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Cognitive and Affective Daily Life Predictors for the Course of Recurrent Depression and the Impact of Mindfulness-Based Attention Training: An Ambulatory Assessment Study.

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1 INTRODUCTION

Major Depressive Disorder (MDD) is a highly prevalent mental disorder and one of the leading contributors to the global burden of disease with high socioeconomic costs, loss in health and social functioning (Whiteford et al., 2013; WHO, 2017). MDD is characterized by a heterogeneous long-term course with high probability of recurrent episodes or chronic developments (APA, 2013; Kuehner & Huffziger, 2013; Ten Have et al., 2018). Consensus definitions used to describe the long-term course of MDD refer to severity and duration of symptoms (see Fig.1). First, symptom severity is categorized in three clinical ranges: Fully symptomatic (acute episode), fully and partly remitted with different criteria used to distinguish fully and partially remitted individuals (de Zwart, Jeronimus, & de Jonge, 2018). Second, remission is defined as a period of two or more months without clinically relevant symptoms following an acute episode of MDD. Third, recovery is described as a sustained period of more than two months in full remission (APA, 2013). Fourth, relapse/recurrence implies a return of symptoms during remission/recovery, respectively (APA, 2013; de Zwart et al., 2018; Frank et al., 1991). Finally, a chronic course of MDD is defined as persisting depressed mood for most of the time for 2 years or longer (APA, 2013). Importantly, DSM-5 implemented persistent depressive disorder (PDD) as a novel diagnostic category of chronic depression and/or dysthymia (APA, 2013; Ildirli, Şair, & Dereboy, 2015).

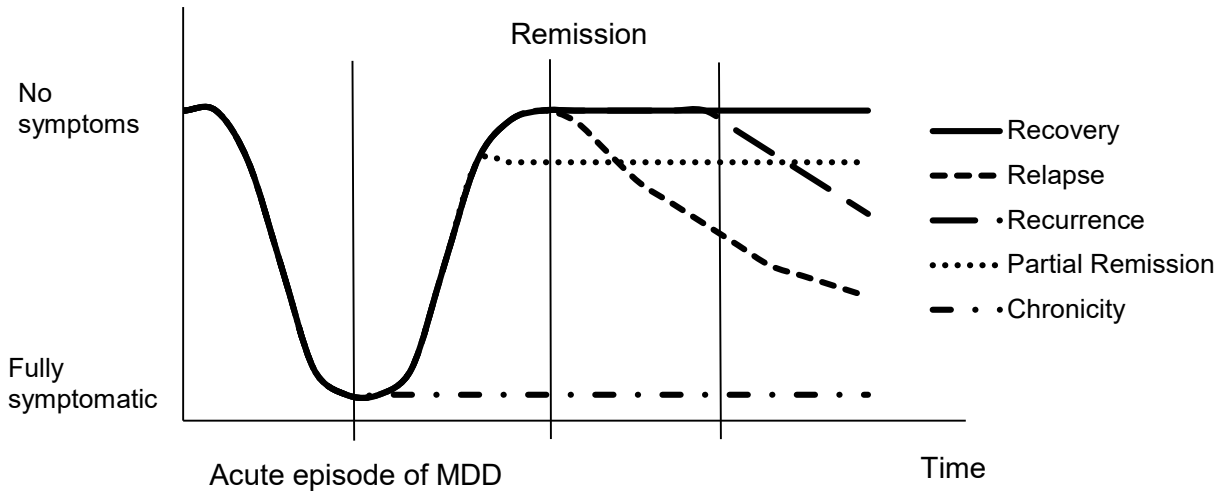

Fig. 1: Varying clinical long-term course of MDD according to DSM-5 and consensus definitions (de Zwart et al., 2018; Frank et al., 1991). No duration thresholds for relapse/recurrence and severity criteria to distinguish partly and fully remitted individuals were included in accordance with DSM-5 (for a critical review see de Zwart et al., 2018).

Definitions of a chronic MDD course in longitudinal research are often based on weeks or percentage of time spent with significant symptoms during follow-up with varying duration criteria (e.g. Pereverseff, Beshai, & Dimova, 2017; Schaakxs et al., 2018; Struijs, Lamers, Spinhoven, van der Does, & Penninx, 2018).

1.1 Predictors for the long-term course of MDD

1.1.1 General risk factors for the long-term course of MDD

In light of the unfavorable course and associated global and personal consequences of MDD the identification of relevant course modifiers is of substantial importance. Population-based studies identified clinical characteristics as important predictors for relapse/recurrence. Particularly, number of previous episodes, severity of the last episode, residual symptoms and medication use were associated with time to relapse/recurrence (Conradi, Ormel, & de Jonge, 2010; Hardeveld et al., 2013; Hoertel et al., 2017; Zajecka, Kornstein, & Blier, 2013). First evidence suggests that a chronic MDD course is predicted by similar clinical variables (for a review see Ten Have et al., 2018). Moreover, first episode characteristics (early age of onset, severity of index episode) are presumably associated with relapse/recurrence and chronicity in formerly depressed individuals (Hardeveld et al., 2013; Pereverseff et al., 2017).

Mixed findings exist in regard to the influence of demographic (age, gender, employment) and environmental (childhood neglect, parental depression, stressful life events) vulnerability factors on both recurrence and chronicity of MDD (Hardeveld et al., 2013; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010; Kuehner, 2017; Paterniti, Sterner, Caldwell, & Bisserbe, 2017; Schaakxs et al., 2018; Ten Have et al., 2018). Longitudinal studies in clinical samples suggest that the course of MDD worsens with age (Schaakxs et al., 2018) while employment seems to foster resilience (Heinz et al., 2018). By contrast, female gender, parental depression and stressful life events predict onset but apparently not the course of depression (Hammen, 2018; Kuehner, 2017; Ten Have et al., 2018), whereas some evidence suggests childhood adversity to be more prevalent in chronic depressed individuals (Barnhofer, Brennan, Crane, Duggan, & Williams, 2014; Liu et al, 2017).

The insignificant influence of stressful life events for the recurrence and chronicity of MDD might reflect a scarring process (Wichers, Geschwind, van Os, & Peeters, 2010). Scar theories of depression assume that internal changes during a depressive episode will increase the risk of recurrence or a chronic course even under only

moderate or no social stress. These internal changes are supposedly encoded at a biological level (Davey et al., 2014; Lythe et al., 2015; Zamoscik, Huffziger, Ebner-Priemer, Kuehner, & Kirsch, 2014). However, changes at psychosocial, cognitive or emotional levels are also possible (Segal et al., 2006; van Rijsbergen et al., 2015; see Bos et al., 2018; de Jonge et al., 2017 for negative results). In this context, it is of particular interest to identify psychological factors that may become scarred after the onset of the disorder, thereby increasing vulnerability for recurrence and chronicity (van Rijsbergen et al., 2015; Wichers, Geschwind, et al., 2010).

1.1.2 Cognitive risk factors for the long-term course of MDD

Historically, cognitive vulnerability is an important risk factor for depression (Hammen, 2018; LeMoult & Gotlib, 2018). Specifically, research findings show that depressed individuals use maladaptive cognitive emotion regulation strategies and are negatively biased in attention and memory processes (LeMoult & Gotlib, 2018). Theoretically, the impaired disengagement hypothesis (Koster, De Lissnyder, Derakshan, & De Raedt, 2011) proposes that depression is associated with difficulties in disengaging from self-referential, repetitive negative thoughts that are cued by internal (sad mood) or external stressors. This prolonged processing of negative self-referential information presumably impairs attention, problem solving and sustains negative affect (Koster et al., 2011). Empirical support for this assumption shows that depressive individuals have difficulties with inhibiting the processing of negative material (Vanderhasselt et al., 2012) and that higher trait rumination was associated with impairments in disengaging from negative compared to positive stimuli (Southworth, Grafton, MacLeod, & Watkins, 2017). Further, neurobiological studies suggest depression specific dysregulation in the Default Mode Network (DMN), a brain structure associated with self-referential processing in depression (for a review see Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012).

First evidence suggests that cognitive impairments might also predict the long-term course of depression (LeMoult, Kircanski, Prasad, & Gotlib, 2017). In a recent meta-analysis, significant cognitive deficits in executive functioning, working memory and processing speed were observed during a first depressive episode with some impairments persisting upon remission (see Ahern & Semkovska, 2017). Individuals with a negative attentional bias showed more depressive symptom worsening over time (Disner, Shumake, & Beevers, 2017), and in remitted depressed (rMDD) individuals' negatively biased self-referential processing after negative mood induction

predicted relapse/recurrence of a depressive episode over three years (LeMoult et al., 2017). Moreover, rMDD compared to healthy control individuals showed increased connectivity of the posterior cingulate cortex (PCC, node in the DMN) with the parahippocampal gyri (PHG, a brain region associated with autobiographical memory) while intensively recalling negative memories (Zamoscik et al., 2014). This hyperconnectivity was even stronger in rMDD individuals with more anamnestic episodes and predicted depressive symptoms during follow-up (Figueroa et al., 2017; Zamoscik et al., 2014). This increased connectivity presumably constitutes a neurobiological correlate of cognitive vulnerability risk factors for relapse/recurrence in depression.

A specific form of self-referential repetitive thinking that has received particular attention in depression research is rumination, defined as the tendency to repetitively and passively think about one's dysphoric mood and its causes and consequences (Lyubomirsky, Layous, Chancellor, & Nelson, 2015; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Rumination is most commonly conceptualized as a cognitive trait measured with the Ruminative Response Scale of the Response Style Questionnaire (Nolen-Hoeksema, 1991; German version Kühner, Huffziger, & Nolen-Hoeksema, 2007). Empirical evidence suggests an association of trait rumination with levels of depressive symptoms and onset of depression (Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008). Further, experimentally induced rumination is associated with subsequent deteriorated mood and maintenance of depression-linked dysfunctional thought content in non-clinical samples (Huffziger, Ebner-Priemer, Eisenbach, et al., 2013; Kuehner, Huffziger, & Liebsch, 2008) and biological response to stress in depressed individuals (LeMoult & Joormann, 2014; LeMoult, Yoon, & Joormann, 2016). Longitudinal studies suggest that trait rumination predicts depressive symptoms in formerly depressed inpatients over four months (Kuehner & Weber, 1999) and lower quality of life, social and occupational functioning in depressed patients after hospital discharge (Kuehner & Huffziger, 2013). Further, rumination mediated the longitudinal effect of reduced autobiographical memory specificity on depressive symptoms (Raes et al., 2006) while post treatment levels of rumination predicted the risk of relapse in MDD individuals during a 12-month follow-up (Michalak, Holz, & Teismann, 2011). Rumination was also associated with a chronic symptom course (Struijs et al., 2018) and more prevalent in chronic depressed individuals over a period of five years (Wiersma et al., 2011). A chronic depression course was also predicted by cognitive

state orientation (Kuehner & Huffziger, 2013), defined as dysfunctional motivational tendency that promotes fixation on negative emotional states and is associated with perseverative cognitive processing of negative events and impaired self-control (Wolff et al., 2016). Recent evidence suggests that rumination is a transdiagnostic vulnerability factor underlying various psychopathologies including eating disorders, anxiety and affective disorders (Aldao & Nolen-Hoeksema, 2010; McLaughlin & Nolen-Hoeksema, 2011; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013). In line with these results, rumination is conceptualized as a subordinate construct of repetitive negative thinking (RNT), defined as repeatedly occurring, uncontrollable, negative thoughts from which it is difficult to disengage (Kaplan et al., 2018; McEvoy, Watson, Watkins, & Nathan, 2013). RNT is defined as a habitual trait assessed with self-report measures such as the “Repetitive Thinking Questionnaire”, (RTQ, McEvoy, Mahoney, & Moulds, 2010; McEvoy, Watson, Watkins, & Nathan, 2013; Samtani et al., 2018) and the “Perseverative Thinking Questionnaire” (PTQ, Ehring et al., 2011 for a critical review see; Samtani & Moulds, 2017). Cross-sectional studies revealed that RNT is associated with the severity of depressive and anxiety symptoms (McEvoy et al., 2017, McEvoy et al., 2018; Spinhoven, Drost, van Hemert, & Penninx, 2015). Further, RNT predicts emotional responses to experimental challenge and symptom improvement during treatment in clinical samples (Kertz, Koran, Stevens, & Bjorgvinsson, 2015; Ruscio, Seitchik, Gentes, Jones, & Hallion, 2011). Longitudinal evidence is scarce and suggests prospective influence of RNT on depressive and anxiety symptoms in clinical samples (Drost, van der Does, van Hemert, Penninx, & Spinhoven, 2014; Spinhoven et al., 2016; Spinhoven, van Hemert, & Penninx, 2018). In sum, these results suggest that transdiagnostic cognitive vulnerability factors, especially maladaptive repetitive thinking - per se or in combination with other risk factors - constitute potential scarring processes during remission in formerly depressed individuals and presumably increase vulnerability towards relapse/recurrence and chronicity.

The differential activation model (Teasdale, 1988) is a cognitive theory aiming to explain the high risk for relapse/recurrence in rMDD individuals thereby considering the above discussed cognitive vulnerability factors (Lau, Segal, & Williams, 2004). This model assumes that maladaptive thinking patterns like RNT or rumination become associated with negative affect during an acute episode of MDD. Supposedly, this association strengthened by repeated MDD episodes remains as potential scarring process during remission (Figueroa et al., 2018; Scher, Ingram, & Segal, 2005; Segal

et al., 2006). The ease with which these learned associations are reactivated is referred to as cognitive reactivity (Cladder-Micus et al., 2018). In line with this model, cognitive reactivity has been shown to predict depressive relapse (Figueroa et al., 2015; Segal et al., 2006) and is linked to higher numbers of previous episodes in remitted individuals (Elgersma et al., 2015). Importantly, this theoretical model to explain relapse/recurrence in depression considers the dynamic interplay between affective states (e.g. sad mood) and cognitive vulnerability (e.g. reactivated maladaptive thinking patterns). This approach is in line with a more dimensional view on depressive vulnerability suggesting a gradual development of risk factors with succeeding numbers of depressive episodes (Wichers et al., 2010).

1.2 Mindfulness: A potentially protective course modifier of recurrent depression

1.2.1 Trait mindfulness and Mindfulness-Based Interventions (MBI's)

A cognitive, potentially protective course modifying factor investigated in the context of chronic and recurrent depression is mindfulness. Derived from Buddhist tradition, it can be defined as "nonjudgmental attention to experiences in the present moment" without fixation on thoughts of past and future (Kabat-Zinn, 2015; Tang, Hölzel, & Posner, 2015). However, a number of mindfulness definitions exists emphasizing different aspects of the construct (for a critical review see Van Dam et al., 2017). Mindfulness can be conceptualized as a multidimensional trait (general tendency to be mindful) that differs between persons (Bergomi, Tschacher, & Kupper, 2013; Medvedev et al., 2016; Park, Reilly-Spong, & Gross, 2013) or as a dynamically changing state (an individual's degree of mindfulness at any particular point of time) that is practiced during mindfulness meditation (Blanke & Brose, 2017). Trait mindfulness is assessed with various self-report measures which capture different aspects of the construct (see review by Sauer et al., 2013). Prominent examples are the multidimensional "Freiburg Mindful Inventory" (FMI, Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006), the "Kentucky Inventory of Mindfulness Skills" (KIMS, Baer, Smith, & Allen, 2004) or the one-dimensional "Mindful Attention and Awareness Scale" (MAAS, Brown & Ryan, 2003). In contrast, state mindfulness has mostly been assessed unidimensionally (e.g. short five-item version of MAAS, Brown & Ryan, 2003) or multidimensionally (see Blanke & Brose, 2017) in experienced meditators compared to non-meditators and during/after repeated meditation practice

within Mindfulness-Based Interventions (MBI's). MBI's are programs, which incorporate elements of mindfulness meditation, yoga and in some cases cognitive behavioral interventions. The most common MBI's are Mindfulness Based Stress Reduction (MBSR, Kabat-Zinn, 1982; Kabat-Zinn, 2005) and Mindfulness-Based Cognitive Therapy (MBCT, Segal, Williams, & Teasdale, 2013) and both have been successfully applied to a wide range of mental health conditions such as stress, pain, depression or substance abuse (Crowe et al., 2016; Khoury, Sharma, Rush, & Fournier, 2015; Kuyken et al., 2016; Li, Howard, Garland, McGovern, & Lazar, 2017). Presumably, cultivating state mindfulness during MBI`s increases trait mindfulness (Kiken, Garland, Bluth, Palsson, & Gaylord, 2015).

Mindfulness is assumed to be a protective factor for the course of depression. The majority of respective supporting research is based on intervention studies using MBI's (see Farb et al., 2018; Kuyken et al., 2016). Preliminary results also indicate that mindfulness as a dispositional trait longitudinally influences the course of depression (Petrocchi & Ottaviani, 2016). The most prominent MBI studied in the context of depression is MBCT a manualized group-therapy program that combines mindfulness meditation with Cognitive Behavioral Therapy (CBT) and was specifically designed to prevent relapse in recurrent MDD (Segal, Williams, & Teasdale, 2013). MBCT is based on the differential activation model (Teasdale, 1988 see Chapter 1.1.2) assuming that the development of mindfulness skills reduces cognitive reactivity by enabling participants to a) recognize automatic activation of dysfunctional cognitive thinking patterns b) disengage from current dysfunctional thoughts by shifting attention to momentary experiences, e.g. concentrate on the breath c) develop meta-awareness (decentering) by observing thoughts as temporary mental events instead of stable aspects of self or reality d) adopt a non-judging attitude towards momentary experienced (Segal et al., 2013).

Meta-analytic studies support the idea that MBCT is effective in preventing depressive relapse particularly in vulnerable individuals with high levels of residual symptoms, with more than three anamnestic depressive episodes, or with childhood trauma (c.f. Kuyken et al., 2016; Piet & Hougaard, 2011; Zhang, Zhang, Zhang, Jin, & Zheng, 2018). A recent meta-analysis compared effects of different forms of CBT and unspecific treatments (psychoeducational support, yoga) on RNT in formerly depressed individuals and control participants. Results demonstrated medium sized and significantly larger effect sizes of MBCT compared to unspecific forms of treatment

(Spinhoven et al., 2018). Moreover, MBCT had a comparable effect to antidepressive medication (Kuyken et al., 2015).

However, less is known about the influence of MBCT on chronicity in depression, since the use of meditation practice is considered to surpass the limited cognitive capacities of depressive patients suffering from acute symptoms (see Fissler et al., 2017 for positive results). Empirical evidence is inconclusive showing MBCT to be no more effective than a wait list control and treatment-as-usual (TAU) intervention in patients with a protracted and chronic course of the disorder (Michalak, Schultze, Heidenreich, & Schramm, 2015), otherwise demonstrating a brief mindfulness meditation training to be more effective than an active control training in reducing depressive symptoms in acutely depressed individuals with a chronic depression course (Winnebeck, Fissler, Gärtner, Chadwick, & Barnhofer, 2017). Furthermore, a combination of MBCT and TAU seems to have beneficial effects on remission rates and quality of life (Cladder-Micus et al., 2018).

1.2.2 Possible effect mechanisms of MBI's

Despite growing evidence for the effectiveness of MBI's it is not fully understood how these evidence-based interventions work and why they are beneficial for the course of depression. Problematically, MBI's like MBCT incorporate a variety of distinct elements presented together under the umbrella term mindfulness (Britton et al., 2018). Consequently, it is difficult to assess their individual contribution to treatment outcomes and one of the largest limitations in mindfulness research is that MBI's have not yet been dismantled into their most basic components (Gu, Strauss, Bond, & Cavanagh, 2015; van der Velden et al., 2015).

Psychological effect mechanisms of MBI's in the context of depression can be derived from the MBCT model (for a review see Alberto Chiesa, Anselmi, & Serretti, 2014). Conclusively, changes of cognitive variables e.g. increase of mindfulness skills, self-compassion, meta-awareness/decentering and decrease of cognitive reactivity and repetitive negative thought (rumination, worry) are supposed effect mechanisms of MBCT (Cladder-Micus et al., 2018; MacKenzie, Abbott, & Kocovski, 2018; MacKenzie & Kocovski, 2016; van der Velden et al., 2015). In line with these assumptions, increases in mindfulness skills after MBCT predicted reduced relapse risk (Michalak, Heidenreich, Meibert, & Schulte, 2008) and mediated the treatment effect on depressive symptoms in rMDD individuals (Batink, Peeters, Geschwind, van Os, & Wichers, 2013; Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010).

Preliminarily results confirmed that when MBCT was compared to antidepressive medication it significantly increased decentering and meta-awareness, however, no associations with follow-up depressive symptoms were found (Bieling et al., 2012) MBCT is more effective in reducing cognitive reactivity compared to TAU (Cladder-Micus et al., 2018) and cognitive reactivity predicted poorer outcomes only for individuals treated with antidepressant medication but not for MBCT participants (Kuyken et al., 2010). Further, trait rumination and depressive symptoms were found to be negatively correlated with mindful breathing exercises (Burg & Michalak, 2011) and decreased rumination following a formal mindfulness practice was associated with reduced depressive symptoms (Hawley et al., 2014; van den Hurk et al., 2012) and with relapse risk (Michalak et al., 2011) and mediated the effect of MBCT on post treatment symptoms of depression in rMDD individuals (Shahar et al., 2010; van Aalderen et al., 2011).

Neuroscientific evidence suggests self-regulatory processes to be enhanced by mindfulness meditation (Tang et al., 2015; van der Velden et al., 2015). More precisely, basic research in non-clinical samples showed that mindfulness meditation alters brain functions in networks that underlie attention control, emotion and self-regulation (Malinowski, 2013; Tang et al., 2015). In line with this, first evidence suggests that emotion regulation is a potential mechanism of change in MBI´s. In a non-clinical sample, daily induced mindfulness compared to suppression and mind-wandering significantly increased subsequent state mindfulness (Garland, Hanley, Farb, & Froeliger, 2015). The degree of state mindfulness achieved during the induction was prospectively associated with increases in trait cognitive reappraisal suggesting that mindfulness may promote emotion regulation by enhancing cognitive reappraisal. Moreover, attention regulation is discussed as another possible effect mechanism of MBI's (Bostanov, Keune, Kotchoubey, & Hautzinger, 2012; Chesin et al., 2016). In a non-clinical sample, a short MBI was effective in improving orienting and executive control indicating that MBI's might be effective approaches to improve individuals' attentional subsystem (Quan, Wang, Chu, & Hou, 2018). Further, Bostanov et al. (2012) investigated the ability to maintain attention on a particular focus with a mindfulness breathing task combined with a mood induction stimuli and a distracting auditory stimulus and found an increase in specific event-related brain potentials (ERPs) only after MBCT but not in the waiting list control group. This finding possibly indicates an improved ability to deploy and maintain attention on a particular focus

during sad mood. Further, mindfulness training specifically improved cognitive inhibition compared to an active and passive control group (Wimmer, Bellingrath, & von Stockhausen, 2016).

Mindfulness is hypothesized to improve attention and emotion regulation by two different forms of meditation, focused attention (FA) practice and open monitoring (OM) practice (Ainsworth, Eddershaw, Meron, Baldwin, & Garner, 2013; Farb, Anderson, & Segal, 2012; Lutz, Slagter, Dunne, & Davidson, 2008). FA meditation is a systematic training of directing and sustaining attention on a chosen object (e.g. the breath), thereby noticing when the mind wanders from the object and disengaging from negative experiences like rumination and negative emotions by redirecting one's attention back to the chosen object (Lutz et al., 2008; Malinowski, 2013). In contrast, OM meditation entails the development of non-reactive awareness of experience, meaning a purposeful shift of attention towards difficult feelings or thoughts. Rather than reducing the occurrence of difficult experiences, OM is thought to change one's relationship to them by promoting a nonjudgmental attitude (Lutz et al., 2008; Malinowski, 2013; Segal et al., 2013). The early phase of mindfulness mediation often comprises FA practice while OM is being practiced with increased meditation experience. In the context of depression, especially focusing on the early stage of FA allows the study of potential effects on impaired core cognitive processes of attentional control in recurrently depressed individuals (see Chapter 1.1.2). Neural correlates of FA, operationalized as mindful breathing exercises, were identified in attention networks, and this effect was moderated by trait mindfulness (Dickenson, Berkman, Arch, & Lieberman, 2013). Evidence from neuropsychological tests in non-clinical samples showed that FA practice was associated with enhanced selective and executive functioning (Chiesa & Serretti, 2011), and specific forms of attention regulation were characterized by maintaining attention and inhibiting secondary, elaborative processes like rumination (Malinowski, 2013; Tang et al., 2015). Possibly, focused attention training is sufficient to activate protective cognitive processes in formerly depressed individuals and might help to foster resilience against depressive relapse.

1.3 Ambulatory Assessment – The role of daily life microlevel processes for the course of recurrent depression

1.3.1 Ambulatory Assessment – a research tool to study daily life experiences

The examination of daily life experiences has the potential to contribute to a better understanding of macrolevel syndromes and diagnoses by identifying microlevel risk factors influencing the onset and course of depression and other mental disorders (Wenzel et al., 2016; Wichers et al., 2014). The method used to assess respective microlevel processes is Ambulatory Assessment (AA, for a review see Myin-Germeys et al., 2018). AA comprises multiple assessments typically collected several times per day in real-world environments (Carpenter, Wycoff, & Trull, 2016; Trull & Ebner-Priemer, 2013). Here, individuals rate their affective states, current thoughts or activities in real-time with paper-pencil or internet diaries or mobile devices (e.g. smartwatch/phone).

Compared to global retrospective ratings, repeated real-time assessments minimize the recall bias of self-reports, which is especially problematic in depressed patients whose memories are often negatively biased by dysfunctional cognitions and who suffer from cognitive impairments (aan het Rot, Hogenelst, & Schoevers, 2012; Vachon, Rintala, Viechtbauer, & Myin-Germeys, 2018). Moreover, possible risk factors for depression occur naturally in interaction with specific contexts and therefore assessments in everyday life situations increase ecological validity and generalizability of results (Trull & Ebner-Priemer, 2013, 2014). Identified AA-patterns can be related to biological processes (e.g., physiological variables) or transsituative psychological traits (Conner & Barrett, 2012; Wenzel, Kubiak, & Ebner-Priemer, 2016). Additionally, resulting longitudinal within person data allow a more reliable representation of levels, fluctuations and interactions of cognitive and affective regulatory processes underlying mental disorders (Trull & Ebner-Priemer, 2014; Wenzel et al., 2016). Therefore, AA provides advanced measures especially for dynamic psychological constructs that fluctuate and change over time (e.g. mood) (Jahng, Wood, & Trull, 2008; Trull, Lane, Koval, & Ebner-Priemer, 2015). For instance, the mean squared successive difference (MSSD) has been used previously to measure affective instability in daily life of different psychopathologies (Trull et al., 2015). It is an index that takes into account three components of instability: temporal order, amplitude and frequency of scores over the day (Jahng et al., 2008; von Neumann, Kent, Bellinson, & Hart, 1941). Finally,

AA measures allow for an advanced modeling of temporal relationship between proposed predictors and outcomes with possible concurrent and lagged associations, which is useful for identifying the time course from risk exposure to clinical outcome (Heagerty & Comstock, 2013). Methodologically, the use of AA technology offers the ability to choose an optimal sampling scheme depending on the research question. Additionally, AA analysis methods, through multilevel modeling, have advanced statistical power (Bolger & Laurenceau, 2013; Carpenter et al., 2016).

1.3.2 Possible transdiagnostic cognitive and affective AA-phenotypes in the context of depression

AA is a promising approach to examine mental states at the microlevel of momentary experience during daily life (Myin-Germeys et al., 2018; Trull et al., 2015; Wichers, 2014) that might be potential risk factors for relapse/recurrence and maintenance of symptoms in different psychopathology including depression.

The Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health (NIMH, see Cuthbert & Kozak, 2013; Insel & Cuthbert, 2015) suggests a dimensional transdiagnostic research framework to investigate mental disorders and related course modifiers. The RDoC framework comprises psychological constructs that are grouped into five higher-level domains of human behavior and functioning considering physiology, molecules, neural circuits, behavior and self-reports. Three domains reflect emotional processes and their regulatory systems (negative valence systems, positive valence systems, arousal and regulatory systems). It has been shown that momentary microlevel experiences assessed with AA are associated with biological markers defined in the RDoC framework, e.g. with neural network activity (e.g. Zamoscik et al., 2014), and with cortisol related (e.g. Huffziger et al., 2013; Stawski, Cichy, Piazza, & Almeida, 2013) and cardiovascular reactivity (e.g. Koval et al., 2013). Compared to retrospective measures, AA appears to measure a different source of knowledge, the experiencing self, that is strongly linked to subjective sensory and body information triggered by everyday situations (for a review see Conner & Barrett, 2012). Thus, AA measures seem appropriate to characterize microlevel regulatory processes during daily life that are - per se or in combination with other characteristics – promising predictors for the long term course of psychopathology in various mental disorders, thereby constituting possible transdiagnostic AA-phenotypes (Wenzel et al., 2016; Wichers, 2014).

Previous research predominantly investigated momentary affective AA-phenotypes in clinical samples with different psychopathologies (Wichers, Wigman, & Myin-Germeys, 2015). Reviews of AA studies concerning affective (aan het Rot et al., 2012) or anxiety disorders (Walz, Nauta, & aan het Rot, 2014) mostly included studies with cross-sectional design indicating a strong association of stress with high levels of daily negative affect (NA) and low levels of daily positive affect (PA) in adults with MDD. For example, compared to healthy control participants male rMDD individuals displayed increased levels of daily life stress reactivity (Husky, Mazure, Maciejewski, & Swendsen, 2009) and students with a history of depression showed increased levels of NA and decreased levels of PA on stressful days (O'Hara, Armeli, Boynton, & Tennen, 2014), suggesting the continued presence of subtle abnormalities during remission that might potentially contribute to future relapse.

A recent meta-analysis investigating affective dynamics across psychopathologies (Houben, Van Den Noortgate, & Kuppens, 2015) showed that lower levels of psychological well-being were associated with both daily life affective instability, the tendency to experience frequent and large mood shifts over time (Jahng et al., 2008; Trull et al., 2015), and emotional inertia, defined as emotional resistance to change (Koval, Sütterlin, & Kuppens, 2015; Kuppens, Allen, & Sheeber, 2010), particularly for NA. Affective dynamics have been studied in different psychopathologies (Trull et al., 2015; Wichers et al., 2015) predominantly in borderline personality disorder (Houben et al., 2016; Santangelo et al., 2014; Trull, 2018). Depressed individuals also seem to display an altered affective dynamic over the day (Thompson et al., 2012; Trull et al., 2015). A recent study demonstrated a distinct intra-day dynamic profile in affective experiences in MDD participants with significantly increased diurnal instability and variation of NA and PA (Crowe, Daly, Delaney, Carroll, & Malone, 2018). Supporting this assumption on a trait level, first evidence suggests that habitual affective instability is associated with a family history of mood disorders (Berenbaum, Bredemeier, Boden, Thompson, & Milanak, 2011) and with depressive symptoms (Bowen, Wang, Balbuena, Houmphan, & Baetz, 2013). Studies with cross-sectional design suggest that depressed individuals compared to healthy controls display higher momentary affective instability (Koval, Pe, Meers, & Kuppens, 2013; Peeters, Berkhof, Delespaul, Rottenberg, & Nicolson, 2006) while inertia of momentary affect appears to be associated with depressive symptoms (Brose, Schmiedek, Koval, & Kuppens, 2015; Kuppens et al., 2010) and with the onset of depression (Kuppens et

al., 2012). Compared to inertia, particularly instability of NA was found to be increased in MDD participants (Thompson et al., 2012).

Recently, an increasing number of AA studies apply a network approach to study microlevel affective experiences and their temporal dynamics and interactions (Myin-Germeys et al., 2018; Wichers et al., 2015). Compared to healthy controls, depressive individuals were characterized by a denser, more strongly connected, affective network structure and showed more interconnection, specifically between negative affective states (Pe et al., 2014; Wigman et al., 2015).

In contrast to affective AA-phenotypes, there is a clear lack of AA studies investigating cognitive risk and protective factors as potential AA-phenotypes in patients with mental disorders. Referring to the RDoC framework, substantially interesting transdiagnostic cognitive AA risk factors are daily life rumination and worry as features of RNT (see Chapter 1.1.2, McEvoy et al., 2013). Worry is characteristic for anxiety disorders (e.g. Newman, Llera, Erickson, Przeworski, & Castonguay, 2013). Contrary to rumination, which refers to stressful events and negative self-referential aspects in the past, worry is future oriented and focuses on possible risks. Both cognitive processes are associated with the subordinate RDoC construct of loss, as part of the negative valence domain (e.g. Cuthbert, 2014). Preliminarily results in clinical samples showed that daily life transdiagnostic perseverative cognition was associated with cognitive rigidity in MDD patients (Ottaviani et al., 2015). Compared to control participants, clinically depressed and anxious individuals were found to be characterized by higher levels of daily life rumination and stress reactivity especially in comorbid cases (Ruscio et al., 2015) and individuals with MDD, Generalized Anxiety Disorder (GAD) and co-occurring MDD-GAD showed elevated levels of momentary rumination and worry (Kircanski, Thompson, Sorenson, Sherdell, & Gotlib, 2015; Kircanski, Thompson, Sorenson, Sherdell, & Gotlib, 2017). Importantly, momentary rumination but not worry was susceptible to the occurrence of daily events. Moreover, exclusively higher momentary levels of rumination predicted subsequent deterioration of affect in depressed and anxious individuals (Kircanski et al., 2017). The negative impact of momentary rumination on subsequent affect is in line with experimental results demonstrating increased NA after induced rumination in the laboratory (Huffziger & Kuehner, 2009) and supports the idea of worry as a cognitive avoidance strategy, maintaining chronic lower levels of NA (Borkovec, Alcaine, & Behar, 2004). Moreover, momentary rumination was associated with higher cortisol secretion over

the day (Huffziger, Ebner-Priemer, Zamoscik, et al., 2013) and with increased PCC-PHG connectivity in rMDD individuals (Zamoscik et al., 2014, see chapter 1.1.2) indicating a link between momentary cognitive vulnerability and biological processes (c.f. Conner & Barrett, 2012). These cross-sectional results support the idea that momentary rumination as a possible transdiagnostic AA-phenotype reflects vulnerability in depression (see Liu & Thompson, 2017).

Comparable with the idea of affective dynamics, also *instability* of momentary cognitive variables like rumination are potential AA-phenotypes in the context of mental disorders including depression. Up to now, the few empirical studies examining unstable cognitive processes in daily life mainly focus on qualitative differences and on the interaction between momentary negative affective and cognitive dynamics. Daily fluctuation of ruminative thinking were investigated in non-clinical samples suggesting that high-trait ruminators showed increased levels of self-focus, unpleasantness, and uncontrollability in their thoughts which in turn predicted increased levels of concurrent negative affect, especially in the evening (Takano & Tanno, 2011). Further, instability of rumination, affect, and their interaction significantly predicted non-suicidal self-injury in a student sample (Selby, Franklin, Carson-Wong, & Rizvi, 2013).

These studies provide preliminary evidence that levels and instability of daily life cognition and affect represent possible AA-phenotypes, which may help to improve the understanding of macrolevel psychopathology (Wichers et al., 2014).

1.3.3 The role of AA-phenotypes for the long-term course of recurrent depression

Research regarding the influence of AA-phenotypes on the long-term course of mental disorders is scarce, apart from studies on schizophrenic disorders (cf. van Os & Reininghaus, 2016). Potentially relevant affective AA-phenotypes for the course of affective and anxiety disorders are levels of positive (PA) and negative affect (NA), affective dynamics, stress reactivity and reward experience (for a review see Wenzel et al., 2016). Stress reactivity and reward experience are characterized as the experience of negative or positive affect in response to negatively or positively appraised events during daily life (Wichers et al., 2014). In the context of affective disorders, an increasing number of AA studies support the prospective influence of affective AA-phenotypes on the clinical course of depression. In a study with rMDD

individuals, levels of NA marginally predicted depressive relapse/recurrence after 1.5 years (Wichers, Peeters, et al., 2010). In patients with recurrent depression, elevated levels of PA persistence at baseline were associated with an improved depression outcome after treatment (Höhn et al., 2013). In adolescents with anxiety disorder and depression, treatment response was significantly better predicted by levels of PA and NA at baseline compared to conventional self-reported symptom measures (Forbes et al., 2012). Further, in currently depressed individuals under antidepressive medication, an early improvement of PA levels was associated with a better treatment response (Geschwind, Nicolson, et al., 2011). In contrast, heightened reactivity to daily life stressors predicted the onset of future depressive symptoms and episodes (Shackman et al., 2016, Wichers et al., 2009). In a cross-sectional study, remitted and depressed individuals displayed higher levels of stress reactivity in social contexts compared to healthy controls indicating heightened trait vulnerability (van Winkel et al., 2015). Finally, blunted reward sensitivity in response to positive events predicted future depressive and anxiety symptoms in rMDD individuals (Wichers, Peeters, et al., 2010), while high reward experience reduced depressive and anxiety symptoms in individuals with early aversive experiences and was marginally associated with a decrease in relapse/recurrence (Geschwind et al., 2010).

Affective instability is also assumed to influence the course of affective disorders. Longitudinally, trait affective instability predicted changes in anhedonic depressive symptoms in a non-clinical sample (Thompson, Berenbaum, & Bredemeier, 2011). In bipolar patients, affective instability at baseline measured as changes in weekly depression and (hypo)mania scores predicted symptoms of depression/mania and a longer time to recover under psychosocial treatment independent of symptom severity (Stange et al., 2016). Particularly instability in depressive affect was prognostically associated with symptoms (higher percentage of weeks in a clinical mood state) and poorer global functioning in adolescents with bipolar disorder over 3 months (O'Donnell et al., 2018). Furthermore, variations in negative affect predicted future depressive symptoms in rMDD individuals (Wichers, Peeters, et al., 2010) and reduced treatment response in depressed individuals in psychotherapy (Husen, Rafaeli, Rubel, Bar-Kalifa, & Lutz, 2016). A longitudinal study showed that greater emotional inertia predicted the onset of clinical depression in youth (Kuppens et al., 2012). Evidence applying the network approach found depressed individuals with persistent compared to remitted depressive symptoms to be characterized by a denser, more strongly

connected symptom network structure including anhedonia during a two year follow-up suggesting that more pronounced associations between symptoms on a microlevel are related to the longitudinal course of depression (van Borkulo et al., 2015).

Evidence for the prospective validity of cognitive AA-phenotypes on the course of depression is scarce and has been predominantly examined in non-clinical samples. Here, higher levels of momentary rumination predicted an increase in depressive symptoms such as sleep disturbances (Kalmbach, Pillai, & Ciesla, 2015), or negative affect (Moberly & Watkins, 2008) over a short period. Further, increase in momentary rumination following stress prospectively predicted depressive symptoms in student samples (Connolly & Alloy, 2017; Vanderhasselt, Brose, Koster, & De Raedt, 2016). Only one study so far investigated cognitive AA variables prospectively in a clinical sample. High entropy, i.e. frequent and unpredictable changes in the interplay between momentary mood and rumination, was related to an increase of depressive symptoms in rMDD individuals during a six-months period (Koster et al., 2015). In contrast, studies investigating the impact of unstable momentary rumination on the long-term course of depression in clinical samples are completely lacking.

1.3.4 AA-phenotypes as possible microlevel mechanisms in MBI's

Affective AA-phenotypes have been proposed as possible microlevel mechanisms of change in MBI's (Garland, Gaylord, & Fredrickson, 2011; Geschwind, Peeters, Drukker, van Os, & Wichers, 2011; van der Velden et al., 2015). In a recent project with different forms of meditation trainings, FA exercises increased daily life PA, and decreased thought distraction over a period of nine months (Kok & Singer, 2017). Further, induced mindful attention during daily life enhanced subsequent mood and was associated with increased positive mood over the day suggesting a beneficial effect of mindfulness attention on daily life mood (Huffziger, Ebner-Priemer, Eisenbach, et al., 2013). Additionally, perceived daily life stress and NA were reduced during MBSR training (Snippe, Dziak, Lanza, Nyklíček, & Wichers, 2017). In a clinical sample, daily life NA was reduced by a brief mindfulness practice compared to a control sham meditation group (Ruscio, Muench, Brede, & Waters, 2016). Moreover, previous RCT studies suggest that MBI's differentially increase levels of momentary positive affect in rMDD individuals (Garland, Geschwind, Peeters, & Wichers, 2015; Geschwind, Peeters, et al., 2011) supporting the idea that mindfulness practice induces microlevel changes in momentary affective experiences. Mediation analysis showed that momentary PA and NA mediated the effect of MBCT compared to a TAU

control group on clinical depression outcome in remitted depressed individuals with three or more previous episodes (Batink et al., 2013).

Similarly, MBI's may influence cognitive processes. Little is known about the role of cognitive AA-phenotypes as possible effect mechanisms of mindfulness training. Previous evidence suggests an increase of daily life positive cognitions (PC) and a strengthened association between momentary PA and momentary PC by MBI's. In a recently proposed theoretical model, mindfulness training is assumed to increase subjective well-being by promoting positive reappraisal, the latter defined as a new interpretation of stressful events as meaningful or positive (Garland et al., 2010; Garland, Geschwind, et al., 2015). Specifically, mindfulness may evoke a broadened scope of attention to internal experiences with possible induction of PA. PA may in turn bias attention to positive environmental events and may generate reappraisal of stressful experiences. The interaction of momentary PA and cognition (reappraisal) may result in the gradual development of well-being referred to as upward spirals (Garland, Farb, Goldin, & Fredrickson, 2015). This model was based on evidence showing that PA in MBCT participants enhanced reward from savoring positive daily life activities (Geschwind, Peeters, et al., 2011). Notably, an RCT study of rMDD individuals showed that MBCT compared to a waitlist control group increases daily life PA and daily life reappraisal (Garland, Geschwind, et al., 2015). Further, daily mindfulness exercises were significantly associated with a more frequent use of positive reappraisal over MBCT training in a non-clinical sample (Garland, Kiken, Faurot, Palsson, & Gaylord, 2017). However, no study so far has tested the effect of MBI's on momentary negative cognitions such as rumination or worry.

Mindfulness is hypothesized to increase self-acceptance, which in term has a salutary effect on subjective well-being (c.f. Jimenez, Niles, & Park, 2010). Preliminary evidence in non-clinical samples showed that the positive link between trait mindfulness and subjective well-being was significantly mediated by trait self-acceptance (Xu, Oei, Liu, Wang, & Ding, 2014). Moreover, in a cross-sectional study trait mindfulness was inversely associated with depressive symptoms and this relationship was fully mediated by trait regulatory processes (Jimenez et al., 2010). Here, trait self-acceptance compared to trait emotion and mood regulation emerged as the strongest mediator. To our knowledge, no study has investigated daily life self-acceptance as a possible AA-phenotype in the context of MBI's.

Subsequently, two studies are described that investigate the influence of possible cognitive and affective AA-phenotypes at the microlevel on the long term course of recurrent depression with a longitudinal design (Study 1) and experimentally tested possible cognitive and affective microlevel changes of AA-phenotypes in formerly depressed individuals during a Mindfulness Based Attention Training (MBAT) in a Randomized Control Trail (RCT, Study 2).

1.4 Research questions and hypotheses

As discussed in chapter 1.3.3, empirical studies provide preliminary evidence that level and instability of daily life cognition and affect display possible AA-phenotypes predicting the long-term course of depressive psychopathology. In this context, particularly affective daily life processes such as NA, PA and instability of NA have been investigated and found to affect the long-term course and treatment response in depression (Höhn et al., 2013; Husen et al., 2016; Koster et al., 2015, Wichers et al., 2010). In contrast, up to date no longitudinal studies have investigated possible effects of levels and instability of daily life cognitions on the long-term course of depression.

Aim of Study 1 was to investigate the possible impact of cognitive and affective AA-phenotypes on the long-term course of clinical depression in a sample of remitted depressed individuals followed-up over a three-year interval. Main hypotheses of Study 1 were as follows:

H1: Cognitive and affective AA-phenotypes together with clinical and cognitive vulnerability trait variables, predict longitudinal depression outcomes, namely time to relapse, chronicity, and maintenance of depressive symptoms over three years in a sample of recurrently depressed individuals.

H2: A fluctuating course (i.e. relapses/recurrences) is predominantly predicted by instability measures of daily affect and cognition, while persistence outcomes are predominantly predicted by mean levels of AA-phenotypes and by trait cognitive vulnerability.

Study 2 aimed to investigate short-term effects of a brief Mindfulness-Based Attention Training (MBAT) compared to an time-matched active control training (Progressive Muscle Relaxation, PMR) within a Randomized Controlled Trail (RCT) on daily life cognitive and affective AA-phenotypes in a new sample of rMDD individuals. In light of meta-analytic results supporting the effectiveness of Mindfulness-Based Interventions particularly for vulnerable individuals with more frequent anamnestic episodes and higher levels of residual symptoms (Kuyken et al., 2016; Piet & Hougaard, 2011) it appears important to understand the contribution of individual subcomponents of MBI's (van der Velden et al., 2015). In this context, focusing on the early stage of focused attention allows to investigate potential effects of such an intervention on impaired cognitive processes of attentional control in rMDD individuals, such as rumination. Rumination has been suggested to provoke inhibitory deficits and

negative bias in attentional control of rMDD (Koster et al., 2011), and the MBCT model suggests an increased reactivation of rumination with subsequent depressive episodes proposing that mindfulness reduces this reactivation (Segal et al., 2013). Moreover, previous RCT studies suggest that MBI's differentially increase levels of momentary positive affect and positive cognitions in rMDD individuals (Garland et al., 2015; Geschwind et al., 2011). In Study 2, we developed a Mindfulness-Based Attention training (MBAT) that consisted primarily of focused attention exercises combined with a baseline and post AA measure. Main hypotheses of Study 2 were as follows:

H3: MBAT compared to PMR differentially influences daily life affect and cognition in rMDD individuals. Specifically, we expected a significant decrease in momentary NA and rumination and an increase in momentary PA and self-acceptance in MBAT compared to PMR.

H4: Further, we expected these effects to be moderated by the number of previous episodes. Specifically, the beneficial effects of MBAT on daily life NA, PA, rumination and self-acceptance were assumed to be more pronounced in highly vulnerable rMDD individuals with a higher number of previous episodes.

2 STUDY I: COGNITIVE AND AFFECTIVE TRAIT AND STATE FACTORS INFLUENCING THE LONG-TERM SYMPTOM COURSE IN REMITTED DEPRESSED PATIENTS

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2.1 Abstract

Background: Major depressive disorder (MDD) is characterized by a high risk for relapses and chronic developments. Clinical characteristics such as residual symptoms have been shown to negatively affect the long-term course of MDD. However, it is unclear so far how maladaptive habitual cognitive traits as well as cognitive and affective momentary states, the latter experienced during daily life, affect the long-term course of MDD.

Method: We followed up 57 remitted depressed individuals (rMDD) six (T2) and 36 (T3) months after baseline. Clinical outcomes were time to relapse, time spent with significant symptoms as a marker of chronicity, and levels of depressive symptoms at T2 and T3. Predictors assessed at baseline included residual symptoms and maladaptive habitual repetitive negative thinking (RNT). Furthermore, momentary daily-life affect and momentary rumination, and their variation over the day were assessed at baseline using ambulatory assessment (AA).

Results: In multifactorial models, residual symptoms and instability of daily-life affect at baseline independently predicted a faster time to relapse, while chronicity was significantly predicted by maladaptive habitual RNT. Multilevel models revealed that depressive symptom levels during follow-up were predicted by baseline residual symptom levels and instability of daily-life rumination.

Conclusions: Our findings indicate that maladaptive habitual RNT, but also affective and cognitive micro-level processes during daily life impact the longer-term course of MDD.

2.2 Introduction

Major depressive disorder (MDD) is a highly prevalent mental disorder characterized by a high risk of chronicity and relapse (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005; Hardeveld et al., 2010; Richards, 2011). In light of the unfavorable long-term course of MDD, it is important to identify risk factors that contribute to the clinical course of the disorder. In previous studies, clinical characteristics such as the number of previous episodes and subclinical residual symptoms have been identified as relevant course modifiers (Hardeveld et al., 2010; Seemüller et al., 2014; Hardeveld et al., 2013). Less is known about the influence of maladaptive habitual cognitive thinking on the long-term course of depression. First evidence suggests that rumination, a cognitive trait defined as a negative pattern of responding to distress by repetitively and passively focusing on the meanings, causes, and consequences of one's depressive symptoms (Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008) predicts symptom severity (Kuehner & Weber, 1999; Gan, Xie, Duan, Deng, & Yu, 2015), as well as a chronic symptom course in depression (Wiersma et al., 2011). Maladaptive habitual thinking styles like rumination or worry are subordinate constructs of the broader concept of trait repetitive negative thinking (RNT) (McEvoy et al., 2013; Ehring & Watkins, 2008). RNT is defined as repeatedly occurring, uncontrollable, negative and abstract thoughts from which it is difficult to disengage and has been considered to represent a potential transdiagnostic cognitive risk factor for various mental disorders (Ehring & Watkins, 2008). Studies suggest that trait RNT is cross-sectionally associated with symptoms and treatment outcomes of depression and anxiety (McEvoy et al., 2013; Kertz, Koran, Stevens, & Björgvinsson, 2015; Spinhoven et al., 2015). Only one study so far has identified the predictive validity of RNT for the 3-year course of depressive symptoms in a nonclinical sample (Raes, 2012). Comparable data in clinically depressed samples is still missing.

In contrast to macro-level risk factors such as trait RNT, possible dysfunctional cognitive and affective momentary state variables reflect mental states at the micro-level of moment-to-moment experiencing during daily life (cf. Trull & Ebner-Priemer, 2013; Conner & Barrett, 2012; Wichers, 2014). The investigation of such momentary experiences and their variability over the day appears important, because there is increasing evidence that they may affect the course of psychopathology at the macro-level (for a review see Wichers, 2014). A promising approach to examine micro-level risk factors in depression is ambulatory assessment (AA) (Trull & Ebner-Priemer, 2013;

Fahrenberg, Myrtek, Pawlik, & Perrez, 2007). Here, individual data is repeatedly collected over a given period of time and in different contexts. During AA, individuals rate their affective states and current thoughts or activities. Thereby, it is possible to assess state-like vulnerability factors in a naturalistic context and to investigate their predictive value for the future course of illness (Wichers, 2014; Wichers et al., 2010).

Several studies have investigated affective state variables showing that MDD patients report less positive and more negative affect in daily life compared to healthy controls (Myin-Germeys et al., 2003; Peeters et al., 2006). Recent efforts undertaken to test predictive effects of momentary affective processes on the course of depression yielded compelling results, substantiating that individual responses to stressful and rewarding events during daily life are associated with future depressive symptoms (Wichers, 2014; Wichers et al., 2009; Geschwind et al., 2010). In addition, depressive individuals seem to display a distinct affective dynamic over the day (Koval et al., 2013; Thompson et al., 2012; Ebner-Priemer & Trull, 2009). Mood instability has predominantly been studied in patients with other psychopathology, such as those with borderline personality disorder (Santangelo et al., 2014; Trull et al., 2015), but first evidence suggests that, for example, variations in negative affect may also have detrimental effects on the clinical course (Wichers et., 2010) and treatment response (Husen et al., 2016) in MDD. Furthermore, by applying a dynamic system framework, we could previously show that high entropy, i.e. frequent and unpredictable changes in the interplay between momentary mood and rumination, was related to an increase of depressive symptoms during six months in remitted depressed (rMDD) individuals (Koster et al., 2015).

There is a clear lack of AA-studies investigating momentary cognitive processes as a potential course-modifying vulnerability factor. One such possibly important cognitive momentary risk factor is daily-life rumination. Up to now, momentary rumination has been predominantly examined in non-clinical samples, thereby demonstrating an increase in depressive symptoms, e.g. sleep disturbances (Kalmbach, Pillai, Roth, & Drake, 2014) or negative affect (Moberly & Watkins, 2008) over a short period. Furthermore, depressive symptoms in a student sample were predicted by the level of momentary rumination (Pasyugina, Koval, De Leersnyder, Mesquita, & Kuppens, 2015). Compared to control participants, clinically depressed and anxious individuals are characterized by higher levels of momentary rumination (Kircanski et al., 2015). In a previous study (Huffziger et al., 2013), we found that momentary rumination was

associated with higher cortisol secretion over the day in rMDD individuals, demonstrating prolonged activation of the bodily stress system in response to rumination with possible detrimental effects on the further course of depression. However, studies explicitly investigating the impact of momentary rumination and its instability over the day on the long-term course of depression in clinical samples are lacking.

In summary, it appears of high importance to investigate the possible predictive value of both trait RNT and momentary affective and cognitive states during daily life for the long-term course of depression. Therefore, the present study aimed to test the predictive validity of such traits and states at baseline on course-related outcomes, i.e., time to relapse, chronicity, and levels of depressive symptoms over three years, in individuals with rMDD. Although clinical predictors were not the focus of the study, we chose to additionally include residual symptom levels at baseline, which are considered a potent clinical predictor for relapse and other poor outcomes in depression (Fava, Fabbri, & Sonino, 2002; Zajecka, 2013; Zajecka et al., 2013), and which also overlap with other clinical predictors such as the severity of the previous index episode (Madhoo & Levine, 2015).

Based on previous research showing that both high entropy and variability in daily-life affect appears to be linked to an increase in depressive symptoms in rMDD individuals (Wichers, 2010; Koster et al. 2015) we expected that a fluctuating course (i.e., relapses) would be predominantly predicted by instability measures of daily life affect and cognition. Up to now, these variability measures have not been tested for the more stringent criteria of relapse. In contrast, first evidence suggests a link between habitual rumination and a chronic symptom course (Wiersma, 2011) leading to the hypothesis that chronicity and symptom level outcomes would predominantly be predicted by trait RNT.

2.3 Methods

2.3.1 Procedure

Participants were recruited by announcements in local newspapers and on the homepage of the Central Institute of Mental Health (CIMH), Mannheim, Germany. After a telephone prescreening, preliminary eligible participants were invited to the CIMH, and a trained clinical psychologist administered the Structured Clinical Interview for DSM-IV axis I (SCID-I, Wittchen, Zaudig, & Fydrich, 1997), see below) as part of the

baseline interview (T1) to assess in- and exclusion criteria. All rMDD individuals had to fulfill either the criteria for at least two lifetime MDD episodes or a previous chronic MDD of at least two years duration. At T1, they had to be remitted from the last episode, i.e., did not fulfill the criteria of a Major Depressive Episode according to DSM-IV, for at least two months. Exclusion criteria were non-affective psychotic disorders, bipolar disorder, substance dependence, current substance abuse, generalized anxiety disorder, and current obsessive-compulsive, posttraumatic stress, and eating disorder according to DSM-IV. In addition to rMDD participants, the study also recruited healthy individuals, which are, however, not subject to the present analyses. Demographic, clinical, and cognitive trait predictors in rMDD individuals were assessed at T1, followed by ambulatory assessment (AA) of affective and cognitive state factors, assessed during the days immediately following the diagnostic baseline interview (see paragraph “Predictor variables”). Follow-ups on the course of clinical depression and depressive symptoms took place at six (T2) and 36 months (T3) after baseline and were conducted by a trained clinical psychologist during a telephone interview. At all measurement points, we assessed diagnostic status and symptom levels and, at T2 and T3, the course of depression since the last assessment.

Importantly, the present study sample of rMDD participants consisted of two consecutively recruited subsamples (subsample 1: Oct 2010 to Apr 2011, subsample 2: Nov 2011 to Nov 2012) from an overarching study. The two subsamples underwent different functional magnetic resonance imaging (fMRI) experiments, conducted after the ambulatory assessment days, which are not subject to the present analyses (see Zamoscik et al., 2014). In addition, the AA of subsample 1 was restricted to the assessment of naturally occurring mood and rumination over the day, whereas in subsample 2 an additional rumination versus mindful self-focus manipulation during AA was conducted. The two AA-procedures are described in the supporting information (S1), together with detailed analyses regarding the comparability of subsample 1 and 2 and the legitimation for their combined inclusion for the present long-term analyses. The study was in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of the University of Heidelberg. All participants gave written informed consent.

2.3.2 Sample recruitment and attrition

Originally, 101 individuals were contacted during the telephone prescreening, of whom eight participants were excluded (n = 2 fulfilling fMRI exclusion criteria (see

above), n = 6 declined to participate). At the diagnostic baseline session (T1), 27 individuals were excluded due to diagnostic exclusion criteria, resulting in a sample of n = 66 remitted depressed (rMDD) individuals with whom the comprehensive baseline assessment was carried out. Of those, one participant dropped out after T1 (could not be reached), and eight individuals dropped out after T2 (n = 1 moved abroad, n = 7 could not be reached). Consequently, 57 of initially recruited 66 participants (86.4%) provided data for all measurement points and were included in the present analyses. Demographic and clinical characteristics at study entry did not differ significantly between participants participating in both follow-ups and those who dropped out during the study, with one exception: there was a significant dropout of participants with lower education levels (n = 9 drop outs vs n = 57 completers: school education < 10y: χ^2 = 5.33, p = .021). In contrast, individuals who completed the study and those who dropped out did not differ with regard to clinical variables at T1 (n = 9 drop outs vs n = 57 completers: BDI-II: t = -.225, p = .823, MADRS: t = -.431, p = .668, number of previous episodes: χ^2 = .085, p = .771).

2.3.4 Outcome measures

The following three outcome measures related to the course of illness were investigated: time to relapse, chronicity and depressive symptom levels. The current diagnostic status at all measurement points (T1-T3) was determined with the SCID-I (Wittchen, Zaudig & Fydrich, 1997). If an individual met criteria for a current major depressive episode (MDE) during the follow-up assessments (T2, T3), we coded the number of weeks since the beginning of the current episode. Additionally, we coded the number of weeks related to the beginning and ending of those depressive episodes occurring exclusively during the follow-up intervals. Thereby, we assessed both pure interval episodes during the T1-T2 and T2-T3 intervals and episodes that were present at T2 and T3.

Time to relapse. For the outcome “time to relapse”, we calculated the number of weeks to the first MDE after T1. Relapse was defined as the recurrence of a depressive syndrome fulfilling criteria of a MDD after T1. This term was used as an umbrella term for relapses (i.e. within six months after remission, n = 1) and recurrences (i.e. after six months, n = 20). Due to the limited sample size, we combined these two outcomes to increase statistical power.

Chronicity. Chronicity was defined as the percentage of weeks spent with significant symptoms (i.e., without distinct symptom relieve) after T1 using the information of the expanded SCID-I at T2 and T3.

Depressive symptom levels. As a measure of levels and course of depressive symptoms we used the self-rated Beck Depression Inventory Revised (BDI-II, Beck, Steer, & Brown, 2006) and the interviewer-rated Montgomery and Asberg Depression Rating Scale (MADRS, Neumann & Schulte, 1989), which both have shown good reliability, validity and sensitivity to symptom changes

Beck, Steer, & Garbin, 1988; Kjærgaard, Arfwedson, Wang, Waterloo & Jorde, 2014; Kuehner, Buerger, Keller, & Hautzinger, 2007). For statistical analysis, we calculated an overall composite score for depressive symptoms by averaging the z-standardized BDI-II and MADRS scores both at T2 and T3, as done in previous research (e.g., (Huffziger et al, 2013; Huffziger, Reinhard, & Kuehner, 2009).

2.3.5 Predictor variables

Demographic and clinical variables. Demographic variables included age, gender and education status. Clinical variables included residual depressive symptoms at baseline (T1) and current use of medication at T1 (the latter to check for possible confounding effects with residual symptoms and outcome measures). Depressive symptoms at T1 were calculated as a composite score of the MADRS and the BDI-II scores (see above).

Trait repetitive negative thinking. Trait repetitive negative thinking (RNT) was measured with the Perseverative Thinking Questionnaire (PTQ, Ehring & Watkins, 2008; Ehring et al., 2011), which is conceptualized as a content-independent measure of RNT. Individuals are asked how they *typically* think about negative experiences or problems. Research has shown that the PTQ has good psychometric properties, i.e. internal consistency, stability, factor-structure and construct validity (Ehring et al., 2011, Ehring, Raes, Weidacker, & Emmelkamp, 2012).

Affective and cognitive state variables. After the baseline interview, affective and cognitive state variables were assessed by AA during the following days. In subsample 1 (n = 28), participants were assessed with personal digital assistants (PDAs, Palm Tungsten E2, Palm Inc.) and the software IzyBuilder (IzyData Ltd., Fribourg, CH) over two consecutive weekdays with ten assessments per day (for detailed description see [37]). AA in subsample 2 (n = 29), was conducted over four consecutive weekdays with ten assessments per day using smartphones (HTC Touch

Diamond 2) and the software MyExperienceIDE by movisens GmbH (Karlsruhe, Germany). The two subsamples completed identical affective and cognitive AA measures (for further details, see supporting information S1). Momentary mood was measured with six bipolar items specifically developed for AA (Wilhelm & Schoebi, 2007) that were collapsed into the three scales “valence” (items “content-discontent”, “unwell-well”), “calmness” (items “agitated-calm”, “relaxed-tense”) and “energetic arousal” (items “tired-awake”, “full of energy-without energy”). Three items (one per subscale) were recoded so that higher values indicate a more positive mood component. These subjective mood scales have shown good reliability and validity (Wilhelm & Schoebi, 2007). Momentary ruminative self-focus was operationalized with the average score of two items developed by Moberly and Watkins (2008): “At the moment, I am thinking about my problems” and “At the moment, I am thinking about my feelings”. These items proved to be suitable for studies with AA-designs (Moberly & Watkins, 2008; Huffziger, Ebner-Priemer, Koudela, Reinhard, & Kuehner, 2012). Figure 2 shows the overall study design.

2.3.6 Statistical analyses

For the AA predictors, we used aggregated scores, i.e. overall means over the respective assessment days, of the momentary scales (valence, calmness, energetic arousal, rumination) together with their averaged instability scores. The latter were calculated according to von Neumann and collegues (von Neumann et al., 1941) using the *mean squared successive difference* (MSSD, see Eq (1)).

$$MSSD(X) = \frac{\sum_{i=2}^{n} (X_i - X_{i-1})^2}{n-1} \quad (1)$$

The MSSD represents instabilities in a time series as an average of all squared successive changes over time. Thereby, MSSD takes into account three components of instability: temporal order, amplitude and frequency of change. A high MSSD score

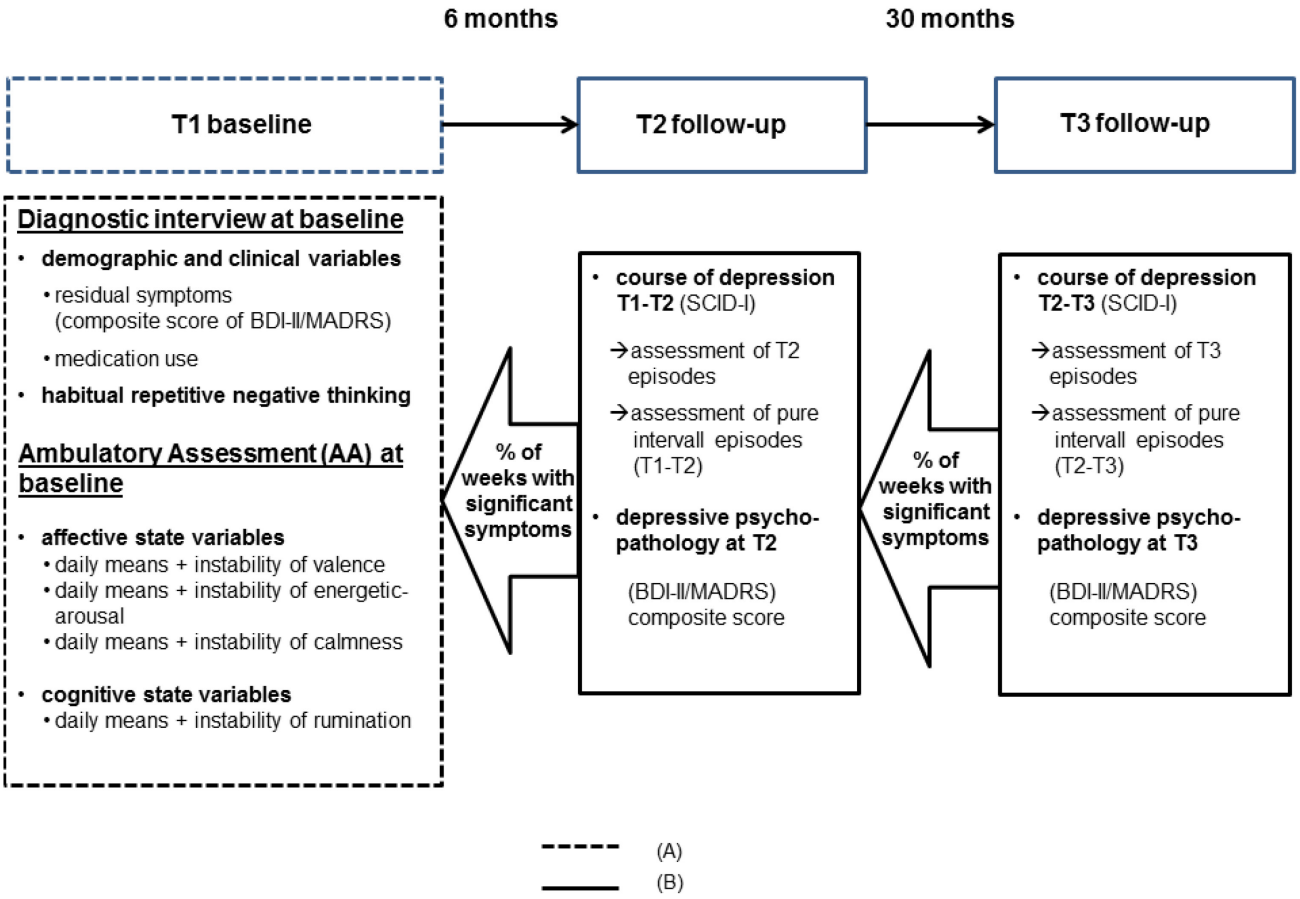

Figure 2: Study design (A) Baseline predictors. (B) Diagnostic information to define outcome variables. BDI-II (Beck Depression Inventory II). MADRS (Montgomery and Asberg Depression Rating Scale). SCID-I (Structured Clinical Interview for DSM-IV Axis 1).

reflects high temporal instability as a result of high amplitudes and high frequency of, e.g., mood swings over the day, corresponding to low temporal dependency (Ebner-Priemer, Eid, Kleindienst, Stabenow, & Trull, 2009; Ebner-Priemer & Sawitzki, 2007; Jahng et al., 2008). MSSD is highly correlated with the standard deviation (SD) (Ebner-Priemer et al., 2009). However, compared to variability, defined as the dispersion of scores from a central tendency, MSSD takes into account gradual shifts in means over time (Ebner-Priemer et al., 2009). For example, while the variability of the mood component “energetic arousal” (Wilhelm & Schoebi, 2007) would be similar for a person with two extreme states of “energetic arousal” in the morning and evening compared to a person with frequent, less extreme swings of “energetic arousal” over the day, MSSD reflects these differences (Ebner-Priemer et al., 2009). MSSDs were calculated for each momentary mood component and for momentary rumination.

For each outcome, we present the results of simple regression analyses, i.e., the association between outcome and each predictor separately in a first step. To

determine the independent contribution of each predictor, we then entered those predictors with a *p*-value of < .05 simultaneously into a multiple model using backward elimination of predictors, and retained all predictors in the model that significantly (p < .05) contributed to the respective outcome.

Effects of predictors on time to relapse were estimated using Cox regressions. To predict chronicity, we applied linear regression analyses with the percentage of weeks spent with significant symptoms as the dependent variable. This outcome was positively skewed and therefore log-transformed to yield a better approximation of a normal distribution. Effects on depressive symptom levels were analyzed by hierarchical linear models with depressive composite scores at T2 and T3 as outcome. For the latter analyses, we first tested main effects of individual predictors and their interaction effect with time (T2, T3) in separate regression models. If the interaction term did not reach statistical significance, we removed this term from the respective models. In a next step we included all significant predictors and significant interaction effects in a multiple model.

In all multiple models described above, subsample status was included as a covariate to control for possible confounding effects of this variable (for further information, see supporting information S1). All statistical analyses were performed using the statistical software IBM SPSS Version 20.

2.4 Results

2.4.1 Participants' characteristics

Demographic, clinical, as well as cognitive trait and state characteristics are presented in Table 1. The mean age at MDD-onset in rMDD participants was 23.8 years (*SD* = 11.2), and 70% of these individuals reported at least 3 lifetime MDD episodes upon entering the study. During the 3-year follow-up period, 28 (49.1%) of the originally remitted depressed patients had suffered at least one relapse into a major depressive episode. Furthermore, the mean proportion of weeks spent with significant symptoms during the 3-year interval was 34.9% (range 1%-95%) with 28% spending more than 50% of the weeks with significant symptoms.

Table 1. Demographic, clinical, cognitive trait and affective and cognitive state characteristics in remitted depressed patients (rMDD) at baseline.

	rMDD (n=57)	
	***mean* (*SD*) / %**	***range (min-max)***
demographic		
age (SD)	43 (10.3)	(23-55)
gender (female %)	70.2 %	
education (% > 9 years)	63.2%	
work situation (% in regular job or education)	68.4%	
marital status (% married or living together)	49.1%	
clinical		
BDI-II[1]	10.6 (8.8)	(0-36)
MADRS[2]	5.8 (4.8)	(0-22)
current psychotherapy	22.8%	
current psychotropic medication[3]	24.6%	
number of previous episodes	3.8 (1.9)	(1-7)
duration of previous hospitalization (weeks)	9.3 (12.9)	(0-75)
residual symptom levels (composite score MADRS[2], BDI-II[1])	0.5 (1.0)	(-0.8-4.1)
habitual negative perseverative thinking		
PTQ[4]	30.8 (14.5)	(0-60)
affective state variables (AA)[5]		
daily-life valence	3.7 (0.9)	(2.4-5.9)
daily-life calmness	3.4 (0.9)	(1.6-5.7)
daily-life energetic arousal	3.4 (0.8)	(1.7-5.4)
instability of daily-life valence	1.3 (0.9)	(0.04-3.8)
instability of daily-life calmness	1.6 (1.2)	(0.2-6.6)
instability of daily-life energetic arousal	1.6 (1.1)	(0.2-5.0)

cognitive state variables (AA)[5]		
daily-life rumination	1.6 (1.1)	(0-4.2)
instability of state rumination	2.9 (2.6)	(0-9.2)

[1]BDI-II BeckDepressionInventory II

[2]MADRS Montgomery and Asberg Depression Rating Scale

[3]Selective serotonin reuptake inhibitors (SSRIs): n = 3 (5.3%), Serotonin-norepinephrine reuptake inhibitors (SNRIs): n = 6 (10.5%), Noradrenergic and specific serotonergic antidepressant: n = 1 (1.8%), Tricyclic antidepressants (TCAs): n = 1 (1.8%), amber: n = 1 (1.8%), Lithium: n = 1 (1.8%), Seroquel: n = 1 (1.8%)

[4]PTQ Perseverative Thinking Questionnaire

[5]AA Ambulatory Assessment

2.4.2 Predictors of time to relapse

Simple Cox regression analyses revealed that higher levels of residual depressive symptoms, as well as higher instability of momentary rumination (AA) and of valence (AA) predicted a shorter time to relapse (Table 2). We further conducted correlational analyses on the relationship between number of previous episodes and predictors. The respective coefficients are: $r = 0.246$ ($p = .067$) for residual symptoms; $r = 0.308$ ($p = .022$) for instability of momentary valence and $r = 0.468$ ($p < .001$) for instability of momentary rumination. Figure 3. shows the corresponding survival curve (remaining in remission), estimated by the product-limit method of Kaplan and Meier, for rMDD individuals with low (A) and high instability (B) of affective valence at T1. In the multiple model, residual symptoms at baseline ($B = .585$, $SE = .187$, Wald = 9.7, $p = .002$), and higher instability of momentary valence (AA, $B = .511$, $SE = .205$, Wald = 6.1, $p = .013$) remained as independent significant predictors of time to relapse in the model.

2.4.3 Predictors of chronicity

Higher levels of residual symptoms at baseline, more trait RNT, and lower levels of momentary energetic arousal (AA) were associated with a higher percentage of weeks spent with significant symptoms in the simple regression analyses (Table 2). In the multiple analysis, only higher levels of trait RNT ($B = .032$, $SE = .009$, $t = 3.37$, $p = .001$) remained in the final model (Table 2).

2.4.4 Predictors of depressive symptom levels

Simple mixed model analyses revealed that higher levels of depression scores (T2, T3) were predicted by more severe residual symptoms, higher levels of trait RNT, higher momentary rumination (AA) and its interaction with time, higher instability of momentary rumination (AA), as well as by lower levels of momentary positive valence, energetic arousal and calmness (AA) during daily life. In the final multiple model, depression scores at baseline (*B* = .503, *SE* = .077, *t* = 6.52, *p* = < .001) and instability of daily-life rumination (AA) at baseline (*B* = .065, *SE* = .031, *t* = 2.11, *p* = .037) were retained as independent significant predictors.

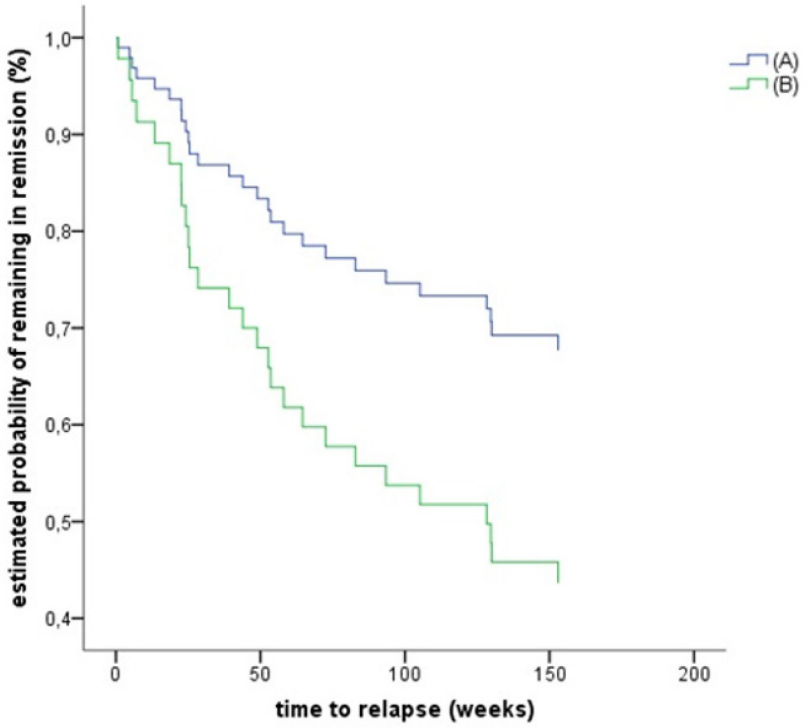

Figure 3: Estimated probability of remaining in remission in rMDD individuals with low and high instability of affective valence at baseline (A) rMDD participants with low instability of affective valence. (B) rMDD participants with high instability of affective valence. Median split for illustrative purposes.

Table 2: Simple and multiple regression models for time to relapse, chronicity, and depression scores (T2, - T3) in remitted depressed patients (rMDD).

outcome variables	**time to relapse after T1[a] (n = 57)**		**chronicity/ % of weeks with significant symptoms after T1[b] (n = 57)**		**composite depression score (BDI-II/MADRS) T2, T3[c] (n = 57)**	
	simple	**multiple[f]**	**simple**	**multiple[f]**	**simple**	**multiple[f]**
	B (SE)	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**
demographics						
age	0.003 (0.019)	-	- 0.001 (0.014)	-	0.007 (0.010)	-
sex	-0.518 (0.388)	-	- 0.547 (0.313)	-	0.236 (0.239)	-
education level	0.040 (0.182)	-	- 0.073 (0.143)	-	-0.102 (0.106)	-
clinical variables						
medication use	-0.116 (0.437)	-	-0.388 (0.337)	-	-0.366 (0.303)	-
residual symptoms at baseline	**0.498 (0.173)****	**0.585 (0.187)****	**0.360(0.135)****	-	**0.522(0.082)*****	**0.502(0.077)*****
trait repetetive negative thinking	0.020 (0.014)	-	**0.037(0.039)*****	**0.032(0.009)*****	**0.024(0.007)*****	-
affective state variables (AA)[d]						
valence	-0.289 (0.240)	-	-0.293 (0.160)	-	**-0.386(0.113)****	-
energetic arousal	-0.189 (0.248)	-	**-0.366(0.181)***	-	**-0.436(0.128)****	-
calmness	-0.291 (0.242)	-	-0.202 (0.169)	-	**-0.338(0.120)***	-

instability of valence	**0.396(0.191)***	**0.511 (0.205)***	0.213 (0.159)	-	0.209 (0.118)	-
instability of energetic arousal	0.156 (0.147)	-	0.165 (0.129)	-	0.064 (0.099)	-
instability of calmness	0.229 (0.131)	-	0.214 (0.119)	-	0.089 (0.091)	-
cognitive state variables (AA)[d]						
rumination	0.275 (0.162)	-	0.185 (0.132)	-	**0.283(0.093)****	-
rumination*time[e]	-	-	-	-	**0.290(0.127)***	-
instability of daily-life rumination	**0.138(0.065)***	-	0.093 (0.057)	-	**0.099(0.042)***	**0.065 (0.031)***

[a] cox regression model

[b] linear regression model

[c] mixed models (hierarchical linear models)

[d] AA Ambulatory Assessment variable

[e] model includes main effects and interaction effect of predictor and time

[f] all multiple models included subsample status as a covariate

*** $p<.001$, ** $p<.01$, * $p<.05$

2.5 Discussion

The present longitudinal study investigated both trait and state predictors for the course of depression in a community sample of remitted depressed individuals with regard to risk of relapse, chronicity and symptom levels during an observation period of three years. We identified a rather unfavorable long-term depression course in our sample. During the 3-year follow-up, approximately half of the sample had suffered a relapse into a Major Depressive Episode, and nearly 30% had spent more than half of the follow-up period with significant depressive symptoms. Rates of relapses and chronicity are largely comparable to those found in previous research (Richards, 2011; Hardeveld et al., 2013; Bukh, Andersen, & Kessing, 2011).

In the present study, a shorter time to relapse was predicted by higher residual symptom levels, higher instability of momentary mood (valence) and higher instability of rumination during daily life (AA) at baseline. In the multiple model, residual symptoms, and higher instability of momentary mood (AA) remained as significant independent predictors. Similar to our results, previous research has identified residual depressive symptomatology as a serious risk factor for relapse (Hardeveld, et al., 2010; Iovieno, van Nieuwenhuizen, Clain, Baer, & Nierenberg, 2011; Kuehner & Huffziger, 2013). Given the high prevalence of residual symptoms during remission (Conradi et al., 2011), even after successful treatment (Zajecka, 2013), this clearly deserves more attention in future relapse prevention efforts for depression. Regarding the predictive role of momentary affective state characteristics for the long-term course of illness, our results showed that a faster time to relapse was predicted by higher instability of momentary mood at baseline, thereby confirming our hypothesis. In previous studies, negative affect variability has been found to predict future negative affective symptoms in rMDD individuals (Wichers et al., 2010) and treatment response in individuals with MDD (Husen et al., 2016). Our longitudinal results confirm and expand these findings by showing that affective instability increases the vulnerability towards relapse (Koval et al., 2013; Trull et al., 2015). This finding has possible clinical implications. While current intervention programs aim to reduce the prolonged negative affect in acutely depressed individuals, fluctuations in everyday affect appear to be linked to a larger susceptibility for relapses or recurrences and could therefore specifically be considered in relapse prevention programs. Clearly, these considerations warrant more rigorous testing in future research.

Chronicity, i.e., the proportion of weeks spent with significant symptoms, was predicted by residual symptom levels, high levels of trait repetitive negative thinking (RNT) and low levels of momentary energetic arousal during daily life (AA) at baseline. In the multiple model, trait repetitive negative thinking was the most powerful and single remaining predictor. These results confirm our hypothesis suggesting that dysfunctional cognitive traits represent an important course moderating factor with regard to the development of a chronic course. Concordantly, high levels of habitual state orientation (Kuehner & Huffziger, 2013), dysfunctional attitudes (Riso, du Toit, Blandino, Penna, Dacey, & Duin, 2003) as well as ruminative thinking (Wiersma et a., 2011) have been found to be heightened in chronic depressed individuals or to predict a chronic symptom course.

Finally, depressive symptom levels at follow-up (T2, T3) were predicted by higher levels of residual symptoms and trait RNT, as well as by virtually all cognitive and affective state variables (AA). Residual symptom levels and instability of daily-life rumination (AA) remained as independent significant predictors in the multiple model. With respect to cognitive state variables (AA), we found that, contrary to our expectation, the instability of daily life rumination over the day (AA) was an even more important predictor for longer-term elevated levels of depressive symptoms than respective mean levels. A question is why higher levels of fluctuation in rumination could be maladaptive with this regard. Possibly, the instability of rumination was related to daily life stressors, which may have mediated the effect on depression symptom levels. However, this has not been investigated in the present study and therefore remains speculative. Our analyses do also not allow to decide whether possible emotional cascades, characterized by reciprocal cycles of rumination and negative affect, or pure cognitive fluctuations in the context of more stable elevated negative mood at baseline, predicted long-term elevated depressed symptoms (cf. Selby et al., 2013a; Selby & Joiner, 2013b). Further research is required on these aspects.

This study has several limitations. First, in order to include patients with a primary diagnosis of MDD, individuals with certain comorbid diagnoses were excluded, which may have led to a somewhat selective sample. Second, we combined samples from two substudies with a somewhat different baseline assessment design. To account for a possible influence of subsample status, we controlled for this variable and could not identify a possible confounding effect in any of the predictor analyses. Third, although dropout rates were satisfactorily low during the three-year period, we observed a

selective dropout of rMDD individuals with lower education levels, thereby reducing the generalizability of our results. Fourth, although all rMDD participants had to be out of episode for at least two months before study inclusion, their residual symptom levels varied markedly. Fifth, we did not control for stressful daily-life events in the present analyses. Thus, it is difficult to conclude how much individual differences in the assessed affective and cognitive states were affected by environmental influences (Koval et al., 2013; Bylsma, Taylor-Clift, & Rottenberg, 2011). Sixth, due to the investigated outcomes, the instability measures had to be aggregated, thereby eliminating the dynamic aspect at the within-subject level. However, MSSD still is a measure of instability, demonstrating differences in emotional fluctuations on the between-subject level (von Neumann et al., 1941; Jahng et al., 2008). Finally, the multiple models showed that single predictors were correlated, and one could argue that the presentation of results from simple models is dispensable. However, we think that these results yield information about predictors that could be relevant for research questions in future studies, which may particularly apply to the daily life measures in hand.

To conclude, our results imply that illness-related characteristics and cognitive vulnerability traits, but also affective and cognitive state variables assessed during daily life, impact the longer- term course of depression. While trait repetitive negative thinking particularly predicted longer-term chronicity, the assessed state variables partly differently affected relapses and levels of depressive symptoms. Our findings imply that particularly those rMDD individuals showing high fluctuations in daily-life affect are susceptible to relapses, while individuals with a more frequent unstable pattern of rumination over the day are especially prone to suffer from persistently elevated symptoms. Importantly, these findings were not attributable to higher residual depression levels at baseline since this course-relevant clinical predictor was also retained in the respective final multiple models. Thereby, the assessed state variables provided independent contributions for the prediction of outcomes.

The present findings have several implications. First, our longitudinal results suggest that mood and rumination instability during daily life, indicating specific patterns of emotional dysregulation (Koval et al, 2013; Trull et al., 2015), might reflect a kind of scarring process (cf. Wichers et al., 2010) in patients with former episodes, which - per se or in combination with other risk factors - increases vulnerability towards relapse and maintenance of depressive symptoms. In fact, both variability parameters

were significantly associated with the number of anamnestic MDE episodes in that the more depressive episodes an individual had experienced in the past, the higher were the current levels of mood and rumination instability. This finding is in line with a more dimensional view on scars, suggesting a gradual development of vulnerability factors with every MDD episode (Wichers et al., 2010). Connected herewith, it has been proposed that ambulatory assessment enables to assess basic regulatory processes such as stress reactivity, reward dependence, and affective instability, which may be relevant for a number of mental disorders (Wenzel et al., 2016). As regards the latter, previous daily life research has investigated affective and cognitive instability features primarily in the context of other disorders such as bipolar disorder (Knowles, Tai, Jones, Highfield, Morriss, & Bentall, 2007), borderline personality disorder (Santangelo et al, 2014; Trull et al., 2015), and non-suicidal self-injury (Selby et al., 2013a; Santangelo et al., 2016). The present study suggests that instability features may also play a role as course-relevant modifiers in major depression, thereby lending support for their role as transdiagnostic endophenotypes (cf. Wenzel et al., 2016). Future longitudinal research testing the role of these AA-phenotypes across mental disorders is clearly warranted. Finally, the study of the dynamic interplay of momentary cognitive and affective variables at the micro-level may help to even better understand determinants of the course of macro-level symptoms and diagnosis (Wichers, 2014; Wichers et al., 2010).

S1 Supporting information

The present study sample of rMDD participants consisted of two consecutively recruited subsamples (subsample 1: Oct 2010 to Apr 2011, subsample 2: Nov 2011 to Nov 2012) from an overarching study. The two subsamples underwent a partly different ambulatory assessment (AA) procedure. The AA of subsample 1 was restricted to the assessment of naturally occurring mood and rumination over the day during two assessment days, whereas in subsample 2 an additional rumination versus mindful self-focus manipulation during four days of AA was conducted. At each of the ten assessments per day, participants rated momentary mood (valence, calmness, energetic arousal), and ruminative self-focus (focus on feelings/ problems) as spontaneous momentary baseline ratings. At the second, third, sixth, eighth and tenth assessment of each day, there was a subsequent 3 min induction of either ruminative (two induction days) or mindful attention (two induction days) via smartphone screen (randomized cross-over design) in subsample 2, in which the individuals had to focus their attention on 10 ruminative or mindful statements, followed by another rating of momentary mood and ruminative self-focus (post-induction ratings). Data from this particular induction part of this study have not been published so far and can therefore not be referred to in the paper. To identify a possible confounding effect of subsample status we performed three sets of analyses.

A): The analyses on predictive effects of the AA variables in the present paper did only include the pre-induction ratings (baseline-ratings), not the post-induction ratings from subsample 2. We conducted hierarchical linear models to check whether the induction day had a significant effect on the mood and rumination pre-induction (baseline) ratings. All models included time and induction day (0 = rumination induction, 1 = mindful self-focus induction) as fixed effects, and random intercepts on the person level. Here, we identified no significant effects of induction day on momentary valence (B = -.04, SE = .06, t = -.623, p = .534), calmness (B =. 01, SE = .07, t = .161, p = .872), energetic arousal (B = -.03, SE = .07, t = -.398, p = .690) and rumination (B = -.11, SE = .09, t = -1.25, p = .211).

B): We further included the variable “subsample” (1 = subsample 1; 2 = subsample 2) as a covariate in all analyses. In fact, this variable showed no significant effect on any of the investigated outcomes (time to relapse: B = .50, SE = .40, Wald = 1.554, p = .213; chronicity: B = .40, SE = .28, t = -1.469, p = .148; symptom levels: B = -.05, SE = .16, t = -.327, p = .744).

C): We conducted additional analyses separately for all outcomes to investigate possible significant interaction effects between subsample status and the corresponding significant predictor variables. Here, we did not identify any significant interaction between respective predictors and subsample status for the outcomes time to relapse (instability of valence x subsample: *B* = -.251, *SE* = .40, Wald = .421, *p* = .516, residual symptoms x subsample: *B* = .317, *SE* = .40, Wald = .698, *p* = .403), chronicity (RNT x subsample: *B* = -.005, *SE* = .02, *t* = -0.237, *p* = .813), and symptom levels (instability of rumination x subsample: *B* = -.024, *SE* = .09, *t* = -0.271, *p*=.787, residual symptoms x subsample: *B* = -.004, *SE* = .17, *t* = - 0.024, *p* = .981).

Altogether, the results of these three sets of control analyses (A): nonsignificant effect of induction day on momentary baseline outcomes, B): nonsignificant effect of subsample status on any of the long-term outcomes after baseline (T1), C): nonsignificant interaction effect of subsample status and predictors on long-term outcomes) showed no indication of a confounding effect of subsample status on any of the presented results, thereby justifying the combination of both subsamples for the present long-term analyses.

3 STUDY II: MINDFULNESS-BASED ATTENTION TRAINING IMPROVES COGNITIVE AND AFFECTIVE PROCESSES IN DAILY LIFE IN REMITTED PATIENTS WITH RECURRENT DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

Publication: Timm, C., Rachota-Ubl, B., Zamoscik, V., Ebner-Priemer, U., Reinhard, I., Kirsch, P., & Kuehner, C. (2018). Mindfulness-Based Attention Training improves Cognitive and Affective Processes in Daily Life in Remitted Patients with Recurrent Depression: A Randomized Controlled Trial. *Psychotherapy and Psychosomatics*, *87*(3), 184-186. doi: 10.1159/000488862.

Mindfulness-Based Cognitive Therapy (MBCT, Segal et al., 2013) has been shown to effectively prevent depressive relapse (Kuyken et al., 2016), particularly in patients with frequent previous episodes (Piet & Hougaard, 2011). However, potential mechanisms underlying MBCT are not fully understood (van der Velden et al., 2015). In this context, possible changes in dysfunctional experiential processes during daily life may constitute promising targets of investigation. First, momentary affective and cognitive vulnerability patterns, measured at the "micro-level" of experience, contribute to the prediction of the "macro-level" long-term course of clinical depression (Timm et al., 2017; Wichers et al., 2010). Second, first evidence suggests that increases in positive affect (PA) and reward sensitivity in daily life following MBCT may increase resilience, thereby reducing risk of relapse, and that changes in momentary PA and negative affect (NA) possibly mediate the efficacy of MBCT (van der Velden et al., 2015). MBCT may also promote an upward spiral of PA and positive cognition (Garland et al., 2015). Research on potential change in cognitive vulnerability in daily life following MBCT is lacking so far.

In parallel, recent research has called for the identification of effects of individual components of MBCT (Malinowski, 2013). For example, focusing on the early stage of focused attention would allow to study potential effects on impaired core cognitive processes of attentional control in recurrent depressed individuals. Particularly depressive rumination, a key cognitive vulnerability factor in the theoretical MBCT model, has been linked to cognitive inhibitory deficits and valence-specific biases in attentional processes (Koster et al., 2011). The MBCT model suggests an increasingly automatic reactivation of rumination by depressed mood with subsequent episodes and proposes that MBCT is specifically effective in reducing these ruminative thinking cycles in patients with frequent episodes (Segal et al., 2013).

The current study aimed to investigate effects of a four-week Mindfulness Based Focused Attention Training (MBAT) compared to an active comparison condition controlling for time and attention (Progressive Muscle Relaxation, PMR) on daily life cognitions and affect in currently remitted individuals with recurrent depression. We particularly expected stronger benefits of MBAT on momentary rumination. With reference to the MBCT model (Segal et al., 2013), we further expected these effects to be stronger in patients with frequent episodes.

The study was a parallel open-label randomized controlled trial (German Clinical Trails Register: DRKS00005222) in remitted depressed (rMDD) individuals with at

least two lifetime Major Depressive Episodes (MDEs, DSM-IV) not fulfilling MDE criteria for at least two months prior to study entry. Exclusion criteria were severe psychiatric comorbid disorders, and mindfulness and/or relaxation practice during the last three months prior to study entry. Diagnostic criteria were assessed with SCID-I. Individuals were randomly assigned to MBAT or PMR (allocation 1:1), stratified according to age and gender, by an independent researcher. Both trainings were manual-based interventions delivered by video-based supervised cognitive behavioral psychologists or Mindfulness-based stress reduction trainers and were held in one weekly session of 50 min for five weeks. Additionally, during the intersession weekdays participants were asked to perform audio-guided home practice of 20 min per day. MBAT elements included practice of mindfulness of the breath and body scan, and PMR elements were strictly parallelized regarding practice duration. Outcomes were assessed smartphone-based by Ambulatory Assessment (AA): Participants rated their momentary affect (PA, NA) and cognitions (rumination, self-acceptance) on 7-point Likert scales over three consecutive weekdays before and after the training with 10 assessments per day (see online supplement). For analyses we applied multilevel linear models with maximum likelihood estimation to the AA-data. Reported analyses are based on the total sample (intention to treat, two-tailed tests).

Seventy-eight rMDD participants (55 females, age: M = 38.3, SD = 11.1, number of previous MDEs: M = 4.5, SD = 2.6) were enrolled. MBAT (n = 39) and PMR (n = 39) groups did not significantly differ in any important baseline variables (age: $t_{(75)}$ = -1.2, p = .223, gender: $\chi^2_{(1)}$ = 0.1, p = .804, education level: $\chi^2_{(1)}$ = 2.7, p = .104, number of previous MDEs: $t_{(76)}$ = 0.5, p = .612, BDI-II: $t_{(65)}$ = -1.5, p=.143, taking antidepressant medication: $\chi^2_{(1)}$ = 1.5, p = .217) and compliance (practice days: $t_{(70)}$ = 1.8, p = .078, therapeutic relationship: patient-rated $t_{(69)}$ = -0.103, p=.919, trainer-rated $t_{(68)}$ = 1.0, p = .332). Finally, three patients per condition (7.7%) dropped out.

For all outcomes we identified significant interactions of Time*Group (Tab. 3). Post-hoc tests demonstrated significant improvements in all outcomes for MBAT, and no change in PA, rumination, and self-acceptance, and increased NA for PMR. The superior effects of MBAT were moderated by the number of previous episodes for all outcomes, indicated by significant 3-way interactions (previous episodes*Time*Group): NA ($F_{(1,3770.2)}$ = 9.8, p=.002), PA ($F_{(1,3779.9)}$ = 28.0, p<.001), rumination ($F_{(1,3785.8)}$ = 4.1, p = .044) and self-acceptance ($F_{(1,3763.1)}$ = 22.8, p<.001). Graphical inspection showed that the more favorable effect of MBAT was particularly

evident in individuals with frequent MDEs (Figure 4). Including age and medication use as covariates did not change the results (all *p*'s remained <.05).

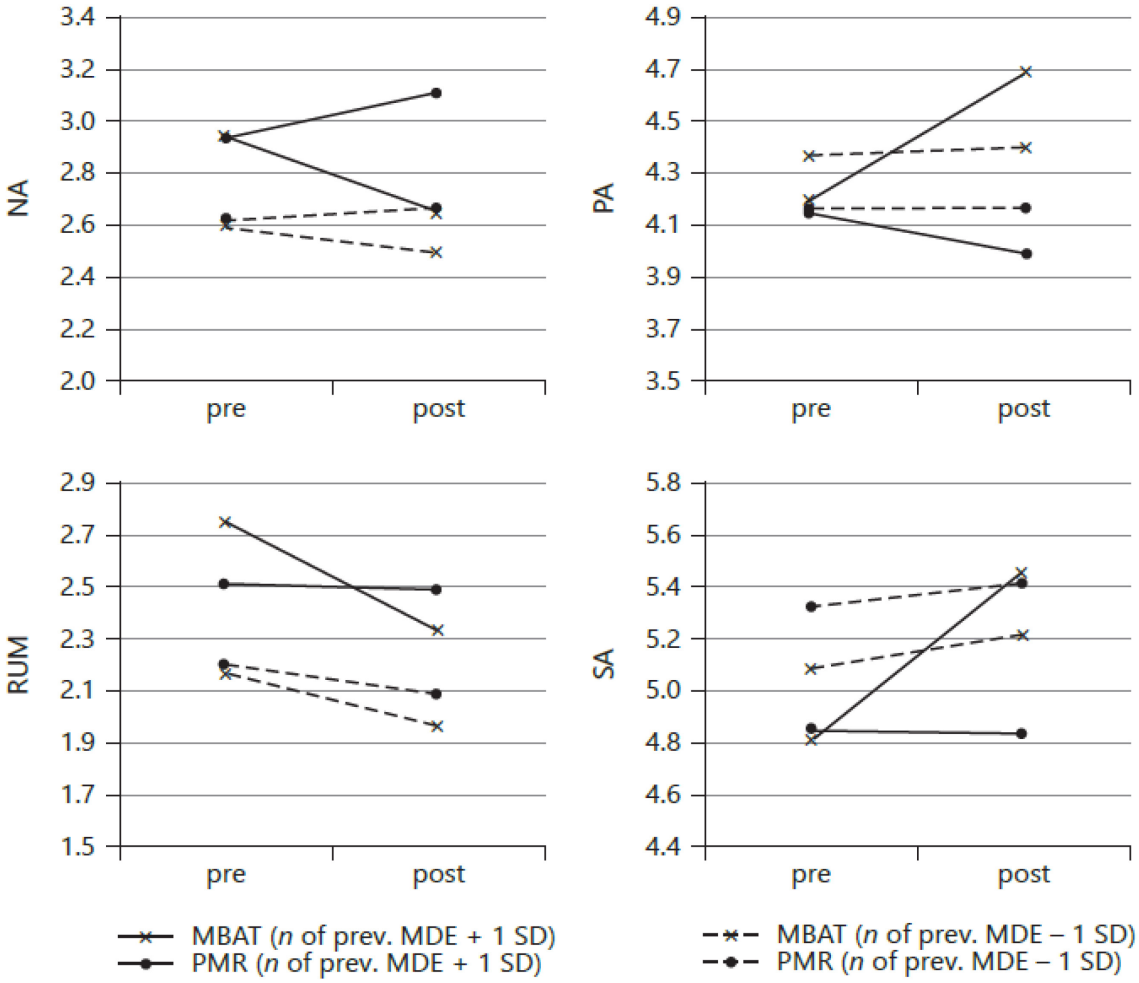

Fig. 4: Estimated scores of outcomes (NA = momentary negative affect, PA = momentary positive affect, RUM = momentary rumination, SA = momentary self-acceptance) during three days before (pre) and after (post) training (MBAT (n = 39) vs. PMR (n = 39)) separately for rMDD individuals with a high (+1SD) and low (-1SD) number of previous MDE. MDE, major depressive episodes; MBAT, mindfulness based attention training; PMR, progressive muscle relaxation

Tab. 3: Differential effects of MBAT versus PMR on momentary cognitive and affective processes

Outcome	Group	Pre assessment	Post assessment	Time x Group[a]				Post Hoc Tests[c] (pre-post per condition)		
				F	*df*	*p*	*Effect size*[b]	*F*	*df*	*p*
Momentary negative affect (NA)	MBAT	2.8 (0.1)	2.6 (0.1)	**41.8**	1, 3764.4	**<.001**	**.29**	**41.2**	1,1938.4	**<.001**
	PMR	2.8 (0.1)	2.9 (0.1)					**8.2**	1,1825.0	**.004**
Momentary positive affect (PA)	MBAT	4.3 (0.1)	4.6 (0.1)	**44.1**	1, 3770.1	**<.001**	**.33**	**55.1**	1,1994.8	**<.001**
	PMR	4.2 (0.1)	4.1 (0.1)					3.5	1,1826.0	.062
Momentary rumination (RUM)	MBAT	2.5 (0.2)	2.2 (0.2)	**10.3**	1, 3774.0	**.001**	**.17**	**42.6**	1,1943.0	**<.001**
	PMR	2.4 (0.2)	2.3 (0.2)					2.2	1,1830.3	.137
Momentary self-acceptance (SA)	MBAT	4.9 (0.2)	5.4 (0.2)	**37.0**	1, 3758.8	**<.001**	**.25**	**80.5**	1,1938.1	**<.001**
	PMR	5.1 (0.2)	5.2 (0.2)					1.4	1,1819.8	.237

MBAT, Mindfulness Based Attention Training, PMR, Progressive Muscle Relaxation. All models include random intercepts.

[a] Models include fixed effects of: day, hours of day (exact time since first assessment), group (PMR = 0, MBAT = 1), time (pre = 0, post = 1), and time*group. Pre and post assessment values of outcomes are presented as estimated means (± *SE*).

[b] Effect sizes were determined by use of standardized outcomes (e.g. standardized NA = NA/SD, whole sample). Thus, the interaction effects are expressed as *SD* units of the dependent variables as a rough approximation to Cohen's *d*.

[c] Models separately for groups include fixed effects of: day, hours of day, time (pre/post

Our findings indicate that a four-week mindfulness-based attention training in contrast to an active control condition was associated with decreased momentary NA and rumination and with increased momentary PA and self-acceptance in daily life, thereby addressing relevant vulnerability factors for the long-term course of clinical depression (Timm et al., 2017; Wichers et al., 2010). Although effect sizes were in the small range, they nevertheless indicate reliable benefits of MBAT during multiple assessments in daily life. Importantly, effects on all outcomes were moderated by number of previous MDEs suggesting that, consistent with the MBCT vulnerability model (Segal et al., 2013), MBAT was particularly effective in individuals with frequent episodes. In this context, it has been suggested that individuals with few episodes might be more vulnerable to recent stressors and require different treatment (Segal et al., 2013). Furthermore, our data indicate that a short PMR training is less suitable to address specific vulnerabilities of individuals with recurrent depression. Clearly, the finding of increased NA in the PMR condition requires further investigation.

In conclusion, our results imply that changes in cognitive and affective processes during daily life measured by AA might represent a subset of mechanisms in mindfulness-based interventions that can be addressed by the training component of focused attention, which appears to be particularly beneficial for those individuals at high risk for relapse (cf. Segal et al., 2013). Further research should study the long-term impact of MBAT on relapse risk associated with respective AA-phenotypes. Understanding such mindfulness-related mechanisms in real-life settings can finally help to establish mechanism-based psychological treatments for relapse prevention as effective alternatives to established but also criticized long-term pharmacological treatments (Vittengl, 2017).

Online supplementary material

Ambulatory Assessment: The Ambulatory Assessment was carried out using Motorola Moto G 1st Generation smartphones with the software movisensXS, version 1.1.1 (movisens GmbH, Karlsruhe, Germany) and was performed on three consecutive weekdays each directly before and after the intervention period. Participants were instructed to turn on the smartphone before 8.00 a.m. on the first assessment day and to leave it on throughout the three-day assessment period. There were ten assessments each day, with the first assessment taking place at 8.00 a.m. and the remaining assessments taking place between 9:00 a.m. and 10:00 p.m. at random time points at least 30 minutes apart. Each assessment was announced by an acoustic signal or vibration alert, and participants were asked to immediately respond to the questions, which took about three minutes to complete. If participants were unable to respond at the time of the signal, they could press a button to delay their response up to 15 minutes. If participants rejected the alarm or ultimately failed to respond to it, the assessment was saved as missing. Participants were provided with written instructions regarding the electronic diary procedure, and the smartphones could not be used for other purposes than responding to the assessments. Altogether, 3847 of 4680 possible assessments were recorded, corresponding to an overall response rate across participants of 82.2%. The Ambulatory Assessment items used in the study are described below.

Momentary rumination (RUM) and self-acceptance (SA): Ruminative self-focus was captured with the item “At the moment, I am stuck on negative thoughts and cannot disengage from them” that captured the uncontrollability facet of rumination (cf. Raes et al., 2008), and momentary self-acceptance with the item “At the moment I accept myself how I am”. Both items were rated on Likert scales from 1 to 7 and were successfully used in previous Ambulatory Assessments (e.g., Kuehner et al., 2017).

Momentary positive (PA) and negative (NA) affect: Momentary positive and negative affect were measured by 12 items derived from the Positive and Negative Affect Schedule (PANAS – Watson, Clark & Tellegen, 1988) and previous Ambulatory Assessment studies (e.g. Bylsma et al., 2011; Nezlek, 2005). These items were balanced in arousal. For positive affect, participants were asked to rate how cheerful, energetic, enthusiastic, satisfied, relaxed and calm they felt and for negative affect how upset, irritated, nervous, listless, down and bored they felt.

4 GENERAL DISCUSSION

The overall aims of the present thesis were the investigation of cognitive and affective daily life AA-phenotypes and their influence on the long-term course of recurrent depression and to identify effects of a brief Mindfulness-Based Attention Training (MBAT) compared to an active control training (Progressive Muscle Relaxation, PMR) on respective daily life processes.

Study 1 investigated the impact of cognitive and affective microlevel processes on the long-term symptom course of rMDD individuals by combining Ambulatory Assessment (AA) data with longitudinal macrolevel outcomes. Level and instability of baseline AA variables were aggregated and used as predictors for time to relapse, chronicity, and maintenance of depressive symptoms over a three-year interval in a community sample of recurrently depressed individuals.

Study 2 examined short-term effects of a 4-week MBAT compared to an active time-matched PMR training within a Randomized Controlled Trail (RCT) on daily life cognitive and affective AA-phenotypes in a new sample of rMDD individuals. Both trainings were manual-based interventions delivered by experienced and supervised trainers and were held in weekly sessions for five weeks. Additionally, participants were asked to perform standardized audio-guided daily home practice per day. Outcomes were assessed with AA on three consecutive weekdays before and after training, in which participants rated their daily life positive (PA) and negative (NA) affect, rumination (RUM) and self-acceptance (SA).

4.1 Important results of Study 1

Results of Study 1 support the hypothesis that cognitive and affective AA-phenotypes together with illness-related characteristics (residual symptoms) and cognitive vulnerability trait variables (repetitive negative thinking, RNT) are linked to the long-term symptom course in recurrently depressed individuals (see Chapter 1.4, H1). Specifically, multiple models revealed that residual depressive symptoms and instability of daily life affect (AA) at baseline independently predicted a faster time to relapse, while residual symptoms and instability of daily life rumination (AA) predicted persistence of depressive symptoms over the three-year interval. Moreover, both instability variables were associated with the number of previous depressive episodes. Finally, chronicity was independently predicted by trait RNT (PTQ, Ehring et al., 2011).

Regarding the role of *affective* AA-phenotypes for the long-term course of

depression, results of Study 1 showed that higher levels of daily life affective instability predicted a shorter time to relapse thereby confirming our hypothesis that a fluctuating course (relapse/recurrence) is predominantly predicted by instability measures of AA (see Chapter 1.4, H2). This finding is in line with previous studies (Husen et al., 2016; Wichers et al., 2010) supporting the assumption that affective instability during daily life can be regarded as a specific vulnerability pattern of emotional dysregulation in recurrently depressed individuals (Thompson et al., 2012; Trull et al., 2015).

Importantly, Study 1 extended previous results by investigating possible effects of daily life *cognitions* on the long-term course of depression demonstrating that instability of momentary rumination together with residual symptomatology predicted depressive symptom levels at follow-up. Conclusively, this result indicates that maladaptive fluctuating patterns of daily life rumination constitute a possible cognitive AA-phenotype for the long-term course of depression. Contrary to our expectation, instability of daily life rumination over the day was a more important predictor for persistent elevated levels of depressive symptoms than respective mean levels (see Chapter 1.4, H2). Clearly, there is a general lack of studies assessing the impact of instability of cognitive vulnerability on the clinical course of depression and further research is required to validate the present findings.

Although instability of daily life affect and rumination were linked to relapse and maintenance of depressive symptoms, it remains unclear whether these AA-phenotypes reflect a premorbid vulnerability marker preceding the onset of MDD or rather a consequence (scar) of prior depressive episodes worsening with subsequent relapses. Importantly, in Study 1 both instability of daily life affect and rumination were correlated with a higher number of previous episodes suggesting that respective AA-phenotypes represent potential scarring processes in patients with recurrent episodes (for reviews see Wichers, 2010, 2014). Supposedly, future longitudinal AA studies investigating individuals who are at elevated familial risk of MDD may help to shed more light on this question.

Finally, Study 1 revealed that trait RNT was linked to a chronic symptom course confirming our hypothesis that a persistent depression course is predominantly predicted by trait cognitive vulnerability (see Chapter 1.4, H2). Similarly, higher levels of cognitive trait variables (state orientation, rumination) have been found to be heightened in chronic depressed individuals or to predict a chronic symptom course (Kuehner & Huffziger, 2013; Struijs et al., 2018; Wiersma et al., 2011).

In general, results of Study 1 revealed that particularly dynamic cognitive and affective daily life processes constitute possible AA-phenotypes affecting relapse/recurrence and maintenance of depressive symptoms. Specifically, our findings imply that rMDD individuals characterized by high fluctuations in daily life affect are more prone to relapses, while an unstable pattern of daily life rumination predicts persistent depressive symptoms. Finally, habitual RNT appears to predict a more pronounced chronic symptom course.

4.2 Important results of Study 2

Hierarchical models identified differential effects of intervention (group*time) for all outcomes (NA, PA, RUM, SA). Specifically, results of Study 2 indicate that a 4-week MBAT in contrast to an active control condition (PMR) was associated with decreased momentary NA and RUM and increased momentary PA and SA, thereby addressing relevant vulnerability factors for the long-term course of clinical depression (cf. Wichers et al., 2010 and Study 1). This finding confirms our hypothesis (see Chapter 1.4, H3) and is in line with previous RCT studies showing that mindfulness training compared to a waitlist control group differentially increases levels of daily life PA (Garland et al., 2015; Geschwind et al., 2011) and that momentary NA and PA mediate the effect of MBCT compared to TAU on clinical depression outcome in rMDD individuals (Batink et al., 2013). Importantly, Study 2 extends existing research revealing that a brief mindfulness-based attention training improves microlevel *negative* cognitions, namely daily life rumination, and beneficially influences daily life self-acceptance (Garland et al., 2015; Jimenez et al., 2010). Within the context of the impaired disengagement model suggesting rumination to be linked to inhibitory deficits and a negative bias in attentional control in recurrently depressed individuals (Koster et al., 2011), the reduction of daily life rumination by MBAT in Study 2 supports the assumption that the early MBI-related stage of focused attention training beneficially influences impaired cognitive processes of attentional control in rMDD individuals.

A particularly important result of Study 2 showed that the beneficial effects of MBAT on all outcomes were moderated by a higher number of previous episodes indicating that especially highly vulnerable rMDD individuals with a higher number of previous episodes benefited from MBAT compared to PMR, independently of participants age. These results confirm our hypothesis (Chapter 1.4, H4) and are consistent with meta-analytic results demonstrating a particular effectiveness of MBCT for highly vulnerable individuals with higher numbers of anamnestic episodes (Kuyken

et al., 2016; Piet & Hougaard, 2011). Moreover, these results clearly support the MBCT vulnerability model suggesting an increased reactivation of rumination with subsequent depressive episodes and proposing that mindfulness training is able to reduce this reactivation (Segal et al., 2013).

Further, results of Study 2 imply that changes in cognitive and affective processes during daily life might represent a subset of mechanisms in MBI's that can be addressed by the early training component of focused attention, which appears to be particularly beneficial for vulnerable individuals with a high risk for relapse (Lutz et al., 2008; van der Velden et al., 2015).

Finally, findings of Study 2 indicate that a short PMR training appears to be less suitable to address specific cognitive and affective microlevel vulnerabilities in rMDD individuals.

4.3 Strengths and Limitations

The present studies investigated important aspects that have been neglected or insufficiently regarded in previous research addressing AA-phenotypes in the context of depression vulnerability. Despite important strengths, both studies have some limitations that need to be mentioned.

Sample characteristics

Both studies examined rMDD individuals, which clearly is a strength and necessary approach to investigate vulnerability markers of depression because it enables the mapping of cognitive and affective alterations in highly vulnerable participants with a history of depression that are on the other hand rather weakly confounded by illness severity. Further, depression is a heterogeneous disorder with high prevalence rates of comorbidity (APA, 2013). In order to include patients with a primary diagnosis of MDD, individuals with certain comorbid diagnoses were excluded in both studies (e.g. eating disorders, obsessive compulsive disorder, substance dependency), which may have led to somewhat selective samples. On the other hand, participants with highly prevalent comorbid diagnoses of anxiety disorders were included. Additionally, future studies could extend the present results by including clinical control groups to investigate whether the identified AA-assessed risk factors are specific to depression or whether they represent possible transdiagnostic vulnerability factors (cf. Kircanski et al., 2017; Santangelo et al., 2014).

Data acquisition

A clear strength of both studies is the use of AA to capture real-life, real-time data with high generalizability by minimizing retrospective bias (cf. Myin-Germeys et al., 2018; Trull et al., 2015; Chapter 1.3.1). AA allows to measure subjective experiences in the context of real-life events (Trull et al., 2013). However, we did not control for stressful daily life events in the analyses of the present studies. Therefore, it is difficult to conclude whether individual differences in the assessed cognitive and affective states were predominantly due to endogenous factors or caused by environmental influences. Considering previous research indicating that daily life stress-reactivity and reward-experience reflect further AA-phenotypes for the course of depression (Shackman et al., 2016; Wichers et al., 2010) and possible microlevel effect mechanisms of MBI's (Garland et al., 2015; Geschwind et al., 2011), future studies should include the assessment of stressful or rewarding daily events.

Strengths and Limitations of Study 1

First, Study 1 used a longitudinal design linking affective and cognitive microlevel predictors to clinical macrolevel outcomes. Due to the investigated outcomes, both levels and instability measures of respective daily life variables had to be aggregated, thereby eliminating the dynamic aspect at the within-subject level. However, aggregated means and MSSDs still demonstrate differences in emotional and cognitive states and fluctuations on the between-subject level (cf. Jahng et al., 2008; Trull et al., 2015). Second, the modest sample size in Study 1 did not allow the differentiation between "relapses" and "recurrences" and their predictors, which should be considered in future research with larger samples. Third, although dropout rates were satisfactorily low during the three-year follow-up period (13.6%), we observed a selective dropout of rMDD individuals with lower education levels, thereby reducing the generalizability of our results. Fourth, it appears to be advantageous to investigate affective AA variables that allow to differentiate between positive and negative affect (cf. Shackman et al., 2016; Wichers et al., 2010). In Study 1, we used bipolar items to assess mood in daily life (Wilhelm & Schoebi, 2007) thereby limiting the interpretation regarding the total range of affective AA-phenotypes.

Strengths and Limitations of Study 2

Previous RCT studies investigating daily life effect mechanisms of MBI's in rMDD samples mainly employed inactive (wait-list control) or treatment-as-usual control groups (Batink et al., 2013; Garland et al., 2015; Geschwind et al., 2011) in order to minimize unspecific selection bias and time effects (Karlsson & Bergmark, 2015). An

important strength of Study 2 was the use of an active control intervention that allows conclusions about specific treatment ingredients by controlling for effects of attention and motivation. Both trainings were highly standardized (manual-based instructions, audio-guided homework) and supervised to ensure adherence and competent treatment delivery. Intention-to-treat analyses ensured the investigation of all participants randomized for treatment.

Study 2 has several limitations. First, AA assessments can influence daily life experiences of participants leading to assessment reactivity and response fatigue that might have biased the results (Trull et al., 2013). On the contrary, compliance rates were satisfactory (82.2%) and attrition rates (7.7%) were low. In addition, a randomized sampling design was administered to minimize predictability of assessments. Second, we did not control for residual symptoms in the final models. However, there were no significant differences between training groups in baseline residual symptoms (BDI-II scores, see Table 3). Third, the strict inclusion criteria of Study 2 may have limited the generalizability of the present results. Fourth, effect sizes of Study 2 were in the small range; nevertheless, they indicate reliable benefits of MBAT during multiple assessments in daily life. Fifth, it should be noted that both participants and trainers were not blind to treatment condition due to practical limitations.

Importantly, Study 2 assessed short-term changes in daily life experiences and it remains to be investigated whether these observed microlevel changes in cognitive and affective states are able to improve the macrolevel symptom course in rMDD individuals (e.g. reduced relapse rate and depressive symptoms, Batink et al., 2013; Geschwind et al., 2011) and to what extend the induced short-term effects of the present MBAT persist for the long-term. Eventually, despite statistical significance, clinical significance may seem less obvious, because decreases and increases in outcomes appeared to be relatively small. However, previous studies and results of Study 1 showed that already small changes in daily life cognition and affect are able to predict clinical outcomes (Geschwind et al., 2011; Wichers et al., 2010).

4.4 Conclusions and future implications

To conclude, results of the present thesis support the assumption that cognitive and affective AA-phenotypes measured at the microlevel in daily life of rMDD individuals predict long-term clinical outcomes at the macrolevel and can be positively influenced by mindfulness-based attention training particularly in those individuals with highest vulnerability for relapses.

Results of Study 1 imply that illness-related characteristics (residual symptoms), trait RNT, but also instability of cognitive and affective AA-phenotypes impact the long-term course of depression. Specifically, dynamic aspects of daily life cognitive and affective experiences seem to increase relapse risk and maintenance of depressive symptoms. Referring to the impaired disengagement hypothesis (Koster et al., 2011), these altered dynamics of cognitive and affective experiences in daily life presumably affect information processing possibly leading to difficulties in disengaging from negative thought that might impair attention and problem solving of rMDD individuals which in turn possibly foster macrolevel residual symptoms such as loss of concentration. From this pattern, vicious circles might evolve, since residual symptoms e.g., concentration, loss negatively influence new experiences in daily life. However, further research is required to validate these assumptions. Here, the combination of microlevel AA and macrolevel longitudinal data seems to promise deeper insights into the mechanisms of respective impaired daily life experiences and their interaction with psychopathological symptoms. Accounting for the fact that within-person relationships between symptoms and everyday experiences vary and may change over time (Sliwinski, 2008), recent research has called for repeated longitudinal assessment of respective microlevel processes regarding psychopathology in the context of a system rather than a category (Nelson et al., 2017). Longitudinal dynamic system models are regarded as useful method to picture dynamic change of symptoms over time (e.g. abrupt vs. gradual onset of depression) and to determine environmental or trait factors influencing these systems (e.g. interpersonal problems) (c.f. Nelson et al., 2017). In recent research, AA data on the microlevel have been used in the context of dynamical system models (Bringmann et al., 2013; Nelson et al., 2017). For example, in a study with depressed individuals and healthy controls van de Leemut et al. (2014) identified characteristic microlevel changes to predict transition from a depressive to a normal state and vice versa. Other studies identified a down regulation of dynamic systems on different levels (affect, cognition and interpersonal skills) in reaction to critical stressors and as possible warning sign of the transition from the normal to a pathological state (Wichers & Groot, 2016; Nelson et al., 2017). The modeling of respective long-term changes in microlevel processes is enabled by so-called Measurement Burst (MB) designs. Such a design includes the repeated assessment of intensive short-term AA-measurements (bursts) together with psychopathological symptoms and traits over longer time intervals (cf. Sliwinski, 2008). Future studies

should include such MB-designs as a novel approach to longitudinally investigate AA-phenotypes per se and to link them to clinical outcomes and macrolevel traits within the framework of depression and transdiagnostic research.

Altogether, a deeper understanding of underlying processes in daily life of rMDD individuals appears necessary to better understand psychopathology of depression, which may also contribute to an improved diagnostic decision-making minimizing unnecessary prolonged treatment or premature end of treatment with increased probability of recurrence.

Results of Study 2 demonstrated that a brief training of mindfulness-based focused attention exercises compared to PMR differentially improved cognitive and affective daily life experiences particularly in individuals with a high number of previous episodes[1]. These results support the assumption that the differential effects of MBAT are most obvious in those individuals with highest vulnerability for relapses. They also imply that changes in cognitive and affective processes during daily life might represent a subset of mechanisms in MBI's that can be addressed by the training component of focused attention particularly in vulnerable individuals with high risk for relapse/recurrent (van der Velden et al., 2015). In a next step, the investigation of the long-term impact of MBAT on clinical outcome e.g. relapse risk associated with respective AA-phenotypes is warranted. More research is needed with regard to active treatment ingredients of MBI's and the degree to which reduced daily life rumination and other AA-phenotypes contribute to recovery from depression and prevention of relapse or recurrence. Understanding such mindfulness-related mechanisms in real-life settings can finally help to establish mechanism-based economical psychological treatments for relapse prevention.

This is the first study to show that a brief training of focused attention can lead to decreased experience of momentary rumination in rMDD individuals supporting the idea that the subcomponent focused attention beneficially influences impaired attentional processes in rMDD by reducing rumination (Koster et al., 2011). Future research could apply objective tests to investigate the relation between changes of

[1] In addition to these results, unpublished analysis controlling for residual symptoms and anamnestic episodes revealed that particularly rMDD individuals with high levels of habitual trait repetitive negative thinking (PTQ, Ehring et al. 2011) and low levels of habitual mindfulness (FFA, Walach et al, 2006) benefited from MBAT compared to PMR with regard to all outcomes (NA, PA, RUM, SA; group*time*moderator: all F scores $p \leq .001$). We performed further supplementary analyses showing that MBAT compared to PMR differentially improved the AA-predictors (microlevel) for longitudinal outcomes (macrolevel) identified in Study 1, namely instability of negative affect (group*time: $F_{(1,3386)} = 4.5$, $p=.034$) and instability of momentary rumination (group*time: $F_{(1,3387)} = 8.4$, $p=.004$).

attentional performance and of daily life cognitive processes after an MBAT training in rMDD individuals.

Furthermore, future studies could extend previous results by investigating the influence of mindfulness-based attention trainings on biological processes that have been linked to daily life rumination in previous studies, such as daily cortisol activity (Huffziger et al., 2013) and DMN hyperconnectivity (Zamoscik et al., 2014). Such an approach could demonstrate whether MBAT induces changes in biological vulnerability markers of recurrent depression that contribute to relapse.

5 SUMMARY

Daily life microlevel processes, assessed with Ambulatory Assessment (AA) have recently shown to contribute to a better understanding of macrolevel syndromes and constitute potential AA-phenotypes influencing onset and course of recurrent depression. Further, cognitive risk factors, such as rumination, have been shown to be linked to impaired attentional processes in remitted depressed (rMDD) individuals presumably resulting in an increased risk of relapse. Mindfulness-Based Interventions aim to improve attentional processes in rMDD individuals and effectively reduce relapse risk in recurrent depression. Based on a longitudinal investigation (Study 1) and a Randomized Control Trail (RCT, Study 2) the present thesis investigated cognitive and affective AA-phenotypes as predictors for the long-term course of recurrent depression and examined effects of a Mindfulness-Based Attention Training (MABT) on respective daily life processes.

Study 1 aimed to investigate the impact of cognitive and affective AA-phenotypes on the long-term symptom course in 57 recurrently depressed individuals during a three-year follow-up interval. Level and instability of baseline AA variables were aggregated and used as predictors for time to relapse, chronicity, and maintenance of depressive symptoms thereby combining AA data with longitudinal macrolevel outcomes. Results of Study 1 indicate that daily life affective instability predicts time to relapse, while instability of daily life rumination appears to influence persistence of depressive symptoms over a three-year interval in recurrently depressed individuals. These findings support the assumption that cognitive and affective daily life processes may represent important AA-phenotypes that are prospectively linked to clinical outcomes in depression.

Study 2 investigated short-term effects of a four-week Mindfulness-Based Attention Training (MBAT) compared to an active control training (Progressive Muscle Relaxation – PMR) on cognitive and affective AA-phenotypes in a new sample of 78 remitted depressed (rMDD) individuals. Both trainings were highly standardized and AA-outcomes (positive and negative affect, rumination and self-acceptance) were assessed three days before and after the trainings each with 10 assessments per day. The RCT study identified significant intervention effects demonstrating a beneficial influence of MBAT compared to PMR on all AA-outcomes with reduced negative affect and rumination and increased positive affect and self-acceptance. The beneficial effects of MBAT were particularly evident in those individuals with more previous

episodes and therewith those at highest vulnerability for relapse. Thus, respective changes in cognitive and affective states may reflect potential mechanisms of action in mindfulness-based intervention research.

Both studies offer new insights into the understanding of daily life cognitive and affective AA-phenotypes as potential vulnerability factors of recurrent depression and their changeability through appropriate interventions.

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