patients a number 2-back task and found that bipolar patients performed more poorly and increased activation in the frontopolar PFC, temporal cortex, basal ganglia, thalamus, and posterior parietal cortex. No reductions in activation were found. Lagopoulos et al (Lagopoulos, Ivanovski, & Malhi, 2007) investigated the encode, delay, and response components of working memory for 3 different load conditions in 10 euthymic bipolar patients and found attenuated patterns of activity in prefrontal brain regions, across all working memory components. Mann-Wrobel et al. (2011) ran a meta-analysis for neuropsychological functioning in euthymic BD, among others investigating working memory. They did find differences between healthy controls and euthymic patients in 8 studies testing with a digit span forward test, and 7 studies testing with a digit span backward test. They conclude that generalized, rather than specific, cognitive impairment characterizes euthymic BD. Monks et al. (Monks et al., 2004) gave 12 euthymic patients a letter 2-back task and found that, while performances did not differ between bipolar patients and controls, patients showed reductions of activation in bilateral frontal, temporal and parietal activation, and increased activation in the left precentral, right medial frontal and left supramarginal gyri. Thermenos et al. (2010) studied 19 euthymic bipolar patients, 18 healthy relatives of bipolar patients, and controls performing a 2-back working memory test and found that both relatives and bipolar patients overactivated the left anterior insula. Relatives also overactivated the orbitofrontal cortex and the superior parietal cortex. Patients, however, did not activate the left frontopolar cortex, as did relatives and controls. The authors conclude that the activity in working memory circuits is affected by activity in emotion regulatory circuits. Schecklmann et al. (2011) investigated 14 depressed bipolar patients with a working memory task with near-infrared spectroscopy and found attenuated activation in the PFC in all working memory loads. Finally, Townsend et al. (2010) measured 13 manic patients, 14 depressed patients, 15 euthymic patients and 14 controls with a 2-back task and found that performance did not differ between groups. However, patients in all three mood states showed significantly

attenuated neural activation in working memory circuits when compared to healthy controls. Taken together, previous research suggests that working memory paradigms find hypoactivation in the PFC, along with worse performance levels for acutely ill patients compared to controls. When patients are measured in a euthymic state, results are contradicting, with some finding remaining performance deficits and hypoactivation, while others report no deficits between euthymic patients and healthy controls and hyperactivation in working memory related brain areas.

It is noteworthy that no studies have been conducted measuring the same patients across mood states, and that group sizes are small. Also, patients were not followed over the natural course of their disorder to find out in which way cognitive deficits, such as working memory deficits, change over time.

1.3.8. Neurophysiological measures of the n-back paradigm

1.3.8.1. Functional near-infrared spectroscopy

The Method called functional Near-Infrared Spectroscopy (fNIRS) is based on two principles: the neurovascular coupling and the optical window (Strangman, Boas, & Sutton, 2002). Neuronal activity is coupled spatially and temporally with a change in the cerebral blood flow and differences in the oxygenation of the blood, a phenomenon called neurovascular coupling (Logothetis & Wandell, 2004). Due to the increased need for oxygen in active neuronal cells, the blood flow in active brain regions rises with a short temporal delay. However, the local rise in oxygenated blood (O_2Hb) flow overcompensates the need for oxygen from the neurons, creating a hyper-perfusion with O_2Hb (Buxton, Uludag, Dubowitz, & Liu, 2004). At the same time, deoxygenated blood (HHb) levels decrease. After a few seconds, the concentration changes of O_2Hb and HHb reach a peak and return to their respective basal levels. This curve is part of the neurovascular coupling and is called the hemodynamic response (see also Figure 3). Hemodynamic responses can differ within a person, as well as between persons in their peak value as well as in their duration (Fox, Snyder, Zacks, & Raichle, 2006; Huppert, Hoge, Diamond, Franceschini, & Boas, 2006). Even the hemodynamic responses between O_2Hb and HHb can differ, Huppert et al (2006) reported up to 2 seconds delay in the peak time of HHb.

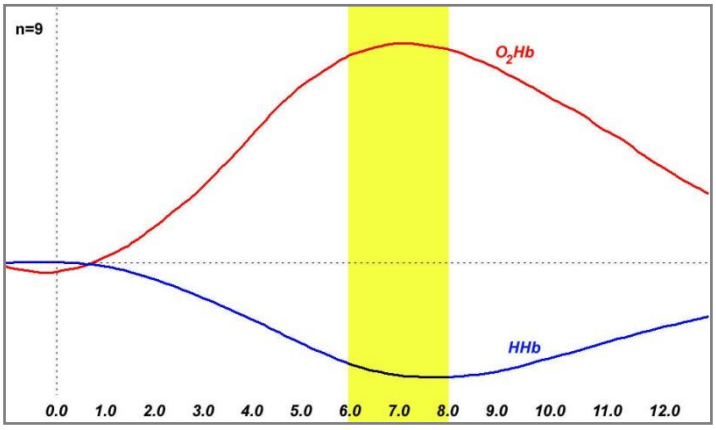

Figure 3. Hemodynamic response of oxygenated and deoxygenated blood with their respective peaks between 6s and 8s after the need for oxygen has arisen within the neurons (Obrig & Villringer, 2003; Strangman, et al., 2002)

The second principle is that of the optical window. It is necessary to know that O_2Hb as well as HHb contain chromophores, which are responsible for their red color through absorption of light of a certain wavelength. Near-infrared light has a wavelength ranging between 650 and 950nm. This wavelength is coupled with the ability to penetrate tissue without the ability to absorb light (Obrig & Villringer, 2003). Therefore the wavelength spectrum of near-infrared light is called the optical window. The chromophores of O_2Hb and HHb have the highest absorption rate of all biological tissue in this spectrum, a characteristic that fNIRS is drawing on.

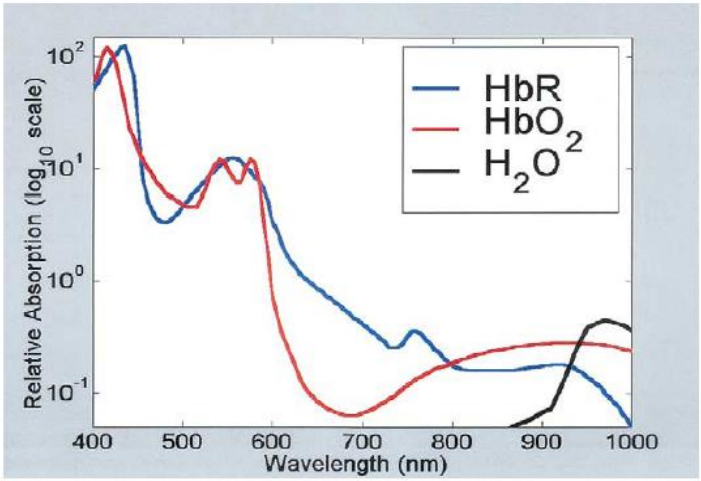

Figure 4. Optical Window displaying the different absorption maxima for oxygenated and deoxygenated blood (Strangman, et al., 2002)

To measure the changes in blood oxygenation levels, optical diodes, called optodes, are placed on the head. The optodes are arranged in plastic space holders, called probe sets, which are then strapped to the head. Each pair of emitter and detectors constitutes a channel. The probe sets are placed on the head according to the electrode positions of the international 10-20 system (Jasper, 1958), which allows for a rough estimation of the brain areas measured (Okamoto et al., 2004).

Some of the optodes emit near-infrared light (emitters) others detect near-infrared light (detectors). The light penetrates scalp, skull, and spinal fluids and is mostly absorbed by the chromophores in O_2Hb and HHb. However, the light does not penetrate farther than the outer cortex region (Ferrari, Mottola, & Quaresima, 2004; Y. Hoshi, 2007), and the spatial resolution is rather small. Light which is not absorbed is caught by the detector. Using a modification of the Lambert-Beer law (Obrig et al., 2000), the interrelation between a weakening of the intensity of the near-infrared light, the concentration of the chromophores, an extinction coefficient, the distance between optodes and the differential path-length-factor at a certain wavelength is calculated. The calculations are based on the assumption, that the diffusion of light in the tissue and the path length factor stay constant.

1.3.8.2. fNIRS and working memory

Several studies have been published researching working memory and working memory components with fNIRS. However, results are mixed, with studies showing increases in ventrolateral prefrontal cortex (vlPFC) and decreases in dlPFC (Koike et al., 2013), or the other way around (McKendrick, Ayaz, Olmstead, & Parasuraman, 2014). Others found increasing activation with increasing working memory load (Ehlis, Bähne, Jacob, Herrmann, & Fallgatter, 2008; Ito et al., 2011; Pu et al., 2012; Schecklmann et al., 2013; Schecklmann et al., 2010; Schreppel et al., 2008; Vermeij, van Beek, Olde Rikkert, Claassen, & Kessels, 2012). One of the most influential studies was published by Hoshi et al. (2003), who found robust activation in vlPFC and dlPFC in an n-back task, which was influenced by the increasing load of that task. Our own workgroup repeatedly used the n-back task and always found robust activation of the PFC depending on working memory load (Kopf, Schecklmann, Hahn, Dresler, et al., 2011).

1.3.8.3. fNIRS in BD

In all, 7 studies have been performed using fNIRS to examine brain activation in bipolar patients. Results, however, are not clear. Kubota et al. (2009) tested bipolar patients in various mood states performing multiple cognitive tasks. They find increased activation of prefrontal

areas compared to controls. Kameyama et al. (2006) investigated 17 bipolar patients who were either euthymic or depressed during a verbal fluency (VFT) and a finger-tapping task. They found decreased activation in the early part of the VFT which increased significantly and then differed in the opposite direction from healthy controls in the late part of the VFT. Matsuo et al. (2004) investigated 9 euthymic patients during a VFT and found a significantly slower increase in activation in the bipolar group. Matsuo et al. (2007) used the same experimental setting with 14 euthymic patients but added a condition where the patients had to inhale carbon dioxide (CO_2) but found no differences between patients and controls in the added condition. The study by Schecklmann et al. (2011) found attenuated brain activation in an n-back task in depressed bipolar patients. Matsubara et al. (2014) had 16 remitted bipolar patients perform an emotional Stroop task and found that patients elicited heightened activation while reading threatening words. While viewing happy words, the activation in patients brains was decreased, and no differences between groups could be observed in the sad condition. Another paper by Takizawa et al. (2014) reports an effort to establish fNIRS activation during a verbal fluency task as a potential biomarker helping to distinguish between patient groups.

Taken together, very little valid research exists studying bipolar patients with fNIRS, and the observations can be summarized as finding overall attenuated brain activation in bipolar patients with fNIRS.

1.3.9. Event-related potentials

Event-related potentials (ERPs) are defined as electrical voltage changes which manifest before, during or after a sensory, motoric or cognitive event in the electroencephalogram (EEG) (Schmidt & Birbaumer, 2005). An ERP therefore is the answer of the brain to an externally or internally produced stimulus, measurable as voltage curves. Amplitudes of ERPs are naturally very small, so that it is necessary to sum them up in order to make them stand out compared to background electrical activity of the brain.

Positive and negative deflections of the ERP are called components. These components can be characterized by means of their polarity (positive or negative), their latency (in milliseconds, ms) or their amplitude (voltage in microvolt, µV). ERP components can be classified into exogenous and endogenous components. Exogenous components, also called primary answers, correlate to the early parts of a potential, and occur within the first 100ms after stimulus onset. They are modeled in their characteristics according to the physical properties of the stimulus (Olbrich, 1989), and are therefore viewed as correlations of primary

sensory processes. The endogenous components, or secondary answers, follow the primary sensory components and are less dependent on the physical properties of a stimulus. Instead, they are influenced by psychological factors, i.e. the salience of a stimulus (Olbrich, 1989). Therefore, endogenous components are considered as neuronal correlates of cognitive or emotional processes. The latency of a potential mirrors the temporal characteristics of the processing of a stimulus, its amplitude is interpreted as the intensity of the processing of that stimulus.

1.3.9.1. ERPs and emotion

The event related potential of this thesis is the late positive potential (LPP). The LPP constitutes a sustained positivity with a relatively late onset (circa 300 ms after the stimulus onset) and is proposed to be able to distinguish between the processing of emotional versus non-emotional stimuli. Compared to the non-emotional stimuli, the emotional stimuli have been shown to elicit a higher positivity in the EEG. The LPP has two components, an early and a late LPP, with the late LPP starting approximately 1000 ms after stimulus onset, whereas the early component starts around 300ms after stimulus onset and lasts until about 600ms after stimulus onset. (Hajcak, Dunning, & Foti, 2009; Hajcak, MacNamara, & Olvet, 2010). The LPP has developed from the P300, a 300ms after stimulus onset occurring positive potential, which has its maximum over parietal sites. The P300 is one of the most extensively studied ERPs (Polich, 2007). It has been used to study i.e. oddball effects, attention modulation, and working memory onset (Hajcak, et al., 2010; Olbrich, 1989). Because of their intrinsic motivational significance, emotional stimuli might be considered natural targets for attention, and therefore soon the relevance of the P300 for emotional stimuli became apparent (Hajcak, et al., 2009). (Hajcak, et al., 2010). Today, the LPP is distinguished from the P300 in that it measures early emotional processing and late emotional regulation correlates.

Studies have shown that the LPP is influenced by concurrent working memory tasks. It reduces the late positive potential. However, if test subjects have high anxiety, this effect is attenuated (MacNamara, Ferri, & Hajcak, 2011).

The neurological correlate of the LPP remains unknown. Hajcak et al. (2010) argues that the LPP may index downstream processes resulting from increased activation of the amygdala, other researchers find complex networks to be correlated with the LPP, depending on the valence that needs to be processed (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012).

1.3.9.2. The LPP in bipolar patients

Up to now, no studies have been done researching the LPP in bipolar patients. This thesis will therefore be the first study on differences in the LPP in patients in their different mood states and compared to healthy controls. One study researched the LPP in MDD and found larger LPPs to higher arousing emotional pictures but no group differences for controls and subjects with a family history of MDD (Jaworska et al., 2012).

1.4. Summary of previous research and hypotheses

The theoretical background of the relevant research findings can be summarized as follows:

BD is characterized by dysfunctional emotion processing and cognitive deficits, and it is not clear whether these deficits still remain in euthymia (1.2).

Studies show abnormalities in the structure and function of key emotional control networks, as well as attenuated function in key cognitive brain areas leading to cognitive deficits (1.3).

Many studies have been done researching cognitive deficits, and working memory in detail, and much more have reported emotional dysfunction. However, the interconnection between these two key domains has not been taken into account. Studies following patients over time and measuring their functionality in the above mentioned key components are sparse or non-existing. The aim of this thesis is to capture the course of BD in patients over different mood states in regard to the two key components, cognitive function and emotional processing. A novel n-back paradigm containing both working memory components and emotional stimuli will be established, a pilot study will be done to show validity of the paradigm, and patients will be recruited in a) an acutely ill phase and b) later on during remission Patients' performance will be measured by two neurophysiological measures, fNIRS and EEG, in order to capture both hypothesized dysfunctional components of the disorder. The hypotheses derived from the study design are as follows:

1. **Working memory function:**
   1.1. Patients show significantly worse performance during an acute phase, compared with healthy controls. Their brain activation will be attenuated compared to controls, and this attenuation will increase with increasing working memory load. Electrophysiological changes in the LPP will be different for patients and controls.

   1.2. Patients will perform on the same level as controls in remission. They will perform significantly better than in the ill phase. Brain activation, however, will still be attenuated compared to controls, and not different from their acute ill phase. LPP differences between patients and controls will not vanish.

2. **Emotion processing:**
   2.1. Patients will show differences in emotional processing compared to controls. They will be slower to react to emotional stimuli and make more errors when compared to controls. Their brain activation will be attenuated for emotional stimuli, and their LPP will be heightened when compared with controls.

   2.2. Performance differences will vanish when patients return to their remitted state, and will not be different from controls anymore. However, brain activation and LPP Amplitude to emotional stimuli will remain different compared to controls.

3. **Interaction between working memory and emotion processing:**
   3.1. The performance in the n-back task will be influenced by the emotional valence of the stimulus presented in the working memory task.

   3.2. This influence will change with increasing working memory load, and the influence will be different for patients compared to controls.

   3.3. This influence and the difference between patients and controls will remain when patients are measured again in their remitted state.

2. Methods

2.1. Study design

At first, a preliminary study was conducted to test whether the paradigm was able to elicit different activation patterns for each condition tested with fNIRS, and establish these activation patterns as a baseline from which patients should differ. After analysis of the prestudy, the main study was conducted as a repeated measures design, with patients being measured in their acute ill phase while being inpatients in the university clinic. These patients were then asked to come back in a fully remitted state at least three months after release from the clinic, and were tested again. Control subjects, which were not identical to the subjects from the prestudy, chosen for their matching with the patients in age, sex, and educational degree, were tested once. Controls were not tested again because of monetary restrictions. It is also reasonable to believe that n-back tests are fairly reliable when retested (Hockey & Geffen, 2004).

The study was reviewed and approved by the Ethics Committee of the University of Würzburg, and all procedures were in accordance with the latest version of the Declaration of Helsinki. All test subjects gave written informed consent after comprehensive explanation of the experimental procedures.

2.2. Test Subjects

2.2.1. Recruiting, inclusion and exclusion criteria

One patient and four controls had to be excluded prior to data analysis after meeting the exclusion criteria.

Test subjects were excluded if they had one of the following: previous history of stroke or traumatic brain injury, as well as previous operations on the head, epilepsy, and diseases influencing their systemic circulation, such as diabetes, to ensure equal interpretation of the fNIRS data. The age range of test subjects was 18-60 years.

Control subjects had to be free of any past or current axis I disorders according to the DSM IV. They were screened with the Mini International Neuropsychiatric Interview (MINI), German version 5.0 (Sheehan et al., 1998).

Bipolar patients were recruited while being inpatients in a specialized bipolar ward at the university hospital psychiatric clinic. Their disorder status was diagnosed and confirmed by 2 psychiatrists and extensive testing with the OPCRIT diagnostic system (McGuffin, Farmer, & Harvey, 1991). Patients disorder status was recorded with the Montgomery Asberger Depression Rating Scale (MADRS) scores (Montgomery & Asberg, 1979) and Young Mania Rating Scale (YMRS) scores (Young, Biggs, Ziegler, & Meyer, 1978).

Included were patients with bipolar I or bipolar II disorder. Patients receiving electroconvulsive therapy were excluded.

Patients coming back at T2 had to be free of symptoms according to DSM IV criteria measured with MADRS and YMRS. Cut-off scores for depression were 9 points in the MADRS and 6 for Mania in the YMRS.

2.2.2. Sociodemographics

To compare state affect between groups, test subjects completed the Positive Affect Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988) before taking part in the experiment. The PANAS comprises of 2 subscales, one measuring positive affect (PA) and one measuring negative affect (NA). The scale consists of 20 items, and each item is rated on a 5-point scale ranging from 1 = very slightly or not at all to 5 = extremely to indicate the extent to which the respondent has felt this way in the indicated time frame. High-NA characterizes subjective distress and unpleasurable engagement, and low NA stands for the absence of these feelings. By contrast, PA represents the extent to which an individual experiences pleasurable engagement with the environment. Thus, emotions such as enthusiasm and alertness are indicative of high PA, whilst lethargy and sadness characterize low PA (Crawford & Henry, 2004). Details on the PANAS and socio-demographic details can be found in Table 1.

Table 1. Socio-demographic details and PANAS scores.
SD indicates the standard deviation.

	Pilot study	Controls	Patients ill	Patients remitted
Sex ♂/ ♀	16/16	18/23	18/28	4/14
Age (mean±SD)	23.6±2.7	39.7±10.8	41.4±11.3	39.6±10.9
Educational degree (median)	3	2	2	2
MADRS (mean± SD)	-	-	21.2±9.8	2±2.6
YMRS (mean± SD)	-	-	4.3±4.2	0.1±0.3
PANAS PA (mean± SD)	-	29.9±5.4	24.6±7.5	26.2. ±4.2
PANAS NA (mean± SD)	-	10.9±2.7	15.9±5.9	12.8±3.8

The pilot study is not included in the following analyses since data is not compared later. Patients and controls did not differ in their sex (Chi^2= .204, *p*= .65), their educational degree (*U*= 909, *z*= -.304, *p*= .76) or their age (t (84) = .78, *p*= .44). However, patients and controls did differ in their respective state affect. Detailed information as to the extent of this difference can be found in Table 2. The possible ramifications of these differences in state affect will be discussed in more detail in section 4 of this thesis.

Table 2. Statistical evaluation of the PANAS scores.
Significant differences are marked in bold.

	t	df	*p* value
PANAS PA			
mild depression vs. controls	-2.49	52	**.016**
depression vs. controls	-5.32	60	**.000**
manic vs. controls	1.13	47	.260
mixed vs. controls	-2.22	47	**.031**
remitted vs. controls	-1.04	58	.303
acute vs. remitted	-1.04	17	.312
PANAS NA			
mild depression vs. controls	4.63	52	**.000**
depression vs. controls	5.09	60	**.000**
manic vs. controls	.82	47	.415
mixed vs. controls	2.21	6.57	.065
remitted vs. controls	1.91	58	.061
acute vs. remitted	2.02	17	.059

2.2.3. Disorder status

Since patients in all mood states were included in this study, it is necessary to make a distinction between different states. Since no clear cut-off scores are defined for the MADRS, a literature search has brought back the following scores which were used in this thesis as well: under 9 points: no depression; 9 – 23 points: mild depression; 23 - 35 points: depression, and over 35 points: severe depression. The same is true for the YMRS, so this study used the following cut-off scores: under 6: no mania; 6 – 12: hypomania; over 12: mania. And finally, patients who had mixed symptoms fitting both categories were labeled as mixed. Numericals of these categorizations can be found in Table 3.

Table 3. Categorization of patients into subgroups according to their disorder status.

mild depression	17
depression	20
severe depression	2
hypomania	9
mania	5
mixed	7

Since there is still ongoing controversy about the impact of the property of the phase on brain activation, patients were splitted into 4 groups: a mild depression group, a depression group also containing the 2 severely depressed patients, a mania group with both manic and hypomanic patients, and a mixed group. The patients grouping can be seen in table Table 4.

Table 4. Categorization of patients for subsequent analyses.

mild depression	12
Depression	20
Mania	7
Mixed	7

2.2.4. Medication

Since this was a naturalistic study, all patients, both acutely ill and remitted, were medicated. A list of all medication data is attached in the supplement. There is much debate over the impact of medication on performance and brain activity. However, a new review by Hafeman et al (2012) summarized previous research and they concluded that, while medication seemed to influence structural MRI studies, it had only limited impact on functional MRI studies. The effects that were found pointed to a heightened blood flow in patients brains, making them

more similar to unmedicated healthy controls than their unmedicated counterparts. If any effects were found in blood oxygenation levels between patients and controls, this would point to a stronger real difference between the groups, due to the increase in type II errors that follows.

2.3. Paradigm

2.3.1. N-back

Participants saw blocks of ten consecutive words presented on a computer screen (see also Figure 5). Two of these words were used as cues and were followed by a target word which was presented one, two or three words after the cue word, to vary the difficulty level and thus the working memory load. When the participants saw the target word, they were instructed to press the space key on a standard keyboard. Each block of ten words comprised one difficulty level. Also the emotional content of the words was varied; the words were positive, negative or neutral. Each block encompassed only one emotional valence. In total, there were three blocks where the emotional valence was negative and the difficulty level was one, meaning the target word followed the cue word directly. Three blocks had a negative emotional valence and the difficulty level was two, meaning there was one word between cue word and target word. Three blocks had a negative emotional valence and the difficulty level was three, meaning there were two words between the cue word and the target word. The same was true for the positive and the neutral emotional valence; therefore, in sum the experiment had 27 blocks. Each block was 20 seconds long, and blocks were separated by a 20-second pause. Within each block, each word was visible for 500 ms, followed by a blank screen, which was also 500 ms long. The difficulty level of the blocks was pseudorandomized, and difficulty levels always varied from one block to another. In the pause preceding a block, the instruction for the task (1-, 2-, 3-back) was presented on the screen.

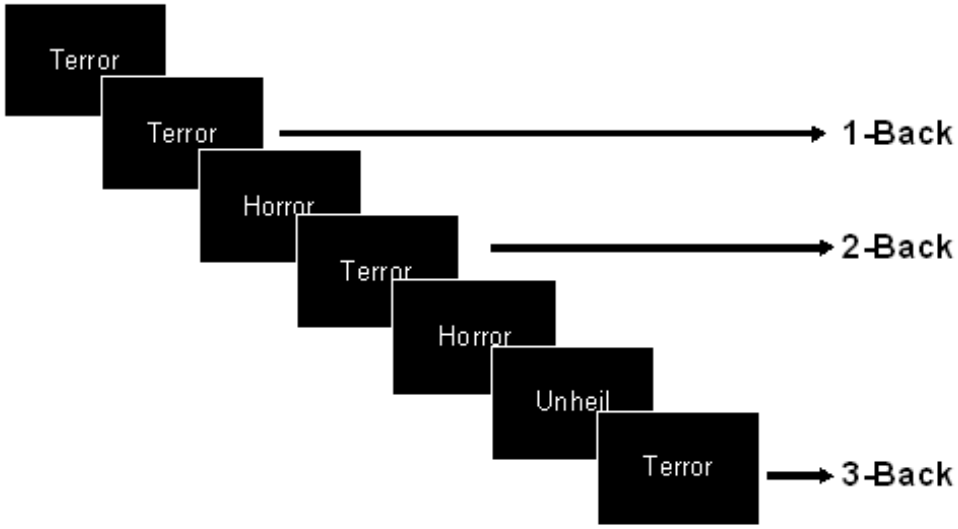

Figure 5. Description of n-back task.

Before the experiment, participants practised the task using one block of each difficulty (1, 2, 3-back). In each block they saw 30 consecutive neutral words in the 1-back condition, the same neutral words in the 2-back condition and in the 3-back condition.

After the experiment, participants were prompted to evaluate the words used for their arousal and valence (words could be rated from 1: very unpleasant to 9: very pleasant and 1: not arousing to 9: very arousing).

2.3.2. Word List

The words (a list of which can be seen in Table 5) were chosen from the Berlin Affective Word List (Vo et al., 2009), were all nouns and matched for valence (positive nouns had a mean valence of 2, negative nouns a mean valence of -2 and neutral words a mean valence rating of 0, with the valence scale spanning from -3 for very negative to 3 for very positive). Mean arousal of emotional words was matched in respect of their valence, meaning the negative and positive words had a mean arousal of 3, the neutral words had a mean arousal of 0 (on a scale from 1: very low arousal to 5: very high arousal). To ensure equal working memory load for all words, phoneme length (5), syllable length (2), and number of letters (6) were matched as well.

Table 5. List of words used in the n-back paradigm.
English expressions are found in the brackets.

negative words	positive words	neutral words
TYPHUS (typhus)	RETTER (savior)	ABLAUF (sequence)
BEFEHL (order)	WISSEN (knowledge)	AFFEKT (affect)
ARREST (warrant)	MUTTER (mother)	BANNER (banner)
TYRANN (tyrant)	GEWINN (win)	GERUCH (smell)
GREUEL (horror)	GEFÜHL (feeling)	KELLER (basement)
SEENOT (distress at sea)	HIMMEL (heaven)	LOSUNG (watchword)
HORROR (horror)	FRIEDE (peace)	STELLE (position)
TRAUMA (trauma)	URLAUB (vacation)	ZEUGIN (eye witness)
TERROR (terror)	SOMMER (summer)	AKZENT (accent)
UNHEIL (calamity)	FREUND (friend)	INHALT (content)

2.4. Electrophysiological measurements

2.4.1. Functional Near-Infrared Spectroscopy

An ETG-4000 Optical Topography system (Hitachi Medical Co., Japan) was used, with a 52-channel array of optodes covering an area of 30 x 6cm of the forehead. The interoptode distance is 3 cm, in order to allow sufficient penetration depth. The array comprises of 17 light emitters (semiconductor laser) and 16 photo-detectors (Avalanche photodiodes).The photo-detectors collect the reflected near-infrared light of its surrounding emitters. A channel is defined as the measuring point of activation, which is the region between one emitter and one detector. The array was fastened to the head by elastic straps. The probe set was placed on the head so that detector optode 26 was on the position for Fpz and aligned to T3/T4 (for emitter optodes 28 and 23), according to the international 10-20 system for EEG electrode placement (Okamoto & Dan, 2005). The array therefore covers both left and right frontal cortex areas.

2.4.2. Electroencephalogram

Continuous EEG was recorded from 5 scalp electrodes placed according to the 10/20 system (Jasper, 1958): Cz, CPz, Pz, CP1, CP2, and both mastoids. The ground electrode was placed on the left part of the scalp in the centroparietal region (corresponding to CP3). The electrooculogram (EOG) was recorded from four facial electrodes: vertical eye movements were measured with two electrodes placed approximately 1 cm above and below the right eye. Horizontal eye movements were measured using two electrodes placed 1 cm away from the outer canthi of each eye. ERPs were recorded with a 64-channel Quick Amp amplifier (Brain

Products, Munich, Germany) and Vision Recorder software (version 2.0, Brain Products, Munich, Germany). Data were referenced online to an average reference including all electrodes. This average referencing is a built-in feature of the Quick Amp and cannot be changed. However, due to the small number of electrodes, the data were rereferenced offline, for details please see the data analysis section. Sampling rate was set to 1000 Hz. All channels were amplified with a band-pass from DC to 200 Hz. The impedances were kept below 5 kΩ.

2.5. Data Analysis

The program SPSS, version 21 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.), was used for all statistical analyses. Details on the statistical tests used can be found in each subsection.

2.5.1. Behavioral Data

3x3 repeated measures analyses of variance (ANOVA) for the difficulty-levels (1-back, 2-back and 3-back) by emotional valence (negative, positive and neutral) were conducted for the reaction time and the errors made in the experiment. In case of non-sphericity, Greenhouse-Geisser adjustment was used. This is true for all data analyses. Respective post hoc t-tests were conducted to evaluate differences between groups.

2.5.2. fNIRS Data

First, the high frequency portion of the signal was removed by applying a moving average (MA) filter with a time window of 1 s. To remove slow drifts, a 3 element discrete cosine transform basis set was then used on the data.

The last five seconds before a block was taken as baseline period. Thereafter, the last 15 seconds of the 20-second block were defined as the activation period, since 5 seconds after the initial trigger the neural response should already be seen in an increase in activation (Logothetis & Wandell, 2004). The mean of oxygenated haemoglobin [O_2Hb] and deoxygenated haemoglobin [HHb] concentrations were computed for each segment and baseline-corrected. Since HHb concentrations did not reveal any new insights into the data, HHb will not be analyzed and discussed further.

We assigned fNIRS channels to specific brain areas according to probabilistic maps (Tsuzuki et al., 2007) and defined regions of interest (ROIs) for both hemispheres. Based on previous work (Kopf, Schecklmann, Hahn, Dresler, et al., 2011; Owen, et al., 2005; Martin Schecklmann, et al., 2010), we defined the dlPFC (Brodman areas 9/10/46) as ROIs. This

corresponds to channels 3, 4, 13, 14, 15, 24, 25, 35, 36, 46 for the right dlPFC, and channels 7, 8, 17, 18, 19, 28, 29, 38, 39, 49 for the left dlPFC. For statistical analyses of the fNIRS data, 3x3 ANOVAs for each ROI were calculated; the within-factors were load (i.e. 1-back, 2-back and 3-back) and emotional valence (i.e. negative, neutral and positive). Subsequently, relevant post hoc tests were conducted. For details on channel placement and ROI location, see Figure 6.

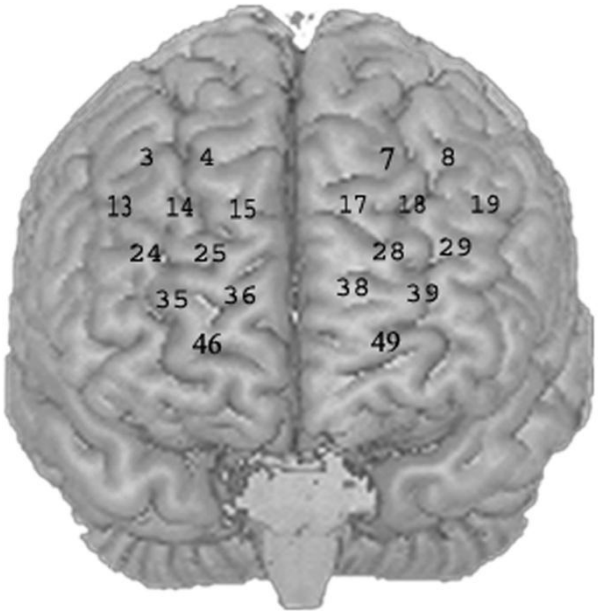

Figure 6. Channel placement on the brain.
Numbers indicate separate channels of the NIRS measurement selected for ROI analyses.

2.5.3. EEG Data

The data were analyzed using Vision Analyzer 2 software (Brain Vision, Munich). Offline, the data were filtered with a Butterworth Zero Phase Filter with a low cut-off of 0.1 Hz and a high cut-off of 20 Hz, eye blink and ocular corrections were conducted according to the Gratton, Coles and Donchin (Gratton, Coles, & Donchin, 1983) algorithm.

The data were then segmented into time windows starting 100 ms before the reference marker (indicated by the onset of a word) and ending 1900 ms after the reference marker.

An automatic procedure built in the analyzer software detected and rejected artefacts: it was specified to reject any voltage steps more than 50.0 µV between sample points, a voltage difference of 300.0 µV within a trial, and a maximum voltage difference of less than 0.50 µV within 100 ms intervals.

After that, the data were re-referenced offline to a combined mastoid reference. Afterwards the baseline was corrected. The baseline, defined as 100 ms before word onset, was subtracted from the signal.

Because the LPP is maximal at centro-parietal sites (Foti & Hajcak, 2008; Hajcak, Dunning, & Foti, 2007; Keil et al., 2002; Weinberg & Hajcak, 2010), it was scored as the average activity from five centro-parietal sites (Pz, CPz, Cz, CP1 and CP2). Based on this research and following our presentation time of the stimuli of 500 ms, we evaluated the window of 350-600 ms after stimulus onset (mean activity). The late portion of the LPP was not analyzed because of the short time each word was visible. The target trials were too small in number and not analysed. In all, 24 trials of every condition went into the analysis.

For the statistical analysis, the same ANOVA as for the fNIRS data was calculated. Relevant post hoc tests were conducted.

3. Results

3.1. Pilot Study

3.1.1. Valence and Arousal Ratings

Repeated measures t-tests for the valence ratings showed significant differences for the valence between negative and neutral words ($t(29) = 9$, $p < .001$), between positive and neutral words ($t(29) = 18.1$, $p < .001$), and between positive and negative words ($t(29) = 18.3$, $p < .001$). Repeated measures t-tests for the arousal ratings showed significant differences for the arousal ratings between negative and neutral words ($t(29) = 7.3$, $p < .001$) and between the positive and neutral words ($t(29) = 7.1$, $p < .001$), but no significant differences between the positive and negative words ($t(29) = 1.9$, $p > .05$). The ratings completed by the participants were done in order to repeat the results from the original study by Vö et al (2009), and to ensure that the actual arousal and valence ratings were equal to the ones already published.

3.1.2. Behavior

A 3x3 repeated measures ANOVA revealed a significant main effect of the difficulty level on the reaction time ($F(1.4, 58) = 31.3$, $p < .001$). A main effect for the factor valence ($F(2, 58) < 1$) or interaction effect could not be found ($F(4, 116) < 1$). Post hoc t-tests for the main effect difficulty revealed significant differences, indicating increasing reaction times with increasing difficulty. All tests were significant ($t(29) > 4.4$, all $p < .001$).

The tests for normal distribution in the error data showed significant p-values for all differences (all $p < .001$). Non-parametric Wilcoxon tests however, show the same results as parametric t-tests for paired samples (see also Table 6). Because we were interested in interaction terms, and the ANOVA is robust against violations of assumptions for parametric testing for $N > 20$ we therefore calculated a 3x3 ANOVA. Results from that ANOVA should be interpreted carefully. The 3x3 ANOVA for the errors revealed a significant main effect for the difficulty level ($F(1.5, 43.9) = 15.6$, $p < .001$). No significant main effect for the valence could be found ($F < 1$). A significant interaction effect for the errors ($F(2.8, 82.1) = 3.7$, $p = .016$) was observed, indicating that word valence influenced the error rate differentially in each difficulty level, the more difficult the task; the more errors were made especially in the negative valence condition. The details of the post hoc t-tests concerning the changes within the difficulty level are presented in Table 6.

Table 6.Non-parametric Wilcoxon and parametric t-test results for errors made. Significant differences are highlighted in bold. Marginally significant differences are written in italics.

Errors		**t-tests**		**Wilcoxon**	
Load	**T**	**df**	***p* value**	**Z**	**Sig.**
1-back					
Negative vs. Positive	-1.438	29	.161	-1	.317
Negative vs. Neutral	-.571	29	.572	0	1.000
Positive vs. Neutral	-1.000	29	.325	-1	.317
2-back					
Negative vs. Positive	.215	29	.831	0	1.000
Negative vs. Neutral	2.058	29	**.048**	-1.705	*.088*
Positive vs. Neutral	1.428	29	.163	-1.429	.153
3-back					
Negative vs. Positive	-1.030	29	.311	-1.035	.301
Negative vs. Neutral	-3.695	29	**.001**	-2.977	**.003**
Positive vs. Neutral	1.869	29	*.071*	-1.642	.101
Valence					
Negative					
1-back vs. 2-back	-1.139	29	.263	-1.342	.180
1-back vs. 3-back	-4.342	29	**.000**	-3.397	**.001**
2-back vs. 3-back	-3.840	29	**.001**	-3.132	**.002**
Positive					
1-back vs. 2-back	-1.438	29	.161	-1.633	.102
1-back vs. 3-back	-3.483	29	**.002**	-2.85	**.004**
2-back vs. 3-back	-2.175	29	**.037**	-1.877	*.060*
Neutral					
1-back vs. 2-back	-3.091	29	**.004**	-2.484	**.013**
1-back vs. 3-back	-2.490	29	**.018**	-2.309	**.021**
2-back vs. 3-back	1.184	29	.245	-0.54	.589

3.1.3. fNIRS

3.1.3.1. Oxygenated Hemoglobin

Four test subjects had to be excluded due to technical artefacts, so all analyses were based on 26 test subjects. The 3x3 ANOVA for the oxygenated haemoglobin revealed a significant main effect for the difficulty level ($F(2, 50) = 4.2$, $p = .021$), no main effect for emotional valence ($F(2, 50) = 1.2$, $p = .3$), but a significant interaction effect ($F(4, 100) = 2.6$, $p = .039$) indicating that the word valence influences the oxygenation in a given difficulty level differentially (

Table 7 and Figure 7). A repeated measures ANOVA with the additional factor hemisphere revealed no differences in activation between the two hemispheres ($F < 1$).

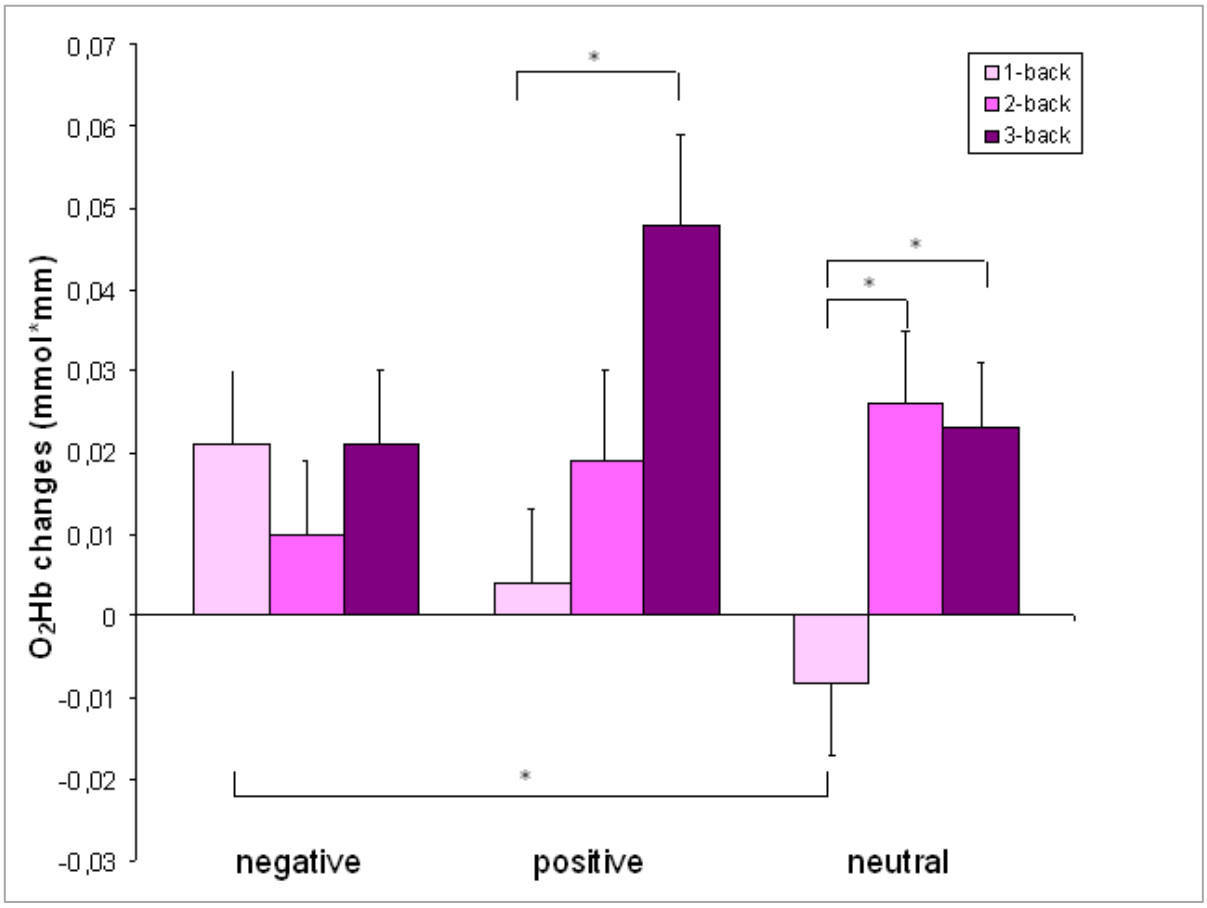

Figure 7. Changes in the oxygenated blood concentration in the ROI.
Bars indicate the standard error. * indicates significant differences between difficulty levels ($p<0.05$)

**Table 7. Post hoc t-tests for the ROI in the oxygenated condition.
Consistent of BA9, BA10, BA46. Significant channels are highlighted in bold.**

Oxyenated hemoglobin changes

Negative	**T**	**df**	***p* value**
1-back vs. 2-back	.835	25	.412
1-back vs. 3-back	-.050	25	.961
2-back vs. 3-back	-1.233	25	.229
Positive			
1-back vs. 2-back	-1.188	25	.246
1-back vs. 3-back	-2.838	25	**.009**
2-back vs. 3-back	-1.813	25	.082
Neutral			
1-back vs. 2-back	-2.382	25	**.025**
1-back vs. 3-back	-2.305	25	**.030**
2-back vs. 3-back	.239	25	.813
1-back			
Negative vs. Positive	1.251	25	.222
Negative vs. Neutral	2.710	25	**.012**
Positive vs. Neutral	.887	25	.383
2-back			
Negative vs. Positive	-.847	25	.405
Negative vs. Neutral	-1.895	25	.070
Positive vs. Neutral	-.561	25	.580
3-back			
Negative vs. Positive	-1.870	25	.073
Negative vs. Neutral	-.166	25	.869
Positive vs. Neutral	1.926	25	.066

3.1.3.2. Deoxygenated Hemoglobin

The 3x3 ANOVA for the deoxygenated haemoglobin replicated the pattern described above. Again, there was a significant main effect for the difficulty level ($F(2, 50) = 14.5$, $p < .001$), no significant main effect for the emotional valence ($F < 1$) and a significant interaction effect ($F(4, 100) = 7.3$, $p < .001$) (Table 8 and Figure 8). Again, the repeated measures ANOVA for the right and left hemisphere revealed no differences in activation between the two hemispheres ($F < 1$).

Table 8. Post hoc t-tests for the ROI in the deoxygenated condition. Significant channels are highlighted in bold.

Deoxygenated hemoglobin changes

Negative	**T**	**df**	***p* value**
1-back vs. 2-back	1.652	25	.111
1-back vs. 3-back	1.563	25	.131
2-back vs. 3-back	-.037	25	.971
Positive			
1-back vs. 2-back	1.934	25	.065
1-back vs. 3-back	4.716	25	**.000**
2-back vs. 3-back	3.749	25	**.001**
Neutral			
1-back vs. 2-back	4.632	25	**.000**
1-back vs. 3-back	2.558	25	**.017**
2-back vs. 3-back	-1.960	25	.061
1-back			
Negative vs. Positive	-1.223	25	.233
Negative vs. Neutral	-2.055	25	**.050**
Positive vs. Neutral	-.748	25	.462
2-back			
Negative vs. Positive	-1.403	25	.173
Negative vs. Neutral	1.742	25	.094
Positive vs. Neutral	2.553	25	**.017**
3-back			
Negative vs. Positive	2.625	25	**.015**
Negative vs. Neutral	-.722	25	.477
Positive vs. Neutral	-4.436	25	**.000**

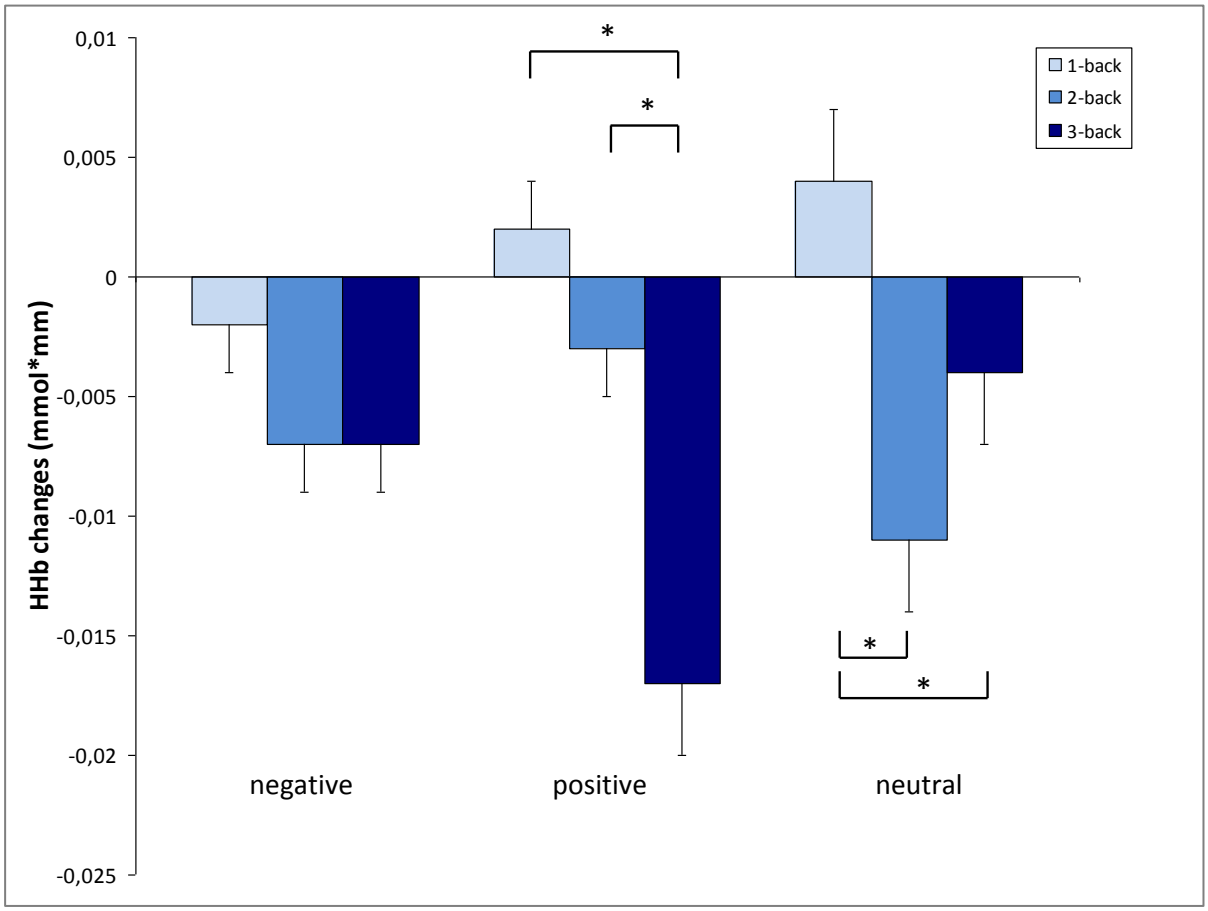

Figure 8. Changes in the deoxygenated blood concentration in the region of interest. Bars indicate the standard error. An asterisk indicates significant differences between conditions.

3.1.4. EEG

The 3x3 ANOVA revealed a significant main effect for the difficulty level (F (2, 58) = 6.9, *p* = 0.002), a significant main effect for the emotional valence (F (2, 58) =5.4, *p* = .007) and a significant interaction effect (F (4, 116) = 2.7, *p* = .036). This indicates that the difficulty level of the working memory task modulates the response to emotionally salient words. Results from the post hoc t-tests can be seen in Table 9, and are also illustrated in Figure 9, and show that in the 1-back task, the LPP is not different between the emotional valence of the words, whereas in the 2-back task, the LPP differentiates between neutral and emotional words but not between the emotional valences. Finally, in the 3-back task it is only possible to dissociate the negative valence within the LPP.

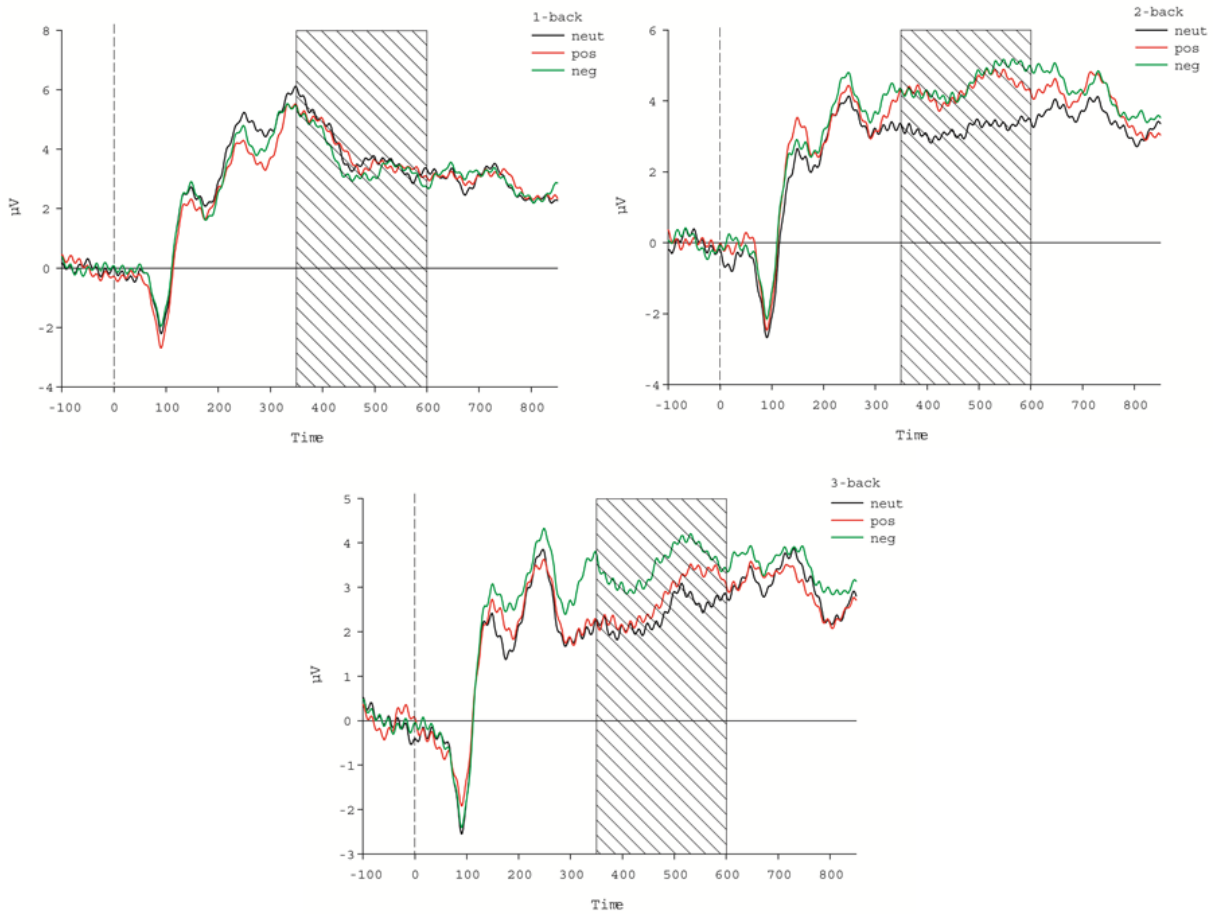

Figure 9. Stimulus locked ERPs averaged at Cz, Pz, CPz, CP1 and CP2 for the valences neutral, negative and positive for the 1-back condition (A), the 2-back condition (B) and the 3-back condition (C).

Table 9. Post-hoc t-tests for the LPP in the different conditions. Significant differences are highlighted in bold.

EEG Data

1-back	**T**	**df**	***p* value**
Negative vs. Positive	1.218	29	.233
Negative vs. Neutral	-0.52	29	.604
Positive vs. Neutral	0.836	29	.41
2-back			
Negative vs. Positive	-0.38	29	.709
Negative vs. Neutral	3.567	29	**.001**
Positive vs. Neutral	2.537	29	**.017**
3-back			
Negative vs. Positive	-1.58	29	.125
Negative vs. Neutral	2.651	29	**.013**
Positive vs. Neutral	0.643	29	.526
negative			
1-back vs. 2-back	-.316	29	.755
1-back vs. 3-back	2.447	29	**.021**
2-back vs. 3-back	3.314	29	**.002**
Positive			
1-back vs. 2-back	-1.811	29	.081
1-back vs. 3-back	.539	29	.594
2-back vs. 3-back	2.872	29	**.008**
Neutral			
1-back vs. 2-back	1.514	29	.141
1-back vs. 3-back	2.765	29	**.010**
2-back vs. 3-back	1.483	29	.149

3.2. Main Study

3.2.1. Valence and Arousal Ratings

3.2.1.1. Acutely ill patients versus controls

To assess group differences for valence and arousal ratings, two 3x5 ANOVAs were calculated for valence ratings and arousal ratings with the between subject factor disorder status.

For the valence, the ANOVA revealed a significant main effect for valence ($F(1.4,119.1)=463.3$, $p<.001$) and a significant main effect for subgroup ($F(4,86)=2.6$, $p=.04$). Post hoc t-tests were conducted for each group, differences can be seen in Figure 10.

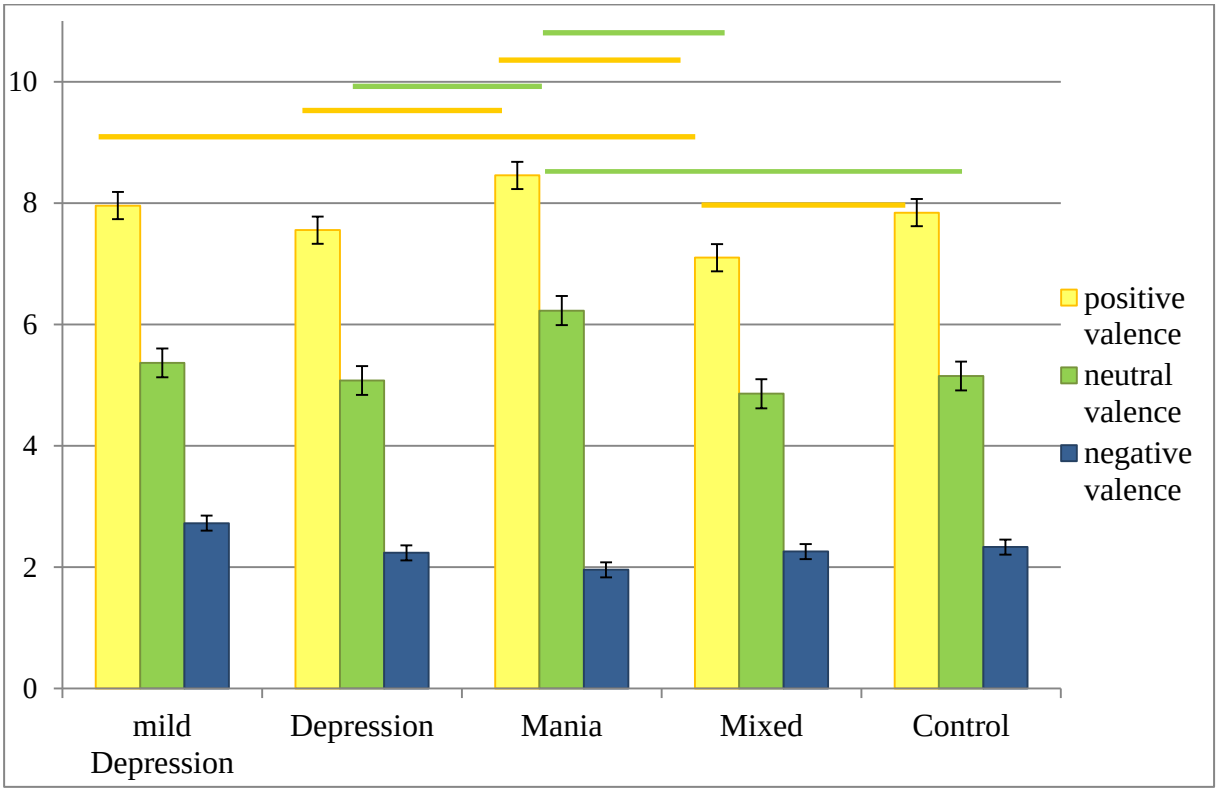

Figure 10. Valence Ratings for patient groups and controls.
Lines above the bars indicate significant differences for the mild depressive group (N=12), the depressive group (N=20), the manic group (N=7), the mixed group (N=7) and the healthy controls (N=45).

Group differences seem to be carried by manic patients who rate positive and neutral words more positive and mixed patients who rate neutral words more negative compared to the other groups.

For the arousal, the ANOVA revealed a significant main effect for arousal ($F(1.7,135,4)=69.8$, $p<.001$). Negative words had the highest arousal, which was significantly

different from the arousal ratings for the positive words (t(85)=6.7, *p*<.001) and from the neutral words (t(85)=17.9, *p*<.001). Positive words were rated as significantly higher arousing than neutral words (t(85)=8.2, *p*<.001). No between group effects were detected.

3.2.1.2. Remitted patients versus controls

The same ANOVAs were also calculated for remitted patients versus controls. For the valence ratings, a main effect of valence was found (F(1.4,76.3)=540.9, *p*<.001). No group differences were detected.

For the arousal ratings, the ANOVA revealed a main effect for arousal (F(1.7,95.6)=65.9, *p*<.001) and a main effect for group (F(1,55)=12.1, *p*=.001). Post hoc t-tests showed that patients always rated words more arousing than controls (t(55)=2.5, *p*=.016 for positive arousal), (t(25.9)=3.2, *p*=.004 for neutral words) and (t(45.7)=2.9, *p*=.005 for negative words).

3.2.1.3. Acutely ill patients versus remitted patients

The 3x2 repeated measures ANOVA for valence revealed a main effect of valence (F(2,32)=406.1, p=<.001). No other effects were significant. Patients did not change their ratings over the course of the disorder.

The 3x2 repeated measures ANOVA for arousal revealed a main effect of arousal (F(2,32)=45.7, *p*<.001). Patients did not change their arousal ratings over time.

3.2.2. Behavior

3.2.2.1. Acutely ill patients versus controls

3.2.2.1.1. Reaction time

A repeated measures 3x3x5 ANOVA was calculated for the factors load and valence, with the between factor disorder status, and detected a significant main effect for the factor load (F(1.8,164)=65.9, *p*<.001) and for the factor disorder status (F(4,82)=3.9, *p*=.005), as well as an interaction effect for valence*load (F(3.2,328)=4.9, *p*=.002). Reaction to 1-back words were fastest, followed by 2-back and reaction to 3-back words took the longest, and this was true for all groups.

To further analyse group differences, groups were analysed separately.

A 3x3x2 ANOVA for mildly depressed and control subjects revealed a significant main effect for load (F(2,102)=77.4, *p*<.001), a significant main effect for disorder status

(F(1,51)=7.7, *p*=.008), a significant interaction effect for load*valence (F(4,204)=5.3, *p*<.001), a marginally significant interaction effect for valence*disorder status (F(2,12)=2.8, *p*=.064) a significant interaction effect for load*disorder status (F(2,102)=3.5, *p*=.033) and a significant interaction for load*valence*disorder status (F(4,204)=3.1, *p*=.014). Post hoc t-test results can be seen in Figure 11 and Table 10.

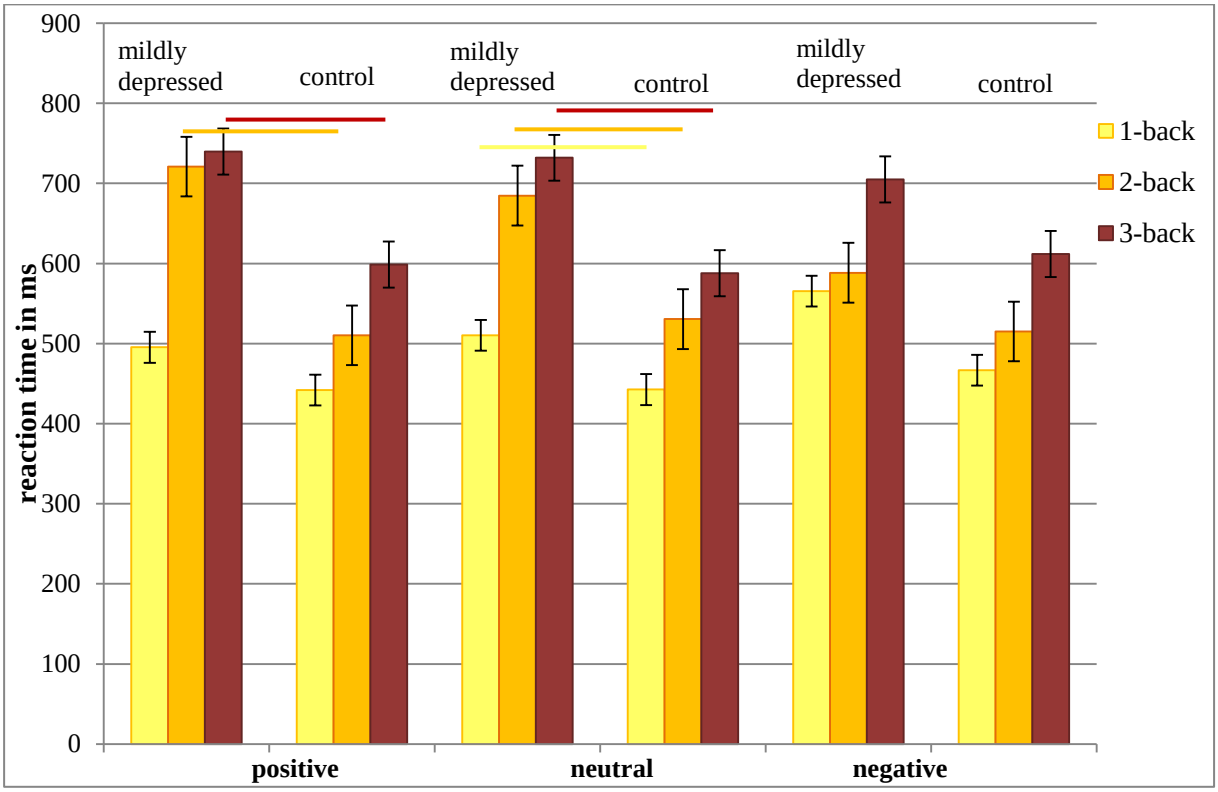

Figure 11. Reaction times for mildly depressed patients and controls. Lines above the bars indicate significant differences.

The 3x3x2 ANOVA for depressed patients and controls revealed a significant main effect for load (F(2,118)=57.4, *p*<.001) and a significant main effect for disorder status (F(1,59)=10.3, *p*=.002). Since there was no valence effect in this ANOVA, different loads were averaged over all valences and only loads were compared in the post hoc t-tests. Results for this can be seen in Figure 12 and

Table 10. Depressed patients were always slower than the controls, no matter of the valence.

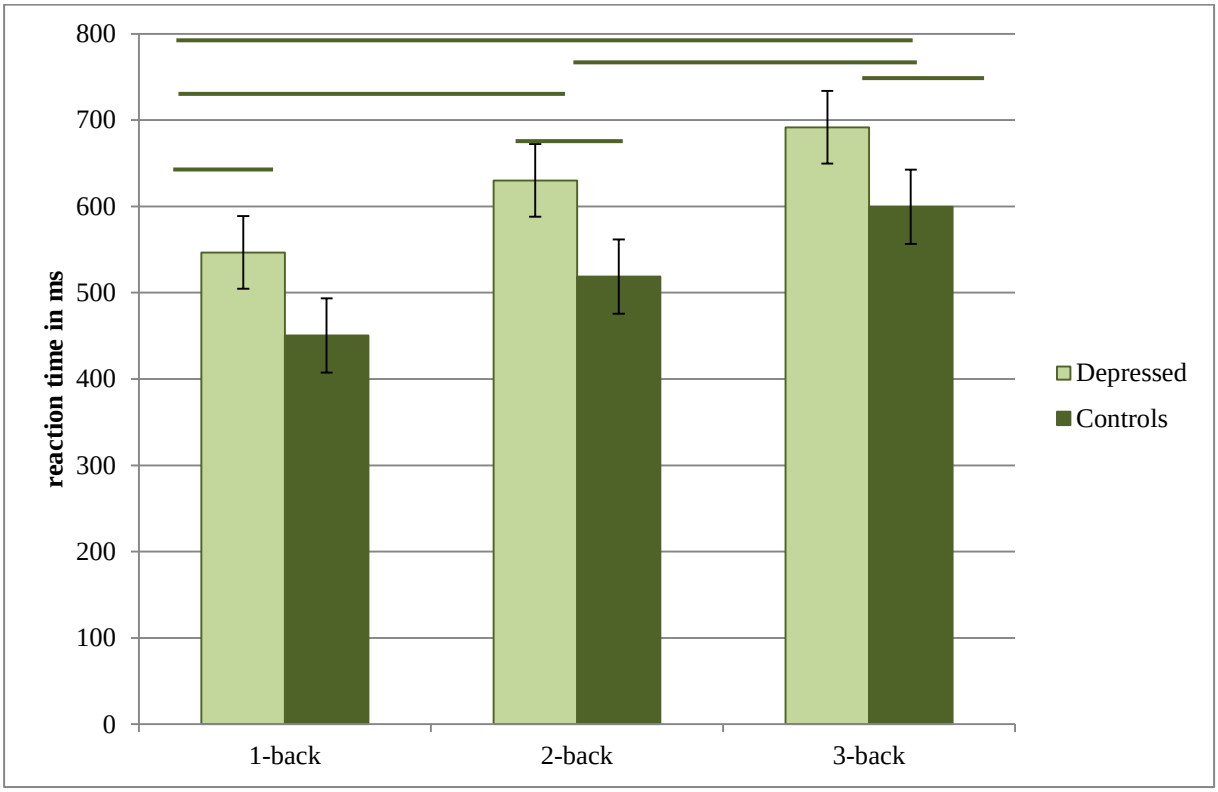

Figure 12. Reaction time differences for depressed and control groups for the load conditions only.
Lines above the bars indicate significant differences.

The 3x3x2 ANOVA for manic patients and controls revealed a significant main effect for load ($F(2,92)=29.4$, $p<.001$). No other effects were significant.

The 3x3x2 ANOVA for mixed patients and controls revealed a significant main effect for load ($F(2,92)=36.8$, $p<.001$), a marginally significant main effect for valence ($F(2,92)=2.5$, $p=.084$), and a marginally significant interaction effect for valence*disorder status($F(2,92)=2.8$, $p=.068$). Since there was no load effect in this ANOVA, different valences were averaged over all loads and only valences were compared in the post hoc t-tests. However, no post hoc t-tests were significantly different between mixed patients and controls.

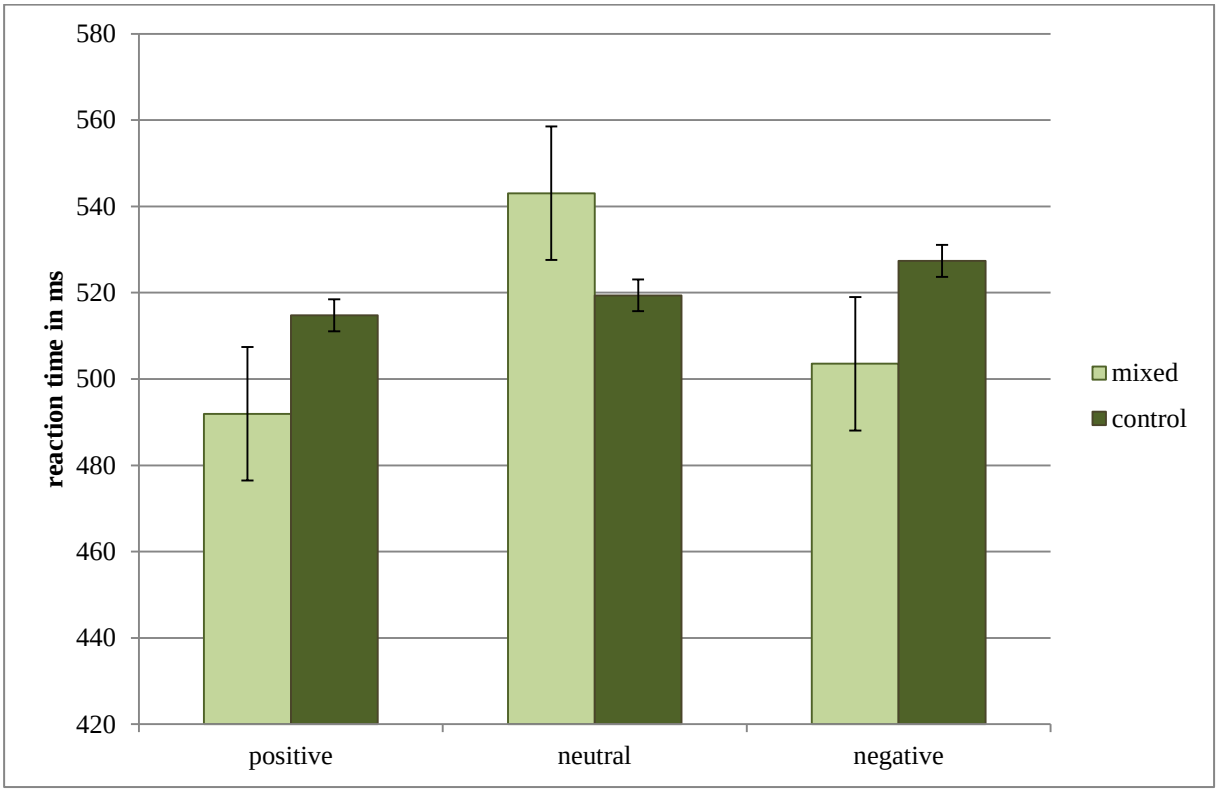

Figure 13. Reaction times for mixed patients and controls in the valence condition. No post hoc t-tests were significant.

Table 10. Post hoc t-tests for REACTION TIME differences between groups. Significant differences are indicated in bold.

Reaction time	t	df	p value
mildly depressed versus controls			
positive			
1-back	1.59	51	0.119
2-back	2.99	13.94	**0.01**
3-back	2.09	13.74	**0.056**
neutral			
1-back	1.73	51	**0.089**
2-back	2.92	51	**0.005**
3-back	2.85	51	**0.006**
negative			
1-back	1.72	13.01	0.109
2-back	1.38	51	0.175
3-back	1.63	51	0.11
depressed versus controls			
1-back	3.24	59	**0.002**
2-back	2.94	59	**0.005**
3-back	2.51	59	**0.015**

3.2.2.1.2. Omission Errors

Since errors tend to be not normally distributed, a Kolmogorov-Smirnoff test for normal distribution was applied, but turned out non-significant, all errors made lay within a normal distribution. Afterwards, a 3x3x5 repeated measures ANOVA was calculated for factors load and valence and between factor disorder status. The main effect for load ($F(1.4, 164)=44.5$ $p<.001$), the main effect disorder status ($F(4,82)=2.9$, $p=.024$) and the interaction effects load*valence ($F(3.1,328)=3.6$, $p=.012$) and load*subgroup ($F(8,164)=2.2$, $p=.027$) turned out significant. The interaction effect valence*subgroup was marginally significant ($F(8,164)=1.9$, $p=.058$). Patients made more errors than did controls, the number of errors depending on their respective subgroup and the valence of the word. The amount of errors in a load condition was influenced by the valence of the presented words.

To further analyse group differences, groups were analysed separately.

A 3x3x2 ANOVA for the mildly depressed group and controls returned a significant main effect for load ($F(1.7,88.4)=22.4$, $p<.001$), a significant main effect for valence ($F(2,102)=4.5$, $p=.013$), and a significant interaction effect for load*valence ($F(3,154.9)=2.9$, $p=.037$). The main effect for disorder status was marginally significant ($F(1,51)=2.8$, $p=.097$). Patients made marginally more errors than controls. Since there were no significant interaction effect for disorder status and load or valence, both load and valence conditions were averaged and then compared between groups with independent t-tests, for results please see Figure 14 and Table 12. Patients did not differ from controls in the load condition in the post hoc t-tests. In the valence condition, patients made more errors when seeing neutral words.

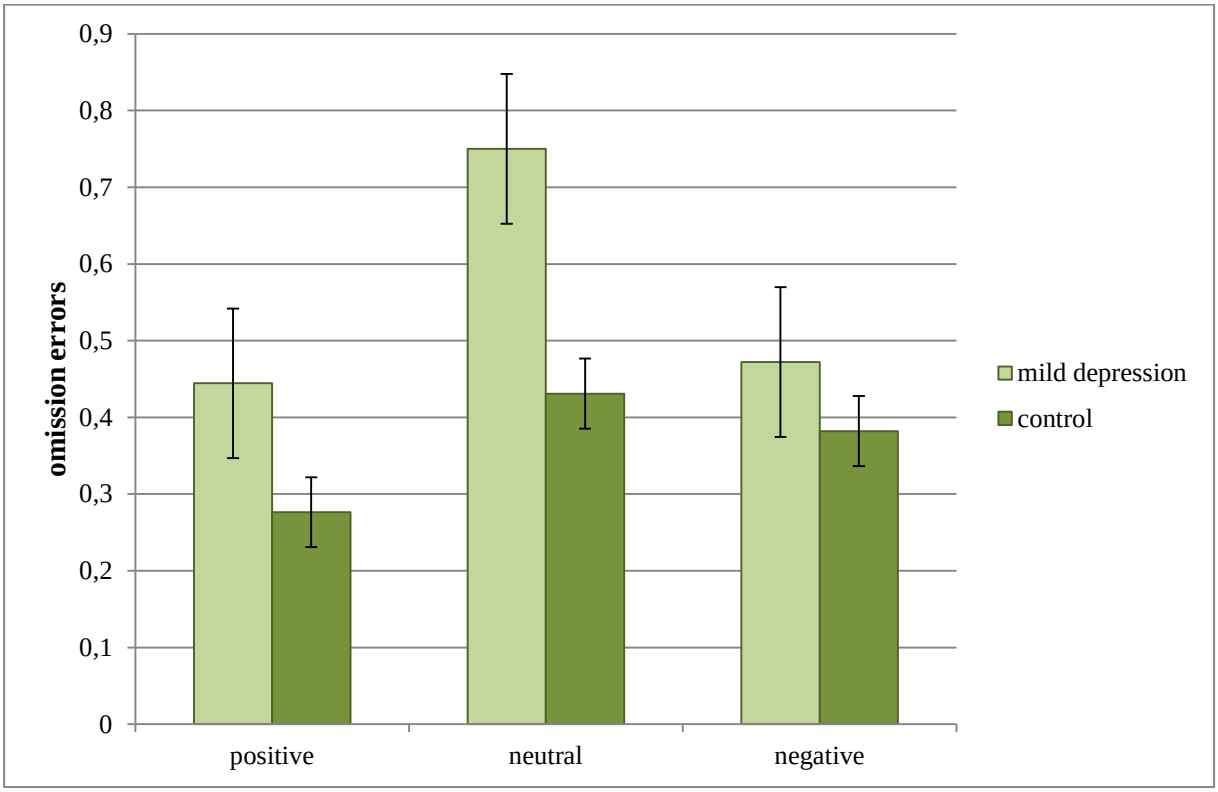

Figure 14. Omission errors for mildly depressed patients and controls for the valence condition. Only the neutral valence produced significant differences.

A 3x3x2 ANOVA for the depressed group and controls revealed a significant main effect for load ($F(1.5,88.9)=27.4$, $p<.001$), a significant main effect for disorder status, a significant interaction effect for load*disorder status ($F(1.5,88.9)=4.7$, $p=.02$), and a significant interaction effect for load*valence ($F(3.2,182.4)=3.6$, $p=.013$). Since no significant effects arose for valence, valences were averaged and only load conditions were compared in the t-tests, for results please see Figure 15 and Table 12. Depressed patients made more errors than controls, and this effect became stronger with increasing working memory load.

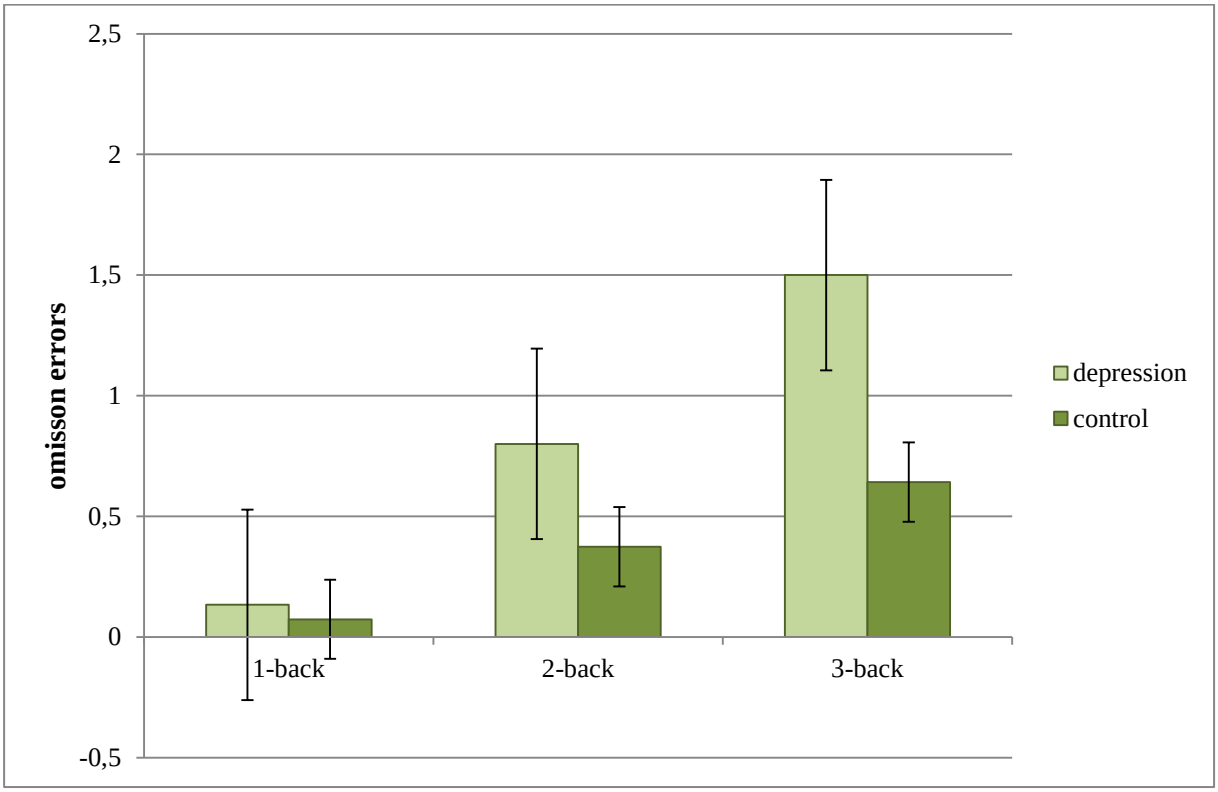

Figure 15. Omission errors for depressed patients and controls in the load conditions. Differences in 2-back and 3-back task were significant.

A 3x3x2 ANOVA for the manic patients and controls revealed significant differences for the main effect load ($F(1.7,80.5)=36$, $p<.001$), a significant main effect disorder status ($F(1,46)=10.7$, $p=.002$), a significant interaction effect for load*disorder status ($F(1.7,80.5)=10.6$, $p<.001$), and a significant interaction effect valence*disorder status ($F(2,92)=6.1$, $p=.003$). Results for independent post hoc t-tests can be seen in Figure 16 and Table 11. Patients made more errors than controls only in the positive and negative valence conditions with increasing working memory load.

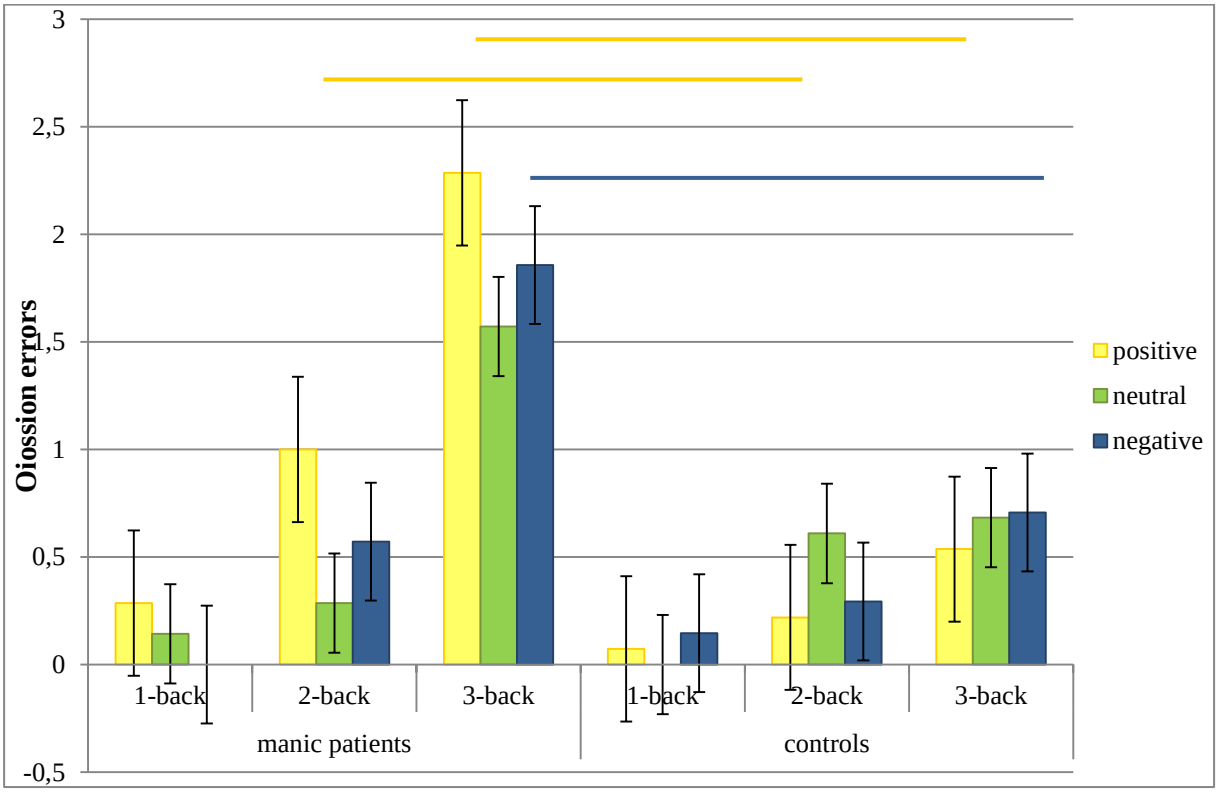

Figure 16. Omission errors for manic patients and controls. Significant changes are indicated by lines above the bars.

Table 11. Post hoc t-tests for manic patients versus controls for OMISSION ERRORS. Significant results are highlighted in bold.

Omission errors	t	df	p value
Mania versus controls			
positive			
1-back	0.731	6.435	0.491
2-back	3.137	46	**0.003**
3-back	2.83	6.49	**0.028**
neutral			
1-back	1	6	0.356
2-back	-1.372	15.219	0.19
3-back	1.331	6.69	0.227
negative			
1-back	-2.619	40	**0.012**
2-back	0.635	6.589	0.547
3-back	2.715	46	**0.009**

The 3x3x2 ANOVA for mixed patients and controls revealed a significant main effect for load ($F(1.7,79.9)=21.3$, $p<.001$), a significant main effect for disorder status ($F(1,46)=7.7$, $p=.008$), a significant interaction effect for load*valence ($F(2.8,130.8)=3.8$, $p=.012$), and a significant interaction effect for load*disorder status

(F(1.7,79.9)=3.6, *p*=.037). With increasing load, mixed patients made more errors compared to the control group. Since no significant effects arose for valence, valences were averaged and only load conditions were compared in the t-tests, for results please see Figure 17 and Table 12. However, no post-hoc t-tests were significant.

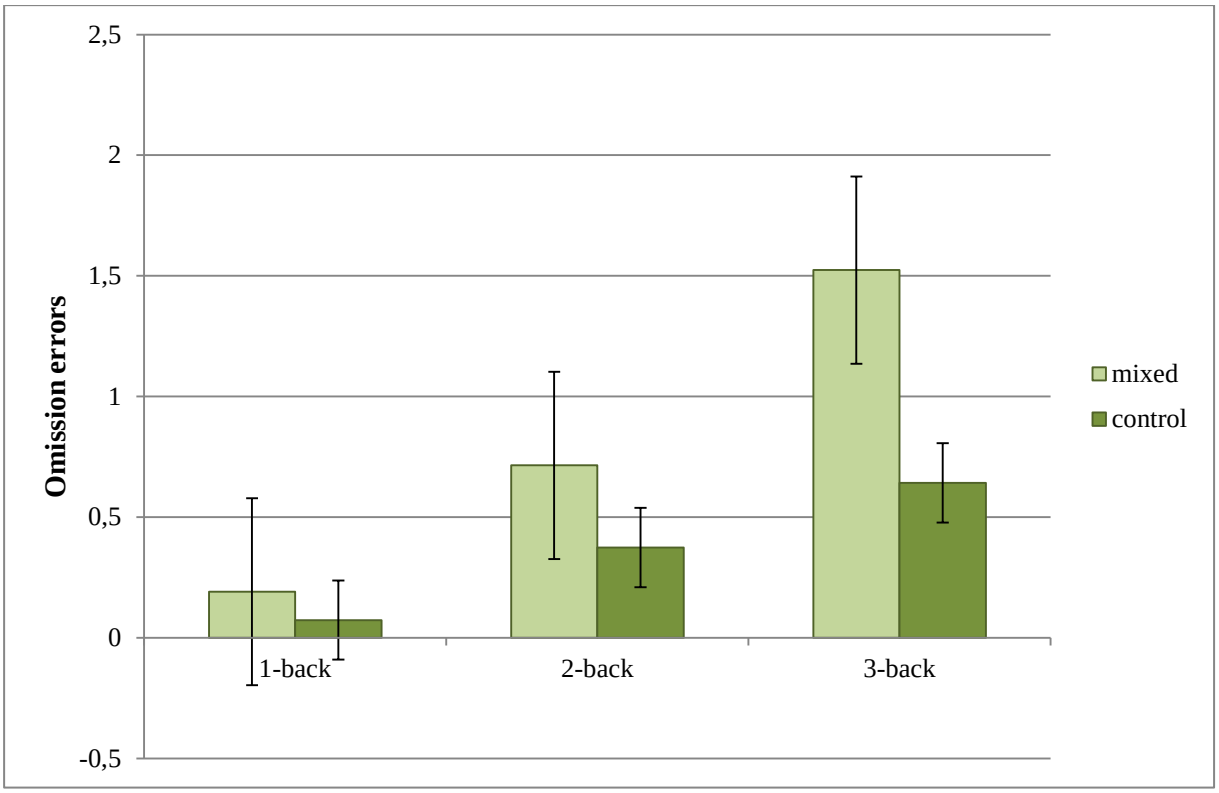

Figure 17. Omission errors for mixed patients and controls.
No post hoc t-tests were significant.

Table 12. Post hoc tests for OMISSION ERRORS for the factors load and valence for each patient group versus the control group.
Significant results are highlighted in bold. Marginally significant results are written in italics.

***Group* vs. Controls**	**t**	**df**	***p* value**
Load			
1-back			
mild depression	.19	51	.844
depression	.70	22.555	.488
mixed	1.15	6.766	.290
2-back			
mild depression	.83	51	.409
depression	2.09	59	**.040**
mixed	1.48	46	.146
3-back			
mild depression	1.35	13.56	.198
depression	2.06	21.22	*.052*
mixed	1.54	6.36	.171
Valence			
positive			
mild depression	1.22	51	.227
neutral			
mild depression	2.02	51	**.049**
negative			
mild depression	.64	51	.524

3.2.2.2. Remitted patients versus controls

3.2.2.2.1. Reaction time

A repeated measures 3x3x5 ANOVA was calculated for the factors load and valence, with the between factor disorder status, and detected a significant main effect for the factor load ($F(2,114)=70.7$, $p<.001$). No other main effects or interaction effects returned significant. For visualisation of the results, please see Figure 18 and Figure 19. Patients as well as controls reacted fastest to 1-back tasks, were slower on 2-back tasks and the slowest on 3-back tasks, irrespective of their emotional valence.

3.2.2.2.2. Omission Errors

A repeated measures 3x3x5 ANOVA was calculated for the factors load and valence, with the between factor disorder status, and detected a significant main effect for the factor load ($F(2,114)=19.6$, $p<.001$). No other main effects or interaction effects returned significant. Results are visualised in Figure 20 and Figure 21. Patients as well as controls made the least

errors in 1-back tasks, more so on 2-back tasks and the most on 3-back tasks, irrespective of their emotional valence.

3.2.2.3. Acutely ill patients versus remitted patients

3.2.2.3.1. Reaction time

A repeated measures 3x3x5 ANOVA was calculated for the factors load and valence, with the between factor disorder status, and detected a significant main effect for the factor load ($F(2,34)=20$, $p<.001$). No other main effects or interaction effects returned significant. For results, please also see Figure 18 and Figure 19. Acute patients did not differ in their performance when they returned to a remitted state.

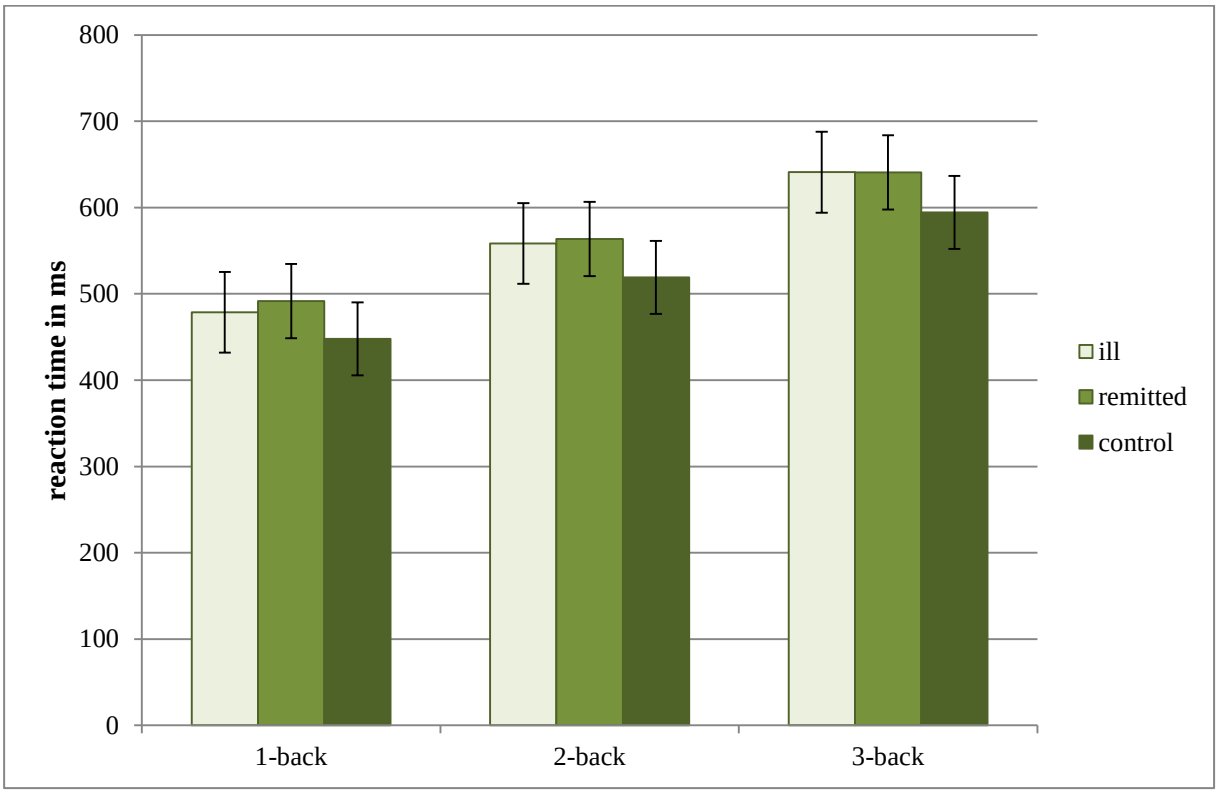

Figure 18. Reaction times for ill patients, the same patients remitted and controls for the load condition.

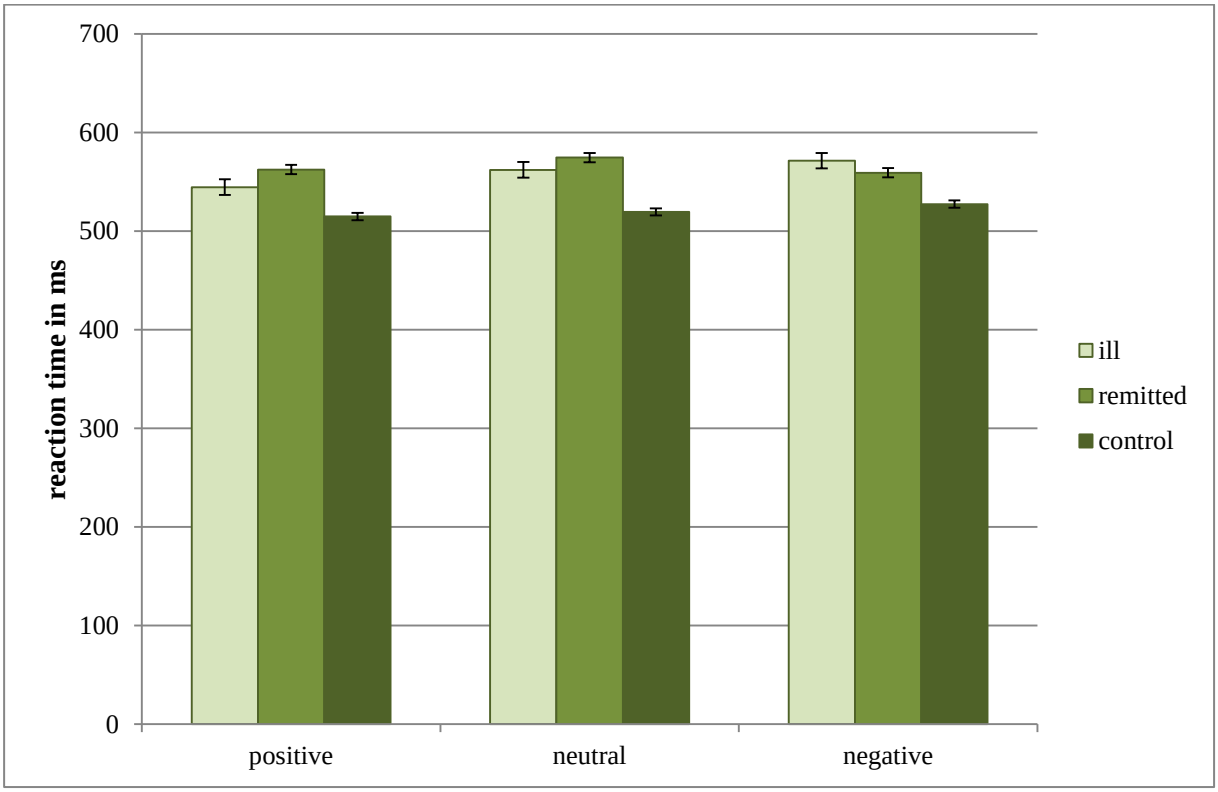

Figure 19. Reaction times for ill patients, the same patients remitted and controls for the valence condition.

3.2.2.3.2. Omission Errors

A repeated measures 3x3x5 ANOVA was calculated for the factors load and valence, with the between factor disorder status, and detected a significant main effect for the factor load ($F(2,34)=18.6$, $p<.001$). No other main effects or interaction effects returned significant. Results are visualised in Figure 20 and Figure 21. Acute patients did not differ in their performance when they returned to a remitted state.

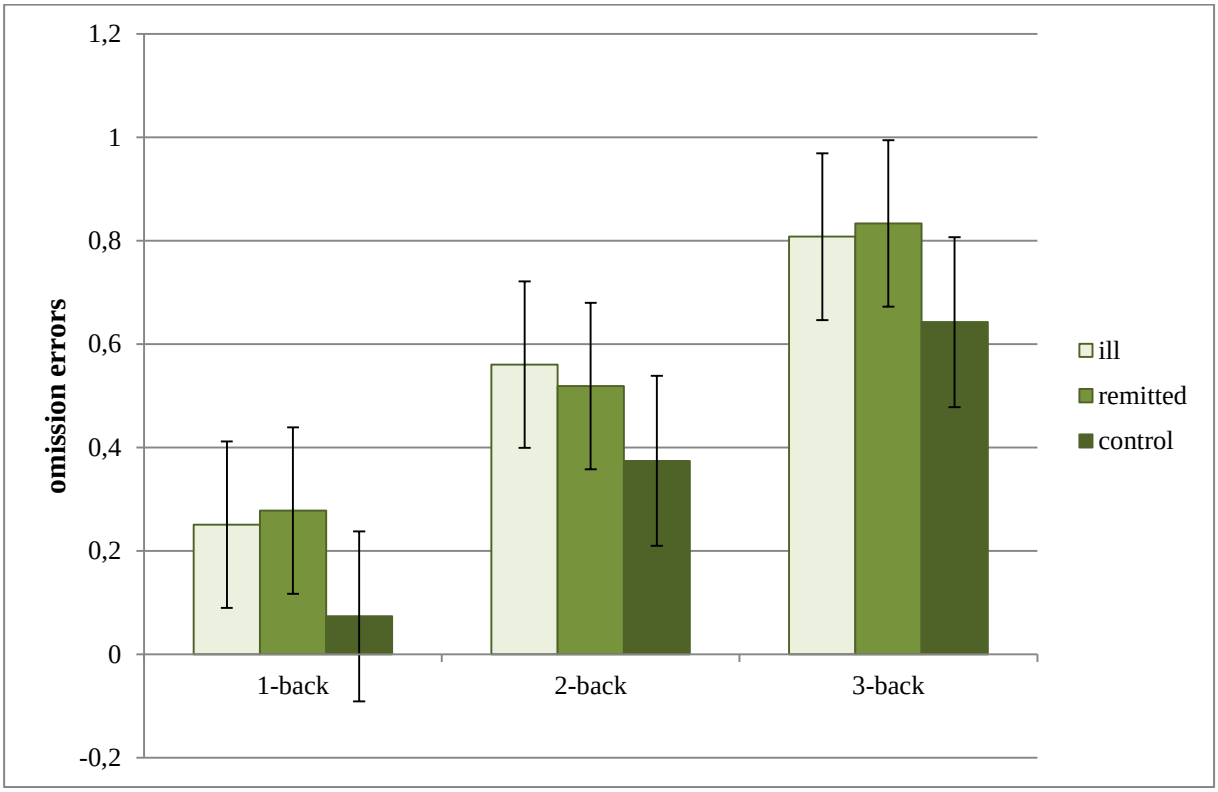

Figure 20. Omission errors for the load condition, comparing ill patients which came back in their remitted state and controls.

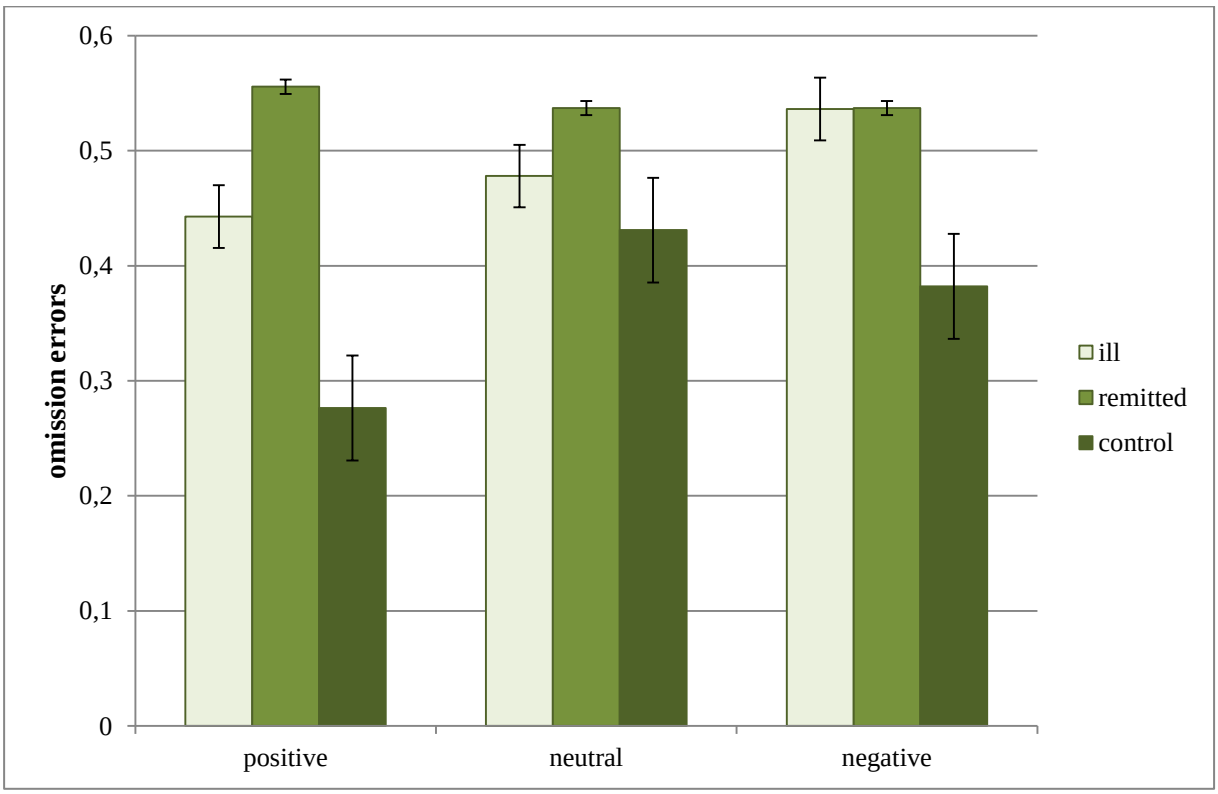

Figure 21. Omission errors for the valence conditions for ill, remitted and control patients.

3.2.2.4. Summary of behavioral results

The statistical analyses of the behavior produced a solid effect of load, i.e. with increasing working memory load. Reaction times and errors increased as well, and this was true for acutely ill patients as well as remitted patients and controls.

Reaction time differences between groups were mainly carried by mildly depressed patients, who were slower than controls in the neutral valence for all load conditions, in the positive load condition only in the 2-back and 3-back tasks, and did not differ at all from controls in the negative condition, no matter how high the working memory load.

Depressed patients were always slower than controls in all three working memory loads, no matter the valence of the word.

Manic patients did not differ at all from controls in their reaction times.

Mixed patients differed from controls in the valence, the took less time than controls to react to positive and negative words, but took longer to react to neutral words.

All patients made more errors than controls. Manic patients produced more errors than controls in respect to the valence of the word, they made the most errors in the negative valence condition, and also significantly more errors in the positive valence condition. All other patients did not differ from controls in respect to valence conditions.

When patients returned to their healthy remitted state, they did not perform differently. However, no differences could be detected when remitted patients were compared to healthy controls, either.

3.2.3. fNIRS

3.2.3.1. Oxygenated Hemoglobin[1]

3.2.3.1.1. Acutely ill patients versus controls

A 3x3x5 repeated measures ANOVA for the dlPFC with between factors valence and load and within factor disorder status revealed significant main effect for load ($F(2,166)=3.9$, $p=.021$), a marginally significant main effect for subgroup

[1] Recent research has shown that oxygenated hemoglobin measures can be artefact prone (Kirilina et al., 2012), an observation that is not made in deoxygenated hemoglobin concentration measures. Deoxygenated hemoglobin concentration was analyzed for this study but did not show any differential activation patterns. Since it is still more common to report oxygenated blood flow changes, it was decided to not discuss deoxygenated blood flow changes further in order to keep the results as readable as possible.

(F(4,83)=2.3, *p*=.072), and a marginally significant main effect for the interaction effect valence*load (F(4,332)=2.1, *p*=.082). No other effects were significant.

The same ANOVA for the vlPFC produced a significant main effect for load (F(2,166)=8.9, *p*<.001) and a significant interaction effect for valence*load (F4,332)=3.03, *p*=.021). No other effects were significant.

Since there were no group differences in the vlPFC, this region was not further analysed.

The 3x3x2 ANOVA for the mildly depressed patients and controls revealed only a significant main effect of disorder status (F(1,46)=7.6, *p*=.008), for results please see Figure 22. No other effects were significant. Mildly depressed patients always activated the dlPFC significantly less than controls.

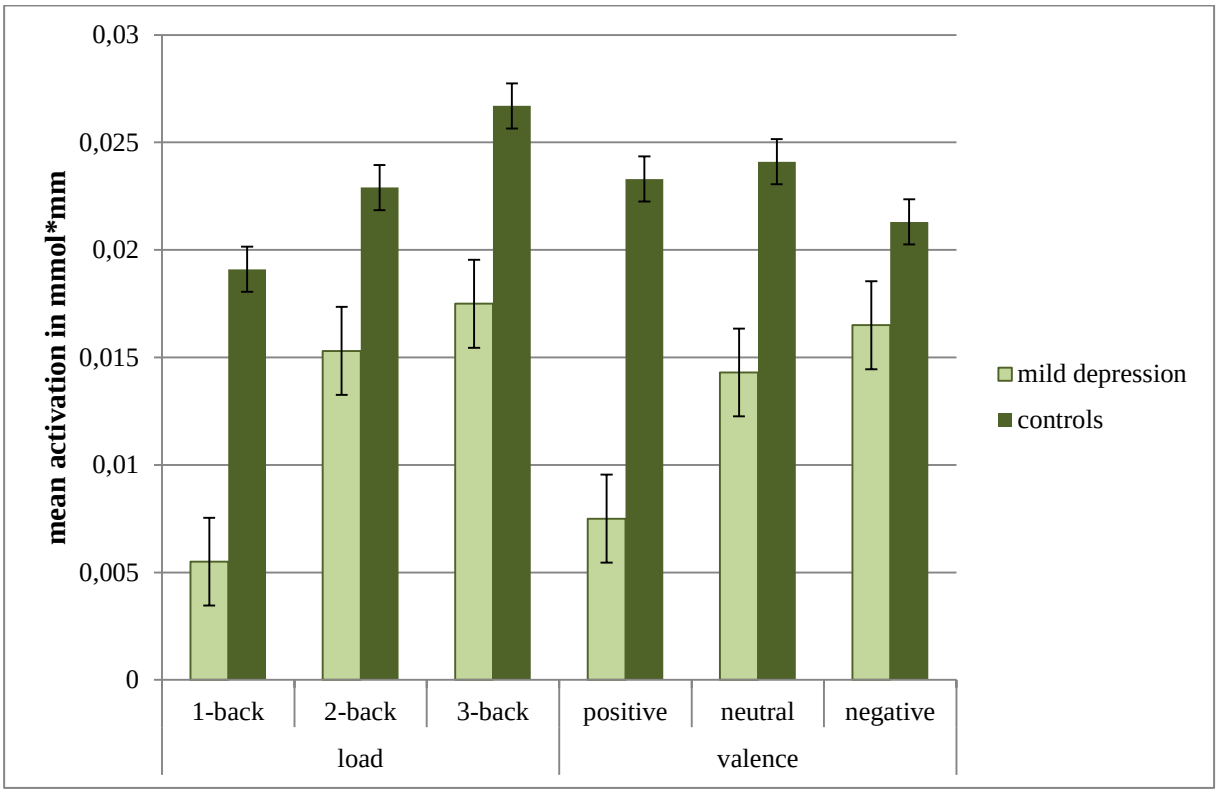

Figure 22. Mean activation for load and valence conditions for mildly depressed patients and controls.

The 3x3x2 ANOVA for depressed patients and controls revealed only a significant main effect for disorder status (F(1,51)=6,1, *p*=.017). Depressed patients activated the dlPFC less than controls. However, as can be seen in Figure 23, activation differences between groups are not carried by 3-back and negative valence.

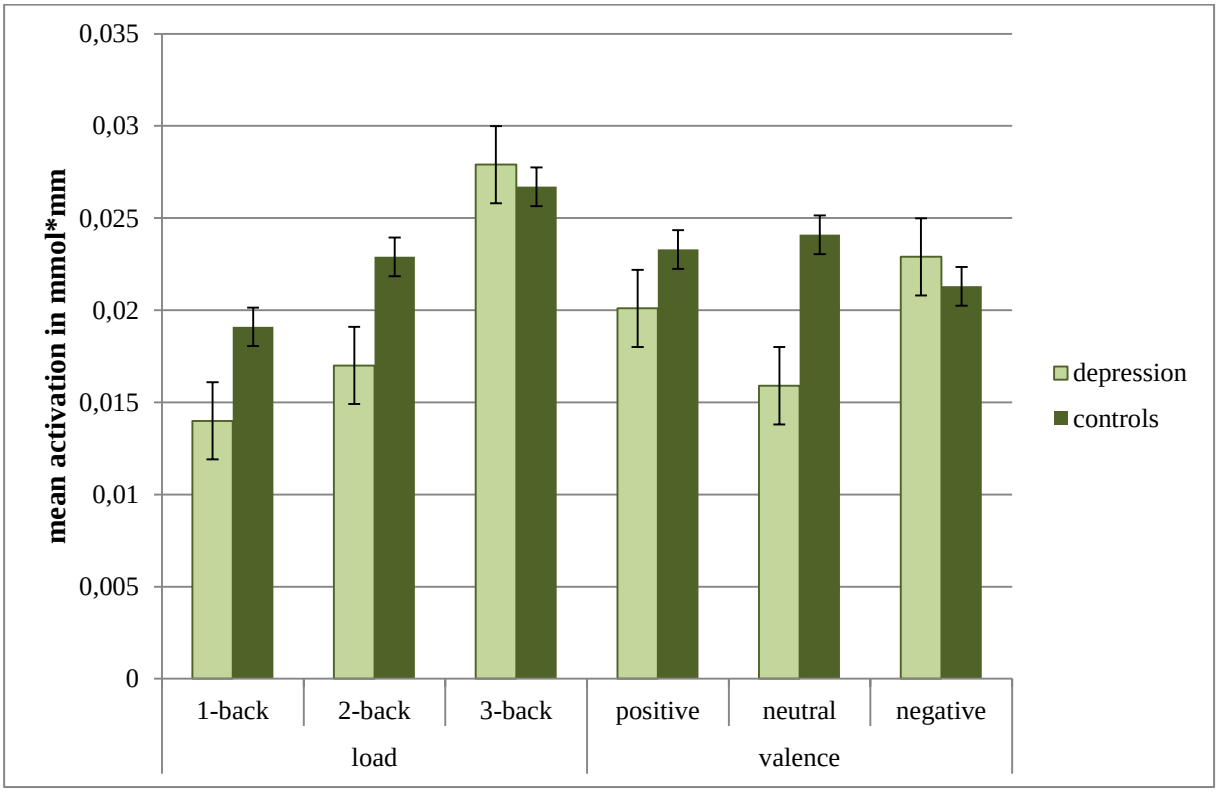

Figure 23. Mean activation for depressed patients and controls for load and valence conditions.

The 3x3x2 ANOVA for manic patients and controls revealed a marginally significant main effect for load ($F(1.8,106)=2.9$, $p=.065$). No other effects were significant. Manic patients do not differ from controls in their activation patterns. Numeric results indicate that manic patients might differ in their activation from controls, please see Figure 24.

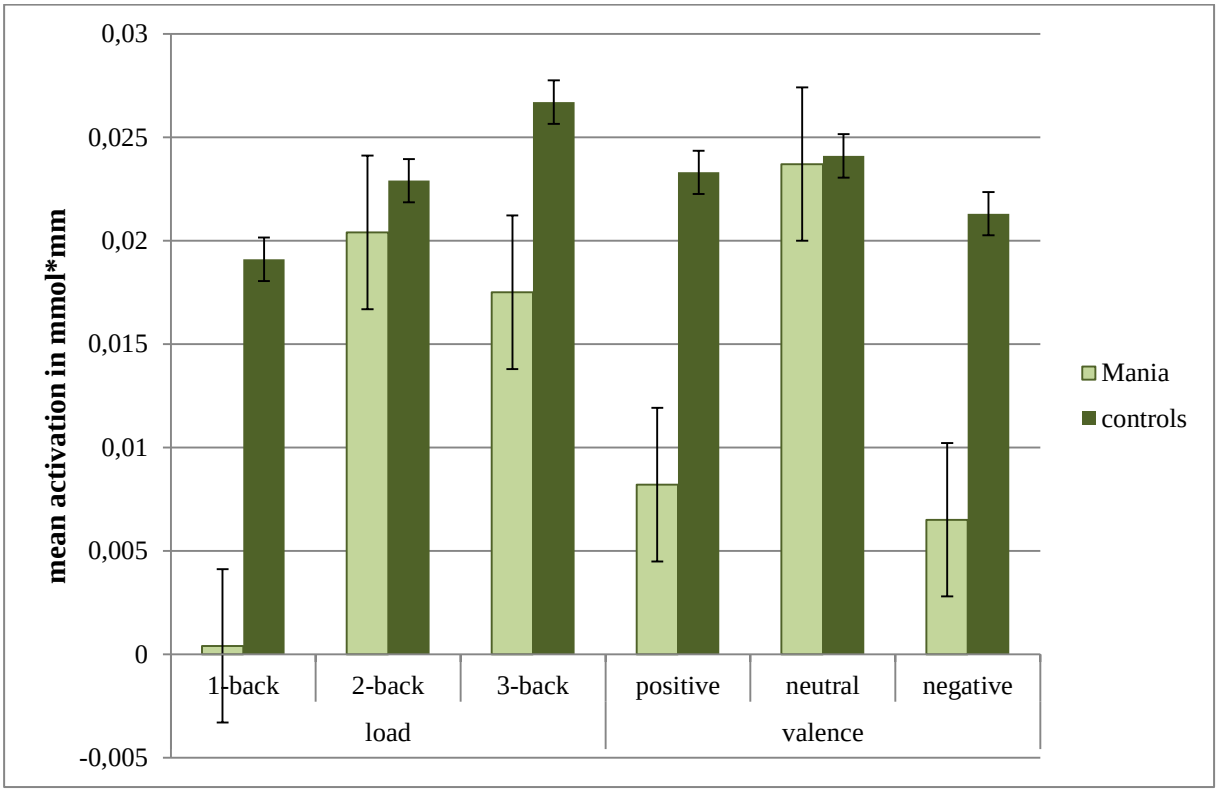

Figure 24. Mean activation for manic patients and controls for load and valence conditions.

A 3x3x2 ANOVA for mixed patients and controls found a significant interaction effect for load*valence (F(4,184)=4.2, *p*=.003) and a significant interaction effect for load*valence*disorder status (F(4,184)=3.2, *p*=.014). Significant post hoc t-test results can be seen in Table 13 and Figure 25 and Figure 26.

Table 13. Post hoc t-tests for dlPFC activation for mixed patients and controls. Significant results are highlighted in bold.

mixed patients vs. Controls	t	df	p value
positive			
1-back	-0.206	46	0.837
2-back	-2.123	46	**0.039**
3-back	-1.135	46	0.262
neutral			
1-back	-2.024	46	**0.049**
2-back	0.721	46	0.475
3-back	0.963	46	0.341
negative			
1-back	-1.326	6.845	0.227
2-back	0.747	46	0.459
3-back	-2.307	46	**0.026**

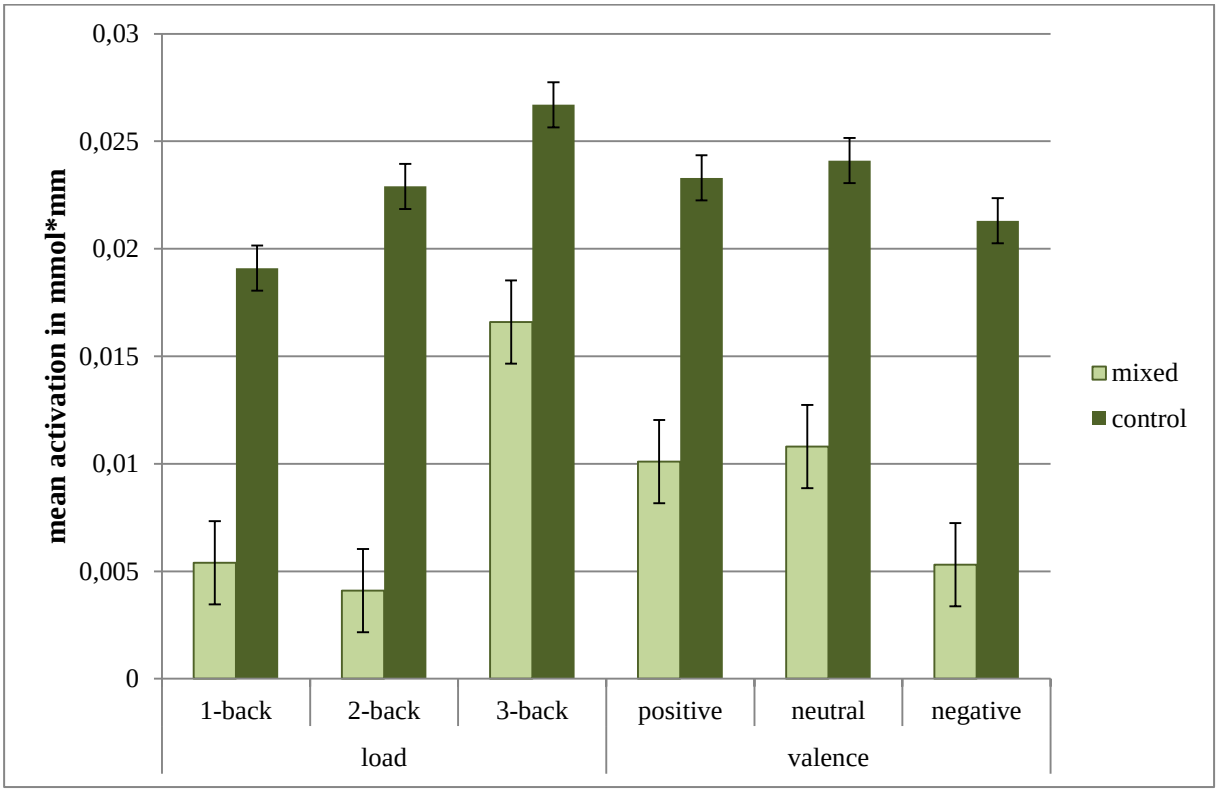

Figure 25. Mean activation for mixed patients and controls in valence and load conditions.

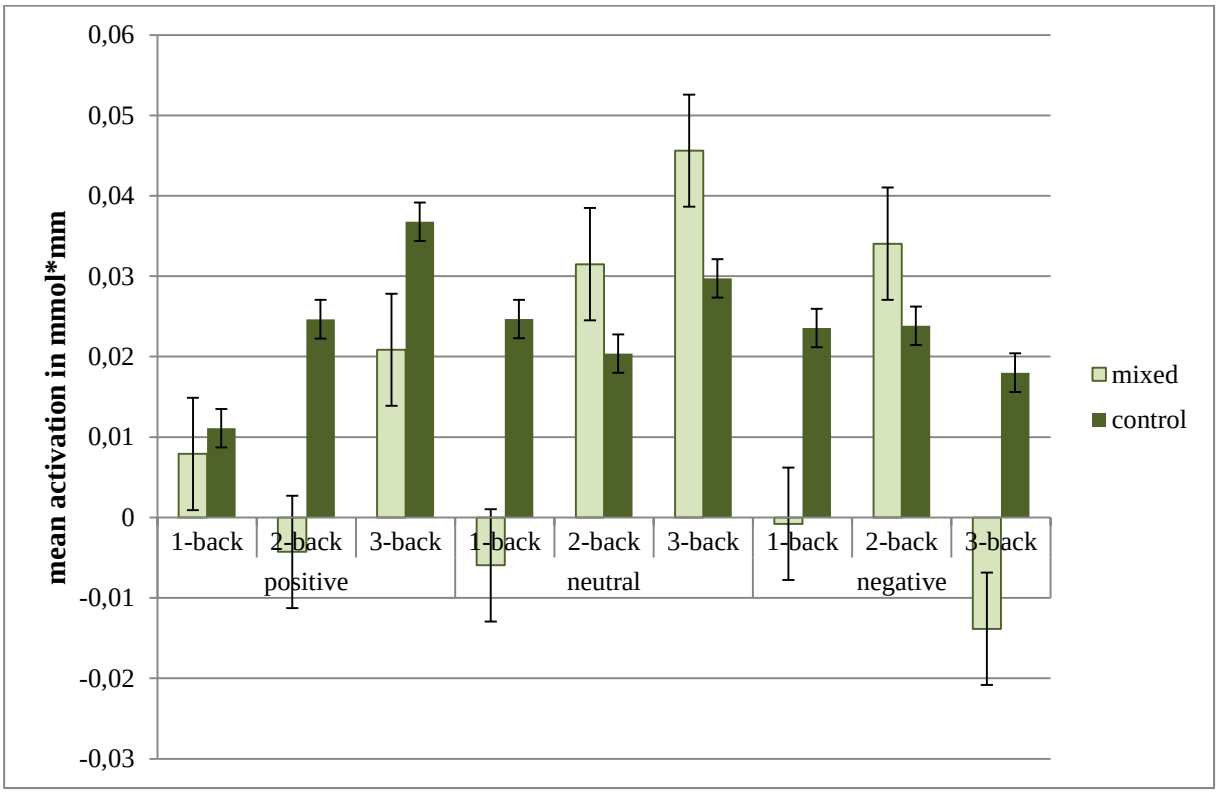

Figure 26. Mean activation for mixed patients and controls, load and valence interactions are displayed.

Since the interaction effect of valence*load was also significant in dlPFC as well as vlPFC analyses, all test subject were analysed together in an ANOVA with the within factors valence and load and no between factor. This seemed also plausible in light of the fact that differences between groups were rather small. For the dlPFC, results returned a significant main effect for load ($F(2,174)=4.7$, $p=.01$) and a significant interaction effect for valence*load ($F(4,348)=2.5$, $p=.041$). Positive and neutral words did not influence the increase of activation produced by the increase in working memory load, negative words, however, actually produced a decrease of activation when working memory load increased.

For the vlPFC, the ANOVA returned only a significant main effect for the factor load ($F(2,174)=9.6$, $p<.001$).

3.2.3.1.2. Remitted patients versus controls

For the dlPFC, a 3x3x5 ANOVA with within factors load and valence and between factor disorder status revealed so significant results at all.

For the vlPFC, that same ANOVA returned a significant main effect for load ($F(1.7,112)=3.9$, $p=.029$) and an interaction effect for valence*disorder status ($F(2,56)=4.7$, $p=.01$). This seems to be driven by the activation of patients to neutral stimuli, whenever they had to react to neutral words, their activation patterns decreased significantly when compared to controls.

3.2.3.1.3. Acutely ill patients versus remitted patients

For the dlPFC a 3x3x2 repeated measures ANOVA for within factors load, valence and disorder status was calculated and returned a significant main effect for the factor load ($F(2,32)=3.3$, $p=.048$). No other effects were significant.

For the vlPFC, the same ANOVA returned a significant main effect for the factor load ($F(2,32)=11.8$, $p<.001$).

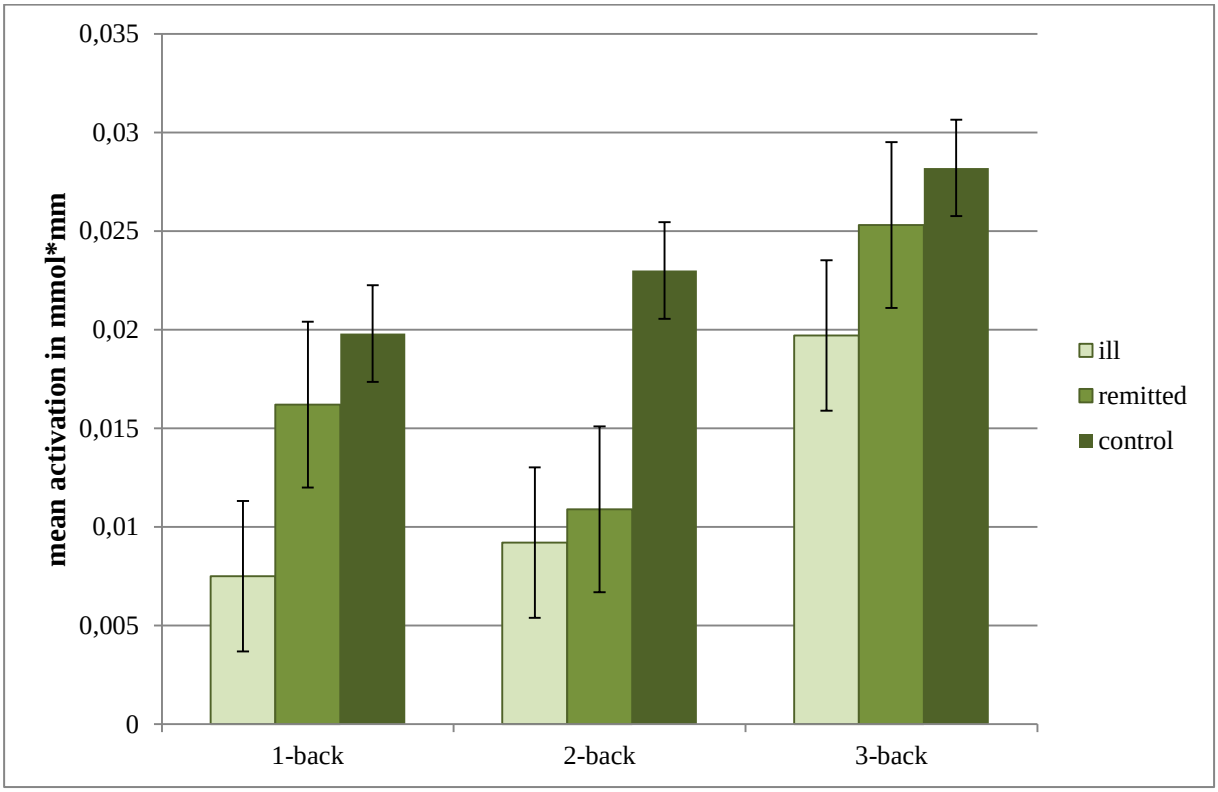

Figure 27. Mean activation for ill and remitted patients and controls for the load condition.

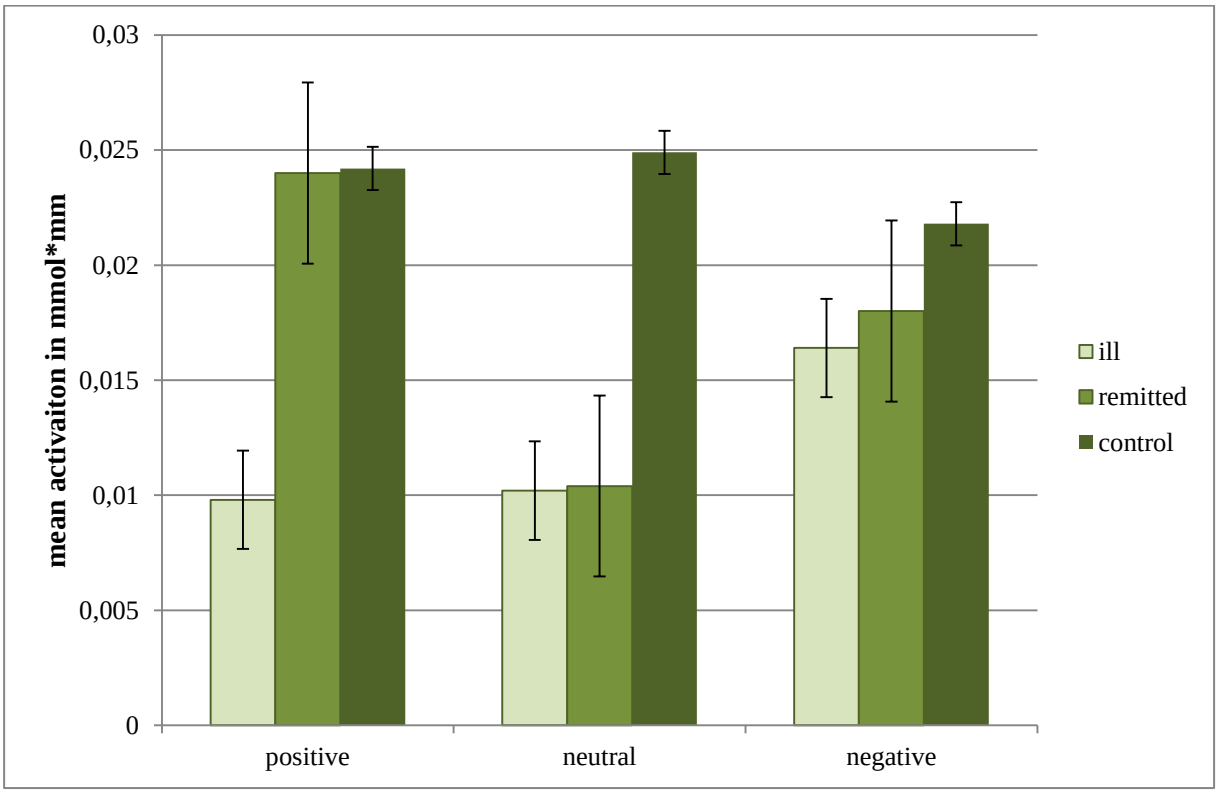

Figure 28. Mean activation for ill and remitted patients and controls for the valence condition.

3.2.3.2. Summary of fNIRS results

The PFC was activated according to each load condition increasingly, and different emotional valences modulated this activation: positive and neutral words did not influence the increase of activation according to the increase in working memory load, however, negative words actually seemed to produce a decrease in activation when working memory load increased. Activation differences between patients and controls were found mainly in mildly depressed patients, who activated the dlPFC less than controls, irrespective of the valence and load conditions. The depressed patients show a less pronounced difference in activation patterns. Manic patients show less activation to 1-back and 3-back working memory loads, and to positive and negative words. Mixed patients seem to always show less activation in the dlPFC than controls, however, activation patterns here are unclear.

When remitted patients are compared to controls, differences in activation mainly disappeared, however, in the neutral valence condition, patients seem to activate less than controls. Differences between ill patients and the same patients in a remitted state could not be detected either.

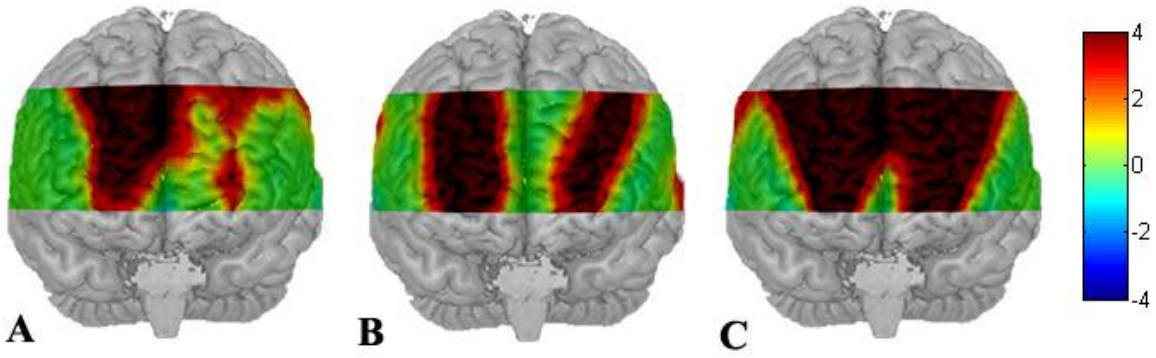

Figure 29. Manipulation check for the working memory condition.
A depicts the 1-back, B the 2-back and C the 3-back activation. Depicted are significant changes in the t-values, all results are corrected for multiple testing with the DAP correction.

3.2.4. EEG

3.2.4.1. Acutely ill patients versus controls

A 3x3x5 repeated measures ANOVA with between factors valence and load and within factor disorder status revealed significant main effect for load ($F(2, 152)=23.9$, $p<.001$), a significant main effect for valence ($F(2,152)=6.6$, $p=.002$),a significant interaction effect valence*load

(F(4,304)=4.9, *p*=.034), and a significant interaction effect valence*disorder status (F(8,152)=2.5, *p*=.012). No other effects were significant.

A 3x3x2 ANOVA was calculated for the mildly depressed patients and controls, with within factors valence and load, and returned a significant main effect for valence (F(2,82)=7.5, *p*=.001) a significant main effect for load (F(1.6,67.2)=14.6, *p*<.001), a marginally significant effect for disorder status (F(1,41)=2.9, *p*=.092), a significant interaction effect for load*valence (F(4,164)=2.9, *p*=.021), and a significant interaction effect for valence*disorder status (F(2,82)=3.8, *p*=.027). Post hoc t-tests for the valences averaged over all load conditions revealed a significant difference only for the negative valence, where mildly depressed patients had a higher LPP compared to controls.

The 3x3x2 ANOVA for depressed patients and controls revealed a significant main effect for load (F(1.6,78)=16.3, *p*<.001), a marginally significant main effect for valence (F(2,94)=2.8, *p*=.066), and a significant interaction effect for load*valence (F(4,188)=2.9, *p*=.023). No other effects were significant.

The 3x3x2 ANOVA for manic patients and controls revealed only a significant main effect for load (F(2,108)=12.5, *p*<.001). No other effects were significant.

The 3x3x2 ANOVA for mixed patients and controls revealed significant main effects for load (F(2,84)=5.4, *p*=.006) and valence (F(2,84)=3.2, *p*=.044).

Graphics of the LPP for all valences for all acutely ill patients and controls can be seen in Figure 30, Figure 31 and Figure 32.

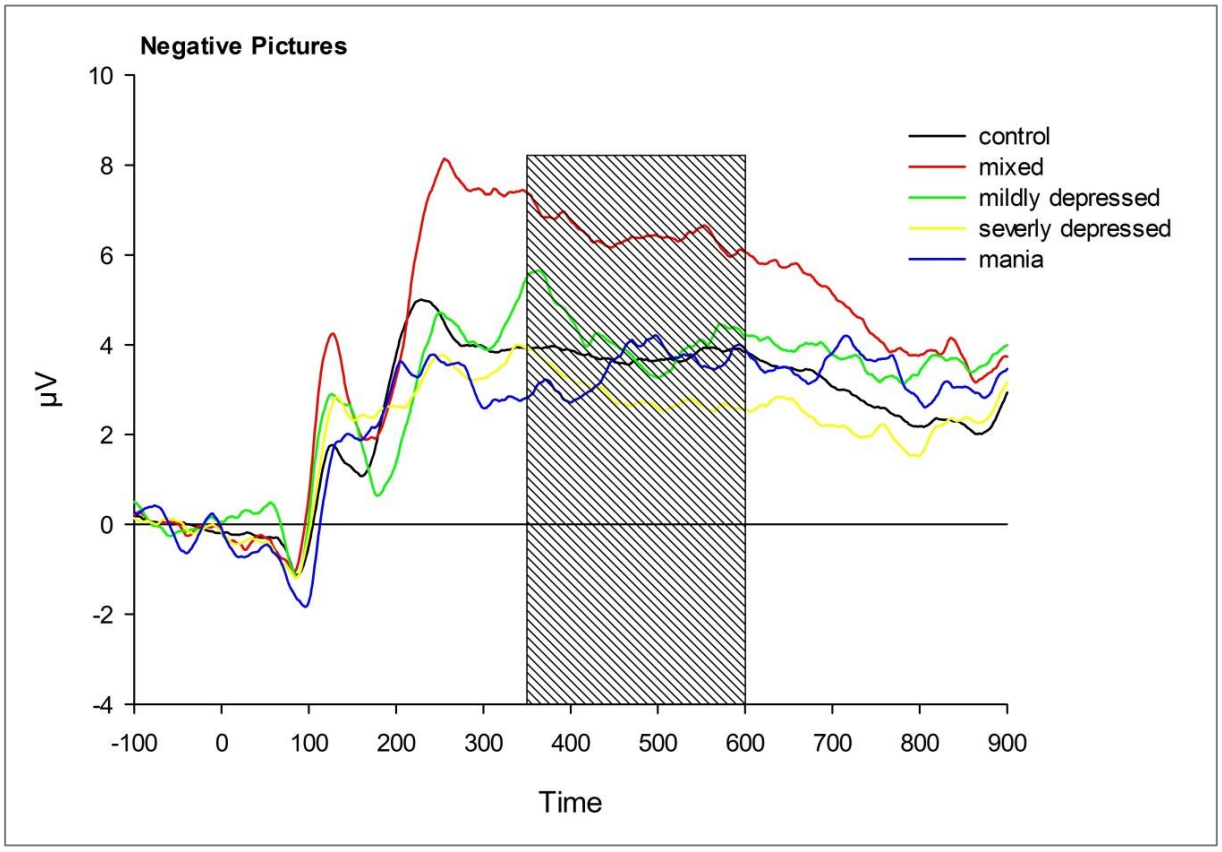

Figure 30. LPP for negative pictures for acutely ill patients and controls.

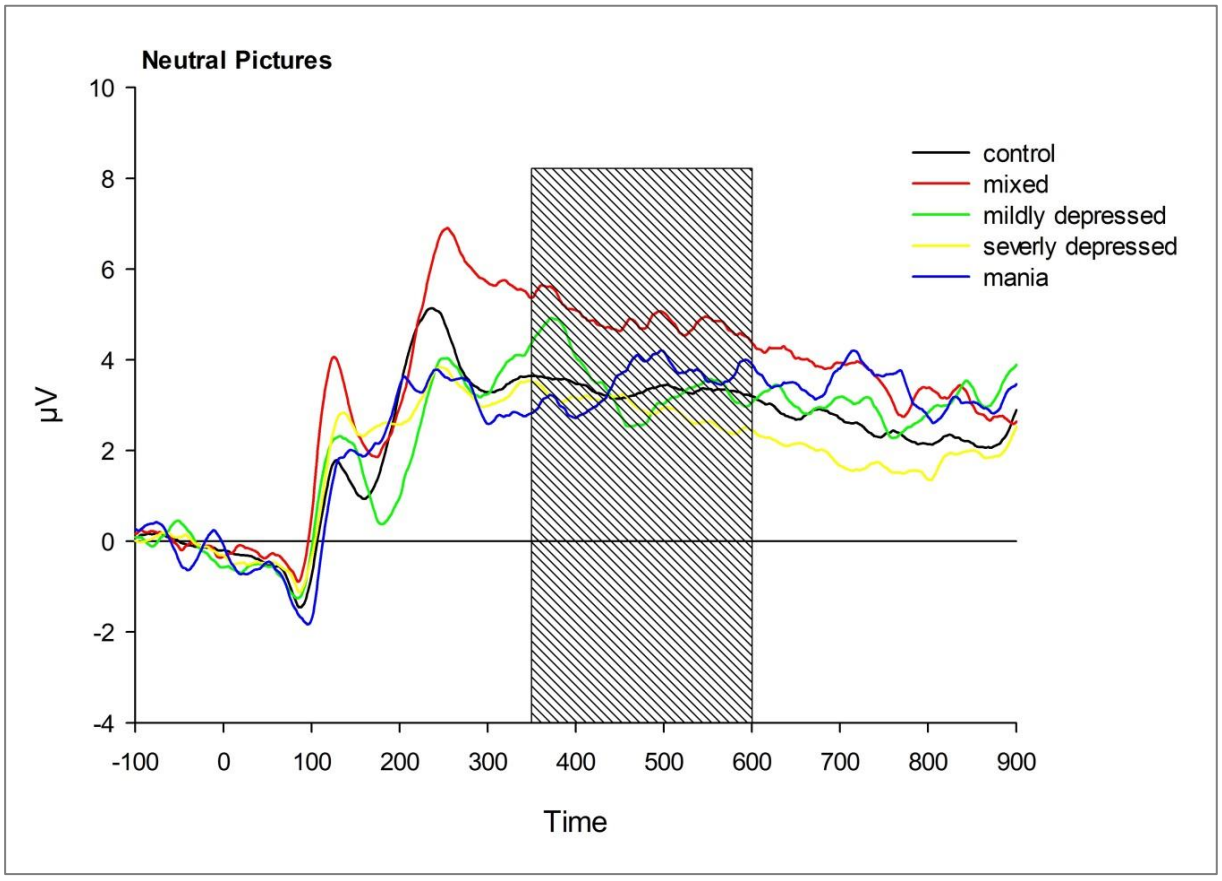

Figure 31. LPP for neutral words for all ill patient groups and controls.

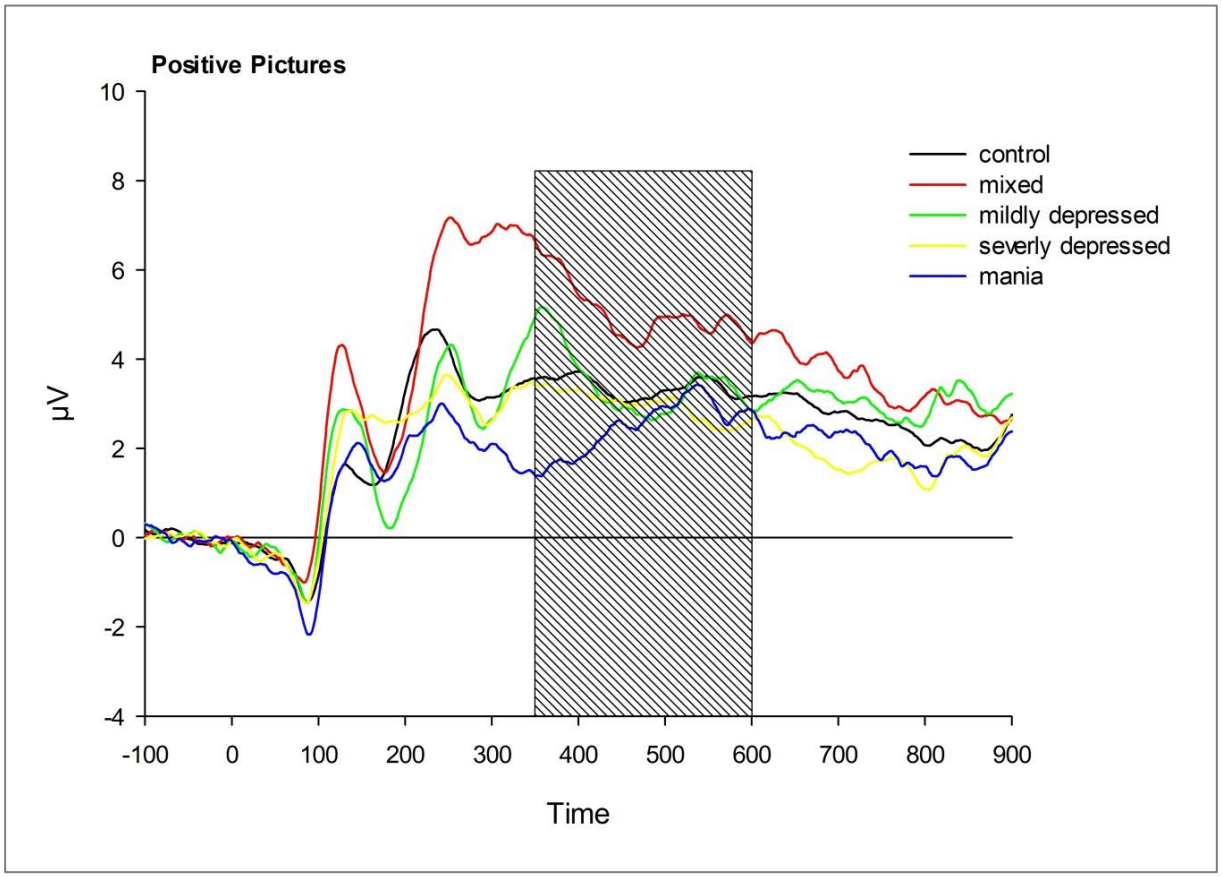

Figure 32. LPP for positive words for all ill patient groups and controls.

3.2.4.2. Remitted patients versus controls

The 3x3x2 repeated measures ANOVA produced a significant main effect for the factor load ($F(2,104)=15.04$, $p<.001$) a significant main effect for the factor disorder status ($F(1,52)=5.09$, $p=.028$) and a marginally significant interaction effect for load*valence ($F(4,208)=2.2$, $p=.071$). For details, please also see Figure 33, Figure 34 and Figure 35.

3.2.4.3. Acutely ill patients versus remitted patients

A 3x3x2 repeated measures ANOVA found a significant main effect for the factor load ($F(2,32)=11.1$, $p<.001$). No other effects were significant. For details, please also Figure 33, Figure 34 and Figure 35.

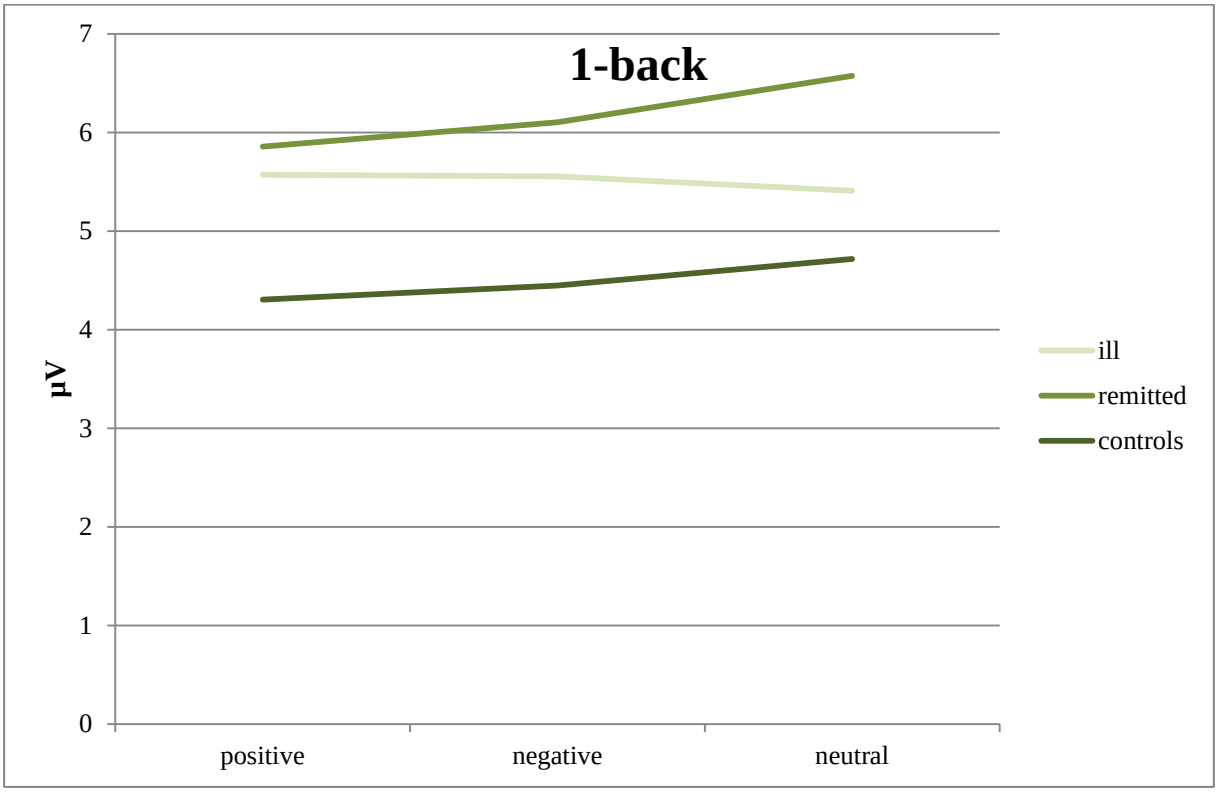

Figure 33. LPP changes in the 1-back load for ill and remitted patients and controls.

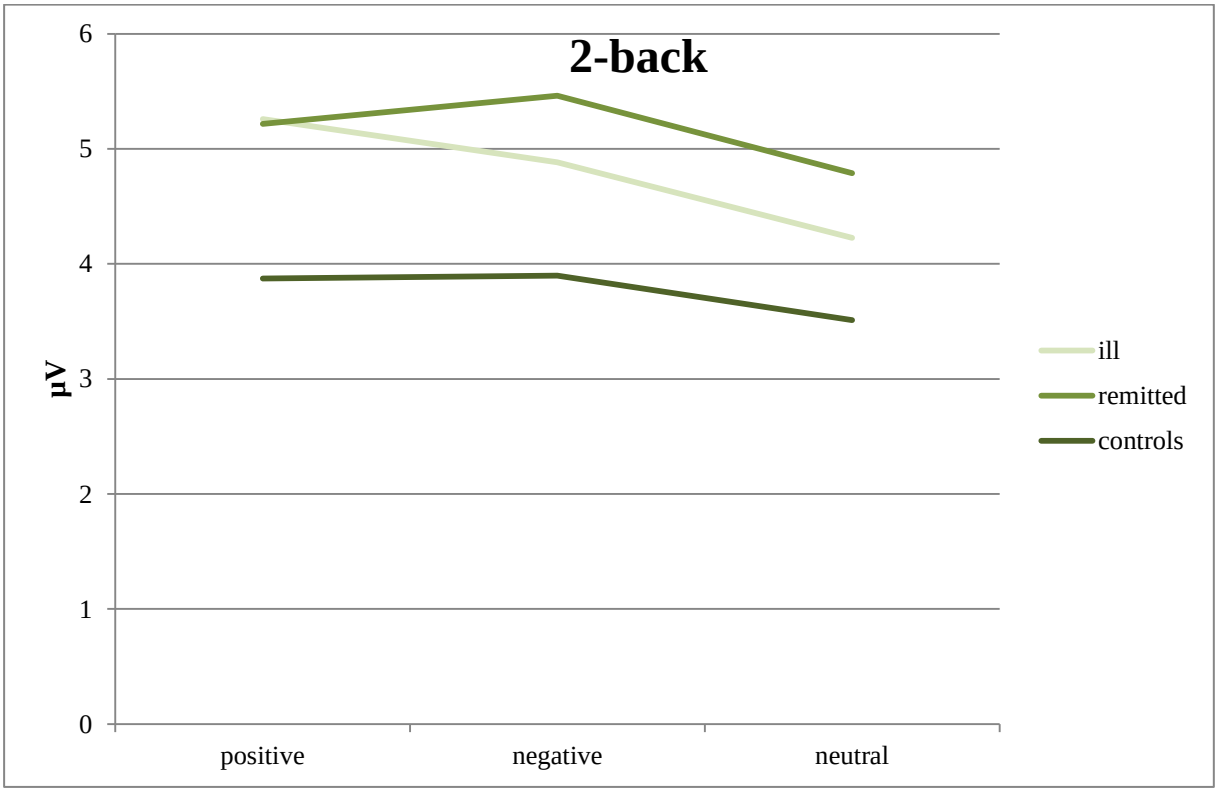

Figure 34. LPP changes in the 2-back load for ill and remitted patients and controls.

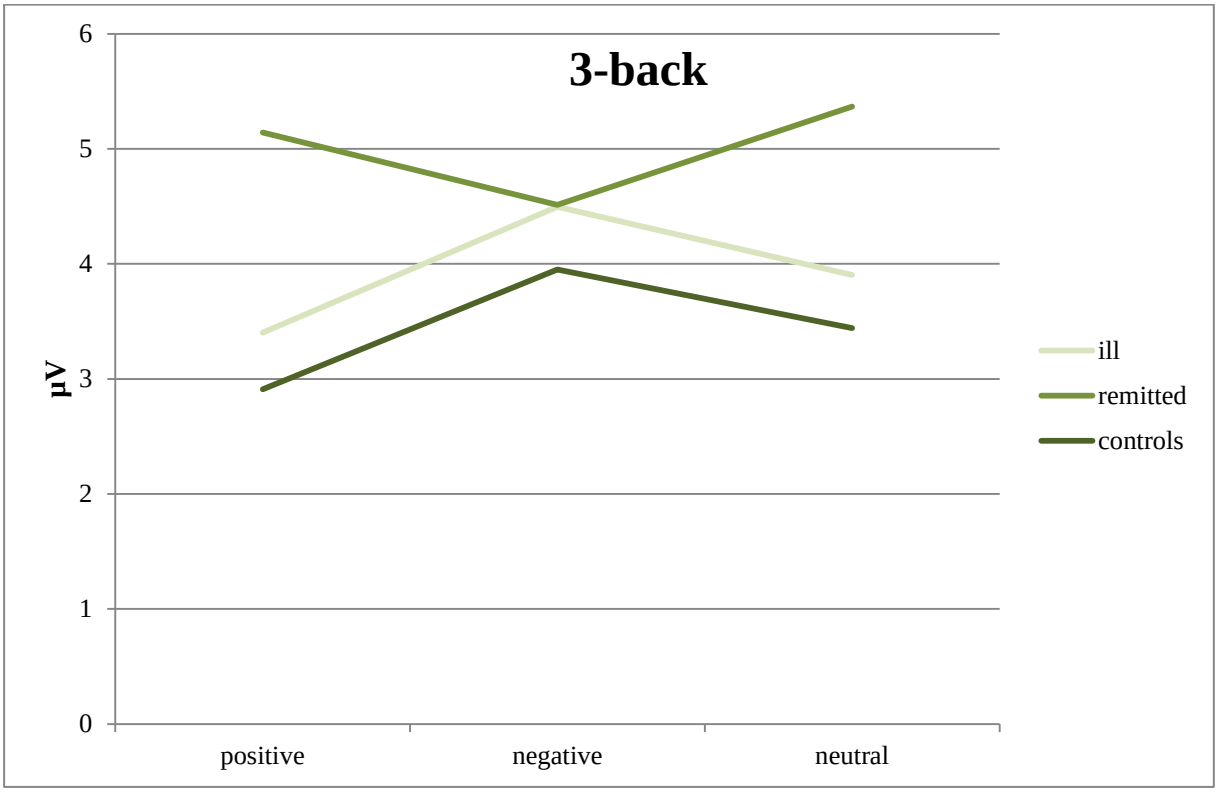

Figure 35. LPP changes in the 3-back condition for ill and remitted patients and controls.

3.2.4.4. Summary of EEG data

The factor load robustly influenced the LLP, leading to a decrease in the amplitude with increasing working memory load. Also, the valence of the word led to differences in the LPP, as negative words produced higher amplitude. Valence differences were influenced by the working memory load, the LPP for the negative valence decreased the least, and the most for positive valences. Only mildly depressed patients differed from controls. When patients were remitted, their LPP did not approximate to that of controls.

4. Discussion

4.1. Pilot study

The first aim of this study was to investigate whether valence of words carefully matched for arousal has an effect on working memory performance. Error data revealed a modulation of performance by word valence. More errors were produced when the word had a negative valence, and that effect was most pronounced in the most difficult 3-back task. Reaction time did not resemble error data, as it increased only as a function of the increasing working memory load. It has been shown that reaction time in an emotional Stroop test was mainly influenced by arousal and not valence (Dresler, Meriau, Heekeren, & van der Meer, 2009). The words used in this study were selected based on their arousal similarities. This could be an explanation for the lack of reaction time effects. However, this would only apply to differences between the emotional conditions, but not to differences with neutral stimuli. Another explanation for this finding could be the small trial size, which may prevent finding significance when effects are small.

The changes in the blood oxygenation level revealed a main effect of task difficulty and an interaction effect for difficulty by emotional valence. Even though the emotional word itself does not change the blood oxygenation as a mean of the valence, it seems to influence the brain activation nonetheless in such a way that the higher the load, the more pronounced the differences between the emotional valences. In detail, while the positive valence does not seem to have any effect on increases of oxygenated blood level, and the brain activation seems to be the comparable to a regular n-back task (Kopf, Schecklmann, Hahn, Dresler, et al., 2011; Martin Schecklmann, et al., 2010), the negative words seem to influence the activation levels so that no change between the different load conditions is detectable. The same pattern becomes even more pronounced in the deoxygenated blood flow changes. This effect of reduced blood flow changes in reaction to negatively valenced stimuli has also been shown by other groups (Perlstein, Elbert, & Stenger, 2002) with emotional pictures, who found reduced activation in the dlPFC for the negative pictures. However, the neutral words induce an unexpected pattern of activation changes, both in oxygenated and deoxygenated haemoglobin levels. From the 1-back to the 2-back condition they increase activation in a manner similar to the positive words. However, as the task becomes even more complicated, the neutral words seize to increase activation: in the 3-back task they cannot be differentiated from the negative words anymore. We expected the neutral words to elicit activation patterns

that show an increase in activation from 1-back to 2-back to 3-back, as can be seen in working memory tasks using letters (Kopf, Schecklmann, Hahn, Dieler, et al., 2011; Martin Schecklmann, et al., 2010).We have no explanation for the discrepant findings so far. We tested whether some participants might have had different evaluation criteria for the words, and aimed to identify outliers within the rating of the words, but the visual inspection could not account for the findings. It is also possible that the different arousal for the neutral words is causing part of the unexpected pattern, and together with the very low difficulty level of the task itself could provide an explanation.

We next analyzed the LPP, and found significant effects of emotion, but also significant effects of difficulty or working memory load and a significant interaction between both. In the 2-back task, the LPP distinguishes between neutral and emotional words very clearly, whereas in the 1-back task that distinction is not detected. In the 3-back task, the only distinction visible in the LPP is for the negative words. It seems that in the easier 2-back condition, the arousal of the word is important for the distinction the LPP can provide, whereas in the most difficult 3-back condition, valence is the key to distinction. We can therefore show that the LPP as well can be influenced by the difficulty level in a working memory task, and differentially for the different emotional valences (MacNamara, et al., 2011). However, contrary to earlier findings by MacNamara and colleagues, when using the stimulus itself as the carrier of the emotional valence, the LPP first becomes larger with increasing working memory load, and only when the load increases further, we observed a decrease in the LPP. That may be due to the different paradigms used, as the study by MacNamara and colleagues used emotional pictures, and they were only used as distractors, not as the stimuli to be remembered themselves, which were strings of letters. But nonetheless, **the main finding of the LPP results** in our study as well as in that of MacNamara et al. (2011) **is that emotion processing is influenced by a simultaneously occurring working memory task, which takes away more and more capacity from emotion processing as the load increases**.

Taken together, our data suggest that it is not only arousal that plays a role in the modulation of working memory but also the valence of the emotional content stored in working memory may play a role in its function. This underlines and extends findings from Levens and Phelps (2008) who used a similar paradigm to show emotion effects on working memory, and furthermore points to the importance of the valence itself.

By integrating the two methods, we conclude that the emotional content of words is influencing working memory performance measured by prefrontal blood flow changes, and that working memory performance is influencing the processing of emotional stimuli.

4.2. Main Study

In order to discuss the main hypotheses, they are stated again at the beginning of this discussion. Afterwards, however, all hypotheses will be discussed for each patient group and the control group at once, to account for the study design, which was set up in order to analyse interactions between working memory and emotion processing.

1. **Working memory function:**
   1.1. Patients show significantly worse performance in their acute ill state, compared with healthy controls. Their brain activation will be attenuated compared to controls, and this attenuation will increase with increasing working memory load. Electrophysiological changes in the LPP will be different for patients and controls.

   1.2. Patients will perform on the same level as controls in their remitted state. They will perform significantly better than in the ill phase. Brain activation, however, will still be attenuated compared to controls, and not different from their acute ill phase. LPP differences between patients and controls will not vanish.

2. **Emotion processing:**
   2.1. Patients will show differences in emotional processing compared to controls. They will be slower to react to emotional stimuli and make more errors when compared to controls. Their brain activation will be attenuated for emotional stimuli, and their LPP will be heightened when compared with controls.

   2.2. Performance differences will vanish when patients return to their remitted state, and will not be different from controls anymore. However, brain activation and LPP Amplitude to emotional stimuli will remain different compared to controls.

3. Interaction between working memory and emotion processing:

3.1. The performance in the n-back task will be influenced by the emotional valence of the stimulus presented in the working memory task.

3.2. This influence will change with increasing working memory load, and the influence will be different for patients compared to controls.

3.3. This influence and the difference between patients and controls will remain when patients are measured again in their remitted state.

Patients indeed did perform worse than controls in their acute ill state. They were slower than controls, and they made more errors. However, the magnitude of the performance differences varied between patient groups.

4.2.1. Depressed patients

Depressed patients were overall slower and made more errors than controls, and that effect increased when the working memory load increased, just as expected. This was also prevalent in the brain activation measured with fNIRS. Patients activated their dlPFC significantly less than controls. Interestingly, this was not true for the 3-back condition as well as the negative word condition, where activations did not differ from controls. The underlying processes are not clear. Maybe patients did try hard to solve the working memory task, and even more so in the 3-back condition, even if that did not sum up to a better performance. The negative valence of a word could be processed with more priority than neutral and positive words, and therefore stimuli with a negative valence would be processed better than other stimuli.

In the LPP, depressed patients did not differ from controls. Reasons for that could be numerous. Depressed patients initially take high doses of medication, and combinations of medication, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antipsychotic medication and lithium for mood stabilization. All these medications are hypothesized to have an influence on brain activation, even if the extent of that effect is unclear (Dodds et al., 2009; Frodl et al., 2011; Hafeman, et al., 2012; Loubinoux et al., 2005; Patin & Hurlemann, 2011). The medication effect could not be controlled for, since this was a naturalistic study and medication differed so much in dose and type between patients. This makes it very hard to find common variables with valid conclusiveness for all patients. Medication effects therefore can only be speculated about. It is quite possible that changes in brain activation and electrophysiology have an onset soon after initiation of the medication,

despite the fact that clinical measures including cognitive performance lag behind. The fact that patients report side effects, such as tiredness, dizziness, and changes in the saliva flow, right after taking the medication for a few times, underlines this theory. Catherine Harmer (2008) discussed in her review of serotonin and emotional processing that antidepressant effects can be seen as early as after the first intake of an SSRI with neuroimaging methods. She describes increased responses to negative facial expressions after the initial start of the pharmacotherapy, which later normalize, and these increased responses induce changes in the patients mood after a few weeks. Interestingly, this can also be seen in the mildly depressed sample discussed next.

4.2.2. Mildly depressed patients

In the group of patients who only showed mild depressive symptoms, performance and activation patterns changed. Patients took longer to react, but only when seeing positive or neutral words. When mildly depressed patients had to react to negative words, they did not differ from controls arguing for biased processing of these stimuli. Also, the increase of working memory load played a role. Differences manifested only in the higher load conditions. An emotional bias could also be seen for omission errors, where mildly depressed patients made more errors when seeing neutral words, and made the least errors when seeing negative words. Working memory performance however was not significantly different for mildly depressed patients and controls. The performance bias in negative stimuli is also reported in other studies (C.-H. Chen et al., 2006; Hulvershorn et al., 2012; Murphy et al., 1999). Again, medication differed very much between patients, making it almost impossible to control for medication effects.

In the fNIRS, mildly depressed patients showed the expected hypoactivations compared to controls. This hypoactivation has been described before (Martin Schecklmann, et al., 2011; Townsend, et al., 2010), and fits the current theory of cognitive deficits due to hypoactivation in the PFC in bipolar patients (Phillips, et al., 2003b). Interestingly, negative valence seemed to elicit the most activation in patients. Again, this has been found before in other studies (C.-H. Chen, et al., 2006; Hulvershorn, et al., 2012). Harmer (2008) discussed this as well, reporting an increased processing of negative or aversive stimuli in the first weeks of treatment, this seems to be true for this study also.

This differential activation for valence could also be seen in the LPP, where mildly depressed patients showed a significantly higher LPP to negative words when compared to controls, but not to other valences, an effect which could not be seen in the load conditions, and therefore

did not point to an overall heightened LPP amplitude. It seemed that the initial anxiogenic effects of SSRI treatment (Harmer, 2008) induce a focus on negative valence, which seems to be processed with priority, as can be seen from the LPP. Stimuli with negative valence are processed sufficiently fast and correct in working memory, and elicit more brain activation.

Taken together, working memory performance seen in depressed patients was poor and not influenced by the valence of a stimulus. They seem to mirror patients' reported blunted affect, where lack of emotional resonance and response upon whatever emotional stimulus is a core symptom. The brain activation measured with fNIRS and EEG seems to be mainly influenced by the medication load. In contrast, patients who report less severe symptoms of depression show differential performance and activation pattern with a focus on negative stimuli, which is in line with patients' reports of regaining their normal feelings and emotional tone, indicated e.g. by patients' ability to cry or experience joy upon adequate experiences despite the ongoing negative, depressive cognitive distortions. The latter of which is also reflected by the preferential processing of negative words. Similar results are discussed by Harmer (2008).

4.2.3. Manic patients

When patients are manic, the picture looks different. They were as fast as controls when reacting to the words, but made the most errors of all patient groups. This fits the manic phenotype of heightened impulsivity, race of thought, distractibility, and reduced conscientiousness that also often results in impaired cognitive performance. Patients especially made more errors in the positive and negative valence conditions. It seems as though patients are more distracted by emotional stimuli. This has also been found before (Murphy, et al., 1999).

The fNIRS results showed no significant effects for the manic patients when compared to controls. However, when looking at the data, manic patients clearly showed less brain activation for positive and negative words when compared to controls. The missing significance of this finding might be due to the small sample size (only 7 patients), which produced a high variance in the data. Even though, strictly taken, post hoc t-tests are invalid in this situation, explorative post hoc t-tests did show significant differences between patients and controls for positive and negative words. Other studies show differences in brain activation in manic patients compared to healthy controls, in working memory tasks as well as in tasks researching neural activation in emotion processing (Foland et al., 2008; Lembke & Ketter, 2002; Townsend, et al., 2010), so that the interpretation of our numeric data is in line with existing literature.

The same might be true for the LPP, where manic patients showed the smallest LPP amplitude of all patient groups in reaction to emotional words, however, no significant group differences arose. This indicates that, unlike it is the case for mildly depressed patients, the emotion processing deficits might be the main contributing factor to their acute ill state. Where mildly depressed patients were better when seeing negative words, and otherwise failed to perform as well as healthy controls, manic patients seemed to be so distracted by emotional valences. They could not process emotional stimuli sufficiently, as seen in the LPP, that they failed to perform like controls. It could seem as though emotional valence of the stimulus increased the overall processing of the stimulus, helping depressed patients to perform more like controls, whereas the same emotional valence distracted manic patients in such a way that they could not perform like healthy controls anymore. Interestingly, this has also been found before in a study by Foland et al. (2008), who found decreased PFC activation to be responsible for the problems in emotion activation.

4.2.4. Mixed patients

The results for mixed state patients compared to healthy controls are ambiguous. Mixed state patients were faster than controls in positive and negative conditions, in line with increased drive as usually present during mixed episodes, yet slower in the neutral condition. However, valence played no role in omission errors for these patients, as they only increased as a function of the working memory load, and they increased much more with increasing load when compared to controls. Their brain activation followed no pattern either. They showed attenuated brain activation compared with controls, however significant differences could only be found for the positive valence in the 2-back task, the neutral valence in the 1-back task and the negative valence in the 3-back task. For the LPP, they showed an overall increase in LPP, but no group differences arose. To add up all these findings, it almost seems as if mixed state patients showed neurophysiological features found in each of the different mood states: the heightened LPP from mildly depressed patients, and attenuated brain activation found in depressed patients, combined with pronounced abnormal emotion processing, which seems to be inefficient as can be seen in the overall high LPP. At the same time, they showed performance differences to differentially valenced stimuli, just like manic patients. When compared to the clinical phenotype of the patients, the data is reflected by their symptom presentation, where patients are anhedonic, show excessive rumination tendencies, but at the same time are anxious and agitated. It has to be taken into consideration that mixed patients are a very heterogeneous group of patients, whose mood state changes very quickly.

Taken together, the hypothesis that patients differ in their performance from controls was correct. This fits the existing research of cognitive deficits (Mann-Wrobel, et al., 2011). The hypothesis that patients show attenuated brain activation cannot be answered that easily. We find significantly reduced brain activation in mildly depressed and mixed patients, as well as numerically reduced brain activation in manic patients. The study by Townsend et al. (Townsend, et al., 2010) found attenuated brain activation in manic and depressed patients and therefore underlines our findings. However, severely depressed patients surprisingly differ. It seems crucial for future research to clearly classify the severity and direction of the mood episode before results can become comparable as episode polarity has a strong differential effect on all of the measures taken, including the LPP. The data on the latter cannot be related to other studies, as there are none. Considering the hypothesis that increased amygdala activation underlies increased LPP amplitudes (Hajcak, et al., 2010), then mixed patients should display the highest amygdala activation, as compared to manic patients, who show the least. This theoretical prediction is going to be tested in fMRI studies in our laboratory. Such an decreased amygdala reactivity might explain manic patients' fearlessness, inappropriate risk assessment and high excitability to emotional stimuli: if the amygdala is hypo-activated, regulation processes cannot properly take place. This has been shown before by Foland et al. (2008) and Hulvershorn et al. (2012), who find abnormal amygdala activity in manic patients just as well.

4.2.5. Remitted patients

Some of the patients came back a second time in a remitted state to take part in the experiment again. Unfortunately, comparability with acutely ill patients is compromised: patients that did come back were in different mood states when they were measured the first time, so that no comparisons between all acute patients and all remitted patients can be made. Therefore, all comparisons with remitted patients will be only with themselves, and cannot be completely conclusive due to the fact that patients differ in their activation and performance patterns when they are in different mood states. In the following part, differences between remitted patients and controls will be discussed, as well as within-differences for patients who were measured in their ill state and again in their remitted state.

Remitted patients did not differ from controls in their behavioral performance. However, remitted patients' performance did not differ from their performance in the acute ill state either. The numerical data shows that indeed, patients did not improve in their performance when remitted, but, if anything, became worse. An explanation could be a selection bias, in

that patients who did come back for a second measurement were different as compared to the other patients in their acute ill state. Indeed, patients who did come back differed significantly in their MADRS scores, they had higher scores as compared to those who did not come back. The other explanation could well be that the small sample size of tested remitted patients produced a much higher variance in the data, which lead to non-significant results. This could also be true in light of the fact that patients did come from different acute ill states. This finding only highlights the importance of investigating the different phases of the disorder separately. However, the hypothesis that remitted patients do not show cognitive deficits anymore cannot be taken as proven, even if no significant differences arose from statistical analyses. An interesting side note is that more severe ill patients seem to be more inclined to take part in studies, presumably because they hope to improve their disorder state, whereas patients who completely remit do not see the need to take part a second time.

For the fNIRS results, brain activation was not significantly different between remitted patients and controls, and not significantly different for acutely ill and remitted patients either. However, numerical data showed an increase in brain activation from ill to remitted to controls for the load condition, but not for the valence condition. When only researching working memory load, remitted patients showed a higher activation than in their acute ill phase, but they were not quite at the level of controls. In the valence condition, remitted patients only showed higher brain activation in the positive valence and the negative valence, whereas the neutral valence did not produce an improvement in brain activation at all for the patients over the course of their disorder. The same picture could be seen in the LPP. No significant results arose when comparing remitted patients to controls, as well as when comparing ill patients to their remitted state. However, when looking at the numerical data, the LPP amplitude overall was higher in ill patients than in controls, and increased even more in remitted patients, hinting at a differential emotion processing overall. It seems as though the direction of the LPP amplitude changes between valences and load conditions are the same, with the exception of the negative valence condition, which increases in controls, as well as in acutely ill patients and decreases in the remitted patients. The implications of these findings are unclear. (MacNamara, et al., 2011) found that working memory decreases the LPP but that this effect was attenuated by increasing anxiety. If emotional valence gets processed with more priority than in control subjects, the LPP does not decrease as much with increasing load. However, in this study, acutely ill patients behaved like controls, and remitted patients showed a decrease in the LPP amplitude for negative words in the 3-back condition, exactly the opposite of what was expected to happen, and what did happen in the ill

patients. Further studies of the LPP with more patients in a remitted state are needed in order to understand the effects of the disorder on the LPP. Possibly the LPP could function as an indicator for a trait of BD, as it is hypothesized to measure emotion processing.

Taken together, the hypothesis that remitted patients return to a level of cognitive functioning where they cannot be distinguished anymore from healthy controls was not correct. While no statistical differences arose between remitted patients and controls, the same was true for the comparison between acutely ill and remitted patients, and the missing statistical difference between remitted patients and controls cannot be used to reject the null-hypothesis. Given the rather small sample sizes for these studies, power issues are most likely to account for these equivocal findings. The same is true for the hypothesis stating that brain activation remains attenuated. This could only be found for the neutral words, not for any other load or valence conditions. For the LPP, remitted patients showed an overall higher LPP amplitude than in their ill phase as well as compared to healthy controls. This might hint at a dysfunction of emotion processing in BD which does not decrease when patients are remitted. Recent research shows that subclinical symptoms in a remitted state are quite prevalent (Vieta, Sanchez-Moreno, Lahuerta, & Zaragoza, 2008). If one takes into consideration that patients with sub-threshold symptoms show attenuated cognitive functioning compared to completely remitted patients, and that our remitted patients were worse ill than the other patients who took part in the experiment, it might well be that this influenced performance and brain activation results.

4.3. Conclusion

If we take into account the proposed model of neurocircuit dysfunction in BD (Phillips, et al., 2003b; Strakowski, et al., 2012), which consists of a hypoactive dorsal system, studied in this thesis using the working memory paradigm, and the overactive ventral system, tested in this thesis with LPP changes due to differently valenced words being shown, then the different disorder states could be interpreted in the following way:

If the brain activation seen in the prefrontal cortex is part of an disturbed dorsal system in BD (Phillips, et al., 2003b; Strakowski, et al., 2012), then the predominantly disturbed system in both mildly and severely depressed patients could be the dorsal system, which show only small changes in the LPP, whereas the predominantly disturbed system in manic and mixed patients is the ventral system, which can be seen in hyperactivation of LPP-related neural correlates in mixed and hypoactivated neural correlates of the LPP in manic patients. When

patients are remitted, the dorsal system regains temporary stability, and can be compared to that of healthy controls, However the ventral system remains dysfunctional and causes the remaining performance deficits. If that is the case, performance deficits can be taken as state markers of the disorder, with pronounced deficits while patients are in an acutely ill phase, and emotion processing deficits could be a trait marker of the disorder, remaining even in full remission. Maybe subsyndromal BD patients would therefore profit from interventions aiming to stabilize the ventral emotion processing system. This would also explain that some patients show a clear manic polarity, and are systemically different from patients who show a clear depressed polarity, including the need for different medication (Popovic et al., 2012).

The theory of the ventral emotion processing system being the one creating the remaining deficits should be researched further. Especially, the interconnectivity of the two systems needs to be implemented in paradigms researching both cognition and emotion, in order to find further proof of this theory. It would be important to study emotion processing deficits in patients over time, in an acutely ill phase as well as in remission. If the emotion processing deficits are indeed trait markers of the disorder, changes in the emotion processing system with changing manic and depressive episodes need to be researched further.

Taken together, this study adds to the knowledge of deficits in working memory and emotion processing in BD. The emotional working memory paradigm established in the framework of the current thesis can be a reliable tool to research functional changes of the two core symptoms in BD over the course of the disease. It is important that patients are measured repetitively during acute phase and remission, in order to fully assess the extent of the cognitive and emotional changes in performance and brain activation. It is even more important that different mood states are studied separately, that medication is taken into account and that sufficiently powered samples are included in order to reliably find differences between groups and changes over time. The LPP needs to be analyzed further in order to establish the source of the potential and create the ability to conclude the underlying neuronal correlates that are disturbed in BD.

4.4. Limitations

There are several limitations that should be kept in mind when interpreting the data. First, since this was a natural study setting, all patients were medicated, with medication varying in type (SSRI, venlafaxine, tricyclic antidepressants, antipsychotics, lithium and other mood stabilizers) and dose. Therefore, medication effects are expected, but cannot be controlled for. Some studies find medication effects on brain activation in working memory and emotion processing studies (Dodds, et al., 2009; Ertugrul et al., 2009; Frodl, et al., 2011; Pavuluri, Passarotti, Harral, & Sweeney, 2010). Especially, Patin and Hurlemann (2011) point to the effects of medication on amygdala function, and clearly state that more research is needed to understand the ramifications of different medication on amygdala activation. Hafeman et al. (2012) review bipolar medication effects in brain imaging studies and conclude that the picture is unclear. Phillips et al. (2008) conclude in their review that medication seems to take no effect on brain activation in bipolar patients. All significant results found in this study therefore have to be interpreted with special care as to the medication effects that possibly change brain activation.

Second, no distinction was made between patients with bipolar I and bipolar II disorder. Numerous studies were conducted addressing possible cognitive differences between bipolar I and bipolar II patients (Ancin, Cabranes, Santos, Sanchez-Morla, & Barabash, 2013; Dittmann et al., 2008; Hsiao et al., 2009; Palsson et al., 2013), but the results are contradictory. A study by Summers et al. (2006) concerning cognition and emotion processing differences between bipolar I and bipolar II patients found that bipolar II patients are cognitively impaired more severely, but no differences between emotion processing tasks were found. They conclude that recurring depressive episodes have a more detrimental effect on cognition. While that fits well into our own data showing that the cognitive system seems to be more impaired in depressed patients, it also justifies the concern that our sample comprised both bipolar I and bipolar II disorder, and we did not distinguish between these patients to retain sufficient power.

Third, the neural underpinnings of the LPP are essentially unknown. All interpretation of LPP data is therefore highly speculative. More research into the origins of this event related potential is needed in healthy controls, in order to be able to correctly interpret LPP findings in patients.

4.5. Outlook

Future research needs to address the interconnectivity of cognitive system and emotion processing system, to provide further evidence for a remaining dysfunctionality of the emotion processing system. While fNIRS is suitable for detecting cognitive deficits, the suitability of the LPP in order to better understand the underlying neural mechanisms is questionable. Maybe another ERP would be better suited to account for both cognitive and emotion processes. Functionality and interconnection of both systems could then function as an endophenotype for BD, which would help to identify genetic polymorphisms influencing both systems. This in turn would help improve treatment options for patients, with personalized medication for different polarities and different mood states, and improved psychotherapy aiming at a better emotion processing.

5. Literature

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6. Appendix

Table 1. ICD and DSM-IV criteria for BD.

ICD 10
F30 MANIC EPISODE
F30.0 Hypomania **A**. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least four consecutive days. **B**. At least three of the following must be present, leading to some interference with personal functioning in daily living: (1) increased activity or physical restlessness; (2) increased talkativeness; (3) difficulty in concentration or distractibility; (4) decreased need for sleep; (5) increased sexual energy; (6) mild spending sprees, or other types of reckless or irresponsible behavior; (7) increased sociability or over-familiarity. **C**. The episode does not meet the criteria for mania (F30.1 and F30.2), bipolar affective disorder (F31.-), depressive episode (F32.-), cyclothymia (F34.0) or anorexia nervosa (F50.0). **D**. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.
F30.1 Mania without psychotic symptoms **A**. A mood which is predominantly elevated, expansive or irritable and definitely abnormal for the individual concerned. This mood change must be prominent and sustained for at least a week (unless it is severe enough to require hospital admission). **B**. At least three of the following must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living: (1) Increased activity or physical restlessness; (2) Increased talkativeness ('pressure of speech'); (3) Flight of ideas or the subjective experience of thoughts racing; (4) Loss of normal social inhibitions resulting in behavior which is inappropriate to the circumstances; (5) Decreased need for sleep; (6) Inflated self-esteem or grandiosity; (7) Distractibility or constant changes in activity or plans; (8) Behavior which is foolhardy or reckless and whose risks the subject does not recognize e.g. spending

sprees, foolish enterprises, reckless driving;

(9) Marked sexual energy or sexual indiscretions.

C. The absence of hallucinations or delusions, although perceptual disorders may occur (e.g. subjective hyperacusis, appreciation of colors as specially vivid, etc.).

D. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

F30.2 Mania with psychotic symptoms

A. The episode meets the criteria for mania without psychotic symptoms (F30.1) with exception of criterion C.

B. The episode does not simultaneously meet the criteria for schizophrenia (F20) or schizo-affective disorder, manic type (F25.0).

C. Delusions or hallucinations are present, other than those listed as typical schizophrenic in F20 G1.1b, c and d (i.e. delusions other than those that are completely impossible or culturally inappropriate and hallucinations, that are not in the third person or giving a running commentary). The commonest examples are those with grandiose, self-referential, erotic or persecutory content.

D. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

A fifth character may be used to specify whether the hallucinations or delusions are congruent or incongruent with the mood:

F30.20 mania with mood congruent psychotic symptoms (such as grandiose delusions or voices telling the subject that he has superhuman powers)

F30.21 mania with mood incongruent psychotic symptoms (such as voices speaking to the subject about affectively neutral topics, or delusions of reference or persecution).

F30.8 Other manic episodes

F30.9 Manic episode, unspecified

F31 BIPOLAR AFFECTIVE DISORDER

Note: Episodes are demarcated by a switch to an episode of opposite or mixed polarity or by a remission.

F31.0 Bipolar affective disorder, current episode hypomanic

A. The current episode meets the criteria for hypomania (F30.0).

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms

A. The current episode meets the criteria for mania without psychotic symptoms (F30.1).

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms

A. The current episode meets the criteria for mania with psychotic symptoms (F30.2).

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:

F31.20 with mood congruent psychotic symptoms

F31.21 with mood incongruent psychotic symptoms

F31.3 Bipolar affective disorder, current episode moderate or mild depression

A. The current episode meets the criteria for a depressive episode of either mild (F32.0) or moderate severity (F32.1).

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), or mixed affective episode (F38.00).

A fifth character may be used to specify the presence of the somatic syndrome as defined in F32, in the current episode of depression:

F31.30 without somatic syndrome

F31.31 with somatic syndrome

F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms

A. The current episode meets the criteria for a severe depressive episode without psychotic symptoms (F32.2).

B. There has been at least one well authenticated hypomanic or manic episode (F30.-) or mixed affective episode (F38.00) in the past.

F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms

A. The current episode meets the criteria for a severe depressive episode with psychotic symptoms (F32.3).

B. There has been at least one well authenticated hypomanic or manic episode (F30.-) or mixed affective episode (F38.00) in the past.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood.

F31.50 with mood congruent psychotic symptoms

F31.51 with mood incongruent psychotic symptoms

F31.6 Bipolar affective disorder, current episode mixed

A. The current episode is characterized by either a mixture or a rapid alternation (i.e. within a few hours) of hypomanic, manic and depressive symptoms.

B. Both manic and depressive symptoms must be prominent most of the time during a period of at least two weeks.

C. There has been at least one well authenticated hypomanic or manic episode (F30.-), depressive (F32.-) or mixed affective episode (F38.00) in the past.

F31.7 Bipolar affective disorder, currently in remission

A. The current state does not meet the criteria for depressive or manic episode in any severity, or for any other mood disorder in F3 (possibly because of treatment to reduce the risk of future episodes).

B. There has been at least one well authenticated hypomanic or manic episode (F30.-) in the past and in addition at least one other affective episode (hypomanic or manic (F30.-), depressive (F32.-), or mixed (F38.00)).

F31.8 Other bipolar affective disorders

F31.9 Bipolar affective disorders, unspecified

F32 Depressive episode

G1. The depressive episode should last for at least 2 weeks.

G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30.-) at any time in the individual's life.

G3. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

Somatic syndrome

Some depressive symptoms are widely regarded as having special clinical significance and are here called "somatic". (Terms such as biological, vital, melancholic, or endogenomorphic are used for this syndrome in other classification.)

A fifth character (as indicated in F31.3; F32.0 and F32.1; F33.0 and F33.1) may be used to specify the presence or absence of the somatic syndrome. To qualify for the somatic syndrome, four of the following symptoms should be present:

(1) marked loss of interest or pleasure in activities that are normally pleasurable;
(2) lack of emotional reactions to events or activities that normally produce an emotional response;
(3) waking in the morning 2 hours or more before the usual time;
(4) depression worse in the morning;
(5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people);
(6) marked loss of appetite;
(7) weight loss (5% or more of body weight in the past month);
(8) marked loss of libido.

In The ICD-10 Classification of Mental and Behavioral Disorders: Clinical descriptions and diagnostic guidelines, the presence or absence of the somatic syndrome is not specified for severe depressive episode, since it is presumed to be present in most cases. For research purposes, however, it may be advisable to allow for the coding of the absence of the somatic syndrome in severe depressive episode.

F32.0 Mild depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the following three symptoms must be present:

(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.
(2) loss of interest or pleasure in activities that are normally pleasurable; (3) decreased energy or increased fatigability.

C. An additional symptom or symptoms from the following list should be present, to give a total of at least four:

(1) loss of confidence and self-esteem;
(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt;
(3) recurrent thoughts of death or suicide, or any suicidal behavior;
(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness

or vacillation;
(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);
(6) sleep disturbance of any type;
(7) change in appetite (decrease or increase) with corresponding weight change).

A fifth character may be used to specify the presence or absence of the "somatic syndrome" (defined on page xx):
F32.00 Without somatic syndrome
F32.01 With somatic syndrome

F32.1 Moderate depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the three symptoms listed for F32.0, criterion B, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least six.

A fifth character may be used to specify the presence or absence of the "somatic syndrome" as defined on page xx:
F32.10 Without somatic syndrome
F32.11 With somatic syndrome

F32.2 Severe depressive episode without psychotic symptoms

Note: If important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such a case.

A. The general criteria for depressive episode (F32) must be met.

B. All three of the symptoms in criterion B, F32.0, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least eight.

D. There must be no hallucinations, delusions, or depressive stupor.

F32.3 Severe depressive episode with psychotic symptoms

A. The general criteria for depressive episode (F32) must be met.

B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D.

C. The criteria for schizophrenia (F20.-) or schizoaffective disorder, depressive type (F25.1) are not met.

D. Either of the following must be present:

(1) delusions or hallucinations, other than those listed atypically schizophrenic in F20, criterion G1(1)b, c, and d (i.e. delusions other than those that completely impossible or culturally

DSM IV TR

Bipolar I Disorder:

The essential feature of Bipolar I Disorder is a clinical course that is characterized by the occurrence of one or more Manic Episodes or Mixed Episodes. Often individuals have also had one or more Major Depressive Episodes.

Episodes of Substance-Induced Mood Disorder (due to the direct effects of a medication, or other somatic treatments for depression, a drug of abuse, or toxin exposure) or of Mood Disorder Due to a General Medical Condition do not

count toward a diagnosis of Bipolar I Disorder. In addition, the episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Bipolar II Disorder:

The essential feature of Bipolar II Disorder is a clinical course that is characterized by the occurrence of one or more Major Depressive Episodes accompanied by at least one Hypomanic Episode. Hypomanic Episodes should not be confused with the several days of euthymia that may follow remission of a Major Depressive Episode. Episodes of Substance- Induced Mood Disorder (due to the direct effects of a medication, or other somatic treatments for depression, a drug of abuse, or toxin exposure) or of Mood Disorder Due to a General Medical Condition do not count toward a diagnosis of Bipolar I Disorder. In addition, the episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary):

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1.inflated self-esteem or grandiosity

2.decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

3.more talkative than usual or pressure to keep talking

4.flight of ideas or subjective experience that thoughts are racing

5.distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

6.increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

7.excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatments) or a general medical condition (e.g., hyperthyroidism).

Note:

Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Criteria for a Mixed Episode

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period:

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Criteria for a Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood:

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1.inflated self-esteem or grandiosity

2.decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

3.more talkative than usual or pressure to keep talking

4.flight of ideas or subjective experience that thoughts are racing

5.distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

6.increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

7.excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. (Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.)

1.Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

Note: In children and adolescents, can be irritable mood

2.Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gains.

4.Insomnia or hypersomnia nearly every day

5.Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6.Fatigue or loss of energy nearly every day

7.Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being ill)

8.Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account

or as observed by others)

9.Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Table 2. Chart depicting the paradigm cell configuration.

affective word / n-back	negative	neutral	positive
1-back	3	3	3
2-back	3	3	3
3-back	3	3	3

Table 3. Post hoc t-tests for differences in VALENCE RATINGS. Significant differences are highlighted in bold.

Mildly depressed vs. control	**T**	**df**	**p value**
Positive	0.397	50	0.693
Neutral	0.878	50	0.384
Negative	0.872	50	0.387
depressed vs. control			
Positive	-1.187	58	0.24
Neutral	-0.447	58	0.656
Negative	-0.327	58	0.745
mania vs. control			
Positive	1.628	45	0.111
Neutral	2.258	6.465	**0.062**
Negative	-0.854	45	0.398
mixed vs. control			
Positive	-1.956	45	**0.057**
Neutral	-1.254	45	0.216
Negative	-0.166	45	0.869
mildly depressed vs. depressed			
Positive	1.495	30	0.145
Neutral	0.916	30	0.367
Negative	0.884	30	0.384
mildly depressed vs. mania			
Positive	-1.422	17	0.173
Neutral	-1.497	17	0.153
Negative	0.897	17	0.382
mildly depressed vs. mixed			
Positive	2.396	17	**0.028**
Neutral	1.076	17	0.297
Negative	0.544	17	0.593
depressed vs. mania			
Positive	-2.631	25	**0.014**
Neutral	-2.356	7.057	**0.05**
Negative	0.626	25	0.537
depressed vs. mixed			
Positive	1.31	25	0.202
Neutral	0.854	25	0.401
Negative	-0.049	25	0.961
mania vs. mixed			
Positive	3.014	12	**0.011**
Neutral	2.741	7.573	**0.027**
Negative	-0.562	12	0.584

Table 4. Medication list of all patients.

Medication

VpNr	Lithium Dosis	Antipsych1 Dosis	Antipsych 2 Dosis	Other mood stabilizers Dosis	SSRI Dosis	TCA Dosis	Benzo Dosis
1			300mg; 5mg				
2	2x 450mg		300 mg	2x 600mg			
3	225mg		300mg			100mg	
4			4mg			25mg, 150mg	3x 0,5mg
5							
6	450, 900mg		300mg		375mg		2x 0,5mg; 10mg
7	450, 900mg						
8	2x 450mg					100mg	0,5mg
9	2x 450mg	2,5mg , 0,5mg	100mg				0,5mg
10			2,5mg				20mg
11	450, 900mg		100mg		300mg, SNRI		
12	2x 450mg					50, 150mg	0,5
13	225, 450mg				10mg		2x 0,5mg ; 10mg
14		250mg		2x 600mg			
15			500mg				
16	2x 450mg	75mg					0,5mg; 20mg
17			5mg				
18	2x 450mg				40mg		
19	2x 450mg		300mg	2x 50mg		75mg	
20	2x 450mg					75mg	10mg
21	2x 450mg			1200mg		25, 50mg	0,5mg
22			100mg	2x 100mg; 2x 800mg		100mg	2x 0,5mg
23							
24	2x450mg		5mg		150mg		0,5mg
25	2x 400mg		200mg		150mg		
26	2x 450mg				300mg	45mg	
27			100mg	600		50mg; ret150mg	1mg
28			10mg; 50mg				
29	2x 600mg		300mg				
30			300, 350mg				
31			200mg; 15mg	500, 600mg			
32	675, 900mg		50mg; 2x 2mg				20mg
33	450, 675mg		20mg	600, 900mg			30mg
34							
35			7,5mg	600, 900mg	300mg		
36			300mg		225mg		0,5mg
37	900mg		100mg; 10mg	100mg	75mg		
38			150mg		300mg		1,5mg
39	1800mg					100mg; 150mg	1,5mg; 10mg
40			300mg	800mg			
41			2x 2,5mg	2x 25, 75mg			1,5mg; 10mg
42			10mg		225mg	30mg	
43	900mg						
44	900mg		300mg				
45	450, 675mg		2,5, 5mg				1,5mg; 10mg
46							
47			4mg, 300mg				

Acknowledgements

I would like to thank several people.

I would like to express my special appreciation and thanks to my advisor Professor Dr. Andreas Reif, you have been a tremendous mentor for me. I would like to thank you for encouraging my research and for allowing me to grow as a research scientist. Your advice on both research as well as on my career have been priceless. I would also like to thank you for your trust in me and my ideas, and for your friendship. Without you, I would not be writing this right now.

I would also like to thank my committee members, Professor Dr. Paul Pauli, and Dr. Martin Herrmann, for serving as my committee members even at hardship. Thank you for your advice and your time.

I would especially like to thank all my coworkers inside and outside the lab at the clinic: Antonia, Lena, Aet, Florian, for providing coffee, sweets and a shoulder to cry on, on countless occasions. When I thought I wanted to throw in the towel, you were there. I cannot believe how lucky I am to have the opportunity to continue working with you, and being friends with you.

Julia, my personal built-in psychotherapist: for always listening to my rants, giving the best advice, sharing my dislike of large datasets nobody knows what to do with. For rooming with me and the “cold asshole”.

All the other people in the lab who have seen me turn into rumpelstiltskin over data, routines, my computer in general and all other research related problems. Thank you for your patience.

I would also like to thank all patients, controls, physicians, and all other people involved in this thesis.

I want to thank my parents for always being there, and believing that I can do it.

Last but not least, I want to thank my boys. You have made me complete.

Curriculum Vitae

Personal Data

Name	Juliane Kopf
Birthday	08.03.1980

Education

2005 – 2010	Study of Psychology at the University Wuerzburg
2010	Diploma in Psychology from the University of Wuerzburg
11/2010 – 02/2014	PhD Student, stipend with the Graduate School "Emotions"

First Author Publications

Kopf J, Schecklmann M, Hahn T, Dresler T, Dieler AC, Herrmann MJ, Fallgatter AJ, Reif A. NOS1 ex1f-VNTR polymorphism influences prefrontal brain oxygenation during a working memory task. NeuroImage. 2011 Aug 15;57(4):1617-23.

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Signature

Affadavit

I hereby confirm that my thesis entitled “Emotion processing and working memory deficits in bipolar disorder: interactions and changes from acute to remitted state.” is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Place, Date Signature

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation „Emotionsverarbeitung und Arbeitsgedächtnisdefizite in der bipolaren Störung: Interaktionen und Veränderungen im Verlauf der Erkrankung.“ eigenständig, d. h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

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