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Affective, Cognitive and Endocrinological Processes in the Daily Life of Individuals with Recurrent Major Depression and Their Course Over Time

Inauguraldissertation

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PREFACE

This thesis is a compilation of three original research articles, which have been published. The publications presented in chapter II and III are based on data of a project on the interplay between momentary affect, cognitions and daily events in individuals with recurrent major depression and healthy individuals, which was funded by the German Research Foundation (DFG, KU1464 8-1 Kuehner). The publication presented in chapter IV is based on data from a previous project using a similar design (DFG, KU1464 4-2) together data from the current project - combined in a measurement burst design - on intraindividual variability and change in the previously named within-person processes.

An adapted version of chapter II has been published as:

Schricker, I. F., Nayman, S., Reinhard, I., & Kuehner, C. (2023a). Reciprocal prospective effects of momentary cognitions and affect in daily life and mood reactivity toward daily events in remitted recurrent depression. *Behavior Therapy*, *54*(2), 274-289. https://doi.org/10.1016/j.beth.2022.09.001

An adapted version of chapter III has been published as:

Schricker, I. F., Nayman, S., Reinhard, I., & Kuehner, C. (2023b). Trait and state effects of different modes of thinking on salivary cortisol in daily life in patients with recurrent major depression and healthy individuals. *Psychoneuroendocrinology*, *155*, 106307. https://doi.org/10.1016/j.psyneuen.2023.106307

An adapted version of chapter IV has been published as:

Schricker, I. F., Nayman, S., Reinhard, I., & Kuehner, C. (2023c). Reactivity toward daily events: Intraindividual variability and change in recurrent depression – A measurement burst study. *Behaviour Research and Therapy*, *168*, 104383. https://doi.org/10.1016/j.brat.2023.104383

Table 1

Overview of the Doctoral Candidate's Personal Contributions in Percentages

	Chapter		
	II	**III**	**IV**
Conception (%)	80	80	80
Literature research (%)	100	100	100
Ethics approval (%)	-	-	-
Animal research proposal (%)	-	-	-
Data collection (%)	100	90	90
Data analysis (%)	100	100	90
Interpretation of results (%)	90	90	80
Manuscript writing (%)	90	90	90
Revision (%)	90	90	90
Figures/Tables	Table 2.1, S1-3 Figure 2.1-2.2	Table 3.1-3.3 Figure 3.1	Table 4.1-4.4, S1 Figure 4.1

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ABBREVIATIONS

AA	Ambulatory Assessment
AIC	Akaike-Information-Criterion
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BDI-II	Beck Depression Inventory Revised
BDNF	Brain-Derived Neurotrophic Factor
BIC	Bayesian-Information-Criterion
B-S	Between-subject
CAR	Cortisol Awakening Response
CBT	Cognitive Behavioral Therapy
CIMH	Central Institute of Mental Health
CRH	Corticotrophine-Releasing Hormone
DFG	Deutsche Forschungsgemeinschaft
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECG	Electrocardiography
EMA	Ecological Momentary Assessment
EMIs	Ecological Momentary Interventions
ER	Emotion Regulation
ESM	Experience Sampling Method
EWMA	Exponentially Weighted Moving Average
GAD	Generalized Anxiety Disorder
GPS	Global-Positioning Systems
GWAS	Genome-Wide Association Studies
HAM-D	Hamilton Depression Scale
HCs	Healthy Controls
HPA	Hypothalamic–Pituitary–Adrenal
ICC	Intra-Class Correlation Coefficient
ICD-11	International Classification of Diseases 11th Revision
JITAI	Just-in-Time Adaptive Intervention
MAAS	Mindful Attention Awareness Scale
MADRS	Montgomery and Asberg Depression Rating Scale

MB	Measurement Burst
MBAT	Mindfulness-Based Focused Attention Therapy
MBCT	Mindfulness-Based Cognitive Therapy
MBI	Mindfulness-Based Intervention
MBSR	Mindfulness-Based Stress Reduction
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MEG	Magneto Encephalogram
MLM	Multilevel-Model
MSEM	Multilevel Structural Equation Model
NA	Negative Affect
NIMH	National Institute of Mental Health
PA	Positive Affect
PANAS	Positive and Negative Affect Schedule
PDD	Persistent Depressive Disorder
PMDD	Premenstrual Dysphoric Disorder
PMR	Progressive Muscle Relaxation
PT	Positive Thoughts
PTQ	Perseverative Thinking Questionnaire
RDoC	Research Domain Criteria
REM	Rapid Eye Movement
rMDD	Recurrent Major Depressive Disorder
	Study 1: Remitted individuals with a History of Recurrent Depressive Episodes
	Study 2: Individuals with Recurrent Depression
RNT	Repetitive Negative Thinking
SCID-I	Structured Clinical Interview for DSM-IV Axis I
SNPs	Single Nucleotide Polymorphisms
T1	Time 1
T-1	Time of the Last Prompt
TE	Time of Event
WHO	World Health Organization
W-S	Within-Subject

CHAPTER I: GENERAL INTRODUCTION

1.1 Epidemiology of Major Depressive Disorder (MDD)

Counting around 280 millions of people worldwide suffering from depression in 2023 (World Health Organization [WHO]), Major Depressive Disorder (MDD) is one of the most prevalent and disabling mental disorders (Guitérrez-Rojas et al., 2020; Le Moult & Gotlib 2019; Remes et al., 2021; Tseng et al., 2023; van der Velden et al., 2023). The lifetime prevalence estimates worldwide range from 2% in China to 21% in France (Guitérrez-Rojas et al., 2020). In addition to the primary disability caused by MDD, including a significant risk for suicidal ideation and behaviours (Borserio et al., 2021), patients with MDD are at a higher risk of developing chronic medical illnesses (Dean & Keshavan, 2017). As a result the economic and medical burden on the world's population is rising (Tseng et al., 2023; Zhang et al., 2023).

1.2 Diagnosis in DSM-5/ICD-11

The symptom profile for the MDD diagnosis is highly corresponding between the two diagnostic systems the Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-5; American Psychiatric Association [APA], 2013) and the International Classification of Diseases (ICD-11; WHO, 2018) (Maj et al., 2020). The shared nine symptoms encompass depressed mood; markedly diminished interest or pleasure in activities; significant change in appetite or weight; insomnia or hypersomnia; psychomotor agitation or retardation; and fatigue or loss of energy; feelings of worthlessness, or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; recurrent thoughts of death, or recurrent suicidal ideation with or without a concrete plan, or suicide attempts or plans. With hopelessness about the future ICD-11 offers one additional symptom compared to DSM-5 (Maj et al., 2020). In both systems, it is essential for at least five of these symptoms to be consistently present throughout most of the day for a minimum of two weeks. Additionally, either a state of depressed mood or a notable reduction in interest or pleasure is an obligatory symptom for

the MDD diagnosis (DSM-5, ICD-11; Maj et al., 2020). Some symptoms not included in either of the two diagnostic systems that could be further components of the depressive syndrome such as anxiety, somatic complaints and irritability are covered by prominent rating scales (e.g., BDI-II, HAM-D, etc.). For anger together with other symptoms such as aggression, irritability and risk taking behaviour, some studies suggest a higher prevalence in men compared to women (Maj et al., 2020).

Despite the concordance in diagnostic criteria between the two diagnostic systems, numerous researchers doubt their efficacy due to the high heterogeneity of MDD (cf. Borserio et al., 2021). The observed heterogeneity in MDD might be one reason for the introduction of different clinical subtypes (e.g., melancholic, psychotic subtype), of which some have been included within the diagnostic systems (Borserio et al., 2021, Maj et al., 2020). Severity serves to further classify the MDD diagnosis. Here DMS-5 and ICD-11 distinguish between mild, moderate and severe MDD on the basis of the number of symptoms, the distress level caused by the symptoms and the level of functional impairment, with ICD-11 offering more detailed criteria (Maj et al., 2020).

1.3 Etiologic Factors for Major Depressive Disorder

There is wide consensus about an interplay of multiple biological, psychological and social or environmental factors in the complex MDD pathogenesis with yet no definite framework as explanatory stand-alone (Tseng et al., 2023; Zhang et al., 2023).

With respect to biological risk factors for MDD onset, findings from heritability studies suggest that genetic factors account for about 30-50% of the risk of developing MDD (Kendall et al., 2021). Candidate gene studies focused on specific genes which were thought to be involved in the pathophysiology of MDD, for example the serotonin transporter (SLC6A4) gene and polymorphisms of the SLC6A4 gene, known as 5-HTTLPR (cf. Kendall et al., 2021; Moncrieff et al., 2022; Shadrina et al., 2018; Stein et al., 2021). Another gene that garnered ample attention is the brain-derived neurotrophic factor (BDNF), responsible for processes controlling neuroplasticity. Reduced peripheral BDNF levels have been ob-

served in MDD (Hing et al., 2018). Single nucleotide polymorphisms (SNPs) are discussed as one possible mechanism explaining such an altered regulation of the BDNF expression (Hing et al., 2018). Nonetheless, in sum, results of candidate gene studies were conflicting and not able to identify a consistent, strong link of one specific gene to depression (Border et al., 2019; Flint, 2021; Kendall et al., 2021). Since previous candidate gene studies have been criticized for insufficient power, a lack of correction for population stratification and low significance levels (cf. Kendall et al., 2021), Genome-Wide Association Studies (GWAS) are conducted as an alternative research method of choice (Flint, 2021). GWAS aim to identify genetic variations (typically SNPs) that are associated with specific traits or conditions across the genome (Uffelmann et al., 2021). Overall GWAS could confirm the highly polygenic nature of MDD. Several genomic loci associated to MDD have been identified, mapping to genes responsible for neurite outgrowth, synaptic function and plasticity, as well as for immunity and inflammation (see Kendall et al., 2021 for a review). However, even though sample sizes in GWAS are commonly very high, GWAS results stem from analysing cohorts where most cases are identified through minimal phenotyping, a method known for its low specificity (Flint, 2021). To date, the variance explained by polygenic risk factors for the etiology of MDD is very low and the causal mechanisms behind these genetic associations yet remain to be explained (Kendall et al., 2021; Ormel et al., 2019).

In addition to the polygenic risk, environmental factors such as early life stress, trauma, or adverse life events play a major role in the etiology of MDD, both independently and in interaction with genetic factors. Despite mixed results from studies on gene-environment interactions, there is evidence supporting the idea that genetic influences can differ depending on particular environmental contexts (Kendall et al., 2021; Remes et al., 2021).

Within the past decades, there has been significant advancements in neuroscience research. However, the pathophysiology of MDD yet remains incompletely understood. Studies have pointed to various mechanisms, including changes in serotonergic, noradrenergic, dopaminergic, and glutamatergic systems, heightened inflammation, abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis activity, vascular alterations, and reduced neurogenesis and neuroplasticity (cf. Dean & Keshavan, 2017)

as well as cognitive decline (Remes et al., 2021). Furthermore, there is good evidence that these different pathways are intertwined (Dean & Keshavan, 2017), making the establishment of a wholesome theory that incorporates the different biological mechanisms particularly challenging.

Physical health conditions, causing pain or disability (e.g., cancer; Remes et al., 2021), have shown to increase the risk of developing MDD. There have also been found significant associations between hormonal dysregulations such as thyroid diseases (i.e., hypothyroidis; Bode et al., 2021) and MDD. Moreover, previous research showed that raised levels of inflammation, due to factors such as pro-inflammatory cytokines or a disordered microbiome, have been linked to MDD (Remes et al., 2021).

To the various psychological factors count personality traits such as neuroticism, sensitivity to rejection, a negative self-concept, rumination and negative emotionality (Remes et al., 2021). Especially *rumination*, a specific subcomponent of repetitive negative thinking (RNT, see below), which can be defined as a tendency to experience recurring thoughts about one's self, feelings, personal concerns and negative experiences, that are difficult to disengage from (Nolen-Hoeksema et al., 2008; Huffziger et al., 2009; Watkins, 2023), is thought to play an important role in the etiology of MDD (Watkins, 2020). In line with this, the response styles theory posits that higher levels of rumination are linked to higher levels of depressive symptoms and an increased likelihood of experiencing depressive episodes. Trait rumination and in particular its most pathological form *brooding* has been linked to elevated connectivity within regions of the default mode network (DMN) during resting state, indicating problems to supress self-referential thinking (Watkins, 2020). Brooding is characterized by negative self-evaluative and comparative thinking about one self, as well as by focusing on a perceived inability to control one’s circumstances and emotions (Bean et al., 2020; Watkins, 2020). Higher levels of brooding have been shown to be characteristic for MDD (Arditte Hall et al., 2019; cf. Hjartarson et al., 2020). Ruminations link to depression might be mediated by a limited ability of problem-solving, as well as insufficient social support (Remes et al., 2021). At the same time, rumination can also serve as a mediator in the causal link between poor attention control and depression (Remes et al., 2021). Moreo-

ver, frequent engagement in rumination interferes with adaptive emotion regulation (e.g., anticipatory reappraisal), making it challenging for individuals to manage their affective reactivity (Nasso et al., 2018). Difficulties in emotion regulation are also discussed to be a significant factor in the onset of MDD (Visted et al., 2018).

Finally, there is ample evidence supporting the significant role played by various social and cultural risk factors in the development of MDD. Among others, childhood adversity, including childhood trauma or abuse, a low socioeconomic status, financial strain, a lack of social support, stressful (major) life events or significant life adjustments, employment problems, exposure to illness, violent crime exposure, substance abuse or dependence, discrimination, (self)-stigma, ethnicity and marital status have been linked to MDD (Remes et al., 2021).

Since the present work addresses the course of recurrent MDD in individuals initially in remission, I will particularly focus on potential vulnerability and protective factors for the clinical course of MDD. A detailed elaboration on mechanisms in the pathogenesis of MDD onsets would exceed the scope of this dissertation.

1.4 Course of MDD

MDD exhibits a notably recurring pattern (Bockting et al., 2015; Bos et al., 2018; Le Moult & Gotlib, 2019; Tseng et al., 2023). As a result, preventing relapses and recurrences of depressive episodes stands as a pivotal challenge in MDD management. The likelihood for an individual, who undergoes a primary depressive episode, to encounter a subsequent episode lies around 40% to 60% (Brouwer et al., 2019; Monroe et al., 2019). This probability increases to approximately 70% for individuals with two episodes and escalates to as much as 90% for those who experienced three episodes (cf. Bockting et al., 2015; Tseng et al., 2023).

According to Bockting et al. (2015), the course of MDD consists of key change points including response, remission, recovery, relapse and recurrence. The concept of *response* is typically utilized to describe progress throughout the treatment process. Most often it is characterized as a proportional

reduction (e.g., 50%) from the initial baseline values of depressive symptom severity, assessed via structured clinical interviews or validated self-report scales (Bockting et al., 2015). In contrast to response, which denotes symptom improvement, *remission* suggests the patient's return to an asymptomatic state of normalcy. This is often determined as the absence of significant symptoms for a specific – yet not entirely consistently defined (cf. Buckman et al., 2018) – period. Furthermore, one can distinguish between stable remission versus partial or unstable remission. According to DSM-5, depression in full remission is diagnosed if an individual has not experienced any "significant signs or symptoms of the disturbance" in the past 2 months (APA, 2013, p. 188; see also: Brouwer et al., 2019; Bockting et al., 2015; Gesicki & Nelson-Becker, 2018). Partial remission is characterized by the remaining of mild ongoing symptoms or by fluctuations between symptom-free and mildly symptomatic phases (cf. Bockting et al., 2015) without meeting the full criteria for major depressive disorder (APA, 2013, p. 188; Gesicki & Nelson-Becker, 2018). At the end of the symptom improvement spectrum lies *recovery*, denoting the end of the initial episode after a prolonged phase of remission (Bockting et al., 2015; Brouwer et al., 2019, de Zwart et al., 2019). Commonly the time to fulfil the status of recovery is defined 6–12 months free of relapses (Bockting et al., 2015).

Lastly, when the current MDE persists for a period of two years or longer, MDD is defined as chronic or persistent, as also implemented in DSM-5 (persistent depressive disorder, PDD) and ICD-11 (persistent (chronic) depressive episode) (APA, 2013; Kuehner et al., 2021; WHO, 2018).

Relapses and recurrences. In previous research, the terms *relapse* and *recurrence* have often been used interchangeably since a consistent definition is lacking (Brouwer et al., 2019). There is agreement, however, that both concepts describe a significant clinical deterioration after a period of symptomatic improvement (Bockting et al., 2015). Furthermore, the term relapse is generally used to describe the reappearance of depressive symptoms as being part of the initial episode (de Zwart et al., 2019). Time wise relapses are allocated after remission but prior to full recovery (Bockting et al., 2015). In contrast to relapses, the term recurrence is applied when an entirely new major depressive episode

(MDE) emerges after a period of remission (Bockting et al., 2015; de Zwart et al., 2019). This period should be defined long enough so that one can assume recovery has already taken place.

Given the current lack of empirical support for the model originally established by Frank et al. (1991) that differentiates relapses from recurrences (Cohen et al., 2023; de Zwart et al., 2019), I will use the terms “relapse” and “recurrence” interchangeably in the present work.

1.5 Risk Factors for Recurrent Depression

Numerous explanations to elucidate why some individuals seem to have an elevated risk for relapses/recurrences of MDEs have been proposed. One of the key ideas is the premorbid vulnerability hypothesis (cf. Bos et al., 2018; Burcusa & Iacono, 2007), indicating that there are individuals inherited with certain traits such as neuroticism and negative cognitive styles that render them predisposed to recurrent MDD, even before the first MDE has emerged and irrespective of the emergence of subsequent MDEs.

Another popular idea is the “scarring” hypothesis, asserting that every subsequent episode leaves enduring effects that amplify susceptibility for future MDEs. The idea of scarring might also explain observed differences between individuals remitted from MDD and those acutely suffering from an MDE (Bos et al., 2018). Plausible causal mechanisms underpinning the scarring hypothesis comprise genetics, HPA axis activity, cognitive mechanisms and stress-related factors (cf. Bockting et al., 2015). Nonetheless, these mechanisms do not necessarily have to be fixed structural changes (Wichers et al., 2010). In their dynamic take on the “scar” concept, Wichers et al. (2010) underscore the modifiability of scars and the role of protective factors to reduce scars and to prevent upcoming MDEs. Bos et al. (2018) run a prospective three-wave population based study and found greater evidence for pre-existing vulnerabilities rather than scars accounting for the observed impairments in mental and physical functioning in their remitted MDD sample.

Buckman et al. (2018) reviewed recent systematic and unsystematic reviews, cohort studies and neurobiological studies in order to get a cohesive framework of risk factors and their influence on recurrences. They identified a history of childhood maltreatment, residual depressive symptoms and a history of recurrences as the main three factors associated with an increased risk for depressive relapses and recurrences. However, in contrast to a common view (cf. Monroe et al., 2019), they did not find evidence for a linear association between the number of previously experiences MDEs and an increased risk for relapses/recurrences (Buckman et al., 2018). This might be partly due to operationalization choices, since MDEs were often treated as a dichotomous variable in the respective statistical models. Moreover, there was strong evidence for comorbid anxiety disorders as well as rumination to represent prognostic indicators for relapses and recurrences. Several studies included in their systematic review also found a younger age of MDD onset, a greater severity and longer duration of the index episode, as well as higher neuroticism to be prognostic factors (Buckman et al., 2018). On a biological level, they further found evidence for dysregulations of rapid eye movement (REM) sleep and HPA axis activity as well as structural changes in neocortical and limbic regions to be associated with a higher risk for relapses and recurrences. In their recent prospective study, Blank et al. (2020) identified neurobiological network predictors for the clinical course in individuals currently remitted from MDD. Their findings suggest that the reward circuit and the DMN serve as both structural and functional indicators predicting recurrences and residual changes in MDD symptoms. Lastly, Buckman et al. (2018) reported stressful life events, cognitive as well as affective and information processing biases, and affective and cognitive reactivity as further potential prognostic risk factors.

In the following, I will elaborate on specific cognitive factors, as well as on social-environmental and endocrinological factors in more detail and discuss their role as possible vulnerability or protective factors for the course of depression.

1.5.1 Macro-Level Risk and Protective Factors

Trait Cognitions. *Repetitive negative thinking (RNT)* is a transdiagnostic pathological process, encompassing phenomena such as rumination and worry (Eisma et al., 2022; Rosenkranz et al., 2020; Samanti et al., 2018; Spinhoven et al., 2018; Wahl et al., 2019; for review: Watkins & Roberts, 2020, Watkins, 2023). RNT is defined as a recurrence of intrusive thoughts, focused on negative content that is subjectively difficult to control and is seen as unproductive, capturing mental capacity (Ehring, 2021; Rosenkranz et al., 2020; Samanti et al., 2018; Wahl et al., 2019; Watkins, 2023). Sharing considerable common underlying mechanisms, the differentiation between worry and rumination lies mainly in their temporal-orientation (Eisma et al., 2022; Kim & Newman, 2023; McEvoy et al., 2013). While worry entails future-oriented negative thoughts about anticipated events potentially causing negatives outcomes (Baik & Newman, 2023; Eisma et al., 2022; Kim & Newman, 2023; McEvoy et al., 2013; Watkins, 2022), rumination is more past- or presence-oriented (Eisma et al., 2022; Watkins, 2023). Rumination has been associated not only with MDD onset and maintenance (LeMoult & Gotlib, 2019; see 1.3), but also with an elevated risk for relapses and recurrences (cf. Bean & Ciesla, 2023; Watkins, 2023; van Kleef et al., 2023; van der Velden et al., 2023). In particular in individuals with a history of (frequent) MDEs, rumination exacerbates existing negative emotional states, maintains and prolongs maladaptive thinking patterns (Bean et al., 2020; Watkins, 2020), which in turn might lead to a downward spiral increasing the risk of depressive relapses (Watkins, 2020). Along these lines, rumination's detrimental effects on the course of MDD stem from the passive and repetitive character of these thoughts (Nolen-Hoeksema et al., 2008). According to the Perseverative Cognition Hypothesis (Brosschot et al., 2006), RNT consistently reactivates cognitive representations of one or several stressful events. As a consequence, psychological and physiological reactions toward the stressor will be extended, even beyond the time of its actual occurrence or, in case of an anticipated stressor, even before the stressor is present (Watkins, 2023). Whenever vulnerable individuals, such as individuals remitted from MDD, are reminded of a personally relevant stressor, it may activate a broad associative

network, thereby reinstating rumination (Zamoscik et al., 2014). Given that stress is a major precipitant of depressive episodes, such prolonged or chronic stress responses might contribute to the recurrence of depression. In particular, Zamoscik et al. (2014) found greater connectivity between the posterior cingulate cortex (PCC, a node in the DMN) and the parahippocampal gyri (PHG) in a sample of individuals remitted from MDD, which was even stronger for those with more previous MDEs. Moreover, increased PCC–PHG connectivity was related to sadder mood and more rumination in daily life, as well as to rumination worsening and a poorer depressive symptom course over the 6-month follow-up period. In their clinical longitudinal cohort study, Spinhoven et al. (2018) found disorder-independent RNT to predict persistence and relapse of MDD and anxiety disorders during a 3-year follow-up period, whereas depression-specific rumination specifically predicted relapse of MDD, and worry specifically predicted relapse of anxiety disorders. Furthermore, Timm et al. (2017) showed that in a sample of individuals initially remitted from recurrent MDD, chronicity, i.e., the proportion of weeks spent with significant symptoms during a 3-year follow-up, was predicted by higher levels of trait RNT. Lastly, van Kleef et al. (2023) investigated the predictive value of trait rumination on depressive relapse in a sample of remitted MDD patients that had experienced at least two MDEs within the last five years. They found that in particular the uncontrollability facet of rumination was significantly associated with relapse at the 18-months follow-up.

Dispositional mindfulness, in contrast, could serve as a protective factor for MDD onset and relapses/recurrences. The concept of dispositional mindfulness is originated in Buddhism and directly influenced by Western philosophy and culture (Rau & Williams, 2023). Jon Kabat-Zinn, founder of the Stress Reduction Clinic of the University of Massachusetts, USA, developed the so called Mindfulness-Based Stress Reduction (MBSR) program. According to Kabat-Zinns secularized representation, dispositional mindfulness can be defined as the general tendency to attend and accept experiences in the present moment non-judgmentally, in which individuals can differ (Kabat-Zinn, 2015; Rau & Williams, 2023).

The majority of research supporting the protective role of mindfulness for psychological wellbeing is based on intervention studies using Mindfulness-Based Interventions (MBI's; see Farb et al., 2018; Kuyken et al., 2016, for an overview see: Zhang et al., 2021). In the context of MDD, Mindfulness-Based Cognitive Therapy (MBCT, Segal, Williams, & Teasdale, 2013) is considered as the most prominent MBI, foremost intended to reduce the risk of depressive relapses (Salomon & Loo, 2023). MBCT is a manualized group-therapy program that helps individuals to build an adaptive attention regulation and present-moment awareness through a combination of mindfulness meditation with Cognitive Behavioral Therapy (CBT). As a consequence, MBCT empowers individuals with recurrent depression to identify and disengage from rumination by redirecting their focus to the present-moment experience (van der Velden et al., 2023). The MBCT vulnerability model posits that with subsequent depressive episodes, rumination becomes more automatically triggered by depressed mood. MBCT might be particularly effective in breaking these cycles of ruminative thinking in patients who had experienced frequent episodes (Segal et al., 2013; cf. Timm et al., 2018). In this vein, previous research has shown that MBCT is effective in diminishing the risk of relapse in individuals with a history of recurrent depression and is therefore endorsed as a preventive treatment (cf. van der Velden et al., 2023; cf. Kuyken et al., 2016; cf. Salmon & Loo, 2023; Zhang et al., 2018). In individuals with recurrent depression, van der Velden et al. (2023) found MBCT interventions to be able to modulate neurocognitive functioning during states of rumination and to mediate an increase in the ability to sustain attention to the present-moment. Moreover, in a sample of individuals remitted from MDD, Timm et al. (2018) found a 4-week mindfulness-based focused attention training to be associated with decreases in momentary rumination and negative affect, as well as with increases in momentary positive affect and self-acceptance, with stronger effects in individuals with a higher number of previous MDEs.

Longitudinal studies investigating the association of dispositional mindfulness with depression are scarce. There are first indications that dispositional mindfulness has predictive value for the course of MDD (Petrocchi & Ottaviani, 2016; Prietro-Fidalgo et al., 2022). In a healthy sample, Petrocci & Ottaviani (2016) investigated the predictive value of different dispositional mindfulness facets (observing,

describing, acting with awareness, non-judging, non-reacting) for depression symptoms over a two year period. They found "non-judging" to be a significant predictor for depressive symptoms after two years. In additional mediation analyses, this association was fully mediated by depressive rumination. Prieto-Fidalgo et al. (2022) conducted a meta-analysis, including mainly healthy samples, of longitudinal predictive associations from facets of dispositional mindfulness to psychological symptoms, including depression and anxiety. They found the facets "acting with awareness" and "non-reacting" to predict a decrease of both depressive and anxiety symptoms over time). These findings hint to a protective role of dispositional mindfulness for the course of depression, however, further research in clinical samples is warranted in order to confirm this notion.

Childhood Adversity and Recent Stressful Life Events. Childhood maltreatment, encompassing emotional, physical, and sexual abuse, as well as emotional and physical neglect, has been prospectively related to MDD (cf. Buckman et al., 2018; Daníelsdóttir et al., 2024; Juwariah et al., 2022; Li et al., 2015; Maj et al., 2020; Mao et al., 2023; Neslon et al., 2017). There is evidence that individuals who have experienced childhood adversity are at higher risk for an earlier MDD onset, more severe symptoms, a higher number of suicide attempts, more likely experience a recurrent and persistent course, and show lower treatment responses (cf. Mao et al., 2023; Nelson et al., 2017; Zisook et al., 2023). Further discussed to be important precipitants for MDD onset as well as potential risk factors for relapses and recurrences are *more recent life events* (e.g., job loss, relationship break-up), typically occurring within the last three months prior to MDD onset (Buckman et al., 2018; Høifødt et al., 2019; Monroe et al., 2019). In order to improve our understanding of the mechanisms underlying relapses/recurrences, Buckman et al. (2018) recommend future research to focus on cognitive and affective reactivity toward stress as well as on HPA axis regulation as a biological stress-marker.

In this context, previous findings suggest more severe ore even threatening life events to be especially prepotent in provoking MDD onset (Monroe et al., 2019). With increasing number of experienced MDEs the association between stressful life events and MDD appears to weaken (Monroe et al., 2019; Stroud, 2018). According to stress sensitization theories, individuals who had already experienced

MDEs become progressively vulnerable for future MDEs, so that eventually MDEs could be triggered rather spontaneously without a distinct major life event preceding (Monroe et al., 2019). In his "kindling hypothesis", Post (1992) describes this heightened susceptibility for subsequent episodes with progressively lesser stress or even without an apparent external stressor as biological vulnerability, which may result from neural sensitization and autonomic dysregulation, such as alterations in the HPA axis (Monroe & Harkness, 2005).

HPA Axis Activity, Basal Cortisol (CAR, Daily Slopes). MDD has been widely linked to dysregulations of the hypothalamic-pituitary-adrenal (HPA) stress axis (Almeida et al., 2021; Gilbert et al., 2017; Huffziger et al., 2013; ter Horst et al., 2019). Cortisol as HPA's primary product is often used as biological stress indicator (cf. Adam et al., 2017; Ahmed et al., 2023; Schlotz, 2019; Zorn et al., 2017). In general, cortisol release is considered as an adaptive biological reaction to stress in order to restore the homeostasis of the human body (Ahmed et al., 2023; Chesnut et al., 2021; Shapero et al., 2019). Along with the activation of the sympathetic nervous system through the release of catecholamines (i.e., adrenaline and noradrenaline), the HPA axis releases the corticotrophine-releasing hormone (CRH) that causes the synthesis and release of the steroid hormone cortisol (Ahmed et al., 2023, Degering et al., 2023; Høifødt et al., 2019). This biochemical cascade initiates a state of arousal and alertness with increased attention focus (Ahmed et al., 2023). In case of longer-term stress exposure, this adaptive stress response needs to be maintained, requiring the provision of additional energy and resources. Once resources are depleted, a state termed allostatic load takes effect (Almeida et al., 2021; Degering et al., 2023; Shapero et al., 2019). Previous research found evidence that long-term stress and consequently sustained high levels of cortisol are linked to hippocampal damage (Degering et al., 2023). Hippocampal damage can result in HPA axis inhibition failure, which in turn leads to progressively higher cortisol secretion in the hippocampus, thereby creating a vicious circle (Degering et al., 2023). In the long-term, when resources for adaptive responses to stressors are depleted, allostatic load reaches the state of exhaustion, which has been associated with several medical conditions such

as cardiovascular, metabolic and autoimmune diseases but also with mental diseases such as MDD (Ahmed et al., 2023; Guidi et al., 2020).

Prior research most commonly found MDD to be associated with heightened HPA axis activation (e.g., Vinkers et al., 2021). However, some studies report the opposite linking MDD to reduced HPA axis activation (cf. Adam et al., 2017; Bockting et al., 2012; Gilbert et al., 2017). These inconsistencies might be partially explained by different MDD subtypes, so that heightened HPA axis activity has been reported to be more pronounced in individuals who are hospitalized and who suffer from MDD with psychotic, melancholic or endogenous features (cf. Booij et al., 2020; Høifødt et al., 2019). However, when MDD becomes a chronic condition, it may be linked to allostatic overload. At a certain point, the adrenal glands reach their production limit and cease releasing cortisol, resulting in HPA hypoactivity (Arnaldo et al., 2022). There is a growing body of evidence indicating that HPA axis dysfunctions represent a trait factor in individuals with MDD that occur before the onset of the disorder, persist even during remission and could potentially serve as a predictive factor for relapses and recurrences (cf. Ancelin et al., 2017; Bockting et al., 2012; ter Horst et al., 2019). With respect to the cortisol awakening response (CAR), different deviations from a typical CAR have been reported in MDD (cf. Linnemann et al., 2023). Høifødt et al. (2019) found increased evening cortisol, but not morning cortisol (single probe directly after getting up), to be associated with higher levels of depressive symptoms in patients with current MDD. However, they did not find differences in cortisol levels between individuals remitted from MDD and healthy individuals, indicating a possible normalization of HPA axis activity once MDD remission sets in. Nevertheless, they also showed that evening cortisol was higher in individuals who had experienced recurrent MDEs compared to those who had experienced only one MDE and healthy individuals. This result, in turn, might offer backing for the idea that increased cortisol levels are not exclusively associated with current depression status, but could serve as a trait marker that predisposes individuals for a recurrent MDD course (Høitfødt et al., 2019). In their systematic review and meta-analysis, Kennis et al. (2020) found increased cortisol levels, measured at different time points (morning, evening, diurnal, nocturnal, reactivity), to have predictive value for the onset of MDD as

well as for relapses and recurrences of MDEs. However, the effect was rather small and became non-significant when outliers and low quality studies were removed. Given the highly dynamic nature of cortisol and the possibility that intraindividual differences might go unnoticed in designs comparing different individuals in their average cortisol levels (between-person design) (cf. Booij et al., 2020), it seems worthwhile to examine not only such between-person associations but also within-person associations of cortisol in daily life (i.e., cortisol levels of an individual at different time points or in different contexts). Such an approach is best implemented undertaking frequent assessments in everyday life as done via Ambulatory Assessment (AA).

In the following, I will introduce AA as a highly suitable research tool to examine potential affective, cognitive, behavioural and physiological predictors at the micro-level for clinical course relevant outcomes such as the deterioration of depressive symptoms or relapses/recurrences.

1.6 Ambulatory Assessment (AA)

Beside the immense heterogeneity in possible MDD subtypes, symptoms experienced by patients underlie considerable variation over time (Schoevers et al., 2020; Thompson et al., 2012). Such fluctuations in psychiatric symptoms – such as affect fluctuations as a marker of emotional dysregulation (Schoevers et al., 2020) – appear to arise from the interplay of person and environment (Reichert et al., 2021). It therefore seems crucial to continually monitor these symptoms and their contextual influences over time in everyday life. This approach enables researchers to identify specific risk factors for psychopathology and increase their understanding of the course of mental illnesses (Beddig & Kuehner, 2020; Brietzke et al., 2019; Reichert et al., 2021; Timm et al., 2017; Wichers, 2014).

Ambulatory Assessment (AA) is used as an umbrella term for a range of real-time data capture methodologies (e.g., Experience Sampling Method [ESM], Ecological Momentary Assessment [EMA]; daily diaries, monitoring of physiological functions e.g., via sensors, global-positioning systems [GPS], and electrocardiography [ECG]) (cf. Reichert al., 2021; Wrzus & Neubauer, 2022; see also: http://www.am-

bulatory-assessment.org). Using ecological valid tools to unravel biopsychosocial processes and observe their unfolding in their natural environment (Wenzel et al., 2016), AA offers many advantages compared to laboratory assessments. In contrast to laboratory research, AA provides real-life data, thereby increasing ecological validity and consequently generalizability of findings (Myin-Germeys et al., 2022; Reichert et al., 2021; Schick et al., 2023; Wenzel et al., 2016). Another advantageous feature of AA is that data can be generated in (near-) real time through momentary self-reports or continuous monitoring of specific physiological processes (Lischetzke & Koenen, 2021; Myin-Germeys et al., 2022; Schick et al., 2023; Wenzel et al., 2016), thereby circumventing the issue of retrospective assessments potentially causing recall bias. Furthermore, AA enables a multi-modal approach via incorporating assessments such as self-reports, physiological processes and physical activity simultaneously (Schick et al., 2023; Velozo et al., 2022; Wenzel et al., 2016).

Ultimately, AA provides intensive longitudinal data that enable researchers to investigate temporal within- and between-person variation in trajectories of variables of clinical interest together with contextual factors (e.g., the occurrence of negative daily events) and identify risk or protective factors for the clinical course of mental disorders (cf. Schick et al., 2023). This kind of generated data allows for an accurate disaggregation of within- and between-subject variance (Lischetzke & Koenen, 2021; Neubauer & Schmiedeck, 2020; Viechtbauer, 2022; Wang & Maxwell, 2015). This seems highly important since previous research has demonstrated that within- vs between-person effects are often independent or even opposing (cf. Cole et al., 2021; Reichert et al., 2021). Therefore, adequate statistical models such as multi-level models are applied that take into account the nested data structure (Schick et al., 2023; Viechtbauer, 2022). Multi-level models further enable to account for between-subject differences in within-subject effects by modelling random slopes and investigate time-lagged associations (Neubauer & Schmiedeck, 2020; Schick et al., 2023).

In the following, I will present an overview of different micro-level factors and processes in daily life assessed via AA that have been identified in previous studies in individuals with MDD and might also play an important role for the clinical course of MDD.

1.6.1 Micro-level Factors and Processes in Daily Life

Momentary Affect and Momentary Cognitions. Within the last years, there has been an increasing trend examining not only average levels of but also dynamic changes in psychologic constructs over time (cf. Bean & Ciesla, 2023). Using this novel approach, important prognostic information about the clinical course of MDD could be revealed by investigating temporal associations of different psychological constructs such as momentary affect and cognitions. With respect to momentary affect, previous research showed that individuals with current but also remitted MDD report higher negative affect (NA; e.g., Thompson et al., 2021), lower positive affect (PA) as well as higher levels of momentary rumination in daily life (e.g., Hjartarson et al., 2022). Substantial evidence supports the idea that momentary rumination serves as a predictor for the deterioration of subsequent affect within non-clinical samples (e.g., Blanke et al., 2021; Connolly & Alloy, 2017; Fang et al., 2019; Pasyugina et al., 2015; Takano & Tanno, 2011). This finding is in concordance with the so far limited amount of research in clinical samples (e.g., Beddig et al., 2020a; Kircanski et al., 2018; Ruscio et al., 2015). When comparing these effects between healthy and clinical samples, findings are inconclusive. In the daily life of women with current MDD, generalized anxiety disorder (GAD) or mixed MDD-GAD effects of momentary rumination on subsequent affect were found to be similarly strong compared to a sample of healthy women (Kircanski et al., 2018). Ruscio et al. (2015) noted stronger predictive value of momentary rumination for subsequent NA, in individuals with current MDD and GAD compared to healthy individuals. Furthermore, Beddig et al. (2020a) identified heightened reciprocal prospective effects of momentary rumination and NA in women with premenstrual dysphoric disorder (PMDD) in comparison to healthy women, particularly during the premenstrual phase.

There is good reason to assume that individuals with a history of recurrent MDEs are particularly vulnerable for a mutual amplification of momentary maladaptive cognitions and (negative) affect (Watkins & Roberts, 2020), which could in turn deteriorate their clinical course. For example, Wichers et al. (2010) found NA in daily life to predict depressive relapses, albeit with only a statistical trend. Van der Velden et al. (2023) describe a heightened cognitive reactivity, where shifts in mood can easily

trigger negative biases and rumination, to be characteristic for recurrent MDD. Following this reasoning, it appears essential to examine the interplay between momentary cognitions and affect in daily life in this high-risk clinical group.

To the best of my knowledge there have only been two studies investigating the interplay between momentary rumination and affect in daily life in individuals remitted from MDD and in individuals with recurrent MDD. Hoorelbeke et al. (2019) showed that PA and resilience, the latter defined as the extent to which individuals considered themselves able to effectively cope with adversity in daily life, were associated with an increase in subsequent positive appraisal and a reduction in subsequent rumination, cognitive complaints, and depressive symptoms. However, rumination did not predict subsequent depressive symptoms or PA. Hjartarson et al. (2022) identified significant mood-related reactivity of rumination in individuals remitted from recurrent MDD but not in healthy individuals. Along their interpretation, in individuals remitted from recurrent MDD, daily NA-fluctuations might automatically trigger subsequent rumination, and this process could lead to a sense of uncontrollability. Following this argumentation, future research should delve further into the uncontrollability aspect of momentary rumination and its association with both NA and PA.

When looking at momentary positive cognitions and their interplay with affect in daily life, research is very scarce. Garland et al. (2010) introduced the upward spiral model, stating that positive emotions are capable of initiating self-reinforcing patterns, termed upward spirals. Positive emotions might broaden individuals' perspectives, diversify their behavioral repertoires, and enhance social openness. Moreover, these effects may reciprocate by fostering increased positive emotions. This could occur since individuals become more attuned to opportunities for engaging in pleasurable events. In a sample of individuals partially remitted from MDD, Garland et al. (2015) found higher daily levels of PA to predict higher levels of positive cognitions at the following day. However, against their expectations, this effect was not reciprocal. Support bolstering the upward spiral model was provided by Layous et al. (2023) who conducted a series of quasi-experiments within five studies. Assigning their participants

(student and online sample) to a rumination, distraction or gratitude condition, they examined manipulation-induced affect changes. In accordance with their assumptions, they found negative effects of the rumination condition, which were the strongest in participants with higher depressive levels at baseline. With respect to the gratitude condition, positive affect was promoted compared to the rumination and the distraction condition. Furthermore, gratitude was related to higher positivity in thought-action repertoires and more positive interpretation of experienced events (Layous et al., 2023). Showing that gratitude was associated with increased NA and increased PA, while distraction was related to decreased NA but either increased or no effect on PA, Layous et al. (2023) once more highlighted that NA and PA cannot be treated as the pure inverse of each other, but that it is important to explore the unique effects of enhancing PA. Overall, In order to identify potential vulnerability as well as protective factors for relapses/recurrences, it seems important to examine (reciprocal) prospective effects of momentary rumination and positive thoughts with affect in the daily life of individuals currently remitted from MDD – in particular in individuals with a history of more frequent anamnestic episodes. So far, there is a clear lack of research within this specific cohort.

Within-person Affective and Cognitive Reactivity toward Daily Events. As stated earlier, (stressful) events occurring frequently in everyday life and more specifically reactivity toward them might be important when discussing potential vulnerability and/or protective factors for the course of MDD. When assessed in daily life, affective or cognitive reactivity is often operationalized as the change in affect (NA, PA) or cognitions (e.g., rumination) in relation to a preceding negative or positive daily event (see for example: Khazanov et al., 2019).

Previous research primarily focused on *affect reactivity* toward stressful or negative daily events and its link to MDD with so far ambiguous results. Some studies showed affect reactivity to be comparable in individuals with current MDD and healthy individuals (e.g., Bylsma et al., 2011; Thompson et al., 2012). However, others found differentiated effects between a clinical group and a control group. While Peeters et al. (2003) showed blunted affect reactivity, demonstrated by lower increases in NA and lower decreases in PA following negative daily events, in individuals with current MDD, Husky et

al. (2009) found higher affect reactivity in individuals remitted from MDD compared to healthy controls. Only a limited number of studies has directly investigated and compared these effects among individuals with current MDD, those remitted from MDD, and healthy controls. Van Winkel et al. (2015) run an AA treatment study and compared individuals non-remitted from MDD, remitted from MDD, and healthy controls, at the 18-month follow-up with respect to their NA- and PA-reactivity toward negative events, activity stress and social stress. They found individuals with current MDD to show higher NA-reactivity toward all three types of stressors compared to healthy controls. In contrast to this, NA-reactivity toward negative events and activity stress in individuals remitted from MDD was similar, but NA-reactivity toward social stress was heightened compared to healthy controls (Van Winkel et al., 2015). However, there was no significant difference in PA-reactivity following negative events, activity stress or social stress between the three groups. In line with these findings, Sheets and Armey (2020) found individuals with current MDD to exhibit heightened NA-reactivity in response to daily perceived stress compared to those who were remitted from MDD or healthy individuals. Additionally, individuals remitted from MDD and healthy controls showed similar levels of NA-reactivity to both interpersonal and non-interpersonal stress, but individuals with current MDD displayed a heightened sensitivity specifically to interpersonal negative events. In contrast, Lamers et al. (2018) observed that the effects of increased anxious (but not sad) mood following negative daily events were more similar between individuals with current MDD and individuals remitted from MDD, and stronger in comparison to healthy controls. Consequently, the evidence regarding a potential emotional sensitization to negative daily events in individuals with (remitted) MDD is inconclusive and requires further exploration.

While there is a clear focus on stressful or negative daily events and their effects on affect in daily life, recent research calls for an emphasis on positive experiences (cf. Santee & Starr, 2022) in order to portray a more comprehensive picture of affective reactivity in daily life. Responsiveness to positive daily occurrences might have the potential to counteract the influence of negative daily events on one's affective state. Indeed, there is already good evidence for a so called 'mood brightening' effect

in both current and remitted MDD (Bylsma et al., 2011; Khazanov et al., 2019; Lamers et al., 2018). Mood brightening is characterized by more pronounced increases in PA and more pronounced decreases in NA following positive daily events in current and remitted MDD compared to healthy individuals.

Previous research rather neglected associations of daily events with subsequent cognitions, which can be defined as *cognitive reactivity*. Initial evidence suggests that cognitive reactivity, yet commonly operationalized as a link between retrospective self-reports about the occurrence of daily events and one's cognitions, is linked to depression maintenance and relapses/recurrences (cf. Cole et al., 2021). AA studies on cognitive reactivity toward daily events in particular in clinical samples are largely lacking. One study so far pointed to a heightened rumination-reactivity in response to negative daily events in MDD (Kircanski et al., 2018). In line with increased cognitive reactivity toward negative daily events, Khazanov et al. (2019) reported cognitive reactivity following positive daily events to be also stronger in individuals with current MDD compared to healthy individuals, as expressed in stronger decreases in momentary rumination.

Cortisol-reactivity toward Daily Events. On a physiological level, stress-reactivity in daily life can be measured as the temporal association between stressful experiences and subsequent levels of saliva cortisol, which can be easily integrated into individuals' everyday lives (Schlotz, 2019). Previous research showed that cortisol levels peak within the next 10-30 min following a stressor (Stoffel et al., 2021). In individuals with current MDD, a blunted cortisol response toward negative daily events was observed when compared to healthy individuals (Peeters et al., 2003). In contrast to negative events in daily life, a potentially beneficial role of positive events on affect and cognitions could be portrayed on a physiological level via decreases in cortisol levels. However, Peeters et al. (2003) did not find significant changes in cortisol levels following positive daily events either in individuals with current MDD or in healthy individuals. So far, there is a lack of studies investigating cortisol reactivity in response to both negative and positive daily events in MDD individuals at high risk for relapses/recurrences.

Cortisol Release in Daily Life and its Associations with Trait and State Cognitions. As indicated by Watkins (2023), *cognitive trait factors* such as RNT could be associated with dysregulated physiological activity and in turn might explain interpersonal differences in cortisol levels beyond clinical status. RNTs or other cognitive traits' (e.g., mindfulness) effects on cortisol release remain underexplored. First evidence showed no significant association of trait rumination with cortisol measured in the daily life of individuals remitted from recurrent MDD and healthy individuals (Huffziger et al., 2013; Zoccola & Dickerson, 2012). However, other studies observed higher RNT in individuals with increased cortisol reactivity toward stressors as well as a delayed stress recovery (cf. Ottaviani et al., 2016; Watkins, 2023; Zoccola & Dickerson, 2012).

Habitual mindfulness could be a protective cognitive trait for a rather adaptive physiological stress response (cf. Manigault et al., 2018a). In the context of acute social stressors, it has been demonstrated to influence affective and cortisol reactions (Brown et al., 2012). Yet, there is scarcity of studies exploring the impact of habitual mindfulness on cortisol release in daily life in the absence of external stressors, in particular in clinical samples. In women with PMDD, Nayman et al. (2022) found no significant association between habitual mindfulness and overall cortisol release during daily life in women with premenstrual dysphoric disorder. In contrast, Manigault et al. (2018a) showed a significant link between acceptance (as a component of habitual mindfulness) and a more robust CAR and a faster decline in evening cortisol in a sample of healthy individuals. Aguilar-Raab et al. (2021) found that a Mindfulness-Based Intervention (MBI) was associated with a more pronounced diurnal cortisol decrease compared to a control condition. Conversely, Beddig et al. (2020) found no group differences in the CAR and in daily cortisol slopes between a mindfulness-based attention training (MBAT) and a progressive muscle relaxation training in individuals remitted from recurrent MDD. However, MBAT mitigated an increase in total cortisol over time, particularly in those patients who exhibited significant improvements in NA and rumination during daily life.

Prior research on cortisol stress-reactivity has widely focused on cortisol reactivity following lab-induced (Gu et al., 2022; Zorn et al., 2017) or external daily life stressors (cf. Schlotz, 2019, Weber et al.,

2022). Specific mechanisms and the extent to which possible internal stressors such as momentary maladaptive cognitions (e.g., rumination or mindwandering) directly influence cortisol reactivity are still neglected research areas (cf. Smyth et al., 2023). Initial findings regarding maladaptive cognitions are inconclusive. To the best of my knowledge, only one study so far has explored the association between momentary content and extent of mindwandering and cortisol in daily life (Linz et al., 2021) in healthy individuals, revealing no significant associations. *Mindwandering* is a phenomenon frequently observed in MDD, which can be understood as self-generated, task-unrelated and context-independent thoughts (Chaieb et al., 2022) or as having difficulty to keep one's attention in the here and now (cf. Hoffmann et al., 2016). However, the relationship between such attention-shifting problems and cortisol activity remains to be addressed in future research. With respect to state rumination, Huffziger et al. (2013) discovered no moment-to-moment effects of rumination on cortisol in individuals remitted from MDD and healthy controls. However, they observed that higher daily means of state rumination were linked to elevated cortisol levels across both groups. In contrast to this, Beddig et al. (2019) demonstrated that state rumination predicted a subsequent within-person increase in cortisol 20 minutes later in healthy women but not in women with PMDD. Finally, in healthy individuals, Aguilar-Raab et al. (2021) explored the influence of momentary (state) mindfulness on concurrently measured cortisol but found no significant association.

In sum, there is a clear lack of studies investigating effects of trait and state cognitions on cortisol release in daily life – irrespective of acute external stressors and in particular in clinical samples such as in individuals with recurrent major depression. Furthermore, it remains to be elucidated whether the more distal effects of trait cognitions on cortisol release in daily life are mediated through the more proximal effects of corresponding state cognitions.

1.6.2 Longitudinal Analysis of Micro-Level Processes Relevant for the Clinical Course of MDD: The Measurement Burst Design

In recent years, psychological research has seen a significant shift from macro-level analyses investigating specific psychological traits toward micro-level analyses, providing a more detailed and dynamic understanding of psychological processes. Applying intensive longitudinal designs, one may examine clinical course related changes in within-person processes (e.g., affective, cognitive or cortisol-reactivity) and how relevant clinical variables at the person level (e.g., number of experienced MDEs) might influence such intraindividual changes in within-person variability over time.

As stated above, AA generates intensive longitudinal data of such micro-level processes during daily life for a rather short time interval (Nestler, 2020). Representing a hybrid of intensive longitudinal designs – in particular AA designs – and more traditional longitudinal designs such as single-measurement multiwave or panel designs (Alessandri et al., 2021; Cho et al., 2019; Nestler 2020; Sliwinski, 2008), the measurement burst (MB) design incorporates repeated “waves” (bursts) of shorter intensive assessment periods (cf. Nestler, 2020; Sliwinski, 2008; Stawski et al., 2015). Consequently, MB designs provide information on change that unfold at a fast scale (e.g., hourly, daily) and at a slower scale (e.g., over bursts/months/years; Cho et al., 2019). Furthermore, MB designs enable researchers to investigate interindividual differences in psychological variables as well as both intraindividual variability within bursts (i.e., short-term fluctuations within an individual) and intraindividual change (i.e., systematic change patterns within an individual) in these micro-level processes over more widely spaced time intervals (e.g., months or years, Cho et al., 2019; Nestler, 2020). Figure 1.1 shows an example of an MB design, built with two bursts.

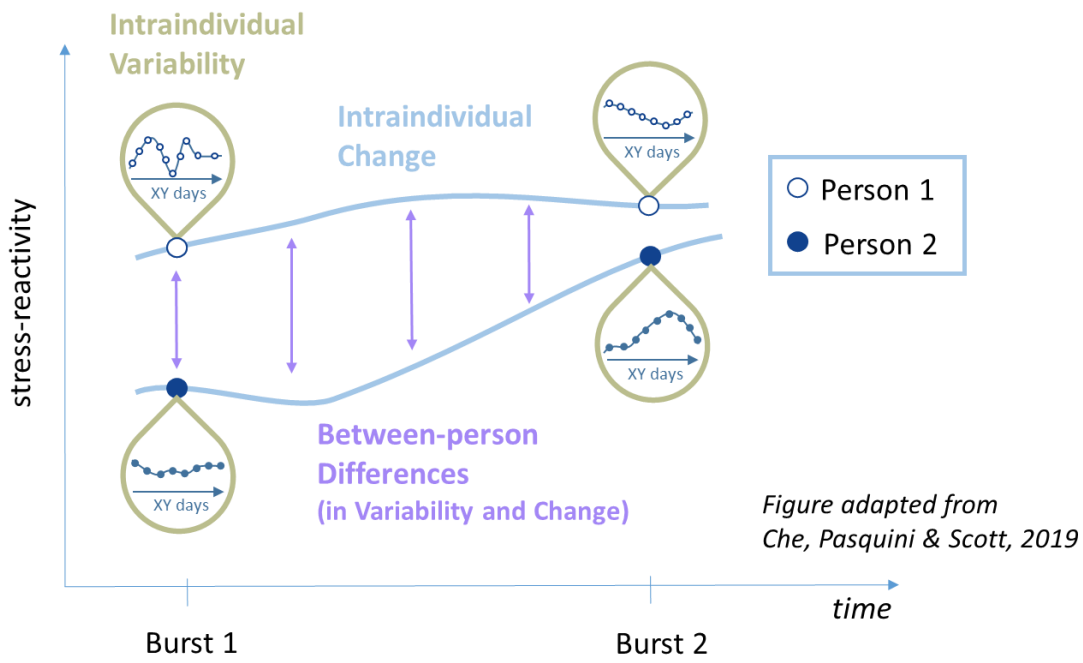

Figure 1.1 Example of an MB Design

MB designs generate data that portray a fairly representative picture of the individual's psychological state by using numerous single observations to build respective scores (e.g., average of negative affect within a burst). With respect to precision and reliability, this approach is superior to traditional longitudinal studies relying on single observations at each wave (Cho et al., 2019). Another major advantage of the MB design is its ability to disaggregate within-person associations at the assessment level from developmental changes over bursts and more stable person-level characteristics at the between-subject level (Patrick et al., 2014).

Initial research on intraindividual change in reactivity toward daily events is limited to healthy samples. In a recent MB daily diary study in a community sample of midlife and later-life participants, stress-reactivity decreased over time (Blaxton et al., 2020). Within individuals, higher global stress perception at the burst level was linked to stronger NA-reactivity toward daily stress. In contrast, Rush et al. (2019) found that stress-reactivity intraindividually increased over time in a large representative US sample. Similarly, Sliwinski et al. (2009) found longitudinal increases in emotional reactivity to daily

stress in aging individuals across the adult lifespan. In bursts with higher perceived stress, stress-reactivity was increased, while no moderation effect of global perceived stress on intraindividual change in reactivity was found.

In sum, previous findings demonstrate the importance to investigate intraindividual change in reactivity over time by also considering more stable slower-scale variables that could moderate intraindividual variability and/or change. However, so far there is a lack of studies investigating intraindividual variability and change in affective, cognitive or endocrinological reactivity toward negative or positive daily events in clinical samples. In particular, monitoring long-term courses of micro-level processes such as cognitive as well as endocrinological reactivity toward daily negative and positive events in individuals with recurrent MDEs might provide first steps to finally identify mechanisms involved in macro-level clinical outcomes of MDD, such as relapses and recurrences.

1.7 Research Questions

The present dissertation focusses on micro-level associations of momentary affect and cognitions as well as affective, cognitive and physiological reactivity toward daily events and internal stressors in individuals with recurrent major depression by a) examining reciprocal prospective effects of momentary affect with momentary cognitions, and affective and cognitive reactivity toward daily negative and positive events in individuals in remission from recurrent major depression, b) examining associations of trait and state cognitions with cortisol release in daily life in individuals with recurrent major depression and testing whether the more distal effects of trait cognitions are mediated by the more proximal effects of state cognitions on cortisol levels, and c) by investigating intraindividual variability and change in reactivity toward daily events over a time period of approximately 4.4 years in individuals initially in remission from recurrent major depression.

Paper 1 examined reciprocal prospective within-person associations between momentary negative and positive affect and momentary rumination and positive thoughts as well as within-person affective and cognitive reactivity toward daily negative and positive events in daily in a sample of individuals

in remission from recurrent major depression. Consequently, Paper 1 targeted the following research questions:

- R1.1: Are there differences in daily affect (negative and positive affect) and cognitions (rumination and positive thoughts) between individuals in remission from recurrent major depression and healthy individuals?
- R1.2: Are there significant reciprocal prospective effects of momentary cognitions and affect, and do individuals in remission from recurrent major depression differ in these effects from healthy individuals?
- R1.3: Are there significant effects of daily negative and positive events on momentary affect and cognitions, and do individuals in remission from recurrent major depression differ from healthy individuals in these effects?

Paper 2 investigated associations of trait as well as state cognitions on cortisol release in daily life in individuals with recurrent major depression and healthy individuals. So far, there has been a lack of research on cortisol-reactivity toward possible internal stressors such as maladaptive cognitions, in particular in clinical samples. Furthermore, it remains to be addressed if the more distal effects of trait cognitions on cortisol release in daily life are mediated by the more proximal effects of respective state cognitions. Therefore, Paper 2 aimed to explore the following research questions:

- R2.1: Are there significant effects of trait repetitive negative thinking (RNT) and trait mindfulness, as well as state mindwandering and state mentalshift problems on salivary cortisol levels in daily life in individuals with recurrent major depression compared to healthy individuals?
- R2.2: Do state mindwandering and state mentalshift problems represent mediators for the impact of trait RNT and trait mindfulness on cortisol release in daily life in individuals with recurrent major depression and healthy individuals?

Paper 3 aimed to explore intraindividual variability as well as long-term changes in short-term within-person processes, in particular in reactivity toward daily events, in a sample of individuals initially in

remission from recurrent major depressive episodes, using a measurement burst design with two bursts, separated by approximately 4.4 years. Paper 3 included the following research questions:

- R3.1: In a clinically diagnosed sample of individuals in remission from recurrent major depressive episodes, is there significant event-congruent affective, cognitive, and cortisol reactivity to daily negative and positive events within bursts?
- R3.2: Do depression levels, measured at the person-level, moderate within-person variability in affective, cognitive and cortisol-reactivity toward daily events within bursts?
- R3.3: Do depression levels, measured at the person-level, moderate intraindividual change in in affective, cognitive and cortisol-reactivity toward daily events over the two bursts?

CHAPTER II: RECIPROCAL PROSPECTIVE EFFECTS OF MOMENTARY COGNITIONS AND AFFECT IN DAILY LIFE AND MOOD REACTIVITY TOWARD DAILY EVENTS IN REMITTED RECURRENT DEPRESSION (STUDY 1)

An adapted version of this chapter has been published as "Schricker, I. F., Nayman, S., Reinhard, I., & Kuehner, C. (2023). Reciprocal prospective effects of momentary cognitions and affect in daily life and mood reactivity toward daily events in remitted recurrent depression. *Behavior Therapy, 54*(2), 274-289. https://doi.org/10.1016/j.beth.2022.09.001"

2.1 Abstract

Major Depressive Disorder is a recurrent condition. Potential risk factors for future episodes are maladaptive cognitions such as rumination and unfavorable reactivity toward negative daily events. Positive thoughts and positive daily events, in contrast, could act as a buffer against mood deterioration. The aim of the present study is (1) to examine differences in daily affect and cognitions in remitted depressed patients with a history of recurrent episodes (rMDD) and healthy controls, (2) to analyse reciprocal prospective effects of momentary cognitions and affect and (3) to investigate effects of daily events on affect and cognitions in both groups. A sample of *N* = 102 participants underwent an Ecological Momentary Assessment (EMA) phase of five consecutive days, where rMDD patients (*n* = 51) and healthy controls (*n* = 51) indicated their momentary rumination, positive thoughts, affect and the occurrence of daily events ten times per day. Via multilevel lag models, we found higher rumination to predict a decrease of positive affect (PA) in the rMDD group, but no effect of rumination on subsequent negative affect (NA) in either group. Higher positive thoughts predicted an increase in PA and a decrease in NA, similarly strong in both groups. Regarding daily events, rMDD patients reported a stronger increase in NA and rumination following negative daily events compared to controls, whereas an observed subsequent decrease of PA and positive thoughts was not moderated by group. Following positive daily events, rMDD patients showed a stronger increase in PA and positive thoughts

and a stronger decrease in NA and rumination than controls. For interventions targeting relapse prevention, our results indicate the implementation of strategies fostering the responsiveness to positive events and the up-regulation of positive affect.

2.2 Introduction

Major Depressive Disorder (MDD) is a recurrent condition, which entails a 40-60% risk of developing a further Major Depressive Episode (MDE) after the initial one. Further, this risk increases to up to 90% for those who experience three or more episodes (Bockting et al., 2015). Buckman et al. (2018) identified three key factors for predicting future depressive relapses and recurrences: childhood maltreatment, residual symptoms and a prior history of depressive episodes. Further potential risk factors include biological aspects (e.g., alterations in neocortical and limbic regions, dysregulation of REM sleep and HPA axis), a history of comorbid anxiety disorders, environmental stress, neuroticism, and specific maladaptive cognitive processes, especially rumination (Buckman et al., 2018).

Remitted depressed patients with a history of recurrent episodes – in the following referred to as rMDD patients[1] - represent a group of particular interest. Besides cognitive impairments and residual depressive symptoms, they show higher habitual rumination, compared to healthy controls (Hjartarson et al., 2022). RMDD patients may be at a high risk of a mutual amplification of rumination and negative affect (NA), producing an emotional cascade (Watkins & Roberts, 2020) which can potentially lead to further clinical deterioration. In contrast to the detrimental effects of this downward spiral, the interplay between positive affect (PA) and positive cognitions might create upward spirals that can act as a countervailing force against deterioration (Garland et al., 2010; Garland et al., 2015).

[1] In the following, we use the abbreviation “rMDD patients” for remitted depressed patients with a history of recurrent episodes (≥2) or shortly for remitted recurrently depressed patients. In distinction to this group, we use the term “remitted MDD patients” for patients with a history of depression, who did not necessarily fulfil the criteria for recurrent depression (i.e., those with ≥1 MDEs in their life). We use the term “current MDD patients” for patients, who were currently suffering from a MDE.

Zooming into the micro-level of MDD can be crucial to examine the moment-to-moment experiencing of dynamic cognitive processes such as rumination, positive thoughts and related constructs (Blanke et al., 2021; Takano & Tanno, 2011; Trull & Ebner-Priemer, 2020) and their interplay with affect in daily life. A powerful tool to detect these within-person processes at the state level is Ecological Momentary Assessment (EMA). By collecting multiple data from everyday life in the individual's natural environment, EMA increases external validity and reduces retrospective bias (Wenzel et al., 2016; Trull & Ebner-Priemer, 2020; Schreuder et al., 2020). The so captured dynamic within-person patterns of potential vulnerability, protective factors and affect as well as their interplay, could eventually explain individual differences in the course of MDD (e.g., Wichers, 2014; Timm et al., 2017).

In the following, we will give a brief overview of the existing evidence in the field of EMA studies on the dynamic interplay between momentary cognitions and affect, as well as of affective and cognitive reactivity toward daily events, mainly in currently depressed or remitted depressed patients.

Prospective effects of Momentary Rumination on Affect

Evidence of momentary rumination predicting affect deterioration is high, particularly in non-clinical samples (e.g., Blanke et al., 2021; Connolly & Alloy, 2017; Fang et al., 2019; Pasyugina et al., 2015; Takano & Tanno, 2011). Only a few studies have investigated these effects in clinical samples (e.g., Beddig et al., 2020a; Kircanski et al., 2018; Ruscio et al., 2015). All of them identified maladaptive effects of momentary rumination on affect. However, obscurity remains regarding group differences in these effects. Kircanski et al. (2018) found similar predictive effects of momentary rumination on affect in daily life in a group of female patients with current MDD, generalized anxiety disorder (GAD) or mixed MDD-GAD, and healthy controls. In contrast, Ruscio et al. (2015) found the effect of rumination on subsequent NA (not PA) to be stronger in patients with current MDD and GAD compared to healthy controls. In line with this, Beddig et al. (2020a) investigated these effects in women with premenstrual dysphoric disorder (PMDD) and found stronger reciprocal prospective effects of rumination and NA in women with PMDD compared to healthy controls, particularly during the premenstrual

phase. Overall, these findings provide first evidence that clinical groups are more sensitive to rumination. It seems essential to investigate if such higher affect reactivity toward maladaptive cognitions is also present during remission - particularly in rMDD patients - and represents a potential vulnerability factor for relapses/recurrences.

To date there have only been two studies on the dynamic interplay between rumination and affect in daily life in remitted MDD and rMDD individuals. Hoorelbeke et al. (2019) investigated different cognitive vulnerability factors (rumination and cognitive complaints), together with protective factors (resilience, positive appraisal, PA), and their interaction in order to predict fluctuations in depressive symptoms in remitted MDD patients. They found that resilience and PA were linked to an increase in positive appraisal as well as a decrease of rumination, cognitive complaints and depressive symptoms at the next assessment. However, rumination showed no predictive value for depressive symptoms and PA. Additionally, Hoorelbeke et al. (2019) found initial evidence that momentary rumination negatively predicts positive appraisal. In a recent EMA study, Hjartarson et al. (2022) found significant mood-related reactivity of rumination in remitted recurrently depressed (rMDD) patients, but not in healthy controls. They concluded that, in these patients, daily fluctuations in NA might trigger subsequent rumination with a high degree of automaticity, leading to uncontrollability. Further research is required to consolidate these findings and to investigate the uncontrollability component of momentary rumination and its interplay with NA as well as with PA.

Prospective Effects of Positive Cognitions on Positive Affect

Regarding the associations of PA and positive cognitions in daily life, current research findings are sparse. In a sample of remitted MDD patients, Garland et al. (2015) showed that higher daily levels of PA predicted subsequent higher levels of positive cognitions. However, in contrast to their hypothesis, they failed to show a predictive value of positive cognitions for subsequent PA. In order to support their upward spiral model (Garland et al., 2010), further research focusing on the temporal interactivity of positive cognitions and affect is needed.

Negative Daily Events and their Influence on Affect

Another potential risk factor, which increases the odds of relapses and recurrences, might be affect reactivity on stressful or negative daily events. However, results on affect reactivity toward negative daily events and its link to current and remitted MDD are mixed. Previous research either showed no differences in affect reactivity following negative daily events between patients and healthy controls (e.g., Bylsma et al., 2011; Thompson et al., 2012) or reported an even stronger mood deterioration in healthy controls compared to current MDD patients (Peeters et al., 2003). In a sample of remitted MDD patients, Husky et al. (2009) found higher affect reactivity in response to previous stressful daily events compared to healthy controls. Only a few studies directly compared these effects for current MDD patients, remitted MDD patients and healthy controls. In some of these studies, heightened mood-reactivity on negative daily events were reported in current MDD patients compared to remitted MDD patients and controls (Van Winkel et al. 2015; Sheets & Armey, 2020). In contrast, Lamers et al. (2018) found the effects of increased anxious – but not sad – mood following negative daily events to be more similar in current MDD and remitted MDD patients and stronger compared to healthy controls. Thus, the evidence concerning potential affective sensitization toward negative daily events in (remitted) MDD is ambiguous and should be further explored.

Positive Daily Events and their Influence on Affect

Given that anhedonia is one of the two cardinal symptoms of depression (American Psychiatric Association [APA], 2013), blunted changes in affect following positive events could be expected. Evidence from laboratory studies support this hypothesis to some degree, as depressed individuals were less reactive to different positive stimuli (e.g., monetary rewards; see Pizzagalli et al., 2009). Nevertheless, these findings have not been replicated in EMA studies, which rather suggested the opposite (Heininga & Kuppens, 2021). Bylsma et al. (2011) identified a so-called “mood brightening” effect, whereby PA was more strongly enhanced and NA more strongly decreased following positive daily events in current MDD patients compared to controls (see also Khazanov et al., 2019). These findings were further

supported by Lamers et al. (2018), who additionally reported the mood brightening effect to be stronger not only in current MDD patients but also in remitted MDD patients compared to controls, possibly pointing to stable tendency even after remission.

Daily Events and their Influence on Cognitions

Finally, it is important to shed light on the predictive value of daily events for momentary cognitions. Kircanski et al. (2018) found that momentary rumination increased after a significant stressful daily event in their clinical group of current MDD, GAD, or MDD-GAD patients, but not in the control group. As for positive daily events, Khazanov et al. (2019) showed that rumination and worry decreased following positive daily events in patients (MDD, GAD, MDD-GAD) and healthy controls and that the decrease in rumination was significantly larger in the patient sample. To date, the associations of daily events with subsequent – especially positive – cognitions in the case of high-risk populations, such as rMDD patients, have been insufficiently examined.

Aims of the Present Study

Taken together, these previous findings raise the question to what extent the interplay of daily negative and positive events, momentary cognitions and affect differs between remitted depressed patients with a history of recurrent episodes (rMDD), and healthy controls. Due to their particularly high risk for relapses and recurrences, rMDD patients are of major interest when investigating potential vulnerability and protective factors in daily life. In addition, previous research mainly focused on negative daily events and maladaptive thoughts and their effects on affect and disregarded temporal within-person associations between positive cognitions, positive affect and positive daily events. To our knowledge, the present study is the first EMA-study providing a comprehensive approach of the interplay between momentary rumination, positive thoughts and affect, as well as of the effects of preceding contextual factors (i.e. daily events) in a sample of rMDD patients compared to healthy

controls. Identified deviations in these within-person dynamics could reveal important prognostic information for the further course of MDD and provide starting points for appropriate relapse prevention.

Consequently the aim of the present study is to (1) examine differences in daily affect and cognitions in rMDD patients and healthy controls, (2) analyze reciprocal prospective effects of momentary cognitions (rumination, positive thoughts) and affect, and possible group differences, and (3) investigate the effects of daily negative and positive events on affect and cognitions, and possible group differences.

2.3 Materials and Methods

Participants

Remitted recurrently depressed (rMDD) patients and matched healthy controls were recruited between October 2019 and October 2021 via online advertisement on the homepage of the Central Institute of Mental Health (CIMH; Mannheim, German), and via print flyers and social media (Facebook, Twitter, various Whatsapp groups). Furthermore, a subgroup of the rMDD patients (n = 46) had already taken part in a former study (Timm et al., 2018) and were re-contacted for a five year follow-up.

Participants were aged between 25 and 62 years. For the rMDD group, the following inclusion criteria applied: a) lifetime episodes of ≥ 2 MDEs, and b) currently not fulfilling MDE criteria for at least the previous two months[2], according to the Structured Clinical Interview for DSM-IV axis I (SCID-I, see below). For both groups, exclusion criteria were a) non-affective psychotic disorders, b) bipolar disorder, and c) current alcohol or substance dependence or abuse. Additionally, healthy controls were excluded when reporting any current or lifetime affective disorder according to SCID-I.

[2] Two patients were included who were in remission for only 5 weeks prior to study inclusion.

The final sample consisted of 102 participants (*M* = 44.14 years, *SD* = 11.42 years; 68.6% female), including *n* = 51 rMDD patients and *n* = 51 healthy controls matched for age, gender and educational degree (see Table 2.1 for additional information).

Table 2.1

Descriptive Demographic and Clinical Characteristics of the Sample by Group

Variables	rMDD (*n* = 51) %/ *M (SD)*	controls (*n* = 51) %/ *M (SD)*	test statistic *T*/ Chi^2
Demographic characteristics			
Age	44.00 (11.64)	44.27 (11.41)	*t* = -0.12
% Female	68.6 %	68.6 %	Chi^2= 0.00
Education (% with high school degree)	72.5 %	68.6%	Chi^2= 0.19
Work situation (% in regular job or education)	72.5 %	92.2%	Chi^2= 6.75*
Marital Status (% married or living together)	52.9 %	62.7 %	Chi^2= 1.01
Clinical Variables			
≥ 3 lifetime MDEs (%)	82.0 %	0.0 %	Chi^2= 70.40***
Previous inpatient treatments (%)	43.1 %	0.0 %	Chi^2= 28.05***
BDI-II	9.14 (7.18)	1.60 (2.37)	*t* = 7.11***
MADRS	6.83 (5.46)	1.80 (2.17)	*t* = 6.13***
Current psychotherapy	41.2 %	3.9 %	Chi^2= 20.67***
Current psychotropic medication	21.6 %	0.0 %	Chi^2= 12.33***

Note. BDI-II = Beck Depression Inventory Revised, MADRS = Montgomery and Asberg Depression Rating Scale, MDE = Major Depressive Episode; *$p < 0.05$; ***$p < .001$.

Procedure

This study is a combined laboratory and Ecological Momentary Assessment (EMA) study. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants provided written informed consent and were compensated with 120€ for completing the study.

Part 1 – Laboratory

After a preliminary telephone screening, eligible participants were invited for an in-person session at the CIMH in Mannheim, Germany. Demographic and clinical variables were assessed via structured interviews and rating scales. In order to assess in- and exclusion criteria, lifetime and current psychopathology were evaluated by a trained clinical psychologist who administered the Structured Clinical Interview for DSM-IV axis I (SCID-I, see *Measures* section). Four participants who could not attend the laboratory session in person because of pandemic contact restrictions were interviewed online using Red Connect (RED Medical Systems GmbH). All participants received a study smartphone and detailed oral and written instructions regarding the electronic diary procedure.

Part 2 – Ambulatory Assessment Phase

EMA was carried out using Motorola G 7 Play smartphones with the software movisensXS, version 1.6.1 (movisens GmbH, Karlsruhe, Germany). The beginning of the EMA phase started on different weekdays; weekends were included in 73.5% of cases. During five consecutive days participants responded ten times per day (between 08:00 am – 10:00 pm) to prompts from their study device. Following a time-stratified random sampling design, participants were signaled once in each 90-min block, except for the first prompt of each day, which always took place at 08:00 am. Participants had the option to delay prompts for 20 min if they were not able to respond right away (e.g., at work or while driving). If reports were not completed within the 20 min time interval, they were coded as missing. At each assessment (Time 1, T1), participants rated their thoughts and feelings and then indicated the occurrence and intensity of a positive and negative daily event since the previous signal (Time of Event, TE). While T1 ratings depicted the individual's current state, TE ratings were retrospective, referring to potential daily events between the last assessment point (T-1) and T1. After completing the EMA-phase, participants returned the study smartphone and filled out a short post-monitoring questionnaire.

Measures

Part 1 – Laboratory

The lifetime diagnosis of recurrent MDD and the current remission status, together with comorbidities and exclusion criteria, were verified using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; Wittchen et al., 1997), which is a structured interview for mental disorders with moderate to high interrater reliabilities (Lobbestael et al., 2011). Demographic and further clinical information, including the assessment of current or past psychotherapy treatment and medication intake, were assessed through a structured interview schedule. Self-rated depressive symptoms were measured with the Beck Depression Inventory Revised, a 21-item questionnaire of depressive symptom severity in the past two weeks (BDI-II; German version: Hautzinger et al., 2009) and the interviewer-rated Montgomery and Asberg Depression Rating Scale (MADRS; Neumann & Schulte, 1989), which have both shown good reliability, validity and sensitivity to symptom change (e.g., Kjaergaard et al., 2014; Kuehner et al., 2007). In the current study, both the BDI-II (α = .87) and the MADRS (α = .83) showed good internal consistencies. For the following statistical analyses, we calculated an overall composite score for depressive symptoms by averaging the z-transformed BDI-II and MADRS scores as done in previous research (e.g., Huffziger et al., 2013; Timm et al., 2017).

Part 2 – Ambulatory Assessment Phase

Positive (PA) and Negative (NA) Affect. At each assessment point, participants rated their current mood on 7-point Likert scales ranging from 1 ("*not at all*") to 7 ("*fully agree*") on 12 items that were balanced in valence (i.e. positive and negative) and arousal (i.e. the degree of activation). These items were derived from the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and from previous EMA studies (e.g., Beddig et al., 2019, 2020a,b; Kuehner et al., 2017; Timm et al., 2017, 2018). For PA, participants were asked how "*cheerful*", "*energet*ic", "*enthusiastic*", "*satisfied*", "*relaxed*" and "*calm*" they felt, and for NA how "*upset*", "*irritated*", "*nervous*", "*listless*", "*down*", and "*bored*" they felt at the moment. PA and NA scores were calculated based on the sum of the respective scale items.

Due to the nested data structure in MLMs, it is necessary to separately calculate reliabilities at different levels of analysis (Nezlek, 2017). We examined both within- and between-subject reliabilities via *lme4* package of R Version 4.1.2 (R Core Team, 2021) based on the formula provided by Bonito et al. (2012), recommended by Nezlek (2017). For NA the within-subject reliability (i.e. the reliability of within-person fluctuations, Neubauer & Schmiedeck, 2020) was .69 and the between-subject reliability (i.e. the reliability of a person's average scores) was .98. For PA the within-subject reliability amounted to .60 and the between-subject reliability to .99. Following guidelines for evaluating reliability (i.e. for trait measures) according to Shrout (1998), between-subject reliabilities were excellent, whereas within-subject reliabilities were of fair to moderate range. In this context, Nezlek (2017) points out to consider more liberal criteria, when interpreting the within-person reliability of EMA scales.

Uncontrollable Rumination. Rumination was assessed on a 7-point Likert scale ranging from 1 ("*not at all*") to 7 ("*fully agree*") with the item "*At the moment before the beep, I was stuck on negative thoughts and could not disengage from them*", thereby capturing the uncontrollability facet of rumination (cf. Beddig et al., 2019, 2020a, b; Kuehner et al., 2017; Timm et al., 2017, 2018).

Positive Thoughts. Participants indicated their experience of positive thoughts at the moment on a 7-point Likert scale ranging from 1 ("*not at all*") to 7 ("*fully agree*") using the item: "*At the moment before the beep, I was thinking about something positive*."

Daily Events. At each signal participants were asked if a negative/positive daily event had occurred to them since the last prompt: "*Did you experience a negative event since the last prompt?", "Did you experience a positive event since the last prompt?*" ("*yes*"/"*no*" each). If they had experienced such an event, they indicated the intensity of the event on a 7-point Likert scale ranging from 1 ("*not at all*") to 7 ("*very*") (cf. van Winkel et al., 2015).

Statistical analyses

All statistical analyses were conducted in IBM SPSS Statistics Version 27. Additionally, R Version 4.1.2 (R Core Team, 2021) with the *lmertest* package was used to determine Pseudo *R-squares* (Raudenbush & Bryk, 2002) as a measure of effect sizes of the multilevel models. Group comparisons (rMDD patients versus healthy controls) regarding demographic and clinical variables were performed using t-tests for continuous and Chi-square tests for dichotomous variables (see Table 2.1). For group comparisons of aggregated EMA variables (NA, PA, rumination, positive thoughts), we used aggregated person-mean scores of the momentary variables and ran analyses of variance (ANOVAs). Additionally we ran t-tests for dependent samples to compare the rate of reported negative and positive daily events per group. For all further analyses, we used multilevel models (MLM), taking the nested data structure into account.

Preliminary analyses showed that, for all dependent variables, a 3-level model yielded a better fit than a 2-level model following the Akaike-Information-Criterion (AIC) and the Bayesian-Information-Criterion (BIC). Consequently, the following data structure applied: assessment points (level 1) were nested within days (level 2), which were nested in persons (level 3). All MLM included random intercepts at levels 2 and 3, which allowed individual baseline levels of the dependent variables to differ between persons and days. All level-1 predictor variables were person-mean centered, which is recommended in order to arrive at an unbiased estimate of the within-person effects (Neubauer & Schmiedeck, 2020). Level-3 variables (except for group status) were centered around the grand-mean.

Two sets of models were run. One set investigated reciprocal prospective effects of momentary cognitions (rumination, positive thoughts) and affect (NA, PA). For this investigation, we built lagged variables for all observations, except for those representing the first response of a day. The other set of analyses examined the effect of negative and positive daily events on daily outcomes (NA, PA, rumination, positive thoughts). For both sets of models, we partitioned time-varying variables into between- (B-S) and within-subject components (W-S). This rather conservative approach ensures the isolation of within-subject effects from variance relating to between-subjects differences in average

levels (Bolger & Laurenceau, 2013). Consequently, all MLM models included a person-mean centered (lagged) level-1 predictor (W-S), the grand-mean centered aggregated person-mean of the level-1 predictor (B-S), and the lagged outcome in order to control for carryover effects. For both sets of analyses we first ran models without interaction terms with group status in order to identify the main effects of predictors on outcomes. In a further step, we added the interaction term of predictors (W-S) and group status (2-way cross-level interaction). In all analyses, the significance level was set at $\alpha = 0.05$. Equation S1 in the Supplemental Material online shows an example of our multilevel models.

2.4 Results

Compliance

The following statistical analyses were based on N = 102 participants (rMDD group: n = 51; control group: n = 51) and 4646 out of a total of 5100 assessment points. The compliance rate across participants was 91.1% (*SD* = 9.4, range 48 - 100%), demonstrating high compliance, which is comparable to prior research (Vachon et al., 2019; Rintala et al., 2019). The proportion of completed assessments did not differ significantly between groups (rMDD group: 89.3%, control group: 92.9%; $t(82.9) = -1.90$, $p = .061$).

Demographic and Clinical Characteristics

Table 2.1 shows that rMDD patients and healthy controls did not significantly differ regarding gender proportion, age, education and marital status. RMDD patients were less often in regular employment or in educational programs, showed higher depressive symptoms (BDI-II, MADRS), and reported being more often currently in psychotherapy compared to healthy controls (all p's < .05). No participant from the control group had been in previous psychiatric or psychotherapeutic inpatient treatment, or was currently under psychotropic medication. Following the exclusion criteria (see *Participants* section) no control participant had experienced any lifetime MDE.

EMA Outcomes

The means, standard deviations (within- and between-person), bivariate within- and between-subjects correlations and the intra-class correlation coefficients (ICCs) of all outcome variables can be found in Table S1. The ICCs of all EMA variables (NA, PA, rumination, positive thoughts) were in the moderate range (.44-.66), indicating that a considerable amount of variance can be attributed to within-person differences.

Group Differences in EMA Variables

Momentary Cognitions and Affect. ANOVAs showed that rMDD patients reported higher momentary rumination (M_{rMDD} = 2.29, SD_{rMDD} = 0.89; $M\_{controls}$ = 1.40, $SD\_{controls}$ = 0.47; $F(1,100) = 40.05$, $p < .001$), higher NA (M_{rMDD} = 2.49, SD_{rMDD} = 0.78; $M\_{controls}$ = 1.73, $SD\_{controls}$ = 0.56; $F(1,100) = 31.36$, $p < .001$), as well as lower PA (M_{rMDD} = 4.31, SD_{rMDD} = 0.80; $M\_{controls}$ = 5.16, $SD\_{controls}$ = 0.73; $F(1,100) = 31.10$, $p < .001$) and lower positive thoughts (M_{rMDD} = 3.84, SD_{rMDD} = 0.98; $M\_{controls}$ = 4.25, $SD\_{controls}$ = 0.86; $F(1,100) = 4.90$, $p = .029$).

Frequency of Daily Events. A total of 1617 events were reported, from which 70.3% were positive daily events. ANOVAs revealed that rMDD patients reported a higher frequency of daily negative events, while both groups did not differ in the frequency of positive daily events. On average rMDD patients indicated the occurrence of daily negative events in 12.6% (SD = 0.93) of assessment points, whereas healthy controls reported the experience of negative events in 8.1% (SD = 0.08) of ($F(1,100) = 6.54$, $p = .012$) Positive events were reported in 25.6% (SD = 0.24) of the assessment points in the rMDD group and in 23.2% (SD = 0.18) of the assessment points in the control group ($F(1,100) = 0.38$, $p = .569$). In both groups, positive events were reported more frequently than negative events (rMDD patients: $t(50) = -4.55$, $p < .001$; healthy controls: $t(50) = -7.23$, $p < .001$).

Reciprocal Prospective Effects of Momentary Cognitions and Affect

The first set of analyses consisted of multilevel lag models, which aimed to investigate reciprocal prospective effects of momentary cognitions and affect in the total sample. Rumination (T-1) did not show predictive value for subsequent NA (b = 0.01, SE = 0.01, p = .295) or PA (b = -0.02, SE = 0.01, p = .166) at T1 as main effects. By contrast, higher positive thoughts (T-1) predicted a decrease in NA (b = -0.02, SE = 0.01, p = .037) and an increase in PA (b = 0.03, SE = 0.01, p = .005) at T1. With regard to the opposite effects of affect on momentary cognitions, higher NA (T-1) predicted an increase in subsequent rumination (b = 0.20, SE = 0.03, p < .001) and higher PA (T-1) predicted a decrease rumination (b = -0.12, SE = 0.02, p < .001) at T1. Conversely, higher NA (T-1) predicted a decrease of subsequent positive thoughts (b = - 0.11, SE = 0.04, p = .001), and higher PA (T-1) predicted an increase of positive thoughts (b = 0.15, SE = 0.03, p < .001) at T1. Additionally, higher rumination (T-1) predicted decreased subsequent positive thoughts (b = -0.07, SE = 0.02, p = .003), and higher positive thoughts (T-1) predicted decreased subsequent rumination (b = -0.04, SE = 0.01, p = .002) at T1 (see Table S2 for additional information).

We further found that group status moderated the prospective effect of rumination (T-1) on subsequent PA (see Table S2). Simple slope analyses revealed that rMDD patients reported a stronger decrease of PA (T1) following higher rumination (T-1) compared to healthy controls (t(3751) = 2.42, p = .015; see Fig. 2.1a for illustration purposes). Moreover, group status moderated the effects of NA (T-1) and PA (T-1) on rumination (T1). Here, the differences in simple slopes showed that the increase of rumination (T1) following higher NA (T-1) was stronger in the rMDD group (t(3375) = -2.24, p = .026; see Fig. 2.1b) and the decrease of rumination (T1) following higher PA (T-1) was stronger in the rMDD group (t(3321) = 2.44, p = .015; see Fig. 2.1c). Effect sizes of main and interaction effects ranged from R^2 = 0.03 - 0.05 (see Table S2).

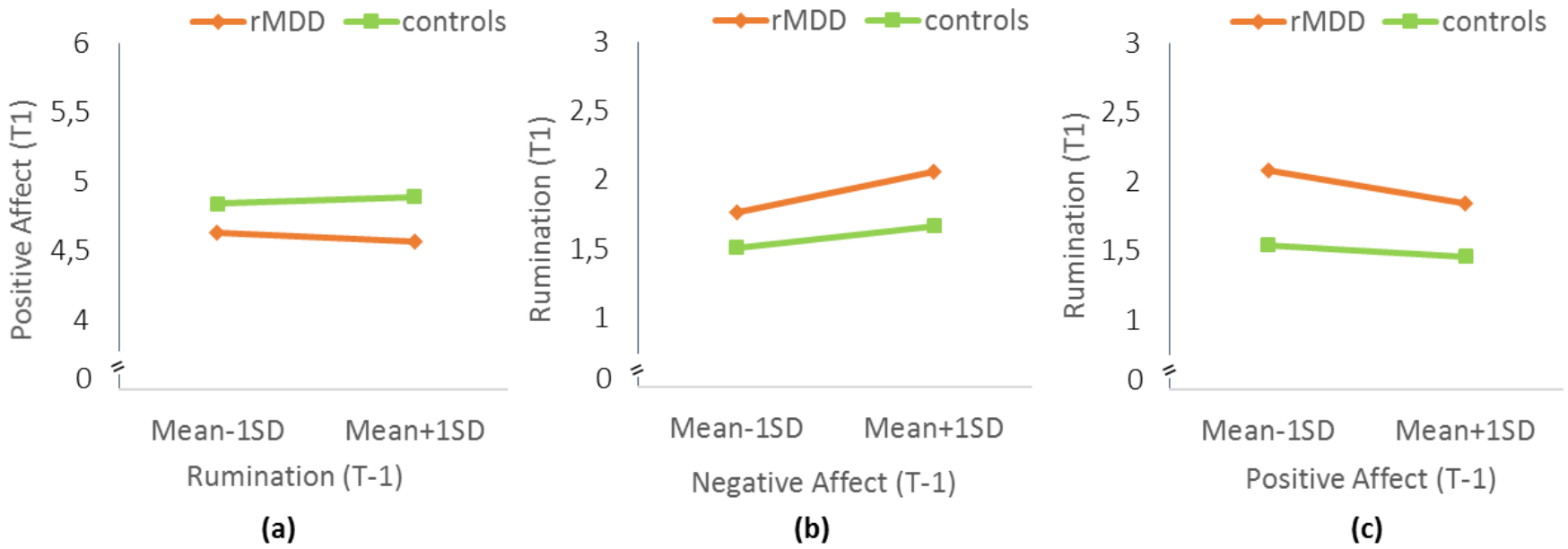

Figure 2.1 Reciprocal prospective effects of momentary rumination and affect

Note. Estimated means scores of a) positive affect (W-S) at T1 following rumination (T-1; W-S) b) rumination (W-S) at T1 following negative affect (T-1; W-S) and c) rumination (W-S) at T1 following positive affect (T-1; W-S) for rMDD patients and healthy controls. Level 1 predictors were person-mean centered and time lagged. Models include random intercepts at level 2 and 3, lagged outcome, between-subjects-effects (B-S) and within-subjects-effects (W-S) and the respective interaction effects of predictor by group.

Daily Events as Predictors of Momentary Cognitions and Affect

In the second set of MLM, we estimated the prospective effects of negative and positive daily events on momentary affect and cognitions. The total sample demonstrated within-subjects' reactivity to previous negative and positive events. Negative daily events since the last prompt (TE) predicted higher NA (b = 0.78, SE = 0.03, p < .001) and rumination (b = 0.98, SE = 0.05, p < .001), and lower PA (b = -0.81, SE = 0.04, p < .001) and positive thoughts (b = -0.87, SE = 0.05, p < .001) at T1. A converse pattern was found for positive events (TE) predicting lower NA (b = -0.23, SE = 0.02, p < .001) and rumination (b = -0.22, SE = 0.04, p < .001) and higher PA (b = 0.41, SE = 0.03, p < .001) and positive thoughts (b = 0.79, SE = 0.05, p < .001) at T1. In a second step, we included interaction terms of daily events by group status (see Table S3). Group status moderated the effects of negative events (TE) on NA and rumination at T1. Simple slope analyses revealed that for rMDD patients reactivity in NA (t(3669) = -3.32, p =.001; see Fig. 2.2a) and rumination (t(3699) = -3.78, p < .001; see Fig. 2.2b) were higher compared to healthy controls. As for reactivity towards positive events, group status was a significant moderator for all outcome variables. RMDD patients showed a stronger decrease in NA (t(3717) = 3.73, p < .001; see Fig. 2.2c) and rumination (t(3717) = 3.46, p = .001; see Fig. 2.2d) and a stronger increase in PA (t(3688) = -4.78, p < .001; see Fig. 2.2e) and PT (t(3736) = -2.04, p = .041; see Fig. 2.2f) compared to controls. Effect sizes for main and interaction effects ranged from R^2 = 0.10 - 0.30 (see Table S3).

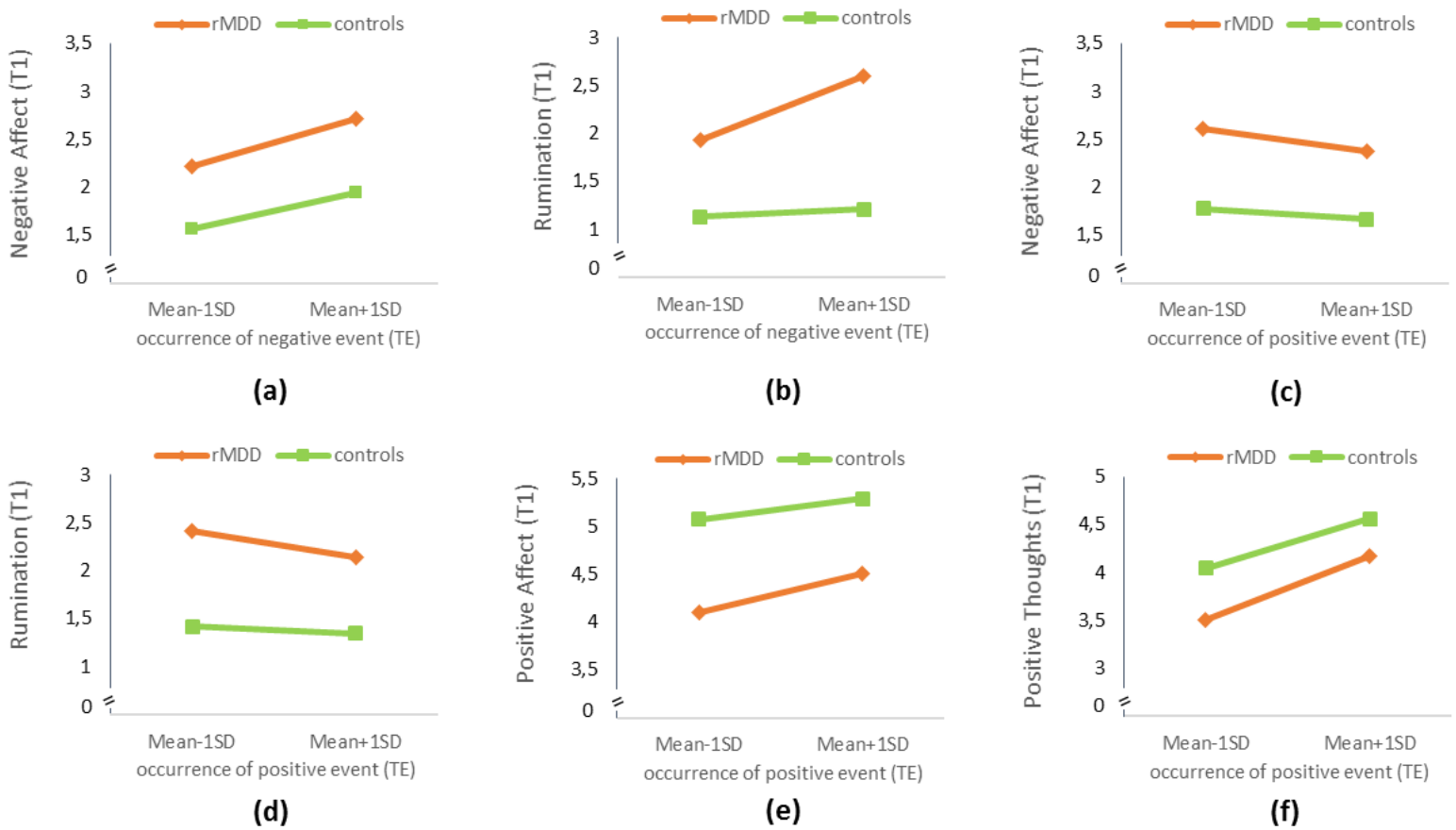

Figure 2.2 Prospective Effects of Daily Events on Momentary Cognitions and Affect

Note. Estimated means scores of a) negative affect (W-S) at T1 and b) rumination (W-S) at T1 following occurrence of negative event (TE; W-S), c) negative affect (W-S) at T1, d) rumination (W-S) at T1, e) positive affect (W-S) at T1 and f) positive thoughts (W-S) at T1 following occurrence of positive event in rMDD patients and healthy controls. Level 1 predictors were person-mean centered. All models include random intercepts at level 2 and 3, lagged outcome, between-subjects-effects (B-S), within-subjects-effects (W-S) of predictors and the interaction effect of event occurrence by group.

2.5 Discussion

The present EMA study aimed to investigate differences in average daily affect and cognitions in remitted recurrently depressed individuals (rMDD) compared to healthy controls, as well as temporal within-person dynamics of momentary rumination and positive thoughts, daily events and affect and potential group differences in these effects. Compared to healthy controls, rMDD patients reported higher levels of negative affect (NA) and rumination, as well as lower levels of positive affect (PA) and positive thoughts. Regarding daily events, rMDD patients reported a higher frequency of negative daily events, whereas no group difference in the frequency of reported positive daily events was found. Furthermore, rMDD patients were more receptive for the prospective negative effect of rumination on PA and showed higher affective reactivity (increased PA, decreased NA) as well as cognitive reactivity (increased positive thoughts, decreased rumination) in response to positive events. Our findings emphasize the importance of positive cognitions and affect in the context of remitted recurrent depression, and should be considered in the evaluation of interventions aiming to prevent relapses/recurrences.

Do RMDD Patients show Impairments in Daily Experiences? (Study Aim 1)

We found that rMDD patients show higher average NA and ruminaton, a finding, which stands in line with previous research (e.g., Hjartarson et al., 2022), and lower average PA compared to healthy controls. These findings should be looked at more closely from the perspective of “scar”-research (Wichers et al., 2010), originally suggesting that scars refer to a variety of alterations (e.g., cognitive, emotional) that develop during an MDE and can result in a heightened vulnerability for further depressive episodes. In the present case, this could indicate that MDEs leave scars, such that affect and adaptive cognitions remain lowered, while maladaptive thoughts remain heightened compared to individuals with no former MDE history. However, given the present study design, we cannot rule out the possibility that these deviations in momentary cognitions and affect represent pre-morbid vulnerability factors (Bos et al., 2018) rather than scars (Wichers et al., 2010). Nevertheless, be it scars or

pre-existing vulnerability factors, both might increase the risk to develop further MDEs and are therefore an important target for investigation. Furthermore, it seems important to mention that according to their dynamic approach to the "scar"-concept, Wichers et al. (2010) understand scars as a modifiable process rather than structural changes and emphasize the role of protective factors for reducing scars and preventing future MDEs.

The finding that rMDD patients report a higher frequency of negative daily events than controls stands in line with prior research on current MDD patients (Bylsma et al., 2011; Lamers et al., 2018; Thompson et al., 2012). In contrast to this, both groups reported a similar amount of positive daily events. This finding to some extent contradicts earlier research on the extended process model of emotion regulation (ER, Gross, 2015), since some studies found that depression was related to reduced exposure to positive events (Khazanov et al., 2019; Vanderlind et al., 2020). Consequently, the similar frequency of reported daily positive events in our study gives a first indication that the first stage of ER, namely the selection of positive situations, may no longer be impaired following remission from depression.

Reciprocal Prospective Effects of Momentary Cognitions and Affect (Study Aim 2)

Our analyses on reciprocal prospective effects of momentary cognitions and affect extend findings of previous research by focusing not only on maladaptive cognitions but also on positive thoughts. Interestingly, we did not find the rather consistently reported negative effect of rumination on subsequent NA (e.g., Blanke et al., 2021; Kircanski et al., 2018; Ruscio et al., 2015), either in rMDD patients or in healthy controls. One reason for this could be that, even though the rMDD group reported higher momentary rumination than controls, it was still low in both groups, which may have accounted for the missing impact of rumination specifically on NA.

We also investigated the effects of NA on rumination and found that NA predicted higher values of subsequent rumination. This effect was significantly stronger in the patient group. These findings support the assumption that rumination denotes a failure to cope with NA (Bean et al. 2021). There is already a consensus for the finding that NA has predictive value for rumination (e.g., Blanke et al.,

2021; Hjartarson et al., 2022). However, findings on respective differences between clinical groups and healthy controls are inconsistent. While there is some evidence demonstrating this effect in healthy controls (e.g., Blanke et al., 2021), Hjartarson et al. (2022) found a significant mood-related reactivity of momentary rumination only in rMDD patients, but not in healthy controls. They reasoned that one aspect of depression vulnerability might be the automaticity of rumination as triggered by daily fluctuations in NA. This high automaticity of the cognitive reaction makes it difficult to control (Hjartarson et al., 2022), which shows uncontrollability to be a key component of rumination (Raes et al., 2008), and, more broadly, of repetitive negative thinking (RNT; Rosenkranz et al., 2020).

Although we could not find a prospective effect of rumination on NA, rumination predicted a decrease in PA, but only in the rMDD group. In earlier research, the focus of (reciprocal) prospective effects of momentary cognitions has mainly been placed on NA. The present finding highlights the importance of also investigating PA in rMDD patients, which is in line with Clark and Watsons`s (1991) tripartite model of depression and anxiety, stating that high levels of NA are associated with depression and anxiety to a similar degree, but that lower levels of PA are specific to depression (Naragon-Gainey, 2019). We also showed that higher PA predicted a significantly stronger decrease of subsequent rumination in the rMDD patient sample. The importance of focusing on positive concepts becomes even more evident when looking at the prospective effects of positive thoughts on subsequent NA and PA and vice versa. In both groups, positive thoughts acted as a countervailing force to rumination, improving subsequent affect in both groups similarly. Furthermore, higher PA and lower NA predicted an increase of subsequent positive thoughts. These results support the upward-spiral model (Garland et al., 2010).

Finally, we looked at the reciprocal effects of both types of momentary cognitions and found that rumination predicted subsequent lower positive thoughts and vice versa. These effects were comparably strong in both groups. This finding can have important implications for therapeutic prevention and intervention strategies, as discussed in the *Implications* section below.

Effect sizes of reciprocal prospective effects of momentary cognitions and affect were generally small, however comparable to recent research on ER-strategies (Wenzel et al., 2021). Moreover, such dynamic associations are repetitive and can occur several times per day, thereby increasing their relevance (Wenzel et al., 2016).

Prospective Effects of Daily Events (Study Aim 3)

The present EMA study further aimed to increase the current understanding of the associations between daily events and affect in daily life. Research on differences in the effects of negative daily events on affect between current MDD patients, remitted MDD patients and healthy controls has to date been ambiguous (see *Introduction* section). In the present study, we found rMDD patients to show heightened reactivity of NA and rumination, since rMDD patients reported stronger increases in NA and rumination following negative daily events. These results are in line with Husky et al. (2009), who also reported heightened NA-reactivity in response to negative daily events in remitted MDD patients, and they partially support the findings from Lamers et al. (2018) who found reactivity in anxious mood to be stronger in both current MDD and remitted MDD patients compared to healthy controls. We did not find any group differences between rMDD patients and healthy controls with regard to either subsequent PA (cf. Van Winkel et al., 2015) or to positive thoughts. Thus, one can assume that rMDD patients are particularly vulnerable for event-congruent feelings and thoughts.

Interestingly, following positive daily events, rMDD patients showed the previously reported “mood brightening” effect (e.g., Bylsma et al., 2011; Khazanov et al., 2019; Lamers et al., 2018; Santee & Starr, 2021), since PA was more strongly enhanced and NA was more strongly decreased following positive daily events in the patient group compared to healthy controls. In addition to mood brightening, we also found a significantly stronger “cognition brightening” following positive daily events in rMDD patients, in so far as these patients reported a stronger increase in positive thoughts and a stronger decrease in rumination. These results conflict with the idea that reactivity is congruent with the valence of daily events but extend previous research, since to our knowledge there is only one previous

study by Khazanov et al. (2019) investigating momentary cognitions following positive daily events. The authors discussed several considerations which might explain the rather counter-intuitive brightening effect in current MDD patients and which could also apply for our sample of rMDD patients. One possible explanation is that rMDD patients might have lower expectations for future events or a lower threshold to appraise positive events as positive compared to healthy controls, both of which are factors that could amplify their reaction to positive stimuli (Heininga & Kuppens, 2021; Khazanov et al., 2019). Another idea comes from affective contrast theory (Newman & Llera, 2011), which states that emotional experiences are heightened when a contrasting emotional experience precedes it.

The phenomenon of mood and cognition brightening in rMDD patients raises some questions since it is not easy to reconcile it with the fact that rMDD patients showed lower average PA and positive thoughts, as well as higher average NA and rumination in daily life. The obvious reason would be that patients on average experience more negative and fewer positive daily events compared to healthy controls, but this was not observed with respect to positive daily events. However, compared to controls, rMDD patients reported more negative daily events, which could potentially overshadow the favorable effects of positive daily events on mood and cognitions. Nevertheless, as already reported (see *Results* section*)*, both healthy controls and rMDD patients reported more positive than negative daily events. A further reason could be that the peak of PA returns more quickly to the baseline after the positive event in rMDD patients compared to controls. This could be due to differences in ER strategies. Depression has already been linked to ER difficulties (Vanderlind et al., 2020), especially the habitual use of ER strategies (Liu & Thompson, 2017). In this context, there is a growing body of research on ER strategies targeting PA, which has been neglected in the past (Silton et al., 2020). For example, Vanderlind et al. (2020) reported that MDD patients are less likely to engage in strategies which maintain or even enhance PA (e.g., savoring) and are more likely to use down-regulation strategies (e.g., dampening, suppression). There is also evidence that remitted MDD patients show greater levels of dampening, similar to current MDD patients and in contrast to healthy controls (Vanderlind et al., 2020). Future research should focus on the use of ER strategies targeting PA following daily

events. This could help to elucidate why rMDD patients cannot increase their average PA up to the level of healthy controls.

Implications

There are several implications that can be drawn from the given results. First, it still seems to be the case that targeting maladaptive thoughts, such as rumination, is important in order to increase affective well-being and reduce depressive symptoms. Rumination might hinder engaging in effective problem solving strategies, and thus might impede overcoming NA (Blanke et al., 2021). In this context, rumination-focused therapy (Watkins, 2015) has already demonstrated efficacy. Given the fact that our data show an even stronger impact of positive thoughts on affect and the idea that positive thoughts could act as a buffer against subsequent rumination, the application of cognitive interventions (CBT; Hofmann & Asmundson, 2017), not only targeting rumination but also positive thoughts – even though speculative - seems promising. Moreover, mindfulness-based cognitive therapy (MBCT; Segal et al., 2018) has been shown to increase momentary positive cognitions and could thus strengthen the link between positive thoughts and PA in daily life (Garland et al., 2015). Therefore, it potentially represents a powerful intervention strategy to reinforce the upward spiral (Garland et al., 2015).

Second, the current data imply that engaging in positive events, e.g. through behavioral activation therapy (Cuijpers et al., 2020; Stein et al., 2021), should be accompanied by attempts to increase the individual's responsiveness once positive emotions have been evoked. There is initial research suggesting beneficial effects of treatments that improve ER strategies of positive emotions (Vanderlind et al., 2021). For instance, favorable effects of savoring, which aims to appreciate and enhance positive experiences on affect, have been reported (Silton et al., 2020). In a recent study, Wenzel et al. (2021) investigated in two non-clinical samples how much variance of momentary affect could be explained by ER strategies (versus event intensity). They found that ER accounted for up to half of the variance of NA and up to a third of the variance of PA. In particular, under-investigated ER strategies (e.g.,

appreciation, mindfulness, acceptance), which aim to up-regulate or maintain PA, added more value in explaining variance in PA compared to NA. Their findings demonstrate the importance of considering ER strategies that are specific for each PA and NA.

Third, the current results can also be translated into Ecological Momentary Interventions (EMIs), which may represent a promising tool for relapse prevention in rMDD patients. So far, there have been only few EMIs, which focus on PA, including PA-feedback, self-monitoring and recommendations for lifestyle changes, and they have yielded mixed results (Heininga & Kuppens, 2021). The future focus should lie on investigating ER strategies targeting positive emotions as moderators on the mood brightening and cognition brightening effects following positive daily events. Finally, there is initial evidence that PA plays an especially important role in the long-term course of depression, since average daily PA (but not NA) and positive social interactions predicted higher well-being ten years later in a sample of MDD patients (Panaite et al., 2021). Future projects should also incorporate multiple intensive phases of micro-longitudinal assessment (measurement burst design; e.g., Stawski et al., 2015) to confirm whether an intensified interplay between momentary cognitions, daily events and affect in rMDD patients is prodromal to future MDEs.

Strengths and Limitations

The present study offers some methodological strengths. To our knowledge, it is the first EMA-study combining the examination of momentary cognitions (rumination and positive thoughts), affect and daily events in a sample at high-risk for future MDEs (rMDD patients) compared to healthy controls. With n = 51 participants per group and 50 assessment points per participant our sample size was rather large, which according to Mathieu et al. (2012) results in a power of > .80 to detect cross-level interactions. Another strength lies in our approach to measure depression by using a composite score of self- (BDI II) and external (MADRS) rating scales in order to avoid possible mono-method bias. Additionally, through providing study-smartphones to all participants we aimed to increase diversity of

the sample (i.e. socio-economic status, age) and minimize technological issues. Another methodological strength can be seen in our conservative approach to include the lagged outcome as a covariate in all multilevel lag models.

Some limitations restrict the scope of the present findings. First, by investigating solely rumination, which is one component of the transdiagnostic construct repetitive negative thinking (RNT, Ehring, 2021), we did not measure other important dimensions of RNT (e.g. worry or post-event processing). Therefore, the specificity of our findings to rumination cannot be firmly established. Second, we assessed momentary cognitions with only one item each. In the case of rumination, we aimed to focus on the uncontrollability facet of it and consequently aligned the measure of positive thoughts correspondingly. The present rumination item has been used in previous research and has shown high predictive value in different clinical samples (see Beddig et al., 2019, 2020a,b, Kuehner et al., 2017; Timm et al., 2018). However, even though single-item measures are common in EMA research, particularly in order to minimize the burden on participants, they clearly restrict the reliability estimation (Mestdagh & Dejonckheere, 2021). Promising initiatives as the *Experience Sampling Method (ESM) Item Repository* (Kirtley et al., 2022) could help researchers to unify their item selection and create reliable short scales for specific constructs. Third, levels of NA and rumination exhibited a restricted range, which could have led to an underestimation of respective effects. Fourth, we measured daily events subjectively (based on personal perceptions) without providing clear instructions or examples of what counts as negative or positive daily event. We chose this approach to avoid a restriction of the individual's scope of perceiving and reporting daily events. Certainly, subjective ratings of daily events can be seen as problematic, because it becomes less evident whether group differences (or the lack thereof) can be accounted for by differences in events experienced, differences in perceptions of events, or both. Future research would profit from context-aware assessment strategies that link the assessment of experiences to specific sensing events (Kubiak & Smyth, 2019). This multi-modal information collection can be implemented by integrating EMA (i.e., subjective assessments) into a broader mobile sensing framework (i.e., GPS-based location tracking, voice records/speech analysis etc.), as

described by Kubiak & Smyth (2019). Moreover, in order to consider the heterogeneity of daily events, future research should distinguish between different types of events (e.g., non-interpersonal versus personal; see: Sheets & Armey, 2020) and consider specific aspects of the situations (e.g., controllability; Wenzel et al., 2021). Fifth, a common problem when assessing daily events is that self-reports on their occurrence are retrospective, since they refer to the time interval between the last prompt (T-1) and the recent one (T1). Since we assessed negative and positive daily events simultaneously with momentary affect, we cannot disregard the possibility that the affect ratings evoked a recall bias for affect-congruent events. Furthermore, the time interval (TE) of daily events differed in length and therefore the impact of daily events on momentary cognitions and affect can vary accordingly. Beyond this, we did not take into account the number of previous negative or positive events when interpreting affect reactivity towards daily events. Here, the accumulation of either positive or negative events could play an important role in affect change (see: Mey et al., 2020). Sixth, because of restricted financial means, we did not include an additional group of current MDD patients, which could have helped to explore potential effects of current depressed mood separable from underlying risk. Finally, our EMA study provided relevant information on moment-to-moment dynamics between cognitions, daily events and affect. However, we cannot draw any conclusions about the long-term stability of these effects nor about their prognostic value for the further course of depression without a follow-up assessment.

Conclusions

The present EMA study builds on previous research investigating the dynamic interplay between momentary cognitions, daily events and affect in a sample of remitted depressed patients with a history of recurrent episodes (rMDD) compared to controls. Results showed that rMDD patients differ from healthy controls in average levels of daily affect and maladaptive cognitions. Our findings further revealed stronger prospective effects of NA and PA on rumination and stronger effects of rumination on

PA in rMDD patients. This might indicate a kind of vulnerability (pre-existing or scar) that could increase the individual's risk for future MDEs. Of particular interest appears to be the replication of the mood brightening effect in the rMDD group and the identification of an additional cognition brightening, since PA and positive thoughts were more strongly enhanced and NA and rumination more strongly decreased following positive daily events. Another key finding is the support for the positive upward spiral model, in terms of a mutual amplification of positive affect and positive cognitions. It remains uncertain why – given these positive effects of positive thoughts on affect and rumination – the overall PA in daily life stays below the level of healthy controls. The given results point towards the importance of integrating therapeutic intervention strategies, which enhance the responsiveness to positive events and the up-regulation of PA. However, the stability of these effects and the mechanisms underlying them still have to be uncovered. Likewise, there needs to be further research, which incorporates multiple extensive longitudinal assessments using measurement burst designs together with assessments of different types of daily events and different ER strategies, in order to reliably unravel vulnerability and improve our understanding of protective factors for the course of depression.

CHAPTER III: TRAIT AND STATE EFFECTS OF DIFFERENT MODES OF THINKING ON SALIVARY CORTISOL IN DAILY LIFE IN PATIENTS WITH RECURRENT MAJOR DEPRESSION AND HEALTHY INDIVIDUALS (STUDY 2)

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3.1 Abstract

Habitual modes of thinking such as repetitive negative thinking (RNT), but also momentary cognitive processes such as mindwandering could be vulnerability factors for the course of Major Depressive Disorder (MDD). On the physiological level, cortisol represents an important biological stress marker of the hypothalamic-pituitary-adrenal (HPA) axis. Being a dynamic and non-invasive measure, salivary cortisol can be assessed in daily life via Ambulatory Assessment (AA). So far, consensus exists on a dysregulation of the HPA axis in MDD. However, findings are ambiguous and AA-studies examining both trait and state level effects of cognitive processes on cortisol release in daily life in patients with recurrent major depression (rMDD) and healthy controls (HCs) are lacking. A sample of 119 (n_{rMDD}= 57, n_{HCs}= 62) participants underwent a baseline session, including self-rated questionnaires (RNT, mind-fulness) followed by a 5-day AA, where participants indicated the occurrence of mindwandering and levels of mentalshift problems ten times per day via smartphone, and collected saliva cortisol samples five times per day. Via multilevel models, we found habitual RNT, but not mindfulness, to predict higher cortisol levels, with the effects being stronger in rMDD patients. State mindwandering and mentalshift problems predicted increased cortisol 20 min later across groups. State cognitions did not mediate the effects of habitual RNT on cortisol release. Our results suggest independent mechanisms of action for trait and state cognitions on cortisol activity in daily life and indicate a

greater physiological vulnerability toward trait RNT and the tendency to experience mentalshift problems in patients with recurrent major depression.

3.2 Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is responsible for physiological adaptation and homeostasis maintenance of the human body (Aguilar-Raab et al., 2021; Turner et al., 2020). HPA's primary product *cortisol* represents an important biological stress-marker (Adam et al., 2017), which due to its noninvasive nature is commonly assessed as salivary cortisol in Ambulatory Assessment (AA) studies (Schlotz, 2019).

While there is consensus that HPA axis dysfunctions are linked to Major Depressive Disorder (MDD), prior findings range from decreased to increased cortisol activity, possibly related to different MDD subtypes (cf. Booij et al., 2020) and clinical status. Regarding basal diurnal cortisol rhythms, MDD has been linked to a flatter diurnal cortisol slope indicating a reduced dynamic activity of the HPA axis (cf. Adam et al., 2017, Gilbert et al., 2017), while both blunted and elevated levels of the cortisol awakening response (CAR) have been reported (cf. Gilbert et al., 2017). With respect to the stress-reactive component of cortisol, previous research has primarily focused on cortisol reactivity following lab-induced (Gu et al., 2022; Zorn et al., 2017) or daily life stressors (cf. Schlotz, 2019, Weber et al., 2022). In contrast, cortisol reactivity toward possible internal stressors such as maladaptive cognitions has mainly been neglected so far (cf. Smyth et al., 2023). Given the heterogeneity of findings in the field of cortisol activity in MDD, it seems worthwhile to examine cognitive *traits* or modes of thinking at the between-person level, which may be linked to adverse physiological consequences (Watkins, 2022) and might account for variations in cortisol levels beyond the clinical status. In addition, since cortisol is of a highly dynamic nature and intraindividual differences could remain unnoticed in between-person designs (cf. Booij et al., 2020), a more fine-grained investigation of its within-person associations with *state* cognitions seems warranted.

Only few studies so far investigated associations of cortisol during daily life with certain cognitive *traits*. Repetitive negative thinking (RNT) such as rumination or worry describes one's tendency to perseverative thinking about negative contents with difficulties to disengage from (Watkins, 2022). While RNT has been linked to numerous dysregulated physiological functions, its effects on cortisol release in daily life remain underinvestigated (e.g., Ottaviani et al., 2016). Both Zoccola and Dickerson (2012) and Huffziger et al. (2013) found no clear associations of more specific depression-related trait rumination with cortisol levels during daily life.

Habitual mindfulness, defined as an intentional and non-judgmental attention shift toward one's current experience, has been suggested to be a protective cognitive trait for an adaptive physiological stress response (cf. Manigault et al., 2018a) and has shown to modulate affective and cortisol responses toward an acute social stressor (Brown et al., 2012). While dispositional mindfulness has mainly been examined in relation to acute stressors, studies investigating its effects on daily cortisol release independent of external stressors are largely lacking. No significant association of habitual mindfulness with overall cortisol release during daily life was found in women with Premenstrual Dysphoric Disorder (PMDD, Nayman et al., 2022). Manigault et al. (2018a) investigated associations of habitual mindfulness components and diurnal cortisol patterns in a healthy sample and found that habitual acceptance was linked to a more robust CAR and a more rapid decline in evening cortisol. In a recent AA-study in healthy individuals, Aguilar-Raab et al. (2021) found a Mindfulness-Based Intervention (MBI) to be linked to a more pronounced diurnal cortisol decrease compared to a control condition without a stress-management component. In contrast, Beddig et al. (2020) found no group differences regarding CAR and daily cortisol slopes between a mindfulness-based attention training (MBAT) and a progressive muscle relaxation training in remitted patients with recurrent major depression. However, MBAT buffered an increase of total cortisol over time particularly in those patients showing marked improvements in negative affect and rumination during daily life.

Regarding effects of state cognitions on cortisol release in daily life, research is similarly scarce. Besides diurnal cortisol profiles, Aguilar-Raab et al. (2021) investigated effects of momentary (state) mindfulness on cortisol, measured concurrently, and found no significant association. Furthermore, initial findings on maladaptive cognitions such as rumination are ambiguous, showing, for example, state rumination to predict a within-person increase in cortisol 20 min later in healthy controls, but not in women with PMDD (Beddig et al., 2019). Huffziger et al. (2013) identified no moment-to-moment effects of rumination on cortisol in patients remitted from major depression and healthy controls, but showed that higher daily means of state rumination were associated with higher cortisol levels across groups.

Mindwandering can be conceptualized as self-generated, task-unrelated and context-independent thoughts (Chaieb et al., 2022). It can also be defined as having problems staying in the here and now, a phenomenon frequently observed in MDD (cf. Hoffmann et al., 2016). Both momentary overall mindwandering and more specific mentalshift problems may represent state indicators of RNT and (inverse) mindfulness. We are aware of only one study so far, investigating momentary content and extent of mindwandering and cortisol in daily life (Linz et al., 2021) in healthy individuals, with no significant associations. However, the link between mindwandering and problems with attention-shifting with cortisol activity has only been insufficiently addressed yet.

Furthermore, it remains to be uncovered if more distal effects of trait modes of thinking on cortisol release during daily life are mediated through more proximal effects of respective state cognitions.

Consequently, the aims of the present study were to examine (a) effects of trait RNT and mindfulness and state mindwandering and mentalshift problems on salivary cortisol levels during daily life, and (b) the role of state mindwandering and mentalshift problems as potential mediators of the effects of trait RNT and mindfulness on cortisol release in patients with recurrent major depression (rMDD) and healthy controls (HCs).

3.3 Method

Design and Participants

Between October 2019 and June 2021, a sample of n = 57 rMDD patients and n = 62 HCs matched for gender, age and educational degree was recruited. RMDD patients had to fulfill the criteria for at least two major depressive lifetime episodes (MDEs) according to the Structured Clinical Interview for DSM-IV axis I (SCID-I), while HCs must not have experienced any lifetime MDE. Joint exclusion criteria were non-affective psychotic disorders, bipolar disorder, current substance use disorder and corticoisteroid based medication intake.

The sample consisted of *N* = 119 participants (*M* = 43.1 years, *SD* = 11.5, range: 24-63; 71% female), and 82.5% of the rMDD patients were currently in remission (SCID-I).

The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University (2017-621N-MA). All participants provided written informed consent and were financially compensated with up to 120 € for study completion.

Study Procedure and Measures

Baseline session. Eligible participants attended a baseline session at the Central Institute of Mental Health in Mannheim, Germany, where in- and exclusion criteria were evaluated by a trained clinical psychologist with the SCID-I. Four participants could not attend the in-person session due to the current Covid-19 contract restrictions and were therefore interviewed remotely using Red Connect (Red Medical Systems GmbH).

In order to assess (a) habitual repetitive negative thinking (RNT) and (b) habitual mindfulness participants filled out (a) the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011) and (b) the Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003; German version: Michalak et al., 2011). Depressive symptoms were assessed using the self-rated Beck Depression Inventory Revised (BDI-II; German version: Hautzinger et al., 2009) and the interviewer-rated Montgomery-Asberg

Depression Rating Scale (MADRS; Neumann & Schulte, 1989). An overall composite score for depressive symptoms was built by averaging the z-transformed BDI-II and MADRS scores (see also Huffziger et al., 2013; Schricker et al., 2023). For all listed measures, Cronbachs amounted to $\alpha \geq .912$ in the present study. Lifetime and current psychopathology were assessed with the Structured Interview for DSM-IV Axis I (SCID-I, Wittchen et al., 1997).

In order to increase sampling accuracy and compliance, participants were given clear instructions on how to use the study phone and on how and when to properly collect saliva samples, by also emphasizing the importance of accurate timing (cf. Schlotz, 2019). Furthermore, we provided phone support for the complete AA-phase and participants were allowed to postpone saliva collection for up to 20 min if inevitable (cf. Schlotz, 2019).

Ambulatory Assessment (AA). AA was carried out using Motorola G 7 Play smartphones with the software movisensXS, version 1.6.1 (movisens GmbH, Karlsruhe, Germany) during five consecutive days. Following a semi-random sampling scheme, participants responded ten times per day to prompts that occurred between 08:00 am – 10:00 pm within 90min time intervals.

State mindwandering was assessed with the dichotomous (*yes/no*) item: "At the moment before the beep, I was thinking about something other than what I was currently doing" (cf. Killingsworth & Gilbert, 2010) and mentalshift problems with the item: "Were you having difficulty shifting focus between activities?" (Marcusson-Clavertz et al., 2022) on a 7-point Likert scale (*not at all - fully agree*).

Cortisol samples were collected 20 min after every second subjective assessment, resulting in five samples per day[3]. Only those subjective assessments were included for analysis which were prompted 20 min preceding saliva collection. Consequently in the present study cortisol reactivity represents the temporal association between state cognitions (mindwandering, mentalshift problems) and salivary cortisol, assessed with a 20 min time lag (cf. Aguilar-Raab et al., 2021; Schlotz, 2019, Stoffel et al., 2021).

[3] We assessed state cognitions at five additional time points, since we used this data within a larger project for further analyses not involving cortisol (see Schricker et al., 2023a,c).

Participants were instructed not to eat, drink anything but water, smoke, physically exercise, and brush their teeth during the 20 min time interval before saliva collection (Schlotz, 2019). Immediately after saliva collection, participants were asked whether they had eaten, drunk anything other than water, smoked, or brushed their teeth (yes/no) and indicated the extent of their physical activity during the last 20 min on a 7-point Likert scale ranging from 1 (“not at all”) to 7 (“very much”). Furthermore we assessed sleep duration in hours and the subjective quality of sleep at every first prompt per day.

Saliva probes were stored in the participants’ home freezers until return to the lab, where samples were frozen at -20°C until their biochemical analysis at the laboratory of Dresden, Germany. After thawing, salivettes were centrifuged at 3,000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). In total 15.4% of saliva probes were analyzed in duplicates. The mean intraassay coefficient for cortisol was 5.1% and the interassay coefficient was 6.2%. In order to adjust for skewness, cortisol raw data was log-transformed. Outliers above 3 standard deviations of the sample mean were winsorized to 3 standard deviations (cf. Schlotz, 2019).

As an incentive, participants were offered the prospect of full financial compensation of 120 € only when responding to at least 80% of prompts, including saliva sampling.

Statistical Analyses

Simple group comparisons on demographics, clinical variables and the aggregated person-means of all central AA-variables (i.e., salivary cortisol, mindwandering, mentalshift problems) were performed with the person-level dataset using t-tests for independent samples for continuous and Chi-square tests for dichotomous variables.

Given the nested data structure with assessment points being nested within days, which in turn were nested within persons, we estimated linear mixed models with restricted maximum likelihood estimation in IBM SPSS Version 28. In empty models, using maximum likelihood estimation, we checked

whether a 3-level model provided a better fit than a 2-level model with assessment points being nested within persons. Since the Hesse Matrix was not positive definite for the 3-level model and the 2-level model showed slightly smaller fit indices (AIC: 4399.065; BIC: 4415.253) than the 3-level model (AIC: 4401.056; BIC: 4422.652), we decided for the more parsimonious 2-level models.

We conducted additional linear mixed models required for the planned multi-level mediation analyses (Baron & Kenny, 1986) by regressing our potential mediators (mindwandering, mentalshift problems) on the focal level-2 predictor variables (RNT, mindfulness). For the dichotomous outcome *mindwandering* we run generalized linear mixed models in R Version 4.1.2 with the *lme4* package (Bates et al., 2014). Mediation analyses were estimated via multilevel structural equation models (MSEMs) with the *lavaan* package (Rosseel, 2012). For the generalized linear mixed model and the MSEMs the maximum likelihood estimation method was used.

All level-1 predictor variables were person-mean centered, and level-2 predictors (except for group status) were centered around the grand-mean. We included the grand-mean-centered person-mean of the level-1 predictors in all models, ensuring a decomposition of within- (WS) and between- subject (BS) effects (Neubauer & Schmiedeck, 2020). The level of salivary cortisol for each individual at each saliva sampling point was the central outcome and was regressed on moment-level variables (level-1) and person-level variables (level-2).

In preliminary analyses, we checked for potential confounders and considered eating, drinking, smoking, physical activity, sleep duration in hours, subjective sleep quality, hormonal contraceptive intake, biological sex, age, comorbidity, current psychotherapy and psychotropic or other medication intake. We further tested for the context effect of the Covid-19 pandemic (pre pandemic versus during pandemic participation). None of the listed confounders were retained in our models, since they showed no significant association with cortisol release in daily life (for a similar approach see Gilbert et al., 2017).

Time of saliva collection was centered around wakening (Stoffel et al., 2021). We tested for a linear and quadratic time effect with maximum likelihood estimation, comparing fit indices (AIC, BIC) and

using a likelihood ratio test. We found the model with the linear and quadratic time effect (AIC: 6810.1, BIC: 6841.2) compared to the more restrictive model with the linear time effect only (AIC: 7119, BIC: 7143.9) to demonstrate a better fit (Chi^2 = 310.96, p < .001). Consequently, all models were fitted using the linear and the quadratic time trend as covariates. All level-1 predictor models were additionally adjusted for the occurrence of negative daily events since the last prompt (WS and BS) in order to identify the net-effect of preceding state cognitions on cortisol levels 20 min later unbiased of potential daily life stressors.

In the process of model building, we tested if random slopes for both level-1 predictors (mindwandering: AIC: 4397.4, BIC: 4456.1; mentalshift problems: AIC: 4405.6, BIC: 4464.3) improved the model fit compared to the more restrictive random intercept models (mindwandering: AIC: 4393.6, BIC: 4440.5; mentalshift problems: AIC: 4401.9, BIC: 4448.8). Using likelihood ratio tests, we found the more restrictive random intercept models to show a better fit compared to the tested random slopes models (mindwandering: Chi^2 = 0.15, p = .813; mentalshift problems: Chi^2 = 0.26, p = .075). Furthermore, we checked if random slopes models with linear time as random effects (mindwandering model: AIC: 4395.0, BIC: 4453.7; mentalshift problems model: AIC: 4401.6, BIC: 4460.3) showed a better fit than the more restrictive random intercept models (mindwandering model: AIC: 4393.6, BIC: 4440.5; mentalshift problems model: AIC: 4401.9, BIC: 4448.8). Likelihood ratio tests revealed that the random intercept models provided a better fit compared to the tested

random slopes models (mindwandering models: Chi^2 = 2.60, p = .189; mentalshift problems models: Chi^2 = 4.31, p = .077). Consequently, all linear mixed models were random intercept models.

Models were built sequentially, by first estimating main effects and in a second step including the interaction term of predictors (WS and BS) by group status in order to test for possible group differences. Finally, using MSEM we checked if significant effects of habitual modes of thinking on cortisol were mediated by state cognitions (i.e., mindwandering, mentalshift problems) 20 min preceding saliva collection.

The following equation shows an example of one final 2-level linear mixed model including a two-way cross-level interaction with group by focal predictor (here: mentalshift problems) predicting cortisol 20 min later. Y_{ij} represents cortisol at measurement occasion *i* for person *j*.

Level-1

$$Y\,(cortisol)_{ij} = \beta_{0j} + \beta_{1j} mentalshift\ problems_{ij}^{W-S} + \beta_{2j} negative\ event_{ij}^{W-S} + \beta_{3j} time\ of\ saliva\ collection_{ij} + \beta_{4j} time\ of\ saliva\ collection_{ij}^{2} + \varepsilon_{ij}$$

The β coefficients represent the intercept and the fixed main effects at level-1, the ε_{ij} denote the residuals at level-1.

Level-2

$$\beta_{0j} = \gamma_{00} + \gamma_{01} group_j + \gamma_{02} mentalshift\ problems_j^{B-S} + \gamma_{03}\ negative\ event_j^{B-S} + \gamma_{04}\ group_j * mentalshift\ problems_j^{B-S} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11} group_j$$

$$\beta_{2j} = \gamma_{20}$$

$$\beta_{3j} = \gamma_{30}$$

$$\beta_{4j} = \gamma_{40}$$

Here the u_{0j} indicates the random intercept for person *j*.

In all analyses, the significance level was set at α = 0.05.

We performed a post hoc power analysis using the web application created by Murayama et al. (2022). Results proposed the present level-2 sample size of *N* = 119 to be sufficient to achieve a power of 80% to detect small to medium effect sizes with α set at .05.

3.4 Results

Compliance

In total 2504 out of 2975 possible subjective assessments were recorded, resulting in a high compliance rate of 92.0%, which is comparable to previous research (for a meta-analysis see Wrzus & Neubauer, 2023). A total of 2809 collected saliva probes out 2975 scheduled probes resulted in a

compliance for saliva cortisol collection of 94.4%, also demonstrating high compliance (cf. Chesnut et al., 2021; Weber et al., 2022). Cortisol values with missing time data were not considered within the statistical analyses. Given this restriction, 89.2% of the scheduled saliva cortisol data could be analyzed.

Demographic and Clinical Characteristics

RMDD patients reported higher habitual RNT and lower habitual mindfulness than HCs (all *ps* < .001, see Table 3.1).

AA-variables

Table 3.2 shows the means, within- and between-standard deviations and the intra-class correlation coefficients of all central AA-variables. On average, rMDD patients reported a higher frequency of mindwandering and higher levels of mentalshift problems (all *ps* < .001). Groups did not significantly differ in cortisol levels (p = .351).

Table 3.1

Descriptive Demographic and Clinical Characteristics and AA-Variables per Group

Variables	rMDD (n = 57) %/ *M (SD)*	HCs (n = 62) %/ *M (SD)*	test statistic *t/ Chi² (df)*
Demographic characteristics			
Age	43.1 (11.8)	43.0 (11.3)	$t(117)= 0.05$
% Female	70.2 %	71.0 %	$Chi^2(1)= 0.01$
Education (% with high school degree)	73.7 %	72.6%	$Chi^2(1)= 0.02$
Marital Status (% married or living together)	57.9 %	62.9 %	$Chi^2(1)= 0.31$
Clinical Variables			
≥ 3 lifetime MDEs (%)	82.1 %	-	-
currently remitted	82.5%	-	-
BDI-II	13.77 (12.05)	1.42 (2.20)	$t(59.6)= 7.62$***
MADRS	9.56 (8.24)	1.78 (2.31)	$t(64.1)= 6.89$***
Current psychotherapy	47.4%	4.8 %	$Chi^2(1)= 28.49$ ***
Current psychotropic medication	26.3 %	-	-
Comorbid diagnosis (%)	57.9%	9.7%	*Chi2(1)= 31.34***
Trait Cognitions			
Habitual RNT	2.02 (1.02)	0.94 (0.65)	$t(92.2) = 6.74$***
Habitual Mindfulness	3.92 (0.80)	4.97 (0.72)	$t(114) = -7.45$***

Note. BDI-II = Beck Depression Inventory Revised, MADRS = Montgomery- Asberg Depression Rating Scale, MDE = Major Depressive Episode, RNT = repetitive negative thinking; *$p < 0.05$; ***$p < .001$.

Table 3.2

Means, Standard Deviations and the Intra-Class Correlation Coefficients (ICCs) of AA-Variables

	M		$SD_{between}$		SD_{within}		test statistic		ICC
	rMDD	HC	rMDD	HC	rMDD	HC	*T(df)*	*p*	
Mindwandering	0.37	0.22	0.25	0.20	0.42	0.36	3.60 (107.6)	< .001	0.55
Mentalshift	2.44	1.37	1.11	0.47	1.06	0.59	6.69 (74.0)	< .001	0.41
Problems									
Cortisol	1.84	1.91	0.41	0.37	0.96	0.98	-1.02 (114)	.312	0.10

Note. $N\_{Persons}$ = 119, $N\_{measurement\ occasions}$ = 2504. *M* = estimated mean values from t-tests for independent samples using the person-level dataset, *SD* = standard deviaton, *ICC* = intraclass correlation coefficient. Cortisol data was log-transformed and winsorized to 3 SDs of the sample mean.

Effects of Traits on Cortisol

RNT predicted higher cortisol levels (*b* = 0.01, *SE* = 2.81E-3, *p* = .031), while mindfulness had no significant main effect on cortisol (*b* = -3.70E-3, *SE* = 3.19E-3, *p* = .251). Group status moderated the effects of RNT (*b* = 0.01, *SE* = 0.01, *p* = .043) but not of mindfulness (*b* = -0.01, *SE* = 0.01, *p* = .196) on cortisol, with stronger effects in rMDD patients compared to HCs (see Table 3.2).

In additional analyses, we explored if the effects of habitual modes of thinking on cortisol in daily life were moderated by current depression levels and found no significant moderation on either the association between RNT and cortisol (*b* = -2.96E-4, *SE* = 2.42E-4, *p* = .224), nor on the association between mindfulness and cortisol (*b* = -1.58E-4, *SE* = 2.30E-4, *p* = .493).

Effects of States on Cortisol

At the WS-level, state mindwandering (*b* = 0.08, *SE* = 0.03, *p* = .003) and mentalshift problems (*b* = 0.03, *SE* = 0.01, *p* = .014)[4] predicted an increase in cortisol levels 20 min later (see Table 3.3, main effect models). The interaction models revealed no moderation of group status on neither the effect of mindwandering (*b* = -0.09, *SE* = 0.05, *p* = .092) nor of mentalshift problems on cortisol (*b* = -0.01, *SE* = 0.03, *p* = .571; see Table 3.3).

At the BS-level, neither mindwandering (*b* = 0.12, *SE* = 0.16, *p* = .455) nor mentalshift problems (*b* = 0.02, *SE* = 0.04, *p* = .640) showed a significant main effect on cortisol release (see Table 3.3), main effect models). Group status did not moderate the association of person-level mindwandering (*b* = -0.09, *SE* = 0.32, *p* = .776), but of person-level mentalshift problems with cortisol release (*b* = 0.23, *SE* = 0.11, *p* = .050). Higher levels of mentalshift problems more strongly predicted higher cortisol levels in rMDD patients compared to HCs (see Table 3.3, interaction effect models).

[4] In sensitivity analyses conducted in R, which included eating, drinking, smoking, physical activity, sleep duration in hours, subjective sleep quality, hormonal contraceptive intake, biological sex, age, comorbidity, current psychotherapy and psychotropic or other medication intake as covariates, we found the main effects of trait RNT (*b* = -0.01; *SE* = 3.02E-3; *p* = .048), state mindwandering (*b* = 0.08, *SE* = 0.03, *p* = .003) and state mentalshift problems (*b* = 0.03, *SE* = 0.01, *p* = .015) on cortisol release to remain significant.

Table 3.3

Effects of Trait and State Cognitions on Momentary Cortisol in Daily Life (separate models)

	Main effect models			Interaction models		
	B	*SE*	*p*	*B*	*SE*	*p*
Traits						
group[a]	-0.15	0.08	.080	-0.11	0.09	.193
RNT	0.01	2.81E-3	.031	2.47E-3	0.01	.624
RNT*group	-	-	-	0.01	0.01	.043
group[a]	-0.11	0.09	.222	-0.11	0.09	.232
Mindfulness	-3.70E-3	3.19E-3	.251	7.86E-4	4.70E-3	.867
Mindfulness*group	-	-	-	0.01	0.01	.196
States						
group[a]	-0.08	0.08	.284	-0.08	0.08	.282
Mindwandering (WS)	0.08	0.03	.003	0.12	0.04	.001
Mindwandering (BS)	0.12	0.16	.455	0.17	0.25	.486
Mindwandering (WS)*group	-	-	-	-0.09	0.05	.092
Mindwandering (BS)*group	-	-	-	-0.09	0.32	.776
group[a]	-0.09	0.09	.309	-0.01	0.09	.898
Mentalshift problems (WS)	0.03	0.01	.014	0.04	0.02	.084
Mentalshift problems (BS)	0.02	0.04	.640	-0.17	0.11	.108
Mentalshift problems (WS)*group	-	-	-	-0.01	0.03	.571
Mentalshift problems (BS)*group	-	-	-	0.23	0.11	.050

Note. RNT = repetitive negative thinking. WS = within-subject (person-mean centered), BS = between-subject (grand-mean centered). All models include random intercepts at level-2, the linear and the quadratic time effect (i.e., time of saliva collection since awakening) as covariates. Level-1 predictor models were further adjusted for the occurrence of negative daily events (WS, BS). Cortisol data was log-transformed and winsorized to 3 SDs of the sample mean. [a] Reference category: healthy control

Again we run additional analyses, investigating a potential moderator role of current depression levels on the effects of state cognitions (WS) on cortisol 20 min later. We found no significant moderation effect on either the effect of mindwandering (b = -2.69E-3, SE = 2.05E-3, p = .191) or of mentalshift problems on cortisol release 20 min later (b = -3.18E-4, SE = 8.50E-4, p = .709; see Table 3.3).

Mediation Models

Additional linear mixed models required for the mediation analyses revealed that trait RNT significantly predicted higher state mindwandering (b = 0.03, SE = 0.01; p = .009) and mentalshift problems (b = 0.03, SE = 0.01; p < .001). Consequently, we calculated two 2-1-1 mediations via MSEM. In these mediation models RNT ($ps \leq .026$), as well as both state mindwandering (p = .001) and mentalshift problems (p = .013) significantly predicted higher cortisol levels. However, we found no significant indirect effects of mindwandering (p = .934) or mentalshift problems (p = .524) on the association of RNT with cortisol (see Figure 3.1a+b).

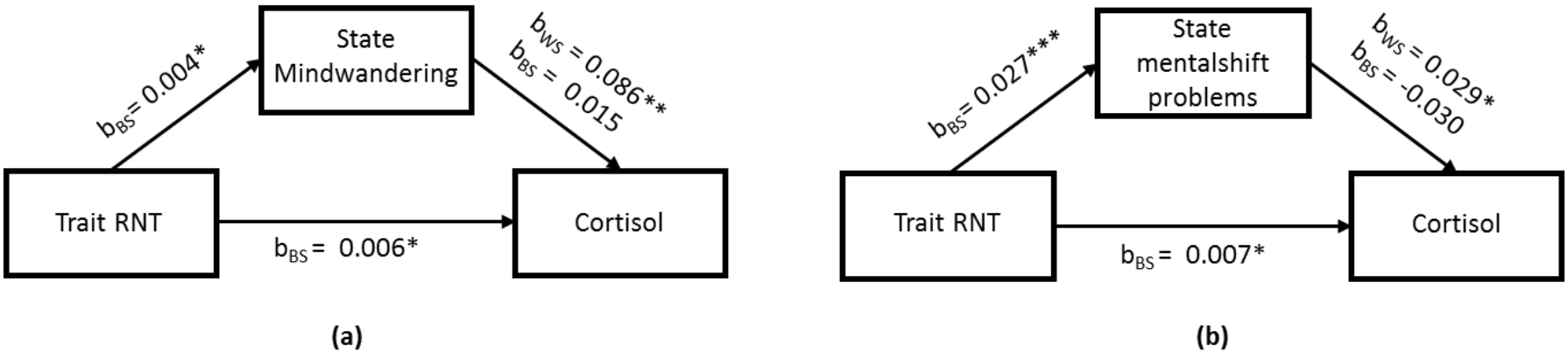

Figure 3.1 Mediation Analyses – Indirect Effects of State Mindwandering and Mentalshift Problems on the Association Between Trait RNT and Cortisol Release

Note. Indirect effects: b_{model_a} = -0.000, p_{model_a} = .934; b_{model_b} = -0.001, p_{model_b} = .524. Total effects: $b_{model\_a,}$ = 0.006, $p_{model\_a,}$ = .020; $b_{model\_b,}$ = 0.006, $p_{model\_b,}$ = .020. MSEMs include group, occurrence of negative daily event (WS, BS) and linear and quadratic time of cortisol collection since awakening as covariates. RNT = repetitive negative thinking. WS = within-subject, BS = between-subject. Cortisol data was log-transformed and winsorized to 3 SDs of the sample mean.*** $p < .001$; ** $p < .01$; * $p < .05$.

3.5 Discussion

Effects of Traits on Cortisol

The finding of higher RNT predicting higher cortisol release in daily life supports the Perseverative Cognition Hypothesis, stating that individuals with greater RNT tendencies show heightened physiological activation (cf. Ottaviani et al., 2016). The predictive value of RNT hints to a potential transdiagnostic nature of the link between perseverative cognitions and cortisol release. The reported effect was stronger in patients with recurrent major depression compared to healthy individuals, indicating their greater physiological vulnerability toward habitual maladaptive thinking.

In contrast, habitual mindfulness showed no effect on cortisol release (see also Nayman et al., 2022). One explanation for these null-findings might be the multi-faceted nature of mindfulness. While we assessed awareness of the present moment using the MAAS, mindfulness also includes acceptance, which is discussed to be a main driving force in reducing biological stress-responses (Manigault et al., 2018a). Moreover, habitual mindfulness might exert effects on cortisol only in the presence of acute stress (Manigault et. al., 2018b).

Effects of States on Cortisol

State mindwandering and mentalshift problems were linked to increases in cortisol activity 20 min later, independent of clinical status. Furthermore, we found that particularly in the patient group, those individuals who tended to experience overall higher levels of mental shift problems also tended to experience higher cortisol levels in daily life. Thus, our results show that mentalshift problems affect cortisol release in daily life both at the within-subject and between-subject level with stronger effects of higher levels of mental shift problems on cortisol release in the patient group, again pointing to heightened physiological vulnerability.

The context of state cognitions such as stressful situations might play an important role for cortisol release (e.g., Linz et al., 2021). However, since we adjusted for negative daily events, we showed that

the effects of state mindwandering and mentalshift problems were independent of daily life stressors (see Huffziger et al., 2013, for similar results on daily rumination and cortisol).

Traits and States show Independent Effects on Cortisol

The fact that the effects of habitual RNT on cortisol were not mediated by state cognitions suggests independent mechanisms of cognitive trait and state factors linked to HPA axis activity during daily life.

State cognitions operate immediately eliciting intraindividual increases in cortisol on the micro-level. Since cortisol activates metabolism (Chojnowska et al., 2021), such *within-person* cortisol increases could be interpreted as a "boost" in energetic arousal and helpful handling stressful experiences in the short term. Consequently, one might assume an increase in cortisol toward preceding state mind-wandering and mentalshift problems – observed to a similar degree in patients with recurrent major depression and HCs - would be an adaptive endocrinological response to internal cognitive stressors. However, while cortisol release as a response to physical stressors helps the individual to mobilize activity, psychological stressors such as maladaptive cognitions are considered biologically unjustified since resources are mobilized for activity that cannot be converted physically (cf. Turner et al., 2020). Therefore, a repeated activation of cortisol in response to these internal stressors during daily life (as demonstrated for mindwandering and mentalshift problems in the present study) may be regarded as disadvantageous.

Irrespective of its short-term purpose, a constant activation of the stress-system over longer periods, has been discussed as an important mechanism linking stress to disease (Weber et al., 2022). Indeed, sustainably high cortisol levels have been linked to hippocampal damage, resulting in HPA axis inhibition failure, which in turn exposes the individual to progressively higher cortisol levels (cf. Degering et al., 2023). Along these lines, one could speculate that *between-persons*, individuals with higher levels of internal habitual modes of thinking such as RNT, show impeded stressor-recovery linked to HPA axis dysfunction, resulting in sustained higher cortisol levels. The stronger link between habitual RNT

and cortisol in individuals with recurrent major depression might reveal prognostic information about the course of illness, which needs to be dissolved in future research.

Limitations

The present study has some limitations. First, even though we collected saliva cortisol 20 min after the subjective assessment of state cognitions, which has some methodological advantages (Stoffel et al., 2021), we cannot draw reliable conclusions about the causality of the association between state cognitions and cortisol 20 min later. Second, compliance rates were high in both groups, however, our attempt to monitor the exact timing of saliva collection was limited and we cannot rule out the possibility that individual saliva probes were not collected directly at the indicated time. Saliva probes with electronic caps recording their opening time might help to surpass this problem (Adam & Kumari, 2009; Schlotz, 2019; Stoffel et al., 2021), but are an expensive alternative. Another more economical solution would be to present participants digit codes via their study smartphone together with the saliva collection prompt, and ask them to record the code on the saliva collection container (Beddig et al., 2019; Schlotz, 2019). Such more objective measures of adherence could increase compliance (Stoffel et al., 2021) and consequently study quality (Kudielka et al., 2003) and may help to avoid underestimation of effect sizes (see Adam et al., 2017). Moreover, informing participants about compliance monitoring has been shown to increase sampling accuracy (cf. Stalder et al., 2022; Stoffel et al., 2021). Third, we did not assess the menstrual cycle phase, which has shown to be a possible confounder for salivary cortisol levels (Schlotz et al., 2019). Fourth, we assessed state cognitions without considering the context in which these cognitions occurred. Future research could profit from simultaneous assessment of current activities or settings. This could be realized either by subjective assessments or more objectively via upcoming AA-techniques such as mobile sensing (Kubiak & Smyth, 2019; Schick et al., 2022). Lastly, with respect to clinical status, our sample of patients with recurrent major depression was heterogeneous, with the majority being currently in remission. In order to improve

our understanding of HPA axis activity and its associations with either acute depressive symptomatology or underlying risk, a differentiation between patients with current and remitted major depression with a larger sample would be insightful.

Conclusions

In sum, we provided first evidence for trait and state cognitive processes to be independently associated with cortisol release in the daily life of patients with recurrent major depression and healthy individuals, and showed a higher physiological vulnerability toward habitual maladaptive thinking in patients with recurrent major depression. In fact, habitual RNT has been implicated in the development, maintenance, and recurrence of major depressive episodes and depressive symptomatology (cf. Watkins, 2022). Our study gives first indications that a permanent hyperactivation of the HPA axis in response to RNT may contribute to a poor clinical course of depression, thereby adding to existing evidence on adverse physiological consequences of RNT in other health conditions (Watkins, 2022). In the context of intervention studies aiming at reducing RNT, such as mindfulness-based interventions (e.g., van der Velden et al., 2023) or RNT-focused cognitive behavioral therapy (cf. Watkins, 2016), it would be important to investigate whether a decrease in RNT is paralleled by a normalization of HPA axis activity during daily life. The study by Beddig et al. (2020) provides a first clue that a mindfulness-based intervention may buffer against heightened HPA activation in patients who respond to the intervention with larger improvements in momentary rumination during daily life.

A mechanism discussed as a contributing factor in both habitual RNT (Watkins, 2022) and mentalshift problems during daily life (e.g., Marcusson-Clavertz et al., 2022) is poor executive control, demonstrated by difficulties in updating, inhibiting, and shifting of working memory contents. Given the demonstrated consistent associations between mentalshift problems with heightened cortisol release both at the within- and between-subject level in the present study, particularly in the patient sample, one could speculate that interventions aiming at improving executive control and cognitive flexibility, which has already been shown - although with small effect sizes – for mindfulness based interventions

(cf. Im et al., 2021), might also reduce cortisol release during daily life. A more in-depth analysis of the interplay of changes in psychological and psychoendocrinological parameters and possible related underlying mechanisms in future intervention studies may help to shed more light on possible causal links in the association between dysfunctional modes of thinking and HPA axis activity during daily life.

CHAPTER IV: REACTIVITY TOWARD DAILY EVENTS: INTRAINDIVIDUAL VARIABILITY AND CHANGE IN RECURRENT DEPRESSION – A MEASUREMENT BURST STUDY (STUDY 3)

An adapted version of this chapter has been published as “Schricker, I. F., Nayman, S., Reinhard, I., & Kuehner, C. (2023). Reactivity toward daily events: Intraindividual variability and change in recurrent depression–A measurement burst study. *Behaviour Research and Therapy*, *168*, 104383.“

4.1 Abstract

In Major Depressive Disorder, first evidence shows heightened mood-reactivity toward daily events. Related longitudinal studies in remitted patients with recurrent major depression are lacking. Long-term changes in such short-term within-person associations can be analysed via measurement burst designs. Two bursts, separated by approximately 4.4 years, consisted of a baseline session and an Ambulatory Assessment (burst-1: 3 days, burst-2: 5 days). Via smartphone, 54 initially remitted patients with recurrent major depression indicated their negative and positive affect, rumination, self-acceptance, and the occurrence of negative and positive daily events ten times and collected saliva cortisol samples five times per day. In bursts with higher depression levels, patients showed blunted negative affect- and cortisol-reactivity and stronger decreases in positive affect and self-acceptance toward negative daily events, as well as stronger increases in self-acceptance following positive daily events. However, patients with higher depression levels demonstrated stronger ruminative stress-reactivity within bursts. Furthermore, patients with higher depression levels showed an increase of affective stress-reactivity over bursts, such that negative affect more strongly increased and positive affect more strongly decreased following negative daily events over bursts. Following positive daily events, patients with higher depression levels showed stronger decreases in negative affect within bursts and a decrease of self-acceptance-reactivity over bursts. To conclude, measurement burst designs enable to examine intraindividual variability and change of micro-level processes, and possible

moderators thereof, potentially providing prognostic information for the course of recurrent major depression.

4.2 Introduction

Depending on the number of previously experienced major depressive episodes, patients in remission from major depression have a risk of about 40-90% for further episodes (Bockting et al., 2015). Consequently, patients currently remitted from recurrent episodes represent a particular high risk group for further recurrences. In order to develop suitable prevention strategies in the longer term, it seems therefore crucial to identify possible vulnerability and protective factors for the course of recurrent depression. Aside from rather stable or slow-scale vulnerability factors (e.g., childhood maltreatment, former depressive episodes, residual symptoms; for an overview see Buckman et al., 2018, Struijs et al., 2021), researchers have shifted their focus more recently toward short-term dynamic within-person processes that occur in the daily life of patients with major depression and which may be associated with longer-term clinical outcomes (e.g., Panaite et al., 2020; Timm et al., 2017). Ambulatory Assessment is a powerful tool to capture such dynamic processes at the micro-level within individuals in real-time, thereby minimising retrospective bias and increasing ecological validity of these assessments (Trull & Ebner-Priemer, 2020).

Ambulatory Assessment covers intensive repeated assessments of such micro-processes during daily life for a given time-window (e.g., a certain number of days). For a longitudinal perspective, a measurement burst approach, incorporating repeated “waves” (bursts) of such intensive shorter measurement phases (cf. Sliwinski, 2008; Stawski et al., 2015) is able to mirror both within-burst variability *and* intraindividual changes in these micro-processes over longer periods of time.

While this approach has largely been applied in studies investigating age-related developmental processes (see for example Blaxton et al., 2020; Sliwinski et al., 2009), its application in clinical psychological science (e.g., for assessing long-term changes in stress reactivity during daily life in clinical popu-

lations) are completely lacking so far. In the present measurement burst study, we will focus on affective, cognitive, and physiological reactivity toward daily events and their longitudinal change in initially remitted patients with recurrent depression.

Due to a lack of longitudinal research, the following overview on existing studies examining daily life reactivity in patients with major depression is restricted to cross-sectional findings from Ambulatory Assessment studies, with a focus on studies reporting on remitted depressed patients.

Stress-Reactivity toward Negative Events in Daily Life in Patients Remitted from Major Depression

One possible vulnerability factor for depressive relapses and recurrences might be a heightened reactivity toward daily stressful events (Monroe et al., 2019; Santee & Starr, 2022). In Ambulatory Assessment research, momentary stress-reactivity in daily life in response to negative *daily* events (mostly minor events, daily hassles) is assessed multiple times per day, and is commonly operationalised as a within-person coupling of a negative daily event with a subsequent affective, cognitive or physiological outcome.

Most studies to date looked at *affective* stress-reactivity in currently depressed patients with ambiguous findings, reaching from blunted (Peeters et al., 2003b) or comparable (Bylsma et al., 2011; Thompson et al., 2012) to increased affective reactivity (Sheets & Armey, 2020) compared to healthy individuals.

In contrast, research on affective stress-reactivity in daily life in patients remitted from major depression are extremely rare. Three studies showed affective reactivity toward negative daily events to be increased (Lamers et al., 2018; Schricker et al., 2023; Wichers et al., 2009), while others found individuals in remission to show negative affect reactivity similar to healthy individuals (van Winkel et al., 2015)

Not only heightened negative and lowered positive affect, but also a frequent occurrence of maladaptive cognitions such as rumination has been reported in remitted depressed patients (e.g., Hjartarson et al., 2022; Struijs et al., 2021). While there is already evidence that *cognitive reactivity* toward negative daily events – yet assessed via retrospective questionnaires – predicts depression maintenance

and relapses or recurrences (cf. Cole et al., 2021), respective Ambulatory Assessment studies are sparse. Initial findings point to increased rumination-reactivity following negative daily events in remitted patients with recurrent major depressive episodes (Schricker et al., 2023), similar to those with current major depression (Kircanski et al., 2018).

In order to portray a physiological reaction to negative daily events, endocrinological stress parameters such as salivary cortisol have been shown to be suitable, since sample collection can be easily integrated into individuals' daily lives (Schlotz, 2019). However, the investigation of *cortisol-reactivity* in patients remitted from major depression has been neglected so far. First findings on patients with current major depression denote a blunted cortisol reaction (i.e., weaker or no cortisol increase) in response to negative daily events compared to healthy individuals (Peeters et al., 2003a).

While all these various studies aimed to capture within-person stress-reactivity, different operationalisations for the assessment of daily events were used, such as dichotomous items asking whether a negative event had occurred since the last prompt, (e.g., Sheets & Armey, 2020) or items asking about the most stressful event that had occurred since the last prompt (e.g., Lamers et al., 2018). Besides differences in study designs, patient samples were defined differently (e.g., clinically diagnosed via structural clinical interviews or via self-reports using depression rating scales). Moreover, previous studies did not regularly decompose reactivity variance into within- and between-subject variation as is recommended for multilevel models (Wang & Maxwell, 2015). This lack of statistical comprehensiveness might account at least partially for inconsistent findings (cf. Cole et al., 2021).

Reactivity toward Positive Daily Events in Patients Remitted from Major Depression

Research on anhedonia, one of the two hallmark symptoms of depression (American Psychiatric Association, 2013), emphasises the role of positive experiences (cf. Santee & Starr, 2022). In fact, reactivity toward positive daily events could act as a countervailing force against the impact of negative daily events on affect.

With respect to *affective reactivity*, a so called 'mood brightening' effect has been identified in currently depressed and in remitted depressed patients (Bylsma et al., 2011; Khazanov et al., 2019;

Lamers et al., 2018; Schricker et al., 2023), reflecting stronger increases in positive affect and stronger decreases in negative affect toward positive daily events compared to healthy controls.

In parallel, a 'cognition brightening' effect has been recently proposed (Schricker et al., 2023). This *cognitive reactivity* is expressed by stronger decreases in rumination and stronger increases in positive thoughts toward positive daily events in both currently depressed (Khazanov et al., 2019) and in remitted depressed patients (Schricker et al., 2023).

Beneficial effects of positive events on mood and cognitions could also be reflected by momentary cortisol decreases. However, analogous to cortisol-related stress-reactivity, *cortisol-reactivity* toward positive daily events is understudied in remitted depressed patients. One study so far reported a lack of cortisol-reactivity both in patients with current major depression and healthy individuals (Peeters et al., 2003a).

The Present Study – A Measurement Burst Study

The present study investigates reactivity toward negative and positive daily events and their intraindividual change over time in a cohort of initially remitted depressed patients with a history of recurrent major depression. Trajectories in micro-level processes such as stress-reactivity over longer periods could reflect digital phenotypes providing unique information associated with the clinical course of the disorder at the macro-level (e.g., regarding recurrences or chronification). This holds true in particular for those individuals with recurrent episodes whose risk for further episodes progressively increases (cf. Moriarty et al., 2022) and for whom it can be expected that clinical depression levels will vary substantially over time. These patients underwent a measurement burst study with two bursts separated by about 4.4 years. As stated above, a measurement burst design enables researchers to investigate within-burst variability and intraindividual change in micro-level processes over bursts (i.e., over longer periods), as well as between-person differences in both (Myin-Germeys & Kuppens, 2021). Furthermore, variables measured on different time-scales can be integrated into one model (Stawski et al., 2019). Since we expected clinical depression levels to change over bursts in the present patient

sample, these levels were investigated as a possible relevant moderator affecting short- and long-term reactivity.

Aims

The present study aims to examine hypothesis driven as well as exploratory research questions. (1) We expected event-congruent affective, cognitive and cortisol-reactivity toward daily events within bursts, (2) aimed to explore a possible moderation role of depression levels on reactivity toward daily events within bursts, and (3) aimed to explore the moderation role of depression levels on intraindividual change in reactivity over bursts, in a clinically diagnosed sample of patients initially remitted from recurrent major depressive episodes.

4.3 Materials and Methods

The present study is a measurement burst study that was built upon two bursts with a mean interval of 4.4 years (range: 3.2 - 5.9 years).

Participants

We re-recruited a sample of recurrently depressed patients from a previous study (Timm et al., 2018, *N* = 78, burst-1) for a follow-up (burst-2). Fifty-four patients from burst-1 agreed to participate in burst-2. All patients had been treated in a clinical in- or outpatient setting and were in remission at burst-1. At burst-1, the following inclusion criteria were applied: a) lifetime episodes of ≥ 2 major depressive episodes according to DSM-IV, b) currently not fulfilling the criteria for a major depressive episode for at least the previous two months prior to study entry, and c) not fulfilling lifetime criteria for a non-affective psychotic or bipolar disorder. For burst-2, all willing participants of burst-1 were included irrespective of their current depression status.

Demographics and clinical characteristics of the final sample of *N* = 54 initially remitted recurrent depressed patients are described in Table 4.1. Non-completers (*N* = 24) did not significantly differ from

the present completer sample with respect to clinical variables at burst-1 (i.e., depression levels, number of previous depressive episodes; all *ps* ≥ .436) and aggregated Ambulatory Assessment variables at burst-1 (i.e., negative and positive affect, rumination, self-acceptance, frequency of negative/positive events, cortisol levels; all *ps* ≥ .127).

Table 4.1

Descriptive Demographic and Clinical Characteristics of the Sample of Patients Initially (at Burst-1) Remitted from Recurrent Depression (N = 54) by Burst

Variables	burst 1 %/ *M (SD)*	burst 2 %/ *M (SD)*	*p*-values
Demographic characteristics			
Age	39.8 (11.4)	44.17 (11.4)	-
% female	70.4%	70.4%	-
Education	70.4 %	70.4%	1.00[a]
(% with high school degree)			
Work situation	75.9 %	74.1%	1.00[a]
(% in regular job or education)			
Marital Status	55.6 %	53.7 %	1.00[a]
(% married or living together)			
Clinical Variables			
≥ 3 lifetime MDEs (%)	75.9%	87.0%	.031[a]
current MDE	0%	14.8%	.008[a]
% experiencing MDE(s)		66.7%	-
after burst-1			
Previous inpatient treatments (%)	46.3%	46.3 %	1.00[a]
BDI-II	8.82 (9.59)	12.35 (11.12)	.002[b]
MADRS	5.02 (5.12)	9.18 (8.45)	.999[b]
Current psychotherapy	11.1 %	42.6 %	< .001[a]
Current psychotropic medication	16.7 %	24.1 %	.388[a]

Note. BDI-II = Beck Depression Inventory Revised, MADRS = Montgomery-Asberg Depression Rating Scale, MDE = Major Depressive Episode. [a] McNemar test. [b] paired t-test for dependent variables.

Procedure

In each burst, participants underwent a baseline session followed by an Ambulatory Assessment phase. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants provided written informed consent and were financially compensated for completing the study.

In the following, we will describe the baseline and Ambulatory Assessment procedures, which were identical for the two bursts except for the length of the Ambulatory Assessment phase, lasting 3 consecutive days at burst-1 and five consecutive days at burst-2.

Baseline Measures

Psychopathology. At burst-1, eligible individuals were invited for an in-person session at the Central Institute of Mental Health in Mannheim, Germany for the assessment of demographic and clinical variables. A trained clinical psychologist administered the Structured Clinical Interview for DSM-IV-TR axis I (SCID-I, German version: Wittchen et al., 1997) in order to assess in- and exclusion criteria, as well as lifetime and current psychopathology. At burst-2, the SCID-I was re-administered.

Depression Symptom Levels. The self-rated Beck Depression Inventory Revised (BDI-II, German version: cf. Kuehner et al. 2022) and the interviewer-rated Montgomery-Asberg Depression Rating Scale (MADRS; Neumann & Schulte, 1989) were used to assess depressive symptom levels at burst-1 and at burst-2. Internal consistencies of both scales were high (BDI-II: $\alpha_{burst\text{-}1}$ and $\alpha_{burst\text{-}2}$ = .94; MADRS: $\alpha_{burst\text{-}1}$ = .82, $\alpha_{burst\text{-}2}$ = .90). For statistical analyses, a composite score for depressive symptom levels was computed by averaging the z-transformed BDI-II and MADRS scores, as done in previous research (e.g., Huffziger et al., 2013; Timm et al., 2017).

Ambulatory Assessment Phase

The Ambulatory Assessment phase started on different weekdays using study-smartphones with the software movisensXS (movisens GmbH, Karlsruhe, Germany). Following a semi-random sampling scheme (Dejonckheere & Erbas, 2021), participants were signaled ten times per day within stratified

90-min windows (min. 60 min - max. 90 min) between 08:00 am and 10:00 pm, except for the fixed first prompt at 08:00 am each day. A delay option for 20 min maximum was offered, in case participants were not able to respond to prompts right away. Assessments which were not completed within this 20-min interval were coded as missing.

Subjective Ambulatory Assessment Measures. At each assessment, participants rated their subjective experiences of affect and cognitions, and indicated if a negative or positive daily event had occurred since the last signal (see Table 4.2). Items were derived from the PANAS (Watson et al., 1988) and from previous Ambulatory Assessment studies (e.g., Beddig et al., 2020; Nayman et al., 2022; Timm et al., 2017). Subjective reactivity was estimated for each prompt, referring to the occurrence of daily events since the last assessment (i.e., within the preceding 90 min).

Saliva Cortisol. Cortisol samples were collected 20 min after every second prompt, resulting in five saliva samples per day. Participants were instructed not to eat, drink anything but water, smoke, physically exercise, and brush their teeth during the 20 min time interval before saliva collection (Schlotz, 2019). Immediately after saliva collection, they were asked whether they had eaten, drunk anything but water, smoked or brushed their teeth (dichotomous items *yes/no* each) and to what extent they were physically active (seven-point Likert scale, 1 = *not at all* to 7 = *very much*) during the last 20 min. Cortisol-reactivity was estimated for every second prompt, referring to the occurrence of daily events within the preceding 90 min + 20 min time lag for saliva collection (cf. Aguilar-Raab et al., 2021; Schlotz, 2019; Stoffel et al., 2021). Only those assessments of negative and positive daily events were included for cortisol-related analyses which were prompted 20 min preceding saliva collection, resulting in five estimates of cortisol-reactivity per day.

Saliva probes were stored in participants' home freezers until return to the lab, where samples were frozen at -20°C until the biochemical analysis at Dresden LabService GmbH, Germany. After thawing, salivettes were centrifuged at 3,000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence im-

munoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 9%. In order to adjust for skewness, cortisol raw data were log-transformed. Furthermore, outliers above 3 SDs of the sample mean were winsorised to 3 SDs (cf. Schlotz, 2019).

Table 4.2

Ambulatory Assessment Items

Construct	*N*	Items	Scale	Range	Reliability	
					burst-1	burst-2
Negative Affect	6	*I feel upset*, *irritated*, *nervous*, *listless*, *down*, *bored*.	7-point Likert scale	1 (*not at all*) to 7 (*fully agree*)	W-S reliability: .57	W-S reliability: .61
					B-S reliability (across bursts): .998	
Positive Affect	6	*I feel cheerful*, *energet*ic, *enthusiastic*, *satisfied*, *relaxed* and *calm*.	7-point Likert scale	1 (*not at all*) to 7 (*fully agree*)	W-S reliability: .63	W-S reliability: .67
					B-S reliability (across bursts): .998	
Rumination	1	*At the moment before the beep, I was stuck on negative thoughts and could not disengage from them.*	7-point Likert scale	1 (*not at all*) to 7 (*fully agree*)	-	
Self-Acceptance	1	*At the moment, I accept myself as I am.*	7-point Likert scale	1 (*not at all*) to 7 (*fully agree*)	-	
Negative and Positive Daily Event	1 each	*Did you experience a negative/positive event since the last prompt?*	dicho-tomous	yes/no	-	

Note. W-S: within-subject, B-S: between-subject. W-S reliability reflects reliability of within-person fluctuations (Neubauer & Schmiedeck, 2020) and B-S reliability represents the reliability of a person's average scores.

Statistical Analyses

Given the nested data structure (i.e., assessments are nested within bursts, which in turn are nested within persons) we ran multilevel models using full maximum likelihood estimation in IBM SPSS version 28 and R Version 4.1.2 (R Core Team, 2021). Reactivity was modeled as the within-person coupling of a negative or positive daily event with a subjective (negative affect (NA), positive affect (PA), rumination, self-acceptance) or endocrinological (cortisol) outcome.

In all three-level models, level-1 predictors (e.g., occurrence of a negative daily event) and burst-level (level-2) predictors (e.g., depression levels) were person-mean centered, which is recommended in order to arrive at an unbiased estimate of the within-person effects (Neubauer & Schmiedeck, 2020). Consequently, level-1 predictors reflect only variation across assessments and across bursts within a person, and level-2 predictors reflect only variation across bursts within a person. The person-means at level-3 were centered around the grand-mean across all assessments, all bursts and all persons.

Exemplarily, the occurrence of a negative daily event (level-1 predictor) was included on all three levels into our models: a) on the assessment-level, where each subjective assessment was centered around the person-mean (W-S1; $neg\_event_{ijk} – neg\_event_{..k}$), b) on the burst-level, where the person-mean per burst was centered around the person-mean across bursts (W-S2; $neg\_event_{.jk} – neg\_event_{..k}$), and c) on the person-level (between-subject level; B-S), where the person-mean of the level-1 predictor was centered around the grand-mean ($neg\_event_{..k} – neg\_event_{grandmean}$). As also shown in Equation 1, neg_event_{ijk} represents the reported negative daily event of a person *k* in burst *j* at the assessment point *i.*

Equation 1 shows an example of one final multilevel model including a three-way cross-level interaction of *burst*moderator*predictor* (here: burst*depression levels (B-S)*occurrence of a negative daily event (neg_event; W-S1) predicting negative affect (NA)).

Level-1 (assessment point level):

$$Y\ (NA)_{ijk} = \pi_{0jk} + \ \pi_{1jk} * (neg\_event_{ijk} - neg\_event_{..k}) + \ \varepsilon_{ijk}$$

Here, Y_{ijk} represents the level of negative affect at assessment point *i* at burst *j* for person *k*. The π coefficients represent the intercept and the fixed main effects at level 1; the ε_{ijk} denote the residuals at level 1.

Level-2 (burst level):

$$\begin{aligned}\pi_{0jk} = \beta_{00k} + \ \beta_{01k} * burst_{jk} + \beta_{02k} * (neg\_event_{.jk} - \ neg\_event_{..k}) \\ + \ \beta_{03k} * (depression\ levels_{jk} - \ depression\ levels_{.k}) \\ + \ \beta_{04k} * study\ day + \ u_{0jk}\end{aligned}$$

$$\pi_{1jk} = \beta_{10k} + \ \beta_{11k} * burst_{jk}$$

with the u_{0jk} representing random intercepts for burst *j* within person *k*.

Level-3 (person level):

$$\begin{aligned}\beta_{00k} = \gamma_{000} + \ \gamma_{001} * (neg\_event_{..k} - \ neg\_event_{grandmean} \ + \ \gamma_{002} * (depression\ level_{.k} \\ - \ depression\ levels_{grandmean}) \\ + \ \gamma_{003} * (time\_weeks\_burst_{.k} - \ time\_weeks\_burst_{grandmean}) + \ v_{00k}\end{aligned}$$

$$\beta_{01k} = \gamma_{010} + \ \gamma_{011} * (depression\ level_{.k} - \ depression\ levels_{grandmean})$$

$$\beta_{02k} = \gamma_{020}$$

$$\beta_{03k} = \gamma_{030}$$

$$\beta_{04k} = \gamma_{040}$$

$$\beta_{10k} = \gamma_{100} + \ \gamma_{101} * (depression\ level_{.k} - \ depression\ levels_{grandmean})$$

$$\beta_{11k} = \gamma_{110} + \ \gamma_{111} * (depression\ level_{.k} - \ depression\ levels_{grandmean})$$

All multilevel models included random intercepts at levels 2 and 3, allowing individual baseline levels of the dependent variables to differ between bursts and persons.

Multilevel models were run sequentially, by first estimating the main effects. In a next step, we added 2-way cross-level interactions of level-1 predictors (i.e., occurrence of daily events; W-S1) *by* depression levels (W-S2 and B-S) as possible clinical moderator variable. In the last step, 3-way cross-level interaction terms of level-1 predictors *by* depression levels (B-S) *by* burst were added[5]. Depression levels (W-S2) represent each person's deviance of depression levels per burst from their person-mean in depression levels over the two bursts, resulting in two estimates per person. The person-level variable of depression levels (B-S) represents the aggregated depression levels over the two bursts centered around the grand-mean, resulting in one estimate per person.

We checked beforehand for significant Ambulatory Assessment specific confounders and included study day into all models with subjective outcomes. For multilevel models with cortisol as outcome, we considered potentially influential covariates (i.e., time, time², eating, drinking, brushing teeth, smoking, physical activity, sleep quality, biological sex, age, and psychotropic medication). We found the linear time effect to be the only significant confounder ($p < .05$) and consequently retained time of saliva collection as a covariate in all subsequent analyses with cortisol as outcome. Models including 2- or 3-way interactions with burst were additionally controlled for time in weeks between bursts in order to adjust for the variance in time lag between the two bursts.

For all these analyses, the significance level was set at $\alpha = 0.05$.

4.4 Results

Compliance

Participants responded to in total 3836 out of possible 4320 assessment points, resulting in a high compliance rate across bursts (cf. Rintala et al., 2019; Vachon et al., 2019). The Ambulatory Assessment compliance rate was 88.3% at burst-1 and 89.1% at burst-2 for subjective assessments. Compliance for cortisol collection was 91.2% at burst-1 and 94.2% at burst-2.

[5] We always estimated the described 2-way and 3-way interactions - even if the lower order effect was non-significant - in order to not miss offsetting effects of the moderator(s).

Descriptives of Ambulatory Assessment Variables

Table S4 shows the means, within- and between-standard deviations, bivariate within- and between-subject correlations as well as the intraclass correlation coefficients (ICCs) per burst.

Ambulatory Assessment variables at burst-1 and burst-2 were compared on the person-level by paired t-tests. Negative daily events were reported at on average 14.5 % (*SD* = 0.15) of prompts at burst-1 and on 13.0% (*SD* = 0.09) at burst-2 ($t(47) = 0.73$, $p = .467$). Positive daily events were indicated at on average 26.3% (*SD* = 0.22) of prompts at burst-1 and on 24.8% (*SD* = 0.24) at burst-2 ($t(44) = 0.46$, $p = .924$). At both bursts, positive daily events were reported more frequently than negative ones (burst-1: $t(44) = -3.73$, $p < .001$; burst-2: $t(49) = -4.11$, $p < .001$).

Reactivity toward Daily Events within Bursts

Within bursts, patients reported higher levels of NA and rumination, and lower levels of PA and self-acceptance toward negative daily events (all *ps* < .001; see Table 4.3). Following positive daily events, higher PA and self-acceptance as well as lower NA and rumination were exhibited (all *ps* < .001, see Table 4). No significant cortisol-reactivity was identified, neither toward negative nor toward positive daily events (*ps* ≥ .241; see Tables 4.3 and 4.4).

Table 4.3

Depression levels (WS2, BS) as a Moderator of Intraindividual Variability and Change in Reactivity toward Negative Daily Events (separate models)

	Negative Affect			Positive Affect			Rumination			Self-Acceptance			Cortisol		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Step 1 – Main effects															
Level 1 – assessment level															
negative event (WS1)	0.87	0.03	< .001	-0.85	0.04	< .001	1.18	0.06	< .001	-0.49	0.04	< .001	0.03	0.04	.449
Level 2 – burst level															
burst[a]	0.33	0.10	.002	-0.14	0.10	.182	0.31	0.14	.027	-0.52	0.17	.003	0.45	0.06	< .001
negative event (WS2)	1.69	0.70	.019	-1.42	0.72	.053	1.98	0.93	.038	0.08	0.15	.945	-0.03	0.41	.939
depression level (WS2)	0.37	0.09	< .001	-0.34	0.09	< .001	0.40	0.11	< .001	-0.60	0.14	< .001	0.08	0.05	.125
Level 3 – person level															
negative event (BS)	1.09	0.93	.247	-1.21	0.90	.184	1.73	1.05	.105	-1.41	1.41	.323	-0.03	0.45	.952
depression level (BS)	0.72	0.12	< .001	-0.63	0.11	< .001	0.52	0.13	< .001	-1.11	0.18	< .001	0.05	0.06	.395
Step 2– 2-way CLIs															
burst[a]*negative event (WS1)	-0.26	0.08	.001	0.40	0.09	< .001	-0.14	0.13	.272	0.25	0.09	.007	-0.18	0.09	.056
burst[a]*depression level (BS)	-0.12	0.15	.432	-0.06	0.15	.690	-0.26	0.20	.196	0.10	0.24	.689	-0.22	0.08	.013
depression level (WS2)* negative event (WS1)	-0.24	0.07	.001	0.37	0.08	< .001	0.06	0.12	.606	0.33	0.09	< .001	-0.21	0.09	.012
depression level (BS)* negative event (WS1)	-0.01	0.05	.792	-0.01	0.06	.877	0.18	0.09	.038	-0.10	0.06	.120	0.11	0.06	.069
Step 3– 3-way CLIs															
burst[a]*depression level (BS)*negative event (WS1)	-0.50	0.12	< .001	0.45	0.13	< .001	-0.09	0.19	.638	0.24	0.14	.075	0.20	0.14	.146

Note. CLIs: cross-level interactions. WS1: within-subject (person-mean-centered), WS2: within-subject (person-burst-mean centered around the person-mean); BS: between-subject (centered around the grand-mean). Models include random intercepts at level 2 (burst) and 3 (person). Additional covariates were study day in all multilevel models with subjective outcomes, time of saliva collection in multilevel models with cortisol as outcome, and time in weeks between bursts in all step 2 and 3 models. [a] Reference category: burst-2.

Depression Levels (W-S2, B-S) as a Moderator of Reactivity toward Daily Events within Bursts

Depression levels at the within- (W-S2) and the between-subject (B-S) level moderated reactivity toward *negative daily events* (see Table 4.3). Depression levels (W-S2) significantly moderated NA-, PA-, self-acceptance- and cortisol-reactivity toward negative daily events. In bursts when patients reported higher depression levels (W-S2; compared to their person-mean), their NA-reactivity (F(1,3740) = 10.17, p = .001) and cortisol-reactivity (F(1,1657) = 6.31, p = .012) were reduced, while PA (F(1,3744) = 20.53, p <. 001) and self-acceptance (F(1,3733) = 14.33, p < .001) more strongly decreased following negative events. No significant moderation effect of depression levels (W-S2) on rumination-reactivity toward negative daily events was found (p = .606).

Depression levels (B-S) significantly moderated rumination-reactivity toward negative daily events (F(1,3748) = 4.29, p < .038). Patients with higher depression levels (B-S; compared to the grand-mean) reported stronger increases in rumination following negative daily events. Effects on other Ambulatory Assessment outcomes were nonsignificant (all p's > .069; see Table 4.3).

Regarding reactivity toward *positive daily events* (see Table 4.4), depression levels at the within-subject level significantly moderated self-acceptance-reactivity, such that in bursts with higher depression levels (W-S2), self-acceptance more strongly increased following positive events (F(1,3727) = 3.98, p = .046). Moderation effects on all other Ambulatory Assessment outcomes were nonsignificant (all ps > .210, see Table 4.4)

Depression levels at the between-subject level significantly moderated NA- and self-acceptance-reactivity (see Table 4). Patients with higher depression levels (B-S) showed stronger decreases in NA (F(1,3733) = -2.51, p = .012) and stronger increases in self-acceptance (F(1,3730) = 11.56, p < .001) following positive daily events. Moderation effects on other Ambulatory Assessment outcomes were nonsignificant (all ps > .500, see Table 4.4).

Table 4.4

Depression levels (WS2, BS) as a Moderator of Intraindividual Variability and Change in Reactivity toward Positive Daily Events (separate models)

	Negative Affect			Positive Affect			Rumination			Self-Acceptance			Cortisol		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Step 1 – Main effects															
Level 1 – assessment level															
positive event (WS1)	-0.40	0.03	< .001	0.57	0.03	< .001	-0.40	0.05	< .001	0.34	0.04	< .001	0.04	0.04	.241
Level 2 – burst level															
burst[a]	0.38	0.11	.001	-0.18	0.11	.114	0.37	0.15	.015	-0.52	0.16	.003	0.45	0.06	< .001
positive event (WS2)	0.18	0.59	.765	-0.11	0.59	.852	1.38	0.77	.078	0.56	0.87	.520	-0.10	0.32	.749
depression level (WS2)	0.45	0.09	< .001	-0.41	0.09	< .001	0.49	0.12	< .001	-0.63	0.14	< .001	0.08	0.05	.120
Level 3 – person level															
positive event (BS)	-0.50	0.43	.249	0.60	0.41	.147	-0.05	0.49	.921	0.91	0.63	.156	-0.14	0.20	.471
depression level (BS)	0.70	0.12	< .001	-0.60	0.12	< .001	0.53	0.14	< .001	-1.05	0.18	< .001	0.04	0.06	.502
Step 2– 2-way CLIs															
burst[a]*positive event (WS1)	-0.01	0.07	.883	-0.19	0.08	.015	0.07	0.18	.574	0.04	0.08	.578	-0.13	0.08	.096
burst[a]*depression level (BS)	0.00	0.17	.985	-0.16	0.16	.316	-0.10	0.22	.643	0.06	0.23	.791	-0.20	0.08	.016
depression level (WS2)* positive event (WS1)	-0.08	0.07	.210	0.01	0.07	.938	-0.05	0.11	.672	0.15	0.07	.046	0.01	0.08	.884
depression level (BS)* positive event (WS1)	-0.13	0.05	.012	0.03	0.05	.526	-0.06	0.08	.500	0.19	0.06	< .001	-0.01	0.06	.824
Step 3– 3-way CLIs															
burst[a]*depression level (BS)*positive event (WS1)	-0.12	0.11	.274	0.03	0.12	.831	-0.01	0.18	.954	0.52	0.12	< .001	0.07	0.12	.585

Note. CLIs: cross-level interactions. WS1: within-subject (person-mean-centered), WS2: within-subject (person-burst-mean centered around the person-mean); BS: between-subject (centered around the grand-mean). Models include random intercepts at level 2 (burst) and 3 (person). Additional covariates were study day in all multilevel models with subjective outcomes, time of saliva collection in multilevel models with cortisol as outcome, and time in weeks between bursts in all step 2 and 3 models. [a] Reference category: burst-2.

Intraindividual Change in Reactivity over Bursts

Over bursts (i.e., over an approximately 4.4 year period), we found significant intraindividual change in NA-, PA- and self-acceptance reactivity toward negative daily events. NA more strongly increased following negative daily events, while PA and self-acceptance more strongly decreased over bursts (all *ps* ≤ .007; see Table 4.3). We did not find significant intraindividual change in rumination-reactivity (p = .272) or cortisol-reactivity (p = .056; see Table 4.3). With respect to reactivity toward positive daily events, within-person reactivity remained intraindividually stable over bursts (all *ps* ≥ .096), except for an increase in PA-reactivity, such that PA more strongly increased toward positive daily events over bursts (p = .015; see Table 4.4).

Depression Levels (B-S) as a Moderator of Intraindividual Change in Reactivity over Bursts

Depression levels (B-S) significantly moderated intraindividual change in NA-reactivity (F(1,3739) = 18.51, p < .001) and PA-reactivity (F(1,3744) = 12.53, p < .001) toward *negative daily events*, but not change in cognitive or cortisol-reactivity (see Table 4.3). Post-hoc simple slope analyses revealed that patients with higher depression levels displayed an increase in NA-reactivity (t(3741) = -5.36, p < .001) and an increase in PA-reactivity (t(3746) = 5.64, p < .001), such that NA more strongly increased and PA more strongly decreased toward negative daily events over bursts. In contrast, patients with lower depression levels demonstrated no intraindividual change in NA-reactivity (t(3729) = 0.60, p = .549) or in PA-reactivity (t(3732) = 0.90, p = .367) over bursts (see Figure 4.1a+b).

With respect to intraindividual change in reactivity toward *positive daily events*, depression levels (B-S) significantly moderated self-acceptance-reactivity (F(1,3726) = 17.44, p < .001), but not NA-, PA-, rumination- or cortisol-reactivity (all *ps* ≥ .274; see Table 4.4). Simple slope analyses revealed that patients with higher depression levels showed blunting self-acceptance-reactivity over time (t(3724) = -3.75, p < .001), insofar as those patients reported self-acceptance to less strongly increase following positive daily events over bursts. In contrast, patients with lower depression levels showed increased self-acceptance-reactivity over bursts (t(3728) = 2.28, p = .023; see Figure 4.1c), insofar as their self-acceptance more strongly increased toward positive events over bursts.

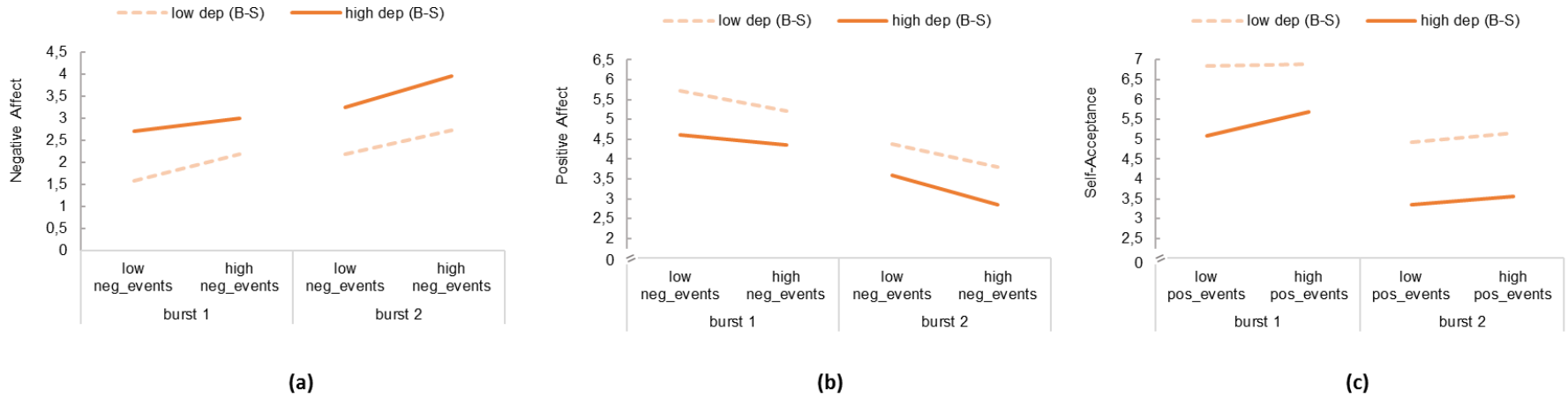

Figure 4.1 Moderation Effects of Depression Levels (B-S) on Intraindividual Change in Reactivity toward Negative and Positive Daily Events

Note. Estimated means of intraindividual change over bursts in a) negative affect (W-S) and b) positive affect (W-S) following negative daily events (W-S) and c) self-acceptance (W-S) following positive daily events (W-S) for initially remitted recurrent depressed patients with low (Mean-1SD) and high (Mean+1SD) depression levels (B-S). Low neg/pos_events: low frequency of negative/positive events (Mean-1SD), high neg/pos_events: higher frequency of negative/positive daily events (Mean+1SD). Models include random intercepts at level 2 and 3, between-subjects-effects (B-S) and within-subjects-effects (W-S), all required 2-way interactions as well as study day and time between bursts in weeks as covariates.

4.5 Discussion

To our knowledge, the present study is the first measurement burst study investigating intraindividual variability and change in subjective and endocrinological reactivity toward daily events in initially remitted patients with recurrent major depression, a sample at high risk for depressive relapses and recurrences. We identified moderation effects of slow-scale depression levels at the within- and the between-subject level on reactivity within bursts and on intraindividual change in reactivity over bursts toward both negative and positive daily events.

In the following, we will discuss main effects and lower-order (2-way) interactions only when they were not subsumed under any higher-order interaction.

Within-Person Reactivity toward Daily Events within Bursts

While we identified event-congruent reactivity toward daily events with respect to all affective and cognitive outcomes (thereby confirming hypothesis 1 with regard to subjective, but not cortisol- reactivity), all main effects of negative daily events were subsumed under higher-order interactions. With respect to positive daily events, we found patients with recurrent depression to experience event-congruent cognitive (i.e., rumination-) reactivity toward positive daily events, which is in line with prior research (see Khazanov et al., 2019). In contrast, we did not find a significant main effect of positive daily events on cortisol. In this context, Peeters et al. (2003a) showed that when compared to healthy controls, patients with current major depression demonstrated a blunted cortisol-response toward negative events. However, in line with our findings, they observed no significant cortisol-reactivity within the group of patients with current depression. This, in turn, highlights the importance of disentangling within- and between-person processes.

Depression Levels as a Moderator of Reactivity toward Daily Events

Our moderation analyses revealed that depression levels (B-S) had no significant moderation effect on self-acceptance or cortisol-reactivity, whereas patients with higher depression levels (B-S) showed

stronger increases in rumination following *negative daily events*. This parallels previous findings showing increased rumination toward stressful daily events in patients with current major depression compared to nondepressed individuals (Kircanski et al., 2018). It furthermore points to variation in event-congruently valenced cognitive stress-sensitivity depending on depressive symptom severity.

The within-person level moderation effect of depression levels on stress-reactivity showed a rather opposing pattern. In bursts with higher depression levels, patients reported blunted negative affect- and cortisol-reactivity. In particular with respect to cortisol, an immediate stress-response followed by a return to homeostasis is seen as adaptive (cf. Peeters et al. 2003a). Consequently, cortisol-blunting might point to a limited capacity to adequately react to stressors in periods (here bursts) with higher depression levels. With respect to negative affect, ceiling effects may account for lowered reactivity.

Furthermore, in bursts with higher depression levels, positive affect and self-acceptance more strongly decreased toward negative daily events. These distinctive responses of stress-related positive outcomes hint to the importance of their consideration in addition to event-congruently valenced outcomes, as already emphasized by Zhaoyang et al. (2019), who found greater positive affect- (not negative affect-) responses to daily stressors to predict steeper increase in depressive symptoms over 18-months.

Overall, these somehow contradictive findings indicate that between persons, patients with higher depression levels showed heightened ruminative stress-sensitivity. Within the individual, in bursts with higher depression levels, event-incongruently valenced affect (positive affect) and cognitions (self-acceptance) more strongly decreased, while event-congruently valenced affective (negative affect) and cortisol-reactivity were blunted. Taken together, these findings also illustrate the need to integrate measures capturing within-person processes into therapeutic interventions. Traditional measures, conceptualized to detect deviations from the norm, might overlook within-person clinical deterioration.

With respect to *positive daily events,* moderation effects of depression levels on reactivity were more coherent. Depression levels at the within-subject level moderated self-acceptance-reactivity and at the between-subject level moderated negative affect reactivity. In bursts with higher depression levels, self-acceptance more strongly increased, and in parallel, patients with higher depression scores reported stronger decreases in negative affect following positive daily events. The latter supports the mood brightening effect (Bylsma et al., 2011). One plausible explanation of such brightening effects in currently depressed and in remitted patients with major depression is based on affective contrast theory (Newman & Llera, 2011), suggesting that emotional experiences are heightened when preceded by a contrasting emotional experience.

Paradoxically, despite an identified brightening in currently depressed and in remitted patients, affected individuals on average report less favorable affect and cognitions in daily life compared to controls (e.g., Khazanov et al., 2019; Schricker et al., 2023). Thus, a question that needs to be raised is *why* brightening does not help to increase these average levels of favorable Ambulatory Assessment outcomes. One possible explanation could be that the impact of negative daily events is stronger and overshadows the beneficial effects of positive daily events (Newman & Nezlek, 2022). A further explanation could be the use of emotion regulation (ER-) strategies unsuitable for maintaining or enhancing positive affect and positive cognitions (e.g., suppression or dampening; cf. Vanderlind et al., 2020).

Intraindividual Change in Reactivity toward Daily Events over Bursts

Over bursts and across patients, we identified significant intraindividual change in self-acceptance-reactivity toward negative daily events, such that self-acceptance more strongly decreased following negative daily events over bursts. Reactivity toward positive daily events remained intraindividually stable, except for an increase in positive affect-reactivity following positive daily events over bursts.

Three-way interaction multilevel models with depression levels as moderator revealed that patients with higher depression levels (but not those with lower depression levels) showed an increase in *affective* (negative & positive affect) stress-reactivity over bursts. Hence, affective stress-sensitivity in

remitted major depression might not reflect a static trait but appears to aggravate over time in those with higher levels of depression. This parallels propositions of stress-sensitisation theories, insofar as minor daily stressors may evoke progressively stronger negative affect (Wichers et al., 2010), thereby potentially increasing vulnerability for relapses and recurrences (cf. Monroe et al., 2019).

In contrast, depression levels did not moderate intraindividual *change* in cognitive or cortisol-reactivity toward *negative daily events*. Linking this finding to the moderation effect of depression levels at the between-subject level on rumination-reactivity within bursts, it appears that while mood-congruent cognitive reactivity is stronger in recurrently depressed patients with higher depression levels, it remains stable over time, irrespective of current depressive symptoms. This observed intraindividual stability of rumination-reactivity toward negative daily events in those patients with higher depression levels most likely reflects a ceiling effect in rumination-reactivity from where there is not much capacity for aggravation.

Furthermore, depression levels did not moderate intraindividual *change* in negative affect-, positive affect-, rumination- or cortisol-reactivity toward *positive daily events*. However, we found a cognition brightening effect (cf. Schricker et al., 2023), such that self-acceptance increases following positive daily events, to blunt over bursts in patients with higher depression levels. This finding expands existing literature on this phenomenon by demonstrating that cognitive brightening is not sustainable over longer periods but that at least in patients with higher depression levels, the threshold to enjoy positive daily events appears to become progressively higher over time. Further research incorporating additional bursts, ideally scheduled within shorter time intervals (e.g., several months), is needed to elucidate the short- and long-term temporal dynamics of stress-reactivity in response to negative events and brightening in response to positive events in patients with recurrent major depression and their impact on macro-level clinical variables.

Strengths and Limitations

To our knowledge, the present study is the first measurement burst study investigating intraindividual variability and change in reactivity toward daily events in a sample of clinically diagnosed patients with recurrent depression at high risk for relapses and recurrences. Using multiple measures (interviewer-ratings, retrospective and prospective self-reports, cortisol), we provided a comprehensive approach to within-person reactivity in recurrent major depression. Nevertheless, the present findings should be considered in the light of some limitations. First, our sample size was only modest. However, given the rather high *N* of assessment points at level-1, a power of .80 to detect cross-level interactions should have been surpassed (Mathieu et al., 2012). Second, we operationalized daily events based on subjective perceptions, which is not flawless, since it does not consider specific contextual factors of reported events (e.g., controllability; Wenzel et al., 2021). Future research would profit from context-aware mobile sensing frameworks, in which subjective and objective Ambulatory Assessment measures could be integrated (Kubiak & Smyth, 2019; Schick et al., 2022). Third, negative events were reported rather infrequently, which can be seen problematic for the reliability of findings and the power to detect effects. This might be especially the case for cortisol-related analyses with fewer data points. Fourth, we assessed daily events retrospectively, referring to the time interval between the last (T-1) and the current assessment (T1). While this approach seems suitable for analyzing associations of daily events with subjective outcomes, it could be more problematic with respect to saliva cortisol, which was collected 20 min after T1, possibly resulting in time intervals varying from around 20 min to 130 min (90 min + 20 min delay option + 20 min time lag for saliva collection). However, as in the present study, cortisol peaks are commonly examined being linked to negative subjective emotional states, where saliva collection is recommended to be scheduled with a time lag of approximately 10-30 min after subjective assessments (Schlotz et al., 2019; Stoffel et al., 2021). In order to improve assessment reliability, future research could consider using event-contingent designs or filter for events that had happened no longer than 30 min ago from saliva collection. Lastly, we did not consider the intensity of negative or positive daily events within our analyses. Doing so could have increased

the validity of our findings. Along these lines we cannot rule out the possibility that patients with higher versus lower depression levels had different thresholds to report negative or positive events.

Implications

By using a measurement burst design, this study demonstrates the importance of differentiating between within- and between-subject effects to overcome the inconsistency of results on reactivity toward daily events in clinical populations (cf. Cole et al., 2021). Beneficial effects of positive events underline the value of scheduling positive activities into the daily life of patients with recurrent major depression. Additionally, the training of emotion regulation strategies addressing up-regulation of positive affect (e.g., savoring, appreciation, mindfulness, acceptance; see Silton et al., 2020; Wenzel et al., 2021) may improve the enjoyment of positive daily events and maintain the subsequent self-acceptance-response. Ecological Momentary Interventions (EMIs) as an emerging tool operating in individuals' daily lives (cf. Schick et al., 2022) may be suitable for relapse prevention. While there is initial evidence on promising efficacy of EMIs for current major depression (Colombo et al., 2019), their efficacy to prevent new major depressive episodes in those with recurrent depression remains to be examined.

Conclusion

Given the potential role of reactivity toward daily events as vulnerability or protective factors for the course of major depression, a prospective investigation of their dynamics and intraindividual change in patients initially remitted from recurrent major depression, who are at high risk for relapses and recurrences, is crucial. We found evidence for a cognition brightening toward positive daily events within bursts in patients with higher depression levels both at the within- and the between-subject level, which however does not seem to sustain over time. Effects on stress-reactivity were less cohesive. In bursts with higher depression levels, patients exhibited blunted event-congruently valenced reactivity and blunted cortisol-reactivity toward negative daily events but increased event-incongruently valenced reactivity. In contrast, patients with higher depression levels generally showed stronger

event-congruently valenced cognitive stress-reactivity within bursts and an event-congruently valenced increase of affective stress-reactivity over bursts. Thus, our findings reflect the complexity of within-person processes and underscore the importance to disentangle within- from between-subject effects. Future research investigating multiple response systems over longer periods via measurement burst designs from different units of analyses (self-report, physiological, neurobiological) will increase our understanding of risk and protective factors for the course of recurrent major depression.

CHAPTER V: GENERAL DISCUSSION

5.1 Summary of the Present Findings

The present series of studies focused on understanding the dynamic interactions between affect, cognition (such as rumination and positive thoughts), and cortisol as a biological stress marker in everyday life among individuals with a history of recurrent depressive episodes. Using Ambulatory Assessment (AA), the studies explored how individuals with recurrent major depression respond to both negative and positive daily events as well as to internal maladaptive thoughts on affective, cognitive, and endocrinological levels compared to healthy individuals. Overall, we aimed to capture the complexity of interindividual variability in these within-person associations on the short- and long-term, emphasizing the role of both momentary and habitual patterns of thought. These findings could provide prognostic value for the course of recurrent depressive disorder and help improve strategies to prevent relapse.

5.1.1 Important Results of Study 1

Study 1 aimed to explore differences in average levels of negative and positive affect, as well as in dysfunctional and positive cognitions, assessed in daily life via AA, in remitted individuals with a history of recurrent depressive episodes compared to healthy individuals. Furthermore, reciprocal prospective effects of momentary rumination, positive thoughts and affect were investigated, as well as affective and cognitive reactivity toward daily negative and positive events, including potential group differences in these effects. Our findings revealed significant differences in affect and cognitions between individuals in remission from recurrent depression and healthy individuals. Those in remission reported higher levels of negative affect and rumination, as well as lower levels of positive affect and positive thoughts. Furthermore, individuals in remission from recurrent depression reported a higher number of negative daily events, while both groups experienced similar rates of positive daily events. Multilevel lag models indicated that momentary rumination predicted a greater decrease in positive

affect among individuals in remission compared to healthy individuals. However, rumination did not significantly predict negative affect in either group. Higher levels of positive thoughts were associated with increases in positive affect and decreases in negative affect and rumination, with effects being comparably strong for both groups. Regarding reactivity toward daily events, individuals in remission experienced stronger increases in negative affect and rumination following negative daily events than healthy individuals, although subsequent decreases in positive affect and positive thoughts were similarly strong in both groups. Following positive daily events, individuals in remission from recurrent depression exhibited greater affective and cognitive reactivity, reflected by more substantial decreases in subsequent negative affect and rumination, alongside stronger increases in subsequent positive affect and positive thoughts.

5.1.2 Important Results of Study 2

Using Ambulatory Assessment, Study 2 investigated associations of trait and state cognitions with salivary cortisol as a biological stress-marker in the daily life of individuals with recurrent major depression and healthy individuals. Via multilevel models, we found trait repetitive negative thinking (RNT), but not mindfulness, to be associated with higher cortisol levels, with the effect being more pronounced in individuals with recurrent depression compared to healthy individuals. State mindwandering and mentalshift problems were significantly associated with increases in cortisol 20 minutes later across groups. Within the group of individuals with recurrent depression, those individuals who generally experienced higher levels of mentalshift problems also tended to have higher cortisol levels in daily life. In a second step, mediation analyses revealed that state cognitions did not mediate the effects of habitual RNT on cortisol release.

5.1.3 Important Results of Study 3

Study 3 is a measurement burst study with two bursts separated by approximately 4.4 years, examining intraindividual variability and change in subjective and endocrinological reactivity toward daily events in in a sample of individuals initially remitted from major depression with a history of recurrent

episodes. Furthermore, we aimed to identify potential moderation effects of slow-scale depression levels on short- and long-term reactivity toward both negative and positive daily events. Within bursts, individuals reported event-congruently valenced affective (negative affect, positive affect) and cognitive (rumination, self-acceptance) reactivity, but no significant cortisol-reactivity. Over bursts, self-acceptance more strongly declined toward negative daily events. Reactivity in rumination and cortisol-reactivity toward negative daily events remained intraindividually stable over bursts. Regarding reactivity toward positive daily events, positive affect more strongly increased in response to positive daily events over bursts. Event-incongruently valenced (i.e., rumination, negative affect) as well as cortisol-reactivity remained intraindividually stable over bursts. In bursts, during which individuals showed higher depression levels, they exhibited reduced reactivity in negative affect and cortisol and more significant declines in positive affect and self-acceptance in response to negative daily events. However, those individuals with higher depression levels displayed stronger reactivity in rumination within bursts and an increase of reactivity in negative affect toward negative daily events over bursts. In response to positive daily events, individuals with higher depression levels showed more pronounced increases in self-acceptance and stronger decreases in negative affect within bursts, as well as a reduction of self-acceptance-reactivity over bursts.

5.2 Rumination and its Interplay with Affect in Daily Life in Remitted Recurrent Major Depression

In Study 1, we investigated reciprocal prospective effects of momentary rumination on subsequent negative and positive affect and on positive thoughts in a sample of individuals in remission from recurrent depression compared to healthy individuals. Despite well-established evidence for rumination's detrimental role in mood in daily life (Baik & Newmann, 2023; Blanke et al., 2021; Kircanski et al., 2018; Ruscio et al., 2015), we did not find a prospective effect of momentary rumination on subsequent negative affect, possibly due to floor effects, as momentary rumination levels were relatively

low. Higher levels of momentary negative affect, however, predicted an increase in subsequent rumination, in particular in individuals in remission from recurrent depression compared to healthy individuals (see also Hjartarson et al, 2022). This aligns with previous research, suggesting that rumination – and, more broadly, repetitive negative thinking - can be triggered by fluctuations in negative affect (Bean et al., 2021; Hjartarson et al., 2022), leading to a vicious cycle where negative affect perpetuates further rumination and emotional dysregulation (Baik & Newmann, 2023; Lu et al., 2024; Watkins & Roberts, 2020). Thus, while rumination may not always predict negative affect directly, the reverse association remains significant in individuals with a history of recurrent depression.

Further findings from Study 1, showing that higher levels of momentary rumination predicted a decrease in momentary *positive affect,* and vice versa, in particular in the group of individuals in remission from recurrent depression, demonstrated once more the importance to set the focus more strongly on positive affect in the context of major depressive disorder (e.g., Hoorelbeke et al., 2019; cf. Naragon-Gainey, 2019, Panaite et al., 2021). Moreover, momentary positive thoughts were shown to be beneficial for subsequent affect in both groups, and momentary affect, in turn, was significantly associated with mood-congruent changes in momentary positive thoughts. In line with this, the upward-spiral model (Garland et al., 2010) suggests that positive affect can enhance psychological resources through a self-reinforcing cycle, making people more resilient to stress and adversity. In the long-term, the repeated experience of such upward spirals could broaden the individual's perspectives and build effective coping strategies for potential stressors (Garland et al., 2010). This is in line with the Broaden-and-Build Theory from Fredrickson et al. (2001), which states that positive affect may broaden individuals in their thoughts and actions, thereby eventually creating more adaptive coping styles (cf., Zhanoyang et al., 2020). Mindfulness and positive reappraisal are important factors within the upward spiral model. Such positive cognitions can further reinforce the positive cycle through enhancing awareness of positive experiences and emotions (Garland et al., 2010). In Study 1, we further showed that higher levels positive thoughts were significantly related to lowered subsequent rumination (and vice versa), independent of clinical depression history. This finding underscores the

capacity of positive cognitions to counteract maladaptive thoughts. Lastly, the constant experience of positive affect and positive cognitions might lead to neurobiological changes in the brain (Garland et al., 2010). This, in turn, may align with the notion that potential scars from past depressive episodes—as suggested for individuals in remission from (recurrent) major depression—could be reversed (see Wichers et al., 2014), putatively through an enhanced activation of the upward spiral. In sum, rumination could fuel a cycle of increasing negative affect, while positive thoughts can enhance mood and reduce rumination, particularly in individuals in remission from recurrent depression. This supports the idea that fostering positive affect can build resilience and potentially reverse the lingering effects of negative affect and maladaptive thoughts on the course of depression.

5.3 Reactivity toward Daily Events: Stress-Reactivity, Mood- and Cognition Brightening in Recurrent Major Depression

5.3.1 Stress-reactivity

In Study 1, individuals in remission from recurrent major depression demonstrated heightened reactivity of negative affect and rumination following negative daily events. Such increased stress-reactivity has already been reported in previous studies (see Husky et al., 2009; Lamers et al., 2018). However, this heightened stress-reactivity seemed to be limited to event-congruent feelings and thoughts (i.e., negative affect and rumination). In Study 3, we found that those individuals with recurrent major depression, who indicated higher depression levels, showed stronger rumination-reactivity in response to negative daily events, a finding which is in concordance with previous research (see Kircanski et al., 2018). Consequently, in particular event-congruently valenced cognitive stress-sensitivity might vary depending on depression severity. At the within-person level, we found that in bursts with higher depression levels, individuals with recurrent major depression showed blunted negative affect reactivity toward negative daily events and cortisol-reactivity; the latter will be discussed in paragraph 5.4. While maintaining positive affect in moments when a negative daily event occurs, is generally beneficial, experiencing normative distress (e.g., increased negative affect) in response to a stressor

may not always be maladaptive (cf. Zhanoyang et al., 2020). Rather than heightened acute negative affect reactivity, prolonged emotional responses to stress or problems shifting negative affect in accordance with changing contexts could contribute to disadvantageous long-term mental health (Zhanoyang et al., 2020). In seeking to explain the phenomenon of blunted stress reactivity, it has been suggested that low stress reactivity may reflect a coping strategy involving disengagement from or downplaying the effects of stressors (Rush et al., 2024). In the long-term this strategy could be dysfunctional, even though there could be benefits to it in the short-term. Interestingly, our results form Study 1 seem rather opposed to the within-person effects on negative affect stress-reactivity. In general, it seems worthwhile to mention, that current theories on stress-reactivity – apart from the fact that many of them relate to laboratory stressors (e.g., context insensitivity theory; Bylsma, 2021) - do not address the importance of disentangling between-person from within-person effects (cf. Cole et al., 2021). This however is essential, since effects can go into opposite directions (Cole et al., 2021) and consequently require more fine-grained theoretical backing. In our case, it is well possible that in comparison with a healthy sample, individuals in remission from recurrent depression demonstrate heightened stress-reactivity. But when we look into a sample of individuals with recurrent depression (majority remitted), it might be that given their anyway increased stress-reactivity, in periods (here bursts) when they experience higher depression levels, their stress-reactivity is blunted due to a prolonged exposure of already higher levels of daily stress. This in turn, might cause a diminished physiological response to stressors (Rush et al., 2024), which will be discussed in more detail in paragraph 5.4.

Another intriguing aspect of stress reactivity comes from Rush et al. (2024), who aimed to explore whether the relationship between stress-reactivity and mental as well as physical health outcomes is better represented by a U-shaped rather than a linear association. Using data from the National Study of Daily Experiences (NSDE), their findings showed that moderate levels of reactivity relative to low or high reactivity were linked to lower psychological distress, fewer chronic conditions, and higher levels of life satisfaction (Rush et al., 2024). Wondering why moderate stress-reactivity appeared to be more

beneficial for mental health than lower stress-reactivity, Rush et al. (2024) reasoned that moderate reactivity could enhance effective coping by promoting a stronger sense of control and mastery when dealing with everyday stressors. According to their argumentation, moderate stress reactivity may indicate an ideal balance between emotional sensitivity and regulation, triggering adaptive biological processes and enabling individuals to respond to stressors appropriately without being overwhelmed or disengaged. Low or blunted stress-reactivity, in turn, could imply a lack of involvement with daily life experiences, also limiting one's engagement in positive activities (Rush et al., 2024). With respect to clinical implications, these findings hint to the application of interventions that focus on improving emotion regulation and coping resources. On the one hand, for individuals who exhibit low stress-reactivity in daily life, interventions that boost emotional awareness and expression (e.g., mindfulness-based interventions) may be beneficial (Rush et al., 2024). On the other hand, individuals with high stress-reactivity could profit from interventions that aim to reduce emotional arousal and distress (e.g., CBT, relaxation; cf. Rush et al., 2024).

5.3.2 Mood- and Cognition Brightening

To date, there is a growing body of research, investigating not only reactivity toward negative daily events but also reactivity toward positive daily events. Results from Study 1 and Study 3 demonstrate additional support for mood brightening and for a further phenomenon, which we referred to as "cognition brightening", as a putative characteristic of major depressive disorder. In Study 1, individuals remitted from recurrent major depression showed higher affective reactivity (increased positive affect, decreased negative affect) as well as cognitive reactivity (increased positive thoughts, decreased rumination) in response to positive events compared to healthy individuals. Study 3 revealed that individuals with recurrent depression indicated a decrease in rumination – termed event-congruent cognitive reactivity - toward positive daily events. This finding aligns with results from Khazanov et al. (2019), who demonstrated that rumination and worry decreased more significantly following positive daily events in individuals with current major depression, generalized anxiety disorder, and comorbid

conditions than in healthy individuals. Moreover, in Study 3, we investigated whether depression levels moderate reactivity toward positive daily events. We could show that at the within-person level, in bursts when individuals reported higher depression levels, self-acceptance more strongly increased following positive daily events compared to bursts when individuals reported lower depression levels. Correspondingly, at the between-person level, individuals with higher depression scores experienced stronger decreases in negative affect toward positive daily events.

In light of these findings, van Loo et al. (2023) examined mood-brightening effects in response to social and active behavior across different levels of depression and anxiety symptoms in a general Dutch population sample. They found all investigated activities (physical activity, being outdoors, social company) to predict increases in positive affect and decreases in negative affect in all groups. However, larger reductions in negative affect after all activities, as well as larger increases in positive affect after being in social company were found in individuals with moderate to severe depressive symptoms (but not anxiety symptoms) compared to individuals with no symptoms. Although their sample consisted of only female participants, this study provides evidence for a mood brightening specifically in depressed but not in anxious mood.

The mood brightening effect at first seems counterintuitive since anhedonia is one hallmark symptom of major depressive disorder (APA, 2013; van Loo et al., 2023), and individuals with current and remitted MDD experience higher average levels of negative affect and lower levels of positive affect in daily life compared to healthy individuals (cf., van Loo et al. 2023; see also Introduction 1.7.1). Furthermore, mood brightening observed in daily life contrasts with the emotion context insensitivity often reported in laboratory studies (see Bylsma et al., 2021 for review), where individuals with major depression typically exhibit blunted emotional responses to positive stimuli compared to healthy individuals (cf. van Loo et al., 2023). One popular explanation for the mood brightening effect, which could also extend to cognition brightening, is the idea that individuals with MDD have a higher threshold for responding to positive activities due to their anhedonic state (cf. van Loo et al., 2023). This would imply

that individuals with (remitted) recurrent MDD detect or report fewer positive daily events, only acknowledging those that are more impactful and elicit stronger affective or cognitive responses. However, in Study 1, we compared individuals in remission from recurrent MDD with healthy individuals and found them to report an equal number of positive daily events, which discards the latter explanation for brightening. Moreover, van Loo et al. (2023) found the mood brightening effect in depression to appear independent of event appraisal, indicating that mood brightening cannot be solely attributed to differences in event appraisals between individuals with MDD and healthy individuals. Differences in emotion regulation strategies are discussed as a further explanation (van Loo et al., 2023). Positive activities might redirect the focus away from maladaptive thoughts such as rumination (Panaite et al., 2022). The fact that individuals with current or remitted depression (vs healthy individuals) are more prone to rumination (e.g., Hjartarson et al., 2022; Watkins & Roberts, 2020) might explain their greater benefit from positive activities (van Loo et al., 2023). Affective Contrast Theory (Newman & Llera, 2011) offers another useful perspective on how to explain mood brightening in depression. It states that the context of emotional experiences is important. A minor daily positive event might have a greater impact on affect when it stands in stark contrast to a previously experienced lower mood. Conversely, if an individual is already in a rather positive mood, the same daily event might not elicit an equally strong affective reaction.

In Study 1, we raised another major concern with respect to mood- and cognition brightening. Why does mood- and cognition brightening not lead to higher average levels of positive affect and positive thoughts in daily life? One idea that we discussed is that negative daily events potentially overpower the effects of positive daily events (Newman & Nezlek, 2022). This could be due to cognitive biases, which are highly prevalent in MDD (LeMoult & Gotlib, 2019) and may amplify the experience of negative daily events (Kircanski et al., 2012; Wichers et al., 2010). Thus, maladaptive thoughts such as rumination, or emotion regulation strategies such as suppression or dampening, which fail to maintain or enhance positive affect and cognition, are more frequently applied (e.g., Vanderlind et al., 2020). Finally, it is also possible that individuals with a history of depressive episodes on average face more

adverse life circumstances such as financial instability, exposure to violence, poor physical health and environmental stressors (Ridley et al., 2020), making positive daily events feel less impactful within the broader context of their lives compared to healthy individuals. However, this notion is rather speculative and warrants further exploration. In sum, even though individuals with recurrent MDD experience stronger reactivity toward positive daily events, their overall emotional landscape could be characterized by persisting depressive patterns that might hinder a sustainable benefit from these daily brightness boosts.

In their recent work, von Klipstein et al. (2023) raised some methodological concerns and aimed to investigate whether the mood brightening effect merely represents an artifact caused by floor effects, in particular with respect to negative affect mood brightening. Indeed, previous research typically found negative affect to demonstrate a restricted range, especially in healthy individuals. Using data from the Netherlands Study of Depression and Anxiety (NESDA), von Klipstein et al. (2023) adjusted their models for non-normality and heteroscedasticity. They found the group differences in negative affect reactivity toward positive daily events, which was identified in the previously unadjusted models, to disappear. According to their results, von Klipstein et al. (2023) reasoned that the floor effect in negative affect score distributions of healthy individuals might serve as one possible explanation for the mood brightening effect. However, in accordance with our findings, they found that positive affect reactivity toward positive events was increased in individuals with current and remitted depression compared to healthy individuals (von Klipstein et al., 2023).

5.3 Cortisol as a Biological Stress-Marker in (Remitted) Recurrent Major Depression

In Study 3, we found that individuals with recurrent depression exhibited blunted cortisol reactivity in bursts with higher depression levels. This pattern aligns with the idea of an exhausted stress system, often observed in chronic stress-related disorders. Typically, adaptive stress responses involve an initial peak in cortisol, followed by a return to homeostasis (Peeters et al., 2003a; Osei et al., 2024; Stoffel et al., 2021; Wesarg-Menzel et al., 2024). Over time, individuals with a history of multiple depressive

episodes may transition from an initial hyperreactive stress response to a more blunted reaction, reflecting a detrimental downregulation of the HPA axis, a topic that will be discussed further later in this section. This is consistent with findings from Peeters et al. (2003a), who showed blunted cortisol responses in individuals with depression suggesting that chronic exposure to stress may lead to physiological wear and tear. One peculiarity needs to be mentioned regarding the findings from Peeters et al. (2003a): When looking at their group of individuals with depression, Peeters et al. (2003a) found no significant cortisol response toward negative daily events. However, in comparison to healthy individuals, their cortisol reactivity was blunted. This underscores the need to disentangle within-person variations (e.g., fluctuating depression levels) from between-person comparisons (e.g., clinical vs. non-clinical samples). Although in Study 3 we used a different approach by examining depression levels as a within- and between-person moderator of cortisol reactivity toward negative daily events, our findings align with Peeters et al. (2003) in demonstrating that depression severity plays a crucial role in cortisol reactivity.

Moreover, we found no significant association between positive daily events and cortisol release, even when considering depression levels. On the neuronal level, a recent meta-analysis of neuro-imaging studies investigating reward processing in major depressive disorder found that depression might be characterized by not only hypo- but also hyper-responses to reward, both depicting abnormalities in the reward circuit (Ng, Alloy & Smith, 2019). Research on cortisol reactivity to positive events in depressed individuals is scarce, possibly because the HPA axis is primarily activated in response to threats (Degering et al., 2023; Wesarg-Menzel et al., 2024). It is possible be that positive events must reach a certain intensity to elicit an endocrine response. Combined with the fact that we did not find proof for a hypersensitivity of the HPA axis for negative events, the lack of cortisol reaction toward positive daily events once more demonstrates the complexity of HPA axis dysregulation in depression.

The classical approach to measuring stress-reactivity through biological markers in daily life involves assessing retrospectively self-reported negative daily events in conjunction with subsequent salivary

cortisol samples (Schlotz, 2019). To examine the notion that not only external but also internal stressors may provoke stress reactions (cf. Smyth et al., 2023), we explored whether maladaptive state cognitions were linked to subsequent cortisol activity in a sample of individuals with recurrent depression compared to healthy controls (see Study 2). Indeed, we found that elevated levels of momentary mindwandering and mentalshift problems predicted increases in cortisol 20 minutes later across both groups. Furthermore, within the recurrent depression group, those individuals with higher overall mentalshift problems exhibited elevated cortisol levels throughout daily life.

While the heightened cortisol reactivity in response to maladaptive thoughts in individuals with recurrent depression (Study 2) may seem at odds with the blunted cortisol response to negative daily events found in bursts of higher depression levels in Study 3, these findings are methodologically distinct and should not be viewed as contradictory. The blunted cortisol response observed in Study 3 among individuals with recurrent depression during episodes of higher depression levels likely reflects an exhausted stress system rather than an anomalous or contradictory pattern. This diminished response may indicate a reduced capacity to mount an adequate stress reaction after repeated stress exposure. Indeed, an extended period of cortisol release due to cumulative or chronic stress can lead to HPA axis overactivity, causing adrenal dysfunction or fatigue, which in turn can result in a state of low HPA axis activity influenced by increased negative feedback sensitivity of the HPA axis (cf. Osei et al., 2024). This condition can be referred to as allostatic overload (cf. Degering et al., 2023; Osei et al., 2024). In contrast, the finding from Study 2 of heightened cortisol reactivity to internal stressors (momentary mind-wandering and mental shift problems) in individuals with recurrent depression compared to healthy controls, emphasizes the need to consider methodological distinctions. Specifically, the blunted response in Study 3 reflects a within-person effect, capturing cortisol fluctuations across episodes of higher depression levels, whereas findings from Study 2 represent a between-person comparison. This differentiation is crucial and highlights the importance of distinguishing between within- and between-person effects to advance our understanding of HPA axis regulation in recurrent depression.

Additionally, we examined the role of trait-level maladaptive cognitions in relation to salivary cortisol. While this does not directly reflect micro-level cortisol reactivity, it may serve as an indicator of chronic stress at the macro-level. We found that trait repetitive negative thinking was significantly associated with higher cortisol levels in both groups, aligning with the Perseverative Cognition Hypothesis (Brosschot et al., 2006; cf. Ottaviani et al., 2016), suggesting that repeated or chronic engagement with repetitive negative thoughts such as rumination and worry and negative daily events can lead to sustained HPA axis activation, even in anticipation of stressors. This effect was more pronounced in individuals with recurrent depression, suggesting a heightened physiological vulnerability. Taken together, these findings from Study 2 indicate that individuals with recurrent major depression may exhibit greater physiological sensitivity to maladaptive cognitions on the micro- as well as on the macro-level.

There is wide consensus in prior research that mindfulness demonstrates an important protective or resilience factor for mental health (Enkema et al., 2020). Surprisingly, in Study 2, trait mindfulness did not show a significant association with cortisol release in daily life (for similar results in a healthy sample see Manigault et al., 2018a). So far, studies investigating dispositional mindfulness in relation to cortisol release in daily life in clinical samples are largely lacking. Nayman et al. (2023) investigated the impact of different emotion regulation strategies at the trait-level on basal cortisol activity in the daily life of women with premenstrual dysphoric disorder. Across cycle phases, there was no significant association with either repetitive negative thinking, reappraisal, or mindfulness and cortisol activity. However, when considering cycle phase as a moderator, higher habitual mindfulness was associated with lower basal cortisol activity, especially in the menstrual phase. One possible explanation for the lack of significant association between trait mindfulness and cortisol release in daily life in Study 2 may be that the beneficial effects of trait mindfulness only take effect in the face of acute stressors. Consequently, mindfulness could act as a stress-buffer, mitigating HPA axis over- and under-responsiveness in the presence of an acute stressor (cf. Manigault et al., 2018a). Indeed, previous research has shown that lower levels of trait mindfulness were associated with a greater likelihood of not mounting

a cortisol response to a social evaluative stressor task but were unrelated to the magnitude of the cortisol response in those individuals who did react (Manigault et al., 2018a). Ultimately, mindfulness may be viewed as an important protective factor in the daily lives of individuals with recurrent depression, helping buffer against the negative impact of negative events in moments when they occur.

In contrast to our assumptions, results from Study 2 showed that the effect of trait repetitive negative thinking was not mediated by state cognitions. This finding demonstrates that there must be distinct mechanisms linking cognitive trait and state cognitions to cortisol activity in daily life. At the *micro*-level, an increase in cortisol in response to a daily stressor is defined as allostasis, a state of adaptive responsiveness to adversity that promotes physiological stability (Osei et al., 2024; Wesarg-Menzel et al., 2024). After the stressor disappears, homeostasis is regained via an inhibitory feedback loop that accurately regulates the HPA axis (Osei et al., 2024; Wesarg-Menzel et al., 2024). It therefore seems reasonable to investigate cortisol stress-*reactivity* in concert with stress-*recovery* (see Wesarg-Menzel et al., 2024). So far, impaired stress-recovery has been shown to be significantly related to major depressive disorder in the laboratory when exposed to a psychosocial stressor (Trierer-Stress-Test; e.g., Burke et al., 2005). To date, there is a lack of guidelines how to best possibly measure and analyze recovery (cf. Degering et al., 2023 in the context of laboratory stress-reactivity) and findings from the laboratory often do not translate into daily life, where potentially more personally relevant events can be assessed with a higher degree of ecological validity (Schlotz, 2019). Assessing endocrinological stress-recovery in daily life, however, would certainly require a higher saliva sampling density within the Ambulatory Assessment design, coming with additional costs and increasing participant burden. Regarding the subjective assessment of affective or cognitive reactivity, implementing both reactivity and recovery assessment seems more feasible. For instance, Velozo et al. (2023) examined time to affective recovery and found that individuals at high risk for a major depressive episode (i.e., individuals in remission from major depression and individuals with subclinical depression symptoms) took longer to recover from stressful daily events compared to healthy controls.

At the *macro*- or trait-level, individuals with higher levels of habitual maladaptive thoughts such as repetitive negative thinking might have impaired stress-recovery. Nonetheless, this notion remains speculative and needs to be addressed in future research.

In summary, our findings illustrate the nuanced cortisol responses in recurrent depression, emphasizing the importance of distinguishing within- and between-person effects. Blunted reactivity during heightened depression episodes may signal cumulative wear on the stress system, while when seen in comparison to healthy individuals, heightened responses to internal stressors point to physiological sensitivity. Additionally, the lack of association between trait mindfulness and cortisol release suggests that mindfulness may serve as a buffer primarily in acute stress contexts. Together, these insights contribute to a more comprehensive understanding of HPA axis regulation in recurrent depression.

5.5 Intraindividual Change in Reactivity

Study 3 revealed that self-acceptance reactivity to negative daily events increased over bursts, meaning that self-acceptance more strongly decreased in response to negative daily events as time progressed, in individuals initially in remission from recurrent depression. This finding contrasts with a recent measurement burst study by Almeida et al. (2023), who demonstrated a normative trend toward improved emotion regulation competency with increasing age. They found that stressor occurrence and affective reactivity generally decreased over a 20-year time span, with younger adults showing a steeper decline in reactivity compared to older adults. In contrast, our sample of individuals in remission did not show this positive trend, suggesting that those with recurrent depression may experience deviations from normative psychological development, specifically regarding stress reactivity. However, we observed stability in reactivity toward positive daily events, with the exception of a stronger increase in positive affect toward positive daily events over bursts.

Depression Levels as a Moderator of Intraindividual Change in Reactivity

Depression levels moderated intraindividual change in stress-reactivity. Individuals with higher depression levels exhibited worsening affective stress-reactivity over time, which indicates that affective reactivity can be interpreted as a dynamic trait and supports stress-sensitization theories (Wichers et al., 2010). This heightened sensitivity to minor stressors could increase the risk of future depressive episodes, though further research is needed to confirm this association by examining both reactivity and changes together with depression status at the macro-level over multiple bursts. Within bursts, individuals with higher depression levels reported greater rumination reactivity to negative daily events, though there was no significant change over the 4.4-year period in cognitive- or cortisol-reactivity. The absence of significant intraindividual change in rumination reactivity could possibly be attributed to a ceiling effect. Individuals with more severe depressive symptoms levels might experience levels of momentary rumination that are already elevated to an extent where there is little room left for further increases.

With respect to intraindividual change in reactivity toward positive daily events, Study 3 revealed that cognition brightening (as also found in Study 1), in particular increases in self-acceptance in response to positive daily events, blunted over two bursts in individuals with higher depression levels. This trend might suggest that the threshold to benefit from positive daily events becomes higher over time, especially in those individuals with higher depression levels. As already discussed for its shorter term purpose (see paragraph 5.3), in particular for the long-term course, cognition brightening seems to be unsustainable. Lastly, depression levels did not moderate intraindividual change in affective-, rumination- or cortisol-reactivity in response to positive daily events. In sum, our findings on intraindividual change in reactivity highlight the complexity of the interplay between current symptomatology and within-person reactivity toward daily events in recurrent depression.

In a recent measurement-burst study, Zhanoyang et al. (2020) investigated positive and negative affect responses to stressors in daily life simultaneously, as well as the predictive value of interindividual differences therein for depressive symptoms trajectories within an 18-month follow-up period in a

community sample. Individuals that experienced stronger decreases in positive affect toward daily stressful events showed stronger increases in depressive symptoms over the following 18 months. To their surprise, stronger increases in negative affect toward daily stressful events did not predict depressive symptoms trajectories. It could be possible that positive affect mitigates negative affect, so that individuals that are able to uphold their positive affect in moments of acute stress may have a long-term mental health benefit (cf. Zhanoyang et al., 2020). As already discussed in paragraph 5.2, according to the upward-spiral model, one can assume that individuals are able to more easily access adaptive emotion-regulation strategies in moments, when they experience higher levels of positive affect (Garland et al., 2010). This, when translated to our clinical sample of individuals in remission from recurrent major depression, could reduce the risk for future depressive episodes. In contrast to our statistical model, Zhanoyang et al. (2020) modeled both positive and negative affect reactivity simultaneously using latent growth curve models, which accounted for issues such as multicollinearity. While their results derive from a healthy sample, their findings emphasize the value of investigating positive affect reactivity toward daily (stressful) events in relation to the course of major depressive disorder.

In this context, Snippe et al. (2023) utilized Exponentially Weighted Moving Average (EWMA) control charts on long-term Ambulatory Assessment data to identify prodromal symptoms of depression among individuals in remission. They found that repetitive negative thinking and high arousal negative affect were the most accurate early indicators of recurrence, detected up to a month prior in a significant portion of their sample. This method holds promise for personalized early detection, facilitating timely interventions to prevent relapses and recurrences. Such findings underscore the importance of identifying specific psychological markers that may signal risk for recurrence, thereby confirming the potential for intraindividual reactivity and change to be equally relevant in individuals with a history of recurrent depression.

5.6. Implications

5.6.1 Research Implications

The present studies offer several important implications for future research, particularly in advancing our understanding of cognitive and emotional regulation in recurrent depression.

Focus on both Maladaptive and Adaptive Thoughts. The present findings emphasize the need for research to continue focusing on maladaptive thoughts, such as rumination, as a central factor in improving affective well-being and reducing depressive symptoms. Interventions like rumination-focused therapy (Watkins, 2015) and cognitive behavioral therapy (CBT; Hofmann & Asmundson, 2017) have demonstrated effectiveness in the context of MDD (cf. LeMoult & Gotlib, 2019). Research should further explore how enhancing positive thoughts can act as a buffer against negative thinking and how techniques such as mindfulness-based cognitive therapy (MBCT; Segal et al., 2018) contribute to reinforcing positive affect and cognition over time, fostering a beneficial upward spiral between the two (Garland et al., 2010). Most of the evidence demonstrating the beneficial role of mindfulness in daily life for individuals with depression stems from mindfulness-based intervention (MBI) studies. MBIs have gained popularity as a method for depressive relapse/recurrence prevention. MBIs focus on teaching individuals to direct their attention to present-moment experiences with a non-judgmental, curious, and accepting attitude, utilizing meditation practices (cf. Linardon et al., 2024). Via this approach, several depression-related processes, such as rumination and emotion dysregulation, may be disrupted (Linardon et al., 2024).

Focusing on Positive Affect. While negative affect triggers immediate survival mechanisms (e.g., endocrine responses) and has well-known long-term detrimental effects on the course of depression, the beneficial impact of sustained positive affect may unfold more gradually, supporting long-term well-being (Panaite et al., 2021). This could be due to its role in promoting more adaptive emotion regulation strategies (cf. van Loo et al., 2023; Zhanoyang et al., 2020). Additionally, the connection

between mentalshift problems in daily life and heightened cortisol release in individuals with recurrent depression (as reported in Study 2) highlights the potential for interventions aimed to improve executive control and cognitive flexibility to regulate HPA axis activity by addressing cognitive dysfunction in daily life (e.g., Im et al., 2021). Thus, future research should explore how sustained positive affect can enhance cognitive flexibility and reduce stress-reactivity, which might have prognostic value for the course of recurrent MDD.

Multimodal Data Integration. The combination of Ambulatory Assessment with advanced neuroscience techniques—such as mobile neuroimaging (e.g., functional near-infrared spectroscopy, portable MEG caps, mobile deep brain recording)—offers new avenues for capturing real-life neural responses (for a more detailed overview see Reichert et al., 2021). Future interdisciplinary research could explore how these tools can integrate multimodal, longitudinal data (subjective, physiological, and neurobiological) to better understand the developmental mechanisms and persistence of depression. Methods such as Exponentially Weighted Moving Average (EWMA) control charts hold promise for early detection of recurrence, with real-time alerts based on indicators like repetitive negative thinking (e.g., Snippe et al., 2023).

Measurement Burst Designs. Future research should consider employing more frequent bursts spaced over shorter intervals to better capture intraindividual variability in high-risk populations, such as individuals in remission from recurrent depression. Assessing reactivity alongside clinical outcomes (e.g., relapses and recurrences) may provide valuable insights into the prognostic value of stress and affect reactivity over time.

5.6.2 Clinical Implications

The findings also have important clinical implications, particularly in terms of enhancing therapeutic strategies with respect to emotion regulation of positive affect and developing personalized interventions for individuals at risk for depressive relapses and recurrences.

Boosting Positive Cognitions and Regulating Cortisol. Clinical interventions targeting maladaptive thoughts, such as rumination, should incorporate techniques that boost positive thoughts to reduce depressive symptoms. Mindfulness-based interventions (e.g., MBCT) show promise for increasing positive cognitions and creating an upward spiral of mood and cognition (Garland et al., 2010). With respect to cortisol, Beddig et al. (2020b) demonstrated the potential of a mindfulness-based focused attention therapy (MBAT) intervention to help individuals with recurrent depression buffer against increased overall cortisol secretion over time. Participants in the MBAT group who showed greater reductions in negative affect and rumination were able to maintain their initial cortisol levels from pre- to post-intervention. In contrast, those with less improvement exhibited cortisol increases similar to those in the progressive muscle relaxation (PMR) group.

Emotion Regulation Focused on Positive Affect. The present findings underscore the value of engaging in positive daily events through interventions like behavioral activation therapy (Cuijpers et al., 2020; Stein et al., 2021). In addition to evoking positive emotions, enhancing the individuals' responsiveness to these experiences through emotion regulation (ER) strategies—such as savoring, appreciation, mindfulness, and acceptance—may improve the maintenance of positive affect (Silton et al., 2020; Vanderlind et al., 2021; Wenzel et al., 2021). One promising strategy might be fantasizing. In a student sample, Besten et al. (2024) found that the frequency and content of mindwandering could be adjusted by self-relevant mood-induction interventions. In particular, compared to a stress induction, fantasizing was related to an increase in positive affect, a decrease in negative affect, as well as to more subsequent future-related, less past-related and less negative thoughts, especially in individuals who were prone to higher levels of negative affect and depressive symptoms. It remains unclear if short fantasizing practice sessions, conceptualized for the laboratory, would have an equally beneficial impact on individuals at high risk for depressive relapses and recurrences, making it an intriguing area for future research. Additionally, the duration of such potential effects needs to be further explored.

Ecological Momentary Interventions (EMIs). Real-time interventions, known as Ecological Momentary Interventions (EMIs) or Just-in-Time Adaptive Interventions (JITAIs), emerge as a promising approach for relapse prevention in high-risk individuals, such as those in remission from recurrent major depressive disorder (Schick et al., 2022). These app-based interventions offer distinct advantages over traditional in-person delivery, particularly in terms of cost, scalability, and anonymity (Linardon et al., 2024; Reichert et al., 2021; Schick et al., 2022). EMIs provide access to therapeutic strategies anytime, regardless of the patient's location, and can be easily tailored to individual needs (e.g., frequency, intensity, content). They also allow for the integration of both passive (e.g., GPS data) and active (e.g., subjective symptom ratings) data collection (Linardon et al., 2024; Reichert et al., 2021; Schick et al., 2022). While initial evidence supports the efficacy of EMIs for managing current major depression (Colombo et al., 2019), further exploration is needed to assess their effectiveness in preventing relapses and recurrences. In this context, the role of positive affect is particularly noteworthy. Although EMIs have shown mixed results in enhancing positive emotions (Heininga & Kuppens, 2021), there is growing evidence that mindfulness apps can effectively reduce symptoms of depression in the short term. However, their long-term effectiveness remains uncertain (Linardon et al., 2024). These apps may be especially beneficial for asymptomatic individuals or those at risk (Linardon et al., 2024). To enhance the effectiveness of future mindfulness-based apps, integrating passive sensing could facilitate the creation of more personalized interventions. Additionally, providing opportunities for direct interaction or real-time support from a psychotherapist via chat can improve user engagement, however, with unclear effects on symptom improvements (Linardon et al., 2024). Furthermore, future interventions could benefit from incorporating emotion regulation strategies that specifically target positive emotions as moderators of mood and cognitive benefits following daily positive events.

5.7 Strengths & Limitations

Together, the present three studies offer several strengths that enhance the robustness and validity of the current findings. First, we adopted a multimodal approach, incorporating multiple measures

such as interviewer ratings, retrospective and momentary self-reports, and cortisol assessments. This comprehensive methodology provides a holistic view of within-person associations and reactivity in recurrent major depression. Moreover, it aligns seamlessly with one of the core foci of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC; Insel et al., 2010) framework, offering valuable insights into the interplay between biological and psychological processes. Our approach also allows for a more nuanced understanding of the interaction between potential risk and protective factors in the course of depression, further enhancing the ecological validity of our findings. In addition, we assessed depression levels using a composite score combining self-reports (BDI-II) and external ratings (MADRS), which significantly reduces the risk of mono-method bias. A notable methodological strength lies in our conservative approach, including the lagged outcome as a covariate in all multilevel lag models, which controls for potential confounding effects of previous measurements. This enhances the accuracy of our findings regarding the dynamic relationships between momentary cognitions, affect, and daily events. Finally, with Study 3, we are among the first to implement a measurement burst design to examine intraindividual variability and changes in affective, cognitive, and physiological reactivity in a clinically diagnosed sample of individuals initially in remission from recurrent major depression. This novel approach in clinical psychological research is particularly innovative for investigating long-term within-person dynamics in depression.

Despite these valuable strengths, certain limitations should be acknowledged when interpreting the given results. Firstly, in all three studies, momentary cognitions were assessed with single items. Although this approach is common in Ambulatory Assessment research to reduce participant burden, it compromises the reliability estimation (Mestdagh & Dejonckheere, 2021). Future studies could benefit from standardized short scales like those suggested by the ESM Item Repository (Kirtley et al., 2022) to enhance measurement consistency.

Regarding the assessment of momentary negative affect and momentary rumination, previous research has shown that the respective scales often exhibit a restricted range, particularily in healthy samples (von Klipstein et al., 2023). Mestdagh et al. (2018) pointed out that when the level of an

Ambulatory Assessment variable is near the extreme ends of the scale, it limits the measure's ability to show fluctuations. This indicates confounding between the means and variances of the respective measure (Mestdagh et al., 2018). In addition, floor effects—where the means are extremely low—or ceiling effects—where the means are extremely high—can lead to violations of the assumptions underlying certain statistical models, such as linear multilevel regression. Addressing these potential violations is essential to avoid drawing erroneous conclusions (cf. von Klipstein et al., 2023). Therefore, it may be an option to use lower-intensity items (e.g., “uneasy”) when measuring negative affect – which however, could hinder a clear differentiation in negative affect within clinical samples -, or to place greater emphasis on assessing positive affect, as positive affect scales do not appear to face the same restriction in range (von Klipstein et al., 2023).

There are several points worth addressing with respect to the assessment of daily events. In Study 1 and 3, the subjective nature of daily event assessments poses a challenge, as it is unclear whether the reported group differences are due to actual differences in experiences or perceptions. We did not assess specific features, such as the type, severity, and persistence of the event or the context in which the event took place. This seems relevant, as research suggests that certain event characteristics—like stressor diversity—may have implications for psychological well-being. For instance, Koffer et al. (2016) found that greater stressor diversity is associated with lower levels of negative affect and weaker links between daily stressor exposure and negative affect. The heterogeneity of events as well as various aspects of the situation in which they occur can be best considered using multi-modal information collection (Kubiak & Smyth, 2019; Wenzel et al., 2016). Implementing context-aware assessment strategies that incorporate both subjective reports and objective mobile sensing data could provide a more comprehensive understanding of responsiveness toward an event (Schick et al., 2023; Smyth et al., 2023). Moreover, we did not account for the cumulative impact of multiple positive or negative events, which could significantly influence affective (e.g., Mey et al., 2020; Schilling & Diehl, 2014; Schilling et al., 2022), cognitive, or even endocrinological changes. A common problem when assessing reactivity demonstrates potential retrospective bias (e.g. Khazanov et al., 2019). Subjective

assessments coincide with the indication of event occurrence, but refer to an event that took place between the current and the last assessment. In particular, with respect to measuring saliva cortisol levels, such retrospective assessment can be seen problematic. While in Study 2, we assessed cortisol levels 20 minutes after the subjective reports of daily momentary cognitions and affect, thereby meeting current recommendations for cortisol-reactivity assessment (Schlotz et al., 2019; Stoffel et al., 2021), in Study 3, the time lag between the reported daily events and saliva collection could strongly vary and therefore deviate from the recommended time interval. Future research could use event-contingent designs in order to increase assessment reliability. Filtering for events that occurred no longer than 30 minutes prior to saliva collection would have been another idea; this however requires a higher sampling density. Compliance rates were overall high, but the monitoring of saliva collection timing was limited, which introduces the possibility of inaccuracies regarding the exact timing of individual samples. To address this issue, using electronic caps to record opening times (Adam & Kumari, 2009; Schlotz, 2019; Stoffel et al., 2021) or implementing a more cost-effective method—such as providing participants with digital codes to note on their saliva collection containers (Beddig et al., 2019; Nayman et al., 2024; Schlotz, 2019)—could enhance adherence, improve study quality, and reduce the risk of underestimating effect sizes (Adam et al., 2017; Kudielka et al., 2003; Stoffel et al., 2021).

Lastly, in Studies 2 and 3 our sample of individuals with recurrent major depression was rather heterogeneous, with the majority currently in partial or full remission. As for studies investigating the long-term course of depression, the sample we chose in Study 3, however, reflects the natural clinical course of individuals with recurrent depressive episodes remitted at baseline with a high risk for further relapses/recurrences. For the analysis of shorter term associations (see Studies 1 and 2), future research would profit from including individuals with current and remitted MDD, as well as healthy individuals in order to more clearly separate the effects of current depressive mood from underlying risk.

5.8 Conclusion

The present studies significantly enhance our understanding of affective, cognitive and endocrinological dynamics in individuals with a history of recurrent depressive episodes, particularly among those in remission. Our findings highlight the crucial role of positive affect and positive cognitions, and their mutual amplification, potentially fostering psychological resilience. The concept of mood- and cognition brightening emerges as a vital mechanism through which individuals can improve their emotional well-being, although questions remain regarding its longer-term sustainability.

The observed interplay between momentary rumination and momentary affect underscores the need for interventions targeting maladaptive cognitive patterns. Our results suggest that addressing rumination may improve emotional responses to daily stressors, with implications for therapeutic strategies aimed at promoting adaptive emotion regulation. Moreover, the variability in cortisol responses in response to daily internal and external stressors indicates that physiological factors should be integrated into future research for a holistic understanding of individual experiences in those at risk for depressive relapses and recurrences.

Additionally, the specificity of our sample, composed primarily of individuals with a history of recurrent major depressive disorder, allows for a deeper exploration of the intricate dynamics between affective, cognitive and physiological processes in daily life. The results suggest that those in remission may still grapple with unique vulnerabilities that can hinder their ability to fully benefit from positive daily events. This underscores the importance of targeting positive emotional experiences as a therapeutic strategy, fostering a greater capacity for joy and appreciation, even amidst underlying risks of recurrence.

I believe our findings provide essential insights for relapse prevention; however, it is important to acknowledge the limitations of our research design. Although the within-person associations at the micro-level have a high-resolution and are ecologically valid, they do not, per se, allow for concrete predictions about long-term mental health outcomes at the macro-level. Future research should aim to bridge this gap by examining the interplay between short-term affective, cognitive, physiological

and ideally neurobiological processes and their implications for the long-term course of depression. As we continue to unravel the complexities of recurrent depression, integrating new insights from pioneering methodological approaches and innovative uses of technology - such as mobile sensing, machine learning, or even artificial intelligence - into clinical practice will be imperative for preventing future depressive episodes and promoting sustained well-being.

SUMMARY

In this dissertation, I explored the affective, cognitive, and physiological dynamics in the daily life of individuals with recurrent depressive episodes compared to healthy individuals. The dissertation is based on three studies, utilizing Ambulatory Assessment methodologies, including a measurement-burst design. These studies aimed to clarify mechanisms of micro-processes in daily life that could increase vulnerability to relapse and suggest potential therapeutic interventions.

Study 1 (Chapter II) examined differences in daily affect and cognitions between individuals in remission from recurrent depression and healthy controls, along with their reactivity to daily negative and positive events. Key findings indicated that higher levels of positive thoughts boosted mood in both groups, while rumination predicted decreases in positive affect specifically in remitted individuals. Remitted individuals showed greater increases in negative affect and rumination following negative events. Notably, positive events elicited a "mood brightening" effect, marked by stronger decreases in negative affect and rumination, along with greater increases in positive affect and positive thoughts. These results highlight the protective role of positive affect and cognitions, suggesting therapeutic approaches that sustain positive mood could support long-term remission.

Study 2 (Chapter III) investigated associations between trait and state cognitions and salivary cortisol as a biological stress marker in daily life. Findings revealed that trait repetitive negative thinking, but not mindfulness, was linked to higher cortisol levels, particularly in individuals with recurrent depression compared to healthy individuals. Additionally, momentary mind-wandering and mental shift problems predicted increases in cortisol levels 20 minutes later. Within the recurrent depression group, higher average levels of mental shift problems were associated with elevated cortisol. Multilevel structural equation models indicated that state cognitions did not mediate the effects of habitual repetitive negative thinking on cortisol release. These results underscore the independent roles of trait and state cognitions as internal stressors activating the hypothalamic-pituitary-adrenal axis, emphasizing the heightened physiological vulnerability of individuals with recurrent depression.

Study 3 (Chapter IV) applied a measurement-burst design to explore intraindividual variability and change in affective, cognitive, and endocrinological responses to daily events over 4.4 years in initially remitted individuals with recurrent depression. Over bursts, negative affect more strongly increased following negative daily events, while positive affect and self-acceptance exhibited a more pronounced decrease. Rumination and cortisol reactivity remained stable in response to negative events. Conversely, positive daily events were linked to a more significant increase in positive affect over bursts. Depression levels served as a moderator of intraindividual variability, with higher depression levels being linked to blunted cortisol responses toward negative events. Additionally, a "cognition brightening" effect was observed, reflected by greater increases in self-acceptance and greater decreases in negative affect toward positive daily events in those individuals with higher depression levels, though this effect seemed unsustainable over bursts. These findings highlight the intricate dynamics of affective, cognitive and endocrinological processes in recurrent depression, emphasizing the need for targeted interventions that account for the stability of these responses and the moderating role of depression levels.

In conclusion, findings from these three studies underscore the importance of fostering positive affect and reducing maladaptive thought patterns in individuals with recurrent depression, providing valuable insights for relapse prevention. Integrating technology and advanced data methods into clinical practice holds promise for tailoring interventions to individual needs and facilitating early detection of relapse risks, thereby promoting more effective and proactive care for those vulnerable to depressive relapses.

ZUSAMMENFASSUNG

In der vorliegenden Dissertation untersuchte ich affektive, kognitive und physiologische Dynamiken von Personen mit einer Vorgeschichte wiederkehrender depressiver Episoden im Vergleich zu gesunden Personen untersucht. Dazu habe ich Ambulantes Assessment, einschließlich einer Measurement-Burst Methodik, eingesetzt. Insgesamt beleuchten die drei Studien Mechanismen, welche die Vulnerabilität für Rückfälle erhöhen könnten, und weisen auf potenzielle therapeutische Interventionen in diesem Kontext hin.

Studie 1 (Kapitel II) untersuchte Unterschiede in Affekt und Kognitionen im Alltag zwischen Personen in Remission von rezidivierender Depression und gesunden Personen sowie deren Reaktivität gegenüber negativen und positiven Ereignissen im Alltag. Als zentrale Ergebnisse zeigten sich, dass ein höheres Maß an positiven Gedanken eine Verbesserung der Stimmung in beiden Gruppen prädizierte, während Rumination insbesondere bei remittierten Personen eine Abnahme des positiven Affekts vorhersagte. Remittierte Personen zeigten nach negativen Ereignissen stärkere Anstiege im negativen Affekt und Rumination. Positive Ereignisse waren mit einer Stimmungsaufhellung, einem sogenannten „*mood brightening*“ Effekt assoziiert, welcher durch stärkere Abnahmen im negativen Affekt und Rumination sowie stärkere Anstiege im positiven Affekt und positiven Gedanken gekennzeichnet war. Diese Ergebnisse heben die protektive Funktion von positivem Affekt und positiven Kognitionen hervor und indizieren, dass therapeutische Ansätze, welche sich auf die Aufrechterhaltung von positivem Affekt konzentrieren, eine langfristige Remission unterstützen könnten.

Studie 2 (Kapitel III) untersuchte Zusammenhänge zwischen habituellen und momentanen Kognitionen im Alltag mit Speichelkortisol als biologischem Stressmarker im Alltag. Die Ergebnisse zeigten, dass habituelles repetitives negatives Denken mit höheren Kortisolspiegeln assoziiert war, insbesondere bei Personen mit rezidivierender Depression im Vergleich zu gesunden Personen. Zudem prädizierten momentanes Mindwandering (Abschweifen der Gedanken) und mentalshift Probleme

(Schwierigkeiten beim Aufmerksamkeitswechsel) einen Anstieg der Kortisolwerte 20 Minuten später. Innerhalb der klinischen Gruppe waren höhere durchschnittliche Niveaus von mentalshift Problemen mit erhöhtem Kortisol assoziiert. Multilevel-Strukturgleichungsmodelle zeigten, dass momentane Kognitionen die Auswirkungen von habituellem repetitiven negativem Denken auf die Kortisolausschüttung nicht mediieren. Diese Ergebnisse unterstreichen die unabhängige Rolle von Trait- und State-basierten Kognitionen als interne Stressoren in der Aktivierung der Hypothalamus-Hypophysen-Nebennieren-Achse und verweisen auf eine erhöhte physiologische Vulnerabilität von Personen mit rezidivierender Depression.

Studie 3 (Kapitel IV) verwendete ein Measurement-Burst Design, um intraindividuelle Variabilität und Veränderung in affektiven, kognitiven und endokrinologischen Reaktionen auf Ereignisse im Alltag über einen Zeitraum von 4,4 Jahren bei initial remittierten Personen mit rezidivierender Depression zu untersuchen. Über die Bursts hinweg zeigte sich eine Zunahme des Anstiegs des negativen Affekts nach negativen Ereignissen, während positive Affekt und Selbstakzeptanz stärkere Abnahmen verzeichneten. Rumination und Kortisolreaktivität blieben gegenüber negativen Ereignissen stabil. Positive Ereignisse waren hingegen mit einem signifikanten Anstieg des positiven Affekts über die Messperioden verbunden. Das Depressionsniveau moderierte die intraindividuelle Variabilität, wobei höhere Depressionswerte mit einer abgeschwächten Kortisolreaktion auf negative Ereignisse assoziiert waren. Zusätzlich wurde ein „cognition brightening“ Effekt identifiziert, welcher sich durch stärkere Anstiege in Selbstakzeptanz und stärkere Abnahmen im negativen Affekt gegenüber positiven Ereignissen bei Personen mit höheren Depressionswerten zeigte. Dieser Effekt erschein über die Bursts hinweg jedoch nicht stabil zu sein. Diese Ergebnisse verdeutlichen die komplexen Dynamiken affektiver, kognitiver und endokrinologischer Prozesse bei rezidivierender Depression und betonen die Notwendigkeit gezielter Interventionen, welche die Stabilität von Reaktivität im Alltag sowie die moderierende Rolle des Depressionsniveaus berücksichtigen.

Schlussfolgernd unterstreichen die vorliegenden Studien die Bedeutung der Förderung positiven Affekts und der Reduktion maladaptiver Denkmuster bei rezidivierender Depression und liefern wichtige

Erkenntnisse für die Rückfallprävention. Die Integration von neuen Technologien und Datenanalysemethoden in die klinische Praxis bietet vielversprechende Ansätze, um Interventionen individuell anzupassen und eine frühzeitige Erkennung von Rückfallrisiken zu ermöglichen. Hierdurch kann eine effektivere, proaktive Versorgung für Personen mit erhöhtem Rückfallrisiko gefördert werden.

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SUPPLEMENTARY MATERIAL

Supplementary Material Chapter II

Model Equation S1

As an example for our multilevel models (here: rumination (RUM; T-1) predicting negative affect (NA; T1), the level 1 model can be described as:

$$Y\ (NA)_{ijk} = \pi_{0jk} + \ \pi_{1jk} * lagged\ RUM_{ijk}^{W-S} + \ \pi_{1jk} * lagged\ NA_{ijk}^{W-S} + \ \varepsilon_{ijk}$$

Here, Y_{ijk} represents the level of negative affect at time *i* at assessment day *j* for person *k*. The π coefficients represent the intercept and the fixed main effects at level 1, the ε_{ijk} denote the residuals at level 1.

The level 2 model can be described as:

$$\pi_{0jk} = \beta_{0jk} + \ u_{1jk}$$

$$\pi_{1jk} = \beta_{10k}$$

$$\pi_{2jk} = \beta_{20k}$$

with the u_{0jk} representing random intercepts for the assessment day *j* within person *k*.

The level 3 model can be described as:

$$\beta_{00k} = \gamma_{000} + \ \gamma_{001} * group_k \ + \ \gamma_{002} * RUM_k^{B-S} + \ v_{00k}$$

$$\beta_{10k} = \gamma_{100} + \ \gamma_{110} * group_k$$

$$\beta_{20k} = \gamma_{200}$$

Here the v_{00k} indicates the random intercept for person *k*.

In all analyses, the significance level was set at $\alpha = 0.05$.

Table S1

Means, Standard Deviations, Bivariate Within- and Between-Subjects Correlations and the Intra-Class Correlation Coefficients (ICCs) of all Outcome Variables

	1	2	3	4
1) Negative Affect	-	-.80**	.83**	-.57**
2) Positive Affect	-.67**	-	-.68**	.71**
3) Rumination	.54**	-.48**	-	-.39**
4) Positive Thoughts	-.37**	.49**	-.31**	-
M	2.11	4.74	1.85	4.05
SD_within	0.62	0.72	0.95	1.26
SD_between	0.78	0.87	0.84	0.94
ICC	0.59	0.57	0.41	0.33

Note. Between-person correlations ($N_{\_Persons}$ = 102) are presented above the diagonal; within-person correlations among daily measures ($N_{\_measurement\ occasions}$ = 4,651) are presented below the diagonal. ***p* < .01.

Table S2

Three-level Models: Reciprocal Prospective Effects of Momentary Cognitions and Affect in Daily Life

Model	Predictor	Outcome	*B (SE)*	*p*	R^2
Step 1	Group[a]	NA (T1)	0.09 (0.10)	.405	0.03
	Rumination (W-S) (T-1)		0.01 (0.01)	.295	
	Rumination (B-S)		0.75 (0.06)	<.001	
	Negative Affect (W-S) (T-1)		0.26 (0.02)	<.001	
Step 2	Rumination (W-S) (T-1) * Group		0.02 (0.02)	.315	0.03
Step 1	Group[a]	RUM (T1)	0.29 (0.10)	.005	0.04
	Negative Affect (W-S) (T-1)		0.20 (0.03)	<.001	
	Negative Affect (B-S)		0.79 (0.06)	<.001	
	Rumination (W-S) (T-1)		0.04 (0.02)	.057	
Step 2	Negative Affect (W-S) (T-1) * Group		0.11 (0.05)	.026	0.04
Step 1	Group[a]	PA (T1)	-0.30 (0.15)	.047	0.04
	Rumination (W-S) (T-1)		-0.02 (0.01)	.166	
	Rumination (B-S)		-0.62 (0.09)	<.001	
	Positive Affect (W-S) (T-1)		0.28 (0.02)	<.001	
Step 2	Rumination (W-S) (T-1) * Group		-0.06 (0.02)	.015	0.04
Step 1	Group[a]	RUM (T1)	0.45 (0.13)	.001	0.03
	Positive Affect (W-S) (T-1)		-0.12 (0.02)	<.001	
	Positive Affect (B-S)		-0.52 (0.07)	<.001	
	Rumination (W-S) (T-1)		0.06 (0.02)	.001	
Step 2	Positive Affect (W-S) (T-1) * Group		-0.11 (0.04)	.015	0.03
Step 1	Group[a]	NA (T1)	0.60 (0.08)	<.001	0.03
	Positive Thoughts (W-S) (T-1)		-0.02 (0.01)	.037	
	Positive Thoughts (B-S)		-0.40 (0.06)	<.001	
	Negative Affect (W-S) (T-1)		0.25 (0.02)	<.001	
Step 2	Positive Thoughts (W-S) (T-1) * Group		-0.02 (0.01)	.263	0.03
Step 1	Group[a]	PT (T1)	0.14 (0.18)	.449	0.03
	Negative Affect (W-S) (T-1)		-0.11 (0.04)	.001	
	Negative Affect (B-S)		-0.75 (0.12)	<.001	
	Positive Thoughts (W-S) (T-1)		0.08 (0.02)	<.001	
Step 2	Negative Affect (W-S) (T-1) * Group		-0.02 (0.07)	.739	0.03

Table S2 (to be continued)

Step 1	Group[a]	PA (T1)	-0.61 (0.11)	<.001	0.05
	Positive Thoughts (W-S) (T-1)		0.03 (0.01)	.005	
	Positive Thoughts (B-S)		0.59 (0.06)	<.001	
	Positive Affect (W-S) (T-1)		0.27 (0.02)	<.001	
Step 2	Positive Thoughts (W-S) (T-1) * Group		0.02 (0.02)	.274	0.04
Step 1	Group[a]	PT (T1)	0.31 (0.16)	.049	0.03
	Positive Affect (W-S) (T-1)		0.15 (0.03)	<.001	
	Positive Affect (B-S)		0.86 (0.09)	<.001	
	Positive Thoughts (W-S) (T-1)		0.06 (0.02)	.001	
Step 2	Positive Affect (W-S) (T-1) * Group		0.05 (0.06)	.363	0.03
Step 1	Group[a]	RUM (T1)	0.79 (0.13)	<.001	0.03
	Positive Thoughts (W-S) (T-1)		-0.04 (0.01)	.002	
	Positive Thoughts (B-S)		-0.26 (0.07)	.001	
	Rumination (W-S) (T-1)		0.08 (0.02)	<.001	
Step 2	Positive Thoughts (W-S) (T-1) * Group		-0.03 (0.02)	.279	0.03
Step 1	Group[a]	PT (T1)	-0.04 (0.21)	.838	0.03
	Rumination (W-S) (T-1)		-0.07 (0.02)	.003	
	Rumination (B-S)		-0.43 (0.13)	.001	
	Positive Thoughts (W-S) (T-1)		0.08 (0.02)	<.001	
Step 2	Rumination (W-S) (T-1) * Group		-0.05 (0.05)	.256	0.03

Note. NA = negative affect, PA = positive affect, RUM = momentary rumination, PT = positive thoughts; W–S: within-subject (person-mean centered), B–S: between-subject (grand-mean centered). Models include random intercepts at level 2 (assessment day) and 3 (person). Time TE = Time of Event (interval between the previous (T-1) and the current (T1) prompt).

[a] Reference category: healthy controls.

Table S3

Three-level Models: Prospective Effects of Daily Events on Momentary Cognitions and Affect

Model	Predictor	Outcome	*B (SE)*	*p*	R^2
Step 1	Group[a]	NA (T1)	0.71 (0.14)	<.001	0.18
	Negative Event (W-S) (TE)		0.78 (0.03)	<.001	
	Negative Event (B-S)		0.81 (0.77)	.292	
	Negative Affect (W-S) (T-1)		0.25 (0.01)	<.001	
Step 2	Negative Event (W-S) (TE) * Group		0.20 (0.06)	.001	0.18
Step 1	Group[a]	PA (T1)	-0.81 (0.16)	<.001	0.16
	Negative Event (W-S) (TE)		-0.81 (0.04)	<.001	
	Negative Event (B-S)		-1.07 (0.87)	.219	
	Positive Affect (W-S) (T-1)		0.36 (0.01)	<.001	
Step 2	Negative Event (W-S) (TE) * Group		-0.14 (0.07)	.055	0.16
Step 1	Group[a]	RUM (T1)	0.84 (0.14)	<.001	0.30
	Negative Event (W-S) (TE)		0.98 (0.05)	<.001	
	Negative Event (B-S)		1.08 (0.79)	.170	
	Rumination (W-S) (T-1)		0.09 (0.02)	<.001	
Step 2	Negative Event (W-S) (TE) * Group		0.38 (0.10)	<.001	0.30
Step 1	Group[a]	PT (T1)	-0.42 (0.20)	.037	0.12
	Negative Event (W-S) (TE)		-0.87 (0.07)	<.001	
	Negative Event (B-S)		-0.07 (1.09)	.946	
	Positive Thoughts (W-S) (T-1)		0.09 (0.02)	<.001	
Step 2	Negative Event (W-S) (TE) * Group		0.03 (0.14)	.817	0.12
Step 1	Group[a]	NA (T1)	0.77 (0.13)	<.001	0.06
	Positive Event (W-S) (TE)		-0.23 (0.02)	<.001	
	Positive Event (B-S)		-0.83 (0.31)	.009	
	Negative Affect (W-S) (T-1)		0.26 (0.02)	<.001	
Step 2	Positive Event (W-S) (TE)* Group		-0.18 (0.05)	<.001	0.06
Step 1	Group[a]	PA (T1)	-0.88 (0.15)	<.001	0.10
	Positive Event (W-S) (TE)		0.41 (0.03)	<.001	
	Positive Event (B-S)		0.92 (0.35)	.010	
	Positive Affect (W-S) (T-1)		0.28 (0.02)	<.001	
Step 2	Positive Event (W-S) (TE)* Group		0.26 (0.05)	<.001	0.10

Table S3 (to be continued)

Step 1	Group[a]	RUM (T1)	0.90 (0.14)	<.001	0.24
	Positive Event (W-S) (TE)		-0.22 (0.04)	<.001	
	Positive Event (B-S)		-0.45 (0.33)	.171	
	Rumination (W-S) (T-1)		0.09 (0.02)	<.001	
Step 2	Positive Event (W-S) (TE)* Group		-0.27 (0.08)	.001	0.24
Step 1	Group[a]	PT (T1)	-0.46 (0.18)	.010	0.13
	Positive Event (W-S) (TE)		0.79 (0.05)	<.001	
	Positive Event (B-S)		1.70 (0.42)	<.001	
	Positive Thoughts (W-S) (T-1)		0.08 (0.02)	<.001	
Step 2	Positive Event (W-S) (TE)* Group		0.21 (0.10)	.041	0.13

Note. NA = negative affect, PA = positive affect, RUM = momentary rumination, PT = positive thoughts; W–S: within-subject (person-mean centered), B–S: between-subject (grand-mean centered). Models include random intercepts at level 2 (assessment day) and 3 (person). Time TE = Time of Event (interval between the previous (T-1) and the current (T1) prompt).

[a] Reference category: healthy controls.

Supplementary Material Chapter IV

Table S4

Means, Standard Deviations, Bivariate Within- and Between-Subjects Correlations, and Intraclass Correlation Coefficients (ICCs) of all Outcome Variables

	burst 1					burst 2				
	1	2	3	4	5	1	2	3	4	5
1) Negative Affect	-	-.75	.80	-.62	-.05	-	-.81	.81	-.79	-.19
2) Positive Affect	-.73	-	-.54	.70	-.05	-.73	-	-.67	.85	.27
3) Rumination	.65	-.56	-	-.49	.03	.65	-.56	-	-.72	.27
4) Self-Acceptance	-.47	.54	-.40	-	.04	-.47	.54	-.40	-	-.11
5) Cortisol	.05	.04	.05	-.10	-	.11	-.06	.05	-.03	-
M	2.89	4.14	2.58	4.80	2.50	2.73	4.14	2.46	5.02	2.06
SD_within	0.88	0.91	1.33	1.19	0.95	0.81	0.87	1.25	0.90	0.95
SD_between	0.92	0.81	1.10	1.30	0.33	0.98	0.96	0.92	1.53	0.33

	Across Bursts				
	Negative Affect	Positive Affect	Rumination	Self-Acceptance	Cortisol
ICC (W-S)	0.34	0.39	0.16	0.43	2.58E-3
ICC (W-S_burst)	0.28	0.28	0.25	0.32	0.16
ICC (B-S)	0.38	0.33	0.59	0.25	0.84

Note. Between-person correlations ($N_{\_patients}$ = 54) are presented above the diagonal; within-person correlations among daily measures ($N_{\_assessment\ points\_burst1}$ = 1,433 and $N_{\_assessment\ points\_burst3}$ = 2,411) are presented below the diagonal.

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Education

since October 2022	**Postgraduate Training in Psychological Psychotherapy (CBT)** IFKV - Institut für Fort- und Weiterbildung in Klinischer Verhaltenstherapie, Bad Dürkheim, Germany
April 2014 – July 2019	**M.Sc. Psychology (1.0) – *Clinical-health oriented focus*** Master's thesis: *Meta-Analysis on mood and emotion induction procedures* (2019). Johannes Gutenberg University, Mainz, Germany
October 2015 – February 2016	**Exchange program of Mainz University** Sponsored by the ERASMUS scholarship of the DAAD M.Sc. Psychology– Clinical Psychology Ramon Llull University, Barcelona, Spain
October 2010 – September 2014	**B.Sc. Psychology (1.3)** Bachelor's thesis: *Holistic and configural face processing in middle-aged adults* (2014). Johannes Gutenberg University, Mainz, Germany
August, 2001 – March, 2010	**Abitur (1.5)** Werner-Heisenberg-Gymnasium, Bad Dürkheim

Clinical Practice & Teaching Experience

since April 2023	**Clinical Psychologist (Internship CBT Training) – Psychiatry Sonnenwende, Bad Dürkheim** Diagnostic assessment, psychotherapy including group therapy and crisis intervention within a multidisciplinary care setting
2012 – 2018	**SPSS Tutor – Johannes Gutenberg University, Mainz** Transferred critical research skills to novice teachers: formulating hypothesis, managing and analysing data using SPSS software, writing conclusions (descriptive/inferential)
2016 -2017	**Teaching Assistant – ESADE - Business and Law School, Barcelona, Spain**

	Responsible for the grading system and group projects in the courses *Business in Society*, *Global Organization*, *Global Operations*, *Managing Ethics and Sustainability* and *Finance* in the *Master of International Management*, *Master of Innovation and Entrepreneurship* and the *Fulltime MBA*
2011-2012	**Teaching Assistant – Johannes Gutenberg University, Mainz** Department: Personality Psychology and Psychological Diagnostics Leading group work and designing research posters

Research Experience

August 2019 – September 2023	**Research Associate – Central Institute of Mental Health Mannheim** PhD Candidate – Department of Psychiatry and Psychotherapy Research Group: Longitudinal and Intervention Research Supervisor: Prof. (apl.) Dr. Christine Kuehner
March 2019 – October 2019	**Research Assistant – Johannes Gutenberg University, Mainz** Department of Work and Organizational Psychology Data analysis and creation of a the final report of a long-term resilience study that evaluated the efficacy of a resilience training for employees of the automobile sector
October 2017 – May 2018	**Research Assistant – Johannes Gutenberg University, Mainz** Department of Educational Science Data management and analyses in the project "*Online self-regulation training for students – a scientifically based instrument to improve learning strategies*"
March 2013 – September 2013	**Research Internship – IFT Institut für Therapieforschung – Munich** Analysing data, writing a final report and designing a conference poster of the current *Phar-Mon* project "*Further development and implementation of a monitoring system for the abuse of medication and other psychotropic substances*."
July 2005	**Schoolinternship** - **GESIS Leibniz Institute for the Social Sciences** Insights in literature research and construction of questionnaires

Completed Projects

August 2019 – March 2024	**Schricker, I. F. & Kuehner, C.** *Long-term course of Ambulatory Assessment (AA-) phenotypes and ecological validation of cognitive processes in patients with recurrent depression (DFG KU1464/8-1).*

Awards

Poster price at the SAA conference (2023), Amsterdam (Netherlands)

3rd poster price at the ZIHUb conference (2022), Heidelberg (Germany)

GLK (Gutenberg Lehrkolleg) award for exceptional student thesis: Bachelor's thesis: Schricker I., & Kurbel, D. (2014). *Holistic and configural face processing in middle-aged adults.*

Membership

German Psychological Society (DGPs)

Mannheim, 30.12.2024

PUBLICATIONS

Peer-Reviewed Publications

Nayman, S., **Schricker, I. F.**, Reinhard, I., Grammatikos, I., & Kuehner, C. (in press). Induced Rumination and Mindful Self-focus in Daily Life across the Menstrual Cycle in Women with and without Premenstrual Dysphoric Disorder. Behaviour Research and Therapy. https://doi.org/10.1016/j.brat.2024.104630

Nayman, S., **Schricker, I. F.**, Reinhard, I., Dreer, J. K., Richter, A. S., & Kuehner, C. (2024). State and trait cognitions differentially affect cyclicity of mood and cortisol in individuals with and without Premenstrual Dysphoric Disorder. *Journal of Psychopathology and Clinical Science, 133*(4), 309–320. https://doi.org/10.1037/abn0000894

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