

**Psychophysiological Working Mechanisms of Mindfulness-
Based Cognitive Therapy: Functional Anterior Brain
Asymmetry and Affective Style**

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Preface

Major Depressive Disorder (MDD) is one of the most frequent psychiatric disorders and is often not limited to a single depressive episode, but involves repeated relapses. Due to the frequent phenomenon of relapse, in recent years, research efforts in clinical psychology have focused on the development and refinement of maintenance psychotherapy, i.e. therapeutic interventions specifically designed to prevent depressive relapse. Mindfulness-Based Cognitive Therapy (MBCT) is a meditation-based group intervention developed to serve this purpose, and has been shown to reduce the relapse risk in patients suffering from recurrent depression. In MBCT, patients engage in meditation exercises to cultivate mindfulness, a meta-cognitive skill characterized by paying attention to the present moment purposefully and in a non-judgmental manner. It has been assumed that the cultivation of mindfulness is associated with a reduction in the sensitivity to spontaneously arising dysphoric states, and in the harmful tendency of rumination, i.e. the excessive thinking about causes of negative mood, both of which have been identified as predictors of depressive relapse.

The prophylactic effect of MBCT has been shown repeatedly and is firmly established. However, until recently, only very few studies have examined the effects of MBCT on physiological parameters indicative of vulnerability in relation to psychological constructs. The current work involves three studies in an attempt to address this issue. The effect of MBCT on a putative neurophysiological marker of vulnerability for the development of MDD was examined in recurrently depressed patients, as well as the relation of this marker to relevant psychological constructs. Functional anterior brain asymmetry (FAA) assessed through the alpha band (8-13Hz) in resting electroencephalogram (EEG) has been identified as a trait indicator of affective style and may represent a diathesis for the development of MDD. Individuals who suffer from and who are at risk for developing MDD have repeatedly been described as displaying stronger relative right-hemispheric anterior cortical activity compared to individuals without a psychiatric history. Despite the fact that FAA is generally

viewed as a stable, trait-like characteristic, few studies have also shown structured mindfulness-training to be associated with beneficial effects on FAA, reflecting a more balanced and positive affective style in healthy and clinical populations. The current work was designed to replicate and extend previous findings on the plasticity of FAA in relation to MBCT. Working mechanisms of MBCT such as alterations in mindfulness and rumination were examined in relation to effects of MBCT on FAA. In addition, the relation of the described parameters was examined on a trait level. Overall, results were supportive of the protective function of MBCT. Effects on brain physiological measures of vulnerability were observed and the examined indices of functional brain asymmetry were shown to be related to psychological constructs of mindfulness and rumination.

In a first study, 19 Patients who were treated with MBCT, did not display any significant alteration in FAA immediately after treatment, or after a two months follow-up period. In contrast, 20 patients of a wait-list control group showed a spontaneous deterioration toward stronger relative right-hemispheric anterior cortical activation over a two months waiting period, which was associated with increased rumination and decreased mindfulness. The following participation in an MBCT course was associated with an increase in relative left-hemispheric anterior activation, indicating increased resilience. Even though in a second study with a similar number of patients, these effects could not be replicated, associations between FAA, rumination and depressive symptomatology were observed in a third study involving 74 participants. In this study, rumination was also identified as a mediator of the known relationship between FAA and depression. This indicates that MBCT attenuates a harmful psychological process, which may function as a link between brain physiological indices of vulnerability and depressive symptomatology. The current work hence provides original results which may foster the integration of physiological and psychological aspects of depressive vulnerability in relation to MBCT.

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1. Major Depressive Disorder

1.1. Definition and Epidemiology

Recent clinical consensus classifies Major Depressive Disorder (MDD) as a mood disorder characterized by abnormalities of affect, cognition, psychomotor activity, and vegetative functions (American Psychiatric Association, 2000a). Typical symptoms of MDD include enduring feelings of sadness, a lack of general interest, loss of appetite and weight, disturbed sleep, psychomotor agitation or slowing, overall lack of energy, feelings of worthlessness and guilt, the inability to concentrate, and suicidal ideation. MDD is diagnosed in case of an individual's experience of a Major Depressive Episode (MDE), the enduring presence of a cluster of at least five of these symptoms. Diagnosis requires symptoms to be present most of the time for at least two weeks, with one of these symptoms being a continuous feeling of sadness or lack of interest. Further, the presence of symptoms needs to be associated with clinically significant distress or impairment in social, occupational or other important areas of life. Symptoms are also required to be no direct physiological effect of a general medical condition, or the use of a substance (e.g. a drug or medication), and not to be better explained by bereavement after the loss of a close person.

Prevalence

MDD is regarded as one of the most prevalent psychiatric disorders and is assumed to become the second leading cause of disability worldwide by 2020, following ischemic heart disease (Murray & Lopez, 1996). Though early cross-national epidemiological studies were limited by the absence of standardized diagnostic assessment tools, the foundation of the International Consortium in Psychiatric Epidemiology of the World Health Organization (WHO) helped to overcome such problems (Kessler, 1999). Coordination of studies through this consortium and the common use of the Composite Diagnostic Interview (World Health Organization, 1997)

which incorporates various classification systems, has yielded internationally comparable data. Based on the results of community epidemiological surveys conducted in ten countries in North and Latin America, Europe, and Asia, Andrade et al. (2003) report a wide variation of prevalence estimates for MDE across countries. Estimates for Japan yielded a life-time prevalence of 3%, in contrast to 16.9% in the United States. The majority of the surveys reported a life-time prevalence of between 5 to 15% with a 12-months/life-time prevalence ratio between 40 to 55%.

Course

The latter finding suggests that MDD is a very chronic disorder, which is supported by the fact that recurrent MDE were reported by nearly 75% of respondents with lifetime MDD (Andrade et al., 2003). Studies in clinical settings report similar estimates, suggesting that at least 60% of individuals who have had one depressive episode will have another, 70% of individuals who have had two depressive episodes will have a third, and 90% of individuals with three episodes will have a fourth episode (American Psychiatric Association, 2000a; Solomon et al., 2000b). Andrade et al. (2003) report a mean duration of MDE of three months. The recurrence of MDD appears to be dynamic in nature. In numerous clinical studies, relapse risk has been described as increasing with the number of experienced episodes and as becoming increasingly autonomous from external stressors (Mazure, 1998; Monroe & Simons, 1991; Post, 1992). Similarly, suicide risk appears to increase with every new episode and it is estimated that there is a probability of 15% that patients suffering from recurrent depression severe enough to require hospitalization, will eventually die by suicide (Keller et al., 1992).

A number of epidemiological studies have found that MDD has an earlier age of onset than other chronic conditions, with the first risk appearing in early adolescence. Even though the median age of onset was estimated to lie between 20 to 25 years, the risk to develop MDD

lasts until old age (Blazer et al., 1994; Christie et al., 1988). Cross-national studies report a consistent course of risk with a very low risk during the early years of life, rising risk during adolescence and the middle to late twenties and subsequent declining risk in later years (Andrade et al., 2003).

Sociodemographic aspects and co-morbidity

Women are more likely to develop MDD than men and MDD appears to be more common among unmarried individuals and in individuals with lower socioeconomic status (Wells et al., 1989; Wittchen et al., 1992). MDD is highly co-morbid with other mental disorders, especially with anxiety disorders (Kessler, 1999; Merikangas et al., 1996). Andrade et al. (2003) report that between 30 to 50% of individuals fulfilling criteria for MDD, also had a history of at least one anxiety disorder. Research further suggests that the age of onset of anxiety disorders is typically earlier than the age of onset of MDD (Merikangas et al., 1996). In line with this observation, it has been found that primary anxiety disorders are strong predictors of a subsequent first onset of MDE (Kessler et al., 2008).

Economic consequences

Considering the aspects described above, it is not surprising that the phenomenon of MDD also has a huge economic impact. There is a vast body of evidence which shows that depressed individuals suffer from diverse functional limitations, such as poorer physical, psychosocial health, and role functioning (Broadhead et al., 1990). Evidence consistently suggests that depression has a negative effect on work productivity and is a factor which dominates health-related lost labor time costs in the United States (McCunney, 2001; Simon et al., 2000). Stewart et al. (2003) estimate the costs for treatment of MDD in the United States to be about 26.1 billion dollars per year, which is outnumbered by costs due to lost productivity of 44-51.5 billion dollars. Lerner et al. (2004) report that at a 6-months follow-

up, employees who were depressed at initial assessments, were more likely to have become unemployed, changed job, and had missed more time at work than healthy controls. Associated mechanisms suggested by the authors included poor job performance and difficulty coping with job pressures. Complementary, it has been shown that employment rates appear to increase after symptom decrease and successful treatment (Lerner et al., 2004; Schoenbaum et al., 2001; Simon et al., 2000).

1.2. Theories of Etiology

Cognitive theories of depression

MDD is a recurrent disorder of complex etiology. It is assumed to be the consequence of a combination of short-term, negative environmental effects (e.g. negative life-events) and long-term diatheses such as genetic and cognitive risk factors (Beck, 2008; Post, 1992). Research in clinical psychology has generally stressed the importance of cognitive and behavioral risk factors in the onset and maintenance of MDD. Since Beck first introduced his cognitive model of depression and related treatment plans (Beck, 1967; Kovacs & Beck, 1978), in particular the concept of vulnerability has been regarded as extremely important (Beck et al., 1979; Teasdale & Dent, 1987). Beck's model integrates three interdependent cognitive structures to explain the occurrence of depressive symptoms: a negative view of the self, world and future, a negatively distorted pattern of information processing, and cyclic self-referent thoughts associated with themes of loss. According to Beck's model, MDD can be causally attributed to the presence of maladaptive cognitive structures which are triggered or activated by stressful life-events (Beck, 1967; Beck et al., 1979). Hence, the model can be classified as a diathesis-stress model. Initial observations yielded overall support for the latter notion through the finding that certain types of negative life events are common precursors of the onset of a variety of clinically relevant depressive symptoms (Brown & Harris, 1978).

According to Beck's original concept, the risk to develop MDD is related to negative experience occurring during childhood, based on which maladaptive, dysfunctional cognitive structures are formed. When individuals with a history of such experience encounter negative life-events later in life, which resemble earlier experiences, the same structures in turn become activated. As a consequence, the individual's attention is likely to be captured by features congruent with the activated structures, leading to a domination of related cognition, perception, and memory. This process may yield the development of a MDE. Once the individual is in such a depressed state, self-referent dysfunctional attitudes or beliefs can be assessed, which previously remained latent and inaccessible. These dysfunctional attitudes are assumed to enduringly control information processing and produce systematic negative attentional and recall bias, as well as cognitive distortions (Beck, 2008). As such, according to Beck's view, depression can be causally linked to the interaction of negative life-events with corresponding maladaptive cognitive structures. These inferred maladaptive structures are generally regarded as stable, with a trait-like quality, and assumed to remain dormant in vulnerable individuals, if the relevant negative life events are not given.

A similar framework is also reflected in other early cognitive models of depression. Abramson et al. (1978) inferred in the learned helplessness theory that depression occurs when a person who experiences a negative life event is under the impression that he is incapable of changing the circumstances of the event. In case of an internal attribution, loss of self-esteem is likely to result. It should be noted however, that the latter assumption may be viewed as applicable to only a subset of individuals suffering from depression, due to the heterogeneity of depressive symptomatology (American Psychiatric Association, 2000a). A stable attribution supposedly yields the persistence of depressive symptoms for a longer period of time. Finally, in case of a global attribution, the depressive cognitions are assumed to have an impact on a huge variety of areas of the individual's life. A later revision of the helplessness theory resulted in the formulation of the hopelessness theory (Abramson, Alloy,

& Metalsky, 1989), which places a special emphasis on hopelessness as the causal basis for depression. According to this theory, an increased likelihood to make stable and internal attributions also increases the likelihood of developing symptoms of hopelessness, while the tendency to make global attributions increases the severity of such symptoms.

Even though there are considerable conceptual differences between these cognitive approaches to the etiology of depression, they share a general cognitive theme. Besides the fact that they ascribe a causal role to hypothesized maladaptive cognitive structures, the theories also overlap in the notion that these cognitive structures are relatively stable, trait-like characteristics. In case of Beck's model, the maladaptive cognitive structures, assumed to be acquired in childhood, are regarded as persistent, dormant traits. These traits reflect a factor of vulnerability, which can be assessed, and manifests in depressive symptoms under adverse conditions. Similarly in the theory formulated by Abramson, the tendency to make certain attributions, i.e. attributional style, is regarded as a stable characteristic which bears a risk for the development of depression. Accordingly, especially in case of Beck's theory, subsequent research intended to test the described notions has adopted the perspective, that at the level of cognitive structures, differences between individuals prone to depression, i.e. individuals with a high vulnerability, and resilient individuals, should be permanently present.

Early evidence against cognitive theories

According to Segal & Ingram (1994), in order to be considered a marker of risk or vulnerability, in line with the suggested cognitive theories of depression, cognitive measures need to satisfy the criteria of sensitivity, specificity and stability. Measures should therefore indicate abnormal cognitive structures in depressed individuals, such abnormal structures should be more frequent in depressed samples than in controls, and measures should not vary considerably with time and clinical status. Surprisingly, despite theories being based on observations in clinical settings, first empirical testing was predominantly regarded as

disconfirming (Coyne & Gotlib, 1983). Empirical studies yielded three kinds of apparent evidence against the described notions:

Firstly, longitudinal studies following depressives over the course of their illness revealed that with the remission of depressive symptoms, also the assumed underlying dysfunctional attitudes and attributions became significantly weaker (Dobson & Shaw, 1987; Dohr, Rush, & Bernstein, 1989; Eaves & Rush, 1984; Seligman et al., 1988). The finding that the presumably stable cognitive structures varied with a patient's clinical status were regarded as first disconfirming evidence, challenging the criterion of stability.

Secondly, studies which compared individuals without a history of depression with individuals who had experienced depression, but were currently in remission, showed that these groups did not differ in dysfunctional attitudes or attributions. Numerous studies revealed that during MDE, measures of negative thinking were shown to be considerably elevated compared to never-depressed controls. However, once patients had recovered, the self-reported level of dysfunctional attitudes did not show significant differences compared to those of healthy controls (Blackburn & Smyth, 1985; Dobson & Shaw, 1987; Dohr et al., 1989; Reda et al., 1985). There were only very few studies which found that measures of dysfunctional attitudes in recovered patients were elevated relative to never-depressed controls (Eaves & Rush, 1984) and these studies have been challenged on the ground of using very short recovery periods (Teasdale, 1988). Hence, the presence of residual depressive symptoms might be an explanation for such results. The described findings seem to be contradicting the cognitive models, since the presumably stable cognitive vulnerability factor would be assumed to be significantly stronger in patients in remission, compared to healthy controls. Consequently, these findings disconfirm the criterion of specificity. Finally, prospective longitudinal studies which were designed to assess whether underlying cognitions put individuals at risk for later depressive episodes did not yield any consistent results. Dysfunctional beliefs and attributions at baseline were no predictor for the onset of depressive

episodes during a 1-year follow-up period in the study of a community sample (Lewinsohn et al., 1981). In another study, depressive self-schemas did not predict the development of depressive symptoms during a follow-up period of four months (Hammen et al., 1985). In sum, early prospective studies did not find that stable cognitions were vulnerability factors that predicted subsequent depression. As such, results of early studies seem to offer only little convincing or consistent support for Beck's original model of vulnerability for the development of depression. Despite the apparent homogeneity of such findings in disconfirming cognitive models of depression at a first glance, a number of possible alternative explanations have been discussed.

Alternative explanations for early disconfirming results

As Teasdale (1988) indicates, at that point of research, final judgment on Beck's theory of depression could not be passed due to various reasons. Those reasons were related to methodological problems of the cited studies, particularly to the fact that the operationalization of the original concepts did not occur congruous with Beck's notions. Segal & Ingram (1994) point out that in essence, cognitive models of depression are diathesis-stress models. Beck's model for instance clearly states that depression is produced by interactions between factors of cognitive vulnerability and aversive conditions, such as negative life-events. Consequently, under ordinary, i.e. neutral conditions, individuals assumed to be vulnerable to develop depression cannot be distinguished from individuals without such vulnerability. Only in the presence of stressors, differences between vulnerable individuals and the general population can emerge and become assessable. The emphasis of this fact bears important consequences for research dealing with vulnerability. Vulnerable individuals can be assumed to be equipped with dormant but reactive cognitive structures, which can emerge and manifest in depressive symptoms only under aversive circumstances. Hence, the only way to properly study the notion of cognitive vulnerability is to focus on the *activation* of negative

self-referent cognitive structures. To effectively operationalize Beck's original notion of vulnerability implies that the reactivation of negative cognitive structures in individuals identified as being at risk, needs to be accomplished through appropriate provocations (Segal & Ingram, 1994). Therefore only the use of construct activation or priming strategies allows the study of vulnerability variables during the time that the patient is asymptomatic. In accord with this line of reasoning, Segal & Ingram (1994) suggest that in order to investigate vulnerability in individuals suspected to be at risk for depression, it is necessary to evaluate the responsiveness of such individuals, once confronted with a negative mood challenge.

Reappraisal: Evidence supporting the cognitive theories

Applied to cognitive theories of depression, this implies that relevant depressive constructs become available and are more readily processed, if their assessment is preceded by constructs with an associative relationship to them. This reasoning is reflected in a proposition by Persons & Miranda (1992), according to which dysfunctional attitudes and attributions are stable traits, independent from an individual's clinical status. Whether dysfunctional cognitions can be reported however, is regarded as dependent on the individual's current mood state. This assertion, also referred to as the "mood-state hypothesis", might explain apparent evidence against cognitive etiological theories. Underlying dysfunctional attitudes would appear to have vanished for individuals in remission, since along with the ceasing of depressive symptoms, relevant concepts become deactivated as well. In support of their assumptions, the authors report that in remitted patients, self-reported dysfunctional attitudes could be reliably changed by confronting patients with a procedure designed to induce a transient sad mood (Miranda & Persons, 1988). Further, in another study, changes in self-reported dysfunctional attitudes correlated with spontaneously occurring mood changes (Miranda, Persons, & Byers, 1990).

Dent & Teasdale (1988) incorporated a similar improvement of the operationalization of Beck's concepts in the "differential activation hypothesis", and further elaborated the original notions. According to the differential activation hypothesis, depression which is mild can be regarded as a normal, non-pathologic phenomenon in response to drastic negative life events. In most cases recovery is very likely to occur. Teasdale (1988) suggests factors in addition to Beck's notions, which may account for a deviation from the normal course of recovery. In particular, Beck's original theory suggests that experienced stressors, in order to cause a MDE, need to sufficiently match the events based on which dysfunctional cognitions were formed (Beck, 1967; Beck et al., 1979). This notion can be used especially as an explanation for the onset of MDE. As indicated, according to the differential activation hypothesis, depression in mild and transient form is common; hence experienced negative events do not necessarily have to tap previous negative experience directly. It is suggested that what is more crucial is the intensity with which information processing is affected by the experienced negative emotional state. Especially the intensity with which the occurring negative mood biases memory, perception and the interpretation of situations is regarded as determining whether clinically relevant depression develops after a negative life-event or not. It is argued that depressed mood makes representations of experiences which may lead to depression more readily accessible. The accessibility of representations yielding general negative interpretations, provides the possibility for a positive feedback loop between depressed mood and negative cognitive processing (Teasdale, 1988). If such a self-perpetuating vicious circle is established, depression is likely to be the consequence. As such, the differential activation hypothesis implies a more global activation of negative constructs through the occurrence of negative life-events than would be predicted by Beck's model. Further, the differential activation hypothesis can be used to explain the maintenance of depression, whereas Beck's model focuses primarily on explaining the onset of MDE. Similar to others (Miranda et al., 1990; Segal, 1988; Segal & Ingram, 1994) emphasizing the need to

readjust research paradigms to match the underestimated aspect of diathesis and stress, Teasdale (1988) claims that cognitive differences between patients with a history of depression but currently in remission, and never-depressed controls may be observed only if they are tested while in a negative mood. In support of this argument, Teasdale & Dent (1987) showed that processes related to global negative self-evaluation were more apparent in mild depressed states in remitted patients.

1.3. Mechanisms of Relapse

Kindling

As mentioned in section 1.1., MDD is often chronic and characterized by frequent recurrence of episodes (Belsher & Costello, 1988; Keller, 2003; Kennedy, Abbott, & Paykel, 2003). With regard to the differential relapse probability according to the number of experienced episodes, for theories intended to describe the course of depression, the distinction between earlier and later episodes is very important (Hammen et al., 1986; Monroe, 1982). In this context, the differentiation between short-term environmental adversities such as stressful life-events and long-term diatheses is of great relevance. A leading hypothesis first articulated by Kraepelin (1921) is that psychosocial stressors play a more prominent role in the initial than in subsequent episodes of the course of MDD. Over the course of illness, the onset of MDE appears to become more autonomous and less based on external stressors. This repeatedly observed pattern has been hypothesized to result from a sensitization process to negative mood states (Post, 1992; Post, Rubinow, & Ballenger, 1986). Paralleling animal electrophysiological models, this idea has been referred to as the “kindling hypothesis” (Goddard, McIntyre, & Leech, 1969). Numerous studies consistently support the kindling hypothesis, according to which there is a greater role for life stress related to the first episode of major depression than to later episodes. In a review of 16 studies of major mood disorders, Post (1992) claims that there are consistent findings that either more psychosocial stressors

were involved in the onset of the first episode than in later ones, or stressors appeared to have less impact on episodes occurring later in the course of illness, after many recurrences, than on the initial episode. In a later review, Mazure (1998) concludes that the majority of studies suggests that negative life events are more common prior to the first episode, compared with later ones. Also subsequent studies on the whole seem to be consistent with the general premise that major life stress has a greater association with the first onset of a MDE relative to a recurrence (Monroe & Harkness, 2005).

Origins of the kindling hypothesis

The origins of the kindling hypothesis are based on observations in clinical settings, results from animal studies, and on more systematic empirical research comparing life stress for people with first onset of MDD to those who experience successive episodes. In case of the animal model this refers to the sensitization of brain tissue. Limbic areas appear to become increasingly sensitive to electrical current which can induce seizures. It has been reported that after repeated applications, formerly sub-threshold current begins to pass the threshold for the elicitation of seizures (Goddard et al., 1969). Electrical kindling has been proposed as paralleling the apparent sensitization found in case of MDD (Monroe & Harkness, 2005). It is of importance to note that stress responses resulting from exposure to chronic stressors, e.g. intermittent shock in animals, have been found to generalize to relatively milder stressors, such as loud noise (Van Dijken et al., 1992).

In humans, imaging studies provide evidence which supports a neurobiological basis of stress-sensitization. Firstly, a reduction in hippocampal volume in recurrently depressed patients compared to individuals without depressive history has been observed. This has been hypothesized to result from toxic effects of stress hormones (Bremner et al., 2000; Shah et al., 1998). Secondly, there have been reports about a negative correlation between the volume of the amygdala and the hippocampus (Sheline, Gado, & Price, 1998). Finally, neuroendocrine

studies have reported that currently depressed patients who had suffered traumatic stress as children, displayed more than six times the adrenocorticotrophic hormone response to mild stress in adulthood than did participants without such experience (Heim et al., 2000). Overall, the results appear to suggest that a history of traumatic events can be associated with a dysfunctional regulation of the hypothalamic-pituitary-adrenal axis. This dysfunctional regulation may sensitize participants for further aversive events.

Kindling and psychological theories of depression: cognitive reactivity

As indicated above, the idea of kindling in humans is rooted in the finding that the association between major life-stress and episode onset weakens from a first episode across successive recurrences. Complementary explanations in cognitive terms have been suggested, according to which the increasing vulnerability to suffer from relapse across episodes is determined by the rising risk of negative patterns of information processing to take place (Segal et al., 1996). The authors argue that over the course of illness, individuals tend to increasingly rely on these patterns of processing. This in turn leads to an easier activation of them in the future, which can be achieved based on increasingly minimal cues. As such, repeated stressors and depressive episodes contribute to progressive changes in information processing that reduce the threshold for triggering recurrence. Congruous with the notion of psychological kindling, early studies have documented a residual form of psychological reactivity to dysphoric mood in formerly depressed patients (Miranda & Persons, 1988; Miranda et al., 1990; Teasdale, 1988). Nevertheless, it should be noted that up to this point a few important questions remained unanswered. Firstly, it appeared to be necessary to verify, whether the reactivity to dysphoric mood indicating vulnerability was a feature present in all patients once they entered the state of remission. Further, if this reactivity in fact represented a moving risk with increasing impact across episodes, it ought to be verified, whether an alteration through treatment was possible. As Hollon (1992) notes, certain forms of treatments for depression

may be more effective than others, since they might target and modify the putative diathesis. Finally, it remained to be established, that the theoretically assumed relation between assessed reactivity and the likelihood for depressive relapse really existed. Although prior work assumed a link and such a connection would be in line with many accounts of relapse, until this point, the association between reactivity to dysphoric mood and later risk for return of depressive symptoms had not been examined directly. The systematic exploration of cognitive reactivity, the relative ease with which maladaptive cognitions or cognitive styles are triggered by mild non-pathological mood fluctuations was yet to be undertaken in appropriate research designs (Ingram, Miranda, & Segal, 1998; Segal & Ingram, 1994).

A first attempt to verify this question was made by Segal, Gemar, & Williams (1999). In this study, patients suffering from MDD either received treatment through pharmacotherapy or cognitive behavioral therapy. Once in remission, in contrast to the group which was treated with pharmacotherapy, patients who had received cognitive behavioral therapy showed significantly less cognitive reactivity. Over a further follow-up interval of 30 months after initial testing, initial cognitive reactivity was predictive of depressive relapse. The result that the type of treatment which patients received appeared to have an effect on the degree with which dysfunctional cognitions were activated during negative mood is of great significance. It seems to suggest that in previously depressed patients, cognitive responses to mild sad moods may be altered by interventions that explicitly target these tendencies. The cited study was also one of the first to show up a direct connection between cognitive reactivity and relapse probability. In terms of the kindling hypothesis however, it still remained to be verified, whether the observed effects resulted from features given prior to the individual developing depression, or whether they represented diminished residual vulnerability from previously suffered episodes. The study further suffered from few methodological problems. Besides the use of a small sample size, the number of stressful life events within the sample was not controlled.

A more convincing study seeking to explore whether alterations in dysfunctional thinking related to negative mood may predict relapse in recurrently depressed patients in remission was provided by Segal et al. (2006). Complementing previous findings, this study showed that changes in dysfunctional attitudes in response to a negative mood provocation differed significantly according to whether patients achieved remission through either antidepressant medication or cognitive behavior therapy. Patients who recovered through antidepressant medication showed increased cognitive reactivity from pre to post-treatment assessments, whereas patients who recovered through cognitive behavior therapy showed a decrease. A subsequent survival analysis revealed, that those patients who showed elevated cognitive reactivity once in remission, also were at a higher risk for depressive relapse. This relation was still given when the number of experienced episodes was controlled. The finding that patients in remission who displayed greater dysfunctional cognitions following a sad mood induction, were at significantly greater risk for relapse during the follow-up period of 18 months, provided the first evidence for the prognostic value of cognitive reactivity. The finding further suggested that effective prevention might be achieved through approaches which are especially designed to target and weaken cognitive reactivity directly. More recent studies provide indirect support for the role of cognitive reactivity in depressive relapse. Antypa, Van der Does, & Penninx (2010) report that cognitive reactivity may underlie the relative stability of suicidal symptoms across episodes, and Barnhofer & Chittka (2010) have identified cognitive reactivity as a mediator of the well established relation between neuroticism and depression.

Rumination

Another important factor to explain relapse in MDD as well as its etiology is the tendency to engage in rumination. In the context of the “response-styles theory”, rumination has been defined as a way of responding to distress which involves a repetitive and passive focus on

symptoms of distress and on the possible causes and consequences of these symptoms (Nolen-Hoeksema & Morrow, 1991; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Even though individuals who tend to ruminate often report to engage in such activities in order to understand the reasons and consequences of their negative moods (Papageorgiou & Wells, 2001), it is by now well established that rumination does not lead to any attempts of active problem solving (Lyubomirsky et al., 1999). In contrast, individuals engaging in rumination have the tendency to continuously think about difficulties and associated affect, without engaging in behavior which might result in improvements of their situation (Nolen-Hoeksema et al., 2008). The themes of thought which occur during rumination typically have negative connotations. Rumination is best classified however as a process of thinking continuously about problems and associated feelings rather than in terms of the specific content (Nolen-Hoeksema et al., 2008).

According to the response-styles theory, rumination amplifies and prolongs negative affect through several mechanisms. Firstly, rumination strengthens the effects of dysphoric mood on cognition. This in turn biases further processing by increasing the probability for using negative thoughts and memories activated by depressed mood to understand a given situation. Secondly, as indicated, rumination interferes with effective problem solving, and with instrumental behavior, yielding increasingly stressful circumstances (Nolen-Hoeksema & Morrow, 1991). Experimental studies which have used rumination inductions have found that rumination is associated with elevated negative mood in patients who already are in a negative mood, but not in case of participants who are in a neutral state at baseline (Lyubomirsky, Caldwell, & Nolen-Hoeksema, 1998). Further, individuals in a negative mood who ruminate, spontaneously retrieve more negative memories from their recent past than do individuals in a negative mood who distract themselves from negative thoughts. They are also under the impression that they have experienced negative events more often, and are highly self-critical and pessimistic about solving their problems (Lyubomirsky et al., 1998).

Rumination appears to play a prominent role in the context of depression, since it has been shown to be associated with a range of maladaptive cognitive patterns. Such cognitive patterns include negative, dysfunctional attitudes, attributional styles and hopelessness (Lam et al., 2003; Nolen-Hoeksema et al., 2008), which contribute to ruminators having more and prolonged periods of depression and a greater likelihood to develop depressive disorders (Nolen-Hoeksema, 2000).

While support for the association between rumination and depression comes from a variety of studies showing up relations between rumination and parameters relevant for depression, studies specifically designed to explore the link between rumination and depression onset and maintenance have produced mixed results. In a study by Nolen-Hoeksema (2000), rumination scores at a first assessment predicted new onsets of MDE over the next year among people who were not clinically depressed initially. However, among people who were already in a MDE at the first assessment, rumination scores did not predict whether they would still be in a depressive episode. Other studies have not found rumination to predict the duration of MDE in patients under treatment (Arnow et al., 2004; Park, Goodyer, & Teasdale, 2004), albeit some report rumination to be predictive (Kuehner & Weber, 1999).

Overall, these findings seem to suggest that rumination may predict the onset of MDE but has less predictive value for its duration. According to Nolen-Hoeksema (2008) the observed findings parallel findings from large nationally representative epidemiological studies which showed that women's greater rates of depression were due to gender differences in first onsets, but not in duration of the episodes (Eaton et al., 1997; Kessler et al., 1993). It is known that women are more likely to engage in rumination than men and these gender differences in rumination have been found to mediate gender differences in depression in some studies (Grant et al., 2004; Nolen-Hoeksema, Larson, & Grayson, 1999a).

2. Treatment of Major Depressive Disorder

2.1. Prophylactic Effects of Cognitive Therapy: Metacognitive Awareness

In recent years, evidence has accumulated, which suggests that cognitive therapy reduces the risk for relapse in MDD. A variety of studies has shown that the prophylactic effect is relatively enduring. The relapse risk for patients who received treatment through cognitive therapy seems to be reduced by approximately 50%, compared to patients who stopped using medication after recovery through anti-depressants (Blackburn, Eunson, & Bishop, 1986; Evans et al., 1992; Kovacs et al., 1981; Simons et al., 1986). Recently, similar prophylactic effects of cognitive therapy compared to treatment through anti-depressant medication and subsequent withdrawal were reported (Hollon et al., 2005). The authors of the latter study argue that cognitive therapy is at least as effective as continuous treatment with medication, the latter being accepted as probably most effective in the prevention of depressive relapse (American Psychiatric Association, 2000b).

Until recently, knowledge as to how the protective effect of cognitive therapy is brought about was rather limited. Hollon et al. (2005) speculate that the answer may lie in the autonomy ascribed to patients who undergo therapy. Patient empowerment is a central element of treatment and patients are continuously encouraged to play an active role. Regular exercises to be done outside the office to test dysfunctional cognitions in combination with preparation for upcoming problems following treatment are very important aspects. The continuous practice of adaptive strategies may yield patients to be protected after therapy.

Theoretical notions of cognitive therapy suggest that depressed patients are characterized by dysfunctional cognitions and that a lower relapse risk can be attributed to a corresponding reduction in such cognitions. Overall, this assertion could not be supported (Barber & Derubeis, 1989). In clinical trials in which treatment through cognitive therapy was associated with longer periods without depressive relapse, at post treatment assessments, there

were frequently no treatment-specific effects on dysfunctional attitudes (Simons, Garfield, & Murphy, 1984).

Teasdale et al. (2002) provide an alternative explanation for the prophylactic effect of cognitive therapy, placing an emphasis on the original, dynamic perspective of the cognitive model. This implies that the assumed diathesis only manifests under aversive conditions. Following the account presented in section 1.2., one may claim that cognitive therapy would yield patients to change their relations to and interpretations of depressive symptoms when confronting potential relapse (Teasdale, Segal, & Williams, 1995). Cognitive therapy would therefore enable a patient to learn to adopt a different perspective on given negative affect, characterized by a more adaptive response. The continuous practice through exercises given in the therapeutic setting may result in the accumulation of a repertoire of protective responses, making it possible for patients to deal better with difficult situations. When facing potential relapse, the availability of such a repertoire may in turn result in a reduced likelihood for maladaptive cognitions to set off the vicious cycle of negative cognitions and affect.

Referring to this argument, the concept of “decentering” is of special relevance (Moore, 1996). It reflects that patients can learn to acknowledge the presence of negative affect and cognition without identifying with either of the two too strongly. The continuous process, which takes place in cognitive therapy, during which patients learn to monitor and assess the accuracy of their cognitions, may bring about a shift towards a more decentered perspective. As a result, patients’ ability to endure negative affective states without an escalation into a depressive episode may be strengthened. Teasdale et al. (2002) label the application of a decentered perspective to negative cognition and affect “metacognitive awareness”. In a series of studies, the authors were able to show that a higher relapse risk was associated with decreased metacognitive awareness. Further, lower scores on a measure of metacognitive awareness in patients than in controls could not be explained by higher

depressive symptoms in patients. In a second study, the authors were able to show that despite the fact that cognitive therapy places an emphasis on altering belief in negative thoughts, it also seems to lead to changes in relationships to negative cognition and affect, in particular to elevated metacognitive awareness. Patients, who had greater problems to adopt a metacognitive perspective in relation to cues relevant for depression, were also more likely to develop an episode of depression during a follow-up period. The authors concluded that relapse prevention through cognitive therapy was probably achieved through increasing patients' abilities to engage in a metacognitive perspective. Hence, increasing metacognitive awareness is likely to partially mediate the prophylactic effect of cognitive therapy (Teasdale et al., 2002).

Since cognitive therapy places a strong emphasis on the change of cognitive structures, the described studies cannot clearly verify, whether the cultivation of metacognitive awareness is indeed the essential component protecting patients from depressive relapse. To verify whether this is the case, one would have to apply training in meta-cognitive awareness without any explicit attempt to change cognitive structures. Segal, Williams, & Teasdale (2002) developed such an intervention. Mindfulness-Based Cognitive Therapy (MBCT) was especially designed to train patients in the cultivation of a metacognitive perspective on negative thoughts and feelings. MBCT also does not include any attempt to alter a patient's belief in the content of cognitions. Compared with treatment as usual (TAU), involving the regular consultation of health professionals when necessary, in a third study by Teasdale et al. (2002), MBCT lead to reductions in depressive relapse in addition to improved skills in adopting a metacognitive perspective.

2.2. Mindfulness-Based Cognitive Therapy (MBCT)

According to Segal et al. (2002), it can be assumed that the likelihood of depressive relapse is decreased, if remitted patients can learn to adopt a metacognitive perspective. MBCT was

specifically designed to teach the necessary skills to recurrently depressed patients in remission (Segal et al., 2002; Teasdale et al., 1995). While a detailed description of MBCT is beyond the scope of this work, in the context of the present research, essential elements and assumed working mechanisms are supposed to be highlighted. MBCT is a group intervention, based on an integration of cognitive therapy for depression (Beck, 1979) and elements of mindfulness meditation (Hanh, 1996), which have previously been utilized in similar treatment programs, such as Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn, 1990). In contrast to cognitive therapy, in MBCT, there is no intention to directly change thought content. In line with the notion of metacognitive awareness, the focus is placed on the alteration of awareness of and relation to thoughts, particularly through the cultivation of mindfulness in contemplative exercises.

The concept of mindfulness in clinical practice

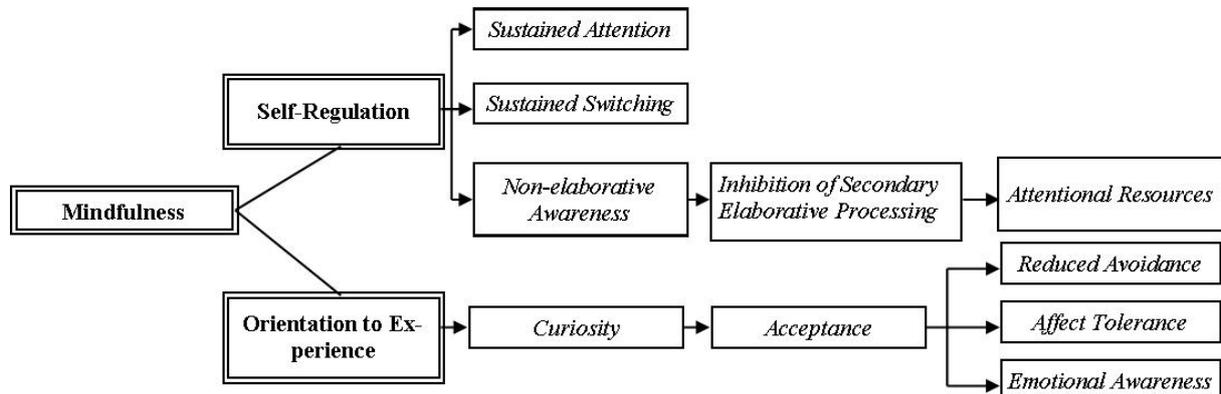
Mindfulness is an English translation of the Pali term “Sati” and originates from Buddhist philosophy. Sati can be conceptualized as expressing awareness and attention, and purposefully focusing on any object or experience that arises within the field of awareness in the present moment (Germer, Siegel, & Fulton, 2005). Traditionally, the cultivation of mindfulness through contemplative practice, such as meditation, is regarded as a mean to achieve an overall cessation of suffering (Hanh, 1996). Mental suffering in this context is viewed as originating from the attachment to virtual moments of permanence, which the human mind is supposed to create from an impermanent reality. Especially the interpretation of fleeting, impermanent phenomena such as cognitions and emotions as static entities reflecting reality, are supposed to create suffering (Germer et al., 2005). Notions of contemporary research in clinical psychology dealing with mindfulness resemble this traditional conceptualization. Here mindfulness is commonly conceptualized as a certain way

of paying attention. Mindfulness implies paying attention purposefully, on a moment-to-moment basis, with a non-judgmental attitude (Kabat-Zinn et al., 1998; Segal et al., 2002).

A model devised by Bishop et al. (2004) illustrates assumed working mechanisms of mindfulness (Fig. 1). According to this model, mindfulness involves two components. The first one is the self-regulation of attention, in a way that keeps attention focused on the present experience. This yields sustained attention and skills in switching between objects of attention purposefully. The latter skill is commonly acquired through the utilization of the breath as an object of reorientation as sensations, cognitions and emotions arise. Since attention is redirected to the breath after such phenomena have been observed and acknowledged, further elaboration upon them is inhibited, which the authors refer to as non-elaborative awareness. This quality of awareness in turn is supposed to inhibit secondary elaborative processing of thoughts. Taking into consideration that attention is a limited resource (Schneider & Schiffrin, 1977), this provides greater resources of attention for processing information of the present moment experience. The second component in this model is a certain orientation toward experience which is accepting, open and curious. This involves a conscious commitment to regard any arising sensations, cognitions and emotions as relevant. During mindfulness exercises, frequent instructions are to observe arising phenomena and subsequently, redirect attention toward physical sensations of the breath. Therefore, the individual engaging in mindfulness exercises does not aim at the induction of a relaxed state, since distressing feelings are regarded as equally important as pleasant ones. Acceptance or openness to reality is to be seen as an active process which is fuelled through non-judgmental contemplation. A consequence of this curious, accepting attitude is supposed to be a reduction in avoidant behavior patterns. At the same time, a familiarization with distressing emotions is supposed to occur, which in turn yields increased affect tolerance. Furthermore, through the active engagement in the contemplation of affect, skills of emotional awareness are supposed to be fostered.

Figure 1. The two-component model of mindfulness

Adapted from Bishop et al. (2004)



In line with Bishop’s conceptualization of mindfulness as enhancing emotional awareness and affect tolerance is the idea, that mindfulness is closely related to abilities of emotion regulation. According to Hayes & Feldman (2004), mindfulness provides a remedy against experiential avoidance and emotional repression on the one hand, and over-engagement involving rumination, worry and obsession on the other. At the same time, the preoccupation with positive experience induced through extreme risk-taking is supposed to be weakened, fostering overall emotional balance. The process of developing this type of emotional balance is not to be regarded as necessarily a linear one. In fact, through the fostered interoceptive exposure of mindfulness practice, a full experience of emotional patterns may occur, which has the potential to frighten practitioners. Hence, initially mindfulness-techniques may actually result in higher distress, until habituation to the new, deepened experiential level of emotions occurs (Hayes & Feldman, 2004; Kumar, Feldman, & Hayes, 2008).

MBCT: course description

MBCT is a skills training course, which takes place in a group setting with up to twelve participants. Initially, patients are interviewed by the instructor. During the interview, psychoeducation concerning depression and depressive relapse is given as well as a rational

for protective effects through participation. The course itself is given in eight sessions of approximately two hours duration, which take place once a week over the course of two months. In addition, extensive homework exercises are to be done by each participant. A central element of MBCT is the practice of mindfulness meditation.

The training of patients to purposefully attend to various internal and external objects of awareness is the focus of sessions one to four. Throughout these sessions, patients are guided to experience, how limited attention paid to experiences of daily life usually is. Further, patients are trained to bring their attention back to focus when their mind starts to wander.

Patients are also supposed to develop an idea of how being in unfocused states may yield negative thoughts and cognitions to become more powerful. In session five to eight, the emphasis of training shifts towards dealing with mood changes. Whenever negative thoughts or feelings are experienced, patients are encouraged to deal with them mindfully. This implies that patients are supposed to increase their awareness of such phenomena, acknowledge their presence and redirect attention to their breathing or other bodily sensations. Generally, there is a strong emphasis on encouraging patients to apply the skills acquired during sessions in settings of everyday life. The latter notion implies a differentiation between formal and informal practice.

Formal practice takes place during the sessions and homework exercises. A central element of formal practice is the so-called “body-scan”, an exercise of about 45 minutes duration. During the body-scan, attention is voluntarily directed towards different parts of the body, according to instructions given by the course leader. Arising phenomena, whatever their quality, are supposed to be regarded with mindful awareness. This formal practice is also a central part of the homework exercises, where guidance occurs through audio CDs. Informal practice is supposed to help the practitioner to transport skills acquired during formal practice into regular, daily situations. Examples of such exercises are mindful eating, walking, or

taking so-called breathing spaces throughout the day, i.e. focusing on the breath for short periods of time. The utilization of such exercises may enable participants to prevent the consolidation of negative thoughts and affect. Patients learn how the establishment and nurturing of self-perpetuating negative cognitions can be disabled. Throughout the whole course, it is stressed that the aim of these mindfulness exercises is not to achieve blissful states, but to mindfully accept any given state.

Since during sessions a lot of time is devoted to practice, a major task of the course instructor is to guide the exercises. Another important function of the instructor is to guide participants in reporting how they experience the exercises and which difficulties might be encountered. Commenting on the reported experience, the instructor also points out how frequently self-referential judgments are passed, and how these reflect the working of ruminative habits of thinking. Comments of the instructor are intended to facilitate the experience of participants that they are often operating in an automatic mode. It is supposed to be learnt that this automatic mode is fuelled by the craving for positive mood and the aversion of negative mood. In addition participants are supposed to realize that constant monitoring of the present state and a comparison of the present state to a desired state, in combination with attempts to solve problems through internal monologue, is maladaptive.

2.3. Effects of Mindfulness-Based Cognitive Therapy

Relapse prevention

Since MBCT was first introduced, several randomized controlled trials (RCTs) have been conducted to verify its efficacy in reducing the risk for depressive relapse. A first RCT was conducted by Teasdale et al. (2000) and included 145 recurrently depressed patients in remission. Results showed that for patients with a history of three or more depressive episodes, MBCT in combination with TAU approximately halved relapse rates over a follow-up period of 60 weeks, compared to patients who received TAU alone. This corresponded to a

medium-sized effect (OR = 0.34, 95% CI = 0.16, 0.76, $p = .008$; Williams, Russell, & Russell, 2008). The observed prophylactic effect was found to be unrelated to whether patients received anti-depressants. It is important to note that MBCT was not protective for all patients included in the sample. Participation was associated with significantly decreased relapse rates only in patients with a history of three or more episodes. This is of special interest considering theoretical accounts of MBCT. Apparently, those patients in whom depressive relapse can be assumed to have reached a relatively high degree of autonomy from external stressors were also those who profited from participating. The authors concluded that MBCT was indeed effective in disrupting processes of reactivation of depressogenic thought patterns in response to negative mood. Theoretically, these processes should play a prominent role for depressive relapse in patients with higher numbers of experienced episodes, whereas in patients with fewer episodes, more drastic negative life events remain necessary to cause relapse. The findings of the described study mirror this assumption.

A second RCT, intended to replicate findings of the first trial was conducted by Ma & Teasdale (2004) with a sample of 75 recurrently depressed patients. The authors were successful in replicating initial results. In patients with a history of three or more previous episodes, the likelihood for depressive relapse was decreased by more than 50% compared to patients who received TAU alone (OR = 0.16, 95% CI = 0.05, 0.52, $p = .002$; Williams et al., 2008). In this case, the protective effects of MBCT were most salient in patients with a history of four or more episodes. Compared to the TAU condition, the effect of MBCT was greatest for MDE which were not preceded by negative life events. It was somewhat weaker for episodes with preceding milder negative life events. Overall, the relapse risk of patients who received MBCT was still higher than that which would be expected according to prevalence rates of the general population. The authors conclude that MBCT is most effective in reducing relapse which occurs independently from external stressors, but that it is probably ineffective in preventing relapse subsequent to severely negative life-events. The authors further assume

that the involved protective mechanism was a disruption of autonomous relapse processes, i.e. the reactivation of ruminative negative thought patterns through negative mood at times of potential relapse. As was the case in the first trial (Teasdale, et al., 2000), patients with only two previous episodes did not benefit from participating in the training. These patients showed a non-significantly greater tendency to suffer depressive relapse following MBCT than did patients who had received TAU. The authors speculate that MBCT hence may be contraindicated for this group of patients. Ma & Teasdale (2004) further note, that it cannot be ruled out that patients with only two previous episodes belonged to a different base population than those with three or more episodes, since patients with two episodes reported a later onset of the first MDE than those with three or more. Also, patients with three or more MDE reported more negative early experiences than those with two.

Both RCTs (Ma & Teasdale, 2004; Teasdale et al., 2000) suffer from several important limitations. As Coelho, Canter, & Ernst (2007) point out, with the given designs, it cannot be verified, whether the protective effects arose specifically through the training of mindfulness skills. Various non-specific effects, possibly brought about by psychoeducation which occurred during the course, received social support within the group, or attention of a therapist, cannot be excluded. In response to such criticism, Williams et al. (2008) argue that the most appropriate control condition would be one allowing for the option of “dismantling”, i.e. one in which treatment in the control condition is the same as the one in the experimental condition, except for the component of interest. Since mindfulness, the component of interest, is supposed to be cultivated through meditation exercises, future studies are planned to use an MBCT format without elements of meditation. Coelho et al. (2007) further criticize that patients allocated to TAU might have suffered from “resentful demoralization”, hence may have experienced an increase in suffering due to the allocation to the comparison and not the treatment condition. However, as Williams et al. (2008) argue, an analysis of data obtained through self-report measures at follow-up assessments did not support this assertion. In their

attempted rebuttal of criticism, the latter authors reanalyzed the data of both clinical trials. Based on this analysis they conclude that MBCT lead to a reduction of depressive relapse between 39-70% during the follow-up period of 12 months (OR = 0.27, 95% CI = 0.14, 0.52, $p < .001$). They also report that MBCT increased the average interval from recovery to depressive relapse by a minimum of 18 weeks, which was associated with a significant decrease in depression scores on self-report measures. Regarding results of the first two RCT assessing MBCT, overall, one may conclude that despite several methodological limitations, MBCT is a form of maintenance therapy which is probably efficacious, since two randomized-controlled trials have shown it to be effective.

A third RCT was conducted by Kuyken et al. (2008), intended to compare the effectiveness of MBCT with maintenance antidepressant medication (mADM). Results of the study showed that over a follow-up period of 15 months, relapse rates in a group of recurrently depressed patients with at least three depressive episodes, treated with MBCT, were marginally lower than in a group of the same patient population which received mADM. This was the case even though patients in the MBCT group were assisted in discontinuing medication. While of the patients treated with MBCT 47% (29/61) relapsed, 60% (37/62) of mADM patients relapsed (hazard ratio = 0.63, 95% CI = 0.39, 1.04). In the MBCT group 75% of patients discontinued medication. Analyses of secondary outcomes revealed that patients who received treatment through MBCT reported significantly less residual depressive symptoms on all follow-up assessments than patients treated with mADM. Patients treated with MBCT also reported significantly better quality of life in physical and psychological domains. The authors conclude that MBCT may offer a promising alternative to the use of mADM. Nevertheless, the design of the indicated study does not allow for any conclusions concerning the working mechanisms of MBCT, and whether it was indeed the mindfulness training specifically, which was associated with positive outcomes.

More recent RCTs to assess effects of MBCT on recurrence of depressive episodes yielded mixed results. Godfrin & van Heering (2010) report that relapse risk in a group of patients treated with MBCT and TAU (30%, 12/40) was significantly lower than that of a group which received TAU alone (68.1%, 32/47; $\chi^2 = 12.5, p < .0005$) over a follow-up period of 56 weeks. For patients of the former group, the time until the occurrence of another depressive relapse was relatively longer. These patients also reported better mood states and an improved quality of life. However, in another RCT intended to independently replicate earlier findings over a follow-up interval of 14 months, only effects on the time until relapse were observed. This time was significantly longer for patients who received MBCT and TAU, than for those who received TAU alone (Bondolfi et al., 2010). Nevertheless, survival rates for both groups were very similar. In case of patients who received MBCT and TAU 29% (9/31) relapsed. For patients who received only TAU 34% (10/29; Fisher's exact test, $p = .78$) relapsed. The latter finding stands in contrast to the first RCTs which reported relapse rates of 66% and 78% in the TAU group (Ma & Teasdale, 2004; Teasdale et al., 2000). Since in the study conducted by Bondolfi et al. (2010), no group differences in terms of clinical history, demographic variables or adjunctive treatment over the follow-up period was observed, the authors point out that differences between health care systems within which the studies were conducted exist. Especially the high availability of psychiatric care in Switzerland may have reduced depressive relapse in the TAU group relative to the other RCTs, which were conducted in the United Kingdom and Canada. This is in line with observed relapse rates for recurrently depressed patients generally being estimated to be higher than those reported by Bondolfi et al. (2010). A notable limitation of the latter study is that similar to the earlier trials, non-specific effects cannot be assessed.

Target mechanisms: rumination and cognitive reactivity

As indicated, several RCTs established that MBCT is probably efficacious in reducing the risk for depressive relapse in recurrently depressed patients. However, in such studies, underlying working mechanisms have not been explored directly. In addition, the lack of appropriate control conditions, other than TAU, does not allow for an attribution of the protective effect of MBCT to increases in mindfulness and associated decreases in cognitive reactivity and rumination. Few studies have attempted to explore the working mechanisms of mindfulness-based interventions, albeit in general they do not place a rigorous emphasis on recurrently depressed patients in remission and on MBCT alone.

Ramel et al. (2004) examined the effects of participation in an MBSR course on self-reported ruminative tendencies in a sample of 23 individuals with life time mood disorder. The authors report that mindfulness practice was associated with decreases in rumination, even when alterations in affective symptoms and dysfunctional attitudes were controlled. The self-reported time spent practicing meditation was predictive of reductions in ruminative tendencies. Similar results were reported by Deyo et al. (2009) in a study which intended to explore the effect of MBSR on mindfulness, rumination and depressive symptoms. In line with the authors' hypotheses, participation in an MBSR course was associated with decreased rumination and symptoms of depression. Kingston et al. (2007) conducted a study to test the effects of MBCT on rumination in recurrently depressed outpatients with residual depressive symptoms. The authors report a significant reduction in depressive symptoms at a one-month follow-up assessment and marginally significant reductions in rumination. Hence, research complementing efficacy studies of MBCT presents relatively homogeneous results, indicating that structured mindfulness training is associated with decreases in ruminative tendencies.

Until this point only one study has assessed the effects of mindfulness training on cognitive reactivity. Raes et al. (2009) examined the relation between trait mindfulness and cognitive reactivity. Further, it was tested for an alteration of cognitive reactivity in response

to MBCT. The authors observed a significant negative correlation between trait mindfulness and cognitive reactivity. This correlation was still given when current levels of depressive symptoms were controlled. In addition, it was found that participation in the MBCT course was associated with a reduction in cognitive reactivity. The reduction was mediated by increased mindfulness.

In sum, cognitive reactivity and rumination, the assumed central processes underlying vulnerability in recurrently depressed patients appear to be changed through mindfulness training. This alteration reflects more adaptive functioning across studies.

MBCT and other psychiatric conditions

Further preliminary evidence for the effectiveness of mindfulness-based interventions comes from studies which explore whether MBCT could be adapted to treat other patient populations, besides recurrently depressed patients. Such attempts which have emerged only recently, appear to be promising. Participation in MBCT courses has been shown to have positive effects in patients suffering from bipolar disorder, treatment resistant, as well as chronic depression (Barnhofer et al., 2009; Kenny & Williams, 2007).

3. Psychobiological Aspects of Depression and Mindfulness

3.1. The approach withdrawal model of hemispheric asymmetry

The notion that trait-like physiological anomalies might be associated with an increased vulnerability for the development of psychopathology such as MDD has received considerable attention. In particular, the study of functional and anatomical brain asymmetries has attracted a lot of interest (Davidson, 2001; Thibodeau, Jorgensen, & Kim, 2006). The earliest accounts which hinted at a hemisphere-specific involvement in emotional processing and regulation are based on lesion studies. Such studies showed that insult to the left hemisphere, especially in anterior regions, could be related to depressive symptomatology. A study which involved patients with unilateral lesions was conducted by Gainotti (1972). The author notes that symptoms indicating negative affect were more likely related to damage in the left than to damage in the right hemisphere. In contrast, abnormal behavior associated with positive affect following insult, was more likely for patients who had suffered damage to the right hemisphere. In another study, Robinson et al. (1984) observed that depressive symptoms were predicted by the proximity of the lesion to the left-hemispheric frontal pole. In contrast, patients who showed mania-like symptoms following brain trauma, were more likely to have suffered tissue damage in right-hemispheric anterior regions. Despite the limited possibilities to appropriately localize sites of insults in these studies, such results seem to suggest that there is a differential involvement of anterior structures in emotional processing, which might be relevant for the discussion of depression. Nevertheless, it should be noted, that not all patients who suffered such tissue damage developed the described symptoms, and inconsistencies were reported (Gainotti, Caltagirone, & Zoccolotti, 1993). Davidson (e.g. 1992, 1995) elaborated a model of hemispheric asymmetry and emotional processing based on such findings. According to this model, effects of unilateral lesions result in the disinhibition of contralateral structures. Hence, left-hemispheric lesions yield the

disinhibition of corresponding right-hemispheric structures. Considering the pattern which emerged in early lesion studies, this implies that anterior portions of the left hemisphere may be structures relevant for the generation of positive affect, whereas right-hemispheric anterior structures may be relevant for the generation of negative affect. This notion has been formulated in terms of the “valence-hypothesis” of hemispheric asymmetry (Hellige, 1993), which assumes a valence-specific functional dominance of each hemisphere. Davidson (1992, 1995) proposed a model which additionally incorporated motivational direction. According to the original version of the “approach-withdrawal model of hemispheric asymmetry”, there is a functional dominance of left-hemispheric anterior structures for positive emotion and approach behavior. In contrast, right-hemispheric anterior structures play a dominant role in the mediation of withdrawal behavior and negative emotion. The model bears special relevance in the context of depression research, since it implies that dominant, trait-like activations of the right prefrontal cortex may represent a diathesis for the development of MDD. This assertion may account for the finding that in early lesion studies not all patients with left-hemisphere damage developed signs of depression. According to Davidson (1992, 1995) the development of depressive symptoms did not occur in all of the patients, since lesions in relevant locations are not sufficient to yield depression. The lesions represent diatheses that alter an individual’s vulnerability to depression by affecting his or her affective style, i.e. the propensity to react to emotion-eliciting stimuli with a certain extent of approach or withdrawal/avoidance-related behavior. Consequently, neither trait-like, left-hemispheric anterior cortical hypoactivation, nor right-hemispheric anterior cortical hyperactivation will suffice for a clinically relevant depression to emerge. Trait-like characteristics associated with a withdrawal/avoidance-related affective style are regarded as interacting with superimposed state-effects. An individual high in vulnerability may develop depression under aversive circumstances. On the other hand, an individual low in vulnerability might also develop depression in case of correspondingly more aversive circumstances.

Davidson (1992, 1995, 2001) suggests that there are two basic neural circuits, one mediating the functional aspects of the approach system, and a second one underlying the withdrawal system. The prefrontal cortex (PFC) has been described as playing an important role in emotion regulation and represents a central element of both systems. On a global level, the left PFC is regarded as mediating approach-related responses and the right PFC as mediating withdrawal-related responses. Davidson & Erwin (1999) further highlight the importance of differentiating the functional roles of structural subcomponents of the PFC and additional non-frontal components. Recent imaging studies indicate that there exists a neural circuit which involves cortical and limbic structures, with prefrontal cortical structures expressing a regulating influence on subcortical components.

Key components of this circuitry seem to include the dorsolateral, orbital, and ventromedial PFC, the anterior cingulate cortex, and the amygdala. In several studies, cognitive effort has been related to increased activation in areas of the PFC, and decreased activation in limbic structures, such as the amygdala, in subjects confronted with affect-eliciting stimuli (Hariri, Bookheimer, & Mazziotta, 2000; Liberzon et al., 2000; Taylor et al., 2003). Levesque et al. (2003) report elevated activation of the dorsolateral and the orbital PFC in relation to efforts to suppress negative affective states induced through short film clips. Ochsner et al. (2002) assessed the neural correlates of cognitive reappraisal of pictures showing extremely negative scenes. Subjects were instructed to reappraise the images in a neutral way, i.e. to reinterpret them in a way that did not yield a negative affective response. The presentation of negative scenes was associated with increased activation in the right amygdala. Reappraisal was associated with increased activity in dorsal and ventral regions of the left lateral PFC and decreased activity in the amygdala. In other studies the suppression of negative affect through cognitive reappraisal was shown to be associated with an activation of the anterior cingulate cortex and the lateral PFC, as well as with a deactivation of the amygdala (Ochsner et al., 2004; Phan et al., 2005). While Urry et al. (2006) could not

replicate the pattern of increased activation in prefrontal areas and the decrease in amygdala activation, Johnstone et al. (2007) report an inverse relationship between the activation of the left ventrolateral PFC and the amygdala during the reappraisal of affective stimuli. This inverse relationship was found to be mediated by the ventromedial PFC. The latter study also included a group of currently depressed subjects. In these participants, the described relationship was not observed. Depressed subjects displayed the contrasting pattern of a positive correlation between activity of the ventromedial PFC and the amygdala. The authors conclude that individuals suffering from MDD may be characterized by a harmful engagement of the right PFC and a lack of engagement of left prefrontal structures relevant for the attenuation of activity in the amygdala in response to negative stimuli.

Keeping these results in mind, one should note that the majority of studies which attempted to test the approach-withdrawal model have used electroencephalographic (EEG) assessments. These studies can be divided into those which test the predictive utility of anterior activation for affective responses, i.e. participants' affective style, mostly in healthy subjects. Secondly, there are those which tested for abnormal patterns of anterior asymmetry in clinical populations, especially in patients suffering from major depression. In the following paragraphs, the former will be reported and discussed, followed by a discussion of the latter.

Functional anterior asymmetry and affective style

In early studies involving EEG assessments, generally, right-hemispheric anterior regions were shown to have special relevance for withdrawal-related, negative affective states. In contrast left frontal regions were activated during approach-related, positive states. EEG studies about anterior brain asymmetry are based on the assumption that the power of the alpha band (8-13Hz) in resting EEG is inversely related to underlying cortical activity (Coan & Allen, 2004). The sensitivity of such assessments to different task demands tapping

lateralized processing mechanisms has been demonstrated in e.g. verbal vs. spatial tasks (Davidson et al., 1990a). Further, functional anterior brain asymmetry (FAA), derived through the power of the alpha band in resting EEG, has been shown to be relatively stable in healthy subjects (Tomarken et al., 1992b).

Davidson & Fox (1989) assessed whether individual differences in FAA were predictive of infants' responses to an affective challenge. In a sample of ten-months old infants, those infants who showed signs of distress, such as crying in response to maternal separation, displayed stronger right-hemispheric anterior activation during a baseline assessment. Similarly, Buss et al. (2003) showed that six-months old infants for whom an extreme pattern of relatively stronger right-hemispheric anterior activity was determined during a baseline assessment, were also those infants who were most likely to display sadness when approached by a stranger. These studies suggest that approach and withdrawal tendencies may already be reflected in childhood temperament and may be detectable in terms of FAA relatively early in life.

FAA has also been explored in relation to facial expressions in adults. In an experiment which involved the assessment of FAA and facial movements, Davidson et al. (1990b) report that expressions of disgust were related to an activation of right-hemispheric anterior areas, compared to a condition in which the expression of happiness occurred. In the latter condition, relatively greater left-hemispheric anterior activation was given. Ekman et al. (1990), conducted assessments of FAA, facial expression, and self-reported emotional experience in response to pleasant and unpleasant film-clips. Duchenne smiles, involving a specific pattern of muscular activity, which have been argued to reflect genuine emotional experience (Ekman, 1992), were displayed more often during the pleasant than the unpleasant clips. Duchenne smiles further predicted the expected approach-related pattern of FAA, while other smiles did not.

Tomarken et al. (1990) conducted a study to verify whether baseline FAA was predictive of emotional responses to films intended to elicit affect. FAA predicted self-reported negative affect congruous with the approach-withdrawal model. Sobotka et al. (1992) manipulated reward and punishment contingencies directly, with the intention to bring about approach and withdrawal-related states. In line with the original notions, reward trials were associated with greater relative left-hemispheric anterior activation, compared with trials during which punishment occurred. In contrast, punishment trials were associated with greater relative right-hemispheric anterior activation.

In another study, Tomarken et al. (1992a) conducted assessments of resting EEG separated by two weeks, in female adults. Participants who displayed extreme relative left-hemispheric anterior cortical activation also reported increased generalized positive affect and decreased negative affect. Similarly, Wheeler et al. (1993) conducted a study in which resting EEG was recorded on two occasions, separated by three weeks. After the second assessment, participants were confronted with film-clips intended to evoke positive and negative affect. In case of subjects who displayed stable FAA across assessments, stronger left-hemispheric anterior activation predicted more intense self-reported positive affect in response to positive films. In contrast, greater right-hemispheric anterior activation at the second assessment predicted stronger negative self-reported affect in response to negative film clips.

Tomarken & Davidson (1994) intended to verify whether FAA could predict differences in repressive defensive coping styles. A repressive coping style had previously been related to a lowered risk for psychopathology (Lane et al., 1990). Those participants who were identified to be repressors displayed FAA indicative of stronger relative left-hemispheric anterior activation, compared to non-repressors.

Jackson et al. (2003) intended to examine the association between FAA and emotion regulation. Participants were confronted with affective and neutral visual stimuli, while eye blink startle data were collected. In addition, startle probes were given after the presentation

of a picture, in order to assess persistence and attenuation of affect following an emotional stimulus. Results revealed that participants who displayed greater relative left-hemispheric anterior activation also showed attenuated startle magnitude after the offset of negative stimuli. The authors interpret their results as supportive for the existence of a mechanism of emotion regulation, which might be mediated by anterior brain structures, especially the left hemisphere.

In sum, despite the use of varying methods, such as different reference schemes during EEG assessments and varying operationalizations of affective style, the cited studies provide a relatively homogenous picture in support of the original notions of the approach-withdrawal model, affective style, and FAA, albeit some attempts of replication failed (Hagemann et al., 1998). Across these studies, different operationalizations of affective style were related to FAA in a way consistent with the original theory. Nevertheless, additional findings lead to a review and adaptation of the original model. Such findings stem from studies which sought to provide converging evidence by combining the approach-withdrawal model with similar constructs.

Sutton & Davidson (1997) assessed FAA on two occasions in college students. In addition, tendencies of behavioral inhibition and activation were assessed. The latter were conceptualized in the context of a model devised by Gray (1994), according to which two broad hypothetical systems determine learning and affect. These two systems have been referred to as the “behavioral activation system” (BAS) and the “behavioral inhibition system” (BIS). The BAS is supposed to be responsible for guiding behavior in response to incentives. The BIS is responsible for guiding behavior in response to threats and novel stimuli. Carver & White (1994) devised a self-report measure to assess individual differences in the strength of the BIS and the BAS. The BAS scale assesses tendencies to experience intense positive affect or behavioral activation, when certain goal-oriented situations are encountered. The BIS scale on the other hand assesses the tendency to experience negative

affect or behavioral inhibition when an individual encounters threats. In the study conducted by Sutton & Davidson (1997), subjects with greater relative left-hemispheric anterior activation reported higher levels of BAS. In contrast, individuals who displayed greater right-hemispheric anterior activation showed higher levels of BIS. While these findings may be interpreted as supporting original notions of the approach-withdrawal model, in subsequent studies, Harmon-Jones & Allen (1997), as well as Coan & Allen (2003) report that FAA predicted BAS, but not BIS scores. Consequently, the BIS may not be related to the withdrawal system. It has been suggested, that besides conceptual differences of the two models, such inconsistencies may be related to the fact that in early studies, motivational direction has been frequently confounded with affective valence (Harmon-Jones & Allen, 1998). Approach-motivation for example does not necessarily imply positive affect. Harmon-Jones & Allen (1998) claim, that dispositional anger represents an approach-related motivational tendency with negative valence. Results of the latter study showed that trait anger was associated with stronger relative left-hemispheric anterior activity. Later studies confirmed this association (Harmon-Jones, 2004a, 2004b). Hence, FAA appears to vary as a function of motivational direction, and not of valence.

The approach-withdrawal model and major depression

While a vast body of research has accumulated which focuses on assessments of affective style in predominantly healthy subjects as reported above, the approach-withdrawal model of hemispheric asymmetry was also tested in relation to MDD. Based on the original notions and the phenomenology of depressive symptoms, it has been suggested that major depression may be classified as a disorder which is characterized by withdrawal-related tendencies (Henriques & Davidson, 1991). Hence, according to the original model, which posits that stronger relative right-hemispheric anterior activity represents a diathesis for the development of depression, individuals with a history of depression and those currently depressed may display

such a pattern of FAA. Allen et al. (2009) have suggested that FAA may represent an endophenotype of depression, which might be independent from clinical status. Studies dealing with this matter can be sorted into several groups. Firstly, there are studies in which scores of self-reported depression are solely correlated with FAA values. In a second category there are studies in which groups are formed based on extremely high and low values on self-report measures of depression. Thirdly, there are studies in which groups of never, formerly or currently depressed participants are compared and in which diagnostic status is determined based on formal diagnostic criteria verified in interviews. Finally, few attempts have been made to use longitudinal designs to examine whether FAA may predict the development of depression.

Though within each methodological framework associations of depression and FAA have been found, several studies yielded inconsistent results (Thibodeau et al., 2006). A brief overview of results according to the described groups is outlined below.

To date, there are numerous reports in which associations between FAA and scores of self-report measures assessing depressive symptoms have been explored. Tomarken & Davidson (1994) report a study involving 90 females in which self-reported depression scores did not contribute any unique variance to FAA. In contrast Jacobs & Snyder (1996) report a significant relationship between self-reported depression and FAA in a sample of 40 males. Similarly Pauli et al. (1999) report an association of stronger relative right-hemispheric activity and elevated depression scores in a sample of eight participants. Diego et al. (2001) found stronger relative right-hemispheric anterior activity to be related to elevated depression scores in a sample of 163 women. The same relationship is reported in studies by Harmon-Jones et al. (2002), and Field et al. (2004b) which included 67 and 92 participants, respectively. In a study by Blackheart et al. (2006) on the other hand, which included 28 participants, depression scores predicted elevated right-hemispheric activity only in parietotemporal regions, but not in anterior ones.

Four studies involving adult participants have been conducted in which groups were created based on extremely high and low self-reported depression scores. The first of these was conducted by Schaffer et al. (1983) and included a sample of 15 individuals. Results indicated that the group of participants with high depression scores also displayed greater relative right-hemispheric anterior activity. Reid et al. (1998) compared a group of 17 participants with elevated depression scores to a group of 19 participants with low depression scores. No significant differences in FAA were obtained. Nitschke et al. (1999) found significantly greater right-hemispheric anterior activity in a group of 12 individuals with elevated depression scores, compared to 14 participants with low scores. Similarly, in a comparison of 160 females with depressive symptoms and 100 controls, Field et al. (2000) report stronger relative right-hemispheric activity for the former group. Field et al. (2004a) also report significantly greater relative right-hemispheric activity for a group of 70 pregnant women with depressive symptoms, compared to 70 controls.

In several studies, formal diagnostic interviews were used in the recruitment of participants. Henriques & Davidson (1990) conducted a study in which FAA between normothymic and never-depressed controls was compared. Subjects with a history of MDD had stronger relative right-hemispheric anterior activation than did never-depressed subjects. The small sample included six previously depressed subjects and eight controls. Results were regarded as supportive of a view according to which FAA reflects a diathesis, independent of clinical status. In another study, Henriques & Davidson (1991) also compared FAA of 15 currently depressed participants and 13 controls, and report that depressed subjects displayed stronger relative right-hemispheric activation than controls.

Allen et al. (1993) conducted a treatment study of individuals with seasonal affective disorder (SAD), involving a sample of four patients suffering from SAD and four controls. Results revealed that even though a relief of behavioral symptoms occurred following treatment through phototherapy, FAA in individuals with SAD differed from controls when

symptomatic and when in remission. Graae et al. (1996) compared a group of 16 currently depressed, suicidal females to 22 controls and found differences in FAA which conformed to the approach-withdrawal model. These differences however were not restricted to anterior regions, but generalized to posterior ones.

Bruder et al. (1997) compared measures of FAA of a group of 19 currently depressed patients with comorbid anxiety disorder and of a group of 25 depressed patients to those of 26 controls. Only the depressed group for which a comorbid anxiety disorder was given differed significantly from controls and displayed stronger relative right-hemispheric anterior activation.

In a frequently cited study, Gotlib et al. (1998) examined differences in FAA among 16 currently depressed, 31 previously depressed, and 30 never depressed participants. Results showed that currently and previously depressed subjects showed stronger relative right-hemispheric anterior activation compared to controls. In the same study, currently and previously depressed patients did not differ from each other in FAA. Results were interpreted as supporting FAA as a trait-marker of vulnerability for depression, independent from clinical status. Baehr et al. (1998) compared FAA of 13 depressed participants and 11 non-depressed participants and report stronger relative right-hemispheric anterior activity in depressed subjects. In contrast Reid et al. (1998) compared FAA of 13 depressed and 14 non-depressed participants and did not observe any significant difference. Debener et al. (2000) assessed FAA in 15 clinically depressed patients and in 22 healthy participants on separate occasions, which were two to four weeks apart. While in both sessions differences in FAA conformed to the original model, groups differed in temporal stability of FAA, which proved not to be retest-reliable in depressed subjects. The latter finding is not in line with the notion of stronger relative right-hemispheric anterior activity represent a trait marker of depression. Deslandes et al. (2008) conducted a study involving elderly participants. A group of 22

currently depressed participants was compared to 14 non-depressed participants. Results revealed that the two groups did not differ significantly in FAA.

Only few longitudinal studies have been conducted to verify directly whether FAA represents a diathesis for the development of depression. Possel et al. (2008) assessed FAA, self-reported anxiety, and symptoms of depression in a group of 80 never-depressed adolescents twice within 12 months. Results revealed that FAA at the initial assessment predicted depressive symptoms one year later. In line with the approach-withdrawal model, stronger relative right-hemispheric anterior activity was predictive of depressive symptoms. Blackheart et al. (2006) assessed depressive symptoms and symptoms of anxiety at a one-year follow-up, subsequent to an initial assessment of FAA. In contrast to results reported by Possel et al. (2008), FAA was not found to predict self-reported depression scores one year later.

In sum, findings on the relation of FAA and depression are more heterogeneous than findings on the relation of affective style and FAA. Several explanations for inconsistent results of studies dealing with FAA and depression have been provided. Firstly, the notion that stronger relative right-hemispheric cortical activity may represent a trait marker of the vulnerability to develop depression does not necessarily imply that all patients who actually develop depression also display stronger relative right-hemispheric anterior cortical activation. Certain trait-like characteristics in anterior activation may increase the vulnerability to develop depression, as they represent an indicator of an individual's affective style. However, this does not imply that all individuals suffering from depression are characterized by a withdrawal/avoidance-related affective style. As noted in section 1.2, according to Teasdale (1988), depressive symptomatology in response to drastic negative life events is a common phenomenon and may develop into an episode of MDD. This may also occur in individuals who are not characterized by stronger relative right-hemispheric anterior activation. As Davidson (1998) points out:

“With particular regard to prefrontal activation asymmetry, we view individual differences in this component of the circuitry as a contributory cause of affective style. As a contributory cause, such differences in prefrontal activation are neither necessary nor sufficient for the production of a specific type of affective style or psychopathology.”

Consequently, since FAA may represent a diathesis, but such a diathesis is not essential for the development of psychopathology, patients suffering from MDD may not always be characterized by stronger right-hemispheric anterior activation. While this argument may account for apparent inconsistent findings, Reid et al. (1998) argue for a necessity to identify putative factors mediating the relation between FAA and MDD, such as temperament, coping styles, and rumination. While this approach has provided few new insights (De Raedt et al., 2008), it does not rule out the fact that according to the approach-withdrawal model, extreme right-hemispheric anterior FAA is not specific for patients suffering from MDD.

3.2. Effects and Correlates of Mindfulness Practice: Attentional Capacity, Neurophysiology and Anatomy

In recent years, numerous studies have explored effects of meditation on attentional capacity, its neurophysiological and anatomical correlates, as well as meditation-related changes in peripheral physiological functioning (Davidson & Lutz, 2008; Luders et al., 2009; Rubia, 2009; Stein, Ives-Deliperi, & Thomas, 2008). A difficulty in interpreting the results of such studies is that the global term meditation refers to a heterogeneous cluster of various contemplative exercises, which frequently differ across studies (Lutz et al., 2008; Rubia, 2009). A relatively consistent finding seems to be the occurrence of a subjectively alert state during meditation, associated with decreased sympathetic activity (Rubia, 2009). This state also appears to differ from normal resting conditions and sleep (Jevning, Wallace, & Beidebach, 1992; Young & Taylor, 1998). Trait effects of meditation practice have been

suggested to include increased attentional performance (MacLean et al., 2010; Slagter et al., 2007), reflected in characteristic changes in event-related potentials in EEG studies (Cahn & Polich, 2006). Repeatedly reported effects also include characteristic functional and anatomical brain changes (Brefczynski-Lewis et al., 2007; Lazar et al., 2005). In light of the emphasis of the present work on mindfulness meditation in clinical practice, below, predominantly the results of studies involving structured, secular trainings based on mindfulness meditation will be reported.

Mindfulness practice and attentional capacity

Jha et al. (2007) conducted a study to assess how mindfulness practice may affect different aspects of attention. The authors tested three different subsystems of attention through behavioral performance, conceptualized as systems of alerting, orienting and conflict monitoring (Posner & Petersen, 1990). Assessments occurred through the “attentional network test” (ANT; Fan et al., 2002), devised to tap the functioning of the indicated systems. The alerting system has been described as being activated during abrupt changes in sensory stimuli and the detection of salient targets. Alerting consists of achieving and maintaining a vigilant or alert state of preparedness. The orienting system is engaged in case of the voluntary direction of attention, in particular during the presentation of cues indicating features relevant for a response. It is responsible for the direction and limiting of attention to a subset of possible inputs. Finally, the system of conflict monitoring is relevant for prioritizing among competing tasks and responses. Jha et al. (2007) report that participants naïve to meditation upon recruitment displayed significantly improved functioning of the orienting system after an eight-week course of MBSR, relative to control participants who did not practice meditation. The authors conclude that mindfulness training in the context of MBSR may improve attention-related behavioral responses by enhancing specific subcomponents of attention.

Similarly, Tang et al. (2007) utilized the ANT to assess effects of a five-day course involving mindfulness meditation in Chinese undergraduate students. Results revealed that the ANT performance of students who received training improved significantly more than that of students who received relaxation training and than that of controls who did not receive any training. In particular, the function of conflict monitoring was significantly improved. The authors conclude that short-term meditation practice involving mindfulness training may yield a higher efficiency of executive function.

Jha et al. (2010) assessed the effects of an eight-week mindfulness course on functioning of working memory capacity. Working memory capacity is closely related to attention (Jha, 2002) and represents the capacity to selectively maintain and manipulate goal-relevant information without getting distracted by irrelevant information over short intervals. Two military groups were assessed during a high-stress predeployment period, one of which underwent mindfulness training. Working memory capacity was assessed with the Operation Span task (Ospan; Unsworth et al., 2005) which involves remembering stimuli such as letters across short time periods while engaging in distracting tasks. Ospan performance has been shown to be highly correlated with the performance on other attentional tasks (Redick & Engle, 2006). In the study by Jha et al. (2010), working memory capacity degraded in the group which did not receive mindfulness training over the eight-week period. Similarly, in the group which received mindfulness training, decreased working memory capacity was observed. In the latter group however, those participants who reported a high practice time showed increased working memory capacity. The authors conclude that mindfulness training may counteract deteriorating cognitive performance during intervals characterized by high stress. In sum, the cited studies indicate that structured trainings focusing on mindfulness may lead to improved executive functions, such as different aspects of attention and working memory.

Anatomical brain changes and mindfulness practice

Several studies examining the effect of mindfulness practice on cortical structure have been conducted. These studies have shown that especially long-term meditation practice may be associated with anatomical alterations. Lazar et al. (2005) for example report that long-term meditation practitioners displayed increased cortical thickness in the anterior insula and sensory cortex, as well as prefrontal regions. Similar results were reported in other studies (Holzel et al., 2008; Luders et al., 2009; Pagnoni & Cekic, 2007). Holzel et al. (2010) also report changes in brain structure possibly related to the participation in an MBSR course. Participation was associated with a decrease in self-reported stress. This decrease predicted decreased gray matter density in the right amygdala. Based on a model which has suggested that the right amygdala may mediate a quick, initial and possibly automatic detection of stimuli, and the left amygdala a more discriminative subsequent one (Morris, Ohman, & Dolan, 1998; Wright et al., 2001), the authors speculate that MBSR might impact the participants' initial reaction to stimuli.

Functional brain changes related to mindfulness practice

Several studies have examined functional brain changes associated with mindfulness-based interventions (e.g. Farb et al., 2007). Of particular interest for the present research are two studies which have explored the effect of MBSR and MBCT on FAA. Davidson et al. (2003) assessed effects of MBSR on FAA in a sample of 25 healthy participants. Pre and post-treatment assessments of resting EEG were conducted under three different mood conditions, neutral, positive and negative. Mood states were induced by having participants write about positive and negative events. The authors report that participants showed a significant pre/post increase in relative left-hemispheric cortical activation obtained for the central electrodes (C3/C4) during baseline assessments and negative mood, and for anterior temporal electrodes (T3/4) during positive mood, relative to a wait-list control group of 16 participants. The

authors claim these results to be the first to show up effects of mindfulness training on FAA. Hence FAA might be regarded as plastic and may be shaped by training. In the same study, a significant increase in antibody titers to influenza vaccine was also found in the treatment group relative to controls. Increased left-hemispheric activation predicted the magnitude of antibody titer-rise to vaccine. The authors however have been criticized for their suggestion of significant effects of meditation on FAA, since effects were actually only observed for central and anterior temporal sites (Travis & Arenander, 2004).

In another study, Barnhofer et al. (2007) explored effects of MBCT on FAA in a sample of individuals with a history of depression characterized by suicidal ideation. Ten participants were treated through MBCT, while 12 were assigned to a TAU condition. Results revealed that the TAU group showed a significant decrease in relative left-hemispheric anterior activation. In contrast, participants who received MBCT did not show any alteration. The authors conclude that MBCT may have helped participants in maintaining a balanced affective style. In light of the small sample size, results of the latter study need to be regarded with caution.

Despite their limitations, it is important to note that both studies indicate, that functional asymmetry assessed in resting EEG in healthy participants and in patients with a history of depression may not be stable, but plastic. In case of the patients involved in the study by Barnhofer et al. (2007), the estimated relapse risk was 90% (American Psychiatric Association, 2000a). One may assume that mindfulness training had a prophylactic effect which was reflected in stable FAA, since in contrast, patients of the TAU group displayed a spontaneous deterioration in FAA. It should be noted however, that few studies have obtained support for retest-stability of FAA in patients currently suffering from or with a history of MDD. Allen et al. (2004) report that patients who were depressed at initial assessments did not show altered FAA on follow-up measures, albeit their clinical status improved through treatment. Also Vuga et al. (2006) report FAA to be relatively stable, even though in the latter

study, clinical status of the participants was not thoroughly assessed. The question whether FAA is stable or may be plastic in recurrently depressed patients therefore requires further exploration.

4. Summary and Aim of the Current Research

Regarding the discussed aspects of MDD, one may sum up that MDD is a very common, highly recurrent disorder, which is dynamic in nature (Andrade et al., 2003; Keller, 2003). Its dynamic and recurrence is particularly related to sensitization processes which occur across episodes, as well as maladaptive behavior patterns such as rumination (Nolen-Hoeksema et al., 2008; Segal et al., 1996). Some patients suffering from MDD may also be characterized by the physiological conspicuity of greater relative right-hemispheric anterior cortical activation in resting EEG, an indicator of a withdrawal/avoidance-related affective style, possibly predisposing for the development of further episodes (Davidson, 2001; Possel et al., 2008). Even though FAA has been claimed to be relatively stable in patients and healthy subjects (Allen et al., 2004b), in patients who are at an extremely high risk for depressive relapse, they may not be stable, but deteriorate, if no counteractive intervention is applied (Barnhofer et al., 2007). Recent developments in clinical psychology have brought forward MBCT, a meditation-based, highly economic form of maintenance therapy, effective in preventing depressive relapse (Segal et al., 2002). Mindfulness training has been shown to yield increased self-reported dispositional mindfulness, and decreased ruminative tendencies (Deyo et al., 2009; Ramel et al., 2004). MBCT may also represent a counteractive intervention, which may be effective in stabilizing FAA in previously depressed patients and in yielding approach-related FAA in healthy subjects (Barnhofer et al., 2007; Davidson et al., 2003).

The aim of the present work was to further explore the plasticity of FAA in patients with an extremely high risk for depressive relapse. Firstly, an attempt was made to replicate findings reported by Barnhofer et al. (2007), according to which FAA may deteriorate in the absence of a counteractive intervention, and is stabilized by MBCT in high-risk patients. In the latter study, measurements of resting EEG occurred solely under a neutral condition. In

contrast, the study by Davidson et al. (2003), which involved healthy participants, also included assessments following the induction of a negative mood and revealed effects of mindfulness training for such a condition from pre to post-treatment assessments. Measuring FAA under different conditions may be informative as to whether treatment effects are also given under aversive circumstances. Hence, a second purpose of the current research was to explore whether treatment effects of MBCT on FAA in recurrently depressed patients would also be observed under aversive conditions. In light of the accounts of depressive relapse, outlined in section 1.3, assessments of resting EEG under negative mood and during a simulation of ruminative thought patterns seem most relevant. In addition, assumed effects were explored during a mindfulness exercise. Following results reported by Barnhofer et al. (2007) and Davidson et al. (2003), pre/post-treatment assessments should at least indicate stability of FAA for all conditions, and might reveal an improvement to stronger relative left-hemispheric anterior activation. For wait-list control groups on the other hand, a spontaneous deterioration, indicated by increased relative right-hemispheric anterior activity, may be expected. Finally, a third purpose was to explore how previously reported changes in self-reported dispositions of mindfulness and rumination brought about by mindfulness training relate to alterations in FAA.

5. Study 1: Effects of MBCT on Functional Anterior Brain Asymmetry during negative Affect and Rumination Challenge

5.1. Hypotheses

In the current study, several assessments of resting EEG, self-reported depression, mindfulness, and rumination were conducted in 42 remitted patients with a history of at least three MDE, prior to and after their participation in an MBCT course. EEG measurements were conducted under several conditions at each measurement point, namely, a neutral condition, following a sad mood induction, and following the simulation of ruminative thought patterns. Participants were randomly distributed between two groups. Both groups received treatment through MBCT at some point during the course of the research project. 22 participants were assigned to a group which did not receive treatment for eight weeks. After the waiting interval, these participants received treatment through MBCT. EEG measures occurred before (Time 1) and after the two-months wait period (Time 2), and again two months later, immediately after the completion of an MBCT course (Time 3). This group will heretofore be referred to as the waiting group (WG). The other 20 participants received treatment immediately upon admission to the study, without a waiting interval. In their case, EEGs were assessed before (Time 1), immediately after the completion of the MBCT course (Time 2), and again two months later (Time 3). This group will heretofore be designated the immediate treatment group (ITG).

Based on previous findings by Barnhofer et al. (2007), it was hypothesized that due to their extremely high risk for relapse (90%; American Psychiatric Association, 2000a), participants of the WG group would show a characteristic change of FAA over time, indicating increased relative right-hemispheric anterior activity, from the Time 1 to the Time 2 assessment. In contrast, due to the known prophylactic effect of MBCT, it was hypothesized that subjects in the ITG would display increased relative left-hemispheric anterior cortical

activity, or retain a stable asymmetry pattern from the Time 1 to the Time 2 assessment. Since MBCT teaches techniques to counteract ruminative tendencies when facing negative mood, it was also assumed that members of the ITG would show increased relative left-hemispheric activity or retain a stable asymmetry pattern following artificially induced negative mood and rumination. In contrast, for the WG group increased relative right-hemispheric anterior activity was expected for both of these conditions.

It was also assumed that the ITG would display an increase in mindfulness, and a decrease in rumination and depressive symptoms, and that an increase in symptoms of depression, and a decrease in mindfulness would occur in the WG from Time 1 to Time 2 assessments. Increased symptoms of depression in the latter group were expected due to the high-relapse risk of the sample, which may be associated with a spontaneous deterioration of clinical symptoms. Since symptoms of depression frequently include a diminished ability to concentrate (American Psychiatric Association, 2000a) and since attentional capacity is a central element of mindfulness (Bishop et al., 2004), a deterioration in mindfulness was expected as well. In case of rumination, no significant alteration was expected, since rumination has been described as relatively independent from clinical status (Nolen-Hoeksema et al., 2008).

MBCT has been shown to have relatively enduring protective effects. Hence, stability or a mild deterioration of FAA toward stronger relative right-hemispheric anterior activity was expected for the ITG during the two-month follow-up period between Time 2 and Time 3 assessments. In contrast, for the WG, which received treatment through MBCT during the same time, a counteractive effect of MBCT was expected, resulting in increased relative left-hemispheric activation.

It was further expected that between the Time 2 and Time 3 assessments, there would be relative stability of self-reported mindfulness, rumination, and depressive symptoms in the ITG, or possibly a mild deterioration in the latter measures. In contrast for the WG, effects of

MBCT were expected to manifest in increased self-reported mindfulness, and decreased ruminative tendencies, as well as decreased depression scores.

Finally, in an exploratory analysis, the relation between an assumed alteration in FAA and self-report measures was examined. In this context, following the conceptualization of mindfulness as described in section 2.2., mindfulness was regarded as approach-related (Bishop et al., 2004). In contrast, following previous suggestions, rumination was hypothesized to represent a withdrawal/avoidance related behavior (Reid et al., 1998). Consequently, a putative increase in asymmetry scores, which represents stronger relative left-hemispheric anterior cortical activation, was hypothesized to be associated with increased mindfulness, and decreased ruminative tendencies and depression scores. An overview of the hypotheses is given in Table 1.

Table 1. List of hypotheses of Study 1

ITG, immediate treatment group. WG, waiting group. LHA, relative left-hemispheric anterior. RHA, relative right-hemispheric anterior. ↑, increase. ↓, decrease. --, stability. Note: For EEG measures, the same pattern is expected to generalize to all conditions, i.e. assessments during the neutral condition, following the negative mood induction and rumination.

<i>Hypothesis</i>	<i>Assessment</i>	<i>Group</i>	<i>Expected Observation</i>
1	Time 1 - Time 2	WG	↑ RHA activity
2	Time 1 - Time 2	ITG	↑ LHA activity / -- asymmetry pattern
3	Time 1 - Time 2	WG	↓ mindfulness, -- rumination, ↑ depression
4	Time 1 - Time 2	ITG	↑ mindfulness, ↓ rumination, ↓ depression
5	Time 2 - Time 3	WG	↑ LHA activity
6	Time 2 - Time 3	ITG	-- / mild ↑ RHA activity
7	Time 2 - Time 3	WG	↑ mindfulness, ↓ rumination, ↓ depression
8	Time 2 - Time 3	ITG	-- / mild ↓ mindfulness, -- / mild ↑ rumination, -- / mild ↑ depression
9	Time 1 - Time 2	ITG, WG	LHA activity predicts ↑ mindfulness, ↓ rumination, ↓ depression
10	Time 2 - Time 3	ITG, WG	LHA activity predicts ↑ mindfulness, ↓ rumination, ↓ depression

5.2. Methods

Participants

Participants were recruited during a period of three months prior to the start of the first intervention via newspaper articles. 70 potential participants who reported past depression but who did not feel depressed at the moment took part in the German version of the Structured Clinical Interview for DSM-IV (Wittchen, Zaudig, & Fydrich, 1997), conducted by a trained clinical psychologist. In order to take part in the study, participants had to be between 18 and 65 years of age, right-handed, meet criteria for at least three MDE and be in at least partial remission. Remission was defined as not meeting the minimum criteria for a MDE within the last four weeks. Exclusion criteria involved not giving or withdrawing informed consent, presence or history of substance abuse, eating or obsessive-compulsive disorder during the last three years, a history of schizophrenia or schizoaffective disorder, any neurological disorder, and borderline personality disorder. Participants also were not included if they had ever practiced any form of meditation on a regular basis.

Participants who were not medicated needed to have stopped using medication at least four weeks prior to the interview and had to agree not to start medication during the course of therapy until the last EEG assessment, unless advised otherwise by a psychiatrist. If participants were medicated, medication had to be stable for at least one month, and participants needed to agree not to change medication or dose during the course of therapy until the completion of the last EEG, unless dose or type was recommended to be changed by a psychiatrist.

In sum, 42 participants were randomly distributed between the ITG and the WG, as indicated in section 5.1. Random assignment involved sending patient initials to an uninvolved researcher at the institute of psychology of the University of Tübingen, Germany, who allocated the subjects following a block randomization and using a random number sequence (Sachs, 1988). Staff conducting the clinical interview and the initial EEG

assessments was blinded to group assignment. When relevant for the analysis, data of patients were only included if they attended at least four sessions of the course, which was the case for all participants. The sample size was determined on the basis of previous studies, which have shown treatment effects of mindfulness-based interventions on functional brain asymmetries to be detectable for group sizes of between twelve and twenty-five participants (Barnhofer et al., 2007; Davidson et al., 2003). The minimum amount of fifteen participants was set for each group. It was not expected that the loss of data due to artifacts and dropouts would exceed 25% and consequently it was decided to recruit at least 40 participants. Since the current study is not a clinical efficacy study, but focuses on psychophysiological effects of MBCT, the sample size may be regarded as appropriate.

Data of participants who showed sufficient quality of EEG data (ITG: $n = 19$, 4 male; WG: $n = 20$, 4 male) did not differ significantly in age (ITG: $M = 51.63$, $SD = 9.88$; WG: $M = 50.95$, $SD = 9.61$, $t[37] = -0.22$), levels of depressive symptoms as measured by BDI (ITG: $M = 12.58$, $SD = 9.36$; WG: $M = 15.05$, $SD = 10.28$, $t[37] = 0.19$), tendencies of symptom-focused (ITG: $M = 20.95$, $SD = 4.06$; WG: $M = 19.35$, $SD = 5.01$, $t[37] = 0.78$) or self-focused rumination (ITG: $M = 16.79$, $SD = 3.41$; WG: $M = 14.45$, $SD = 4.42$, $t[37] = -1.84$) as assessed by RSQ, or mindfulness as assessed by FFA (ITG: $M = 31.95$, $SD = 5.27$; WG: $M = 31.20$, $SD = 4.99$; $t[37] = -0.45$) at Time 1 assessments (all $ps > .05$).

Groups were also comparable regarding the age of onset of the first MDE (ITG: $M = 25.8$, $SD = 8.5$; WG: $M = 27.9$, $SD = 8.5$, $t[37] = 0.76$), proportions of participants currently using anti-depressant medication (ITG: yes 8/no 11; WG: yes 11/no 9, $\chi^2 [1,39] = 0.65$), and the number of experienced MDE (ITG: $Mdn = 4$, range = 3-9; WG: $Mdn = 4$, range = 3-20, $U = 162.5$, all $ps > .05$). In the ITG, seven participants dropped out of the study after the Time 2 assessment and were lost for the follow-up measure at Time 3. During the respective treatment periods, participants attended one group session of MBCT per week. In total, four courses were given by a therapist with extensive experience in treatment via MBCT and

MBSR, which followed the original protocol (Segal et al., 2002). Participants of the ITG and the WG were distributed between two courses, respectively. All participants were advised to consult their medical doctor or other sources of help, if they felt they needed to, hence to seek medical treatment as they usually would. The study was approved by the ethics committee of the faculty of medicine, University of Tübingen.

Self-report measures

Questionnaires administered before and after treatment included German versions of the Beck Depression Inventory (BDI-II; Hautzinger, Keller, & Kühner, 2007), a self-description questionnaire which measures the severity of depression symptoms during the last two weeks, the Response Styles Questionnaire (RSQ-D; Kühner, Huffziger, & Nolen-Hoeksema, 2007), a self-report measure of trait rumination and the tendency to distract oneself when confronted with negative mood, and the Freiburger Fragebogen zur Achtsamkeit (FFA; Walach et al., 2003), a self-report measure of trait mindfulness.

The RSQ-D consists of three subscales, symptom-focused rumination, self-focused rumination and distraction tendencies. In the current research, only data obtained with the first two of these subscales was evaluated, since mindfulness training, thought to decrease rumination, also implies that patients try to accept negative emotions without engaging in distractive activities. As such, distraction tendencies might not fit the treatment model of mindfulness-based interventions. During each experimental session subjects also received the state version of the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996), a measure of positive and negative affect.

Procedure

At each assessment, the self-report measures BDI, RSQ-D and FFA were completed. Subsequently, brain electrical activity (EEG), and electrooculogram (EOG) was recorded

during three resting conditions in the following order: neutral (baseline condition), following the induction of a sad mood (sad mood induction) and following a rumination simulation during which subjects had to ignore ruminative statements played over loudspeakers (rumination challenge). Each measurement consisted of eight one-minute resting trials, four with eyes open and four with eyes closed, presented in counterbalanced order (COCOOCOC). After the completion of the first half of each condition, subjects received the PANAS. The negative mood induction was a combination of established mood-induction procedures by Clark & Teasdale (1985) and Broderick (2005). Subjects listened to a piece of music, known to bring about transient dysphoric states for eight minutes (Martin, 1990), and were instructed to recall a time of their life during which they felt sad. Intermixed with the music were 20 negative self-referential statements, with progressively increasing depressing content, spoken by a male-voice. Subjects also received a booklet which contained the same statements and were instructed to read along with what they heard (one statement per page, 15 seconds each). Following the measurement periods after the sad mood induction, subjects listened to four additional statements, intended as a reactivation of the sad mood, which was assumed to have weakened during the measurements. After the four statements, subjects listened to mood incubation instructions, which have been demonstrated to enhance the effects of standard mood induction procedures (Zoellner, Sacks, & Foa, 2003), for three minutes.

Prior to the rumination simulation, which lasted for 20 minutes, subjects were instructed to focus on their breath and physical sensations associated with it for five minutes. The rumination simulation was based on a procedure adapted from Lyubomirski & Nolen-Hoeksema (1995) which has been successfully used in German subjects (Kuehner, Holzhauser, & Huffziger, 2007) before. Subjects were informed that they would hear some irritating statements, which would try to distract them from their breath. The task was to ignore the statements and keep attention focused on the breath. The average length of the 25 statements was 8.5 seconds. Each statement was followed by three 1.5-second bursts of white noise,

related to a different research question, which is to be reported elsewhere. In total, each assessment session lasted for approximately 70 minutes.

Electrophysiological recording

EEG was recorded from 28 sites using a 32-channel system with active Ag/AgCl electrodes (ActiCap; Brain Products, Gilching, Germany). The sites included Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, Cz, C3, C4, T7, T8, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, Oz, A1 and A2. During recording, all sites were referenced to the nose. For data analyses, it was re-referenced off-line to an average mastoid (A1/A2) reference. Four electrodes at supra and infraorbital sites surrounding the left eye and at the outer canthi of each eye were used to monitor blinks and eye movements. Impedances were kept below 7 k Ω for the EEG and below 10 k Ω for the EOG electrodes during the whole recording. EEG was amplified with a BrainAmp Standard (Brain Products, Gilching, Germany; bandpass = 0.05 and 40 Hz, 50 Hz notch filter in) with 16 bit A/D conversion, a resolution of 0.1 μ V, and digitized at a rate of 200 Hz.

Electrophysiological analysis

EEG and EOG signals were semi-automatically scored and portions of data containing blinks were deleted using a rejection criterion of $\pm 75\mu$ V. When artifact was identified on a given channel, data from all channels were removed. Analysis followed standard procedures (Allen, Coan, & Nazarian, 2004a). Each 1-minute segment was divided into epochs of 1.28 seconds (50% overlap). Artifact-free epochs were extracted through a Hamming window which tapered data at the distal 10% of each epoch to avoid spurious elements of spectral power, and subjected to a fast Fourier transform to derive measures of spectral power density (μ V²/Hz) in 0.5Hz bins. Spectra were averaged over all artifact-free epochs of a 1-minute trial. Power density in the alpha band (8-13Hz) was computed by averaging power density values across

all the half-Hz bins within the alpha band. A natural log transformation was used to normalize the values of a given trial. Weighted means were computed separately for eyes-open and eyes-closed baselines for each participant. Weighting occurred based on the number of artifact-free chunks within each baseline. The average of the eyes-open and eyes-closed baselines was computed to generate a composite measure of EEG power density. Finally, asymmetry scores were computed for two different sites (two electrode pairs), fronto-polar (Fp1/Fp2) and frontal (F3/F4), by subtracting power density in the left from power values in the right hemisphere site. Because the present report focuses on frontal EEG asymmetry, data from non-frontal leads are not reported. When a participant had fewer than ten artifact-free chunks for a given baseline, that baseline was not included in the computation. In line with Tomarken et al. (1992b), subject-selection criteria were applied and subjects were rejected from the analysis, if there were less than 15 artifact-free chunks across the eyes-open or the eyes-closed trials of a condition. The application of this criterion resulted in the rejection of data of one member of the ITG and of two members of the WG. At Time 1, Time 2 and Time 3 assessments, there was no difference in the average number of segments per participant across groups for any condition (all $ps > .05$).

Statistical analysis

Due to the fact that in the ITG seven patients were lost for the Time 3 assessment, two separate statistical analyses were conducted. The first one focused on effects between the Time 1 and Time 2 assessment, and included a sample size of 19 (4 male) participants in the ITG and 20 (4 male) participants in the WG. In the second analysis, assessments from all three measurement points were considered. The latter analysis included a sample of 12 (4, male) participants in the ITG and 20 participants in the WG.

Analysis 1

The analysis focused on interactions between Group (ITG versus WG) and Time (Time 1 versus Time 2). Multivariate repeated-measures analysis of variance (MANOVAs) were computed for the two electrode pairs for each condition, and main effects and interactions were examined. Follow-up univariate analyses of variance (ANOVAs) were conducted separately for each electrode pair. For the data obtained through self-report measures, ANOVAs were computed with the factors Time and Group. To evaluate effects of the mood induction and rumination challenge on state affect, ANOVAs with the factor Mood (neutral, negative) and Rumination (neutral, rumination) were conducted. Greenhouse-Geisser corrected degrees of freedom were used for the evaluation of F ratios when homogeneity of variance was not given. In an exploratory data analyses boxplots were used to ensure that data did not contain any outliers.

Analysis 2

This analysis was congruent with the first analysis, with the only difference that the factor Time included three levels (Time 1 vs. Time 2 vs. Time 3).

5.3. Results

Self-report measures

Analysis 1

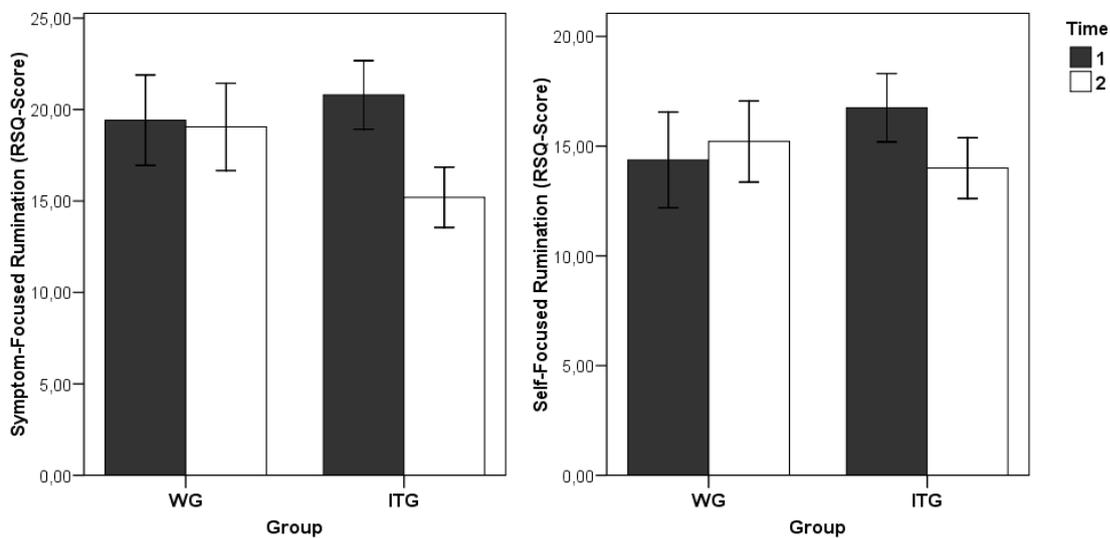
An evaluation occurred of self-report measures of rumination, mindfulness and depression at Time 1 and Time 2, and of self-report measures of positive and negative emotional states across conditions, at the same measurement points.

There was a significant main effect of Time on symptom-focused rumination ($F[1,37] = 21.36, p < .001, \text{partial } \eta^2 = 0.37$), and on mindfulness ($F[1,37] = 6.82, p < .05, \text{partial } \eta^2 = 0.16$). The main effect on symptom-focused rumination was accompanied by a significant

Time by Group interaction ($F[1,37] = 15.06, p < .001, \text{partial } \eta^2 = 0.29$; Fig. 2). The Time by Group interaction was also significant for self-focused rumination (Time: $F[1,37] = 9.20, p < .01, \text{partial } \eta^2 = 0.20$; Fig. 2), and marginally significant for depression (Time: $F[1,37] = 3.26, p = .08, \text{partial } \eta^2 = 0.08$).

Fig. 2. Mean scores of rumination

Mean scores of the subscales of symptom-focused and self-focused rumination of the Response Styles Questionnaire displayed separately by group and time. Error bars reflect 95% confidence intervals. ITG, immediate treatment group. WG, waiting group. RSQ, response styles questionnaire.



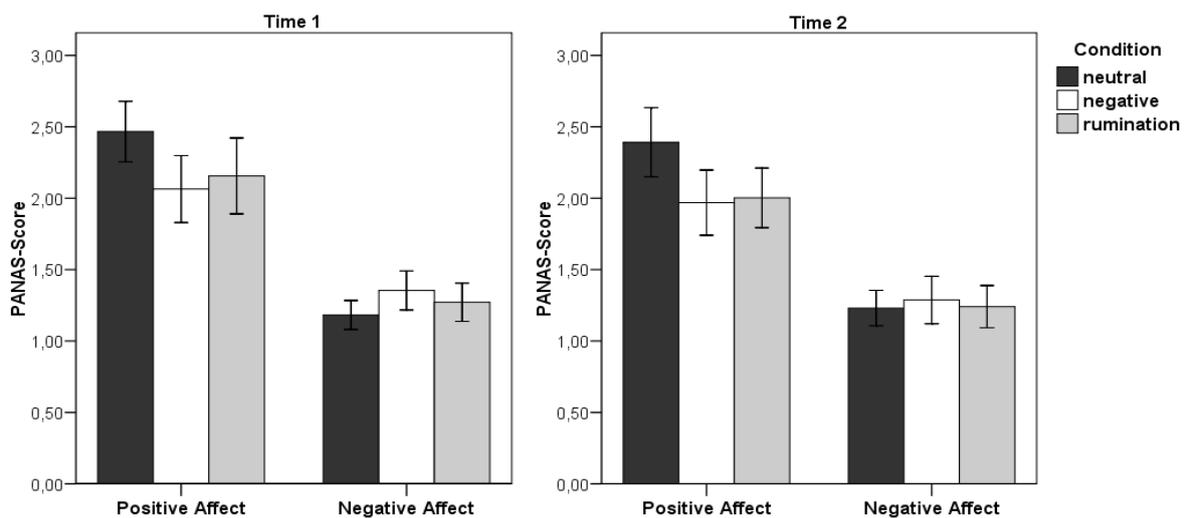
To examine the interaction effects, Bonferroni-corrected simple comparisons were computed. Since the possibility for four simple comparisons was given, results with a p -value below 0.025 were considered significant. The comparisons revealed a significant decrease in rumination scores from Time 1 to Time 2 in the ITG (symptom-focused rumination: $M_{I-J} = 5.74, SE = 0.92, p < .001$; self-focused rumination: $M_{I-J} = 3.00, SE = 0.83, p < .01$), whereas there was no significant change in the WG (symptom-focused rumination: $M_{I-J} = 0.50, SE = 0.99$; self-focused rumination: $M_{I-J} = -0.90, SE = 0.97, \text{all } ps > .05$).

As indicated, there were no significant Time by Group interactions for mindfulness and depression. However, based on our strong prediction for the ITG to display increased mindfulness after the training, and the observed marginally significant interaction for depression scores, changes for each group were evaluated for the respective measures. Simple comparisons showed that there was an increase in mindfulness in the ITG ($M_{I-J} = -4.74$, $SE = 1.76$, $p = .015$), with a similar change in the WG, which did not reach significance ($M_{I-J} = -0.80$, $SE = 1.22$, $p > .05$). There also was a significant decrease in depression scores in the ITG ($M_{I-J} = 7.16$, $SE = 2.26$, $p < .01$) while a similar change in the WG was not significant ($M_{I-J} = 4.50$, $SE = 2.29$, $p > .05$).

A graphic illustration of the effects of the negative mood induction and rumination challenge on positive and negative state affect is presented in figure 3. When comparing effects of the mood induction and rumination challenge to baseline, at Time 1 assessments, there was a highly significant main effect of Mood ($F[1,37] = 29.92$, $p < .001$, partial $\eta^2 = 0.45$) and a significant main effect of Rumination ($F[1,37] = 6.62$, $p < .05$, partial $\eta^2 = 0.15$) on positive emotional state, indicating a less positive emotionality in the negative mood and rumination conditions than in the neutral conditions. There also was a significant main effect of Mood ($F[1,37] = 13.53$, $p < .01$, partial $\eta^2 = 0.27$) on a measure of negative emotional state, which resulted from higher negative emotionality in the negative condition than in the neutral condition. The same effect of Mood ($F[1,37] = 19.03$, $p < .001$, partial $\eta^2 = 0.34$) and Rumination ($F[1,37] = 13.43$, $p < .01$, partial $\eta^2 = 0.27$) on positive emotionality was also found at Time 2.

Fig. 3. Mean scores of positive and negative affect

Mean scores of the subscales of positive and negative affect of the Positive and Negative Affect Schedule displayed separately by condition and time. Error bars reflect 95% confidence intervals. PANAS, Positive and Negative Affect Schedule.



Analysis 2

In analysis 2, an evaluation occurred of self-report measures of rumination, mindfulness and depression at Time 1, Time 2 and Time 3, as well as of self-report measures of positive and negative emotional states across conditions at the respective measurement points.

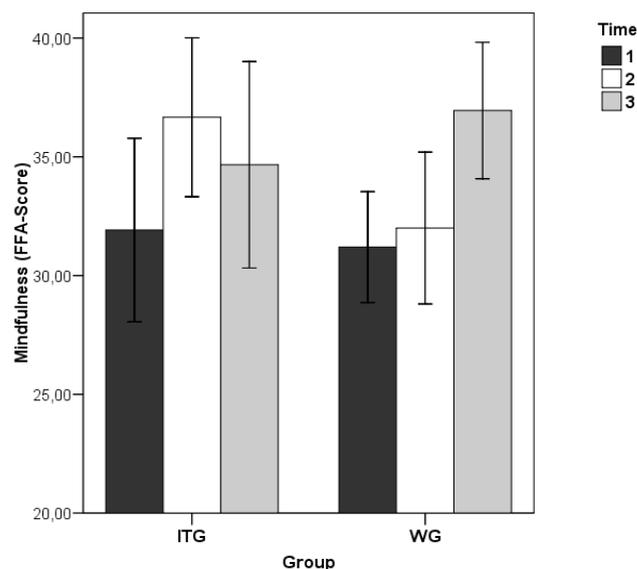
There was a significant main effect of Time on symptom-focused rumination ($F[2,58] = 6.51, p < .01, \text{partial } \eta^2 = 0.18$) and on mindfulness ($F[2,58] = 4.16, p < .05, \text{partial } \eta^2 = 0.13$). The former was qualified by a significant linear trend ($F[1,29] = 9.25, p < .01, \text{partial } \eta^2 = 0.24$). There were no significant Time by Group interactions, albeit the interaction for mindfulness was marginally significant ($F[2,58] = 2.88, p = .06, \text{partial } \eta^2 = 0.09$; Fig. 4). To evaluate the latter effect in detail, Bonferroni-corrected simple comparisons were computed. Since in this case four simple comparisons were performed following the time course of measurement points, results with a p -value below 0.0125 were considered significant. The comparisons revealed that the effect was characterized by a marginally significant increase in

mindfulness in the ITG from Time 1 to Time 2 ($M_{I-J} = -4.80$, $SE = 1.67$, $p = .016$), and a subsequent non-significant decrease ($M_{I-J} = 2.00$, $SE = 2.39$, $p > .05$) from Time 2 to Time 3. In addition there was a non-significant increase from Time 1 to Time 2 in the WG as indicated in Analysis 1, and a subsequent marginally significant increase from Time 2 to Time 3 in the same group ($M_{I-J} = -4.95$, $SE = 2.04$, $p = .026$).

Fig. 4. Mean scores of mindfulness

Mean scores of mindfulness displayed separately by group and time. Error bars reflect 95% confidence intervals.

ITG, immediate treatment group. WG, waiting group. FFA, Freiburger Fragebogen zur Achtsamkeit.

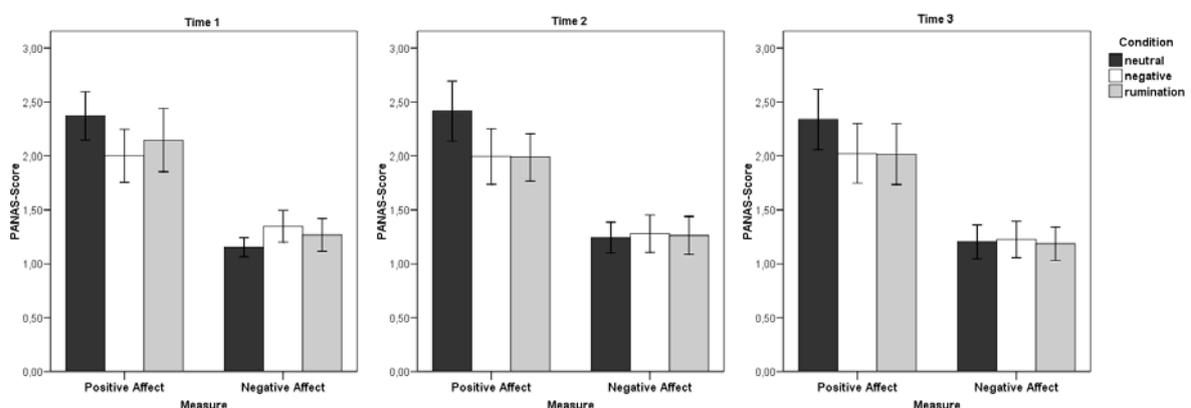


The comparison of self-reported state affect after the negative mood induction and the rumination challenge to reports at baseline as displayed in figure 5 revealed, that there was a significant main effect of Mood on positive and negative affect at Time 1 (positive affect: $F[1,30] = 19.53$, $p < .001$, partial $\eta^2 = 0.39$; negative affect: $F[1,30] = 13.17$, $p < .001$, partial $\eta^2 = 0.31$), indicating the same effects on emotionality as in Analysis 1. The effect of Rumination was not significant in case of positive affect ($F[1,30] = 2.63$, $p > .05$, partial $\eta^2 =$

0.08), and marginally significant for negative affect ($F[1,30] = 3.23, p = .09$). At Time 2, the same main effect of Mood was given for positive affect ($F[1,30] = 17.78, p < .001, \text{partial } \eta^2 = 0.37$). In addition, there was a significant main effect of Rumination on positive affect ($F[1,30] = 18.38, p < .001, \text{partial } \eta^2 = 0.38$), indicating lower positive emotionality following the mood induction, compared to baseline. At Time 3, significant effects of Mood ($F[1,30] = 12.43, p < .001, \text{partial } \eta^2 = 0.29$) and of Rumination ($F[1,30] = 8.51, p < .01, \text{partial } \eta^2 = 0.22$) on positive affect were given, indicating a more negative emotionality in both conditions.

Fig. 5. Mean scores of positive and negative affect

Mean scores of the subscales of positive and negative affect of the Positive and Negative Affect Schedule displayed separately by condition and time. Error bars reflect 95% confidence intervals. PANAS, Positive and Negative Affect Schedule.



Brain electrical activity measures

Analysis 1

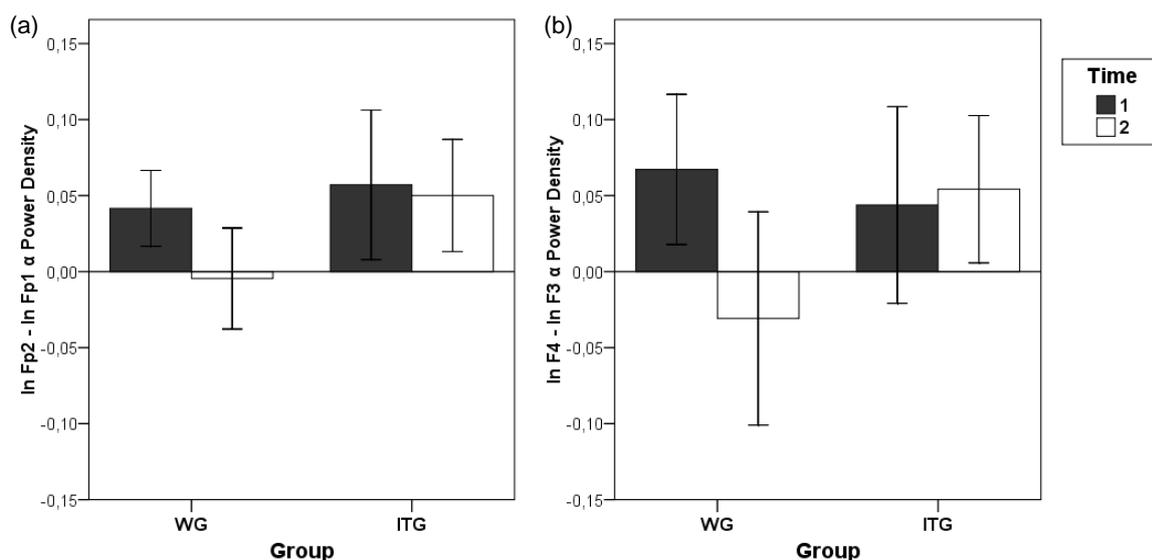
The omnibus MANOVA showed that there was a significant main effect of Time ($F[2,36] = 5.71, p < .01, \text{partial } \eta^2 = 0.24$) and a significant Time by Group interaction ($F[2,36] = 5.30, p < .05, \text{partial } \eta^2 = 0.23$) from Time 1 to Time 2 measures for the baseline period assessments.

Separate ANOVAs for each electrode pair showed that the main effect of Time ($F_{p1/Fp2}$:

F[1,37] = 8.32, $p < .01$, partial $\eta^2 = 0.18$; F3/4: F[1,37] = 5.31, $p < .05$, partial $\eta^2 = 0.13$) and the Time by Group interaction (Fp1/Fp2: F[1,37] = 4.51, $p < .05$, partial $\eta^2 = 0.11$, Fig. 6a; F3/F4: F[1,37] = 8.12, $p < .01$, partial $\eta^2 = 0.18$, Fig. 6b) were given for both electrode pairs. Bonferroni-corrected simple comparisons revealed that the interaction obtained for the frontopolar leads was characterized by a significant decrease ($M_{I-J} = 0.046$, SE = 0.012, $p < 0.01$) in asymmetry scores in the WG, whereas asymmetry scores did not change significantly in the ITG ($M_{I-J} = 0.007$, SE = 0.14, $p > .05$). Similarly, for the interaction obtained for the frontal leads there was a significant decrease in asymmetry scores in the WG ($M_{I-J} = 0.098$, SE = 0.032, $p = 0.01$), whereas there was no significant change in the ITG ($M_{I-J} = -0.01$, SE = 0.02, $p > .05$). At Time 1 assessments, there were no significant group differences for any electrode pair (all $ps > .05$).

Fig. 6. Mean scores of functional anterior alpha-asymmetry during baseline assessments

Mean scores for electrode pair Fp1/Fp2 (a) and F3/F4 (b), displayed separately by time and group. The ordinate represents a metric of right – left log-transformed power density. Higher numbers on this metric indicate greater relative left-hemispheric activation. Error bars reflect 95% confidence intervals. ITG, immediate treatment group. WG, waiting group.

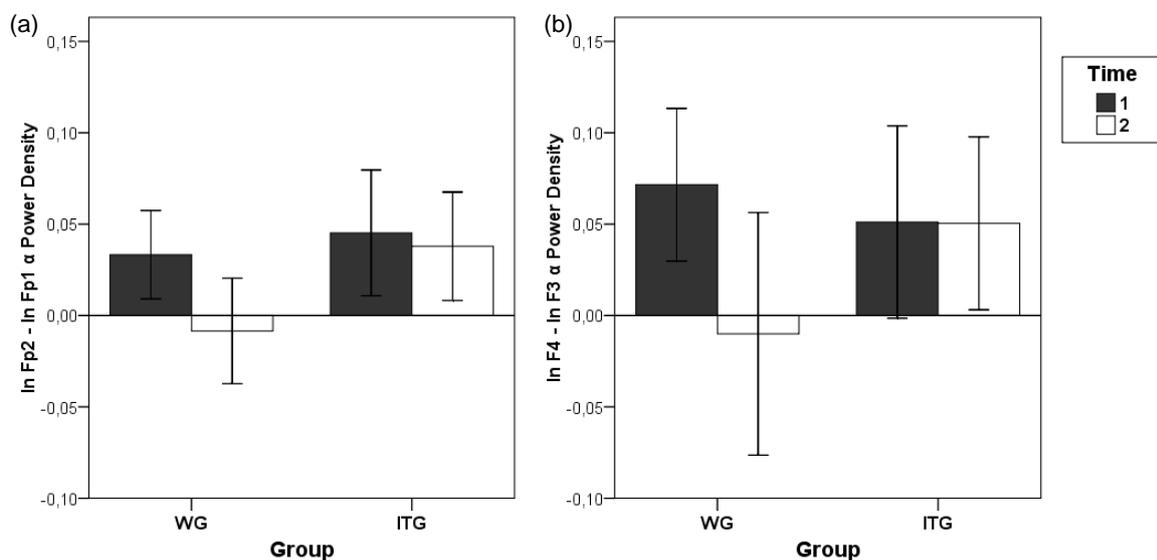


For the assessments following the negative mood induction, the omnibus MANOVA showed both, a significant main effect of Time ($F[2,36] = 5.90, p < .01, \text{partial } \eta^2 = 0.25$) and a significant Time by Group interaction ($F[2,36] = 3.70, p < .05, \text{partial } \eta^2 = 0.17$). Follow-up

Fig. 7. Mean scores of functional anterior alpha-asymmetry following the negative mood induction

Mean scores for electrode pair Fp1/Fp2 (a) and F3/F4 (b), displayed separately by time and group. The ordinate represents the same metric of asymmetric activation as in Fig. 6. Error bars reflect 95% confidence intervals.

ITG, immediate treatment group. WG, waiting group.

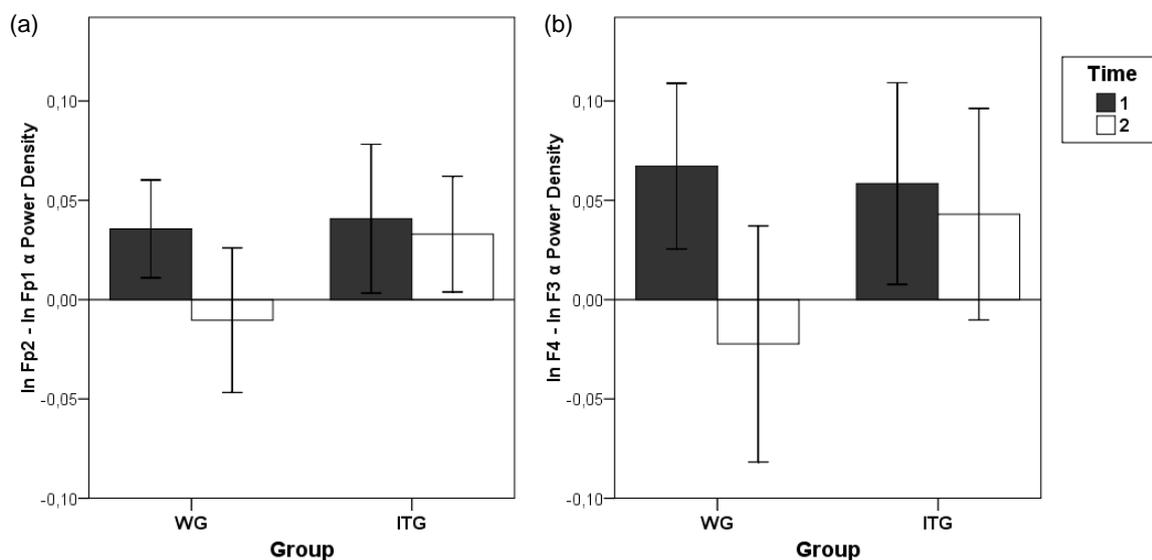


ANOVAs showed a significant main effect of time (Fp1/Fp2: $F[1,37] = 9.92, p < .01, \text{partial } \eta^2 = 0.21$; F3/F4: $F[1,37] = 4.42, p < .05, \text{partial } \eta^2 = 0.11$) and a significant Time by Group interaction (Fp1/Fp2: $F[1,37] = 4.89, p < .05, \text{partial } \eta^2 = 0.12$, Fig. 7a; F3/F4: $F[1,37] = 4.27, p < .05, \text{partial } \eta^2 = 0.10$, Fig. 7b) for both electrode pairs. Bonferroni-corrected simple comparisons revealed that the Time by Group interaction obtained for the frontopolar leads was produced by a significant decrease in asymmetry scores ($M_{I-J} = 0.042, SE = 0.011, p < 0.01$) in the WG, whereas asymmetry scores did not change significantly in the ITG ($M_{I-J} = 0.007, SE = 0.011, p > .05$). The interaction obtained for the frontal leads was characterized by a marginally significant decrease in asymmetry scores in the WG ($M_{I-J} = 0.082, SE =$

0.030, $p = .013$), and a small non-significant decrease in the ITG ($M_{I-J} = 0.001$, $SE = 0.025$, $p > .05$). At Time 1 assessments, no group differences were present for any electrode pair (all $ps > .05$).

Fig. 8. Mean scores of functional anterior alpha-asymmetry following rumination challenge

Mean scores for electrode pair Fp1/Fp2 (a) and F3/F4 (b) following the rumination challenge, displayed separately by time and group. The ordinate represents the same metric as in previous figures. Error bars reflect 95% confidence intervals. ITG, immediate treatment group. WG, waiting group.



For the assessments following the rumination challenge, there was a highly significant main effect of Time ($F[2,36] = 10.07$, $p < .001$, partial $\eta^2 = 0.36$) and a significant Time by Group interaction ($F[2,36] = 5.05$, $p < .05$, partial $\eta^2 = 0.22$). When change for each electrode pair was examined, there was a significant main effect of Time (Fp1/Fp2: $F[1,37] = 10.46$, $p < .01$, partial $\eta^2 = 0.22$; F3/F4: $F[1,37] = 10.53$, $p < .01$, partial $\eta^2 = 0.22$) and a significant Time by Group interaction (Fp1/Fp2: $F[1,37] = 5.29$, $p < .05$, partial $\eta^2 = 0.13$, Fig. 8a; F3/F4: $F[1,37] = 5.25$, $p < .05$, partial $\eta^2 = 0.14$, Fig. 8b) for both sites. Bonferroni-corrected simple comparisons showed that the interactions were produced by a significant decrease in asymmetry scores in the WG at both sites (Fp1/Fp2: $M_{I-J} = 0.046$, $SE = 0.013$, $p < 0.01$; F3/F4: $M_{I-J} = 0.090$, $SE = 0.024$, $p < 0.01$), whereas there were no significant changes in the

ITG (Fp1/Fp2: $M_{I,J} = 0.008$, $SE = 0.011$; F3/F4: $M_{I,J} = 0.015$, $SE = 0.022$, all $ps > .05$). At Time 1 assessments, no group differences were present for any electrode pair (all $ps > .05$).

Analysis 2

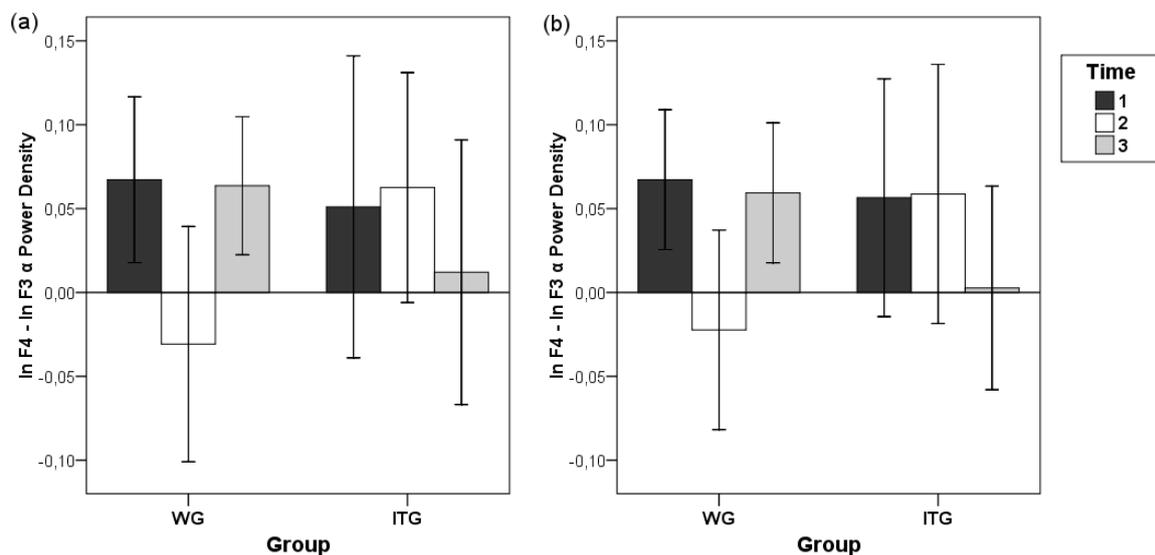
The omnibus MANOVA showed that there was a significant Time by Group interaction ($F[4,27] = 2.77$, $p < .05$, partial $\eta^2 = 0.29$) across measurements from Time 1, Time 2 and Time 3 for the baseline period assessments.

Separate ANOVAs for each electrode pair showed that this interaction was marginally significant only at the frontal electrodes (Fp1/2: $F[2,60] = 0.92$, $p > .05$, partial $\eta^2 = 0.03$; F3/F4: $F[2,60] = 2.85$, $p = .07$, partial $\eta^2 = 0.09$, Fig. 9a), which was qualified by a significant quadratic trend ($F[1,30] = 6.97$, $p < .05$, partial $\eta^2 = 0.19$). Bonferroni-corrected simple comparisons revealed that the observed pattern was characterized by a significant decrease in asymmetry scores in the WG from Time 1 to Time 2 ($M_{I,J} = 0.098$, $SE = 0.032$, $p < 0.01$), as indicated in Analysis 1, as well as a subsequent marginally significant increase from Time 2 to Time 3 ($M_{I,J} = -0.094$, $SE = 0.039$, $p = 0.027$). In the ITG, asymmetry scores did not change significantly from Time 1 to Time 2 ($M_{I,J} = -0.012$, $SE = 0.029$, $p > .05$), or Time 2 to Time 3 ($M_{I,J} = 0.05$, $SE = 0.062$, $p > .05$).

In case of the assessments following the negative mood induction, the MANOVA revealed a marginally significant main effect of Time ($F[4,27] = 2.50$, $p = .07$, partial $\eta^2 = 0.19$). For assessments following the rumination challenge, there was a significant main effect of Time ($F[4,27] = 4.64$, $p < .01$, partial $\eta^2 = 0.41$) and a marginally significant Time by Group interaction ($F[4,27] = 2.73$, $p = .05$, partial $\eta^2 = 0.29$, Fig. 9b). Follow-up ANOVAs for each electrode pair showed that the interaction was only significant for the frontal electrodes ($F[2,60] = 3.58$, $p < .05$, partial $\eta^2 = 0.11$). Bonferroni-corrected simple comparisons further showed that the observed pattern was characterized by a significant decrease in asymmetry scores in the WG from Time 1 to Time 2 ($M_{I,J} = 0.090$, $SE = 0.024$, p

< .01), as indicated in Analysis 1, as well as a subsequent marginally significant increase from Time 2 to Time 3 ($M_{I,J} = -0.082$, $SE = 0.035$, $p = .032$). In the ITG, there was no significant change in asymmetry scores from Time 1 to Time 2 ($M_{I,J} = -0.002$, $SE = 0.026$, $p > .05$) or from Time 2 to Time 3 ($M_{I,J} = -0.056$, $SE = 0.057$, $p > .05$).

Fig. 9. Mean scores of functional anterior alpha-asymmetry during baseline and following rumination challenge. Mean scores for electrode pair F3/F4 during baseline (a) and following the rumination challenge (b), displayed separately by time and group. The ordinate represents the same metric as in previous figures. Error bars reflect 95% confidence intervals. ITG, immediate treatment group. WG, waiting group.



Relations among measures

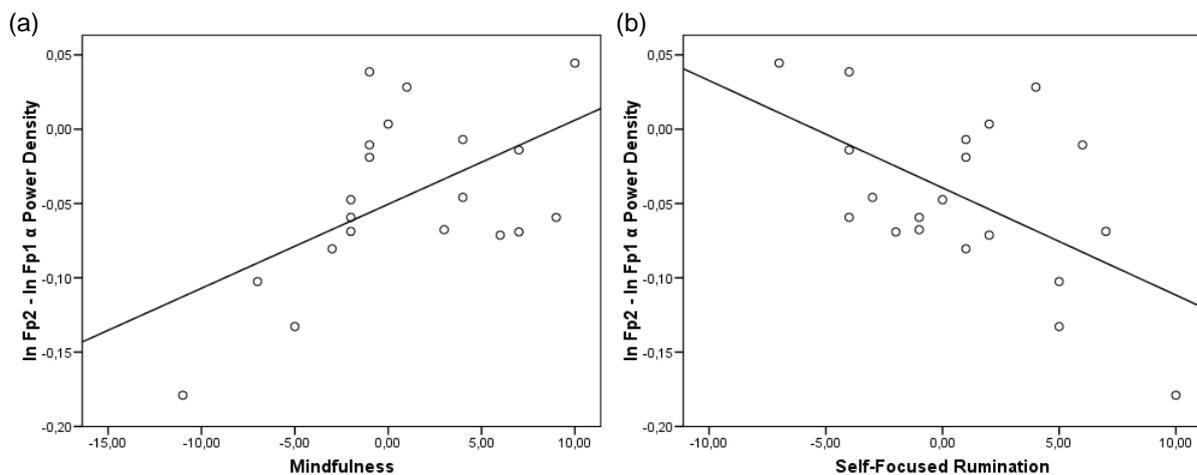
In an exploratory analysis, attempts were made to assess the relation between changes in FAA, and changes on the self-report measures of mindfulness, rumination and depression. Change scores of activation asymmetry following the rumination induction and of the self-report measures were computed for each subject, and the obtained scores were correlated. Due to Bonferroni correction, correlations at the significance level of $p < .0083$ (one-tailed) were considered.

Analysis 1

In the WG, subjects who displayed increased relative right-hemispheric anterior cortical activation (decreased asymmetry scores) at fronto-polar electrodes after rumination challenge from Time 1 to Time 2 assessments, showed decreased mindfulness ($r = .548, p = .006$, Fig. 10a) and increased self-focused rumination ($r = -.557, p = .005$, Fig. 10b). In case of symptom-focused rumination, a marginally significant correlation was obtained ($r = -.507, p = .012$). There was no relation between any of these variables in the ITG (all $ps > .05$).

Fig. 10. The relation between alterations in mindfulness, rumination, and FAA

Scatter plot of the relation between alterations in mindfulness (a), self-focused rumination (b), and alpha power density at electrode pair Fp1/Fp2 during rumination challenge from Time 1 to Time 2 in the WG. No significant associations of these variables were observed in the ITG.



Analysis 2

In case of change scores between Time 2 and Time 3 assessments, in the WG, those participants who displayed increased relative left-hemispheric anterior activation at fronto-polar electrodes following the rumination challenge at post-treatment assessments, also displayed a marginally significant decrease in symptom-focused ($r = -.462, p = .020$) and self-focused rumination ($r = -.462, p = .015$), as well as depressive symptoms ($\tau = -.296, p =$

.034). In the ITG no significant correlations were obtained from Time 2 to Time 3 assessments.

5.4. Discussion

The main goal of the current study was to explore effects of MBCT on indices of mindfulness, rumination and affect, particularly on FAA. FAA has been shown to be indicative of global affective style, may be plastic, i.e., shapeable by training such as mindfulness meditation (Davidson et al., 2003), and deteriorate towards stronger relative right-hemispheric anterior activity in recurrently depressed patients in remission, in absence of a counteractive intervention (Barnhofer et al., 2007). In these regards, our findings have several implications. Firstly, we replicated results obtained by Barnhofer et al. (2007) using a larger sample. For EEG assessments which occurred under a neutral condition, members of the ITG were able to keep a balanced pattern of FAA, from Time 1 to Time 2 assessments, whereas members of the WG showed a shift to stronger relative right-hemispheric anterior activity, indicative of increased vulnerability and withdrawal/avoidance-related affective style (Coan & Allen, 2004; Davidson, 2004). Secondly, it can be reported for the first time, that also under conditions of negative mood and rumination, i.e., conditions particularly detrimental for individuals with recurrent depression, patients treated with MBCT were able to retain a balanced pattern of FAA. In contrast to patients of the ITG, who retained a stable asymmetry pattern from Time 1 to Time 2 assessments, members of the WG group showed a deterioration toward stronger relative right-hemispheric anterior activity during the waiting period.

The observed shifts in asymmetry may be attributed to the high risk for relapse in the WG, which is an explanation also given by Barnhofer et al. (2007). MDD has been described as a highly recurrent illness with the risk of recurrence progressively increasing with every successive episode, and with episodes becoming increasingly independent from major life

stressors (Solomon et al., 2000a). Hence, internal processes such as cognitive reactivity and rumination may become more powerful in yielding depressive relapse throughout its course. For patients included in our study, the risk for relapse has been estimated to be 90% (American Psychiatric Association, 2000a). Since patients for MBCT studies are generally selected during remission, and the risk for relapse is very high, one may expect that without an effective treatment, their condition will deteriorate with time, which might be indicated by stronger relative right-hemispheric anterior activity. While this claim was only speculative in the study by Barnhofer et al. (2007), we have obtained some preliminary support for it, since rumination, an indicator of vulnerability (Kuehner, Liebisch, & Huffziger, 2009), which has been shown to predict MDE (Ito et al., 2006; Kuehner & Weber, 1999; Nolen-Hoeksema, Morrow, & Fredrickson, 1993), predicted anterior right-hemispheric activity at fronto-polar sites following rumination challenge in the WG. In addition, in the latter group, lower mindfulness scores at Time 2 assessments, which might be interpreted as weakening of a mechanism protecting against depressive relapse (Michalak et al., 2008), predicted the relative activity of the right-frontal lobe at the same site and under the same condition. The interpretation however is limited by the fact, that contrary to the initial predictions, no significant deterioration in self-reported depression, and no decrease in mindfulness scores occurred in the WG from Time 1 to Time 2.

Effects on self-report measures were given in the ITG, participants of which received MBCT treatment from Time 1 to Time 2, and showed decreased ruminative tendencies and increased mindfulness. The latter findings support the interpretation of a protective effect of MBCT, since they reflect an elevated resilience in the ITG. Consequently, according to the results, both, psychological and physiological alterations from Time 1 to Time 2 are in line with the hypothesis of a protective effect of MBCT.

Results obtained from Time 2 to Time 3 assessments further extend previous findings provided by Davidson et al., (2003) and Barnhofer et al. (2007), and are completely novel.

Most importantly, treatment through MBCT in the WG, subsequent to the waiting period, was associated with increased relative left-hemispheric anterior activity, while in the ITG, which had already received treatment, no change, and in particular no significant deterioration in FAA was observed at the two-month follow-up assessment. These novel findings indicate elevated resilience after training, as well as a more positive and balanced affective style, respectively. In addition to the physiological effect, members of the WG also displayed a significant increase in self-reported mindfulness following MBCT, which further indicates increased resilience.

Importantly, MBCT applied during remission is efficient in preventing relapse in recurrent MDD patients (Ma & Teasdale, 2004; Teasdale et al., 2000). Especially in the WG however, patients were not in optimal remission any longer, when MBCT started. Nevertheless, the positive electrophysiological effect of MBCT was highly pronounced in this group. This does not prove a clinical effect, but the present data indicate that it may be worth applying MBCT not only to patients in optimal remission, but also to those who already exhibit signs of arising psychological impairment.

The present findings have further implications for the role of FAA in depression research. It has been suggested that FAA may be regarded as a putative endophenotype for depressive risk, which is independent from current clinical status (Allen et al., 2009). Smit et al. (2007) have argued that FAA as an endophenotype for depression should possess several features. Among others, FAA should be stable, heritable, and correlated with the phenotype of interest. While some support has been provided for the criteria of heritability, stability, and the correlation with the risk for depression (Allen et al., 2004b; Coan & Allen, 2004; Davidson & Irwin, 1999; Smit et al., 2007; Vuga et al., 2006), a few studies (Barnhofer et al., 2007; Davidson et al., 2003), as well as the current research indicate that FAA is not necessarily stable, but can be modified by training. Results by Barnhofer et al. (2007) and of the current study support a view of FAA in MDD as plastic, which suggests that in a

population at extremely high risk for depressive relapse, FAA may change toward stronger relative right-hemispheric anterior activity, if no counteractive intervention is applied. Since in the current study, rumination, a predictor of depressive relapse also significantly predicted changes in FAA, but depression symptoms as assessed by BDI did not, one may speculate that rumination might mediate an association between the rather heterogeneous cluster of diagnostic criteria of MDD and abnormal FAA. Contrary to this assumption, Drevets et al. (1992) have hypothesized that increased blood flow in the left frontal cortical region may be a correlate of ruminative processes, due to the involvement of language-related associative operations. Similarly Reid et al. (1998) speculate that depressed individuals who engage in rumination display stronger left-hemispheric anterior activity. However, to date, no research has been conducted to evaluate the relation of dispositional rumination and FAA in recurrently depressed individuals in remission. Our preliminary findings of contrary associations of FAA and rumination on the one hand, and FAA and mindfulness on the other suggest, that the concepts of rumination and mindfulness may be placed within the framework of the approach-withdrawal model of hemispheric asymmetry, and that rumination might be withdrawal-related, whereas mindfulness may be approach-related in recurrently depressed patients. Despite the intuitively reasonable argument that rumination should be associated with left-hemispheric activity, this view ignores the known influence of rumination on affect (Nolen-Hoeksema et al., 2008). Rumination involves language-related associative processing, but is also intertwined with emotional responses and depression symptoms. Therefore ruminative ideation needs to be discussed in relation to the approach-withdrawal model and FAA. If rumination has a mediating function, one can assume that it is especially manifested in patients after several recurrent depressive episodes, as in the current sample. Ma & Teasdale (2004) have reported that MBCT is effective in preventing autonomous, internally provoked recurrence in patients with three or more MDE. Since relapse becomes increasingly autonomous from life stressors with successive episodes (Post, 1992), patients included in the

current study with at least three MDE are probably prone to relapse as a result of internal processes, such as rumination. Another reason why the relation between rumination and FAA needs further exploration is that rumination is known to be more common in women than in men (Nolen-Hoeksema, Larson, & Grayson, 1999b), as is MDD (Weissman & Olfson, 1995). Gender-specific findings on FAA (Accortt & Allen, 2006) might at least partially be related to ruminative ideation. To thoroughly verify these speculations however is beyond the scope of the current study and requires further research.

Several limitations of this study have to be noted. The sample size was still relatively small and applied subject selection criteria reduced it further. On the other hand, the application of these criteria provides some confidence that the obtained effects are genuine ones. Since strict criteria based on previous literature were used (Tomarken et al., 1992b), the data analysis followed a sound procedure. Importantly, with the current design, non-specific effects of the applied intervention cannot be ruled out. The observed consistent effects on mindfulness and rumination in relation to treatment nevertheless indicate that the intervention was probably successful. In addition, it is important to note that negative life-events were not controlled and experience with cognitive therapy for depression was not ruled out.

To conclude, the current study confirmed that even a very short course of MBCT has significant positive effects on concurrent indices of emotionality, including functional brain asymmetry. The data further permit to putatively suggest that the increasing emotional stability following MBCT training may be mediated by the suppression of harmful behavior patterns such as rumination, and increases in protective factors, such as mindfulness. Further, the latter behavior patterns might also show systematic relations to FAA in the context of the approach-withdrawal model of hemispheric asymmetry. MBCT may represent a form of maintenance psychotherapy with a relatively enduring protective effect, which may manifest in the stability of FAA. A longitudinal design with a longer follow-up period however is

necessary for a better evaluation of the stability of its electrophysiological and psychological effects.

6. Study 2: Effects of MBCT on Functional Anterior Brain Asymmetry during negative Affect and Mindfulness Support

6.1. Hypotheses

Based on Study 1, the current study was conducted to replicate previous findings, and to incorporate an additional condition, under which mindfulness training may express effects on FAA. Several assessments of resting EEG, self-reported depression, mindfulness, and rumination occurred in recurrently depressed patients in remission prior to, and following the participation in an MBCT course. EEG assessments took place under several conditions at each measurement point. In contrast to Study 1, the negative mood induction was followed by a condition during which patients were supported by mindfulness instructions, with the intention to enable them to stay in a mindful state. Hence, assessments were conducted in a neutral condition, following a negative mood induction, and following a condition in which mindfulness support was provided. While the first two conditions were identical with those of Study 1 in order to replicate previous results, the latter was incorporated to provide novel information with regard to the question, whether treatment effects of MBCT on FAA generalize to states of mindful awareness.

As was the case in Study 1, participants were allocated to an ITG or a WG. In this case, 19 participants were allocated to immediate treatment, whereas 16 were only treated after a waiting interval of eight weeks. Assessments in the ITG occurred immediately before treatment started (Time 1), and upon completion of the course (Time 2). In case of the WG, assessments occurred prior to (Time 1) and following the waiting interval (Time 2), as well as after the completion of the MBCT course (Time 3). An overview of the hypotheses is provided in Table 2.

Table 2. List of hypotheses of Study 2

ITG, immediate treatment group. WG, waiting group. LHA, relative left-hemispheric anterior. RHA, relative right-hemispheric anterior. ↑, increase. ↓, decrease. --, stability.

Note: For EEG measures, the same pattern is expected to generalize to all conditions, i.e. assessments during the neutral condition, following the induction of a negative mood, and mindfulness support.

<i>Hypothesis</i>	<i>Assessment</i>	<i>Group</i>	<i>Expected Observation</i>
1	Time 1 - Time 2	WG	↑ RHA activity
2	Time 1 - Time 2	ITG	↑ LHA activity / -- asymmetry pattern
3	Time 1 - Time 2	WG	↓ mindfulness, -- rumination, ↑ depression
4	Time 1 - Time 2	ITG	↑ mindfulness, ↓ rumination, ↓ depression
5	Time 2 - Time 3	WG	↑ LHA activity
6	Time 2 - Time 3	WG	↑ mindfulness, ↓ rumination, ↓ depression
7	Time 1 - Time 2	WG	↑ RHA activity predicts ↓ mindfulness, ↑ rumination, ↑ depression
8	Time 1 - Time 2	ITG	↑ LHA activity predicts ↑ mindfulness, ↓ rumination, ↓ depression
9	Time 2 - Time 3	WG	↑ LHA activity predicts ↑ mindfulness, ↓ rumination, ↓ depression

Based on the rationale outlined and results obtained in Study 1, as well as results reported by Barnhofer et al. (2007), it was expected that the WG would display elevated relative right-hemispheric anterior cortical activity at Time 2 compared to Time 1 assessments, i.e. signs of increased vulnerability. In contrast, for participants of the ITG, stability of FAA, or a shift toward stronger relative left-hemispheric anterior activity was expected, as both have been reported to be associated with structured mindfulness training (Barnhofer et al., 2007; Davidson et al., 2003). In line with the hypotheses of Study 1, it was also expected that the WG would display increased self-reported depressive symptoms at Time 2, as well as decreased mindfulness and stable ruminative tendencies. In contrast, for the ITG, decreased self-reported depression and rumination, as well as increased self-reported mindfulness were expected at Time 2. In the current study, unlike Study 1, Time 3 assessments occurred only in case of the WG. The same counteractive effect of MBCT was expected to be expressed in an

increase in relative left-hemispheric anterior cortical activity at Time 3, compared to Time 2. Similarly, a decrease in self-reported rumination and depression, as well as elevated self-reported mindfulness was expected to be observed at Time 3 assessments. The respective expected changes in FAA were further hypothesized to predict alterations in self-report measures in line with the approach-withdrawal model of hemispheric asymmetry, as outline in Study 1. Increased relative left-hemispheric anterior cortical activation, i.e. an increase in a neural correlate of approach-behavior, was expected to predict decreased rumination and depression, and increased mindfulness.

6.2. Methods

Participants

Recruitment of participants followed the same procedure as in Study 1. The same inclusion and exclusion criteria were applied, and medication status was handled accordingly. In sum, 42 participants were recruited and allocated to an ITG or a WG. Out of these, seven participants dropped out after the Time 1 assessment, leaving 35 participants who completed at least the Time 1 and Time 2 assessments. Participants with sufficient quality of EEG data at Time 1 (ITG: $n = 19$, 5 male; WG: $n = 16$, 6 male), did not differ significantly in age (ITG: $M = 46.26$, $SD = 8.37$; WG: $M = 41.50$, $SD = 10.78$, $t[33] = -1.47$), levels of depressive symptoms assessed by BDI (ITG: $M = 9.79$, $SD = 9.98$; WG: $M = 12.19$, $SD = 9.21$, $t[33] = 0.73$), tendencies of symptom-focused (ITG: $M = 19.53$, $SD = 4.38$; WG: $M = 19.88$, $SD = 5.33$, $t[33] = 0.21$) or self-focused rumination (ITG: $M = 15.84$, $SD = 3.91$; WG: $M = 16.31$, $SD = 4.29$, $t[33] = 0.34$) as measured by RSQ, or mindfulness as assessed by FFA (ITG: $M = 34.00$, $SD = 7.06$; WG: $M = 30.56$, $SD = 10.64$; $t[33] = -1.14$; all $ps > .05$). Groups were also comparable in the age of onset of the first MDE (ITG: $M = 30.53$, $SD = 9.25$; WG: $M = 25.19$, $SD = 5.69$, $t[33] = -2.00$), proportions of participants currently using anti-depressant medication (ITG: yes 13/no 6; WG: yes 11/no 5, $\chi^2 [1,35] = 0.0004$), and the number of

experienced MDE (ITG: Mdn = 5, range = 4-15; WG: Mdn = 6, range = 5-20, $U = 119.5$, all $ps > .05$).

Another four patients were lost in the WG for Time 3 assessments. Hence, at Time 3, data of 12 participants (6 male) was available. As was the case in Study 1, during the respective treatment phases, participants attended one group session of MBCT per week. All participants received the instruction to consult their medical doctor or other sources of help if they felt they needed to, hence to seek medical treatment as they usually would.

Self-report measures

The included self-reported measures were the same as in Study 1.

Procedure

At each measurement point, self-report measures were completed and subsequently, resting EEGs were recorded. EEG recording occurred under three resting conditions in the following order: neutral (baseline condition), following the induction of a sad mood (sad mood induction) and following a period during which subjects attended to instructions of mindfulness meditation, guiding their attention toward their breath and bodily sensations (mindfulness support). The sad mood induction was the same as in Study 1. In the mindfulness support condition, participants listened to a recording which started with a brief introduction to mindfulness meditation on the breath. Participants were told that in a few moments, they would hear statements, which would help them to keep their attention focused on their breath and bodily sensations. They further received the instruction to follow the suggestions of the statements and to redirect their attention to their breath and bodily sensations, as soon as they felt they lost focus, without judging themselves for lapses of concentration. Following the introduction, 25 statements were played, with typical instructions used in guided mindfulness meditation (Segal et al., 2002). Statements were

formulated by the MBCT therapist, who delivered the treatment, and read by a male voice, following the same time course as the statements of the rumination condition in Study 1. The average length of the 25 statements was 8.5 seconds. Each statement was followed by three 1.5-second bursts of white noise, related to a different research question, to be reported elsewhere. In sum, the duration of assessments at each measurement point was approximately 70 minutes.

Electrophysiological recording and analysis

Electrophysiological recording and analysis followed the same procedure as described in Study 1. At Time 1 and Time 2 assessments, no significant difference in the average number of artifact-free EEG data segments per participant was given for any condition across groups (all $ps > .05$).

Statistical analysis

Since in the current study, assessments at Time 3 only occurred in the WG and no follow-up measure was involved for the ITG, two separate analyses were conducted. The first one involved alterations which occurred between the assessments at Time 1 and Time 2. The second analyses focused on effects within the WG and involved all three measurement points.

Analysis 1

Multivariate repeated-measures analyses of variance (MANOVAs) were computed for the two electrode pairs for each condition, and main effects and interactions were examined with a focus on interactions between Group (ITG versus WG) and Time (Time 1 versus Time 2). Separate follow-up ANOVAs were computed for each electrode pair. For the self-report measures, ANOVAs were conducted with the factors Time and Group. To evaluate effects of the mood induction and mindfulness support on state affect, ANOVAs with the factor

Condition (neutral, negative mood, mindfulness support) were conducted for positive and negative affect at both measurement points. As was the case in Study 1, Greenhouse-Geisser corrected degrees of freedom were used for the evaluation of F ratios when homogeneity of variance was not given, and boxplots were used to ensure that data did not contain any outliers.

Analysis 2

In this analysis, effects within the WG were considered only. A MANOVA was conducted for the two electrode pairs, examining a main effect of Time (Time 1-3). Subsequently, separate ANOVAs were computed for each electrode pair. In case of the self-report measures, separate ANOVAs were conducted with the factor Time. To test for effects of the mood induction and mindfulness support on state affect, ANOVAs with the factor Condition were conducted at each measurement point.

6.3. Results

Self-Report Measures

Analysis 1

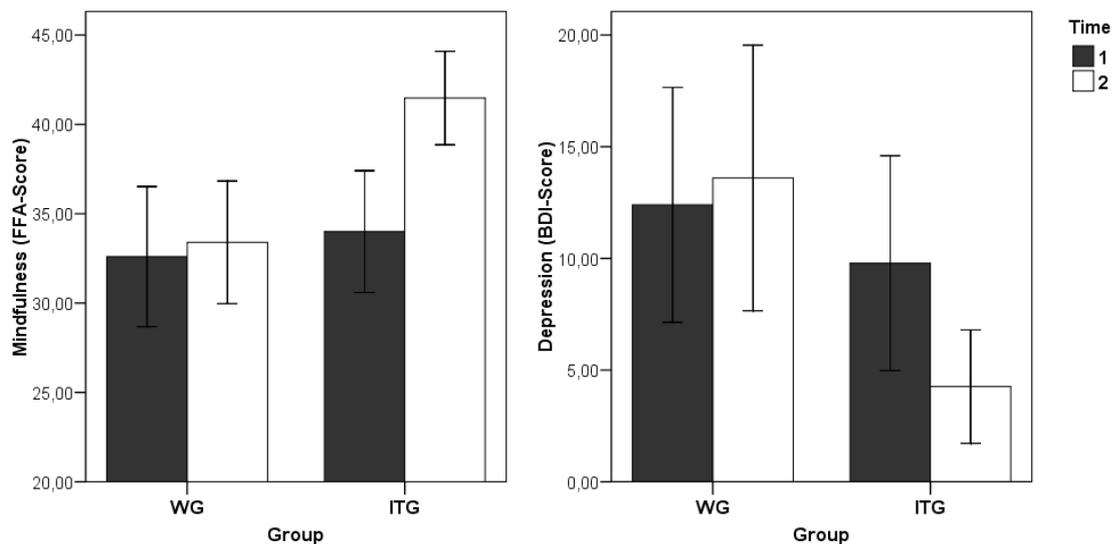
The ANOVAs revealed a significant main effect of Time on symptom-focused rumination ($F[1,33] = 4.79, p < .05, \text{partial } \eta^2 = 0.13$) and a highly significant effect of Time on mindfulness ($F[1,32] = 16.32, p < .001, \text{partial } \eta^2 = 0.34$). There also was a significant Time by Group interaction for mindfulness ($F[1,32] = 10.62, p < .01, \text{partial } \eta^2 = 0.25$) and for depression ($F[1,33] = 4.26, p < .05, \text{partial } \eta^2 = 0.14, \text{Fig. 11}$).

To examine the interaction effects, Bonferroni-corrected simple comparisons were computed. Since the possibility for four simple comparisons was given, results with a p -value below .0125 were considered significant. Bonferroni-corrected simple comparisons showed that the interaction for mindfulness was characterized by a highly significant increase in

mindfulness in the ITG ($M_{I-J} = -7.47$, $SE = 1.66$, $p < .001$), whereas mindfulness did not change significantly in the WG ($M_{I-J} = -0.8$, $SE = 0.94$, $p > .05$) from Time 1 to Time 2. The interaction for depression was characterized by a significant decrease in the ITG ($M_{I-J} = 5.53$, $SE = 1.95$, $p = .011$), and a non-significant increase in self-reported depressive symptoms in the WG ($M_{I-J} = -0.94$, $SE = 0.71$, $p > .05$).

Fig. 11. Mean scores of mindfulness and depression

Mean scores of self-reported mindfulness and depression displayed separately by group and time. Error bars reflect 95% confidence intervals. ITG, immediate treatment group. WG, waiting group. FFA, Freiburger Fragebogen zur Achtsamkeit. BDI, Beck Depression Inventory.



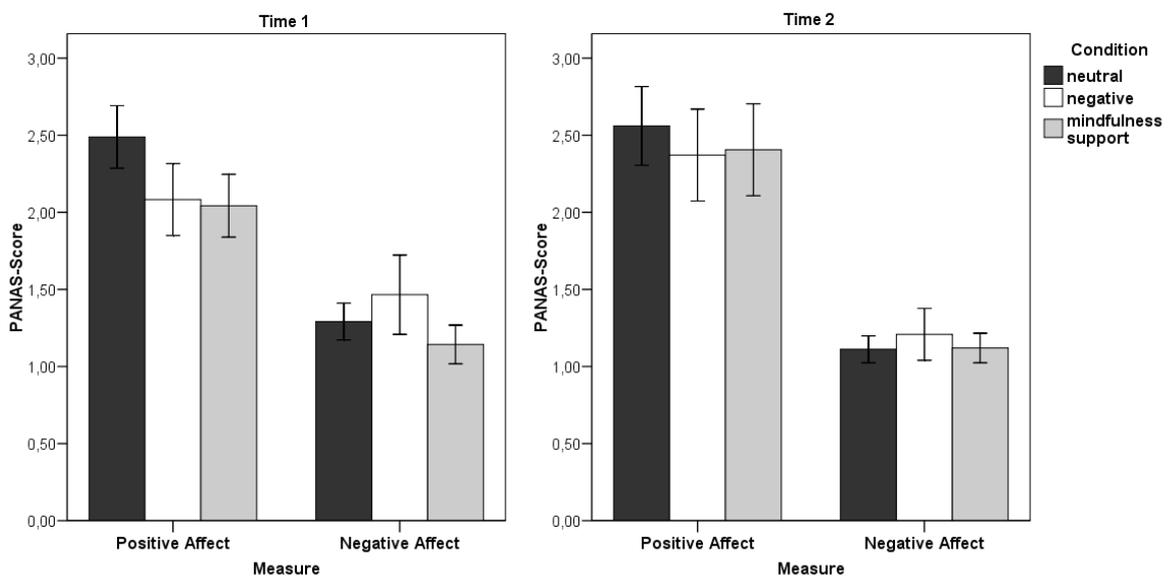
Mean scores of positive and negative affect across conditions at Time 1 and Time 2 are displayed in Figure 12. When comparing effects of the mood induction and subsequent mindfulness support to baseline, at Time 1 assessments, there was a highly significant main effect of Condition ($F[2,68] = 12.66$, $p < .001$, partial $\eta^2 = 0.27$) on positive affect, qualified by a significant linear trend ($F[1,33] = 20.64$, $p < .001$, partial $\eta^2 = 0.39$). The trend was produced by significantly reduced positive affect following the mood induction ($M_{I-J} = 0.41$, $SE = 0.08$, $p < .001$), and a subsequent non-significant decrease following the mindfulness support condition ($M_{I-J} = 0.04$, $SE = 0.11$, $p > .05$).

For the measure of negative affect, there was a significant main effect of Condition ($F[2,66] = 5.09, p < .01, \text{partial } \eta^2 = 0.13$), qualified by a significant linear ($F[1,33] = 9.69, p < .01, \text{partial } \eta^2 = 0.23$) and quadratic trend ($F[1,33] = 4.56, p < .05, \text{partial } \eta^2 = 0.12$). Simple comparisons showed that the observed pattern was qualified by a non-significant increase in negative affect following the mood induction ($M_{I-J} = -0.19, SE = 0.12, p > .05$), and a subsequent significant decrease following the mindfulness support ($M_{I-J} = 0.43, SE = 0.13, p = .016$).

At Time 2 assessments, there was no significant main effect of Condition ($F[2,66] = 1.7, p > .05, \text{partial } \eta^2 = 0.05$), on positive affect. Simple comparisons revealed however, that there was a marginally significant decrease in positive affect following the negative mood induction ($M_{I-J} = 0.19, SE = 0.08, p = .03$), and a subsequent non-significant increase following the mindfulness support ($M_{I-J} = -0.37, SE = 0.12, p > .05$).

Fig. 12. Mean scores of positive and negative affect

Mean scores of the subscales of positive and negative affect of the Positive and Negative Affect Schedule displayed separately by condition and time. Error bars reflect 95% confidence intervals. PANAS, Positive and Negative Affect Schedule.



Analysis 2

In case of this analysis, a significant main effect of Time on self-focused rumination ($F[2,22] = 3.69, p < .05, \text{partial } \eta^2 = 0.25$) with a significant linear trend ($F[1,11] = 8.17, p < .05, \text{partial } \eta^2 = 0.43$) was observed. There also was a marginally significant main effect of Time on symptom-focused rumination ($F[2,22] = 3.24, p = .06, \text{partial } \eta^2 = 0.23$), with a significant linear trend ($F[1,11] = 5.54, p < .05, \text{partial } \eta^2 = 0.34$).

The main effect of Time on self-focused rumination was characterized by a non-significant decrease from Time 1 to Time 2 ($M_{I-J} = 1.21, SE = 0.94, p > .05$) and a subsequent non-significant decrease from Time 2 to Time 3 ($M_{I-J} = 2.57, SE = 2.13, p > .05$). The marginally significant main effect of Time in case of symptom-focused rumination was characterized by a marginally significant decrease from Time 1 to Time 2 ($M_{I-J} = 2.50, SE = 1.22, p = .07$) and a subsequent non-significant decrease from Time 2 to Time 3 ($M_{I-J} = 0.83, SE = 1.44, p > .05$).

When comparing effects of the mood induction and subsequent mindfulness support to baseline, at Time 1 assessments, there was a highly significant main effect of Condition on positive affect ($F[2,22] = 6.41, p < .01, \text{partial } \eta^2 = 0.37$), qualified by a significant linear trend ($F[1,11] = 10.74, p < .001, \text{partial } \eta^2 = 0.49$). Bonferroni-corrected simple comparisons showed that the trend was produced by significantly reduced positive affect following the mood induction ($M_{I-J} = 0.54, SE = 0.15, p < .01$), and a subsequent non-significant increase following the mindfulness support condition ($M_{I-J} = -0.13, SE = 0.19, p > .05$). For the measure of negative affect, there was no significant effect of Condition ($F[2,22] = 2.05, p > .05, \text{partial } \eta^2 = 0.16$). At Time 2 assessments, there was no significant effect of Condition on positive ($F[2,22] = 0.96, p > .05, \text{partial } \eta^2 = 0.08$) or negative affect ($F[2,22] = 0.98, p > .05, \text{partial } \eta^2 = 0.09$).

At Time 3, a marginally significant main effect of Condition on positive affect ($F[2,10] = 3.39, p = .08, \text{partial } \eta^2 = 0.40$) was observed, which was produced by a non-

significant decrease in positive affect following the sad mood induction ($M_{I-J} = 0.22$, $SE = 0.13$, $p > .05$), and a subsequent non-significant increase after the mindfulness support condition ($M_{I-J} = -0.13$, $SE = 0.20$, $p > .05$). There was no significant effect of Condition on negative affect (all $p > .05$).

Brain electrical activity measures

Analysis 1

The omnibus MANOVA showed that there was a significant main effect of Time on FAA for the assessments following the sad mood induction ($F[2,28] = 4.21$, $p < .05$, partial $\eta^2 = 0.23$). Separate ANOVAs for each electrode pair revealed that the main effect was significant only for frontopolar electrodes [Fp1/Fp2: ($F[1,29] = 7.83$, $p < .01$, partial $\eta^2 = 0.21$); F3/F4: ($F[1,29] = 0.49$, $p > .05$, partial $\eta^2 = 0.03$)], and qualified by a significant decrease in asymmetry scores from Time 1 to Time 2 ($M_{I-J} = 0.057$, $SE = 0.020$, $p < 0.01$, Fig. 13a). At Time 1, there was a marginally significant difference in asymmetry scores for frontopolar leads between groups ($t[29] = -1.91$, $p = 0.07$). There also was a main effect of Time on FAA during the neutral condition, albeit it failed to reach significance ($F[2,28] = 2.86$, $p = .07$, partial $\eta^2 = 0.17$).

Analysis 2

No significant effects were observed.

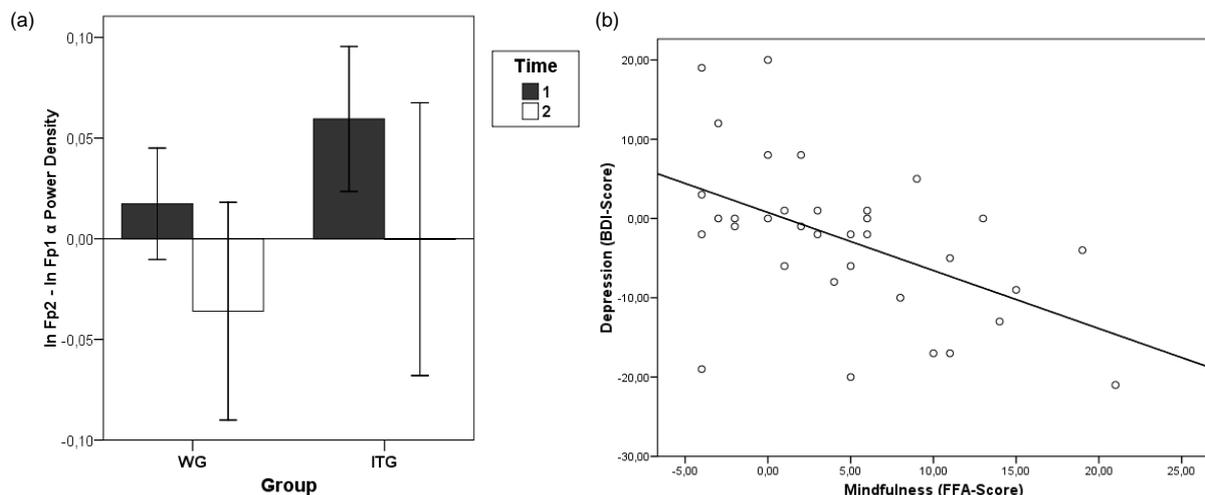
Relations among measures

To evaluate associations among measures, change scores for FAA at frontopolar electrodes and self-report measures from Time 1 to Time 2 were computed and correlated. There was no significant association between FAA and self-report measures. However, mindfulness was

found to be a predictor of decreased depression scores across groups, as indicated by post hoc correlation analyses ($\tau = -.373, p = .001, \text{Fig. 13b}$).

Fig. 13. Mean scores of FAA and the relation between mindfulness and depression

a) Mean scores of functional anterior alpha-asymmetry for electrode pair Fp1/Fp2 following the negative mood induction, displayed separately by time and group. The ordinate represents a metric of right – left log-transformed power density. Higher numbers on this metric indicate greater relative left-hemispheric activation. Error bars reflect 95% confidence intervals; b) Scatter plot of the relation between alterations in mindfulness and depression from Time 1 to Time 2 in both groups. ITG, immediate treatment group. WG, waiting group. FFA, Freiburger Fragebogen zur Achtsamkeit. BDI, Beck Depression Inventory.



6.4. Discussion

The purpose of the current study was to replicate previous findings of treatment effects of MBCT on measures of affect, rumination, mindfulness, and FAA in recurrently depressed patients in remission. In addition to the replication of earlier findings, a further goal was to explore whether treatment effects of MBCT also generalize to conditions characterized by state mindfulness.

With regard to the findings of treatment effects on FAA as reported in previous studies (Study 1; Barnhofer et al., 2007), the current research does not provide a consistent replication

of previous results. While patients with a history of MDD who participated in an MBCT course displayed stable FAA, whereas patients assigned to waiting conditions displayed spontaneous deteriorations toward stronger relative right-hemispheric anterior activity in previous studies, in the current research, stability and deteriorations were observed regardless of group status in various conditions. In particular, for assessments which occurred under the neutral condition and following the provision of mindfulness support, changes in FAA observed from Time 1 to Time 2 were only marginally or not significant, respectively. In contrast, for the assessments which occurred following the negative mood induction, i.e. a condition particularly detrimental for recurrently depressed patients, a deterioration in FAA was observed, which was not group-specific. This heterogeneous pattern of results restricts interpretations, since the basic premise of a spontaneous deterioration in FAA during the waiting period was not consistently met.

Several interpretations of the current findings are possible. Firstly, one may claim that the observed deterioration toward stronger relative right-hemispheric activity in the negative mood condition may indicate that the treatment was not successful. If this was the case, it would be congruous with previous reports to find deteriorated FAA at Time 2 in both groups. While this claim may appear sensible with regard to results of earlier studies (Study 1; Barnhofer et al., 2007), it is challenged by the finding that patients of the ITG reported significantly reduced depressive symptoms and increased mindfulness at Time 2 (Fig. 11). The claim of non-effectiveness is further challenged indirectly by the observation that increased mindfulness was predictive of decreased depressive symptoms at Time 2 assessments for the whole sample, a finding which is supportive of the known protective effect of mindfulness (Raes et al., 2009). Hence, the deterioration in FAA in the ITG can hardly be attributed to a failure of the MBCT courses to improve the participants' subjectively judged condition.

In order to obtain further information about the nature of the main effect of Time, which was observed for assessments following the negative mood induction in Analysis 1, in a post hoc analysis, the alteration in FAA was examined separately for each group. This analysis revealed that the deterioration in FAA was marginally significant in both groups (both $p = .06$; Fig. 13a). Two inferences can be derived from this observation. On the one hand, there is no indication that the treatment had any effect on FAA, despite the alleviation of depressive symptoms and increased mindfulness. On the other hand, a spontaneous deterioration in the untreated group approached significance. Hence, while these results do not provide any support for a prophylactic effect of MBCT on FAA, they do provide limited support for FAA not being stable in recurrently depressed patients in remission. The observation of a spontaneous deterioration is congruent with earlier findings (Study 1; Barnhofer et al., 2007), albeit it did not generalize to the neutral condition. A similar post hoc analysis of the marginally significant effect of Time on FAA under the neutral condition however revealed, that the deterioration in FAA was significant for frontopolar electrodes ($p = .03$). This result may be regarded as further support for the instability of FAA in recurrently depressed patients, even though this conclusion is clearly limited by the fact that the analysis was only post hoc and that a significant main effect of Time on FAA in the neutral condition was lacking.

Observations made in the WG at Time 3 assessments also do not support the notion that the prophylactic effect of MBCT may manifest in improvements toward stronger relative left-hemispheric anterior activation subsequent to deterioration. In Analysis 2, no significant effects were observed altogether. A post hoc analysis showed that the deterioration in FAA at frontopolar sites, which was given in the WG from Time 1 to Time 2 in Analysis 1, was also reflected in a marginally significant decrease in asymmetry scores at the same measurement points in those 12 participants who were available for Analysis 2 ($p = .06$). This was the case despite the fact that in Analysis 2, the negative mood induction was not successful at Time 2

assessments. Nevertheless, the subsequent increase in asymmetry scores from Time 2 to Time 3 failed to reach significance ($p = .33$), albeit again the negative mood induction was not successful. In sum, in the current research, counteractive effects of MBCT on previously deteriorated FAA as reported in Study 1 could not be replicated.

In addition, contradicting the original hypotheses, no associations were observed between alterations in FAA and self-reported mindfulness, rumination, and depression. Therefore, the current study also failed to provide new evidence on the relation of mindfulness and rumination to the approach-withdrawal model of hemispheric asymmetry.

Finally, a novel observation was made for the introduced condition of mindfulness support. In the context of previous studies on effects of mindfulness-based interventions on FAA (Study 1; Barnhofer et al., 2007; Davidson et al., 2003), to date, this was the first time that patients were supported with mindfulness instructions. Participants of the WG did not display a deterioration for this condition from Time 1 to Time 2. While this observation contradicted initial assumptions of this study, it remains to be verified whether the previously reported spontaneous deterioration in FAA generalizes to such an appetitive condition, for which stability of FAA might occur in untreated patients as well. Due to the heterogeneous pattern of results with regard to altered FAA from Time 1 to Time 2 across conditions, as well as the lack of a spontaneous deterioration in FAA for the mindfulness support condition in the WG, one cannot verify whether the observed stability in the ITG was in any way related to the treatment through MBCT.

In sum, the current study is the third to provide support for the instability of FAA in recurrently depressed patients in remission. Even though results were not as robust as in Study 1, they indicate that this patient population may display increased relative right-hemispheric anterior cortical activation over time, a pattern which has previously been shown to predict depression (Possel et al., 2008), and which has been hypothesized to be a precursor of depressive relapse, reflecting increased vulnerability (Barnhofer et al., 2007). Contradicting

results of earlier studies (Study 1; Barnhofer et al., 2007), the present research does not support the notion that the known prophylactic effect of MBCT (Ma & Teasdale, 2004; Teasdale et al., 2000) is reflected in stable FAA. Further, no support was provided for a systematic relation between rumination and mindfulness on the one hand and FAA on the other, in the context of the approach withdrawal model of hemispheric asymmetry. Notable limitations of the current research are the same as those of Study 1, in particular that a small sample size was involved.

7. General Discussion of Study 1 and Study 2

With regard to previous studies on structured mindfulness-based interventions and their effect on maladaptive behavior patterns and FAA, to this point, the current research has provided novel findings, as well as mixed results in terms of the replication of earlier observations.

7.1. Effects of MBCT on indices of affect and affect regulation

In line with previous reports (Deyo et al., 2009; Raes et al., 2009; Ramel et al., 2004), a consistent finding of Study 1 and Study 2 was the association of mindfulness training and improvements on concurrent indices of emotion and emotion regulation. Study 1 successfully replicated the attenuating effect of mindfulness training on ruminative tendencies. Even though there was no such effect on rumination in Study 2, significantly increased self-reported mindfulness and decreased depression were observed in the latter study. Mindfulness is regarded to be inversely related to rumination (Nolen-Hoeksema et al., 2008). Hence, results of Study 1 and Study 2 implicate consistently, that the participation in MBCT courses is beneficial for recurrently depressed patients in remission, leading to improved psychological functioning. The current research therefore further strengthens the growing body of evidence which suggests, that the known prophylactic effect of MBCT (Godfrin & van Heeringen, 2010; Ma & Teasdale, 2004; Teasdale et al., 2000; Williams et al., 2008) is closely related to the extenuation of maladaptive traits, such as rumination, and the consolidation of protective ones, such as mindfulness.

7.2. Effects of MBCT on functional anterior brain asymmetry

In terms of FAA, its plasticity in recurrently depressed patients, as well as its alterations through mindfulness training, the current research has provided mixed results. Study 1 was successful in replicating findings by Barnhofer et al. (2007), and showed that the prophylactic

effect of MBCT may manifest in stable FAA, counteracting a spontaneous deterioration toward stronger relative right-hemispheric anterior activation. This finding was not only replicated, but shown to generalize to conditions which are known to be detrimental for recurrently depressed patients, i.e. negative mood and rumination. Study 1 provided further novel findings, since an initial spontaneous deterioration in FAA could be counteracted by subsequent mindfulness training, and since stability in FAA following training was relatively enduring. In addition, results of Study 1 suggest that rumination may represent a behavioral trait associated with neurophysiological correlates of withdrawal. Rumination may therefore vary systematically with FAA, and may be ascribed the characteristic of a withdrawal/avoidance-related trait in the context of the approach withdrawal model of hemispheric asymmetry (Davidson, 2001), albeit, a more thorough investigation is necessary to confirm this notion. Results of Study 2 on the other hand represent only a partial replication of earlier observations, and disconfirm several previous findings. In Study 2, the finding of a spontaneous deterioration in FAA toward stronger relative right-hemispheric activity in recurrently depressed patients could be replicated for the sad mood condition only, notably a condition detrimental for the involved participants. Nevertheless, in the neutral condition, and in the condition in which mindfulness support had been provided, no significant deterioration occurred. Hence Study 2 provides some limited support for a spontaneous deterioration of FAA in recurrently depressed patients, reflecting a more withdrawal-related affective style. Nevertheless, the prophylactic effect of MBCT manifesting in stable FAA, contrasted with deterioration in the absence of treatment, could not be replicated. The same was true for the counteractive effect of MBCT on previously deteriorated FAA, and an association of FAA and rumination.

The instability of FAA in recurrently depressed patients

For brain physiological measures, the main consistent finding across Study 1 and Study 2 was the instability of FAA in untreated recurrently depressed patients, characterized by a spontaneous deterioration over time. This pattern was initially assumed to be observed based on findings by Barnhofer et al. (2007). In the context of the present research, to explore the psychophysiological mechanisms of the prophylactic effect of MBCT, the fact that this pattern was observed in Study 1 and Study 2 may be seen only as a limited success. Nevertheless, with regard to the fact that it has been repeatedly asserted, that FAA in MDD is relatively stable, the finding is of great significance. Measures of FAA reflect state as well as trait-components (Hagemann et al., 2005; Hagemann et al., 2002). In this context, it is important to point out again that there exists some support from studies using within-subjects designs for a high retest-stability of FAA and its independence from clinical status in MDD. Allen et al. (2004b) conducted a study specifically designed to address this issue and found that patients who were experiencing an MDE when admitted, displayed relatively stable FAA despite symptom-alleviation through treatment on several follow-up measures. Since this study involved a larger sample size than the current research, results reported in Study 1 and Study 2 need to be regarded with caution, albeit results obtained by Allen et al. (2004b) do not necessarily have to be generalizable to patients in remission. Similarly, in a study examining the long-term stability of FAA in individuals with a history of depression, Vuga et al. (2006) found FAA to be moderately stable. In the indicated study, however, it was not specified whether participants were in a state of remission at initial assessments or not. Further, as the authors note themselves, the use of a vertex reference scheme, which is problematic for numerous reasons (Hagemann, Naumann, & Thayer, 2001) limits conclusions to be drawn from this finding. Importantly, the design of neither of the two studies (Allen et al., 2004b; Vuga et al., 2006) can rule out the possibility that FAA in recurrently depressed patients in remission may shift to stronger relative right-hemispheric anterior activity spontaneously,

indicating increased vulnerability, as reported and suggested by Barnhofer et al. (2007). In this sense, both Study 1 and Study 2 extend the existing body of literature on the issue of a questionable stability of FAA in individuals suffering from recurrent MDD. To thoroughly address the issue of retest-stability in this population however is beyond the scope of this work, for it requires a larger scaled study to provide appropriate statistical power. Further, numerous additional factors which might have had an impact on FAA were not controlled, e.g. the time of the day during which recording took place, seasonal effects and negative life events. Future research is necessary to verify whether findings on the plasticity of FAA turn out to be robust.

The relation of the prophylactic effect of MBCT and stable FAA

It remains to be verified, why the replication of the prophylactic effect of MBCT in physiological terms, initially reported by Barnhofer et al. (2007), was successful in Study 1, while a replication failed in Study 2. Several reasons may account for the failure to replicate earlier results in Study 2, some of which can be tested post hoc, while others remain speculative due to the design of the involved studies.

For sample characteristics which were not assessed during the diagnostic interviews or during the course of the study, but which may have had an impact on groups across studies, merely speculations are possible. It is a shortcoming of both studies, that the experience with cognitive therapy was not assessed systematically. As described in detail in section 2.1., cognitive therapy itself is known to express prophylactic effects in recurrently depressed patients, reducing the likelihood of depressive relapse (e.g. Hollon et al., 2005). Teasdale et al. (2002) suggest that the cultivation of metacognitive awareness during cognitive therapy may be a critical element of this prophylactic effect. The fact that experience with cognitive therapy was not assessed systematically in the current sample makes it impossible to test, whether the positive outcomes in Study 1, in contrast to mixed results in Study 2, were

causally linked to patients' treatment experience prior to the MBCT intervention. While random assignment to the immediate treatment and the waiting condition probably ruled out any relevant group differences in terms of experience with cognitive therapy within studies, it is possible that differences across studies were given. For instance, in Study 2, the involvement of relatively more patients with such experience compared to Study 1 may have yielded these patients to be more protected from autonomic processes causing relapse (Teasdale et al., 2002). Results of Study 1 indicated that increased rumination might be associated with stronger relative right-hemispheric activity. Hence, it is conceivable, that an effect of former cognitive therapy, yielding greater protection from internal relapse mechanisms such as rumination, resulted in a more pronounced stability in FAA, which was observed for the neutral condition in Study 2. On the other hand, the apparently successful treatment in Study 2 probably would have added to such an effect, and hence, deterioration in FAA which occurred during the negative mood condition in Study 2, and which was not group-specific, can hardly be sensibly explained by this reasoning.

Another possibly relevant factor which was not assessed may be the occurrence of negative life events throughout the study. As noted in section 1.3., major life stress has a greater association with the first onset of a MDE relative to a recurrence (Monroe & Harkness, 2005). Hence depressive relapse appears to become increasingly autonomous from external stressors (Post, 1992). Nevertheless, this does not imply that life stress has no impact in later stages of MDD. It is possible that during the course of the research project, negative life events were more common for participants in Study 1, leading to a more pronounced deterioration in FAA in these patients. This may have accounted for a more consistent pattern of alterations of FAA, indicating increased withdrawal tendencies across all conditions in the WG from Time 1 to Time 2 assessments. In contrast, in Study 2, the absence of such events may have accounted for a more inconsistent pattern, with relative stability of FAA for the neutral condition. Barnhofer et al. (2007) do not provide any information as to whether

negative life events were given during the course of their study. Hence, it cannot be rule out, that such events affected the alterations of FAA reported by the authors.

While these accounts are bound to remain speculative, the possibility for post hoc testing is provided for others. Factors which appear particularly relevant in the determination of the course of MDD are, as indicated in section 1.3. and 2.1., the number of previously experienced MDE, as well as medication status (American Psychiatric Association, 2000a; Post, 1992). Focusing on the inconsistency across Study 1 and Study 2, which was given for FAA assessed during the neutral condition, one may argue, that patients involved in Study 1 had a psychiatric history of more MDE than patients involved in Study 2. This may explain why a deterioration in FAA was given in the former, but not in the latter. The sample characteristics however reveal that the number of experienced MDE was relatively balanced across Study 1 (ITG: Mdn = 4, range = 3-9; WG: Mdn = 4, range = 3-20) and Study 2 (ITG: Mdn = 5, range = 4-15; WG: Mdn = 6, range = 5-20). Patients assigned to the WG in Study 1 did not have a history of significantly more MDE than patients of the WG in Study 2 ($p > .05$). Consequently, the amount of experienced MDE cannot explain that the deterioration in the WG differed across studies for the neutral condition. Regarding medication status, one may argue that a more consistent deterioration in FAA was related to patients of the WG in Study 1 receiving relatively less anti-depressants than patients of the WG in Study 2. The sample characteristics show however that the relative amount of medicated and non-medicated participants was balanced (Study 1: yes 11/no 9; Study 2: yes 11/no 5, $\chi^2[1,36] = .71$, $p > .05$). Neither differences in medication status nor the amount of previously experienced MDE could explain inconsistent alterations in FAA across studies. Further putatively useful variables which were available for post hoc analyses were sex ratio, level of trait rumination and mindfulness given at initial assessments, age, and age at onset of the first episode. With regard to the sex ratio, a post hoc analysis appears necessary due to the elevated risk in women to suffer from depression, and gender-specific findings on rumination and FAA

(Accortt & Allen, 2006; Nolen-Hoeksema et al., 2008; Wells et al., 1989). It also seems feasible to test for group differences in rumination and mindfulness across studies at baseline, since this may provide information about initial differences in vulnerability. Finally, age and age at onset of the first episode in particular may be helpful to discriminate between different base populations of MDD patients (Ma & Teasdale, 2004). These post hoc analyses showed that sex ratios per group did not differ significantly across studies (ITG Study 1: 15 female/4 male, ITG Study 2: 14 female/5 male, $\chi^2[1,38] = .15$; WG Study 1: 16 female/4 male, WG Study 2: 10 female/6 male, $\chi^2[1,36] = 1.36$, all $ps > .05$). The comparison of initial levels of symptom-focused, self-focused rumination, and mindfulness as reported in sections 5.2 and 6.2 did not yield any significant results, as did the comparison for the age of onset of the first MDE (all $ps > .05$). Patients of the WG of Study 1 were significantly older than those of the WG of Study 2 (Study 1: $M = 50.95$, $SD = 9.61$; Study 2: $M = 41.50$, $SD = 10.78$, $t[34] = 2.78$, $p < .01$). In contrast, patients of the ITG did not significantly differ in age across studies (Study 1: $M = 51.63$, $SD = 9.88$; Study 2: $M = 46.26$, $SD = 8.37$, $t[36] = 1.81$, $p > .05$). In sum, given the data at hand, the only characteristic which could be identified to differ was the age of participants of the WG across studies. An interpretation of this difference as to whether different base populations were involved appears exaggerated. Consequently, clear reasons for the failure to replicate previously reported effects of MBCT on FAA in Study 2 could not be identified with the information about the groups at hand. Those reasons remain speculative, and it is necessary that relevant variables are more thoroughly assessed in future research.

To this point, the current research could not clearly verify, whether prophylactic effects of MBCT indeed manifest in stable FAA counteracting a spontaneous deterioration. Nevertheless, the consistent observations of improvements in psychological functioning, i.e. decreased trait rumination and increased mindfulness, support the usefulness of MBCT for patients suffering from recurrent MDD. With regard to the relation of FAA and psychological functioning in the context of MBCT, a peculiar finding in Study 1 was a strong association

between alterations in FAA and rumination, as well as FAA and mindfulness. This association may be potentially useful in strengthening the interpretation of a prophylactic effect of MBCT manifesting in stable FAA, for if it turns out to be a robust one, MBCT would express effects on a putatively withdrawal/avoidance-related behavioral trait in case of rumination, and an approach related behavioral trait in case of mindfulness. While the association between the indicated variables was only observed in a very small sample in Study 1 across two assessments, Study 3 intended to verify this notion with methodologically more sound methods.

8. Study 3: The Relation of Trait Functional Anterior Brain Asymmetry, Mindfulness and Rumination

8.1. Hypotheses

With regard to the inconsistent results of Study 1 and Study 2, the purpose of Study 3 was to examine the relation between FAA, mindfulness and rumination as traits. Information on this matter may be potentially useful to verify whether the effect of MBCT, possibly manifesting in stable FAA, indeed indicates elevated resilience, despite disconfirming results of Study 2. Even though Reid et al. (1998) pointed out the importance to identify the relation between rumination and FAA, to date, no study has been conducted to deal with this matter directly. Based on the observations made in Study 1, in which shifts toward stronger relative right-hemispheric anterior cortical activation in the WG were predictive of elevated rumination and attenuated mindfulness (Fig. 10), one may suggest that rumination represents a withdrawal-related trait, whereas mindfulness may represent an approach related trait in recurrently depressed patients. MBCT has been repeatedly shown to increase trait mindfulness and decrease ruminative tendencies (Deyo et al., 2009; Jain et al., 2007; Kingston et al., 2007; Michalak et al., 2008; Ramel et al., 2004). According to results of Study 1, in the context of the approach withdrawal model of hemispheric asymmetry (Davidson, 1992, 1995, 2001), reported effects of MBCT, which counteract a spontaneous deterioration in FAA, may in part be accounted for by a trained adaptive alteration in mindfulness and rumination. Hence, if associations between FAA on the one hand, and rumination and mindfulness on the other can be revealed to be robust on a trait level, this may foster attempts to integrate assumed protective working mechanisms of MBCT with the approach withdrawal model of hemispheric asymmetry.

In Study 3, analyses of the associations of FAA, mindfulness, rumination and depression on a trait level were conducted in three groups. The first two groups comprised

participants of Study 1 and Study 2, respectively. The third group comprised participants of Study 1 and Study 2 combined. Due to the contrasting results obtained in Study 1 and Study 2, one cannot rule out the possibility that patients of the respective studies represent separate base populations, albeit putatively distinct characteristics remain speculative, as noted in section 7.2. Hence, in the current study, separate, as well as combined analyses were conducted for the two samples. Brain physiological measures obtained during a neutral resting condition at initial assessments, and trait self-report measures completed upon admission to the study were utilized. Based on the rationale outlined above, higher trait mindfulness was expected to be predictive of stronger relative left-hemispheric anterior cortical activation, indicating higher approach tendencies. In contrast, higher trait rumination was assumed to be predictive of stronger relative right-hemispheric activation, reflecting an avoidance-related affective style and higher withdrawal tendencies. The outlined associations were expected to generalize across all three samples. In line with suggestions of section 5.4, a further goal was to assess whether putative relations between FAA and self-reported depression were mediated by rumination or mindfulness.

8.2. Methods

Participants, self-report measures, procedure, electrophysiological recording and analysis

As indicated, data of participants of Study 1 (n = 39, 8 male) and Study 2 (n = 35, 11 male) were included in the analyses of the current study. Information about recruitment and sample characteristics are given in sections 5.2., and 6.2. Self-report data were obtained with the Response Styles Questionnaire (RSQ-D; Kühner et al., 2007), a self-report measure of trait rumination, the Freiburger Fragebogen zur Achtsamkeit (FFA; Walach et al., 2003), a self-report measure of trait mindfulness, and the Beck Depression Inventory (BDI-II; Hautzinger et al., 2007). The procedures of the relevant studies are outlined in sections 5.2., and 6.2. Data included in the current study was obtained through assessments which took place under a

neutral condition at Time 1 in both studies. Electrophysiological recording and analysis followed the same procedure as described in detail in Study 1, however, asymmetry measures were computed for seven different sites (electrode pairs), i.e. frontopolar (Fp1/Fp2), lateral and medial frontal (F7/F8, F3/F4), medial frontocentral (FC1/FC2), medial central (C1/C2), medial centroparietal (CP1/CP2) and medial parietal (P3/P4).

Statistical analysis

Due to the fact that it cannot be ruled out that patients involved in Study 1 and Study 2 represent distinct base populations of recurrently depressed patients, statistical analyses were conducted for three groups, i.e. participants included in Study 1 (Sample 1), participants of Study 2 (Sample 2), and a group combined of the two (Combined Sample). The analysis was the same for each group.

Similar to a procedure described by Hewig et al. (2004), general linear models (GLM) with repeated measures were used to test the hypotheses. These models involved two categorical topographic factors, i.e. Region and Laterality. Data obtained through the respective self-report measure was entered as a continuous predictor variable, since this has been argued to be a statistically more sound procedure than a median split due to the avoidance of statistical artifacts (Aiken & West, 1991; Bissonnette et al., 1990).

The factor Laterality had two levels, left vs. right. The factor Region had seven levels (one frontopolar position: Fp1/Fp2; two frontal positions: F3/F4, F7/F8; one frontocentral position: FC1/FC2, one central position: C1/C2, one centroparietal position: CP1/CP2, and one parietal position: P3/P4). Each z-transformed self-report scale, i.e. symptom-focused rumination ($Rumination_{Sym}$), self-focused rumination ($Rumination_{Self}$), and Mindfulness was entered as a continuous predictor, in separate models. The analysis focused on three-way interactions between topographic factors and the self-report scales, albeit two-way interactions between Laterality and the self-report scales were considered as well. The three-

way interactions were used to test the assumption that the regression between alpha activity and the self-report score varied as a function of Region and Laterality. The p levels of all effects were Huynh-Feldt corrected.

For each significant interaction, post hoc correlations between the respective questionnaire and alpha asymmetry measures were computed. The three hypotheses outlined in section 8.1. imply the occurrence of three-way interactions of the two topographical factors and the respective questionnaire scale. As noted in Study 1 and Study 2, higher values on the asymmetry index reflect stronger relative left-hemispheric cortical activation, i.e. approach-related affective style. Hence, post hoc analyses should reveal significant positive correlations between Mindfulness and asymmetry measures for anterior scalp locations, as well as significant negative correlations between Rumination_{Sym} and Rumination_{Self} and asymmetry measures for anterior scalp locations. Significant two-way interactions of Laterality and self-report measures may still be informative with regard to the hypotheses, albeit they do not allow for the specification that the predictive value of lateralized alpha-power was given for anterior sites and not for posterior ones.

8.3. Results

Descriptive intercorrelations of the self-report measures for each sample are presented in Table 3. There were significant negative correlations between Mindfulness and Rumination_{Sym} in all three samples, corresponding to the known antagonistic effect of mindfulness on rumination. Similarly, consistent negative correlations between Mindfulness and Rumination_{Self} were obtained, albeit they did not reach significance. Rumination_{Self} and Rumination_{Sym} showed significant positive correlations in all three samples, reflecting the congruency of the constructs. Depression was negatively correlated with Mindfulness across all samples, with significant values in Sample 2 and the Combined Sample, in line with the known effect of mindfulness to protect from depression. Depression further showed a

consistent pattern of significant positive correlations with Rumination_{Sym} and Rumination_{Self} across all samples, in accord with the known detrimental effect of rumination on symptoms of depression.

Table 3. Descriptive Intercorrelations

Descriptive intercorrelations of self-report measures by sample. Rum_{Sym}, symptom-focused rumination. Rum_{Self}, self-focused rumination. * $p < 0.05$. ** $p < 0.01$.

<i>Measure</i>	<i>Sample 1</i>			<i>Sample 2</i>			<i>Combined Sample</i>		
	Mindfulness	Rum _{Sym}	Rum _{Self}	Mindfulness	Rum _{Sym}	Rum _{Self}	Mindfulness	Rum _{Sym}	Rum _{Self}
Rum _{Sym}	-.399*			-.434**			-.417**		
Rum _{Self}	-.146	.520**		-.203	.525**		-.176	.522**	
Depression	-.241	.379*	.287*	-.670**	.435**	.298*	-.547**	.471**	.354**

Sample 1

There was a significant three-way interaction, Region \times Laterality \times Rumination_{Sym} ($F[6,192] = 3.84, p = .019, \text{partial } \eta^2 = 0.11$). The post hoc correlation analysis revealed that the interaction was characterized by significant negative correlations between Rumination_{Sym} and asymmetry measures obtained for frontopolar and frontolateral sites (Fp1/Fp2: $r = -.30, p = .042$; F7/F8: $r = -.37, p = .02$), as well as medial central sites (C1/C2: $r = .29, p = .047$). The interaction Region \times Laterality \times Rumination_{Self} was not significant ($F[6,192] = 2.26, p = .11, \text{partial } \eta^2 = 0.07$), as were the interactions Region \times Laterality \times Mindfulness ($F[6,192] = 1.98, p = .13, \text{partial } \eta^2 = 0.06$), and Region \times Laterality \times Depression ($F[6,192] = 1.25, p = .30, \text{partial } \eta^2 = 0.03$). There were no significant two-way interactions.

Sample 2

There was a marginally significant three-way interaction, Region \times Laterality \times Rumination_{Self} ($F[6,204] = 2.48, p = .06, \text{partial } \eta^2 = 0.07$), and a significant two-way

interaction Laterality \times Rumination_{Self} ($F[1,34] = 6.45, p = .02, \text{partial } \eta^2 = 0.16$). Post hoc correlations revealed a significant negative correlation between Rumination_{Self} and asymmetry measures at frontolateral, as well as medial central and medial centroparietal sites (F7/F8: $r = -.355, p = .02$; FC5/FC6: $r = -.463, p = .002$; C1/C2: $r = -.377, p = .01$; CP1/CP2: $r = -.349, p = .02$).

The three-way interaction, Region \times Laterality \times Rumination_{Sym} was not significant ($F[6,204] = 1.74, p = .16, \text{partial } \eta^2 = 0.05$). However, there was a marginally significant two-way interaction Laterality \times Rumination_{Sym} ($F[1,34] = 4.11, p = .051, \text{partial } \eta^2 = 0.11$). The post hoc correlation analysis indicated significant negative correlations between Rumination_{Sym} and asymmetry measures at lateral frontal, medial frontocentral, as well as medial central sites (F7/F8: $r = -.364, p = .015$; FC1/FC2: $r = -.286, p = .045$; C1/C2: $r = -.328, p = .025$).

The three-way interaction Region \times Laterality \times Mindfulness, ($F[6,204] = 1.72, p = .17, \text{partial } \eta^2 = 0.05$), was not significant, however the two-way interaction Laterality \times Mindfulness was highly significant ($F[1,34] = 17.328, p < .001, \text{partial } \eta^2 = 0.34$). Post hoc correlations showed that it was characterized by significant positive correlations between Mindfulness and asymmetry measures obtained for frontopolar, lateral and medial frontal, medial frontocentral, and medial central sites, while the correlation for medial centroparietal and parietal sites were not significant (Fp1/Fp2: $r = .62, p < .001$; F7/F8: $r = .47, p = .002$; F3/F4: $r = .53, p = .001$; C1/C2: $r = .42, p = .005$; CP1/CP2: $r = .290, p = .08$; P3/P4: $r = .25, p = .15$).

The three-way interaction Region \times Laterality \times Depression was not significant ($F[6,204] = 1.34, p = .26, \text{partial } \eta^2 = 0.04$). However, the two-way interaction Laterality \times Depression was significant ($F[1,34] = 7.94, p = .008, \text{partial } \eta^2 = 0.19$). The post hoc correlation analyses showed that there were significant negative correlations of Depression and asymmetry measures derived from frontopolar, frontolateral, and medial central

electrodes (Fp1/Fp2: $r = -.52, p = .001$; F7/F8: $r = -.48, p = .001$; C1/C2: $r = -.328, p = .025$), while no significant relations with other sites were obtained (all $ps > .05$).

Combined Sample

In the combined sample, a marginally significant three-way interaction, Region \times Laterality \times Rumination_{Sym} ($F[6,408] = 2.12, p = .09, \text{partial } \eta^2 = 0.03$), was observed. The post hoc correlations indicated significant negative associations between Rumination_{Sym} and asymmetry measures at frontolateral sites (F7/F8: $r = -.31, p = .005$).

The three-way interaction Region \times Laterality \times Rumination_{Self} ($F[6,408] = 1.39, p = .22, \text{partial } \eta^2 = 0.02$) was not significant, as was the interaction Region \times Laterality \times Mindfulness ($F[6,408] = 1.17, p = .32, \text{partial } \eta^2 = 0.02$). The three-way interaction Region \times Laterality \times Depression was also not significant ($F[6,408] = 1.45, p = .23, \text{partial } \eta^2 = 0.02$). However, the two-way interaction Laterality \times Depression was marginally significant ($F[1,71] = 3.00, p = .08, \text{partial } \eta^2 = 0.05$). In this case, post hoc correlation analyses indicated that Depression correlated negatively with asymmetry scores obtained for frontopolar and lateral frontal sites (Fp1/Fp2: $r = -.310, p = .004$; F7/F8: $r = -.415, p < .001$).

Explorative mediation analysis

The current results allow for a mediation analysis, to investigate whether the association between FAA and Depression is mediated by Rumination, as has been speculated in section 5.4. In particular, in the Combined Sample, the constellation of correlations between FAA, Rumination_{Sym}, and Depression allows the identification of Rumination_{Sym} as a putative mediator. As displayed in Table 3, showing the descriptive intercorrelations of the respective self-report measures, there was a significant positive correlation between Depression and Rumination_{Sym}. The post hoc correlation analyses of the marginally significant two-way interaction Laterality \times Depression further revealed significant negative correlations of

Depression and asymmetry scores at frontopolar and frontolateral sites. In addition, the post hoc correlation analysis of the marginally significant two-way interaction Laterality \times Rumination_{Sym} revealed that Rumination_{Sym} was negatively correlated with asymmetry measures at frontopolar and frontolateral sites. A conceptual outline of the observed relations is displayed in Fig. 14. Detailed regression analyses of the described constellations are provided in Table 4.

Table 4. Regression analyses testing rumination as a putative mediator of the relationship between FAA obtained for frontolateral sites (F7/F8) and depressive symptoms.

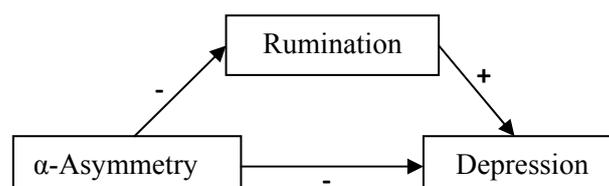
Variables	β	T	Total R ²	F
Dependent Variable: Depression				
FAA	-.42***	-3.85	.17	14.80***
Dependent Variable: Rumination _{Sym}				
FAA	-.31**	-2.64	.09	6.96**
Dependent Variable: Depression				
Rumination _{Sym}	.25*	2.16	.35	18.11***
FAA	-.43***	-3.72		

*** $p < .001$

** $p < .01$

* $p < .05$

Fig. 14. Conceptual outline of the relationships of symptom-focused rumination, depression and FAA Relations as they were observed in the Combined Sample. α -Asymmetry reflects values obtained for asymmetry measures at frontolateral sites (F7/F8). Note: higher values on this index reflect stronger relative left-hemispheric anterior cortical activation, indicative of approach-related affective style.



To investigate whether the path from FAA to depressive symptoms was mediated by Ruminations_{Sym}, a mediation analysis was performed (Baron & Kenny, 1986). A Sobel test was conducted (Sobel, 1982) to assess the indirect effect of the independent variable on the dependent variable through the mediator. The raw regression coefficients and standard errors were used with FAA and Ruminations_{Sym} predicting Depression. The results were significant and confirmed that Ruminations_{Sym} functioned as a partial mediator between FAA and Depression ($z = -2.26$, $SE = 0.48$, $p = .02$).

8.4. Discussion

The main goal of the current study was to assess the relation between FAA, mindfulness, rumination and depression on a trait level in recurrently depressed patients. Reid et al. (1998) have suggested to verify the role of rumination as a putative mediator of the relation between FAA and depression, and Study 1 revealed that alterations in FAA may be systematically related to alterations in mindfulness and rumination. While in Study 1, this claim was rather speculative since the relationship was only observed in a small group of patients, the current study provides new information using larger samples.

The relation of FAA, rumination, mindfulness and depression on a trait level

Firstly, results of the current study indicate that symptom-focused rumination in particular may vary with FAA. The three-way interaction between the topographic factors and symptom-focused rumination, which was observed in Sample 1, clearly indicates that the predictive utility of alpha power density for levels of symptom-focused rumination differed by hemisphere and location, and was particularly pronounced in anterior regions. Even though no further significant findings emerged for this sample, the results suggest that symptom-focused rumination reflects a withdrawal-related behavioral trait in line with conceptualizations of the approach-withdrawal model of hemispheric asymmetry (Davidson,

1995, 1998, 2001). With regard to the quality of ruminative behavior as described in detail in section 1.3, this categorization is sensible. The excessive reflection about their difficulties and associated affect yields withdrawal and prevents ruminators from engaging in behavior which might result in improvements of their situation. Consequently, approach tendencies, possibly reflected in effective problem solving strategies and instrumental behavior are undermined (Nolen-Hoeksema et al., 2008). In the current study, the occurrence of a marginally significant three-way interaction between topographic factors and self-focused rumination in Sample 2, as well as a marginally significant three-way interaction involving symptom-focused rumination in the Combined Sample, further give some, albeit limited support for results obtained in Sample 1.

While the results obtained for rumination are relatively homogenous across the involved samples, support for mindfulness as an approach-related trait in recurrently depressed patients is somewhat weaker. Despite the strong association of alterations in FAA and mindfulness as reported in Study 1, as well as an increase in relative left-hemispheric anterior activation through mindfulness training in healthy participants as reported by Davidson et al. (2003), there was no significant three-way interaction of topographic factors and mindfulness in either sample. Nevertheless, in Sample 2, a hemisphere-specific effect was observed in case of mindfulness, indicating that mindfulness was predicted by stronger relative left-hemispheric cortical activation, which approximates suggestions of the approach-withdrawal model. While the absence of a three-way interaction does not allow to conclude that the predictive utility of anterior regions was substantially pronounced compared to that of posterior ones, post hoc correlation analyses showed that associations were somewhat more pronounced in frontal areas. The latter finding is congruent with what one would expect according to the approach-withdrawal model, if mindfulness reflected an approach-related trait.

Similarly, the significant two-way interaction between laterality and depression observed in Sample 2, which was also marginally significant in the Combined Sample, was congruent with predictions of the approach-withdrawal model of hemispheric asymmetry and in line with previous reports (Davidson, 1998; Gotlib et al., 1998; Henriques & Davidson, 1990, 1991). In this case, the predictive utility of anterior asymmetry measures was also more pronounced.

In sum, these results replicate previous findings, in showing that depressive symptoms may be associated with neural correlates of withdrawal. Further, rumination may be classified as a withdrawal-related behavioral trait, which is associated with stronger relative left-hemispheric anterior cortical activation on a trait level. While the known antagonist of rumination, mindfulness (Deyo et al., 2009; Jain et al., 2007; Kingston et al., 2007; Ramel et al., 2004), did not show such a clear relation to FAA, in the current study it was shown to be related to stronger relative-left hemispheric cortical activation. Even though this association was not specific for anterior versus posterior sites, it approximates notions of the approach-withdrawal model.

Rumination as a mediator of the relation between FAA and depression

The current study provides further entirely novel results, since the relation between stronger right-hemispheric anterior activation and depressive symptoms was shown to be partially mediated by symptom-focused rumination. The latter finding has several implications.

Firstly, on a theoretical level, it strengthens the utility of the approach-withdrawal model of hemispheric asymmetry in predicting motivational direction (Davidson, 1995, 1998, 2001). On a behavioral level, rumination, which is typical for MDD, can clearly be regarded as withdrawal-related (Nolen-Hoeksema et al., 2008). The current study provides initial support for this claim, by showing up neural correlates, which would be expected accordingly.

Secondly, these results extend the approach-withdrawal model. There have been failures to replicate the relation between FAA and depression (e.g. Reid et al., 1998). While the authors of the latter study could only speculate on putative mediators between FAA and depression, results of the current study suggest that such inconsistencies might be accounted for by rumination. Participants of the latter study may not have displayed enough a tendency to ruminate, and consequently may not have shown the expected association. In this sense, future studies dealing with the relation between FAA and depression need to incorporate measures of rumination.

Limitations of the current study may be seen in the fact that still a relatively small sample size was involved and that no complementary measures of mindfulness, rumination and depression with convergent validity were used to consolidate the observations.

9. General Concluding Remarks and Future Directions

Concluding remarks about the results obtained across studies are necessary with regard to the usefulness of results of Study 3 to partially resolve some of the difficulties which arose through inconsistent results obtained in Study 2.

While Study 1 most importantly reported a spontaneous deterioration and subsequent improvement of FAA through MBCT, as well as associations in the alteration of FAA, mindfulness and rumination, Study 2 in part failed to replicate a spontaneous deterioration, associated changes in self-report measures, as well as the prophylactic effect of MBCT. Even though, as outlined in section 6.4, reasons for these inconsistencies remain speculative, Study 3 provides further support for results obtained in Study 1, especially in terms of the observed relationship between FAA, rumination and mindfulness.

The finding of Study 3, according to which particularly rumination and to a lesser extent mindfulness varies with FAA, provides indirect support for the observation in Study 1, that stronger rumination and weakened mindfulness in the WG at Time 2 assessments were associated with an increase in a neural correlate of withdrawal and a decrease in a correlate of approach, respectively. The results of Study 3 may hence also be seen as indirect support for the relation between a protective effect of MBCT being reflected in FAA.

Is there a double dissociation between FAA, mindfulness and rumination?

With regard to the latter notion, one should point out that the relation between FAA, mindfulness and rumination varied according to whether it was assessed dynamically across sessions as was the case in Study 1, or whether it was assessed on a trait level. In the former case, the relation may be non-linear, or it may only be presented at a certain level of vulnerability in terms of FAA. Firstly, even though in Study 1, a significant decrease in rumination and increase in mindfulness occurred from Time 1 to Time 2 in the ITG, there was no increase in relative left-hemispheric cortical activation. In contrast, Davidson et al. (2003)

report elevated left-hemispheric activation in a group of healthy participants following mindfulness training. While results obtained in healthy participants do not necessarily generalize to the patient population involved in the current work, considering the results reported by Davidson et al (2003), and those of Study 3, one may expect that decreased rumination and increased mindfulness through training are associated with elevated left-hemispheric cortical activation. Nevertheless, such an alteration did not occur in the ITG in Study 1, where a stable pattern of FAA was observed across assessments.

Secondly, despite the fact that there was no significant increase in rumination or decrease in mindfulness in participants of the WG in Study 1 from Time 1 to Time 2 assessments, in the latter group a significant deterioration in FAA occurred, which was associated with only insignificant alterations in rumination and mindfulness. In the same group, a marginally significant decrease in rumination during training from Time 2 to Time 3 was associated with elevated left-hemispheric anterior cortical activation, albeit this association was only marginally significant as well. In contrast, associations on a trait level as reported in Study 3 were clearly given in case of rumination. Hence, these results indicate a differential association of rumination (and possibly mindfulness) and FAA in the context of dynamic assessments related to MBCT and in the context of associations assessed on a trait level. While associations at a trait level appear to be robust in recurrently depressed patients, in the context of MBCT, there appears to be a double dissociation between rumination and FAA which is reflected in the finding that the relation between rumination and FAA vanishes when the vulnerability in terms of FAA is relatively low. The latter observation might also be accounted for by a ceiling effect which occurred in the ITG from Time 1 to Time 2 assessments, so that at a certain point of diminished rumination and elevated mindfulness, a further elevation in left-hemispheric activation ceases to occur. In this sense, it may be possible that the observed relations between the described parameters in the current study might be specific for the patient population of recurrently depressed patients, for whom

patterns of FAA have been reported to differ from never-depressed participants (Gotlib et al., 1998). Hence future research needs to verify whether the pattern of relations particularly on a trait level is the same in healthy participants as the one reported in the current research. Similarly, taking a more dynamic perspective it may be assumed that alterations of rumination and mindfulness through mindfulness-based interventions may be differentially associated with alterations in FAA in healthy, never-depressed individuals, in a way that is distinct from results reported here.

The functional mechanisms of MBCT

In conclusion, the current research supports previous reports of a protective function of MBCT manifesting in reduced rumination and elevated mindfulness. The prophylactic effect of MBCT may also be reflected in the maintenance of a stable pattern of FAA, counteracting a spontaneous deterioration. Further, rumination has been identified as a mediator of the relation between FAA and depression. Consequently, MBCT specifically targets a mediator of the relationship between a brain physiological conspicuity indicative of affective style, which possibly predisposes for the development of MDD.

Future Directions

With the methods applied in the current work, useful novel information on the functional working mechanisms of MBCT was gained. Nevertheless, future studies need to be enhanced in various ways to be able to address the issue of brain asymmetries in relation to MDD more directly. EEG measures have their advantages over imaging techniques such as fMRI in a practical way, when it comes to the assessment of larger groups. Nevertheless, the hypothesized neural circuitry underlying the approach and withdrawal systems, which is supposed to be tapped by alpha asymmetries, cannot be assessed in detail. Based on results by Davidson et al. (2003), Barnhofer et al. (2007), and those of the current work, it appears

feasible to conduct a study with a similar design regarding patient-flow and treatment, but to include fMRI assessments. In particular, findings provided by Johnstone et al. (2007), who report on compromised emotion regulation in patients suffering from MDD in an fMRI study appear promising. In the latter study, it was demonstrated that healthy control subjects display left-lateralized activation of the PFC when instructed to downregulate negative affect. In contrast, depressed participants showed a bilateral activation on the same task. Interestingly, in the former group, the activation pattern of the PFC was associated with decreased activation in the amygdala. No such inverse relationship was observed for depressed participants, who in contrast showed a positive association between the activation of areas of the PFC and the amygdala. In total, these results were interpreted as an indication of a pathophysiological over-engagement of right-hemispheric prefrontal areas in MDD. They seem to resemble the vast body of literature on frontal asymmetries in the EEG domain. The application of a similar method as the one utilized by Johnstone et al. (2007) in combination with an intervention such as MBCT might provide useful information, as to which alterations in brain functioning in patients suffering from MDD are related to positive treatment outcomes.

10. References

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11. Appendix

Abbreviations

ANOVA	Analyses of Variance
ANT	Attentional Network Test
BAS	Behavioral Approach System
BIS	Behavioral Inhibition System
BDI	Beck Depression Inventory
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
EOG	Electrooculogram
FAA	Functional Anterior Brain Asymmetry
FFA	Freiburger Fragebogen zur Achtsamkeit
fMRI	functional magnetic resonance imaging
GLM	General Linear Model
ITG	Immediate Treatment Group
mADM	maintenance Antidepressant Medication
MANOVA	Multivariate Analysis of Variance
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
OR	Odds Ratio
Ospan	Operation Span Task
PANAS	Positive and Negative Affect Schedule
PFC	Prefrontal Cortex
RCT	Randomized Controlled Trial
RSQ	Response Styles Questionnaire
SAD	Seasonal Affective Disorder
TAU	Treatment as Usual
WHO	World-Health Organization
WG	Waiting Group

12. Zusammenfassung der Dissertationsschrift

Die Arbeit beschäftigt sich mit den psychophysiologischen Wirkmechanismen der Achtsamkeitsbasierten Kognitiven Therapie zur Rückfallprophylaxe bei unipolaren Depressionen (engl.: Mindfulness-Based Cognitive Therapy; MBCT; Segal et al., 2002). Depressionen stellen ein dynamisches psychiatrisches Störungsbild dar, bei dem Rückfälle sehr häufig vorkommen, wobei die Rückfallwahrscheinlichkeit mit jeder erlebten depressiven Episode weiter steigt. Über die Episoden hinweg werden Rückfälle außerdem immer autonomer, d.h. unabhängiger von negativen Lebensereignissen (Keller, 2003; Post, 1992). Als Rückfallmechanismen wurden in diesem Zusammenhang wiederholt die kognitive Reaktivität, sowie die Rumination beschrieben. Der Begriff kognitive Reaktivität bezieht sich auf die Tendenz von Patienten, vor allem im remittierten Zustand, auf spontane, relativ milde negative Stimmungen mit extrem negativen Gedankenmustern zu reagieren, die charakteristisch für depressive Episoden sind (Segal et al., 2006). Bei der Rumination handelt es sich um das bei depressiven Menschen sehr typische Verhalten des exzessiven Grübelns über die Gründe und Konsequenzen ihrer negativen Stimmungen (Nolen-Hoeksema et al., 2008). MBCT wurde entwickelt, um sowohl der kognitiven Reaktivität, als auch der Rumination bei rezidivierend depressiven Menschen in Remission entgegenzuwirken. Bei dieser Form der Erhaltungstherapie, die im Rahmen einer Gruppe von zehn bis zwölf Patienten stattfindet, werden Teilnehmer darin trainiert Achtsamkeit zu kultivieren. Bei letzterer handelt es sich um ein aus der buddhistischen Philosophie stammendes Konzept, das eine nicht bewertende, die Wahrnehmung des gegenwärtigen Augenblicks erfassende Geisteshaltung beschreibt (Bishop et al., 2004). Diese wird vor allem durch säkularisierte Formen buddhistischer Achtsamkeitsmeditation trainiert.

MBCT trägt nachweislich zur Reduktion des Rückfallrisikos bei (Ma & Teasdale, 2004; Teasdale et al., 2000). Dieser Effekt ist besonders ausgeprägt bei Patienten, für die

autonome Rückfallmechanismen angenommen werden können. Obwohl die Effektivität von MBCT in verschiedenen Studien belegt wurde, ist bisher jedoch relative wenig über physiologische Korrelate des Achtsamkeitstrainings bekannt.

Ein hirnphysiologisches Merkmal, das im Kontext von Depressionen besonders relevant ist, ist das der funktionellen anterioren Asymmetrie (FAA), gemessen anhand des Alpha-Frequenzbandes im Ruhe-Elektroenzephalogramm (EEG). FAA wurde als Indikator globalen affektiven Stils (Davidson, 1992, 1995) und als möglicher physiologischer Vulnerabilitätsmarker für die Entwicklung von Depressionen identifiziert. In klinischen Studien konnte teilweise gezeigt werden, dass akut depressive und remittierte depressive Patienten durch eine stärkere, relative rechtshemisphärische frontale kortikale Aktivierung im Vergleich zu gesunden Kontrollpersonen gekennzeichnet sind (Gotlib et al., 1998; Henriques & Davidson, 1990, 1991). Dieses Aktivierungsmuster wird in der Regel über die Stärke des Alpha-Bandes identifiziert, das im Ruhe-EEG als invertierter Indikator tonischer kortikaler Aktivierung betrachtet wird (Allen et al., 2004a). Obwohl die FAA generell als relativ stabiles Eigenschaftsmaß gilt (Tomarken et al., 1992b), konnte in einigen Studien auch gezeigt werden, dass strukturiertes Achtsamkeitstraining einen Effekt auf funktionelle Asymmetrien hat (Davidson et al., 2003). An Patienten mit depressiver Vorgeschichte konnte demonstriert werden, dass die Teilnahme an einem MBCT Kurs mit einer stabilen FAA assoziiert war, wohingegen Patienten einer Wartelistenkontrollgruppe spontane Verschlechterungen zu einer stärkeren relativen rechtshemisphärischen Aktivierung zeigten, die für erhöhte Vulnerabilität spricht (Barnhofer et al., 2007).

In der vorliegenden Arbeit sollten bisherige Befunde über die Plastizität der FAA repliziert und erweitert werden. Wirkmechanismen von MBCT, wie verringerte Ruminationstendenzen und erhöhte berichtete Achtsamkeit, wurden dabei in Beziehung zu Veränderungen der FAA in rezidivierend depressiven Patienten untersucht. Insgesamt stützen die Ergebnisse den prophylaktischen Effekt von MBCT. Stabilisierende Effekte von MBCT

auf FAA, die spontanen Verschlechterungen über einen Zeitraum von zwei Monaten entgegenwirkten, konnten in einer ersten Studie demonstriert werden. Bei 19 Patienten, die durch MBCT behandelt wurden, zeigten sich weder unmittelbar nach der Therapie, noch zwei Monate nach Ende der Therapie signifikante Veränderungen der FAA. Im Gegensatz dazu zeigten 20 Patienten einer Wartelistenkontrollgruppe eine spontane Verschlechterung hin zu einer stärkeren relativen rechtshemisphärischen Aktivierung während einer Wartezeit von zwei Monaten. Die anschließende Teilnahme an einem MBCT Kurs ging bei diesen Patienten mit einer verstärkten relativen linkshemisphärischen Aktivierung einher. Bei der zuvor Beobachteten Verschlechterung sagten FAA-Werte stärkere Ruminationstendenzen und verringerte Achtsamkeit voraus. Obwohl eine zweite Studie mit einer ähnlichen Patientenzahl diese Effekte nicht erneut replizieren konnte, wurden Assoziationen von FAA, Rumination und Depression als Eigenschaftsmaße in einer dritten Studie mit 74 Teilnehmern gezeigt. In dieser Studie wurde Rumination als Mediator der bekannten Beziehung zwischen FAA und depressiver Symptomatik identifiziert. Insgesamt liefert die Vorliegende Arbeit also Ergebnisse, die die Nützlichkeit von MBCT stützen. Außerdem werden Befunde geliefert, die zur Formulierung eines integrativen Modells physiologischer und psychologischer Aspekte von Depressionen beitragen können.