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Source distribution of neuromagnetic slow wave and alpha activity in depressive patients: therapy-dependent changes

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Content

Zusammenfassung.

Viele elektroencephalographische Studien berichten über abnorme Gehirnaktivität bei depressiven Patienten. Jedoch haben wenige magnetoencephalographische Studien anormale neuromagnetische Aktivität während der Depression untersucht, und keine Studie hat bis jetzt neuromagnetische Aktivität vor und nach der psychotherapeutischen Intervention analysiert. Außerdem bestätigen die neuesten Untersuchungen im Neuroimaging die Effektivität verschiedener Interventionen in der Normalisierung von regionalen Gehirnabnormitäten während der Depression. Diese Studie verwendet das Magnetoencephalogramm (MEG), um die abnorme regionale Aktivität bei depressiven Patienten und die Veränderung der Aktivität nach der psychotherapeutischen Behandlung zu untersuchen.

Gemäß des derzeitigen Standes der Literatur wird im Delta- and Thetaband erwartet, dass depressive Patienten eine Verminderung der Aktivität in der anterioren Region und eine Vergrößerung der Aktivität in der posterioren Region im Ruhezustand im Vergleich zu Kontrollen zeigen. Im Alphaband wird erwartet, dass depressive Patienten eine anteriore Asymmetrie bezüglich einer stärkeren Aktivität in der linken Hemipshäre und posteriore Asymmetrie bezüglich einer stärkeren Aktivität in der rechten Hemisphäre im Vergleich zu Kontrollen aufweisen. Dazu wird ein Zusammenhang zwischen abnormer neuromagnetischer Aktivität und Symptomatik erwartet. Nach der Therapie wird eine Veränderung der Aktivität in Richtung Normalisierung bei depressiven Patienten erwartet. Zudem wird ein Zusammenhang zwischen dem Effekt der Behandlung, evaluiert in der Veränderung der Symptomwerten, und der Normalisierung der neuromagnetischen Aktivität erwartet.

Das MEG wurde bei 24 Patienten, die gemäß den Kriterien der ICD-10 (Internationale Klassifikation psychischer Störungen) die Diagnose der psychischen und Verhaltensstörungen erfüllten, während einer Ruhezustand vor und am Ende der Therapie durchgeführt. Die Schwere der Symptomatik wurde mit Hilfe zweier Beurteilungsskalen (Beck Depression Inventory- BDI, und Brief Psychiatric Rating Scale- BPRS) an beiden Messpunkten geschätzt. Vor der Behandlung bekamen alle außer vier Patienten Medikamente. Die Gruppe der Patienten wurde mit 24 gesunden Probanden ähnlichen Alters verglichen.

Die Analyse zeigt, dass die meisten depressiven Patienten eine mäßige Depression (gemessen mit BDI) vor der Therapie aufweisen. Patienten, die mit der rezidivierenden depressiven Störung (F33) diagnostiziert wurden, zeigen eine größere Schwere der Depression im Vergleich zu Patienten, die mit depressiver Episode diagnostiziert wurden (F32). Am Ende der Therapie ist eine Verminderung der Symptomatik zu beobachten. Vor der Therapie ist die Schwere der Depression mit längerer Dauer der psychotherapeutischen Behandlung verbunden.

Wie erwartet zeigen depressive Patienten eine reduzierte Aktivität in der präfrontalen Region and eine erhöhte Aktivität in der parietalen Region im Delta- and Thetaband im Vergleich zu Kontrollen auf. Jüngere depressive Patienten weisen mehr Deltaaktivität in der parietalen Region der rechten Hemisphäre auf. Im Alphaband werden ähnliche Muster einer verringerten Aktivität in präfrontalen Region and einer vermehrten Aktivität in der parietalen Region beobachtet. Jedoch zeigen depressive Patienten keine anteriore und posteriore Asymmetrien auf. Entgegen den Erwartungen zeigen Depressive frontale Asymmetrie in Richtung einer höheren Alphaaktivität in der rechten Hemisphäre.

Vor der Behandlung weisen Patienten mit einer F33 Diagnose eine ausgeprägtere frontale Reduktion im Deltaband und eine ausgeprägtere parietale Erhöhung im Theta- und Alphaband im Vergleich zu Patienten mit F32 Diagnose auf. Diese Ergebnisse demonstrieren, dass im Vergleich zu depressiver Episode, rezidivierende depressive Störung zusammen mit größerer Schwere der Depression mit größerer Anormalität der langsamen Aktivität und Alphaaktivität verbunden ist.

Nach der Therapie zeigen depressive Patienten nicht nur Symptomverbesserung, sondern auch eine Erhöhung der Aktivität in der rechtspräfrontalen Region und eine Reduzierung der Aktivität in der rechtsparietalen Region im Deltaband im Vergleich zu vor der Therapie. Diese Ergebnisse bestätigen die Hypothese, dass der Effekt der Behandlung, evaluiert durch Symptomverbesserung, von einer Normalisierung der Deltaaktivität in der präfrontalen und parietalen Regionen der rechten Hemisphäre bei depressiven Patienten begleitet wird. Nach der Therapie zeigen nur die Patienten mit F32 Diagnose eine Verkleinerung in der rechtsparietalen Thetaaktivität und nur die Patienten mit F33 Diagnose eine Verkleinerung in der linksparietalen Alphaaktivität im Vergleich zu vor der Therapie.

Lateralitätsindizes im Alphaband zeigen keine Veränderungen vor und nach der Therapie. Jedoch ergibt die Analyse der Gruppen mit unterschiedlichen

Asymmetriemustern, dass depressive Patienten mit höherer linksfrontalen Alphaaktivität vor der Therapie die Asymmetrie in Richtung höherer rechtsfrontalen Alphaaktivität nach der Therapie signifikant verschieben.

Vor der Therapie zeigen Korrelationen zwischen Thetaaktivität und Symptomatik entgegen den Hypothesen, dass eine Reduktion in der linkspräfrontalen Region und eine Erhöhung in der rechtsparietalen Region mit geringerer depressiven Symptomatik assoziiert sind. Auch verringerte Alphaaktivität in der linkspräfrontalen Region ist mit weniger depressiver Symptomatik verbunden. Nach der Therapie ist die Normalisierung der Deltaaktivität in den präfrontalen und parietalen Regionen der rechten Hemisphäre nicht mit einer Symptomverbesserung verbunden. Auf der anderen Seite ist die Verringerung der rechtsfrontalen Deltaaktivität mit deutlicheren Verbesserungen der Depressionssymptomatik assoziiert. Zudem ist die Veränderung hin zu einer Reduktion der Alphaaktivität in dem rechtspräfrontalen Region und der Deltaaktivität in dem rechtsfrontalen Region mit höherer Symptomverbesserung verbunden.

Diese Arbeit ist die erste Studie, welche neuromagnetische Aktivität nach der psychotherapeutischen Intervention untersucht, und die erste, die einen Beweis aus dem MEG dafür liefert, dass Psychotherapie in der Lage ist, die regionale Gehirnaktivität bei depressiven Patienten zu normalisieren. Dennoch hat diese Studie auch ihre Beschränkungen. So könnten die Medikamente bei denjenigen Patienten, die mit Medikamenten, deren Effekte unbekannt sind, behandelt wurden, Einfluß auf die Ergebnisse gehabt haben. Die Befunde dieser Studie müssen daher durch eine Stichprobe von depressiven Patienten ohne Medikation bestätigt werden. Zudem könnte sich die Richtung des Zusammenhangs zwischen anormaler Aktivität und Symptomatik verändern, wenn die Korrelationen mit BDI und BPRS für die gesamte Stichprobe einschließlich depressiver und gesunder Probanden berechnet werden.

Summary.

A number of electroencephalographic studies have demonstrated abnormal brain activity in depressed subjects. However, very few magnetoencephalographic studies investigate abnormal neuromagnetic activity in depression, and no study to date has examined neuromagnetic activity before and after psychotherapeutic intervention. Furthermore, recent neuroimaging research confirms the effectiveness of various interventions in the normalization of regional brain abnormalities in depression. This study uses magnetoencephalography (MEG) to examine abnormal regional activity in depressed patients and to investigate the change in activity after cognitive-behavioral therapy.

Following the literature, depressed patients are expected to show diminished anterior and augmented posterior resting activity in the delta and theta bands compared to controls. In the alpha frequency band, depressed patients are expected to show an anterior asymmetry towards greater left activity and a posterior asymmetry towards greater right activity, compared to healthy subjects. In addition, abnormal neuromagnetic activity is expected to correspond to higher symptomatology. After therapy, depressed patients are expected to demonstrate a change in abnormal regional activity towards normalization. Moreover, treatment effects, evaluated by change in symptom scores, are expected to relate to a change in neuromagnetic activity in the direction of normalization.

The MEG was measured in 24 inpatients meeting the criteria for a ICD-10 (International Statistical Classification of Diseases) diagnosis of mental and behavioral disorders during a resting period prior to psychotherapeutic intervention and at the end of therapy. The patients' clinical status was assessed with Beck Depression Inventory (BDI) and Brief Psychiatric Rating Scale (BPRS) at both time points. Before treatment all but four patients received medications. The patient group was compared to 24 healthy subjects, similar in age to the depressive patients.

Analysis of symptomatology shows that most depressed patients have moderate depression as measured by BDI scores before treatment. Patients with a diagnosis of recurrent depressive disorder (F33) have a higher level of depression severity than patients with a diagnosis of depressive episode (F32). At the end of therapy, the BDI and BPRS scores reveal a decrease in symptomatology relative to the beginning of

therapy across all depressed groups. Before treatment, a higher level of depression severity is related to longer duration of psychotherapeutic treatment.

Present findings demonstrate, consistent with expectations, that depressed patients display reduced prefrontal and enhanced parietal delta and theta activity, compared to controls. Furthermore, younger depressed patients display more delta power in the right parietal region. In the alpha band, the same patterns of reduced left prefrontal and enhanced parietal activity are observed. Finally, contrary to expectations, depressed patients fail to demonstrate abnormal alpha asymmetry.

Before therapy, frontal delta reduction and left parietal theta and alpha enhancement are more pronounced in patients with a F33 diagnosis than in patients with a F32 diagnosis. These results demonstrate that, compared with depressive episode, recurrent depressive disorder, together with higher depression severity, is associated with greater abnormalities in resting slow wave and alpha activity.

After therapy, in addition to symptom improvement, depressed patients show an increase in delta power in the right prefrontal region and a decrease in the right parietal region relative to the beginning of treatment. These results confirm the hypothesis that treatment effects, evaluated by symptom improvement, are accompanied by normalization of delta activity in the prefrontal and parietal regions of right hemisphere in depressed patients.

Although theta and alpha activity did not change form pre- to post-treatment, there were significant decreases in the right parietal theta activity in patients with a F32 diagnosis and in the left parietal alpha activity for patients with a F33 diagnosis at the end of therapy relative to the beginning. However, there were no significant changes in alpha activity laterality indices from pre- to post-treatment. Nevertheless, examining groups with opposite asymmetry patterns reveals that depressed patients with greater left frontal alpha activity at the beginning of treatment significantly shift the asymmetry pattern towards greater right frontal alpha activity at the end of treatment.

Before therapy, correlations between theta power and symptomatology reveal, contrary to expectations, that decreased power in the left prefrontal region and increased power in the right parietal region are associated with lower depression severity. Also, decreased left prefrontal alpha power is associated with less severe depression. After therapy, normalization of delta power in the prefrontal and parietal regions of the right hemisphere is not associated with symptom improvement. On the

other hand, change towards a decrease in the right frontal delta activity and in the right prefrontal alpha activity from pre- to post-treatment is associated with greater symptom improvement.

This is the first study to investigate neuromagnetic activity after psychotherapeutic intervention, and the first to provide evidence from MEG that psychotherapy is able to normalize the regional brain activity in depressed patients. Nevertheless, this study does have some limitations. Most notably, because depressives in the present study were also treated with medication and the effects of these medications on neuromagnetic activity are unknown, these medications may have influenced the results. The findings of this study must be confirmed in a sample of depressed patients not on medication. In addition, the direction of relationships between abnormal neuromagnetic activity and symptomatology may change if the correlations with BDI and BPRS have been computed for the sample as a whole (combining depressed and control participants).

1. INTRODUCTION.

Brain oscillations play a key role in understanding brain dynamics and human information processing. Because these oscillations vary considerably as a function of neurological and psychological condition, the study of these oscillations in psychiatric disorders, such as depression, may provide a better understanding of neural circuitry dynamics and have broad implications for treatment. This study examines the role of brain oscillations in depressive patients to both identify dysfunctional brain regions and to establish the effects of pyschotherapeutic intervention.

Previous studies have demonstrated the importance of certain types of brain oscillations in brain dysfunction. Studies suggesting that slow oscillatory rhythms often appear in the vicinity of a structural lesion have provided researchers the first clues about the potential importance of these rhythms in neurological disorders[1]. These important findings have led researchers to examine the role of slow wave activity in psychological disorders such as depression and schizophrenia. As a result, abnormal slow wave activity has been reported in psychopathological conditions (Fehr et al., 2001, 2003; Wienbruch et al., 2003), suggesting that a concentration of focal magnetic slow waves may indicate dysfunctional brain areas in psychiatric patients.

A number of studies have found different patterns of regional brain activity when comparing depressed and non-depressed subjects. There remains little consensus in the literature, even after controlling for different research techniques. Some studies find abnormal increased regional activity compared to controls, while other studies find abnormal decreased activity. Astoundingly, several other studies find no significant difference in brain activity between depressed persons and controls. This suggests that research in this field remains uncertain about the relationship between brain activity and depression, and indicates that more work must be done. Insights from functional neuroimaging studies of depression may ultimately localize specific brain regions, elucidate treatment mechanisms, and guide pathophysiology-based classification of depression.

[1] For recent studies examining slow wave activity in patients with brain lesions, see De Jongh et al. (2001), Hensel et al. (2004); Meinzer et al. (2004); Vieht et al. (2000).

Although the findings of different studies do not completely converge, it is possible to observe some consistencies. Abnormal brain activity has been found mostly in the anterior and posterior regions. In the frontal and prefrontal cortex, a reduction in metabolism and cerebral blood flow (Baxter et al., 1989; Bench et al., 1992; Ebert, Feistel and Barocka, 1991; Martinot et al., 1990), and electric slow wave activity (Flor-Henry, Lind and Koles, 2004; Wienbruch et al., 2003) has been found in depressed persons. Also atypical increased activation in the parietal region has been identified in electroencephalographic (EEG) studies (Dierks et al., 1993, Flor-Henry, Lind and Koles, 2004).

In addition, abnormal patterns of asymmetric activity in depression have been observed in many EEG studies. Depressed persons show greater left than right frontal alpha power (Allen et al., 1993; Gotlib, Ranganath and Rosenfeld, 1998; Henriques and Davidson, 1991) and greater right than left parietal alpha power (Bruder et al., 1997; Debener et al., 2000) compared to controls. This evidence is consistent with neurological studies indicating that the severity of depressive symptomatology is correlated with lesions in the left frontal (Morris et al., 1996; Robinson and Downhill, 1995; Shimoda and Robinson, 1999) and right parietal regions (Sinyor et al., 1986; Fedoroff et al., 1992); and regional cerebral blood flow studies showing that clinically depressed participants demonstrate relative decreases in the left frontal (Baxter et al., 1989; Bench et al., 1992; Ebert et al., 1991; Gonul et al., 2004; Martinot et al., 1990) and right parietal (Bonne et al., 2003) areas when compared to non-depressed controls.

Moreover, studies relating symptomatology to the dysfunctional nature of regional brain activity suggest that severity of depression strongly correlates with decreased activity in the left prefrontal region (Baxter et al., 1989; Bench et al. 1993; Galynker et al., 1998; Wienbruch et al., 2003). Greater left compared to right frontal alpha power has also been shown to correlate with depression symptoms (Diego, Field and Hernandez-Reif, 2001; Schaffer, Davidson and Saron, 1983). However, a relationship between the parietal region and depression severity is not invariably found (Bruder et al. 1997; Metzger et al., 2004). These findings require further investigation.

Identification of dysfunctional brain regions in depression may ultimately provide not only a diagnostic aid in psychiatry, but also the means to monitor treatment. Recent research confirms the effectiveness of different therapeutic

interventions in the normalization of regional brain abnormalities in depression. If alterations of local slow wave activity indicate a dysfunctional condition in the corresponding brain region, reversibility or at least partial change may be expected during a spontaneous or therapy-supported recovery. Findings suggest that the psychotherapeutic approach has the potential to modify the dysfunctional neural circuitry associated with various psychiatric disorders (Nakatani et al., 2003; Paquette et al., 2003). PET studies confirm that psychotherapy can lead to adaptive regional brain metabolic changes in depressed persons (Brody et al., 2001; Martin et al., 2001).

Although various neurological, cerebral blood flow and EEG studies indicate certain regional brain abnormalities in depressed persons, there are very few studies in depression which investigate brain activity using magnetoencephalogram (MEG). This study investigates differences in neuromagnetic brain activity between patients with affective disorders and healthy subjects. First, I examine patterns of abnormal regional activity in depression and compare the findings with other research in this area employing different imaging techniques. Previous studies of depression have found abnormal activity in the prefrontal, frontal, and parietal regions; however, these results have yet to be confirmed using MEG. Moreover, I examine atypical anterior and posterior asymmetry in depression, something MEG studies have not yet investigated.

Secondly, I examine the relationship between regional abnormalities and depressive symptomatology. Some studies, but not all, suggest that regional abnormal activity correlates with symptomology. Again, these studies have mostly employed other imaging techniques.

Thirdly, I investigate the changes in brain activity in the delta, theta and alpha frequency bands in relation to symptom change in depressed patients during the course of a stationary psychiatric treatment including cognitive-behavioral therapy. No MEG study to date has examined changes in neuromagnetic brain activity as a result of psychotherapeutic intervention in depression.

1.1. Description and function of brain oscillations.

Most general dynamics in the brain are governed by the brain's natural oscillations, which provide basic links to brain functions (Basar et al., 2001). Brain oscillations vary considerably as a function of neurological and psychological condition. Differences in brain arousal systems determine fundamental differences in temperament, personality and cognition, as well as vulnerability to psychiatric disorders (Knyazev et al., 2003; Robinson, 2000).

Changes in arousal are normally accompanied by modifications of the electric and magnetic activity that can be recorded with EEG and MEG. In the alert, activated state cortical activity is characterized by low voltage fast activity. With a decreased activation, there is a gradual slowing in the overall frequency of the EEG/MEG, while its amplitude increases. Rhythmic oscillations in the alpha (9–13 Hz) and theta (4–9 Hz) range characterize drowsiness and superficial sleep. In the deepest phase of sleep, large irregular delta waves (0–4 Hz) dominate the EEG/MEG (Basar, 1998; Steriade, 1999b).

1.1.5. Neural basis of EEG and MEG.

MEG and EEG are noninvasive techniques for investigating neuronal electric and magnetic activity in the living human brain. Bioelectric neural currents arise in the pyramidal neurons of the cerebral cortex (Nunez, 1981). These currents produce excitatory postsynaptic potentials and inhibitory postsynaptic potentials along the dendritic tree of the pyramidal neurons. Current flow within the pyramidal neurons is called the primary current. The intracellular currents produce compensatory extracellular currents in the extracellular tissues called secondary currents. Because these extracellular currents are symmetrically distributed around the neuron, their magnetic fields cancel because of symmetry, leaving only the primary currents as the source of MEG fields in most circumstances. The secondary currents, also known as volume currents, propagate throughout the body in a manner determined by the conductivity of each tissue. EEG records potential differences arising from secondary currents when electrodes are attached to the scalp or implanted into the brain (Barkley, 2004; Hämäläinen et al., 1993).

Membrane potential changes of cortical pyramidal cells depend mainly on two factors: on the synaptic inputs reaching the cells and on the functional state of the different ion channels in their membrane. The most potent synaptic input reaches the cortex from the thalamus; thus thalamic activity has a very strong influence on cortical EEG/MEG. The thalamus has two modes of operation: oscillatory and transmitting modes (McCormick and Bal, 1997; Steriade and Deschenes, 1984). In the first mode, relay cells fire rhythmic high-frequency bursts inducing rhythmic waves in the cortical EEG in the alpha-theta range. In the transmitting mode, irregular activity of the relay cells is accompanied by cortical desynchronization. Switching between these modes depends on the membrane potential of the thalamic relay and reticular neurons. Their membrane potential in turn is set by different ascending modulatory systems. Activity in these systems promotes relay mode in the thalamus (McCormick, 1992). The same modulatory influence also reaches the cortex through direct projections. These inputs provide the other important factor in the regulation of cortical EEG in addition to the synaptic input from the thalamus.

The four major transmitters (cholinergic, noradrenergic, serotonergic, and histaminergic) have modulatory actions promoting responsiveness of the cortical and thalamic cells (Detari, 2000). An exception is acetylcholine, which inhibits GABAergic neurons in the reticular nucleus of the thalamus (McCormick, 1992). The anatomies of these systems share common characteristics. The cell bodies are located in more or less circumscribed parts of the brain stem and basal forebrain; all innervate extended areas of the brain with monosynaptic projections and probably all participate in some generalized function. However, the cholinergic component has been traditionally thought to have the greatest importance for maintaining arousal because observations that large slow waves, indistinguishable from those seen during deep sleep (Longo, 1966), are induced by the muscarinergic antagonists, atropine or scopolamine. Such effects are not seen after the manipulation of the other systems. In addition, acetylcholine alone is capable of maintaining a high level of EEG activation during REM sleep, when the other systems are silent or show very little activity (McCormick, 1992; Steininger et al., 1999).

1.1.2. Alpha rhythm (8-12 Hz).

Oscillatory EEG/MEG activity, such as the waking-alpha rhythm, is thought to entail reverberating activity in thalamo-cortical and cortico-cortical circuits (Larson et al., 1998; Lopes da Silva et al., 1973, 1980; Steriade, Jones and Llinas, 1990). The visual cortex and the lateral geniculate nucleus of the thalamus have been found to generate highly coherent alpha oscillations with significant phase shifts (Klimesch, Pfurtscheller and Schimke, 1992; Klimesch, Schimke and Pfurtscheller, 1990).

Steriade and colleagues (1985, 1987) suggest that only the nucleus reticularis is capable of producing spindle oscillations (7 to 14 Hz). Moreover, Steriade and Deschenes (1984) conclude that an inverse relationship exists between cellular activity in the thalamus and cortical oscillations of 7 to 14 Hz. In other words, activity in the nucleus reticularis is inversely correlated with cortical alpha rhythms. Two recent studies by Larson et al. (1998) and Lindgren et al. (1999) demonstrate robust inverse correlations, indicating that greater thalamic metabolism is correlated with decreased alpha power. Furthermore, this relationship has been established in healthy subjects, but not in depressed patients, possibly indicating a deficit in thalamocortical connectivity in depressives (Lindgren et al., 1999).

Alpha synchronization is a state in which millions of cortical neurons oscillate synchronously with the same phase and within a comparatively narrow frequency band. Desynchronization seems to imply that different oscillators within the alpha band are no longer coupled and start to oscillate with different frequencies. Alpha synchronization occurs during alert wakefulness, whereas desynchronization reflects actual cognitive information processes (Basar, 1997).

Lower alpha desynchronization (in the range of about 6–10 Hz) is obtained in response to a variety of non-task and non-stimulus specific factors (Gevins et al., 1997, Weiss and Rappelsberger, 1996) which may be best subsumed under the term “attention” (see also Shaw, 1996). Upper alpha desynchronization (in the range of about 10–12 Hz) is topographically restricted and develops during the processing of sensory-semantic information (Klimesch, 1996, 1999; Klimesch, Schimke and Schwaiger, 1994; Klimesch et al., 1997a, 1997b).

The reported findings suggest that alpha frequency is an indicator of cognitive and memory performance (Basar, 1998). This conclusion is also supported by the fact

that alpha frequency increases from early childhood to adulthood and then decreases with age, similar to brain volume and general cognitive performance (Bigler et al., 1995; Willerman et al., 1991). Opposite alpha rhythm, theta frequency decreases from early childhood to adulthood and then increases with age. However, a pronounced decrease in alpha and increase in theta in the elderly may be due to age related neurological disorders and not to age per se (Breslau et al., 1989; Harmony et al., 1995; Hubbard, Sunde and Goldensohn, 1976).

1.1.3. Theta rhythm (2-8 Hz).

The hippocampus is one of several limbic cortical structures that is considered to be a generator of the theta rhythm (Basar, 1998; Kirk, 1998; Bland, 1986). Fujita and Sato's (1964) intracellular analysis of pyramidal cells in hippocampus indicates that 85% of the impailed neurons show rhythmic slow oscillations of the membrane potential that are synchronous with theta waves; the positive and negative phases recorded extracellularly in the pyramidal cell body correspond to the hyperpolarization and depolarization of the intracellular rhythm. Although Fujita and Sato (1964) indicate that the cells firing synchronously with theta are pyramidal neurons, Fox and Ranck (1981) later demonstrate that very few hippocampal cells with theta-like discharge properties can be antidromically driven from stimulation of hippocampal projection pathways, which is a further indication that theta cells are interneurons. Furthermore, Vertes (1982) reports in 24 separates studies that brainstem reticular formation stimulation elicits a theta rhythm in the hippocampus. Very few brainstem sites outside the reticular formation have been shown to affect the hippocampal EEG.

A series of experiments have demonstrated that even in a human scalp EEG, the theta band responds selectively to the encoding of new information into episodic memory. This effect was first demonstrated by Klimesch et al. (1994, 1997c), suggesting that a close relationship between theta synchronization and the encoding of new information reflects theta activity that is induced into the cortex via cortico-hippocampal feedbackloops. Further evidence for this interpretation comes from a study by Gevins et al. (1998), who use a new method to spatially sharpen the EEG with magnetic resonance imaging-based finite element deblurring. These authors

found a frontal midline theta rhythm which increases with increasing memory load. Most interestingly, dipole models localized this signal to the region of the anterior cingulate cortex, which is linked with the hippocampal formation via complex feedbackloops.

Today, event related theta oscillations can be considered important building-blocks of functional signaling in the nervous system related to cognitive and emotional processing and cortico–hyppocampal–limbic interaction (for review see Basar, Schurmann and Sakowitz, 2001). A strong theta band power increase during concentrated task performance (Sasaki et al., 1996), attention (Dietl et al., 1999) and affective processing (Aftanas et al., 1998, 2001, 2003; Aftanas and Golocheikine, 2001) has been reported.

It is important to note that there are two different types of theta synchronization. One type of synchronization is related to an increase in power within a narrow frequency band in the range of peak theta frequency. The second form of theta synchronization refers to irregular slow activity related to an increase in power over a broad range. It appears plausible to assume that the narrow band synchronization during regular rhythmic theta activity reflects event-related theta synchronization that is closely linked to the encoding of new information (or "recoding" during REM), whereas the broad band increase in theta power reflects a state in which the ability to encode new information is reduced or even blocked (e.g., during the hypnagogic state, in slow wave sleep or in demented subjects) (Buzsaki et al., 1992).

1.1.4. Delta rhythm (0,5-4 Hz).

Low-frequency rhythms that characterize slow-wave sleep consist of several types of synchronized oscillations: spindles (7–14 Hz), which are generated in the thalamus and appear during early sleep stages (Steriade, McCormick and Sejnowski, 1993); two types of delta waves (1–4 Hz), which are generated in the thalamus (Steriade, McCormick and Sejnowski, 1993) and the neocortex (Amzicha and Steriade, 1998, 2002), and are more prominent during late stages of non-REM sleep; and slow oscillation (usually 0.6 to 1.0 Hz). The latter, which has been described in intracellular recordings of cortical neurons in anesthetized cats (Steriade, Nunez and Amzicha, 1993), is marked by a continuous alternation of the membrane potential

between two voltage levels: a depolarized and a hyperpolarized one. The membrane depolarization is due to synchronous synaptic activities in the cortical network (Amzica and Steriade, 1995), and is made mainly of excitatory and inhibitory postsynaptic potentials (Steriade, Nunez and Amzicha, 1993). Each depolarizing-hyperpolarizing cycle of the cellular slow oscillation corresponds, at the EEG level, to a K-complex ((KC); Amzica and Steriade, 1997, 1998). Through its long-range synchronization, the slow oscillation has the ability to trigger and to group thalamically-generated spindles and two delta (1–4 Hz) oscillations.

Most *in vitro* (McCormick, 1992; McCormick and Pape, 1990) and *in vivo* (Curro Dossi, Nunez and Steriade, 1992; Nunez et al., 1992; Steriade, Curro Dossi and Nunez, 1991) studies have revealed an intrinsic oscillation of thalamocortical neurons within the frequency range of EEG delta waves (1-4 Hz). The only thalamic neurons with documented intranuclear collaterals, the dorsal lateral geniculate, have been shown to display rhythmic synaptic potentials at the delta frequency (Nuñez, Amzicha and Steriade, 1992; Soltesz and Crunelli, 1992). The basic mechanism relies on the interplay between two currents, available in virtually all thalamocortical cells at hyperpolarized membrane potentials (below −70 mV): the low-threshold transient Ca^{2+} current (I_t) and the hyperpolarization-activated current (I_h). The afterhyperpolarization of the I_t activates the I_h, which in turn triggers the I_t, promoting the rhythmicity of this oscillation (McCormick and Pape, 1990; Soltesz et al., 1991).

In contrast to large networks of cortical cells generating the slow (<1 Hz) oscillation, individual thalamocortical neurons produce a clock-like delta oscillation. Being generated in individual neurons, the oscillation still has to undergo a synchronizing process in order to reach the cortex coherently and hence to diffuse into the EEG. Since it is generally accepted that thalamocortical neurons are not synaptically coupled, an extrathalamic structure is expected to assume the synchronizing task. It has been shown that the cerebral cortex may synchronize the clock-like delta in the thalamus (Steriade, Curro Dossi and Nunez, 1991) and that the cortically generated slow oscillation resets the clock-like delta oscillation in thalamocortical neurons (Steriade et al., 1993). The slow oscillation is synchronized over wide cortical territories (Amzica and Steriade, 1995) and will therefore send synchronized excitations in many thalamic nuclei that will, in turn, start simultaneous sequences of clock-like oscillations. It was demonstrated that reduced temporal jitter of thalamic delta is obtained at more negative membrane potentials (Curro Dossi,

Nunez and Steriade, 1992). Under these circumstances, more synchronized delta cycles from the thalamus may reach the cortex and be reflected in the EEG as delta wavelets following a KC and contributing to the polymorphic pattern of slow wave sleep (also for reviews see Steriade, 1999a, 2002).

The rhythmic spike-bursts of thalamic and neocortical neurons that are present during slow wave sleep oscillations could assist in specifying and reorganizing the brain circuitry, and could contribute to the strengthening of synaptic contacts that carry behaviorally relevant information. Moreover, the low-frequency oscillations followed by persistent changes in neuronal excitability within thalamocorticothalamic loops can be expressed in normal conditions, but can eventually develop into pathological conditions (Steriade and Timofeev, 2003; Grenier et al., 2003).

1.2. Brain oscillations and pathology.

Similar to the interpretation of slow oscillatory rhythms during sleep stages as deafferentation of the cortex due to thalamic hyperpolarisation (Steriade, 1997), abnormal focal slow wave activity in the waking state might indicate functional deafferentation in the sense of reduced information processing and impaired neuronal network communication in affected brain regions (Gloor, Ball and Schaul, 1977; Amzica and Steriade, 1997).

Grey Walter (Walter, 1936) was the first to assign the term “delta waves” to particular types of slow waves recorded in the EEG of humans and used this term to describe pathological potentials due to cerebral tumors. Tumors are associated with massive damage to neurons and, since cortico-cortical connections provide the majority input to the cortex itself (DeFelipe and Fariñas, 1992), it is likely that the region circumscribing them acts as a relatively deafferented area. Electrical stimulation of activating brain-stem structures, as well as of the thalamus, disrupts the slow oscillation (Steriade, Amzicha and Nunez, 1993), and the thalamically-generated intrinsic delta (Steriade, Curro Dossi and Nunez, 1991). Thus, the persistence of delta waves around pathologic brain tissue may reflect deafferentation (Ball, Gloor and Schaul, 1977; Gloor, Ball and Schaul, 1977). Functional cortical deafferentation achieved during sleep and surgical or pathologic deafferentation may have similar

effects on the cortical activity by enhancing the production of slower (<4 Hz) oscillations (Amzicha and Steriade, 1998).

The first studies on pathological slow waves using MEG have been reported by Lewine and Orrison (1995), Orrison et al. (1995) and Lewine et al. (1995) analyzing 1-4 Hz oscillations in a large group of patients with brain lesions. In patients with neoplasms with a mass effect, dipoles were located at tumors margins. For pathophysiological reasons this is a plausible location for generators of abnormal electric activity. Also, a study by De Jongh et al. (2001) including five patients with a cerebral tumor, showes a location of asymmetric dipole distributions describing abnormal slow-wave activity in the affected hemispheres, adjacent to or within the tumor tissue. Dipoles describing delta and theta activity were located ipsilateral to lesions. Dipole positions might therefore give clinically relevant information. For example, many patients with cerebral tumors suffer from epilepsy. Delta wave sources might indicate locations of irritative zones in epileptic patients. Gallen et al. (1997) investigated the use of abnormal low-frequency magnetic activity for presurgical evaluation in epileptic patients. The results obtained in a group of 13 patients with cortical space-occupying lesions provide strong support for the assumption that both delta and theta abnormal EEG activities are the counterparts of two different pathophysiological processes, lesion and edema respectively (Fernandez-Bouzas et al., 1999).

The relationship between slow wave brain activity and brain lesions also has been established in the studies of Vieth and colleagues (1995, 1996, 2000). The authors analyze 2-6 Hz slow-wave oscillations in patients with white matter lesions (Vieth et al., 1995). MEG data were bandpass-filtered according to the EEG band and dominant signals were selected using principal component analysis. They find that delta activity is associated with white matter lesions. In the next study, for an accurate source localization, Vieth et al. (1996) transform the MEG coordinate system to the magnetic resonance imaging (MRI) system using a surface fit of the digitally measured head surface and the reconstructed surface of the MRI scan. All source localization procedures were tested using structural brain lesions, which were verified by imaging techniques (MRI or computed tomography (CT)), showing the results in close topographical relation to the lesions.

The abnormal EEG activity in patients with a chronic subdural hematoma is characterized by the presence of focal slow waves on the side of the hematoma

(Tolonen and Sulg, 1981) and therefore, an injury to the thalamus has been considered to be the cause for the abnormal EEG activity (Gloor, Ball and Schau, 1977). Following these findings, Tanaka and colleagues (1998) evaluate the correlation between the cerebral blood flow (CBF) reduction using the CT method and topographic EEG changes in ten patients having a chronic subdural hematoma with hemiparesis and/or a mental disturbance. Cerebral blood flow values correlate negatively with the presence of delta and theta waves and positively with alpha waves. On the side with the hematoma, the brain wave activity correlate significantly with thalamic flow, and the correlation is greater than with the hemispheric or cortical flow. The correlation of EEGs with thalamic flow, which was maximally reduced, seems to substantiate the assumption that the thalamus is primarily injured by brain distortion due to the compression from hematoma and that the remote areas are secondarily deactivated by a transneural depression ("diaschisis") originating from the dysfunctioning thalamus. Thalamic involvement seems to be the cause of the neurologic dysfunction and the abnormal EEG activity in chronic subdural hematomas. Also, the consistent correlation of delta and alpha waves with CBF in the central, temporal, and occipital regions has been seen in brain ischemia (Nagata et al., 1989).

EEG data from aphasic patients with a left hemisphere infarct or bleeding confirms a focus of delta activity in the affected (left) hemisphere (Hensel et al., 2004). Meinzer et al. (2004) shows the same result in aphasic patients by means of MEG recordings, suggesting increased delta activity in the left hemisphere and in the vicinity of the structurally obvious lesion, as verified by structural MRI.

EEG changes typically present in patients with Alzheimer's disease (AD) include increased power in the theta and delta bands, but decreased power in the alpha band (Berendse et al., 2002; Buchan et al., 1997; Coben, Danziger and Storandt, 1985; Dierks et al., 2000; Duffy, Albert and McAnulty, 1984; Fernandez et al., 2002; Penttilä et al., 1985; Robinson et al., 1994, for review see Jeong, 2004). In patients with AD, researchers relate EEG slowing and many cognitive symptoms to the atrophy of cholinergic and monoaminergic neurons, which have been implicated in the etiology of AD because markers for both transmitters are consistently reduced in the brains of AD patients (Dringenberg, 2000; Dringenberg, Diavolitsis and Noseworthy, 2000; Soininen et al., 1992). This observation is consistent with a large number of animal studies that have provided evidence that the loss of cholinergic, and

also of monoaminergic inputs to the cortical mantle can result in EEG slowing and loss of desynchronization (Drindenberg et al., 2002; Vanderwolf and Baker, 1986). Some EEG changes are found to be a sensitive index of degree of cognitive impairment, especially reflected in increased absolute and relative power in the theta band, with delta increasing in later stages of cognitive deterioration (Prichep et al., 1994).

The focal slow wave activity explained by metabolic or blood flow changes consequent upon the structural lesion has been attributed to pathological or dysfunctional neural tissue (Niedermeyer and Lopes da Silva, 1987; Lewine and Orrison, 1995). This brain activity may not only result from neurologic disease but also may appear in certain psychopathologic conditions. For example, augmented slow wave activity has been reported for psychiatric patients with posttraumatic stress disorder (PTSD; Teicher et al., 2002; Begic et al., 2001), with attention-deficit/hyperactivity disorder (Barry, Clarke and Johnstone, 2003; Clarke et al., 1998) and schizophrenia (Canive et al., 1998; Clementz et al., 1994; Elbert et al., 1992; Harris et al., 1999, 2001; Koshino et al., 1993; Mientus et al., 2002; Rockstroh, Elbert and Berg, 1997; Shagass, 1991; Sponheim et al., 2000; Winterer and Herrmann, 1995; Wuebben and Winterer, 2001). This is complemented by mapping slow wave generators in the EEG or MEG, which in schizophrenic patients disclosed a clustering in temporal and parietal regions (Canive et al., 1998; Fehr et al., 2001, 2003; Sperling et al., 2002; Wienbruch et al., 2003) and in anterior areas (Pascual-Marquis et al., 1999), whereas in PTSD patients an increase of theta activity is observed over central region (Begic et al., 2001). The dysfunctional nature of focal slow wave is also suggested by the relationship to symptomatology. Lewine et al. (2002) and Wienbruch et al. (2003) find that enhanced left-temporal MEG-theta activity in schizophrenic patients is associated with hallucinatory symptoms, and Sperling et al. (2002) report a high correlation between focal magnetic delta concentration and productive psychotic symptoms.

In contrast to these findings, Coutin-Churchman et al. (2003) conclude that a decrease in slow wave activity can be regarded as a specific sign of brain dysfunction. In their study, they demonstrate a reduction of delta and theta power in a large sample of different psychiatric patients with varying disorders, but mostly depression. Moreover, a delta-theta decrease is correlated with cortical atrophy as seen in MRI.

With regard to abnormal alpha activity, reduction has been found in schizophrenia (Sponheim et al., 2003), in attention-deficit/hyperactivity disorder (Barry, Clarke and Johnstone, 2003; Clarke et al., 1998), in obsessive–compulsive disorder (Bucci et al., 2004) and in Alzheimer's disease (Bennys et al., 2001; Ihl et al., 1993; Maurer and Dierks, 1992; for review see Jeong, 2004). Lower alpha power and increased slow wave activity have been found in children with reading disabilities and attention deficit/hyperactivity disorder (Chabot et al., 2001; Hughes and John, 1999; Scarpa and Raine, 1997).

The present results call for an investigation of whether abnormal slow wave and alpha activity charcterize pathological or dysfunctional brain regions in neurologic and psychiatric disorders. EEG/MEG alterations may be considered highly suggestive of the presence of neuronal atrophy or malfunctioning, and thus important in the overall management of any patient with a mental health disorder. Identification of dysfunctional brain regions in different psychopathologic conditions might ultimately provide a diagnostic aid in psychiatry.

1.3. Regional brain abnormalities in depression.

Recent research using various methodologies has investigated the link between depression and patterns of cortical activation. Some studies have used different functional neuroimaging techniques to examine brain activation in depressed persons compared to healthy subjects, while others have reported affective responses in patients who have incurred localized brain damage. The most consistent finding of these studies suggests that depressed patients show abnormal brain activation in the anterior region, primarily in the left hemisphere, and in the posterior region, mainly in the right hemisphere.

1.3.1. Depression associated with brain lesions.

Research on depressive syndromes in patients with brain lesions was initially motivated by the observation that affective disturbances are common among brain damaged patients (for reviews see Davidson, 1984; Silberman and Weingartner, 1986; Tucker, 1981). For example, approximately 25% of patients who have suffered an acute stroke also develop major depression (Robinson et al., 1983), while another 40% experience a minor depression or dysthymia (Eastwood et al., 1989). Older literature examining damage from stroke and lesions of the left hemisphere indicates that following such injury there is increased depression, dysthymia and negative emotions expressed through tears and dysphoric mood changes. In contrast, lesions of the right hemisphere have been associated with the inability to understand and interpret the emotional states of others, excessive laughter and joking, and inappropriate behavior in social settings including pathological laughter (Sackeim et al., 1982). Observations by Robinson and colleagues (Robinson and Benson, 1981; Robinson and Szetele, 1981; Robinson and Price, 1982; Robinson et al., 1983; Robinson et al., 1984; Shimoda and Robinson, 1999; for a review, see Robinson and Downhill, 1995; Rosenthal et al., 1998) of brain-damaged patients have suggested that the severity of post-stroke depression is associated with left-hemisphere lesions in the frontal pole. The authors also find that right-hemisphere posterior lesions are similar to left-hemisphere frontal lesions in that they tend to produce depression (Robinson and Szetele 1981; Robinson et al., 1984). A study by Fedoroff et al. (1992) establishes the same result, indicating an association between major depression and left dorsolateral frontal lesions in patients with traumatic brain injury. Right parietal-occipital lesions are also associated with depression, however, to a lesser extent. This evidence has also been confirmed in a study by Morris et al. (1996) showing that patients with lesions involving left hemisphere prefrontal or basal ganglia structures have a higher frequency of depressive disorder than other left hemisphere lesions or those with right hemisphere lesions.

Orbitofrontal cortex lesions are associated with abnormalities in a wide range of affective behaviors including depressed mood, anger, affective instability, irritability, and anxiety symptoms, frequently observed in major depression disorder patients (Grafman et al., 1986, 1996). Humans with lesions that include the subgenual

prefrontal cortex demonstrate abnormal autonomic responses to emotional experiences, inability to experience emotion related to concepts that ordinarily evoke emotion, and impaired comprehension of the adverse consequences of pernicious social behaviors (Damasio et al., 1990; Bechara et al., 1996).

Thus, the most consistent finding among these studies is that the likelihood of depression is greatest in patients with left anterior lesions (Robinson and Price, 1982; Robinson et al., 1984; Starkstein et al., 1987; Astrom et al., 1993; Eastwood et al., 1989; Finkelstein et al., 1982).

1.3.2. Brain imaging studies.

Functional imaging studies of depression, using positron emission tomography (PET) and magnetic resonance imaging (MRI) techniques, have consistently demonstrated regional blood flow and metabolic abnormalities (Davidson and Henriques, 2000; Davidson et al., 1999, 2002; Drevets, 2000; Heller and Nitschke, 1997, 1998; Soars and Mann, 1997). Although several studies indicate that patients with major depression show increased metabolism and cerebral blood flow in the ventrolateral prefrontal cortex, (Brody et al., 2001; Drevets, 1995, 1998; Mayberg et al., 1997,1999; Baxter et al. 1987; Biver et al., 1994; Buchsbaum et al., 1986; Cohen et al., 1992; Drevets et al., 1992; Ebert et al., 1991; Wu et al., 1992), most investigators report a decrease in metabolic activity in the dorsolateral and medial areas of the prefrontal cortex (Baxter et al., 1987; 1989; Bench et al., 1992, Biver et al., 1994; Cohen et al., 1989, 1992; Curran et al., 1993; Dolan et al., 1993; Drevets et al., 1997, 1998; Ebert et al., 1991; Ketter et al., 1996; Kennedy, Javanmard and Vaccarino, 1997; Mayberg, 1997; Mayberg, 1994, Mayberg et al., 1999). Other studies have found lower glucose metabolism and regional cerebral blood flow (rCBF) in the anterior cingulate (Bench et al., 1992; Curran et al., 1993, Mayberg, 1994; Drevets et al., 1997; Kumar et al., 1993; Ito et al., 1996; Oda et al., 2003), lateral frontal regions (Vasile et al., 1996), inferior frontal area (Austin et al., 1992) and orbital frontal region (Kumar et al., 1993) of depressed unipolar patients. Using MRI, several studies observed that orbitofrontal cortex volumes in patients with major depressive disorders are smaller than those in controls (Bremner et al., 2002, Lacerda et al., 2004, Lai et al., 2000; Taylor et al., 2003). MRI data in depression also indicate

the presence of white-matter structural abnormalities in the frontal lobes (Leuchter et al., 1997) suggesting that white-matter lesions may disrupt fiber tracts linking cortical and subcortical structures and hence could compromise the function of systems responsible for mood regulation.

Depression has been linked to abnormalities in activation of prefrontal regions, mostly in the direction of decreased bilateral or predominantly left-sided activation (see reviews Davidson et al., 1999; George, Ketter and Post, 1994). Many studies (Baxter et al., 1989, Biver et al., 1994, Bench et al., 1995) use PET to measure reduced rCBF in the left prefrontal cortex in patients with major depression compared to controls. Patients suffering from major depression with psychotic features show decreased rCBF in the left subgenual anterior cingulate cortex relative to both non-psychotic depressed patients and healthy controls (Skaf et al., 2002). Both psychotic and nonpsychotic depressed patients show significantly lower rCBF values in the left and right superior frontal cortex, and left anterior cingulate cortex compared to those of controls (Gonul et al., 2004). In addition, the researchers report a strong association between the severity of depression and decreased activity in the left prefrontal region (Baxter et al., 1989; Bench et al., 1993; Galynker et al., 1998).

Regions of decreased metabolism in the inferior parietal (Drevets et al., 1992; Mayberg, 1994) and anterior parietal (Sackeim et al., 1990) regions have also been identified. The reduced cerebral blood flow in the inferior parietal region in untreated depressed patients is associated with deficits in attention and memory (Dolan et al., 1993). Another study by Berman et al. (1993) finds relatively decreased blood flow in the left parietal region and relatively increased in the right parietal region, whereas Bonne et al. (2003) demonstrates reduced rCBF in the right parietal and occipital lobes in depressed subjects compared with controls. Other studies fail to find significant abnormalities in parietal glucose metabolism (Kling et al., 1986; Hagman et al., 1990), blood flow (Maes et al., 1993; Mayberg et al., 1994; Vasile et al., 1996), frontal metabolism (Kling et al., 1996) and blood flow (Berman et al., 1993; Maes et al., 1993) in depressed unipolar patients.

Thus, while there are inconsistencies among studies concerning the exact nature of cerebral blood flow and glucose metabolism abnormalities, the results of these brain imaging studies converge to suggest that prefrontal, frontal and parietal cortical areas are abnormal in patients with affective disorders indicating a reduction of metabolism and blood flow.

1.3.3. EEG and MEG studies.

A large number of studies have assessed baseline EEG activity in depressed and nondepressed subjects in a rest condition, meaning subjects were alert but not performing a task. Such assessments have been denoted "resting EEG" in the literature (for review, see Tomarken and Keener, 1998). The relationship between depression and regional brain activity has been investigated primarily in the alpha band, but relationships in the delta and theta bands have been examined as well.

1.3.3.1. Abnormal slow wave activity in depression.

Findings in the delta and theta frequency bands are not very consistent. Some studies have found that depressed subjects have less delta and/or theta activity than non-depressed subjects (Pozzi et al., 1995; Passynkova and Volf, 2001; Mientus et al., 2002; Volf and Passynkova, 2002; Wienbruch et al., 2003; Lubar, Congedo and Askew, 2003). For example, decreased slow wave activity is observed in the posterior region in subjects with seasonal affective disorder (Passynkova and Volf, 2001; Volf and Passynkova, 2002). A recent EEG study using low resolution electromagnetic tomography (LORETA) to detect cortical activity in various psychiatric disorders finds a reduction in delta and theta activity for unmedicated depressive inpatients compared to controls in the anterior cingulate cortex (Mientus et al., 2002). Using the same technology, Lubar, Congedo and Askew (2003) report less delta power in the right middle temporal gyrus, but not in the anterior cingulate of unmedicated chronically depressed subjects. The differences between these two studies may have arisen from gender differences in the subject populations. The mixed gender sample in the Mientus et al. (2002) study contrasts with the exclusively female sample in Lubar, Congedo and Askew (2003) study. Wienbruch et al. (2003) investigate MEG activity in medicated mixed gender inpatients with affective disorder. They find that depressives have reduced delta and theta activity in the frontal and prefrontal regions relative to controls and schizophrenic patients. Suppression of left prefrontal slow wave activity is associated with severity of depression.

In contrast to these findings, other investigators have demonstrated more delta (Knott and Lapierre, 1987; Dierks et al., 1993; Kwon et al., 1996) and more theta

(Luthringer et al., 1992; Sloan and Fenton, 1993; Kwon et al., 1996; Llinas et al., 1999) activity in depressed patients compared to controls. In addition, Pollock and Schneider (1990) and Nyström (1986) establish positive correlations between slow wave activity and depression severity. Pozzi et al. (1993) also find enhanced theta activity in depressive patients with Alzheimer's disease (AD) compared to non depressed patients with AD. A study by Kwon et al. (1996) establishes higher EEG power in depressives in the right hemisphere. More delta activity is found in the posterior region in depressed patients, compared to controls (Dierks et al., 1993). Finally, neither delta nor theta has consistently distinguished depressed from control groups in the studies of John et al. (1988), Visser et al. (1985), Pollock and Schneider (1990), Reid, Duke and Allen (1998) and Pizzagalli et al. (2002).

Differences between studies may have resulted from age differences, as age may positively covary with increased risk for cognitive impairment or dementia. Dahabra et al. (1998) find a correlation between (enhanced) slow wave activity and cognitive impairment in older depressive patients irrespective of the duration of illness, structural abnormalities and clinical remission. Pozzi et al. (1995) control for the influence of age and dementia by comparing depressive patients with and without dementia; they find an increase in delta and theta activity (relative to controls) in demented depressives but a reduction in non-demented depressives. Furthermore, in a study by Brenner et al. (1986) depressed patients differ from demented patients, having less delta and theta activity.

Many of the EEG studies cited above use different recording and analytical procedures, which probably accounts for a substantial proportion of the variability among studies. Recently Flor-Henry, Lind and Koles (2004) use more electrodes to increase spatial resolution of the source-current density in their EEG study. They also use a spatial filter prior to the LORETA transformation, which has been shown to be effective for enhancing differences between EEG populations. They find that the pattern of reduced current density in the delta band of unmedicated depressed men is generally lateralized to the frontal region and left hemisphere, and increased source power is lateralized to the right hemisphere and right parietal region during the resting condition compared with matched controls.

Following the findings of these studies, depressed individuals demonstrate abnormal brain activity primarily in the anterior and posterior regions in the delta and theta frequency bands.

1.3.3.2. Brain asymmetry in the alpha band.

There are more studies which investigate electrical brain activity in depression in the alpha band than in the delta and theta bands, probably because prominent researchers have argued that delta and theta activity is not as strongly and consistently related to emotion as alpha (Davidson, 1988). Over 25 years ago Davidson and his colleagues (1979) suggested that the experiences of positive and negative affect are associated with differential patterns of asymmetrical frontal electrical activity in the alpha frequency band. More recently, they proposed that different asymmetrical patterns of activation in the anterior cortical zones bias a person's emotional reactivity and increase a person's vulnerability to particular types of psychopathology (Davidson and Tomarken, 1989; Davidson, 1992a; Wheeler, Davidson and Tomarken, 1993). Neuropsychological models of dispositional affect and psychopathology (Davidson, 1992b, 1994; Heller, 1993; Heller et al., 1997) led a growing number of researchers to investigate the brain activity patterns of hemispheric specialization associated with depression in the alpha frequency band.

It is important to note that brain activation in these studies is investigated under the assumption that activity within the alpha range (typically 8–13 Hz) is inversely related to underlying cortical activation. The assumption seems reasonable because decreases in alpha tend to be observed when underlying cortical systems engage in active processing (see part 1.1.2. in this work.; Shagass, 1972; Davidson, 1988; Davidson, Jackson and Larson, 2000; Ray and Cole, 1985). Accordingly, EEG and metabolic measures may compliment each other in terms of their relationship to cortical asymmetry, while increased cerebral metabolism measured by PET is correlated with increased power in delta–theta (less than 7 Hz), but is inversely correlated with alpha (8–12 Hz) activity (Leuchter et al., 1999).

1.3.3.2.1. Relationship between asymmetry and emotion.

Davidson and his colleagues have proposed a biological model of affective behavior, stating that asymmetrical effects of anterior lesions on affective behavior reflect the functions of two different motivational systems (Davidson, 1984, 1992a, 1992b, 1992c, 1994, 1998; 2000, 2004; Davidson and Tomarken, 1989, Wheeler, Davidson and Tomarken, 1993). According to this model, the left frontal region

specializes in approach behavior, which is associated with the experience and expression of positive emotions. The right frontal region, on the other hand, specializes in withdrawal behavior, associated with the experience and expression of negative emotions.

Most EEG studies have found support for the relationship between cerebral activation and emotion (for reviews see Shankman and Klein, 2003; Coan and Allen, 2004). Tomarken et al. (1992a) administer the trait version of the Positive and Negative Affect Scales (PANAS; Watson, Clark, and Tellegen, 1988) and find that the right-frontally activated subjects report less positive and more negative affect than their left-frontally activated counterparts. Jacobs and Snyder (1996) also report an association between relative right-sided cortical activation and increased generalized negative affect (PANAS). Other researchers have found positive affects such as joy and interest are associated with relatively greater left frontal cortical activation, and negative affects such as sadness and disgust are associated with relatively greater right frontal activation (Davidson, 1993; Davidson et al., 1990). When asked by researchers to report affective responses to emotional film clips, individuals with greater right frontal activation respond with more intense negative affect to negatively valenced films, and individuals with greater left frontal activation respond with more intense positive affect to positively valenced films (Tomarken, Davidson and Henriques, 1990; Wheeler, Davidson and Tomarken, 1993). Coan, Allen and Harmon-Jones (2001) use a voluntary directed facial action to elicit approach (joy and anger) and withdrawal (disgust, fear and sadness) related emotions. Withdrawal-related emotions do result in the expected relative right frontal activation compared to a control condition, but approach-related emotions do not result in a comparable relative left frontal activation. This may suggest that withdrawal emotions are more easily evoked than approach emotions using the directed facial action task. Relatively higher left frontal activation has also been shown during states of induced anger, a negative, but presumably approach-related affect (Harmon-Jones and Sigelman, 2001). Other studies indicate that greater relative left frontal activation characterizes individuals with higher behavioral activation sensitivity (i.e., heightened approach motivation; Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997; Coan and Allen, 2003), but, in one instance, lower behavioral inhibition sensitivity (i.e., reduced withdrawal motivation; Sutton and Davidson, 1997).

These findings suggest that EEG asymmetries index a person's propensities for reacting in predictable ways to emotionally evocative stimuli. Davidson (1998) has called this propensity "affective style", and he has proposed that an individual's particular affective style may create a risk for psychopathology. A person with relative right-sided tonical activation in the frontal region should demonstrate a marked negative affect with high affective reactivity to negative stimulation, low response to positive stimuli, and high vulnerability to depression. In contrast, a person with relative left-sided anterior activation should show a distinct positive affect with high affective reactivity to positive stimulation, low response to negative stimuli, and low vulnerability to depression. Hypoactivation in the left anterior region is predicted to increase a person's vulnerability to behavior and emotion associated with deficits in the approach system. Depression and sadness are both expected to result from such approach-related deficits (Davidson, 1994, 1998).

Clark and Watson (1991) characterize depression as having a high negative affectivity and a low positive affectivity. Numerous studies have found that individuals with major depression report significantly higher levels of negative affectivity than nondepressed individuals (Hirschfeld et al., 1983; Kendler et al., 1993). Brown et al. (1998) find that not only a negative affectivity, but also a positive affectivity is significantly related to a diagnosis of depression. Decreased dispositional positive affect is found in depressed persons (Watson, Clark and Carey, 1988). Furthermore, low positive affectivity distinguishes depressed patients from anxiety patients (Lonigan, Carey and Finch, 1994; Clark, Watson and Mineka, 1994).

Davidson (1994, 1998) has proposed that an overactivation of the withdrawal system, which outputs an excess of arousal and negative affect in response to aversive stimuli, is characteristic of anxiety. However, recent studies have indicated that both dysphoric college students and subjects meeting criteria for major depression exhibit decreased responsiveness to reward, suggesting a deficit in approach-related behavior, and an increased responsiveness to punishment, suggesting an abnormality in their withdrawal systems as well (Henriques and Davidson, 2000). This, however, is consistent with Tomarken and Keener's (1998) theory that the depression can be seen as an underactivation of the approach system and/or an overactivation of the withdrawal system. For example, in a study by Nitschke et al. (2004) negative memory bias in depressed participants is inferred from their association between right prefrontal activity during the sad narrative and memory performance, consistent with

research implicating the right prefrontal region in withdrawal-related unpleasant emotions.

Similarly, Heller and colleagues (Heller, 1993; Heller, Etienne and Miller, 1995, Heller et al., 1997; Heller and Nitschke, 1998; Nitschke et al., 1999) have postulated a system located in the frontal lobes that may modulate the valence dimension of emotion. A second system located in the right parietotemporal region, may be involved in the modulation of emotion-related autonomic arousal. Following this valence-arousal model, relatively stronger activation of the right frontal cortex is expected to be associated with a bias towards negative emotion, and high activation of the right parietotemporal cortex is expected to be associated with high autonomic arousal. This model predicts that whereas depression and anxiety may manifest a similar pattern of anterior activity, they will be associated with opposing levels of activity in the right posterior region. Furthermore, anxiety is comprised of two distinct though related processes, anxious apprehension and anxious arousal, and these processes are reflected in EEG asymmetries as relatively greater left frontal and right parietal activation, respectively. In particular, Heller and Nitschke (1998) have argued anxiety coupled with negative affective valence should be associated with the pattern of right frontal activation that other researchers have found in their studies of frontal EEG asymmetry and anxiety. Thus, ultimately Heller and colleagues argue that anxiety can become manifest in frontal EEG asymmetry as either relatively greater left frontal, relatively greater right frontal, or relatively greater right parietal activation, depending on the relative presence or absence of anxious apprehension, anxious arousal and negative affect.

Based on the findings of an association between states of emotion and cerebral activation, anterior asymmetry reflects a “diathesis” for depression (Davidson, 1993). In the case of EEG and negative affect, this model proposes that less left relative to right frontal activation would be correlated with a biological predisposition to patterns of emotional reactivity characterized by negative affect. Presumably those individuals who exhibit hypoactivation of the left frontal region and who, therefore also demonstrate elevated responsivity to negative stimuli, may be at increased risk for experiencing episodes of depression. Given that a major characteristic of depressed persons is their increased sensivity to negative stimuli (Lewinsohn, Lobitz, and Wilson, 1973) and their withdrawal from positive stimuli (Feldman and Gotlib, 1993),

it is reasonable to expect left frontal hypoactivation (or right frontal hyperactivation) in these persons.

1.3.3.2.2. Relationship between asymmetry and depression.

Most EEG studies indicate that depressed persons differ from healthy persons in patterns of cerebral activity in the alpha frequency band (Davidson and Henriques, 2000). Atypical brain asymmetry in depression is most often localized in the anterior region, but posterior asymmetry has also been emphasized.

1.3.3.2.2.1. Anterior asymmetry.

A robust and replicable finding from EEG studies of depression is an abnormal pattern of asymmetric activity due to increased alpha activity of left relative to right frontal regions (for reviews, see Davidson and Henriques, 2000; Davidson, 1995, 1998b; Davidson et al., 2002; Tomarken and Keener, 1998). In an early study comparing the resting levels of EEG activation in currently depressed and nondepressed college students, Schaffer, Davidson and Saron (1983) find that depressed persons have significantly greater left than right (L>R) frontal alpha activity, while nondepressed subjects show the opposite pattern. More recently, individuals with elevated scores on the BDI (Baehr et al., 1998) or on the CES-D (Center for Epidemiological Studies Depression Scale; Diego, Field and Hernandez-Reif, 2001) are found to have the same asymmetry pattern towards L>R frontal alpha activity. Moreover, several researchers have identified a link between relatively less right frontal resting activity - or relatively gretaer left frontal resting activity - and depression severity (Diego, Field and Hernandez-Reif, 2001; Schaffer, Davidson and Saron, 1983). Schaffer, Davidson and Saron (1983) find that higher scores on the Beck Depression Inventory (BDI) are associated with L>R frontal activity in their sample of undergraduate research participants. L>R frontal activity is also found to correlate with higher levels of depression in women, as measured by the CES-D (Diego, Field and Hernandez-Reif, 2001).

Greater left than right frontal alpha activity has also been found in clinically depressed patients (Henriques and Davidson, 1991). However, Henriques and Davidson (1991), examining the relationship between severity of depression and

frontal EEG asymmetry within a clinical sample, have found that frontal asymmetry is unrelated to severity. Coan and Allen (2004) argue that there are methodological explanations for the differences between these studies. In the case of Schaffer, Davidson and Saron (1983), the BDI is used not as a measure of severity, but as a selection tool to identify those with considerable depression. In the case of Henriques and Davidson (1991), by contrast, the selection is accomplished by clinical interview to derive extreme groups, with BDI scores examined within groups. Henriques and Davidson (1991) do not compute correlations with the BDI for the sample as a whole (combining depressed and control participants), as participants are selected on the basis of depressive symptoms. Had Henriques and Davidson (1991) split their clinical sample into high and low BDI scores, group membership would have remained unchanged and they would have found the same relationship as found by Schaffer, Davidson and Saron (1983), with high-BDI participants characterized by L>R frontal alpha activity.

Also, Lubar, Congedo and Askew (2003) observe a pattern of higher fronto-lateral and medial frontal asymmetry (increased alpha, 10-12 Hz, current density in the left hemisphere as compared to the right hemisphere) in medication-free chronically depressed females. The major findings of investigations of unipolar depression are essentially replicated in a sample of women with bipolar seasonal affective disorder who showes L>R frontal alpha activity (Allen et al., 1993). Differences in frontal asymmetry between genders are investigated by Miller et al. (2002). They find support for the relationship between depression and midfrontal asymmetry scores reflecting greater left frontal activity, but only for women with a documented clinical history of childhood-onset depression. Men with a history of childhood depression show the opposite pattern of extreme relative right midfrontal asymmetry.

Researchers have attempted to determine if frontal alpha asymmetry is stable over time in depressed subjects. Allen et al. (2004) examine the internal consistency and test-retest stability of resting EEG alpha (8-13 Hz) asymmetry in 30 women diagnosed with major depression at 4-week intervals for 8 or 16 weeks. Asymmetry scores generally display good internal consistency and exhibit modest stability over the 8- and 16-week assessment intervals. Furthermore, intraclass correlation stability estimates suggest that although some trait-like aspects of alpha asymmetry exist in depressed individuals, there is also evidence of changes in asymmetry across

assessment occasions that are not closely linked to changes in depressive severity. In another study, Debener et al. (2000) examine 15 medicated depressed patients on two occasions separated by 2 weeks. They find that, although depressed subjects exhibit lower test–retest stability of frontal EEG asymmetry than controls, no systematic mood-dependent changes in asymmetry occur across sessions in these depressed patients. The most obvious difference between the two studies is that patients in Allen et al. (2004) receive no medication, whereas those in Debener et al. (2000) receive a variety of antidepressant compounds. Most receive benzodiazepines, raising the possibility that the variability in the depressed patients between the two studies could reflect the acute effects of the initiation of the medication trial. These two studies tentatively suggest some trait-like stability in frontal EEG asymmetry across time in depressed subjects, but provide no evidence to suggest that variation in frontal EEG asymmetry across measurement occasions is due to changes in clinical status.

If frontal EEG asymmetry is indeed relatively stable over time in previously depressed subjects (Debener et al., 2000; Allen et al., 2004) and in nondepressed samples (Tomarken et al., 1992b; Hagemann et al., 2002), one would expect to observe evidence of L>R frontal activity in currently euthymic individuals with a history of depression. Henriques and Davidson (1990) test a group of normothymic subjects who are diagnosed as having a previous episode of depression and compare them with matched control subjects who have no history of depression. The common observation of an altered pattern of asymmetric activation in frontal region in the direction of L>R activity has been replicated in previously depressed subjects compared to never-depressed subjects. The same result of L>R frontal activity in the previously depressed subjects is replicated by Henriques and Davidson (1988) and Pollock and Schneider (1989).

Electrophysiological data indicate that L>R frontal alpha activity, which has been found in the acutely depressed subjects compared to controls (Davidson, Schaffer and Saron, 1985; Schaffer, Davidson and Saron, 1983; Henriques and Davidson, 1991), also distinguishes previously depressed from never-depressed control subjects (Henriques and Davidson, 1990). These findings demonstrate a pattern of augmented left-sided anterior activity which may predict vulnerability to depression rather than reflect changes in activity subsequent to depression; depressives exhibit these patterns even after recovery from the depressed state (Tomarken and Keener, 1998).

Gotlib, Ranganath and Rosenfeld (1998) have extended these previous findings reported by Henriques and Davidson (1990, 1991) by directly comparing all three groups - currently depressed, remitted depressed and never depressed subjects – in the same study. The three groups of subjects differ with respect to depressive symptomatology: currently depressed subjects obtain significantly higher IDD (Inventory to Diagnose Depression) symptom scores than do both the previously depressed subjects and the never depressed subjects, who do not differ significantly from each other. Currently and previously depressed subjects show L>R frontal alpha activity relative to never-depressed controls, but do not differ significantly from each other. Importantly, the data obtained in this study indicate that, despite a significantly higher level of depressive symptoms in the currently depressed subjects, these subjects do not differ from their remitted depressed counterparts with respect to EEG asymmetry. Moreover, despite the fact that remitted depressed subjects do not differ with respect to depressive symptoms from the never-depressed controls, they do exhibit signficantly greater left compared to right hemisphere activity. These results provide support for Davidson's (1993) postulation of frontal alpha asymmetry as a state-independent marker of vulnerability to depression.

An assessment of at-risk populations who have not yet manifested depression represents a more direct test of whether L>R frontal activity indicates vulnerability. One such population is children of depressed parents. L>R frontal activity has been found in infants of depressed mothers compared to infants of nondepressed mothers (Dawson et al.,1992, 1997; Jones et al., 1997a, 1997b; Tomarken, Simien, and Garber, 1994). Field et al. (1995, 2000) have achieved similar effects, reporting L>R frontal activity in depressed versus non-depressed mothers, and correspondingly similar differences in their respective infants. Also, adolescents whose mothers have a history of depression demonstrate the hypothesized pattern of L>R frontal activity compared to adolescents whose mothers are lifetime-free of psychopathology (Tomarken et al., 2004).

However, the observation in EEG studies of an altered pattern of asymmetric activity in anterior scalp regions in the direction of L>R frontal alpha activity in depressed subjects is not invariably found (Graae et al., 1996; Kentgen et al., 2000, Pizzagalli et al., 2002; Pollock and Schneider, 1990). The expected L>R frontal activity in depression is not seen in the study of Flor-Henry, Lind and Koles (2004). Their results suggest exactly the opposite: decreased activity of the left frontal lobe

and increased activity of the right frontal lobe. Their result, however, may be influenced by the fact that their sample includes subjects with major depression with psychotic (schizoaffective and bipolar) features. Finally, Reid, Duke and Allen (1998) find no significant differences in frontal activity between depressed and nondepressed participants in either college students having high Beck Depression Inventory scores or in individuals diagnosed with DSM-III-R depression.

This failure to observe asymmetric frontal activation in depression has been attributed to both methodological and diagnostic issues. First, Reid, Duke and Allen (1998) suggest that frontal alpha asymmetry has been most evident with short 2 min vs. 8 min EEG recordings. They examine data from the first 2 min of the 8 min recording period to determine whether any differences in asymmetry are present at the beginning of the recording period, but not consistently throughout the 8 min. Decreased left frontal activation is observed in the depressed individuals compared with control subjects at the lateral-frontal and mid-frontal sites only in first 2 min, but not throughout the entire 8 min recording. Next, several studies suggest that L>R frontal activity may not be specific to depression, characterizing those with significant anxiety as well (Davidson et al., 2000; Heller et al., 1997; Wiedemann et al., 1999). In a study by Bruder et al. (1997) anxious depressed patients show L>R frontal anterior than non-anxious depressed patients and controls. Non-anxious depressed patients show no differences with controls, indicating that frontal alpha asymmetry is more evident in unipolar depressives with anxiety features.

Findings suggest that a pattern of L>R frontal alpha activity characterizes depressed individuals both when symptomatic (Bell et al., 1998; Gotlib, Ranganath, and Rosenfeld, 1998; Henriques and Davidson, 1991; Schaffer, Davidson, and Saron, 1983), as well as during normothymic periods (Allen et al., 1993; Gotlib, Ranganath and Rosenfeld, 1998; Henriques and Davidson, 1990), although not without exception (Reid, Duke and Allen, 1998). These studies raise the possibility that resting frontal EEG asymmetry may be a relatively stable traitlike marker that distinguishes depressed individuals from never-depressed individuals, and one that does not vary simply as a function of whether individuals are symptomatic.

The finding that depressed patients differ from nondepressed controls in several (Allen et al., 1993; Baehr, Rosenfeld, Baehr, and Earnest, 1998; Gotlib, Ranganath and Rosenfeld, 1998; Henriques and Davidson, 1991; Schaffer, Davidson and Saron, 1983), but not all (Reid, Duke and Allen, 1998), studies is consistent with a diathesis

stress model, with L>R frontal activity tapping a nonnecessary risk factor for the onset of depression. According to this reasoning, individuals with L>R frontal activity are at risk for depression, but not all depressed participants will demonstrate a pattern of L>R frontal activity, as depression is highly heterogeneous. Further, among those with L>R frontal activity, current clinical state should not alter the diathesis tapped by frontal asymmetry. Investigations finding a pattern of L>R frontal activity in formerly depressed but currently euthymic patients provide evidence in support of this interpretation (Allen et al., 1993; Gotlib, Ranganath and Rosenfeld, 1998; Henriques and Davidson, 1990), as do findings that clinical severity is unrelated to frontal asymmetry (Henriques and Davidson, 1991).

Other researchers, however, have failed to replicate the relationship between depression severity and resting frontal EEG asymmetry (Bruder et al., 1997; Graae et al., 1996; Reid, Duke and Allen, 1998; Tomarken and Davidson, 1994). In addition, some studies of patients with unilateral brain lesions fail to show increased depressive symptomatology associated with left anterior lesions (see Gainotti, 1989). The fact that some patients, who show both clear evidence of a left anterior lesion and a lack of depressive symptomatology, have been identified indicates that increased alpha activity in this region is clearly not sufficient for the production of depressive symptomatology. Henriques and Davidson (1991) propose that L>R frontal alpha activity either naturally occuring or lesion induced, represents a diathesis that increases a person's vulnerability to depression. Only when the requisite enviromental stress occurs, however, is the vulnerability expressed. This view, therefore, recognizes the existence of persons with a depressogenic pattern of frontal activation who do not show any of the symptoms of depression. However, at least a subset of persons who are already depressed ought to possess the diathesis and therefore may show L>R frontal activity in comparison to controls.

1.3.3.2.2.3. Posterior asymmetry.

Comparisons between depressed and non-depressed subjects indicate not only a pattern of abnormal asymmetry in the anterior region, but also a similar pattern in the posterior region. The most consistent findings, demonstrating that depressed subjects differ from controls in the increased right relative to the left (R>L) parietal alpha activity, have been obtained in EEG studies.

Much depression research has shown increased EEG power in the right hemisphere (Koles, Lind and Flor-Henry, 1994; Kwon et al., 1996; Knott et al., 2001; Volf and Passynkova, 2002). Greater right than left posterior alpha power is observed in currently (Davidson et al., 1987; Tucker et al., 1981; Bruder et al., 1997; Heller et al., 1995; Reid, Duke and Allen 1998; Kentgen et al., 2000) and previously (Henriques and Davidson; 1988; 1990) depressed subjects compared to controls. Debener et al. (2000) also note a temporally stable posterior EEG asymmetry in depressed patients not evident in the anterior EEG. Abnormal parietal alpha asymmetry is supported by evidence that depressed people display deficits in cognitive functions associated with the right hemisphere on neuropsychological tests and in lateralised tachistoscopic paradigms (for reviews, see Heller, 1993; Heller and Nitschke, 1997; Flor-Henry, 1976; Tucker, 1981; Davidson, Chapman, Chapman and Henriques, 1990). A study by Henriques and Davidson (1997) demonstrate that depressives' impaired performance on a spatial task is significantly predicted by R>L parietal activity. Nondepressed controls show less right than left parietal activity compared with depressed subjects during spatial task performance.

Not all studies have been able to confirm this result (Schaffer, Davidson and Saron, 1983; Henriques and Davidson, 1991). Schaffer, Davidson and Saron (1983) find that the pattern of alpha activity in the parietal regions does not differ significantly between depressed and control subjects, although the direction of the means indicates that controls show less right than left parietal activity. Also, Henriques and Davidson (1991) do not find differences between depressives and control subjects in posterior asymmetry. The opposite asymmetrical distribution of greater left than right alpha activity in the parietal region has been found in depressed patients with seasonal affective disorder (Passynkova and Volf, 2001). Heller et al. (1995) have suggested that the failure of some EEG studies to find evidence of R>L parietal alpha activity in depression could due to opposing effects of anxiety on parietotemporal activity. Bruder et al. (1997) have observed that depressed groups without comorbid anxiety show R>L posterior activity, whereas depressed group with comorbid anxiety show the opposite asymmetry. In a study by Kentgen et al. (2000) comorbid anxiety disorders increase the posterior alpha asymmtery within the major depression patient group showing R>L parietal activity.

It is also important to note that for the most part, EEG studies have examined resting, or baseline activity. Davidson (1993) has pointed out that baseline levels of

frontal asymmetry may reflect individual tendencies toward a valenced affective response, but this relationship may not be observed in the absence of a specific environmental elicitor. Thus, he emphasizes the need to examine the relationship between individual differences in patterns of asymmetry and affective response to emotionally challenging tasks. As applied to the pattern of posterior findings, these considerations suggest the possibility that more robust differences in posterior brain activity might be yielded by studies measuring brain activity while participants perform tasks for which depressed people show decreased ability.

Moreover, many studies fail to find a correlation between R>L parietal activity and depression severity as measured by the BDI (Bruder et al., 1997) and CES-D (Diego, Field and Hernandez-Reif, 2001). According to Henriques and Davidson (1990), R>L parietal activity may directly contribute to certain symptoms of depression, such as poor orienting and deficits in social skills, which require the decoding of nonverbal, expressive behavior. It remains questionable whether these types of symptoms are reflected in self-reported measurements.

On other hand, if right posterior regions of the brain prove to be dysfunctional in depression, Heller and Nitschke (1997) expect that depressed people would have difficulty processing narrative information, a task that has been shown to rely, in part, on this area of the brain. The right posterior region is suited for processing contextual, relational and global information, whereas the left posterior region for systematic processing of details (for review see Heller and Nitschke, 1997). Depression and sad affect are associated with better performance on some detail-oriented tasks than is pleasant affect. Indeed, Heller and Nitschke (1997) propose that R>L parietal alpha activity in depression might result in the tendency to utilise left hemisphere information-processing strategies. This is consistent with the findings that right brain-damaged patients tend to violate the overall reality of a verbal narrative in favour of irrelevant details (Grossman, 1988).

Findings of posterior asymmetry in depressed subjects and its relationship to depression severity remain more elusive than the findings in anterior asymmetry. Although many hypotheses exist concerning abnormal posterior asymmtery in depression, the empirical evidence remains unclear. This could be explained by the fact that brain lesion studies suggest that the parietal cortex, like the frontal cortex, tends to produce depression, but to a lesser extent (Fedoroff et al., 1992). In addition, the fact that these two regions have different functions may explain why empirical

results in the regions differ. The anterior region is strongly related to emotion, whereas the parietal region reflects more cognitive processing such as the spatial selection in a visuomotor task (Shibata and Ioannides, 2001). Depression is an affective disorder, so dysfunction in the frontal region may be expected, whereas dysfunction in the parietal region may appear only when cognitive disabilities are present.

The tendency to investigate the posterior cortex as well as the anterior cortex can be explained by the connectivity between these two brain areas. Many researchers find evidence that the orbitofrontal cortex receives projections from the temporoparietal cortices which contribute to integrating viscerosensory information with affective signals (Morecraft, Geula and Mesulam, 1992; Price, 1999). On the basis of connectivity, both regions may fulfill the same function. Anterior and posterior areas are both involved in decision-making (Damasio, 2003; Miller and Cohen, 2001; Platt and Glimcher, 1999) and verbal working memory (Deldin et al., 2001). Because these functions usually deteriorate in patients suffering with major depressive disorder, depressives may show brain activity abnormalities not only in anterior region, but also in the posterior region.

1.4. Treatment effect on regional brain abnormalities in depression.

If abnormal slow wave activity indicates a dysfunctional condition in the corresponding brain region, due to either structural or functional lesions, reversibility or at least partial change may be expected during a spontaneous or therapy-supported recovery. Evidence of such a change comes from recent studies of brain damaged patients, which indicate a change in slow wave activity over the course of recovery or treatment. For example, Hensel et al. (2004) report a decrease in EEG-delta amplitude in the hemisphere containing a lesion and spontaneous language recovery during the first year following a stroke in aphasia patients. In a MEG study by Meinzer et al. (2004), patients with chronic aphasia show alterations in perilesional delta activity after speech and language therapy.

These findings suggest that abnormal slow wave activity in the vicinity of brain lesions may be normalized by therapeutic intervention. Moreover, the normalization

of abnormal slow wave activity may be related to improvement in brain function. The functional capabilities of the affected brain area can potentially be restored or re-integrated into certain neural networks. Improvement in brain function through treatment may be related to brain plasticity. Treatment enables the nervous system to reorganize neural pathways and adapt to changing circumstances, and may become more effective as the brain demonstrates greater plasticity (Peled, 2004).

Plasticity allows the cerebral cortex to coordinate brain activity even after a region has suffered damage. Processes distributed in the cerebral cortex must allow local areas to function within the large-scale anatomical structure of the brain so as to satisfy competing requirements for stability and flexibility. In order to generate adaptive behavior within changing unpredictable environments, the cortex as a whole must be able to rapidly coordinate the activities of variable assemblages of areas that can collectively express consensual information that is appropriate for the functional requirements of cognition (Peled, 2004).

Researchers must rely upon advanced imaging technologies such as fMRI and MEG combined with sophisticated signal analysis methods directed toward detection of altered neural complexity (Kircher et al., 2004) to assess neuropathologies and effects of plasticity when studying mental disorders and treatment effects. For example, EEG abnormalities in patients with Alzheimer's disease (AD) directly reflect anatomical and functional deficits of the cerebral cortex damaged by the disease (Jeong, 2004). Thus, the investigation of EEG dynamics provides fruitful clues about the neuropathology of AD. Moreover, coherence analysis of the EEG in AD allows noninvasive assessment of synaptic dysfunction. Synaptic plasticity is critical for brain functions affected by diseases such AD, particularly learning and memory. A number of studies suggest that disturbances of synaptic connections may underlie numerous neurological and psychiatric disorders including AD (Masliah and Terry, 1993), schizophrenia (Feinberg, 1983), epilepsy (Sutula, 1990), and Parkinson's (Donnan et al., 1991). A decrease in functional connectivity and its correlation with the degree of dementia suggest that EEG coherence studies of AD may help understand the association between synaptic plasticity and cognitive performance (Cook and Leuchter, 1996).

Other studies have also demonstrated that focusing on plasticity may prove fruitful. Coherency alterations in the gamma band of EEG from schizophrenia patients (Breakspear et al., 2003) are presently being established and plasticity alterations are

being revealed as the underlying mechanisms of antidepressant and anxiolitic medications (Charney, 2004).

Major depressive disorders have traditionally been considered to have a neurochemical basis, but recent studies have associated these complex disorders with regional reductions in central nervous system volume, as well as in the numbers and/or sizes of glia and neurons in discrete brain areas (for review, see Manji et al., 2001). Although the precise cellular mechanisms underlying these morphometric changes are unknown, the data indicate that major depressive disorders are associated with impairments of structural neuroplasticity and cellular resilience. A number of preclinical and clinical studies have shown that antidepressants and mood stabilizers exert major effects on signaling pathways that regulate neuroplasticity and cell survival (D'Sa and Duman, 2002; Manji et al., 2001, 2003; Nestler et al., 2002, Young, 2002). Antidepressant effects also appear to induce an EEG profile characterized by increases in delta and theta activity and decreases in alpha activity in depressed patients (Knott et al., 1996; Knott and Lapierre, 1987; Saletu et al., 1980).

However, other forms of nonpharmacological therapeutic intervention, such as electroconvulsive therapy (ECT), music and massage therapy, biofeedback, psychotherapy and meditation, may have similar effects on a patient's EEG/MEG profile. Researchers have not yet fully assessed how different therapies affect neuroplasticity; but recent research confirms the effectiveness of various therapeutic interventions in the normalization of regional brain abnormalities in depression. The efficacy of ECT has been related to the induction of postconvulsive EEG/MEG delta and/or theta activity (Luber et al., 2000; Mäkelä, 1997; Salmelin et al., 1997), while alpha activity does not appear to respond to treatment (Heikman et al., 2001). Music and massage therapy applied to depressed adolescents results in the augmentation of their relative right frontal alpha activity, suggesting that relative decreases in the magnitude of psychopathology can result in corresponding increases in relative right frontal resting activity (Jones and Field, 1999; Field et al., 1998). Baehr et al. (1999) show that it is possible to use EEG biofeedback (neurofeedback) to train individuals with depressive disorders to shift the asymmetry ratio from the left side to the right side or to reduce it. Also, Rosenfeld et al., (1996) demonstrate that day-to-day fluctuations in EEG asymmetry predicted the direction of change in affective responses to EEG biofeedback training over the course of the training sessions.

These findings show that the different therapeutic interventions such as ECT, music and massage therapy or biofeedback are able to change the state of brain activity in depressed individuals. In addition, reseachers in psychiatry consider questions pertaining to the neurobiological effects of psychotherapy (Corrigan, 2004; Gabbard, 2000; Kandel, 1999; Thase, 2001). The learning about oneself that occurs in psychotherapy may in itself influence the structure and function of the brain, as Kandel (1999) suggests. This allows researchers to broaden the understanding of psychiatric interventions by regarding them as having a biopsychosocial nature.

With respect to this issue, recent PET findings indicate that cognitive and behavioral modifications, occurring in a psychotherapeutic context, can lead to adaptive regional brain metabolic changes in patients with major depression (Brody et al., 2001; Martin et al., 2001), obsessive-compulsive (Baxter et al., 1992; Nakatani et al., 2003; Schwartz et al., 1996) or anxiety disorders (Furmark et al., 2002; Paquette et al., 2003).

Brody et al. (2001) find that patients with unipolar major depression, after treatment with either paroxetine or interpersonal psychotherapy (IPT), show normalization of abnormal metabolic activity with decreases in the left and right prefrontal cortex, and increases bilateral inferior temporal lobe. Martin et al. (2001) also find changes after treatment with venlafaxine or IPT. Only IPT treatments, however, lead to an increase in limbic blood flow in right posterior cingulate, while both treatments increase basal ganglia blood flow. When used in the treatment of obsessive—compulsive disorder, both behaviour therapy and fluoxetine appear to produce a decrease in cerebral metabolic rates in the right caudate nucleus (Baxter et al, 1992; Nakatani et al., 2003). These studies indicate that the changes in functional brain activity following pharmacotherapy and psychotherapy are remarkably similar.

Cognitive-behavioral therapy (CBT) also has the potential to modify the dysfunctional neural circuitry associated with anxiety disorders. Paquette et al. (2003) use fMRI to measure regional brain activity before and after effective CBT in subjects suffering from a spider phobia as they viewed film excerpts depicting spiders. The right dorsolateral prefrontal cortex and the right parahippocampal gyrus were significantly activated before CBT but not after CBT. Futhermore, a fMRI study recently carried out by Beauregard et al. (2001) has confirmed the hypothesis that the dorsolateral prefrontal cortex is a key brain structure implicated in voluntary self-regulation of emotion (see also Davidson et al., 2000). According a PET study by

Johanson et al. (1998), an increase in frontal rCBF is correlated with the use of cognitive strategies to cope with a phobic situation. In this context, the dorsolateral prefrontal activation before CBT noted by Paquette et al. (2003) relates to the use of proactive metacognitive strategies aimed at self-regulating the fear and anxiety evoked by the phobogenic stimuli.

Evidence from psychotherapy suggests that CBT may achieve its long term beneficial effect by increasing awareness of triggers, such as negative thoughts and distressing feelings. That is, it is the awareness itself, rather than an ability to engage in rapid cognitive restructuring that helps to prevent relapse in depressive illness (Segal et al., 2002). The anterior cingulate cortex (ACC) is highly significant for emotional processing, and, on the basis of its interaction with the ventral and dorsal subdivisions of ACC and with adjacent prefrontal cortex, rostral ACC is suggested to be the important neurobiological substrate for this healing process (Corrigan, 2004). The ability to be aware of one's own emotional state has also been demonstrated by imaging techniques to be a feature of rostral ACC (Lane et al., 1997; Beauregard et al., 2001). In addition, rostral ACC allows humans to focus not only on their own mental state but on the mental state of others (Gallacher and Frith, 2003; Vogeley et al., 2001). The empathic attunement of the therapist and the patient's focused attention on his distressing emotions will both involve activation of rostral ACC.

After CBT, people who have recovered from depression do not respond to small changes in mood by large increases in negative thinking because, as a result of treatment, they accept temporary sadness as an appropriate and evanescent emotional response to an event, without progressing to judgements of the emotional state, dysfunctional attitudes, negative cognitions, and prolonged low mood. The absence of activation in the dorsolateral prefrontal cortex (see Paquette et al., 2003) provides strong support for the view that CBT reduces phobic avoidance by decreasing cognitive misattributions and catastrophic thinking at the level of the prefrontal cortex (Gorman et al., 2000).

Like psychotherapy, meditation is practiced by many to facilitate their health and adaptation to medical illness. It may be viewed as a form of systematic training in a self-regulatory approach to stress reduction and emotion management (Bishop, 2002, Kabat-Zinn et al., 1992; Reibel et al., 2001). In recent years, there have been various studies on the behaviors of the mind during meditation using EEG. During meditation, experienced meditators are reported to demonstrate increased alpha and

theta power (Corby et al., 1978, Delmonte, 1984, Kubota et al., 2001; Travis, 2001; Woolfolk, 1975), particularly in the frontal area (Takahashi et al., 2004; Tassi and Muzet, 2001; Young and Taylor, 1998). Successful meditative experience appears to be mediated by a switching-off mechanism of external attention, as indicated by slower alpha synchronization over the frontal cortical region (Aftanas and Golocheikine, 2001). The percent change in slow alpha power in the frontal area has been associated with enhanced internalized attention, whereas the percent change in fast theta power in the frontal area reflects enhanced mindfulness (Takahashi et al., 2004). Davidson et al. (2003) indicate that meditation, as a method designed to increase positive affect, seems to be able to change the anterior asymmetry towards a decrease in the left anterior alpha activity in heatlhy subjects. Based on this finding, one may propose that meditation be effectively applied to depressed persons with greater left than right frontal alpha activity.

Although psychotherapy is successful in altering emotional distress, the biological mechanism by which it achieves this has not been the subject of intensive neurobiological investigation. Liggan and Kay (1999) emphasize that psychotherapeutic effects are based on synaptic plasticity which occurs during the process of memory consolidation. Post and Weiss (1997) posit that mechanisms involved in neuronal learning memory, such long-term potentiation and long-term depression of excitatory postsynaptic potentials (Buonomao and Merzenich, 1998), are used in the molding of personality and behavior based on experience. They postulate that for higher order processes such as emotional memory, neuroplasticity occurs at increasingly larger numbers of synapses and at cell assemblies with increasing mechanistic complexity and self-organization. Nonetheless, discussing the neurobiology of such self-organizing plastic systems may begin to change conceptual approaches to psychopathology. It may open new avenues of therapeutics for major psychiatric illnesses critically dependent on higher order learning and memory mechanisms. Moreover, MEG studies, such as this one, may provide new key insights into how neuronal plasticity functions in depression, and may elucidate how therapy works to reduce brain dysfunction.

1.5. The aim of the study.

This MEG study investigates the patterns of slow wave and alpha activity in depressed patients by comparing patients to the healthy subjects, relating patterns of activity to symptomatology, and observing changes in activity after psychotherapeutic intervention (cognitive-behavioral therapy) in relation to symptom improvement.

1.6. Hypotheses.

Hypothesis 1:

a) Following the literature, depressed subjects demonstrate decreased slow wave activity in the prefrontal and frontal regions (Wienbruch et al., 2003), and increased activity in the parietal region (Dierks et al., 1993; Flor-Henry, Lind and Koles, 2004). Compared to healthy subjects, depressed patients are expected to show diminished anterior and augmented posterior resting activity in the delta and theta bands 1) relative to controls, and 2) related to symptoms.

b) EEG studies find greater left than right frontal alpha activity (Gotlib, Ranganath and Rosenfeld, 1998; Lubar, Conged and Askew, 2003) and greater right than left parietal alpha activity (Reid, Duke and Allen, 1998; Kentgen et al., 2000) in depressed subjects compared to controls. Given that alpha activity is inversely related to underlying cortical activation, authors interpret these findings as a left anterior and right posterior hypoactivation in depression (Davidson, Jackson and Larson, 2000). This interpretation fits well with other lesion and functional neuroimaging studies findings. Studies of brain-damaged patients suggest that left-hemisphere lesions in the frontal pole and right-hemisphere posterior lesions are associated with depression (Fedoroff et al., 1992; Shimoda and Robinson, 1999). Reduction of metabolism and blood flow have been observed in the left prefrontal (Biver et al., 1994; Bench et al., 1995) and right parietal (Bonne et al., 2003) regions in depressed subjects compared to controls. Following these findings, an increase in left anterior and right parietal alpha activity in depressed patients compared to controls is expected in the present study. Asymmetry towards greater left anterior and greater right posterior activity are

also expected in depressed patients compared to controls. In addition, these abnormal patterns of regional activity are expected to correspond to higher symptomatology prior to treatment.

Hypothesis 2:

PET studies indicate that psychotherapy and antidepressant therapy can lead to adaptive regional brain metabolic changes in depressed persons (Brody et al., 2001; Martin et al., 2001). Meditation also has been found to produce increases in theta and alpha power in the frontal region (Tassi and Muzet, 2001; Takahashi et al., 2004), and to alter anterior asymmetry towards a decrease in the left anterior alpha activity (Davidson et al., 2003) in healthy subjects. With regard to these findings, after psychotherapy, depressed patients are expected to demonstrate a change in abnormal regional activity towards normalization. It is also reasonable to expect that treatment effects, evaluated by change in symptom scores, will be related to a change in neuromagnetic activity in the direction of normalization.

2. METHOD.

The MEG was measured using a 148-channel whole-head neuromagnetometer (MAGNES WH 2500, 4D Neuroimaging, San Diego, USA) during a 5-min resting period prior to therapeutic intervention (after a diagnostic interview and within seven days after admittance), and again at the end of therapy and/or discharge from the hospital. The clinical status was assessed with BDI and BPRS at both time points.

2.1. Subjects.

Thirty-one inpatients were recruited from the local Center for Psychiatry. Following the first MEG reading, data from two probands were removed from the study due to artifacts (see 2.3.1.). 26 test subjects took part in the MEG recording following therapy. Data from two patients with bipolar affective disorder (F31) were excluded from further analysis.

On average patients were 46 years old - the youngest person was 30 and the oldest was 63. The sample consisted of 16 females and 8 males. Twenty-three patients were right-handed and one was left-handed according to the Edinburgh Handedness Questionaire (Oldfield, 1971), which asks subjects to demonstrate hand use on various actions (such as using a broom, brushing teeth, writing, etc.). The patient group was compared to 24 healthy subjects (14 females, 10 males), who all were determined to be right handed according to the same handedness test and did not differ from depressive patients in age (mean age of control group 41 (range 29 – 65 years); $t(1,46) = 1.63$, $p = .11$)).

2.1.1. Diagnosis.

All patients met the criteria for a ICD-10 diagnosis of mental and behavioral disorders (International Statistical Classification of Diseases; Dilling et al., 1993; see also http://www3.who.int/icd/vol1htm2003/fr-icd.htm). The diagnoses fell in the categories F3 (mood (affective) disorders; N = 21), and F4 (neurotic, stress related and somatoform disorders; N = 3; see table 1).

Eleven patients met the criteria for a recurrent depressive disorder with current moderate or severe episodes. One of these patients displayed the diagnosis agitated depression, two had suicidal tendencies, and three had comorbid diagnoses such as eating disorder, panic (with social phobias) and obsessive-compulsive disorders. Ten patients met criteria for a moderate or severe depressive episode, with four of them suffering from a comorbid diagnosis like alcohol abuse, Parkinson's disease, disorders of somatization and posttraumatic stress. Mixed anxiety and depressive disorder, neurasthenia and adjustment disorder with prolonged depressive reaction were rare diagnoses (one proband each; see table 2.1.).

Diagnosis		Comorbid diagnosis	Number of patients
F3 Mood (affective) disorders			**21**
F32 Depressive episode			10
F32.1	Moderate depressive episode (MDE) without somatic syndrome		2
	MDE without somatic syndrome	F10 Alcohol abuse	1
	MDE without somatic syndrome	G20 Parkinson's disease	1
	MDE with somatic syndrome	F45.0 Somatization disorder	1
F32.2	Severe depressive episode (SDE) without psychotic symtpoms		4
	SDE without psychotic symtpoms	F43.1 Posttraumatic stress disorder	1
F33 Recurrent depressive disorder (RDD)			11
F33.1	RDD, current episode moderate		1
	RDD, current episode moderate	F50.8 Eating disorder.	1
	RDD, current episode moderate	F41.0 Panic disorder and F40.1 Social phobias	1
F33.2	RDD, current episode severe		5
	RDD, current episode severe with suicidal tendencies		2
F33.9	Agitated depression	F42 Obsessive-compulsive disorder	1
F4 Neurotic, stress related and somatoform disorders			**3**
F41.2	Mixed anxiety and depressive disorder		1
F43.21	Adjustment disorder with prolonged depressive reaction		1
F48.0	Neurasthenia		1
		Total	24

Table 2.1. Diagnostic subgroups and comorbid diagnoses of patients according to ICD-10.

2.1.2. Medication.

At the time of the first MEG-recording, twenty patients were under current medication (see table 2.2.). They were receiving tricyclic antidepressants (N = 6), tetracyclic antidepressants (N = 1), selective serotonin reuptake inhibitors (SSRI; N = 2), neuroleptics (NRL; N =1), a combination of the tricyclic antidepressant and NRL (N = 5), a combination of the tricyclic antidepressant and SSRI (N = 3), and a combination of SSRI and NRL (N = 2).

Nr.	Code	Diagnosis	Number of hospitalisations	Medication pre	Medication post	Duration of therapy
1.	001	F33.1; Fear and panic condition, social phobias	5th	-	TCA;NRL	10
2.	002	F32.1	First	TTA	-	5
3.	003	F32.1; Alcohol abuse	First	SSRI;NRL	-	14
4.	004	F48.0	First	TCA	-	9
5.	006	F32.1; F45.0	First	TCA;NRL	-	6
6.	007	F33.2	2nd	TCA;NRL	-	15
7.	008	F33.2	First *	TCA;NRL	-	10
8.	009	F33.2	First	-	TCA	7
9.	011	F32.2	6th	-	-	9
10.	012	F32.1; Parkinson's	First	TCA	-	4
11.	013	F41.2	First	TCA	-	4
12.	014	F33.1	2nd	SSRI	-	21
13.	015	F32.1	Not available	TCA	-	4
14.	017	F32.2	First *	SSRI	SSRI;NRL	18
15.	018	F43.2	First	TCA;NRL	-	7
16.	019	F33.9; F42.0; F60.6	5th	TCA;NRL	SSRI;NRL	22
17.	020	F33.1; F50.8	First *	-	-	14
18.	022	F33.2	4th	TCA	-	11
19.	023	F32.2	First	TCA;SSRI	TCA;SSRI	10
20.	024	F32.2; PTSD	First	TCA;SSRI	-	4
21.	025	F33.2	3rd	TCA;SSRI	SSRI	11
22.	026	F33.2	3rd	SSRI;NRL	SSRI;NRL	7
23.	027	F32.2	5th	NRL	-	18
24.	030	F33.2	3rd	TCA	-	14

* ambulatory treatment earlier

Table 2.2. Medication details at the time of pre- and post-treatment. Abbreviations for medications: TTA – tetracyclic antidepressant, TCA – tricyclic antidepressant, SSRI – selective serotonin reuptake inhibitor, NRL – neuroleptic.

At the time of the second MEG-recording only seven patients were on medication (see table 2). They were receiving tricyclic antidepressants (N = 1), SSRI (N = 1), a combination of the tricyclic antidepressant and NRL (N = 1), a combination of SSRI and NRL (N = 3), and a combination of the tricyclic antidepressant and SSRI (N = 1). All but two patients who received medication after treatment also had received medication before treatment.

2.1.3. Number of hospitalizations.

At the time of examination, 10 probands suffered their first bout with depression and were in treatment for the first time. Three patients had already had an earlier depressive phase and were treated with ambulatory psychotherapy. Ten patients were treated repeatedly (see table 2.2.). There was no information available for one person.

2.1.4. Duration of therapy.

The treatment length for the study was defined as the time from the pre-examination to the post-examination. Duration of therapy varied between 4 and 22 weeks around a mean of 10.5 weeks (see table 2.2.).

2.1.5. Symptomatology.

The symptom severity of depression for each patient was assessed at the beginning and the end of therapy by the Beck Depression Inventory (BDI; Beck et al., 1961) and by the psychologist or psychiatrist in charge by means of the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986).

The BDI is a 21-item self-report instrument that assesses the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression (see appendix 1). The answers range from 0 to 3 (0 = minimal, 3 = severe). The boundaries for the severity of the depression are given in table 2.3. (Beck et al., 1961).

Bounds	Severity of Depression
Up to 15 Points	Mild Depression
From 15-30 Points	Moderate Depression
More than 30 Points	Severe Depression

Table 2.3. Boundaries for the BDI, Beck et al. (1961) with regard to the severity of depression.

The BPRS measures the severity of the general psychopathology. Twenty four distinct symptoms such as Delusions, Hallucinations, Thought Disorders, Blunted Affect, Emotional Withdrawal, Hostility, Depression, Anxiety, and Suicidality are in the BPRS. Psychotherapists rate patients' severity of symptoms on 24 items (see appendix 2). The estimated intensity of the pathology is given on a ratings scale from one to seven (one = none; 2-3 = very mild, mild; 4-5 = moderate; 6-7 = severe, extremely severe). For one patient, no BDI or BPRS ratings are available.

2.2. Data collection.

Before recording, all patients were familiarized with the recording environment, informed about the procedure, and gave written consent to participate in the experiment. Then the patient received verbal information and instructions about the recording. Subjects were asked to stay awake during the measurement and not to engage in any specific mental activity while looking at a colored fixation mark on the ceiling of the magnetically shielded room to avoid eye and head movement.

Next, the coils were attached to determine the head shape of the patient. For artifact control, eye movements (electrooculogram) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye using a Synamps amplifier (NEUROSCAN, Sterling Virginia). The electrocardiogram was monitored via electrodes attached to the right collarbone and the lowest left rib. The patient's head shape was digitized prior to each measurement. The subject's head position relative to the pickup coils of the sensor was estimated before and after each measurement. The MEG was recorded with a 678.17 Hz sampling rate, using a band-pass filter of 0.1–200 Hz. MEG recordings were obtained in a supine position. A video camera installed inside the magnetically shielded room

allowed monitoring the person's behavior and compliance at any time throughout the experiment.

After each MEG measurement participants were paid 10 Euro.

2.3. Data analysis.

2.3.1. Data reduction and artifact correction.

For the 5-min recording, the number of sample points was reduced by factor 16 and noise corrected. Artifacts in the data caused by heartbeat and eye movement were eliminated. Heartbeats were removed using a specific Program cardiac_remove. After the data was converted into binary format (BESA), eye blink artifacts were corrected (Berg and Scherg, 1994; Ille, Berg and Scherg, 2002). Eye blinks were averaged separately, using pattern search. Artifact topographies were defined from the averaged data by setting the forward low cutoff 0.5 Hz filter. The artifact signal was subtracted from the original MEG data.

Fast Fourier Transformation (FFT) was applied to identify sources of brain activity in the frequency domain. The MEG signals were divided into sections of 1024 points by applying a running window with 50% overlap. To reduce leakage between neighboring frequency bands, a Hanning window was applied to each section. The signals from each section were transformed to delta (1.5-4 Hz), theta (4.1-8 Hz) and alpha (8.1-12 Hz) frequency bands using FFT. Then the Fourier transformed signal was applied to the minimum norm estimate (MNE) algorithm (see Hauk et al., 2002) resulting in the source distribution. MNE were calculated using the program MATLAB.

2.3.2. Minimum norm estimate.

MNE is an inverse method reconstructing the primary current that underlies an extracranially recorded time-locked brain potential (for details, see Hämäläinen and Ilmoniemi 1994; Hauk, 2000; Hauk et al., 1999, 2002; Jensen and Vanni, 2002; Moratti, Keil and Stolarova, 2004; Uutela, Hämäläinen and Somersalo, 1999). This linear estimation technique assumes that the data vector **B**, which contains the recorded magnetic field distribution over the sensors, can be described as the product

of the lead-field matrix **G**, which specifies the sensor's sensitivity to the sources located, for example, on a shell, and a current density vector **q** of these sources plus a noise component **n**: **B** = **Gq** + **n**. The MNE algorithm produces an estimate of **q**, which explains most of the data **B** and minimizes the sum of the currents **q** with respect to the 2-norm, which is obtained by multiplying the pseudoinverse of **G** with the data **B**. To reduce the variance of the current estimates, the Tikhonov-Phillips regularization procedure was applied during the pseudoinversion of the lead-field matrix.

The lead-field matrix **G** was computed for each participant, based on information on the center of a fitted sphere to the digitized head shape, and the positions of the MEG sensors relative to the head. A spheric shell 1 at 80% radius of the head relative to its center with distributed 350 dipole locations served as source space. Each of the 350 dipole locations consisted of two perpendicular dipoles oriented tangentially to the shell surface. This resulted in two MNEs for each dipole location. Computing the MNE leads to an estimation of dipole strength for each of the two perpendicular oriented dipoles at each location resulting in an activity estimation distributed over the shell. Using FFT algorithm, power was estimated separately for each dipole orientation in each frequency band. The square root of the sum of squares of the power for the two orientations served as a measure of the total power at one location.

All power values were log-transformed to achieve a Gaussian distribution (John et al., 1987). Then individual z-transformations were calculated for each subject by subtracting each power value at one dipole location from the mean power values of all dipole locations and dividing by the standard deviation. This transformation allows better evaluation of regional differences. The power values were viewed using the program BPLOT.

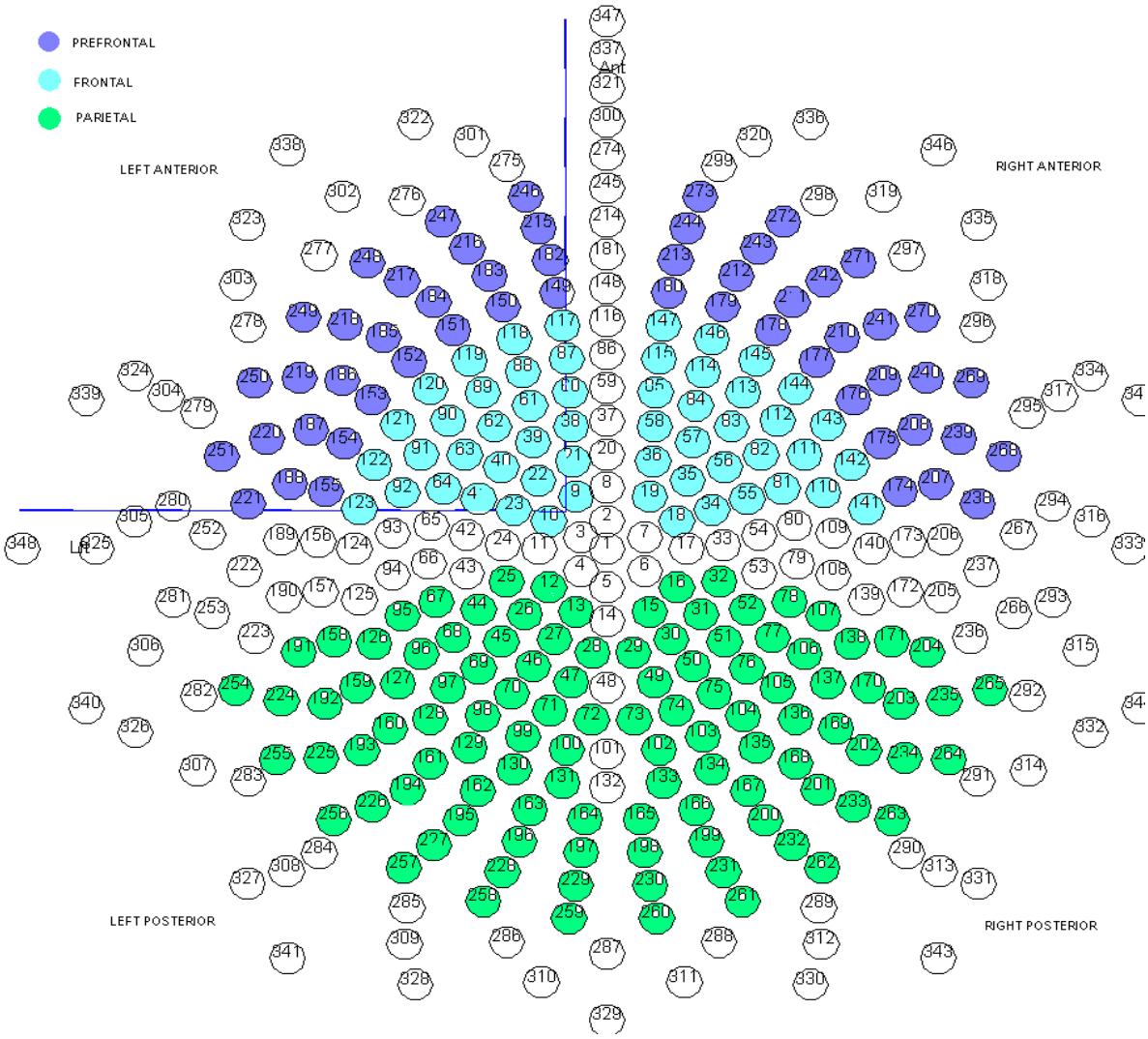

Figure 2.1. MNE shell 1 with distributed 350 dipole locations projected onto a plain. Blue shadings depict the anterior region, divided into prefrontal and frontal, and green shadings depict posterior region.

For statistical analyses, the log- and z-transformed MNEs were averaged further across the left and right hemispheres and regions of interest (ROI). Following the literature on the anterior and posterior regions, the anterior area of the brain was divided into left and right prefrontal and frontal regions, and the posterior area into the left and right parietal regions. The six regions of interest were defined with respect to source distribution on the shell (see figure 2.1.): the left and right prefrontal regions each include 27 dipole locations, the left and right frontal region also have 27 dipole locations each, and the left and right parietal regions contain 54 dipole locations each.

2.3.3. Statistical analysis.

Differences in the pattern of power between groups were evaluated separately for the delta, theta and alpha frequency band using analyses of variance (ANOVA) with repeated measures. The two-way ANOVA was computed using GROUP (depressed patients vs. controls) as the between-subjects variable and HEMISPHERE (left vs. right) as the within-subjects variable. The differences between groups in regions of interest (ROI: prefrontal vs. frontal vs. parietal) were also examined with three-way ANOVA. The three-way interaction was decomposed in separate two-way ANOVAs (GROUP X HEMISPHERE) computed for each region. Sources of interactions were verified by post hoc Bonferroni t test. To examine brain asymmetry, a repeated measures ANOVA was computed for HEMISPHERE (left vs. right) and ROI in each group.

Asymmetry was examined by means of the laterality index (LI), i.e. the difference between right and left power divided by the absolute value (because the *z scores* include negative and positive values) of sum of these powers (R-L/|R+L|). A score of zero represents hemispheric symmetry, a negative score represents greater activity in the left relative to the right hemisphere, and a positive score represents greater activity in the right relative to the left hemisphere. Laterality ratios were computed for regions of interests. Repeated measures ANOVA were computed for GROUP (depressed patients vs. controls) as the between-subjects variable and with laterality ratios of ROI (prefrontal vs. frontal vs. parietal) as within-subjects variable. The same interaction analysis was performed for diagnostic groups (F32 and F33) and for groups with high and low BDI scores.

The effects of treatment were examined for the patient group with repeated measures ANOVA. Within-subjects factors were the two MEG recordings (MEASUREMENT) before (pre) and at the end of treatment (post). This analysis was performed for the left and right hemispheres and regions of interest. The effects were also examined between different diagnoses (F32 and F33) and high vs. low BDI groups.

Based on the LI, the depressive patients were divided into two groups in the left and right hemispheres and every region of interest. The first group consisted of individuals with negative scores, while the second group contained individuals with

positive scores. Changes in activity from pre- to post-treatment were observed separately within each group and hemisphere/region.

To investigate a relationship between brain activity and the severity of depression, Pearson Product Moment correlations were computed. Correlations between depressed patients' brain activity and the severity of depression as measured by the BDI and BPRS were examined for each ROI prior to therapy. To investigate the relationship between treatment effects and symptom improvement, correlations were performed for the change in power (subtracting pre- from post-treatment) and change in symptom ratings (subtracting pre score from post score).

All analyses were run in the statistical packages SPSS 10.0 and StatView 5.0.

3. RESULTS

3.1. Symptomatology

3.1.1. Beck Depression Inventory.

At the beginning of therapy, 8 of the total 23 depressed patients, for whom BDI scores are available, show severe depression, another twelve demonstrate moderate, and three display mild depression (see table 3.1.). The mean BDI-value of all 23 patients (26.96) indicates moderate depression.

The depressed patients are split in two groups: high and low BDI according to pre-treatment scores. The high group contained 11 patients with BDI scores above the median (28). The low group contained the remaining 12 patients scoring 28 or lower on the pretreatment BDI.

Severity of depression	Pre-treatment	Mean	Post-treatment	Mean
Mild	3	12.67	18	8.56
Moderate	12	24.83	5	19.20
Severe	8	35.5	0	-

Table 3.1. Number of depressed patients at various degrees of depression and the mean of BDI scores at the beginning and end of therapy.

After treatment, the BDI-values point to mild depression in 18 patients and to moderate depression in another 5 (see table 3.1.). The mean BDI-value of all patients (10.87) point to mild depression.

A paired t test of BDI scores between pre- and post-treatment reveals a significant difference, $t(22) = 8.28$, $p < .001$. Figure 3.1. displays a clear improvement in symptoms as measured by BDI-values between pre- and post-tests in all patients (except two). On average the BDI-values fell by 16.09 points between the pre- and post-tests (the BDI-value before therapy is subtracted from the BDI-value after therapy for every patient).

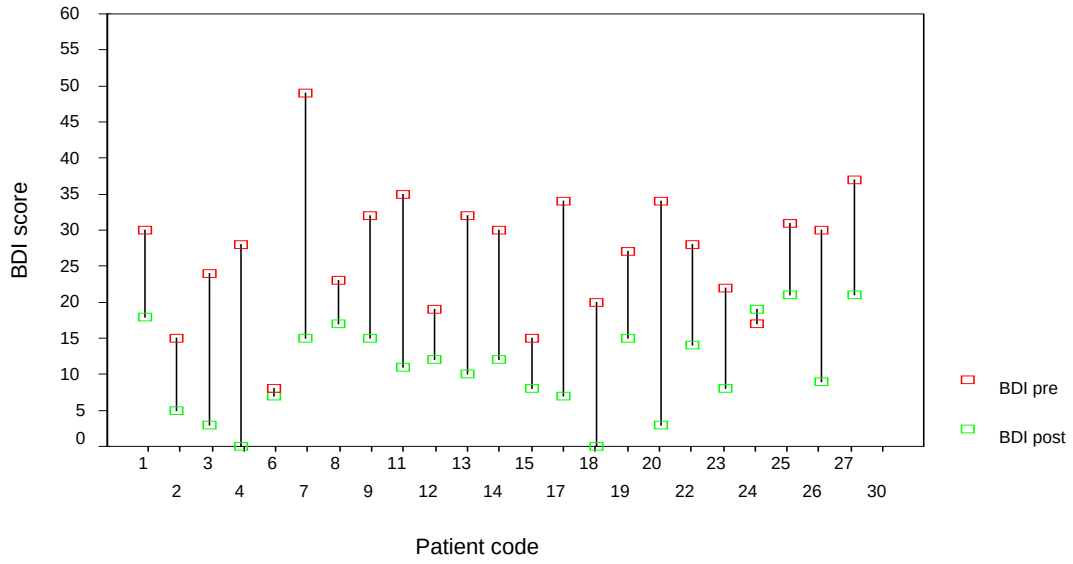

Figure 3.1. BDI-Scores before and after therapy for each patient.

Figure 3.2. displays the mean BDI scores separately for depressed patients with depressive episode (F32) and recurrent depressive episode (F33) diagnoses. An analysis comparing patients diagnosed with F32 and those diagnosed with F33 reveals a significant difference before treatment, $t(18) = -2.33$, $p < .05$, with a F33 diagnosis displaying higher BDI scores (mean = 31.4; n = 10) than depressed patients with a F32 diagnosis (mean = 22.6; n = 10).

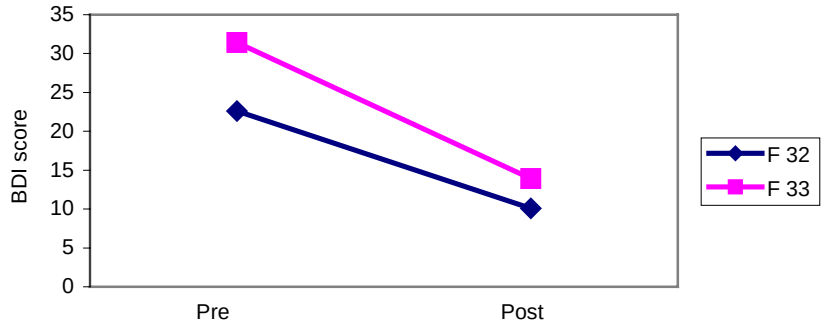

Figure 3.2. BDI scores for depressed patients with F32 and F33 diagnoses at the beginning and end of therapy.

BDI scores at the beginning of treatment correlate positively with duration of therapy ($r = .533$, $p < .01$), indicating that a higher level of depression before therapy is related to longer treatment duration (see figure 3.3. left); and with the number of hospitalizations ($r = .429$, $p < .05$), indicating that persons treated stationary more often have a higher BDI scores before therapy (see figure 3.3. right).

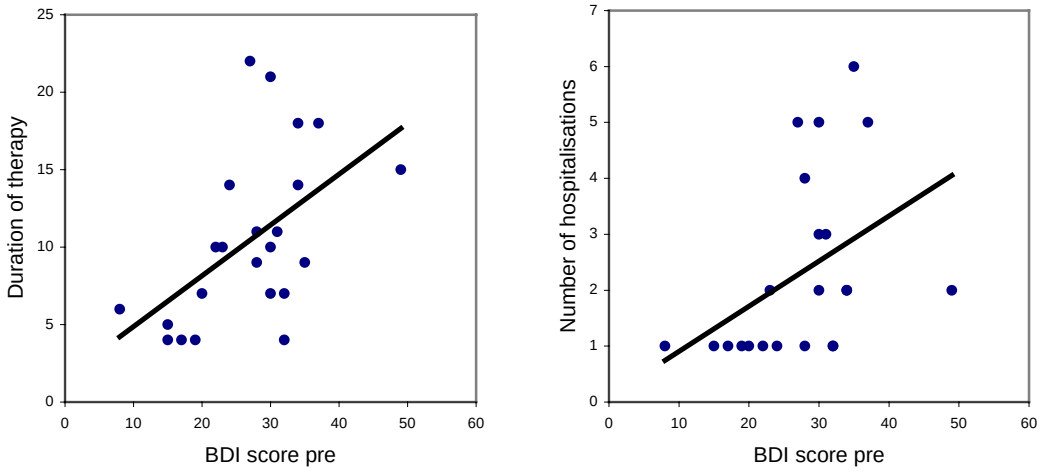

Figure 3.3. Scatterplot of single-subject distribution of BDI scores before treatment relative to duration of therapy in weeks (left) and relative to number of hospitalizations (right).

3.1.2. Brief Psychiatric Rating Scale.

The mean BPRS-score in the 23 patients prior to treatment is 40.25 and following treatment 30.17. A paired t test between pre- and post-treatment BPRS scores reveals a significant difference, $t(22) = 5.43$, $p < .001$. Figure 3.4. illustrates the reduction in BPRS scores after treatment in 18 patients, almost no reduction (1 point)

in two patients, and worsening of symptoms in three patients. On average the BPRS-scores change by 10.65 points (BPRS-score before therapy subtracted from BPRS-score after therapy).

There is little difference in BPRS scores between diagnostic groups (see figure 3.5.). The effect of treatment is slightly greater in patients with a F32 diagnosis compared to those with a F33 diagnosis (mean F32 = 16,8, mean F33 = 10,8), though the difference is not significant.

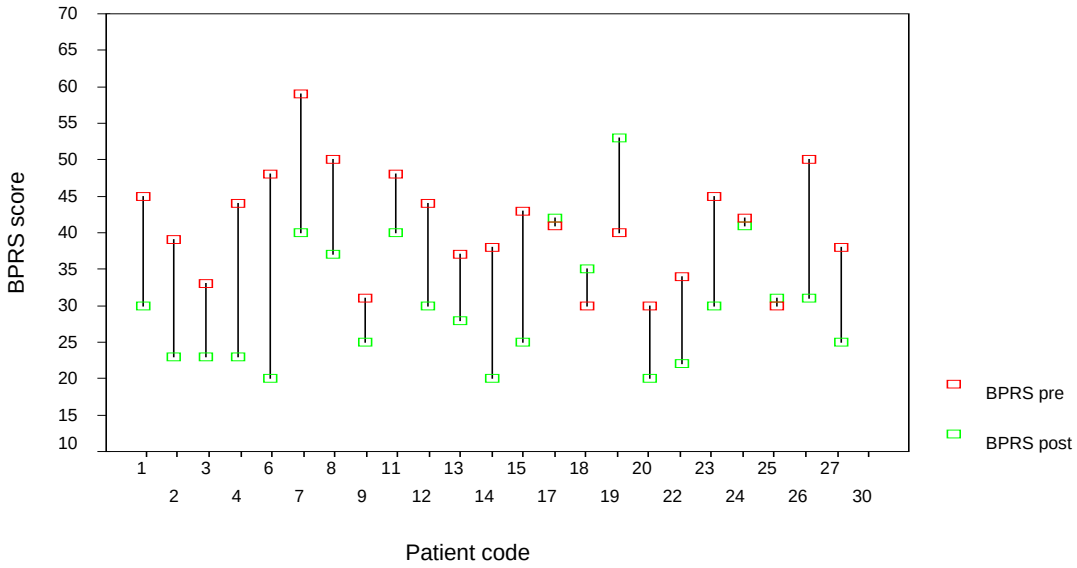

Figure 3.4. BPRS-Scores before and after therapy for each patient.

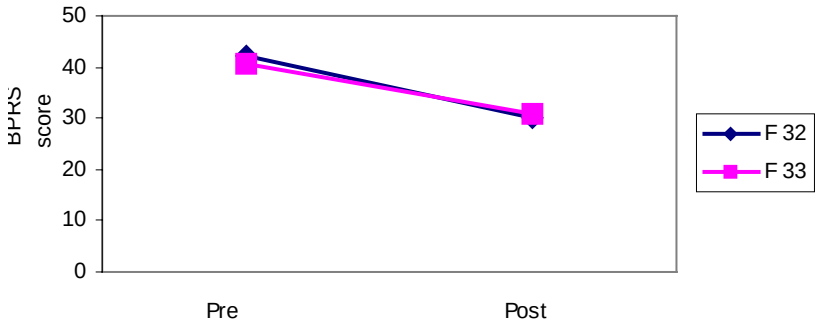

Figure 3.5. Pre- and post-treatment BPRS scores separated by F32 and F33 diagnosis groups.

3.1.3. Summary

Most depressed patients show moderate depression as measured by BDI scores at the beginning of therapy. Patients with a diagnosis of recurrent depressive disorder have a higher pre-treatment BDI scores than patients with a diagnosis of depressive

episode. At the end of therapy, the BDI and BPRS scores reveal a decrease in symptomatology relative to the beginning of therapy across all depressed groups.

Interestingly, before treatment a higher level of depression is related to longer therapy duration. Other relationships show that persons who are treated stationary more often have a higher BDI score both before and after therapy.

3.2. Brain activity in different frequency bands.

3.2.1. Delta band.

3.2.1.1. Group comparison before treatment.

Figure 3.6. displays delta power for depressed patients and healthy subjects. The figure suggests that patients shows more delta activity than controls in the left hemisphere. ANOVA reveals a significant effect for GROUP ($F(1,46) = 10.22$, $p < .01$), but no significant HEMISPHERE x GROUP interaction. Post hoc Bonferroni t-test confirms the group effects in the left hemisphere ($t(46) = 3.29$, $p < .01$), indicating that depressed subjects have more left-sided delta power than controls.

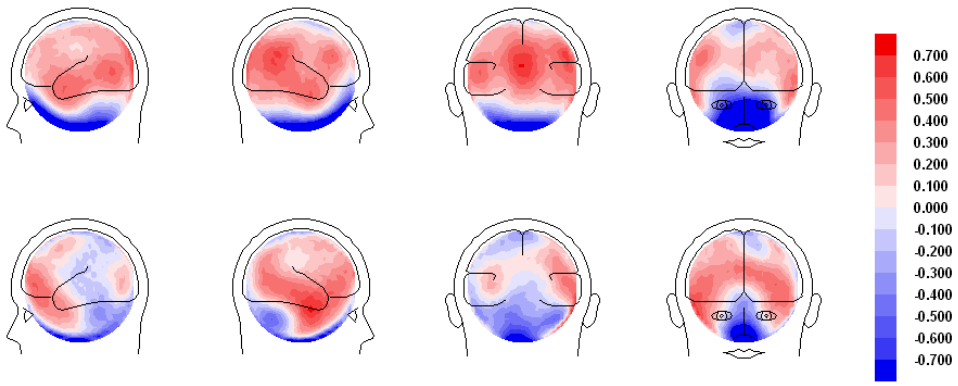

Figure 3.6. Distribution of delta power values for depressed patients (top row: left, right, back, front; left = right; n = 24) and controls (bottom row: left, right, back, front; left = right; n = 24).

Enhanced delta power in patients is confined to the posterior brain regions, while they demonstrate less delta in the anterior regions than controls. Statistical analysis of averaged delta power in ROI confirms a significant ROI x GROUP interaction ($F(2,92) = 6.47$, $p < .01$), resulting from a decrease of delta activity in the patient group over right prefrontal region ($t(46) = -2.52$, $p < .05$) and an increase over left ($t(46) = 4.43$, $p < .001$) and right ($t(46)=3.23$, $p < .01$) parietal regions relative to healthy subjects (see figure 3.7.).

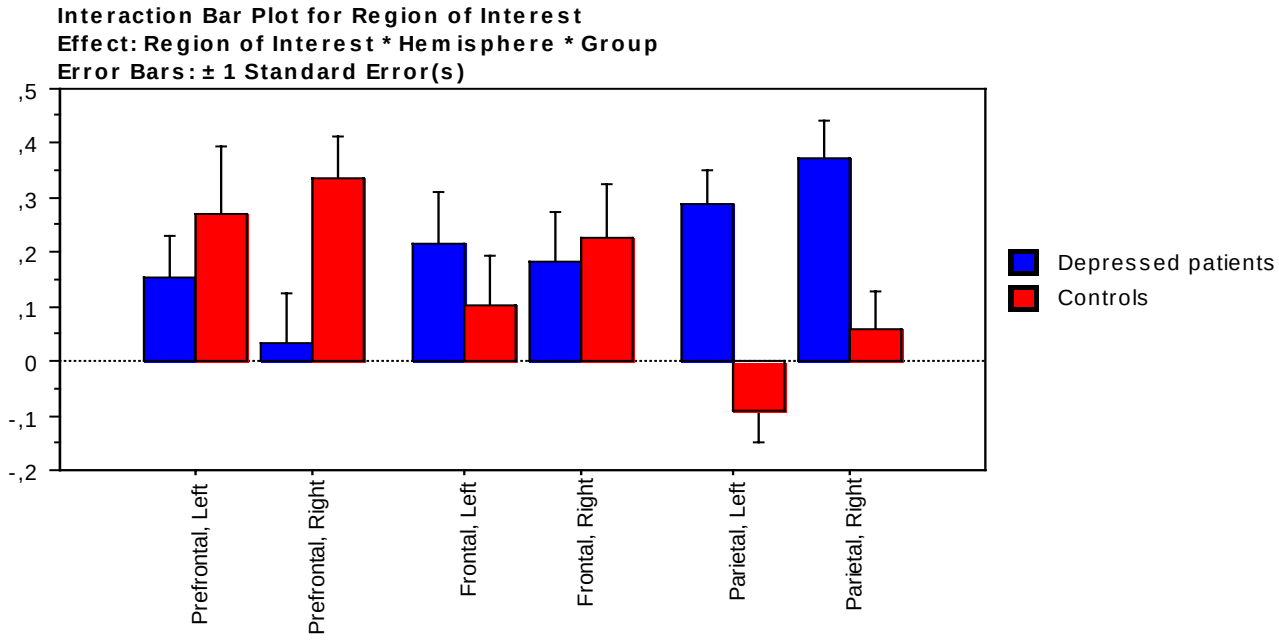

Figure 3.7. Mean delta power split by region and hemisphere for depressed patients and controls.

Although figure 3.7. suggests more left than right prefrontal and frontal delta power in patients and more right than left delta power in controls, anterior asymmetry fails to reach significance. Delta asymmetry is significant only for the controls in the parietal region ($F(2,46) = 3.67$, $p < .05$), with more delta activity in the right relative to the left parietal region ($t(23) = -2.22$, $p < .05$).

The distribution of delta activity for depressed patients with the diagnoses depressive episode (F32) and recurrent depressive disorder (F33) are shown in figure 3.8. As evident from this figure, patients with a F33 diagnosis demonstrate less delta in the anterior region and more delta in the posterior region relative to the patients with a F32 diagnosis (ROI x DIAGNOSIS, $F(2,38) = 5.02$, $p < .05$). Post hoc Bonferroni t-tests confirm the differences in the frontal region: patients with a F33 diagnosis display less delta activity in the frontal region of the left ($t(19) = 2.69$, $p <$

.05) and right (t(19) = 2.39, p < .05) hemispheres compared to patients with a F32 diagnosis (see figure 3.9.).

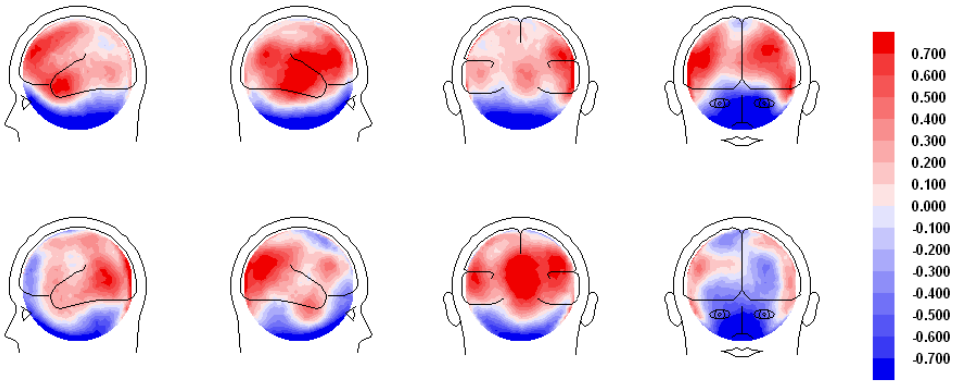

Figure 3.8. Distribution of delta power values for depressed patients with F32 diagnosis (top row; n = 10) and with F33 diagnosis (bottom row; n = 11).

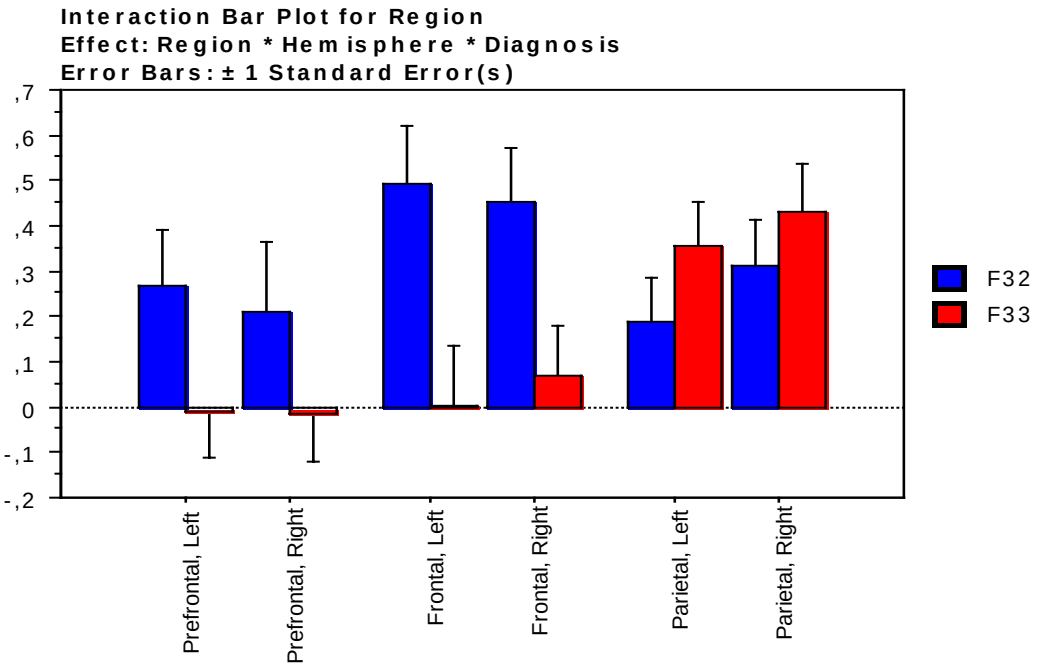

Figure 3.9. Mean delta power split by region and hemisphere for patients with diagnosis of depressive episode (F32) and recurrent depressive disorder (F33).

The age of depressed patients is negatively correlated with right parietal delta power at the beginning of therapy ($r = -.451$, $p < .05$), indicating that older depressed patients show less right parietal delta activity before treatment (see figure 3.10.).

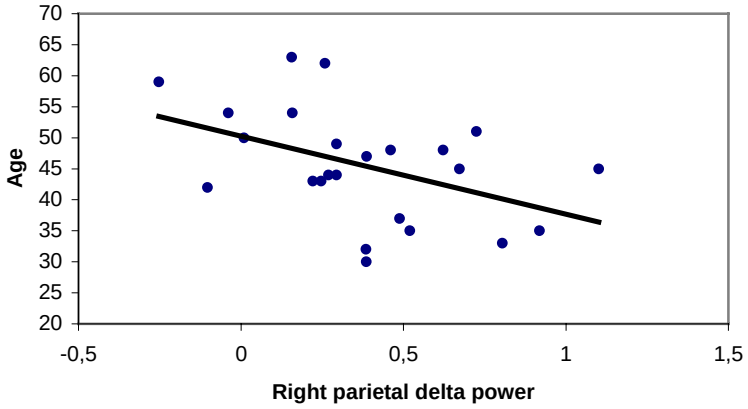

Figure 3.10. Scatterplot of single subject distribution of mean delta power in the right parietal region relative to age.

3.2.1.2. Delta activity changes after treatment.

As suggested by figure 3.11., delta activity changes from pre- to post-treatment in the right hemisphere, although this is not confirmed by the interaction HEMISPHERE x MEASUREMENT.

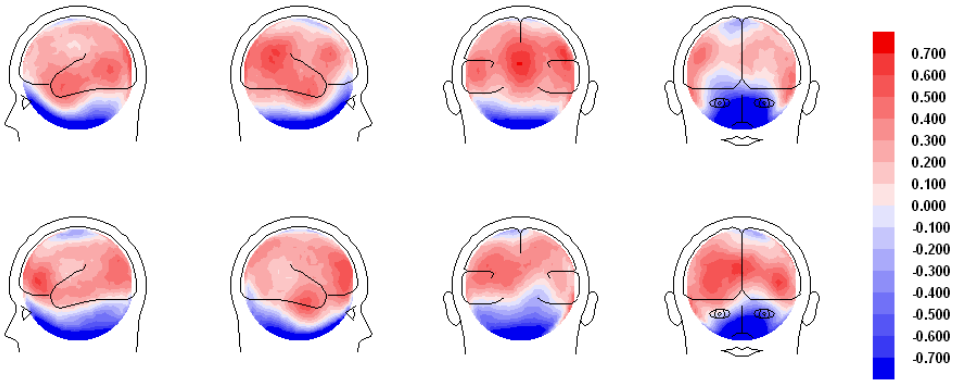

Figure 3.11. Distribution of delta power values for depressed patients at the beginning (top row; n = 24) and the end of therapy (bottom row; n = 24).

When broken down for ROI, differences between pre- and post-treatment delta power are confirmed for the right hemisphere (ROI x MEASUREMENT x HEMISPHERE, $F(2,46) = 4.75$, $p < .05$): after treatment depressed patients show an increase in delta power in the right prefrontal region ($t(23) = -2.72$, $p < .05$; see figure 3.12.) and a decrease in the right parietal region ($t(23) = 2.49$, $p < .05$; see figure 3.13.).

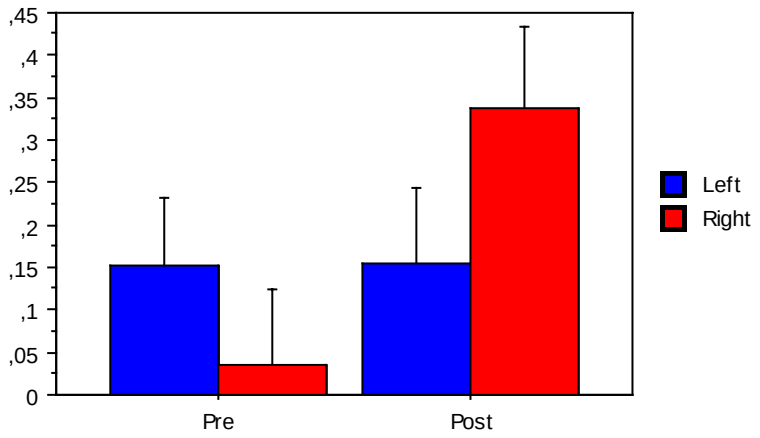

Figure 3.12. Mean delta power split by time of MEG recording (pre vs. post) and hemisphere in the prefrontal region (bar plots with standard errors).

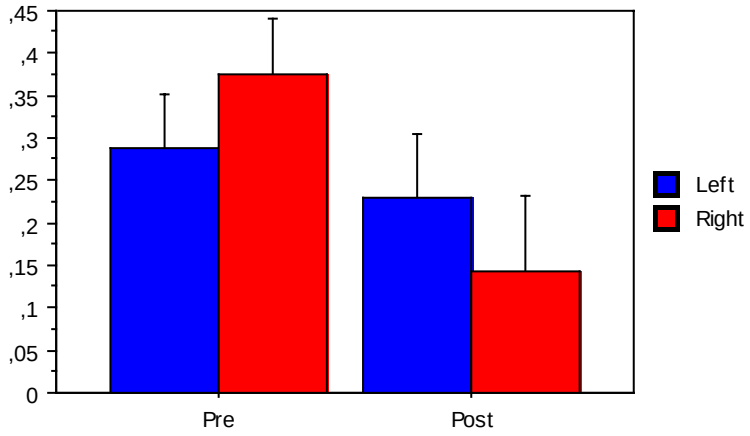

Figure 3.13. Mean delta power split by time of MEG recording (pre vs. post) and hemisphere in the parietal region (bar plots with standard errors).

Comparing high and low BDI groups, ANOVA reveals a signficant ROI x MEASUREMENT x HEMISPHERE ($F(2,42) = 4.31$, $p < .05$) interaction. As can be seen in figure 3.14., after treatment, depressives with low BDI scores show more prominent change in delta power in the right hemisphere compared to patients with high BDI scores. Further analysis demonstrates significant effects for MEASUREMENT in the right prefrontal ($F(1,19) = 4.66$, $p < 0.05$) and right parietal ($F(1,19) = 10.21$, $p < 0.01$) regions. In the right prefrontal region, both groups show an increase in delta power, however significant change at the end of therapy compared to the beginning has been found only for patients with low BDI scores ($t = -2.66$, $p < .05$). In addition, in the right parietal region, the low BDI group displays a significant decrease of delta power ($t = 2.87$, $p < .01$) at the end of therapy compared to the beginning. Hence, a tendency towards normalization in the prefrontal and parietal regions of the right hemsiphere is more pronounced in patients with low BDI scores.

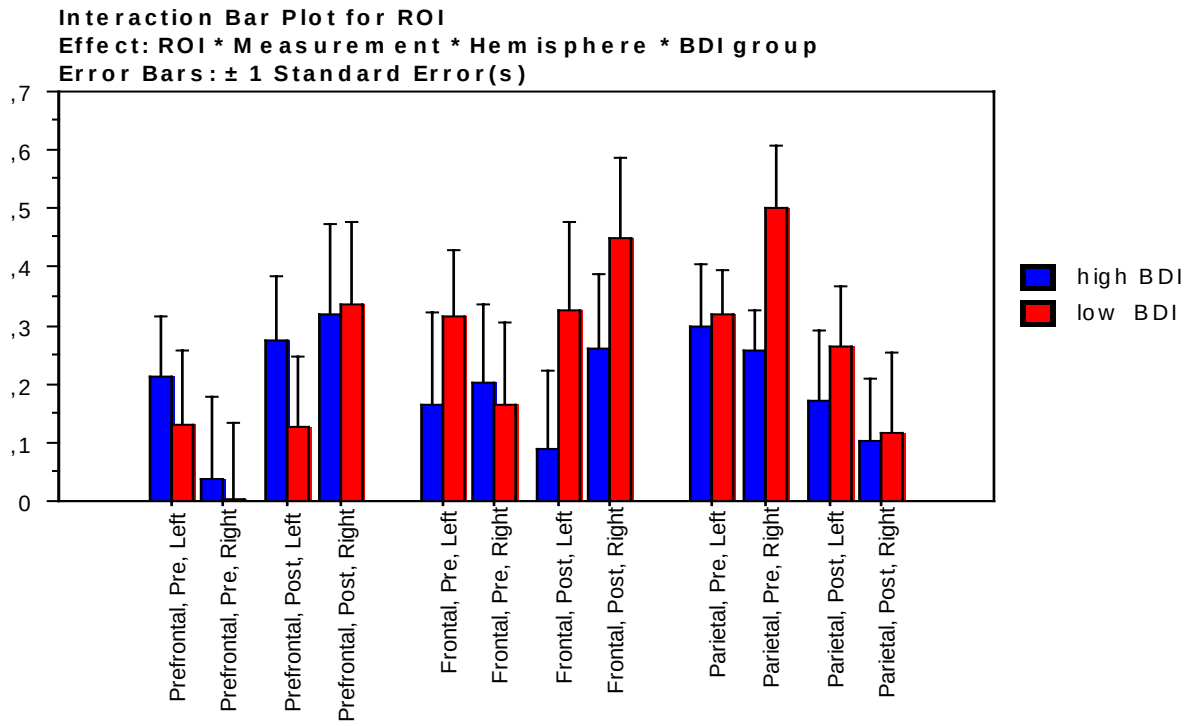

Figure 3.14. Mean delta power split by hemisphere and region for patients with low (n = 12) and high (n = 12) BDI scores from pre- to post-treatment.

3.2.1.3. Relationship between delta power and symptom ratings.

Figure 3.15. illustrates the correlation coefficients for each dipole and BDI and BPRS scores in the delta frequency band at the beginning of therapy. A positive correlation in the right frontal region is evident at the beginning of therapy. However, as shown in table 3.2., correlation coefficients for means of power in ROI and BDI scores do not reach significance.

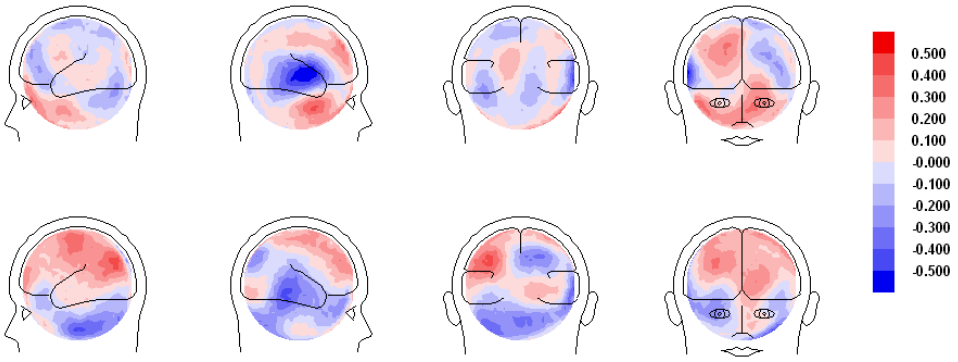

Figure 3.15. Distribution of correlation coefficients for delta power and symptom scores at the beginning of therapy (n = 23). Top row displays relation to pre-treatment BDI scores, bottom row - to pre-treatment BPRS scores. The map is created by calculating the correlation for each dipole. The color scale displays correlation coefficients: blue indicates negative correlations, red – positive correlations.

As can be seen from bottom row in figure 3.15., before treatment more delta activity in the left parietal region is associated with the higher scores. However, this correlation does not reach significance (see table 3.2.). As can be seen in table 3.2., there is a moderate positive, but not significant, correlation between left hemisphere and BPRS score, which indicates that higher delta power in the left hemisphere is associated with more symptoms of general psychopathology.

	Left				Right			
	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	-.126	.056	-.121	-.113	-.138	-.078	.166	-.132
BPRS	.408	.074	.325	.228	-.109	-.203	.311	-.142

Table 3.2. Correlation coefficients between mean delta power in ROI and BDI / BPRS scores prior to therapy (n = 23).

Laterality indices of prefrontal delta activity correlate negatively with pre-treatment BPRS scores ($r = -.453$, $p < .05$), demonstrating that before therapy, a

higher BPRS score is associated with more left than right prefrontal delta power (see scatterplot in figure 3.16.).

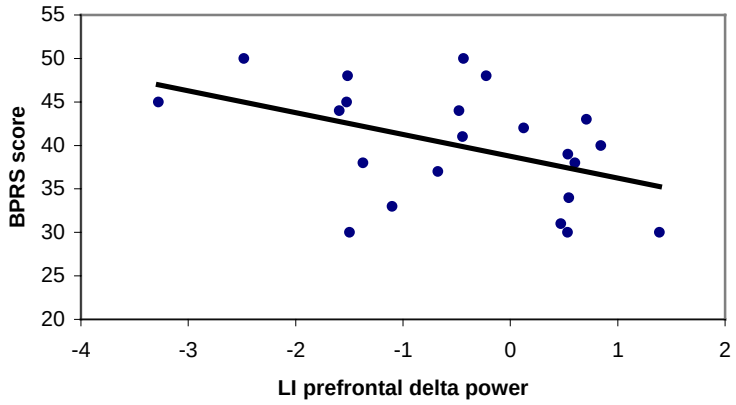

Figure 3.16. Scatterplott of single subject distribution of mean LI delta power in the prefrontal region relative to BPRS score at the beginning of therapy.

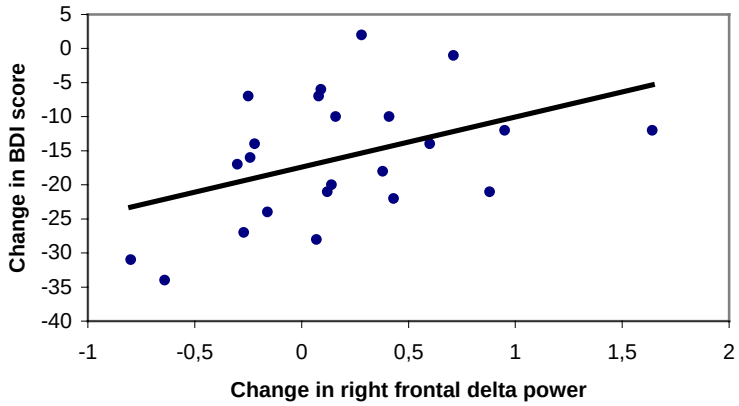

Figure 3.17. Scatterplott of single subject distribution of change (post-pre) in delta power in the frontal region relative to change (post-pre) in BDI scores.

	Left				Right			
Change	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	-.047	.149	.184	-.273	.212	.200	**.434***	-.134
BPRS	-.131	.202	-.010	-.271	.006	.365	.191	-.344

* Correlation is significant at the .05 level.

Table 3.3. Correlation coefficients between change in mean delta power in ROI from pre- to post-treatment (post – pre) and change in BDI / BPRS scores (post – pre; n = 23).

As seen in table 3.3., symptom improvement correlates positively with change in right frontal delta power indicating that decreases in right frontal power from pre- to post-treatment are associated with greater improvement in depression symptoms (see scatterplot in figure 3.17.).

3.2.1.4. Summary.

Results indicate that depressed patients exhibit more delta power in the left hemisphere compared to healthy subjects. In addition, depressives display more delta power in the right and left parietal regions and less in the right prefrontal region compared to controls. Asymmetry with less left than right parietal delta activity is found in healthy subjects. Lower left and right frontal delta power is more pronounced in patients with a diagnosis of recurrent depressive disorder compared to patients with a diagnosis of depressive episode. Furthermore, older depressed patients show less right parietal delta power.

After treatment, depressed patients show an increase in delta power in the right prefrontal region and a decrease in the right parietal region relative to the beginning of treatment. These results confirm the hypothesis that treatment effects are accompanied by normalization of activity in the prefrontal and parietal regions of the right hemisphere. The normalization of delta power in the right hemisphere is more pronounced in patients with low BDI scores.

Before therapy, correlations reveal no relationship between activity and symptomology excepting the correlation between laterality indices of prefrontal delta activity and pre-treatment BPRS scores, demonstrating that before therapy, a higher BPRS score is associated with more left than right prefrontal delta power. From pre- to post-treatment, decreased right frontal delta power is associated with greater improvement in depression symptoms.

3.2.2. Theta band.

3.2.2.1. Group comparison before treatment.

As can be seen from figure 3.18., which displays theta power in depressed patients and healthy subjects, depressives demonstrate more theta power relative to controls in both hemispheres. Although there is a significant effect for GROUP ($F(1,46) = 17.5$, $p < 0.001$), a post hoc Bonferroni t-test only confirms the difference between groups in the right hemisphere ($t(46) = 2.13$, $p < .05$).

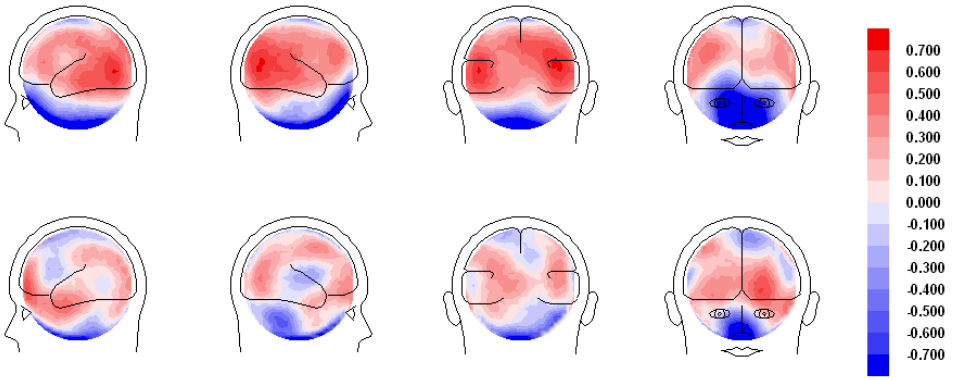

Figure 3.18. Distribution of theta power values for depressed patients (top row: left, right, back, front (left = right); n = 24) and controls (bottom row: left, right, back, front (left = right); n = 24).

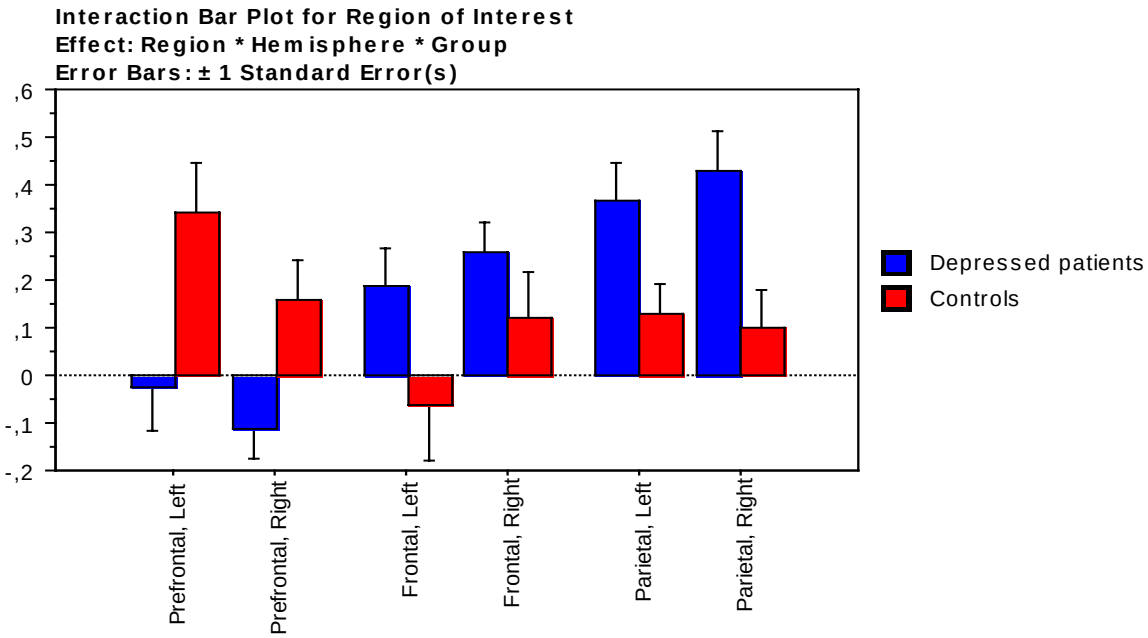

Figure 3.19. Mean theta power split by region and hemisphere for controls and depressed subjects.

The focus of enhanced theta power as displayed in the figure 3.18. is observed in the parietal region, whereas the focus of reduced theta power is seen in the prefrontal region in depressed patients compared to controls. The averages of power

for the ROI in figure 3.19. display clear differences between groups. Effects are significant for the interactions ROI x GROUP ($F(2,92) = 8.54$, $p < .001$) and ROI x HEMISPHERE ($F(2,46) = 4.92$, $p < .01$). Moreover, a post hoc Bonferroni t-test confirms larger parietal (right, $t(46) = 2.89$, $p < .01$, and left, $t(46) = 2.34$, $p < .05$) and lower prefrontal (right, $t(46) = -2.55$, $p < .05$, and left, $t(46) = -2.67$, $p < .05$) theta activity in depressed patients compared to controls.

As shown in figure 3.20., patients with a F33 diagnosis display less theta in the right anterior region and more theta in the left posterior region compared to patients with a F32 diagnosis (ROI x HEMISPHERE x DIAGNOSIS, $F(2,38) = 3.68$, $p < .05$). Post hoc Bonferroni t-tests only confirm the difference between diagnosis groups in the left parietal region ($t(19) = -2.29$, $p < .05$; see figure 3.21.).

Comparing depressives with high and low BDI scores, ANOVA reveals a significant effect for ROI ($F(2,21) = 10.3$, $p < .001$). In the right parietal region, patients with low BDI scores show greater theta activity than patients with high BDI scores ($t(21) = 2.05$, $p < .05$; see figure 3.22.).

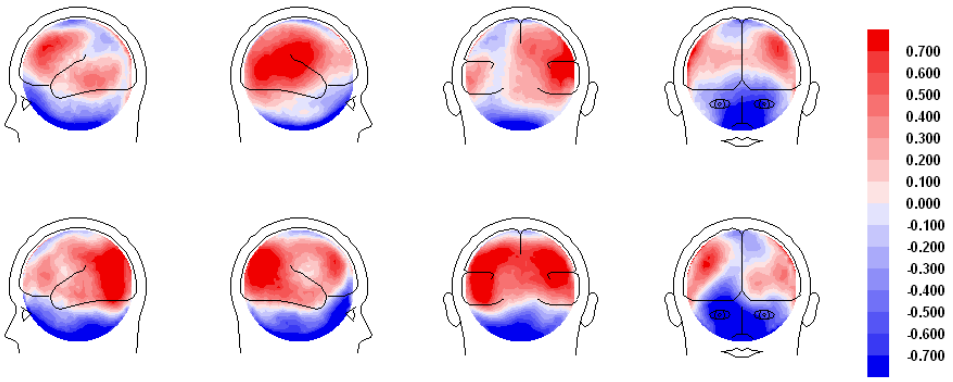

Figure 3.20. Distribution of theta power values for depressed patients with the F32 diagnosis (top row; n = 10) and with the F33 diagnosis (bottom row; n = 11) at the beginning of therapy.

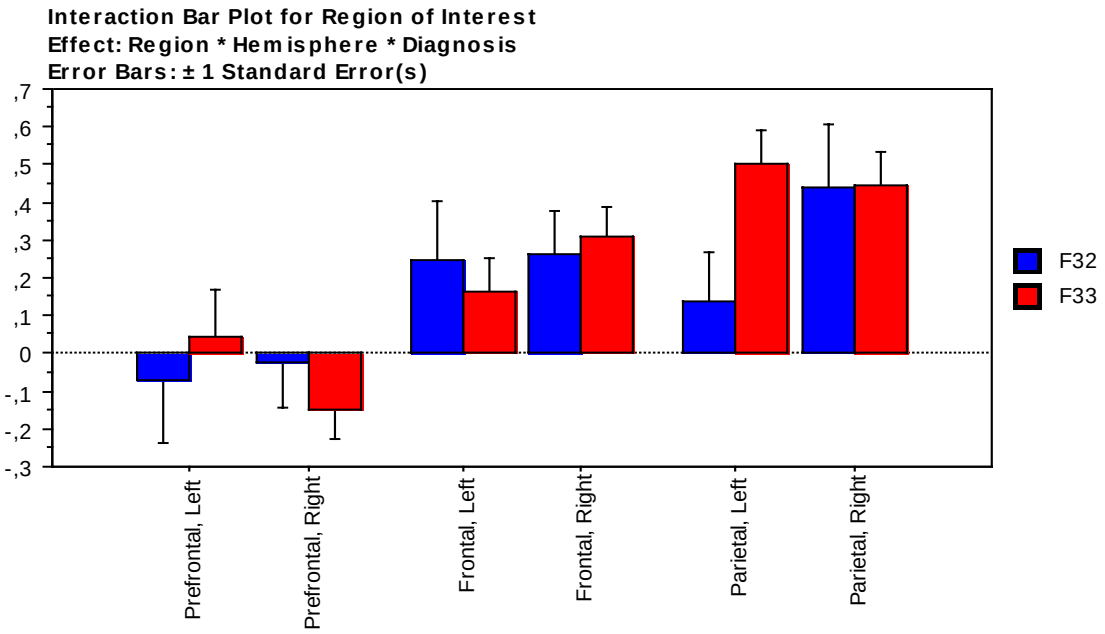

Figure 3.21. Mean theta power split by region and hemisphere for depressed patients with the diagnosis of depressive episode (F32) and recurrent depressive disorder (F33).

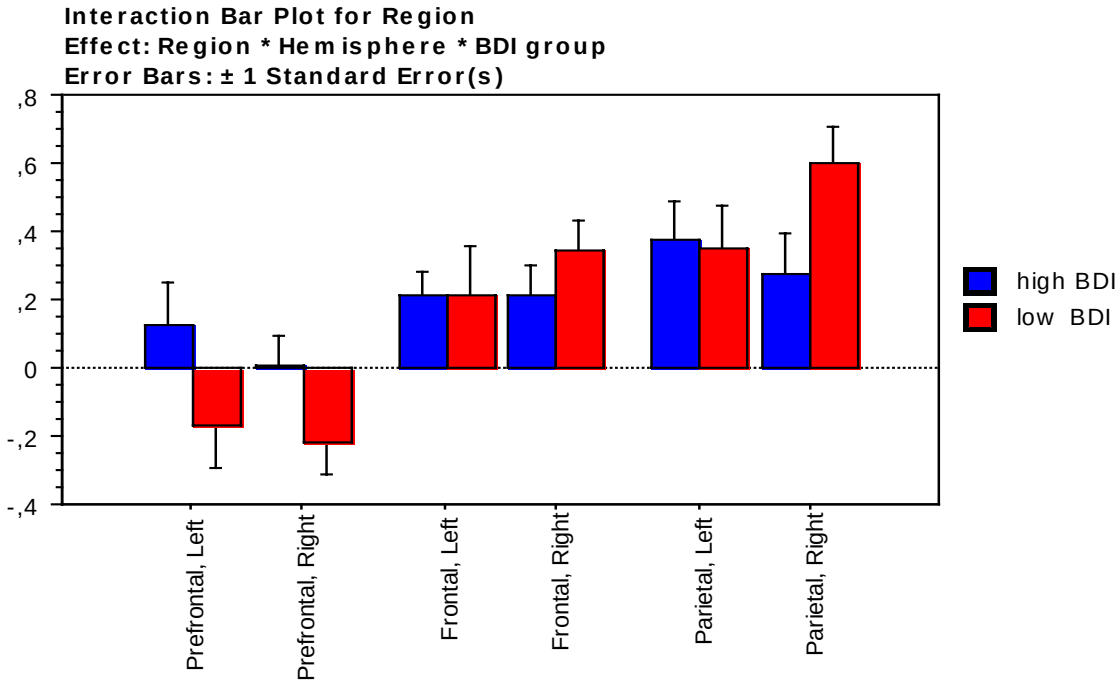

Figure 3.22. Mean theta power split by region and hemisphere for depressed patients with high (n = 11) and low (n = 12) BDI scores.

3.2.2.2. Theta activity changes after treatment.

As can be seen from figure 3.23., theta activity after treatment increases in the right anterior region and decreases in the posterior region relative to before treatment, but these differences are not significant.

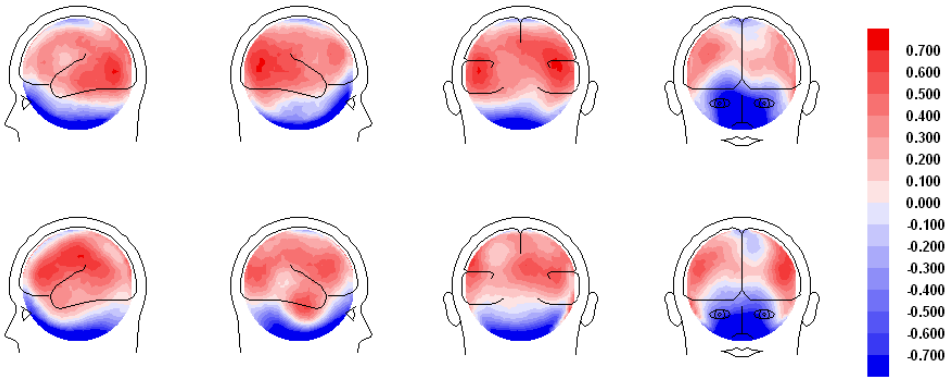

Figure 3.23. Distribution of theta power values for depressed patients at the beginning (top row; n = 24) and the end of therapy (bottom row; n = 24).

Treatment induced effects do differ between diagnoses, because ANOVA reveals a significant MEASUREMENT x HEMISPHERE x ROI x DIAGNOSIS interaction ($F(2,38) = 4.46$, $p < 0.05$) which is displayed with a bar plot in figure 3.24. Further analysis demonstrates significant effect for MEASUREMENT in the right parietal region ($F(1,19) = 4.62$, $p < 0.05$). After treatment, a more prominent tendency towards normalization is suggested for patients with depressive episodes. They show a significant decrease in the right parietal region ($t = 2.74$, $p < .05$), relative to before treatment.

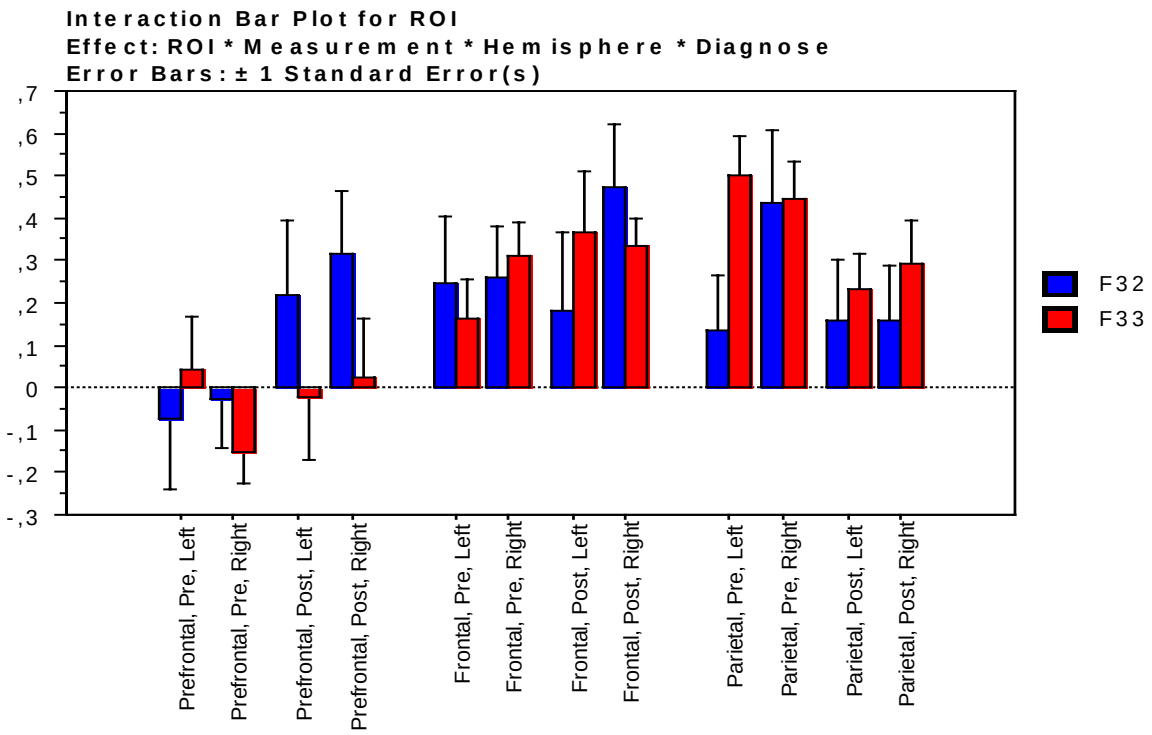

Figure 3.24. Mean theta power split by hemisphere and diagnosis for depressed patients before and after therapy (F32: depressive episode, F33: recurrent depressive disorder).

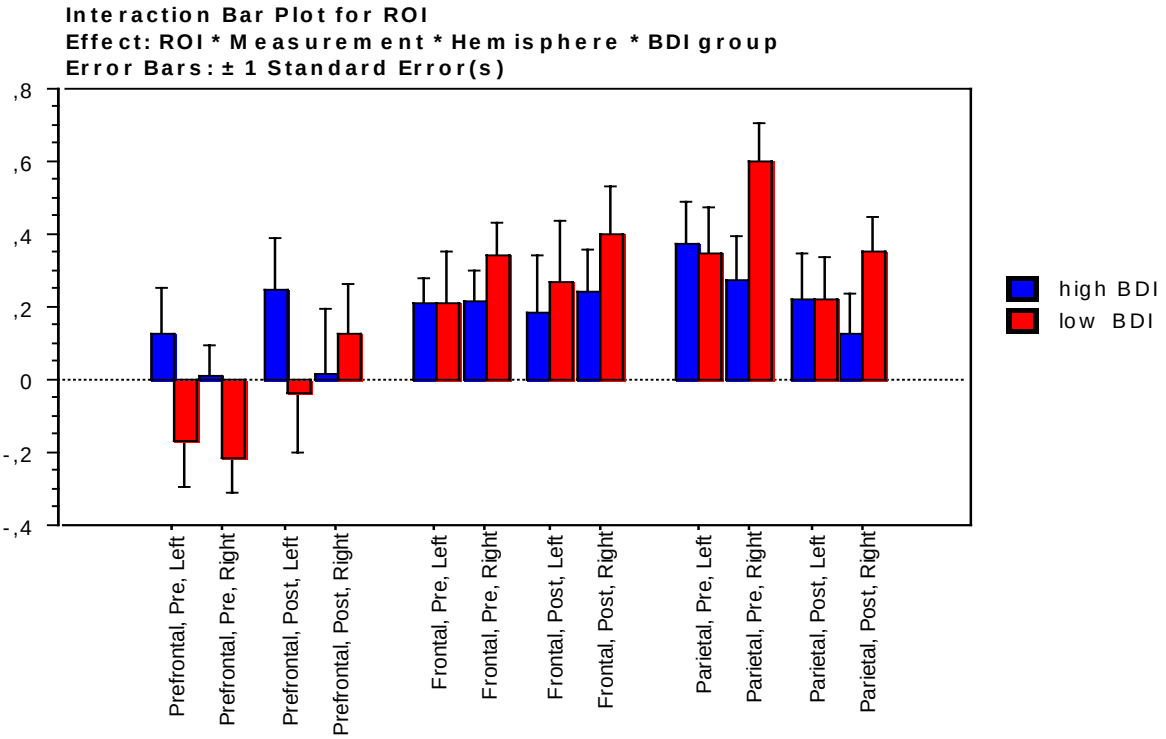

Figure 3.25. Mean theta power split by region, hemisphere and BDI group before and after therapy.

Analysis of high and low BDI groups reveals a significant effect for ROI ($F(2,42) = 5.53$, $p < .001$). As seen in figure 3.25., depressives with low BDI scores show an increase in the right prefrontal region and a decrease in the right parietal region, however there are significant effects only for latter region: MEASUREMENT ($F(1,21) = 4.79$, $p < 0.05$) and BDI GROUP ($F(1,21) = 5.53$, $p < 0.05$). Depressed patients with low BDI scores display a significant decrease of theta power in the right parietal region at the end of therapy compared to the beginning ($t = 2.49$, $p <. 05$). However, there are no significant effects for patients in the high BDI group.

3.2.2.3. Relationship between theta power and symptom ratings.

The correlation coefficients between theta power and BDI scores in the figure 3.26. show a positive correlation in the left hemisphere at the beginning of therapy, mainly in the prefrontal region, and a negative correlation in the right hemisphere, mainly in the parietal region (see table 3.4.). These relationships indicate that a higher level of depression before treatment is associated with more theta power in the left hemisphere and left prefrontal region and with less theta in the right hemisphere and right parietal region (see scatterplots in figures 3.27. and 3.28).

	Left				Right			
	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	**.421***	**.464***	.042	.076	**-.489***	.219	-.094	**-540****
BPRS	.127	.077	.071	-.047	.039	-.041	**.438***	-.066

** Correlation is significant at the 0.01 level.
* Correlation is significant at the 0.05 level.

Table 3.4. Correlation coefficients between mean theta power in ROI and BDI / BPRS scores prior to therapy (n = 23).

As can be seen from the bottom row in figure 3.26., the right frontal theta activity correlates positively with BPRS scores before treatment, indicating that a higher level of general psychopathology is associated with more theta power in the right frontal region (see table 3.4. and scatterplot in figure 3.29.).

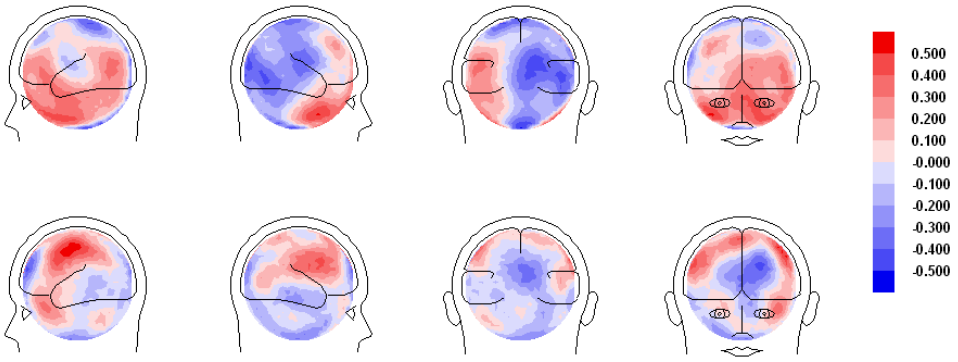

Figure 3.26. Distribution of correlation coefficients for theta power and symptom scores at the beginning of therapy (n = 23). Top row displays relation to pre-treatment BDI scores, bottom row - to pre-treatment BPRS scores. The map is created by calculating the correlation for each dipole. The color scale displays correlation coefficients: blue indicates negative correlations, red – positive correlations.

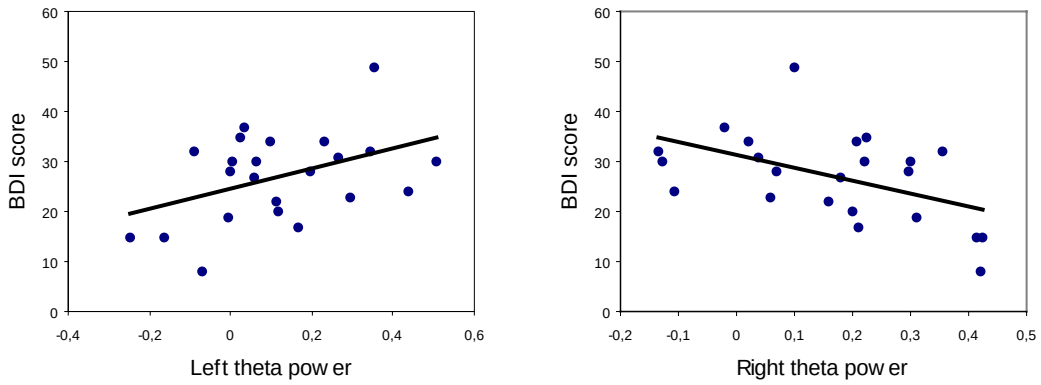

Figure 3.27. Scatterplott of single subject distribution of theta power in the left (left) and right (right) hemisphere relative to BDI scores at the beginning of treatment.

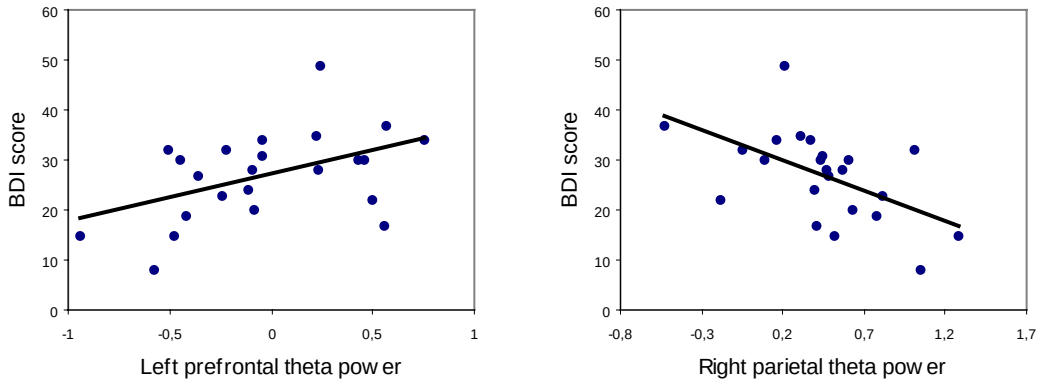

Figure 3.28. Scatterplott of single subject distribution of theta power in the left prefrontal (left) and right parietal (right) regions relative to BDI scores at the beginning of treatment.

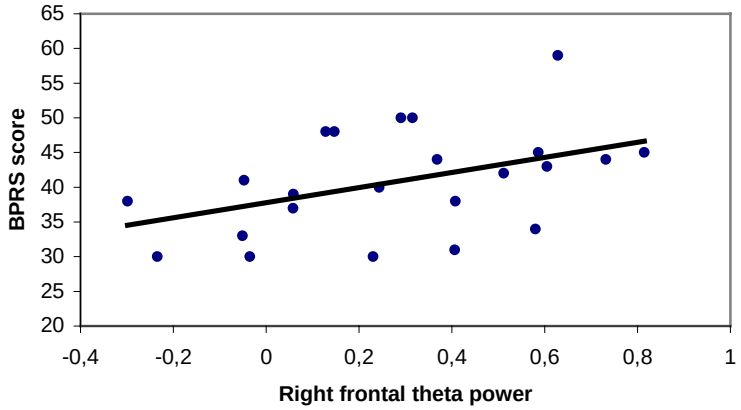

Figure 3.29. Scatterplott of single subject distribution of theta power in the right frontal region relative to BPRS scores at the beginning of treatment.

As shown in table 3.5., change in theta power from pre- to post-treatment does not correlate with symptom improvement.

	Left				Right			
Change	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	.304	.367	.096	.043	-.210	.404	.066	-.389
BPRS	-.130	.017	-.379	-.128	.158	.237	.001	-.042

Table 3.5. Correlation coefficients between change in mean theta power in ROI from pre- to post-treatment (post – pre) and change in BDI / BPRS scores (post – pre; n = 23).

3.2.2.4. Summary.

Results from the theta band confirm the hypothesis that depressed patients exhibit less activity in the prefrontal (left and right) regions and more activity in the parietal (left and right) regions compared to controls. Furthermore, depressed patients show greater theta activity in the right hemisphere relative to healthy subjects. Within the patient group, depressed patients with a F33 diagnosis demonstrate more theta power in the left parietal region than patients with a F32 diagnosis. Patients with low BDI scores have greater theta activity in the right parietal region compared to patients with high BDI scores.

Depressed patients show no significant change in theta activity from pre- to post treatment. However, after therapy, patients with a F32 diagnosis show a decrease in the right parietal region, relative to before treatment. Also depressed patients with low BDI scores show a decrease in the right parietal region after treatment relative to before treatment.

Correlations of theta activity with symptoms scores demonstrate that, contrary to expectations, abnormal theta power is associated with lower depression severity. At the beginning of therapy, decreased theta power in the left hemisphere and left prefrontal region, and increased theta power in the right hemisphere and right parietal region are associated with a lower level of depression. Moreover, more right frontal theta power is associated with higher level of general psychopathology. Change in theta power from pre- to post-treatment does not correlate with symptom improvement.

3.2.3. Alpha band.

3.2.3.1. Group comparison before treatment.

As evident from figure 3.30., depressed subjects display more alpha power than controls, mainly in the right hemisphere. Although the repeated measure ANOVA reveals a significant main effect GROUP ($F(1,46) = 7.86$, $p < .01$; but no interaction GROUP x HEMISPHERE), a post hoc Bonferroni t-test confirms a significant difference between groups only in the right hemisphere ($t(46) = 2.55$, $p < .05$).

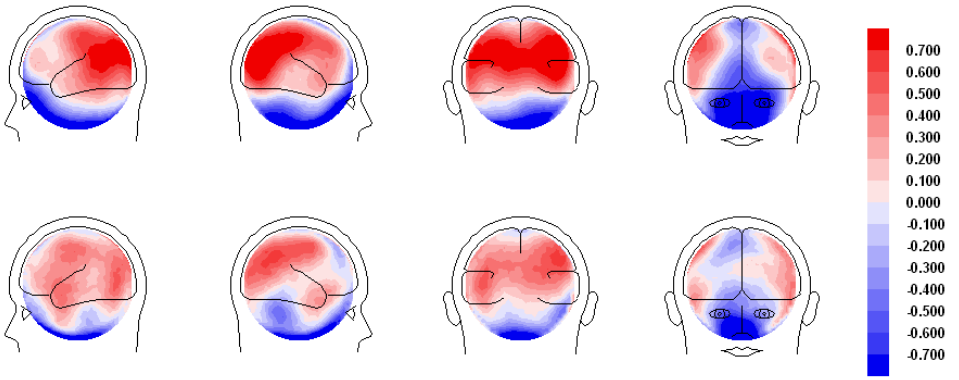

Figure 3.30. Distribution of alpha power values for depressed patients (top row: left, right, back, front (left = right); n = 24) and controls (bottom row: left, right, back, front (left = right); n = 24).

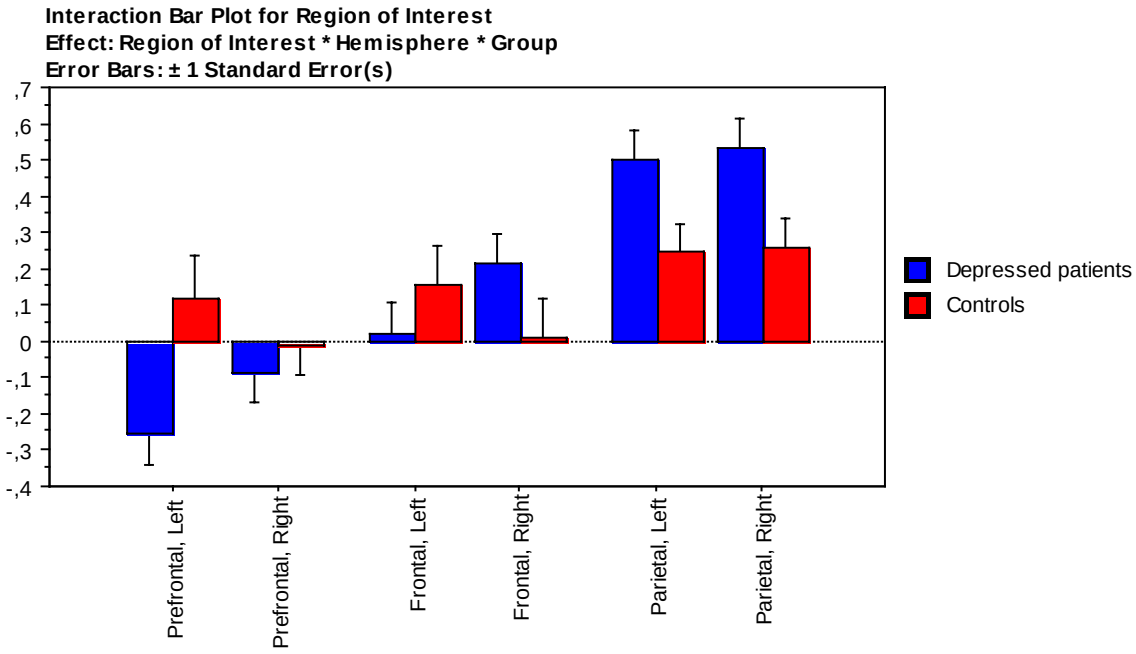

Figure 3.31. Mean alpha power split by region and hemisphere for depressed patients and controls.

Figure 3.30. also indicates that group differences in the alpha power are apparent in the anterior and posterior regions with depressives exhibiting less anterior and more posterior activity compared to controls. The ANOVA reveals significant interactions of ROI x GROUP ($F(2,92) = 4.21$, $p < .05$) and HEMISPHERE x GROUP ($F(1,46) = 4.29$, $p < .05$). Post hoc Bonferroni t-tests confirm a significant difference between groups in the left prefrontal region ($t(46) = -2.48$, $p < 0.05$) and parietal region (left, $t(46) = 2.34$, $p < .05$, and right, $t(46) = 2.39$, $p < .05$), suggesting that depressed subjects show reduced alpha power in the left prefrontal region, and enhanced alpha power in the parietal region compared to healthy subjects (see figure 3.31.).

The pattern of anterior asymmetry in depressives is indentified by ANOVA performed only for the depressive group: a main effect HEMISPHERE ($F(2,46) = 3.67$, $p < .05$) explains the difference between the left and right hemispheres in the frontal region ($t(23) = -2.72$, $p < .05$), while there is no significant ROI x HEMISPHERE interaction in healthy subjects. Thus, depressed patients show more right than left frontal alpha activity at the beginning of therapy.

Laterality indices of alpha power are plotted in the figure 3.31. Depressed patients, when compared to controls, display anterior and posterior asymmetry with more right than left prefrontal and frontal alpha power, and more left than right parietal alpha power. However, ANOVA reveals no significant differences between groups.

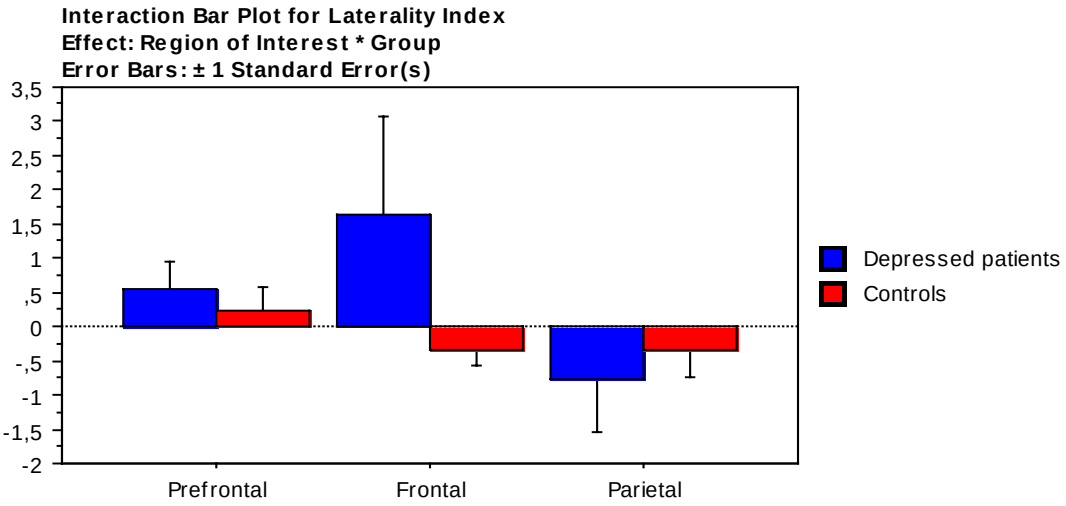

Figure 3.31. Mean alpha power laterality indices for depressed patients and controls. Positive scores indicate greater right than left power, negative – greater left than right power.

Depressed patients with a F32 diagnosis display more right, but less left frontal power compared to patients with a F33 diagnosis. The latter demonstrate more left parietal power than patients with the F32 diagnosis (see maps in figure 3.32.). The differences are not strong enough to be confirmed by an interaction ROI x HEMISPHERE x DIAGNOSIS. However there are significant effects for ROI ($F(2,19) = 13.33$, $p < .0001$) and HEMISPHERE ($F(1,19) = 5.75$, $p < .05$). A post hoc Bonferroni t-test confirms the difference in the left parietal region indicating that patients with recurrent depressive disorder exhibit more alpha power than patients with depressive episode: $t(19) = -2.18$, $p < .05$ (see figure 3.33.).

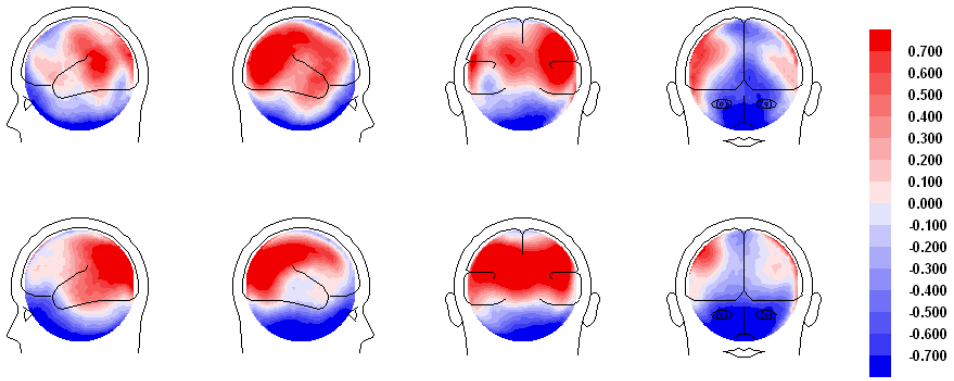

Figure 3.32. Distribution of alpha power values for depressed patients with F32 diagnosis (first row; n=10) and with F33 diagnosis (second row; n=11) at the beginning of therapy.

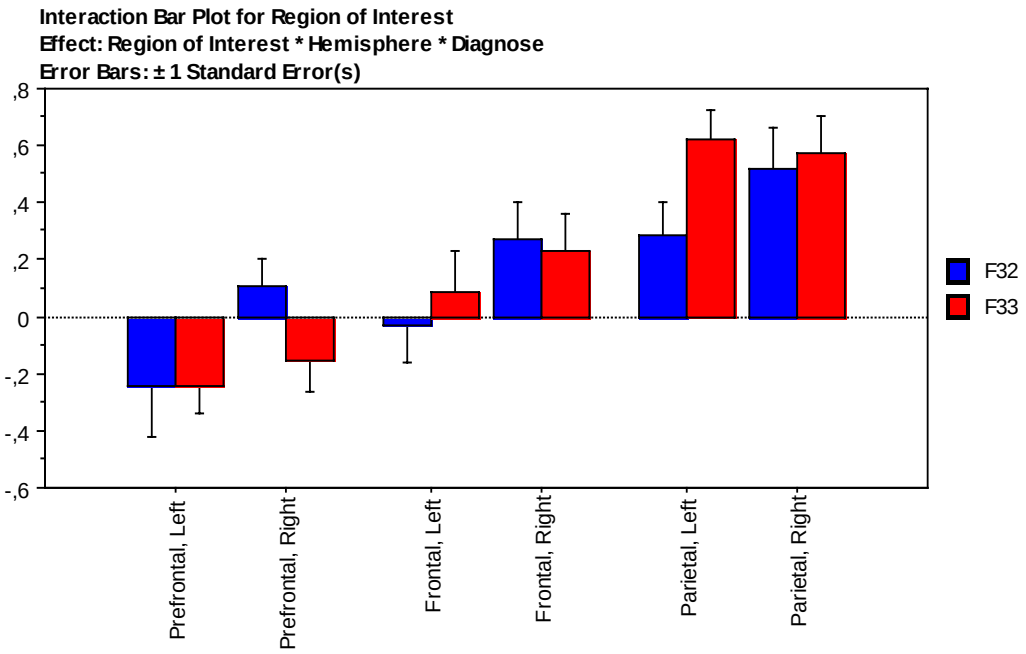

Figure 3.33. Mean alpha power split by region and hemisphere for depressed patients with a depressive episode diagnosis (F32; n = 10) and with a diagnosis of recurrent depressive disorder (F33; n = 11).

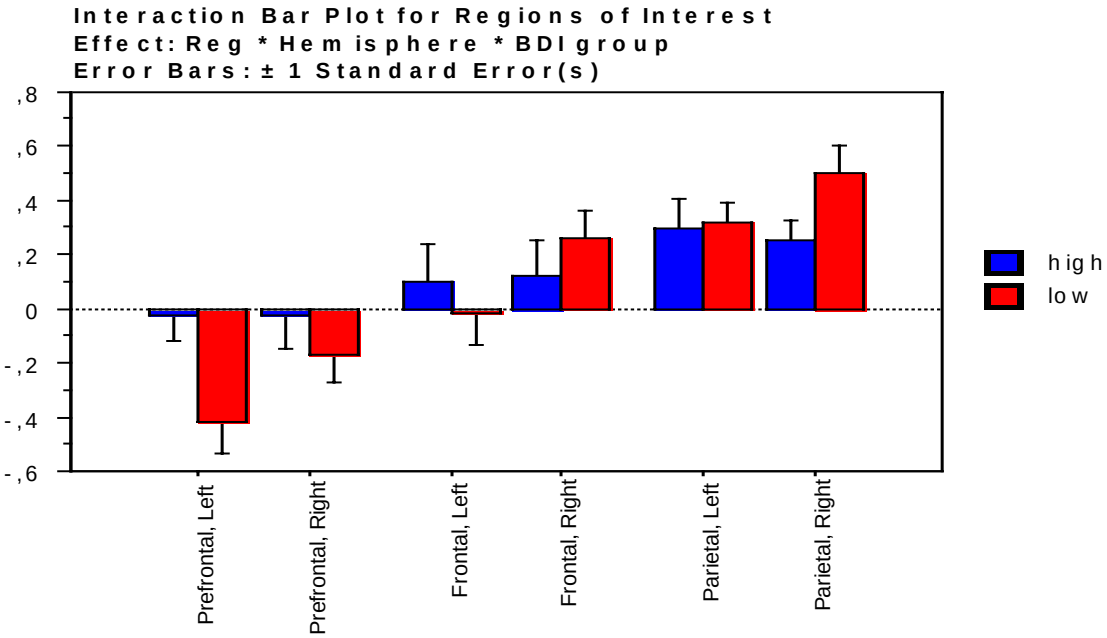

Figure 3.34. Mean alpha power split by region and hemisphere for patients with high (n = 11) and low (n = 12) BDI scores.

Analysis of depressed patients with high and low BDI scores reveals a significant interaction HEMISPHERE x BDI GROUP ($F(1,21) = 6.04$, $p < .05$) and a significant effect for REGION ($F(1,21) = 14.75$, $p < .001$). Depressives with low BDI scores show less alpha power in the left prefrontal region ($t(21) = -2.55$, $p < .02$; see figure 3.34.), compared to the high BDI group.

3.2.3.2. Alpha activity changes after treatment.

The change in alpha power between pre- and post-treatment is presented in the figure 3.35. Although it seems that depressed patients display an increase in alpha power in the left anterior region and a decrease in the left posterior region at the end of therapy relative to the beginning, these effects are not confirmed by ANOVA.

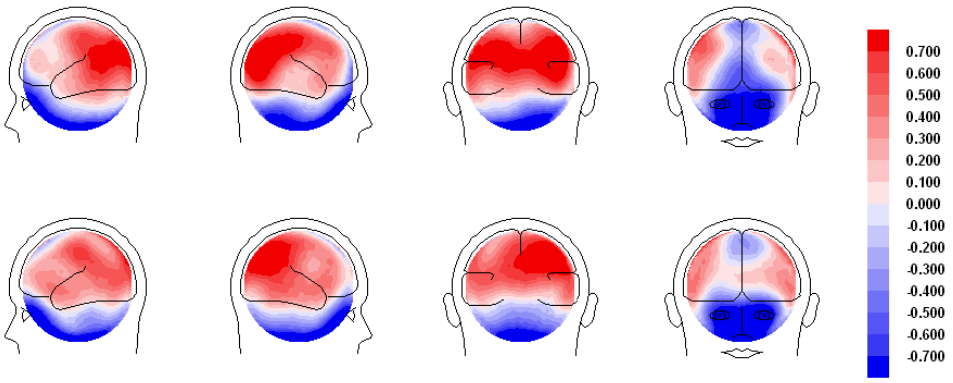

Figure 3.35. Distribution of alpha power values for depressed patients at the beginning (first row; n = 24) and the end of therapy (second row; n = 24).

There are no significant effects in the alpha power LI from pre- to post-treatment. However, examining groups with opposite asymmetry patterns, depressed patients with greater left than right frontal alpha power at the beginning of treatment shift the asymmetry pattern towards greater right than left frontal alpha power at the end of treatment ($t = -2.13$, $p < .05$). Figure 3.36. demonstrates that opposite frontal asymmetries change from pre- to post-treatment towards symmetry, however the effect is only significant for the group with more left than right alpha power (the

effect for the group with an asymmetry pattern towards greater right alpha power is not significant due to a larger standard deviation).

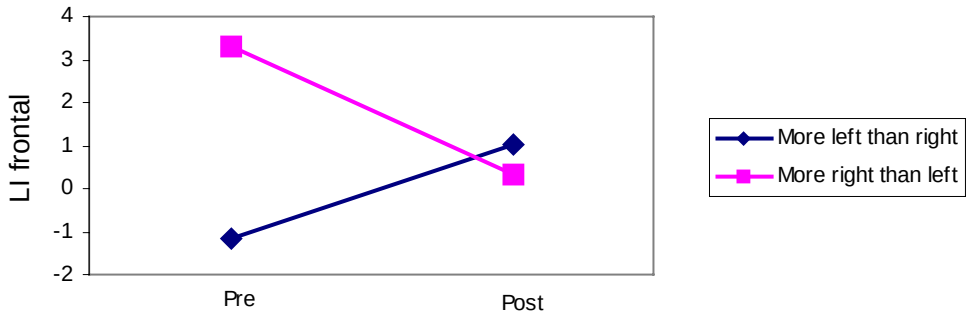

Figure 3.36. Change of LI in the frontal region in depressed patients with more left than right (n = 9) and with more right than left (n = 15) alpha power from pre- to post-treatment.

Comparing different diagnosis groups, ANOVA reveals a significant effect for ROI ($F(2,38) = 13.91$, $p < 0.001$). As shown in figure 3.38., a prominent increase of alpha power in patients with a F32 diagnosis can be observed in the left prefrontal and frontal regions at the end of therapy, whereas patients with a F33 diagnosis show a clear decrease in alpha power in the left parietal region. However, there is only significant effect in the left parietal region for DIAGNOSIS ($F(1,19) = 5.49$, $p < 0.05$). Separate analyses in each group demonstrate a significant decrease of alpha power in the left parietal region in patients with a F33 diagnosis at the end of therapy compared to the beginning ($t = 1.82$, $p < .05$).

In addition, ANOVA reveals a significant ROI effect ($F(2,42) = 19.18$, $p < 0.001$) for groups with high and low BDI scores. In figure 3.39., a more prominent increase in alpha power in the left prefrontal region in depressives with low BDI scores can be seen after treatment, whereas depressives with high BDI scores show a decrease in the left parietal region. Statistical analysis demonstrates significant effects for BDI GROUP ($F(1,21) = 6.26$, $p < 0.05$) in the left prefrontal region and for MEASUREMENT ($F(1,21) = 4.37$, $p < 0.05$) in the left parietal region. Hence, depressives with low BDI scores show an increase of alpha power in the left prefrontal region ($t = -1.99$, $p < .05$) at the end of therapy compared to the beginning, whereas depressives with high BDI scores show a decrease in the left parietal region ($t = 1.86$, $p < .05$).

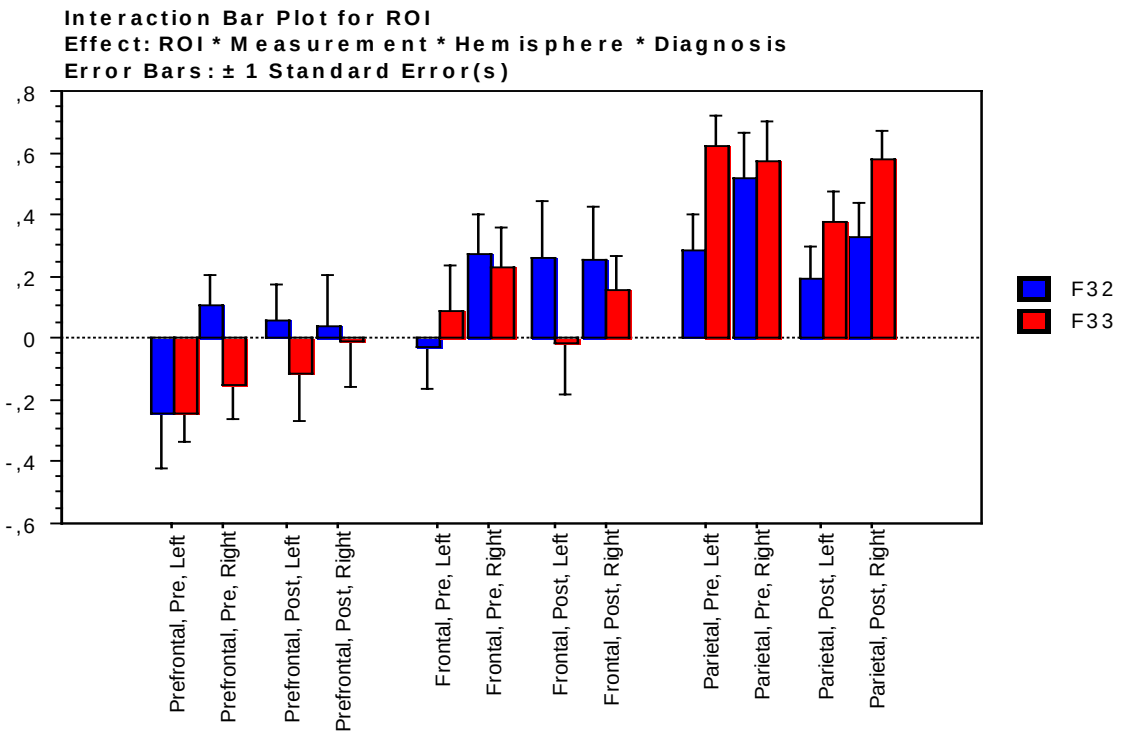

Figure 3.38. Mean alpha power split by hemisphere and diagnosis group (F32 and F33) before and after treatment.

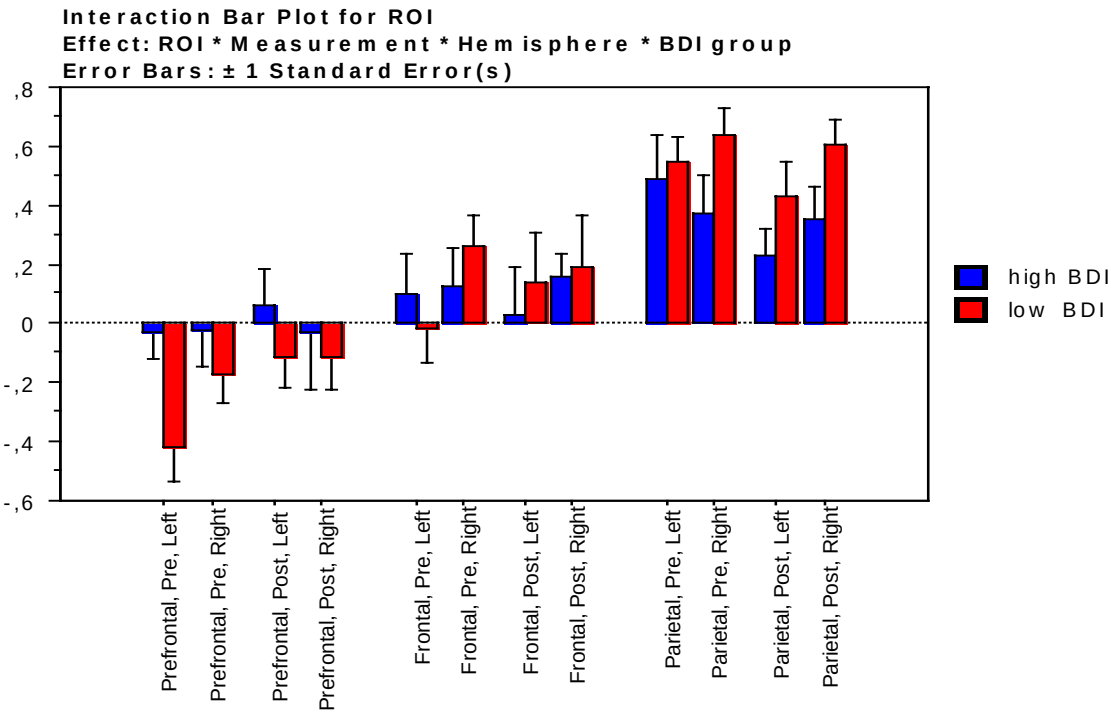

Figure 3.39. Mean alpha power split by hemisphere and BDI group (high and low) before and after therapy.

3.2.3.3. Relationship between alpha power and symptom ratings.

Figure 3.40. suggests a positive relationship between BDI scores and prefrontal (mainly left) alpha power and a negative relationship between BDI scores and right parietal alpha power. Correlation analyses only reveal a positive relationship at the beginning of therapy with less alpha activity in the left prefrontal region varying with less severe depression (see table 3.6., also see scatterplot in figure 3.41. right). There is also a negative correlation between pre-treatment BDI scores and right hemisphere alpha power at the beginning of therapy (see table 3.6.). This negative correlation demonstrates that before treatment, less alpha power in the right hemisphere is associated with higher levels of depression (see scatterplot in figure 3.41. left).

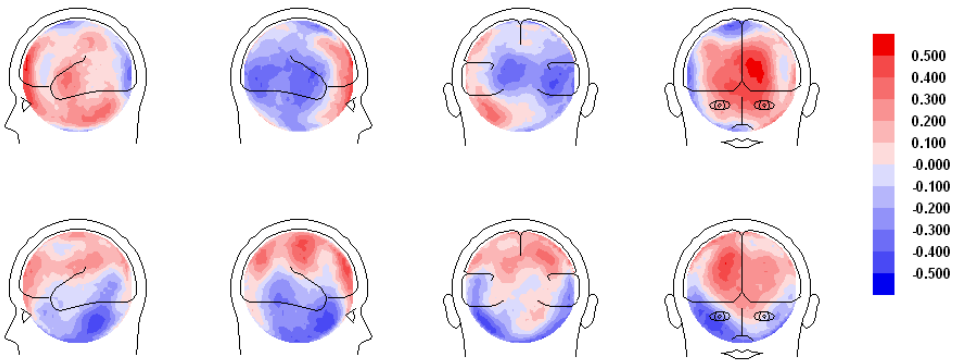

Figure 3.40. Distribution of correlation coefficients for alpha power and symptom scores at the beginning of therapy (n = 23). Top row displays relation to pre-treatment BDI scores, bottom row - to pre-treatment BPRS scores. The map is created by calculating the correlation for each dipole. The color scale displays correlation coefficients: blue indicates negative correlations, red – positive correlations.

As can be seen from the bottom row in figure 3.40., right frontal alpha power at the beginning of therapy correlates positively with pre-treatment BPRS scores. Correlation analysis of ROI confirms these results. In table 3.6., the relationships

presented indicate that before therapy a higher BPRS score is associated with more alpha power in the right frontal region (see also scatterplot in figure 3.42. left).

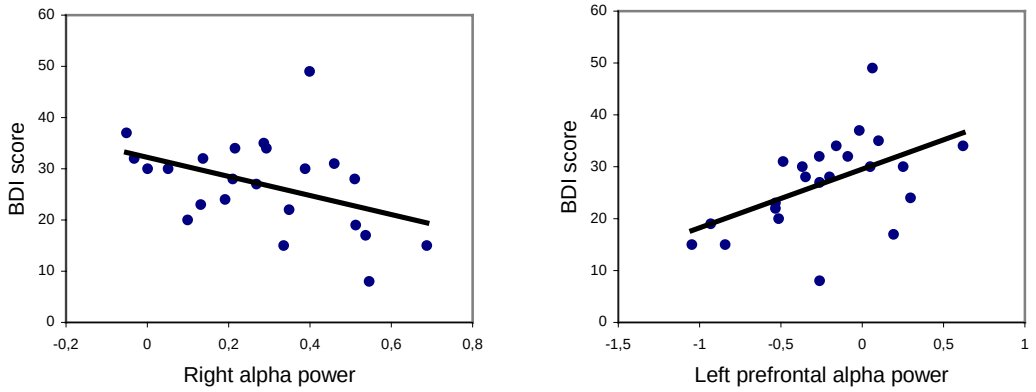

Figure 3.41. Scatterplott of single subject distribution of alpha power in the right hemisphere (left) and left prefrontal region (right) relative to BDI scores at the beginning of treatment.

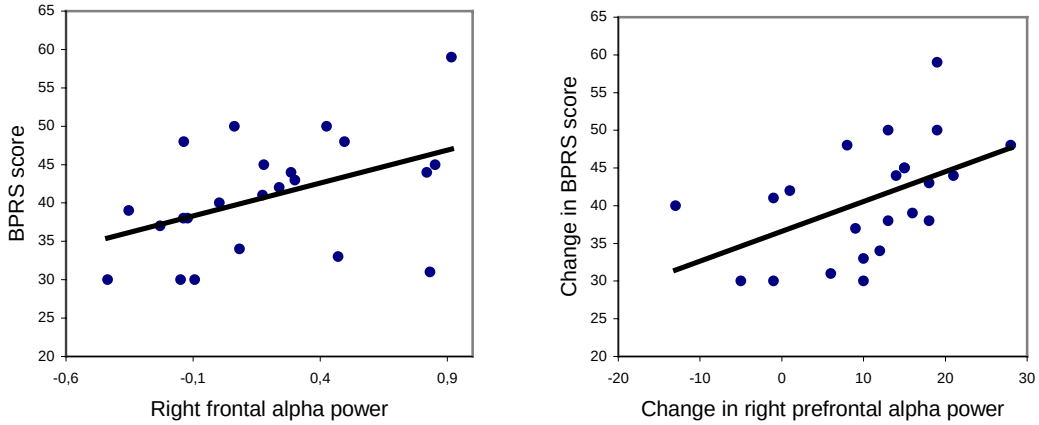

Figure 3.42. Left: scatterplott of single subject distribution of alpha power in the right frontal region relative to BPRS scores at the beginning of treatment. Right: scatterplott of single subject distribution of change in alpha power in the right prefrontal region (post-pre) relative to change in BPRS scores (post-pre) at the beginning of treatment.

	Left				Right			
	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	.281	**.515***	.198	-.059	**-.423***	.096	-.025	-.365
BPRS	.182	.112	.258	.014	.263	-.091	**.450***	.097

* Correlation is significant at the 0.05 level.

Table 3.6. Correlation coefficients between mean alpha power in ROI and BDI / BPRS scores prior to therapy (n = 23).

As shown in table 3.7., change towards a decrease in right prefrontal alpha power from pre- to post-treatment is associated with greater symptom improvement of general psychopathology (see also scatterplot in figure 3.42 right).

	Left				Right			
Change	Hemisphere	Prefrontal	Frontal	Parietal	Hemisphere	Prefrontal	Frontal	Parietal
BDI	.133	.118	.391	-.191	-.115	.122	.331	-.383
BPRS	-.296	-.242	-.258	-.162	.206	**.417***	.198	-.075

* Correlation is significant at the 0.05 level.

Table 3.7. Correlation coefficients between mean alpha power in ROI and BDI / BPRS scores prior to therapy (n = 23).

3.2.3.4. Summary.

Statistical analysis of alpha activity reveals that depressed patients show more right hemisphere alpha power than controls. Results also indicate that depressed subjects have less alpha power in the left prefrontal region and more alpha power in the right and left parietal regions compared to healthy subjects. Moreover, depressed patients show more alpha power in the right frontal region relative to the left frontal region. Reduced left prefrontal alpha power is pronounced in depressed patients with low BDI scores compared to those with high BDI scores, whereas augmented left parietal alpha activity is more pronounced in patients with a diagnosis of recurrent depressive disorder compared to patients with a depressive episode.

Correlations demonstrate that abnormal alpha power is associated with lower depression severity. Evidence indicates that enhanced right hemisphere alpha power and reduced left prefrontal alpha power is associated with lower depression severity. A positive correlation is also found in the right frontal region indicating that less right frontal alpha power is associated with a lower level of general psychopathology.

As in the theta frequency band, depressed patients also show no significant change in alpha band from pre- to post treatment. At the end of therapy, a change of alpha power is observed, implying an increase in the left prefrontal region in depressed patients with low BDI scores, whereas a decrease in the left parietal region is demonstrated by patients with high BDI scores. Furthermore, after therapy, patients with a F33 diagnosis show a decrease of alpha power in the left parietal region.

Although the pattern of asymmetry in depressives does not change after treatment, when examining groups with opposite frontal asymmetry patterns,

depressed patients with greater left than right frontal alpha power at the beginning of treatment significantly shift their asymmetry pattern towards greater right than left frontal alpha power by the end of treatment.

Decreases form pre- to post-treatment in right prefrontal alpha power are associated with greater symptom improvement of general psychpathology.

4. DISCUSSION.

The present MEG study investigates slow wave and alpha activity in patients with affective disorder by comparing depressives to healthy subjects, relating abnormal activity to symptomatology, and observing the change in activity after psychotherapy treatment in relation to symptom improvement.

The findings confirm hypothesis 1a, suggesting that depressed patients show decreased theta power in the left and right prefrontal regions, decreased delta power in the right prefrontal region, and increased delta and theta activity in the left and right parietal regions, compared to controls (see table 4.1. for a summary of results). However, the relationship between brain activity and symptomatology is unexpected. Reduced prefrontal and increased parietal theta activity is associated with less severe depression. Moreover, delta activity does not correlate with symptomatology.

As expected, depressed patients show enhanced right parietal activity in the alpha frequency band, however, contrary to hypothesis 1b, depressed patients demonstrate reduced left prefrontal alpha activity compared to controls (see table 4.1.). In addition, decreased left prefrontal alpha activity is related to a lower level of depression, whereas alpha activity in the right parietal region does not correlate with symptomatology.

The failure to find differences between groups in anterior and posterior asymmetry does not confirm the hypothesis 1b, which states that depressed patients demonstrate asymmetry patterns towards greater left anterior and right posterior activity in the alpha frequency band compared to healthy subjects. Depressed patients show frontal asymmetry towards more right frontal compared to left frontal alpha power.

At the end of treatment, depressed patients, parallel to symptom improvement, show an increase in delta activity in the right prefrontal region, but a decrease in delta activity in the right parietal region relative to the beginning of treatment. These results confirm the second hypothesis, which states that treatment effects, evaluated by symptom improvement, are accompanied by normalization of slow wave activity in the prefrontal and parietal regions of the right hemisphere. However, change from pre- to post-treatment towards normalization in delta activity is not related to symptom improvement after therapy (see table 4.1.).

Brain activity	Before treatment				Change after treatment			
	Compared to controls	Between diagnosis groups	Between high and low BDI groups	Correlation with symptoms	In depressed patients	In diagnosis groups	In high and low BDI groups	Correlation with symptom improvement
Delta	L ↑							
	PFR R ↓				PFR R ↑		Low ↑	
	PT L, R ↑				PT R ↓		Low ↓	
		F33 FR L, R ↓						BDI FR R +
Theta	R ↑			BDI ↓				
	PFR L, R ↓			BDI L ↓				
	PT L, R ↑	F33 L ↑	Low R ↑	BDI R ↓		F32 R ↓	Low R ↓	
				BDI L +				
				BPRS FR R +				
Alpha	R ↑			BDI ↓				
	PFR L ↓		Low L ↓	BDI ↓			Low ↑	BPRS PFR R +
	PT L, R ↑	F33 L ↑				F33 L ↓	High L ↓	
				BPRS FR R +				

Table 4.1. Neuromagnetic brain activity in depressed patients (compared to controls, between F32 and F33 diagnoses and between high and low BDI groups) in different frequency bands before and after treatment. Abbreviations: L – left hemisphere, R – right hemisphere, PFR – prefrontal region, FR – frontal region, PT – parietal region, ↑ - increase, ↓ - decrease, + - positive correlation, F33 – diagnosis of recurrent depressive disorder, F32 – diagnosis of depressive episode. Results in red confirm the hypotheses and blue indicates that hypotheses are not confirmed.

Despite some inconsistent findings in the present MEG study, the data suggest that the prefrontal and parietal cortices are dysfunctional in depression. Findings that, in a resting condition, depressed patients show a decrease in neuromagnetic activity compared to healthy subjects in the prefrontal region and an increase in the parietal region are supported by other neurological, cerebral blood flow and EEG/MEG studies investigating anterior and posterior abnormalities in depression. The findings and limitations of the present study will be discussed below with regard to previous research and possibilities for further investigation.

4.1. Anterior and posterior abnormalities in depressed patients.

4.1.1. Slow wave activity.

Depressed patients in the current study show increased delta activity in the left hemisphere compared to healthy subjects. This is in accordance with findings of brain lesion studies, which report that depression after stroke is more frequently observed in

patients suffering damage to the left hemisphere (Starkstein and Robinson, 1989). However, observations from the theta frequency band contradict the above results indicating more theta activity in the right hemisphere of depressed patients compared to controls. Nevertheless, this finding is consistent with demonstrations that right hemisphere lesions also can produce depression, only to a lesser extent than left hemisphere lesions do (Fedoroff et al., 1992; Robinson et al., 1984; Sackeim et al., 1982).

Most neurological and neuroimaging research suggests left anterior dysfunction in depression (Davidson, 2003; George, Ketter and Post, 1994; Rosenthal, Christensen and Ross, 1998). Although in the delta band there is a difference between groups in the right prefrontal region, in the theta band, depressed patients show reduced left and right prefrontal activity. These results replicate findings from a previous MEG study by Wienbruch et al. (2003) demonstrating decreased theta activity in the prefrontal region in patients with affective disorder. EEG studies indicating reduced slow wave activity in the anterior region are also in line with this finding (Flor-Henry, Lind and Koles, 2004; Mientus et al., 2002). EEG sleep studies indicate that delta activity and slow wave sleep are usually diminished during sleep in depressives compared to controls (Armitage et al., 2001). In addition, many PET studies find evidence for decreased metabolism and blood flow in the dorsolateral and medial prefrontal cortex in depressed subjects (Bench et al., 1992; Biver et al. 1994; Cohen et al., 1992; Curran et al., 1993; Dolan et al., 1993; Drevets et al., 1998; Ebert et al. 1991; Gonul et al., 2004; Mayberg et al., 1999; Skaf et al., 2002). Reduced cortical volume in the prefrontal (Kumar et al., 1997, 1998), subgenual prefrontal (Drevets, Price and Simpson, 1997) and frontal regions (Coffey et al., 1993) are found in depressed subjects. In addition, various MRI studies report also reduced activity in the anterior areas (Bremner et al., 2002; Drevets et al., 1997; Kumar et al.,1997, 1998; Lai et al., 2000; Lee et al., 2003).

Present results reveal significant group differences in the left and right parietal regions with augmented delta and theta activity in depressed patients. This finding confirms hypothesis 1a, which argues, based on a recent EEG study by Flor-Henry, Lind and Koles (2004) that posterior activity increases in depressed patients. Also, an early study by Dierks et al. (1993) demonstrates an increase in delta activity in the posterior region of depressed patients, compared to controls. The findings of neuroimaging studies are also in line with these results. Berman et al. (1993) show

increased blood flow in depressed subjects in the right parietal region, while Ballmaier et al. (2004) observe increases in cortical gray matter in the parietal lobes in depressed elderly women. However, studies with depressed subjects with seasonal affective disorder show decreased slow wave activity in the posterior region (Passynkova and Volf, 2001; Volf and Passynkova, 2002).

In the present study, patients with a F33 diagnosis have more depression symptoms and demonstrate more abnormal theta activity in the left parietal region, compared to patients with a F32 diagnosis. Furthermore, patients with a F33 diagnosis show less delta activity in the right and left frontal regions. These results demonstrate that recurrent depressive disorder is associated with greater abnormalities in resting slow wave activity than depressive episode. Jindal et al. (2002) find that patients with recurrent forms of major depression have greater disturbances of sleep continuity, REM sleep, and diminished slow wave sleep as compared to single-episode patients. Greater abnormalities in recurrent depressive disorder are consistent with both an illness transduction model (Post, 1992) and the possibility of phenotypic expression of a more virulent form of affective illness (Drevets, Ongur and Price, 1998).

Earlier research suggests that increased slow wave activity in the delta and theta frequency bands appears in EEG as well as MEG, usually near structural brain lesions, and may indicate a dysfunctional state in neuronal tissue (Lewine and Orrison, 1995). Furthermore, as seen in MRI, abnormal decreased slow wave EEG activity in patients with different psychiatric disorders is associated with cortical atrophy (Coutin-Churchmal et al., 2003). Following these findings, it is possible that in the present study, abnormal deviations in slow wave activity towards a decrease in the prefrontal region and an increase in the parietal region in depressed patients are markers of dysfunctional neuronal tissue in these brain areas.

Dysfunctional tissue in depression may be related to serotonergic, noradrenergic and other neurotransmitter systems abnormalities (Drevets and Price, 1997; Kanner, 2004; Manji, Drevets and Charney, 2001). Neurochemical research suggests that the disruption of monoaminergic neurotransmitter systems, which are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits, may be critical in the pathophysiology of major depressive disorder (Drevets, 2001; Manji et al., 2003; Nestler et al., 2002). Studies of the prefrontal cortex in depressed patients reveal changes in monoamine receptors, transporters and related second messenger systems (Biver et al., 1997; Klimek et. al., 1997; Pacheco et al.,

1996; Stockmeier et al., 1998) suggesting parallel cellular changes in the cortical projection areas of monoaminergic neurons. Postmortem studies in patients with depression indicate glial reductions in the subgenual region of the prefrontal cortex (Ongur, An and Price, 1998) and complex neuronal abnormalities in distinct layers of the orbitofrontal cortex (Rajkowska, 2000; Rajkowska et al., 1999). The decrease in slow wave activity in the prefrontal region (in delta band right-sided and in theta band bilateral) in depressed patients found in this study may be a sign of neuronal atrophy or malfunctioning, possibly related to monoaminergic network dysfunction in depression.

Animal experiments have shown that the lowering noradrenergic and serotonergic systems levels produce EEG slowing (Vanderwolf and Baker, 1986). In addition, it has been demonstrated that reduced cholinergic and monoaminergic neurotransmission increases slow wave EEG activity in patients with Alzheimer's disease (AD) (Soininen et al., 1992). Considering these findings and evidence that noradrenergic and serotonergic systems are also consistently reduced in the brains of depressed patients (Manji et al., 2002), decreased prefrontal slow wave MEG activity in depressed patients cannot be related to dysfunction in these neurotransmitter systems. On other hand, animal studies suggest that cholinergic and monoaminergic drugs are effective in reversing EEG slowing (Detari, 2000; Dringenberg et al., 2002). Moreover, treatment with acetylcholinesterase inhibitors, such as tacrine, that improve the cognitive symptoms of AD, also produces a partial normalization of the EEG such as a suppression of theta and delta power (Jelic et al., 1998). Since, in the present study, almost all patients receive various medication, including antidepressants, SSRIs and neuroleptics, it is possible that medication influences cortical activation by diminishing slow wave activity in the prefrontal cortex.

Given the findings that during the waking state, slow waves generated in a damaged brain region characterize pathological or dysfunctional neural tissue (Vieth et al., 2000), augmented focal slow wave MEG activity in frontal and parietal regions of schizophrenia patients has been related to dysfunctional tissue in these brain areas (Fehr et al., 2003; Wienbruch et al., 2003). In a recent study by Wienbruch et al. (2003) and in the present study, depressed patients exhibit decreased MEG slow wave activity in the prefrontal region compared to controls, which raises a question about why depression seems to be associated with abnormal decreased delta and theta

activity while other pathological conditions are associated most often with abnormal increased activity.

Dementia is often accompanied by symptoms of depression, and demented depressives show an increase in delta and theta activity compared to controls (Pozzi et al., 1995; Matousek et al., 2001). Non-demented depressives show a reduction of slow wave activity compared to controls (Pozzi et al., 1995; Brenner et al., 1986; Wienbruch et al., 2003) and compared to patients with multi-infarct dementia (Sloan and Fenton, 1993). According to these findings, absence of dementia in depressed patients could be one explanation for attenuated activity in the prefrontal region, and this would not indicate the pathological tissue in this brain area.

Again, in AD patients it has been demonstrated that more pronounced right temporoparietal MEG slow wave activity is associated with worse cognitive performance (Fernández et al., 2002). Another study by Matousek et al. (2001) finds that, compared to frontal lobe syndromes (emotional bluntness, impaired control, loss of judgement), the intensity of parietal lobe syndromes (apraxia, sensory aphasia, visual agnosia, visuospatial disability) in dementia is correlated more strongly to the EEG slow activity. The EEG is, therefore, most valuable in the early-onset type of Alzheimer's disease, in which the parietal lobe syndrome is dominant and the EEG abnormality is proportional to the degree of dementia. Hence, it is possible that in the present study, accenuated delta and theta power in the posterior region in depressed patients may be an early indicator for the onset of dementia and degenerative processes in neuronal networks.

Dementia may be one explanation of alterations in abnormal slow wave activity in depressed subjects, however the question remains unanswered without empirical evidence. Comparing depressed patients to patients with neurodegenerative diseases would allow researchers to better identify neuropathological brain areas and to detect the intensity of impairment in relation to slow wave activity.

A large literature suggests that the pattern of brain activity associated with depression is intrinsically related to many of the cognitive charcteristics that have been described in depression (Heller and Nitschke, 1997). Reduction in anterior activity in depressed subjects has been related to bias or deficits on cognitive tasks that involve functions of the anterior brain regions (Heller and Nitschke, 1997). Various studies have indicated that depressed people are poor problem solvers (Hartlage et al., 1993). Using a mathematical estimation task, Slife and Weaver

(1992) show that both induced depression and psychometrically defined depression are associated with inaccurate predictions about problem-solving abilities in relation to the task, as well as with inaccurate ratings of performance. Damasio (2003) points out that patients with damage to prefrontal cortex show an inability to make appropriate decisions in situations in which the outcomes are uncertain, such as making financial investment or entering an important relationship. The author also proposes that this defect might be due to the impairment of an emotion-related signal. When these patients face a given situation they fail to activate an emotion-related memory that would help them choose more advantageously among competing options.

Furthermore, various studies indicate that less left than right anterior activity is associated with unpleasant affect and sad mood states (Davidson, 1998; Sackeim et al., 1982; Tomarken et al., 1992a; Wheeler, Davidson and Tomarken, 1993). PET studies also demonstrate that sadness decreases activation in the dorsolateral prefrontal cortices (Damasio et al., 2000). In addition, Liotti et al. (2000) and Mayberg et al. (1999) find negative associations between induced sadness and activity in the dorsolateral prefrontal cortex. During an induced happiness condition, a pattern of asymmetry towards greater right parietal activity in the low theta band (3.5-5.45 Hz) is observed in healthy men (Crawford, Clarke and Kitner-Triolo, 1996). In the current study, control subjects show more delta power in the right parietal region compared to the left parietal region.

Research that has examined cognitive characteristics related to induced pleasant and unpleasant affect suggests that unpleasant affect is associated with a decrease in the cognitive processes related to frontal lobe function (Isen, 1990). Clore, Schwarz and Conway (1994) assume that sad affect is associated with a reduction in abstract thinking, less cognitive flexibility and fewer novel responses. Given these findings, depresed patients in the present study with abnormal decreased delta and theta activity in the prefrontal regions may also show impairments in cognitive organization.

In subjects with major depression, negativity of slow waves in the left hemisphere and parietal regions are more often observed during working memory in response to negative stimuli compared to positive stimuli (Deldin et al., 2001). Although depressive cognition is characterized by a deficit in the processing of positive information (Sloan et al., 1997), in the current study, abnormal increased parietal slow wave activity in depressed patients, found during resting condition, may

indicate a bias towards remembering more negative information compared to positive information. Moreover, this bias may be increased for patients with recurrent depressive disorder, as left parietal theta augmentation is more pronounced in patients with a F33 diagnosis than in patients with a F32 diagnosis.

In the present study, a negative correlation between right parietal delta power and age indicates that older depressed patients exhibit less delta power in the right parietal region. In normal subjects, the same relationship is found between delta power and age (Polich, 1997).

4.1.2. Alpha activity.

The finding that depressed patients show reduced left prefrontal activity in the alpha band compared to controls goes against hypothesis 1b, which states that increased left anterior alpha activity in depressed patients. Moreover, depressed patients show asymmetry towards less alpha power in the left frontal compared to the right frontal region. However, these findings replicate results reported in an EEG study by Flor-Henry, Lind and Koles (2004), which finds decreased alpha power in the left frontal region and increased alpha power in the right frontal region in depressed subjects. Kano et al. (1992) and Volf and Passynkova (2002) also find decreased alpha power in the frontal region of patients with affective disorders compared to controls. Given evidence that increased cerebral metabolism measured by PET is inversely correlated with alpha activity (Leuchter et al., 1999), these findings are in line with the studies which demonstrate increased metabolism and cerebral blood flow in the ventrolateral prefrontal cortex in depressed persons (Biver et al., 1994; Brody et al., 2001; Cohen et al., 1992; Drevets, 1998; Drevets et al., 1995; Ebert et al., 1991; Mayberg et al., 1999; Wu et al., 1992).

According to Davidson's approach-withdrawal model (Davidson, 1994, 2004), relatively less left frontal activity corresponds to an increased trait tendency to approach, whereas relatively less right frontal activity corresponds to an increased trait tendency to withdraw (Tomarken, Davidson, and Henriques, 1990; Wheeler, Davidson, and Tomarken, 1993). In addition, a left-sided medial region of the orbital frontal cortex appears responsive to rewards, whereas a lateral right-sided region appears responsive to punishments (Kawasaki et al., 2001; O`Doherty et al., 2001).

On the basis of these findings, depression is related to a deficit in the approach system of motivation (Davidson, 1998) and less responsiveness to rewards (Henriques and Davidson, 2000), both of which are associated with greater left anterior activity. It is suprising first, that our sample of depressed patients fails to demonstrate abnormal anterior asymmetry, and second, that they show less alpha power in the left prefrontal region compared to controls. Following the model, one interpretation could be that less activity in the left prefrontal region means an abnormal increased trait tendency to approach and a more intense response to affectively positive stimuli and reward. This is contrary to common views of depression with a high negative affectivity and a low positive affectivity (Clark and Watson, 1991). On other hand, Harmon-Jones (2004) finds that certain types of anger under specific conditions may be associated with less left prefrontal activity.

The finding that depressed patients show more right than left frontal alpha activity mirrors findings by Koek el al. (1999). In that study, the authors find that such an asymmetry is associated with mania. However, in the current study, there is no evidence that the patients in the sample suffer from mania. Nevertheless, eleven patients in the current study suffered recurrent depression and seven of these patients suffered a severe episode (F33.2). According to the ICD-10 (http://www3.who.int/icd/vol1htm2003/fr-icd.htm), patients with this disorder often experience manic episodes, and as depression becomes more severe, manic episodes become more likely.

Because depression is a remarkably heterogenous disorder, it may be that the decrease in alpha power in the left prefrontal region found in this study reflects some subtypes of depression. It is possible that less left frontal alpha activity is associated primarily with certain symptoms or patterns of depression, which may have been common across prior studies reporting this finding. Although participants in the present study were carefully screened, patients comprising this depressed group could possibly have been somewhat atypical compared to other samples in previous studies. Considering that in this sample, 3 patients meet diagnostic criteria for neurotic, stress related and somatoform disorders and that other patients, who meet criteria for mood (affective) disorders, have comorbid diagnoses (see table 2.1.), it is possible that the decrease in alpha power in the left prefrontal region reflects this variety of symptomatology. On one hand, it is a limitation of this study that it does not include a

homogenous sample, but, on other hand, this demonstrates the highly variable nature of depression.

Major depressive episodes are several-week- to several-year-long periods in which conscious mental activity is dominated by persistent dysphoric emotions and thoughts, which coexist with disturbances of motivated and psychomotor behavior, sleep, appetite, energy, and libido. Despite the application of the descriptive term "depression", the dominant emotional symptoms of major depressive episodes can instead include anxiety, irritability, or anhedonia (inability to experience pleasure or reward) (Drevets, 2001; Drevets and Todd, 1997). In addition, research demonstrates considerable comorbidity among depression and anxiety, which share a core of common symptoms and genetic liability (Mineka, Watson, and Clark, 1998). Heller et al. (1997) suggest that the experience of anxiety may be related to asymmetry in ways that are opposite to that expected in depression alone (Heller et al., 1997). According to Heller's (Heller et al., 1997; Heller and Nitschke, 1998; Nitschke et al., 1999) valence-arousal model, anxiety is comprised of two distinct though related processes, anxious apprehension and anxious arousal, and these processes are reflected in brain asymmetries as relatively less activity in the left anterior and right posterior regions. The current study finds less left prefrontal alpha power in depressed patients, which may suggest symptoms of anxious apprehension in the patients making up the sample, assuming Heller et al.'s findings are correct.

A PET study by Osuch et al. (2000) finds that severity of anxiety symptoms in depressed patients is positively correlated with regional cerebral glucose metabolism in the left anterior cingulate regions[2]. Moreover, PET studies using normal subjects, in which depressive symptoms are induced during scanning, have demonstrated an association between anxiety (induced by medication, visual imagery, or recall of anxiety-provoking situations) and increased activity in the left anterior cingulate gyrus (Benkelfat et al., 1995; Chua et al., 1999; Gottschalk et al., 1992; Kimbrell et al., 1999, Wik et al., 1991). The anterior cingulate and ventral prefrontal cortex have also been found to have increased rCBF in patients with anxiety disorders (obsessive-compulsive disorder, simple phobia and posttraumatic stress disorder) when their symptoms are provoked (Rauch et al., 1997).

[2] Cerebral metabolism measured by PET correlates inversely with alpha activity (Leuchter et al., 1999).

It is difficult to conclude that the present findings speak to the nature of the combined influence of anxiety and depression, because there is no evidence that the depressed patients in the current sample have anxiety symptoms. However, in the present study some patients' diagnoses include anxiety symptoms (see table 1, for example F41.2) and some have comorbid diagnoses such as PTSD, panic disorder and obsessive-compulsive disorder. It is possible that this sample may have included a few participants with covered symptoms of anxiety. Considering the findings of other studies (Heller et al., 1997), decreased left prefrontal activity in depression may reflect a dimensional structure for relevant symptoms that is substantially similar for depression and anxiety or a combination of shared and unique features of the two constructs. Further confirmatory evidence regarding the potential role of the left prefrontal region in depression comorbidity is required.

In EEG research, conducted by Bruder et al. (1997), depressed patients with a comorbid anxiety disorder show greater left parietal alpha activity, whereas patients with no diagnostic comorbidity show less left parietal alpha activity. In the present investigation, depressed patients demonstrate abnormal increased alpha power in the left parietal region. Furthermore, Graae et al. (1996) find increased activity in the left posterior region in adolescents who attempted suicide. In the present study ten patients with a diagnosis of recurrent depressive disorder, of which two have suicidal tendencies, display more abnormal alpha power in the left parietal region compared to patients with a depressive episode.

In the right hemisphere and right parietal region, depressed patients show more alpha power compared to controls. Many EEG studies have shown increased power in the right hemisphere (Knott et al., 2001; Koles et al., 1994; Kwon et al., 1996; Prichep and John, 1992). In addition, present findings of increased activity in the right posterior region are in agreement with studies indicating more right posterior activity in depression (Allen et al., 1993; Bruder et al., 1997, 1999; Henriques and Davidson, 1990; Keller et al., 2000; Kentgen et al., 2000). Other neuroimaging studies demonstrate decreased cerebral blood flow in the right posterior region (Uytdenhoef et al., 1983) and in the midtemporal cortex (Post et al., 1987; Drevets et al., 1992) in depressed subjects.

A number of studies suggest that the right posterior region is involved in depression as evidenced by selective impairment on right hemisphere tasks (Rubinow and Post, 1992; Silberman, Weingartner and Post, 1983), right-hemisphere deficits in

paradigms using lateralized presentation of stimuli such as dischotic listening and tachistoscopic techniques (Bruder, 1995), and reduced attentional biases in favor of the right hemisphere on the Chimeric Faces Task (Levy et al., 1983; Keller et al., 2000). Henriques and Davidson (1997) find that depressed subjects showing a deficit in the performance of a spatial task compared to nondepressed controls display more activity in the posterior regions of the right hemisphere during spatial performance, whereas in posterior scalp regions, controls have a pattern of relative less right-sided activity during this task. With regard to these findings, it is possible that in the current study, depressed patients with bilaterally increased power in the parietal region may have some impairment in spatial cognitive functioning.

Moreover, there is a large literature describing deficits in social functioning (Lezak, 1995), and in the ability to express and interpret emotional information (Borod, 1993; Bowers, Bauer and Heilman, 1993) after damage to the right hemsiphere. This suggests that the processing of emotional material is an aspect of cognition modulated by posterior regions of the right hemisphere. Problematic interpersonal behaviours, such as slow and monotonous speaking, poor eye contact, poor timing in verbal interchanges, and use of awkward gestures, are all phenomena of depression (Barnett and Gotlib, 1988) that have been described in patients with right hemisphere damage (Lezak, 1995).

In addition, a PET study by Damasio et al. (2000) in which emotions are induced by the recall of personal emotional episodes, sadness and fear decrease activation in the inferior parietal lobule and parieto-occipital region, and only sadness increases activation in the orbitofrontal region. Similar patterns of neuromagnetic activity in the alpha band in the left prefrontal and parietal (left and right) regions have been found in the current investigation in depressed patients[1].

The present findings of greater alpha power in the posterior region correspond with other neuroimaging studies showing reduced regional blood flow and metabolism in areas of the lateral temporal and the parietal cortex in depression (Drevets et al., 1992). Although blood flow and metabolic abnormalities in depression may reflect pathophysiological changes in synaptic transmission associated with altered neurotransmitter synthesis or receptor sensitivity (Drevets, 1997; Raichle,

[1] Again, this assumes that increased cerebral metabolism measured by PET is inversely correlated with alpha activity.

1987), abnormal alpha power in the parietal region in depressed patients in the present study may also indicate some pathophysiological changes in synaptic transmission.

The present MEG study does not confirm the hypothesis that depressed patients demonstrate an anterior asymmetry towards greater left than right alpha power compared to healthy subjects. This result replicates the findings from other EEG studies indicating the absence of anterior alpha asymmetry in depressed subjects compared to controls (Graae et al., 1996; Kentgen et al., 2000, Pollock and Schneider, 1990; Reid, Duke and Allen, 1998).

The lack of anterior asymmetry in depressed subjects compared to controls may indicate that asymmetry reflects broad dispositional characteristics, but it does not serve as a biological marker for depression. In other words, people, such as those found in this study, may develop depression despite the lack of anterior asymmetry. This assumption contradicts the diathesis-stress model of EEG activity and depression (Davidson, 1998), which postulates that resting anterior asymmetry reflects a predisposition for the development of depression. The basis of this model is that individual differences in prefrontal asymmetry are most appropriately viewed as diatheses that bias a person's affective style, and then in turn modulate an individual's vulnerability to develop depression. This model is used to help predict vulnerability to psychopathology because virtually all forms of major mental illness involve some abnormality of emotion. It is suprising that the present sample of depressed patients with affective disorder does not show this asymmetry. It is possible that anterior asymmetry was present in these patients before they became ill, but has since diminished. This proposition can be further investigated by examining whether healthy subjects with anterior asymmetry develop some types of psychopathology later in life.

It remains too early to conclude that resting frontal asymmetry directly relates to a risk for depression, because this relationship is mediated by other variables, including temperament (Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997), coping styles (Kline et al., 1998; Tomarken and Davidson, 1994), shyness and social anxiety (Schmidt, 1999), socioeconomic status (Tomarken et al., 2004), cognitive dissonance arousal (Harmon-Jones, 2004), reassurance seeking (Minnix et al., 2004), immune function (Kang et al., 1991) and genetic factors (Allen et al., 1997).

In addition, the data do not confirm the hypothesis that depressives show greater right than left posterior alpha power compared to controls. This finding replicates

results from other studies which fail to find posterior asymmtery in depressed subjects (Schaffer, Davidson and Saron, 1983; Henriques and Davidson, 1991). Although depressed patients show a bilateral increase in alpha power in the parietal region compared to controls, this does not imply an asymmetry.

There may be several explanations for the failure to find abnormal anterior and posterior asymmetry in this sample of depressed patients. Most EEG studies and the present MEG study have examined resting, or baseline activity. Davidson (1993) points out that baseline levels of frontal activation asymmetry may reflect individual tendencies toward a valenced affective response, but this relationship may not be observed in the absence of a specific environmental elicitor. If frontal alpha asymmetry is strongly related to emotions, during the resting condition, there is no situational provocation, and the level of baseline state-emotion is rather low. It is plausible that frontal asymmetry would be present examining the relationship between individual differences in patterns of asymmetry and affective response to emotionally challenging tasks. As applied to the pattern of posterior asymmetry findings, these considerations suggest the possibility that more robust differences in posterior brain activity might be yielded by studies measuring brain activity while participants perform tasks for which depressed people show decrements.

Additional methodological approaches highlighted by Davidson (1993), such as the use of extreme groups and classification of participants according to the affect measures as opposed to the brain asymmetry measures, would also be useful in finding the differences in asymmetry patterns.

4.2. Treatment effects.

This MEG study is the first to demonstrate that abnormal neuromagnetic activity in the prefrontal and parietal regions of the right hemisphere changes toward normalization in depressed patients treated with cognitive behavior therapy. These findings are in line with other neuroimaging studies showing normalization of regional brain metabolic changes in patients with major depression disorder after interpersonal psychotherapy (Brody et al., 2001; Martin et al., 2001).

There is growing evidence from neuroimaging and postmortem studies that severe mood disorders, which have traditionally been conceptualized as

neurochemical disorders, are associated with impairments of structural plasticity and cellular resilience (Helmut, 2003). Antidepressive medications probably act by enhancing neuronal plasticity (Kolb et al., 2003), allowing the brain system to readapt to neurocomputational requirements thus reducing ensuing mood disturbances. Not only medication, but also psychotherapy in general (as a learning experience) leads to changes in synaptic plasticity (Liggan and Kay, 1999) through a retraining of implicit memory systems (Liggan and Kay, 1999; Amini et al., 1996). It could be proposed that the normalization of neuromagnetic delta activity in depressed patients after therapy reflects some aspects of brain plasticity that underlie adaptive processes of neuronal network activity (Peled, 2004).

In a combined fMRI/MEG study, positive emotional processing affect activation in the lateral orbitofrontal/prefrontal cortex (Northoff et al., 2000). In addition, PET studies demonstrate increased activation in right orbitofrontal cortex and widespread reductions in bilateral temporal-parietal regions during induced happiness (Damasio et al., 2000; George et al., 1995). In the present study, following psychotherapy the same patterns of increased delta activity in the right prefrontal region and decreased delta activity in the right parietal region are observed in depressed patients.

The few PET studies which examine associations between regional brain activity and major depression disorder symptoms directly find positive correlations between cognitive performance and rCBF in the medial prefrontal cortex (Bench et al. 1993; Dolan et al., 1994). These findings provide evidence that neuropsychological deficits in depression are associated with the function of the medial prefrontal cortex. Brody et al. (2001) demonstrate that improvement in cognitive disturbance is associated with increasing dorsolateral prefrontal cortex metabolism in depressed outpatients who undergo treatment with either paroxetine or interpersonal psychotherapy. It is possible that at the end of therapy, increased delta power in the right prefrontal region may indicate improvement in cognitive performance for depressed patients in present investigation.

Examining groups with opposite asymmetry patterns, depressed patients with greater left than right frontal power at the beginning of treatment shift significantly towards greater right than left frontal power at the end of treatment. The same result has been demonstrated after meditation in healthy subjects (Davidson et al., 2003). Furthermore, Otto, Yeo and Dougher (1987) point out that cognitive-behavioral therapies for depression, involving primarily verbal procedures, may help activate the

language-dominant left hemisphere by providing the patient with the means to use verbal skills to re-interpret negative events. Hence, subjects with a hemispheric imbalance favoring right- over left-hemisphere activation benefit most from cognitive therapy because it helps reactivate the language-dominant (left) hemisphere. When considering the assumption that alpha power correlates inversely with cortical processing, which means that greater alpha power reflects less cortical activation and less alpha power reflects higher cortical activation, the present study's findings support this result by demonstrating that psychotherapy may be effectively applied to depressed persons, who have an asymmetry pattern of less left than right frontal activation.

In the theta and alpha frequency bands, depressed patients show no changes from pre- to post-treatment. However, after therapy, patients with a F32 diagnosis show a decrease in the right parietal region relative to before treatment, whereas patients with a F33 diagnosis show no significant change of theta activity. This result may reflect better cognitive functioning after therapy in patients with a F32 diagnosis.

Depressed patients with a F33 diagnosis show more left parietal alpha power compared to patients with a F32 diagnosis and demonstrate a significant decrease in left parietal alpha power at the end of therapy relative to the beginning of therapy. With regard to the earlier presumption that greater left parietal alpha power may be a possible indicator of anxiety symtoms in depressed patients (Bruder et al., 1997; Graae et al., 1996), treatment effects towards a decrease in left parietal alpha power after treatment may indicate the reduction of anxiety in patients.

Treatment effects in the delta frequency band are more apparent in patients with low BDI scores than in patients with high BDI scores. Although depressed patients with low BDI scores have greater theta activity in the right parietal region compared to patients with high BDI scores before treatment, at the end of treatment, only patients with low BDI scores show a significant change of activity towards a decrease in the right parietal region relative to the beginning. In the alpha frequency band, normalization effects in the left prefrontal region are observed in patients with low BDI scores and in the left parietal region in patients with high BDI scores. These findings suggest that psychotherapy is less effective in severely depressed patients and highlight the importance of early intervention in depression.

Relative to the beginning of therapy, an increase of alpha power in the left prefrontal region is observed at the end of therapy, but only in low BDI group.

According to EEG studies in meditation (Aftanas & Golocheikine, 2001; Takahashi et al., 2004), increased alpha power after psychotherapy in the anterior area may reflect enhanced internalized attention. It is plausible that an increase in alpha power in the left prefrontal region is achieved because of the empathic attunement of the therapist and the patient's focused attention on his negative thoughts and distressing emotions. In depressed subjects, impaired modulation of the left prefrontal cortex has been associated with impairment in the ability to shift emotional and cognitive sets appropriately, such that they maintain a negative thought pattern or mood (Quintana 1989, Goldman 1987). It could be proposed that increased left prefrontal alpha power after psychotherapy in depressed patients with low BDI scores is related to enhanced attentional focus on all the components of an emotional experience that lead to healing allowing resolution of negative affect associated with memories, negative cognitions and entrenched schemas (Corrigan, 2004).

In the present study, because almost all patients (21) receive medication before treatment and after treatment only six patients receive medication, it is possible that medication influences change in regional activity from pre- to post-treatment. Saletu et al. (1980) find selective serotonin reuptake inhibitor (SSRI) and imipramine to increase slow wave activity, while Sperling et al. (2000) do not report an increase in slow wave activity in the patient group treated with tricyclic antidepressants. General slowing of EEG frequencies has been reported as a consequence of neuroleptic medication (Koshino et al., 1993; Malow et al., 1994). Because patients in this study receive various medications, including SSRI, antidepressants and neuroleptics, and considering the findings of various effects of medication, there is a problem in the interpretation of the treatment effect in the current study.

4.3. Relationship between neuromagnetic activity and symptomatology in depressed patients before and after therapy.

This study's findings suggest that reduced slow wave activity in the right prefrontal region does not correlate with severity of depression or general psychopathology. However, theta power in the left prefrontal region correlates positively with BDI score, indicating that decreased left prefrontal theta activity is associated with a lower level of depression. These findings do not confirm the

hypothesis that abnormal slow wave activity in the anterior region relates to higher symptomatology. Moreover, this result does not replicate the findings of Wienbruch et al. (2003), who suggest that suppresion of left prefrontal slow wave activity correlates with more severe depression.

Contrary to the formulated hypothesis that abnormal slow wave activity in the posterior region relates to higher symptomatology, this study indicates that more theta power in the right parietal region and greater asymmetry towards higher right parietal theta power are associated with less depression severity. Also, depressed patients with low BDI scores show greater theta power in the right parietal region compared to patients with high BDI scores. This fails to replicate the results of Deldin et al. (2001), who show that increased depressive symptomatology is associated with greater slow wave activity in the parietal region. In addition, Dierks et al. (1993) report a positive correlation between theta activity in the posterior region and clinical global impressions. On other hand, Knott et al. (2000) fail to find an association between theta power in the posterior region and depression severity.

The relationship between the right hemisphere and BDI score shows that an increase in theta activity in the right hemisphere is associated with a lower level of depression symptoms. Also, depressed patients with low BDI scores show greater theta power in the right parietal region compared to patients with high BDI scores. In contrast, a study by Dierks et al. (1993) demonstrates that, in depressed patients, more theta power in the right hemisphere is associated with higher depression severity as measured on Hamilton Depression Scale (Ham-D; Hamilton, 1960).

Despite these surprising and inconsistent findings, there is one relationship which indicates that abnormal increased delta activity in the left hemisphere is associated with a higher level of general psychopathology. Unfortunately, this correlation was high, but not significant (see table 5). Other correlations reveal that more theta power in the left hemisphere varies with more severe depression. Although relatively few, if any, studies have attempted to examine relationship between EEG and severity of clinical depression, a number of early investigations have shown increased theta to be characteristic of depressed patients compared to normal controls (Pollock and Schneider, 1990; Kwon et al., 1996). Increased theta power has also been shown to correlate positively with motor, but not verbal, intellectual or emotional aspects of retardation in depression (Nieber and Schlegel, 1992; Nyström, Matousek and Hällström, 1988). Moreover, the present study finds a relationship

indicating that increased right frontal theta power is associated with a higher level of general psychopathology. This finding is in line with the study by Knott et al. (2000) indicating that increasing relative theta power values in the frontal region are associated with increasing Ham-D ratings.

The present study also reports that abnormal alpha power in the left and right parietal regions is not associated to depression severity. Studies which investigate EEG posterior alpha asymmetry in depression also fail to find a relationship between severity of depression and posterior asymmetries (Bruder et al., 1997; Diego, Field and Hernandez-Reif, 2001; Graae et al., 1996; Metzger et al., 2004). These findings may indicate that increased activity in parietal region is clearly not sufficient for the production of depressive symptomatology. On other hand, according to Henriques and Davidson (1990), an increase in right posterior activity may directly contribute to certain symptoms of depression, such as poor orienting and deficits in social skills, which require the decoding of nonverbal, expressive behavior. It remains questionable whether these types of symptoms are reflected in BDI and BPRS measurements.

Depressed patients with low BDI scores show less left prefrontal alpha power compared to patients with high BDI scores. Moreover, the positive correlation between left prefrontal alpha power and BDI score indicates the same relationship: less left prefrontal activity is associated with less severe depression. This finding is in line with other studies indicating that more left anterior activity is related to higher depression severity (Schaffer, Davidson and Saron, 1983; Diego, Field and Hernandez-Reif, 2001).

Depressed patients in the current study show frontal asymmetry towards greater right alpha power. Moreover, increased right frontal alpha power is associated with a higher level of general psychopathology. This finding that right frontal alpha power is associated with general psychopathology, but not with depression severity, may suggest that the present pattern of frontal asymmetry in depressed patients, contrary to the pattern reported in previous studies of depression (Henriques and Davidson, 1991; Gotlib, Ranganath and Rosenfeld, 1998), could reflect symptoms which are not directly related to depression, but are related to other psychopathologies.

The findings of the present study demonstrate that, in depressed patients, abnormal neuromagnetic activity is inversely related to depression severity. Other neuroimaging studies also report such a relationship. They find that although blood flow and metabolism are abnormally elevated in the lateral and posterior orbital

cortices during depression, the magnitude of the physiological activity in these regions correlates inversely with ratings of depression severity and negative thought frequency (Drevets et al., 1992).

At the end of therapy, parallel to the normalization of regional neuromagnetic activity, depressed patients show clear improvement in symptoms of depression and general psychopathology. However, normalization towards an increase in delta power in right prefrontal region and a decrease in the right parietal region from pre- to post-treatment is not associated with symptom improvement.

Positive correlations between symptom improvement and change in delta power in the right frontal region and in alpha power in the prefrontal region indicate that decreases in right frontal and right prefrontal activity from pre- to post-treatment are associated with greater symptom improvement. In a study by Brody et al. (2001), improvement in depression symptoms (anxiety, psychomotor retardation, tension and fatigue) is also associated with decreasing ventral frontal lobe metabolism in depression.

4.4. Limitations of present investigation and future directions.

Several explanations may exist for the inconsistency in the direction of the relationship between abnormal neuromagnetic activity and symptomatology in the current study. First, correlations with BDI were not computed for the sample as a whole (combining depressed and control participants). There is no information about the depression level in the control group. Other research, however, has demonstrated variations in BDI scores among study participants not suffering from clinical depression (Schaffer, Davidson and Saron, 1983; Diego, Field and Hernandez-Reif, 2001). It may be that control group BDI scores would have been higher than expected had they been measured, even though no one in the control group suffered clinical depression. This could influence the relationships found in this study.

Second, the BDI is one of the most widely used mental health measures, but it may contain some flaws. Although its readability is estimated to be at a fifth to sixth grade level (Teri, 1982; Berndt, Swartz and Kaiser, 1983), a study by Sentell and Ratcliff-Baird (2003) demonstrates that overall, even high-school level readers had considerable comprehension problems with many BDI response alternatives, revealing a high level of comprehension difficulty. It may be that patients in this study

had problems understanding the propositions and misinterpreted the meaning of words or phrases. On other hand, it is difficult to test these observations in the present investigation because self-reported measures were conducted by the psychotherapists and not by members of the research team.

A third possible explanation for the inverse correlation between abnormal neuromagnetic activity and depression severity is omitted variable bias. A source of variability is introduced by the clinical heterogeneity inherent within the depressive syndrome, as diverse signs and symptoms may have distinct neurophysiological correlates (Drevets and Todd, 1997). For example, brain images of a depressed patient exhibiting prominent anxiety, obsessive ruminations, insomnia, and psychomotor agitation may be quite different from those of a patient who predominantly manifests apathy, inactivity, excessive sleep, and psychomotor slowing. Following the evidence that patterns of left anterior activation are discrepant for depression and anxiety (Heller and Nitschke, 1998; Heller et al., 1997), it may be that the patients in the current sample showing increased activity in the left prefrontal region suffer from anxiety as well as depression. Unfortunately, the study does not measure anxiety levels in patients, leaving no way to control for the effects of anxiety on brain activity. Because depression and anxiety may be correlated, and because there is no way to control for anxiety given the present data, the analysis may be attributing the effects of anxiety to depression, and thus producing this unexpected correlation. Future research in this area should control for patients' anxiety levels, either by carefully screening the sample, or by measuring patients' anxiety. Given the heterogeneity of depression, it will be imperative in the future to conduct large sample studies that are explicitly designed to address this issue.

In addition to controlling for anxiety, the ideal study would control for a number of possible factors that may influence brain activity in addition to depression, such as neurodegenerative processes and cognitive impairment. Studies to date, including the present study, have tended to focus on one of these factors and have assumed that the other factors are randomly distributed throughout the sample and controls. However, this is unlikely. Neuropathological and psychological disorders may be correlated with one another. In other words, if a patient has one disorder, he or she is more likely to suffer from a second or third disorder as well. At the same time, controls are more likely to not suffer from any of these conditions.

Moreover, it remains unclear whether the patterns of regional neuromagnetic activity found in the present study as characteristic of depression are present regardless of mood state. Miranda et al. (1990) argue that dysfunctional attitudes are traits (i.e. vulnerability factors) that are mood-state dependent. Specifically, previously depressed people show more dysfunctional beliefs than never-depressed people when in an induced or naturally occurring unpleasant mood, but not when in a pleasant mood. Similarly, Teasdale and Dent (1987) find that after a negative mood induction, remitted depressives exhibit a memory bias for unpleasant words, whereas subjects with no history of depression do not; without the negative mood induction, no group differences emerge. Following this pattern, depressed subjects might display greater left prefrontal alpha activity than never-depressed subjects only when in an unpleasant mood. It will thus be crucial to measure current mood, as well as depression, in future research examining treatment effects and depression.

Other limitations include potential threats to the internal validity of the findings. Although major depression disorders are systematic diseases with deleterious effects on multiple organ systems (Musselman et al., 1998), other variables might account for observed differences between depressives and controls, such as risk factors for cerebrovascular disease, overall medical illness burden, and also the level of cognitive impairment. Moreover, in this study, it was not possible to examine gender differences, because the sample contains to few men. Future studies with larger samples will need to control for this potentially important variable.

Clinical neuroscientific investigations into the biology of mood disorders struggle with the limitation that psychiatric nosology remains at a syndromatic level, in which nonspecific behavioral signs and symptoms (e.g. insomnia, fatigue, low mood, impaired concentration), rather than pathophysiology, are used to define major depressive disorder (MDD). Consequently, specific links between syndrome and pathophysiology may not exist, and the MDD diagnostic criteria are expected to encompass an etiopathologically heterogenous group of disorders. Not surprisingly, the diagnosis of MDD has generally proven insufficient for identifying subject samples with reproducible neuroimaging abnormalities (Drevets, 2001). This is reflected in the present study. Abnormal regional neuromagnetic activity in depressed patients is inversely associated with symptoms of depression. Hence, to manage depression effectively, one needs to understand the neurobiology of emotion along its many dimensions – molecular, cellular, cognitive and sociocultural – and apply this

understanding to well-characterized disease phenotypes and genotypes (Damasio, 1997).

Studies by Brody et al. (2001) and Martin et al. (2001) suggest that the changes in functional brain activity following pharmacotherapy and psychotherapy are remarkably similar. Considering this evidence, data from this study confirm the normalization of neuromagnetic activity in depressed patients following psychotherapy and medication. One of the main limitations of this study is that the findings cannot distinguish between alterations in brain activity due to psychotherapeutic intervention or medication, however the results demonstrate that normalization is an effect of treatment, either psychotherapy or medication. The primary problem is that patients with clinical depression usually receive medication, and it is not clear to what extent medication affects one region over another, or how this might consequently influence the focal concentration of activity, making the effect of medication difficult to control for. In this study the psychotherapy is the main independent variable, because brain activity is measured before and after therapy. The effect of medication, on the other hand, is difficult to test because many patients were on medication before the beginning of the study. To draw the more precise conclusions, future research must to try investigate only depressed subjects not receiving medication prior to psychotherapy.

Another possible method for drawing more precise conclusions about psychotherapy's effect on neuromagnetic activity would be to observe neuromagnetic activity change during the course of treatment. For example, future studies may repeat MEG recordings when patients begin to feel improvement, but have not yet fully recovered. It also may be reasonable to repeat the MEG measurement one month after treatment (in the recovery phase) to investigate the stability of treatment normalization in regional activity.

Finally, various studies sample a restricted set of brain regions. Because regions of interest are not consistent from one study to the next, it is plausible that there will be inconsistencies in brain activity findings in depression. Neuroimaging studies in depression report that the ventrolateral part of prefrontal cortex shows increased metabolic activity (Brody et al., 2001; Drevets, 1995, 1998; Mayberg et al., 1997,1999), whereas dorsolateral and medial parts of prefrontal cortex display decreased activity (Baxter et al., 1987; 1989; Bench et al., 1992, Biver et al., 1994; Cohen et al., 1989, 1992; Curran et al., 1993). Variations in precision of localization

of cortical activation from study to study could account for better identification of activity in certain brain regions.

5. CONCLUSIONS.

This is the first study to investigate neuromagnetic activity after psychotherapeutic intervention, and it provides evidence that psychotherapy is able to normalize regional brain activity in depressed patients. This study reports group differences between normal subjects and patients, revealing MEG abnormalities in depression which point to brain dysfunction. These findings are one piece of information which must be integrated in the whole clinical picture of depressed patients. Diagnosis using MEG features may accurately predict response to therapy in patients previously diagnosed by clinical criteria, and MEG may be a useful diagnostic aid for evaluating neurophysiopathology and a helpful tool in therapeutic management.

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