Aberrant brain activation and coupling in Depression – Links between Psychopathology and Neurophysiology

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Abstract

Major Depressive Disorder (MDD) is the most common mental disorder and ranging under the top three of the most disabling diseases worldwide. Although various treatments exist for MDD, about 30 to 40 % of the patients don't respond. A better understanding of the neurobiological correlates of MDD might lead to the development of new and the improvement of existing treatments. The dissertation at hand is dedicated to the aim of a better understanding of aberrant brain functioning and coupling in MDD. Further, we sought to investigate the behavioral and cognitive-affective underpinnings that lead to aberrant brain functioning and coupling in MDD, in terms of depressive rumination.

In total this work comprises four studies. In our **first study,** we investigated the functional connectivity (FC) during resting state (rsFC) and task performance of the Trail Making Test (TMT) in subjects with late-life depression (LLD) and healthy controls (HC). FC was assessed via functional near-infrared spectroscopy (fNIRS) in areas of the cognitive control network (CCN). While we observed an expected pattern of change in FC in the healthy controls with relatively low FC during resting-state and an increase during task-performance, subjects with LLD showed an opposite pattern, with relatively high FC during resting-state and decreases during task-performance. Further, depressed and non-depressed subjects differed significantly during resting-state (LLD>HC) and the executive demanding condition of the TMT (HC>LLD). While these results were interesting from a standpoint of pathophysiological changes in FC, we couldn't give a final explanation for the observed FC patterns in LLD. As a possible explanation, we assumed that some kind of depressive cognitive process could lead to hyper-connectivity within the CCN during resting-state that further disturbs cortical coupling during task performance. As depressive rumination is such a cognitive process that is common in depression, we developed a resting-state questionnaire to assess state rumination for subsequent studies.

In **study two**, we investigated rsFC within subjects with MDD and HC with a parietal probeset covering parts of the default mode network (DMN), CCN and dorsal attention network (DAN). Further, we investigated in how far state- and trait rumination explained the differences between depressed and non-depressed subjects in rsFC. In contrast to our first study, we observed an opposite pattern of FC differences between the groups: within the parietal cortex, depressed subjects showed reduced FC in comparison to HC in a widespread bilateral network. While state rumination showed rather restricted effects, the measures of trait rumination showed wide-spread effects. Further, FC was negatively correlated with state- and trait rumination.

Since our results so far were restricted to non-experimental between-subject associations, that don't allow the investigation of causal relationships, we further designed a study in which we sought to induce rumination with the Trier Social Stress Test (TSST).

In **study three**, we investigated the hemodynamic changes during the TSST in high and low trait ruminators in the CCN, further, we examined in how far state rumination would be induced through the TSST. Relationships between hemodynamic responses and state rumination were examined with a mediation analysis. As expected, we found increases in state rumination through the TSST. Further, these increases were higher in the high-trait ruminators. On a cortical level, low ruminators showed higher cortical activation in the stress condition than the high ruminators in the right inferior frontal gyrus (IFG). Further, group differences in post-stress state rumination were mediated by the cortical reactivity in this region. Subject with high IFG reactivity showed less state-rumination following the TSST.

In **study four**, we further investigated in the same study cohort, if rsFC before and after stress would show an expected pattern with higher baseline FC in the high trait ruminators and a higher reactivity in rsFC in subjects with high increases in state rumination. As expected, baseline levels of rsFC were increased in the high-ruminators like in our first study for the LDD group. However, although state rumination increased in the high trait ruminators more

strongly than in the low trait ruminators, rsFC only increased in the latter group. Since we didn't observe a co-variation of change scores between rsFC and state rumination, we concluded that the effect of rumination on FC changes would be an indirect one.

In the general discussion of this dissertation, I propose a model of indirect prolonged stress effects in high ruminating subjects that lead to higher stress levels and subsequently to permanent changes in FC. This model would explain the observed effects in our study and is in line with current research of FC alterations in chronic stress. I further outline, in how far the presented results and the research of biological underpinnings could improve the current theory development of mental diseases as well as treatment planning.

Zusammenfassung

Bei der Majoren Depression handelt es sich um eine häufig vorkommende psychische Störung, welche weltweit zu den drei am stärksten einschränkenden Erkrankungen zählt. Obwohl eine Vielzahl an Behandlungsmöglichkeiten existiert, schlagen herkömmliche Behandlungsmethoden bei 30 bis 40 % der Patienten nicht an. Die Erforschung der neurobiologischen Grundlagen von Depression könnte zu der Entwicklung neuer und der Verbesserung bestehender Behandlungsmöglichkeiten beitragen. Die vorliegende Dissertation ist dem Ziel gewidmet, die Deviationen hinsichtlich kortikaler Aktivierung und funktioneller Konnektivität bei depressiven Patienten besser zu verstehen. In diesem Zusammenhang wurden die verhaltensbezogenen und kognitiv-affektiven Prozesse, welche mit Veränderungen in der Aktivität und funktionellen Konnektivität in spezifischen Hirnarealen einhergehen, untersucht. Hierbei lag ein besonderes Augenmerk auf dem Prozess des depressiven Grübelns (engl. *rumination*).

Diese Arbeit umfasst insgesamt vier Studien. In unserer **ersten** Studie untersuchten wir, inwiefern sich Probanden mit Depression im Alter von gesunden Kontrollprobanden hinsichtlich ihrer funktionellen Konnektivität während Ruhemessungen und während der Durchführung des Trail Making Tests voneinander unterschieden. Die funktionelle Konnektivität wurde dabei mittels funktioneller Nahinfrarot Spektroskopie (fNIRS) im kognitiven Kontrollnetzwerk erfasst. Bei den gesunden Probanden zeigte sich wie erwartet eine relativ geringe funktionelle Konnektivität während der Ruhemessung und einem Anstieg während der Aufgabenbewältigung. Konträr dazu zeigten die Patienten eine relativ hohe funktionelle Konnektivität im Ruhezustand und eine verringerte funktionelle Konnektivität während der Aufgabenbewältigung. Weiterhin unterschieden sich die beiden Gruppen während der Ruhemessung (Patienten>Kontrollen) und der schwierigen Bearbeitung des Trail Making Tests (Kontrollen>Patienten) signifikant voneinander. Als mögliche Ursache für die berichteten Ergebnisse diskutierten wir die Rolle des kognitiven Prozesses der Rumination und entwickelten einen Ruhemessungs-Fragebogen, um momentanes (engl. *state*) Grübeln in den folgenden Studien zu erfassen.

In unserer **zweiten** Studie untersuchten wir die funktionelle Konnektivität während Ruhemessungen bei Patienten mit einer Majoren Depression und gesunden Kontrollprobanden in einem parietalen Probeset welches Teile des somatosensorischen Netzwerkes, des Default Mode Netzwerkes und des dorsalen Aufmerksamkeitsnetzwerkes erfasste. Weiterhin untersuchten wir, inwiefern Unterschiede in der funktionellen Konnektivität zwischen Patienten und gesunden Probanden durch momentanes (*state*) und habituelles (engl. *trait*) Grübeln erklärt werden können. Im Vergleich zu unserer ersten Studie beobachteten wir hier einen umgekehrten Gruppeneffekt: Patienten mit einer Majoren Depression zeichneten sich während der Ruhemessung durch eine verringerte funktionelle Konnektivität im parietalen Kortex aus. Während die Effekte des momentan erfassten Grübelns in der linken Hemisphäre fokussiert waren, wies sich habituelles Grübeln durch weit gestreute Effekte im gesamten bilateralen parietalen Kortex aus. Zudem zeigten sich negative Korrelationen zwischen dem momentanen und habituellen Grübeln und der Stärke der funktionellen Konnektivität.

Da unsere Ergebnisse an dieser Stelle auf nicht experimentellen Zwischensubjekteffekten beruhten, planten wir im Folgenden eine Studie zur Induktion momentanen Grübelns mittels des Trier Sozialen Stress Test (TSST), um eine kausale Beurteilung der Wirkung von momentanen Grübeln auf die funktionelle Konnektivität und Hirnaktivierung zu ermöglichen.

In Studie **drei** untersuchten wir Unterschiede in der hämodynamischen Antwort zwischen hoch und niedrig Grüblern im Kognitiven Kontrollnetzwerk während des TSST. Hierzu wurden zwei studentische Stichproben mit hoher und niedriger habitueller Grübelneigung rekrutiert. Zusammenhänge zwischen der kortikalen Aktivierung und momentanem Grübeln wurden anhand einer Mediationsanalyse überprüft. Wie erwartet, ließ sich – gemessen mittels des Ruhemessungs-Fragebogens – durch den TSST momentanes Grübelverhalten induzieren, welches bei Probanden mit hoher habitueller Grübelneigung besser gelang als bei Teilnehmern mit einer niedrigen habituellen Grübelneigung. Auf kortikaler Ebene zeigten sich Unterschiede in der Aktivierung während des TSST: Habituelle niedrig-Grübler wiesen sich durch eine stärkere Aktivierung

des rechten inferioren frontalen Gyrus (IFG) aus. Weiterhin zeigte sich, dass Gruppenunterschiede bezüglich des momentanen Grübelns nach Durchführung des TSST durch die kortikale Reaktivität im IFG mediiert wurden. Hierbei zeigten Probanden mit einer hohen IFG Reaktivität weniger momentanes Grübeln nach der Stressinduktion.

In Studie **vier** untersuchten wir in der gleichen Kohorte, inwiefern sich die funktionelle Konnektivität während Ruhemessungen vor und nach der Stressinduktion in den Gruppen unterscheidet. Außerdem überprüften wir, ob es einen Zusammenhang zwischen den induzierten Veränderungen im momentanen Grübeln und funktioneller Konnektivität gibt. Wie erwartet, zeigte sich wie schon in unserer ersten Studie bei Depressionen im Alter, dass sich habituelle hoch-Grübler durch eine erhöhte funktionelle Konnektivität im Kognitiven Kontrollnetzwerk zur Baseline auszeichnen. Es zeigten sich jedoch nur bei den Probanden mit einer geringen Grübelneigung Anstiege in der funktionellen Konnektivität durch den TSST. Es zeigte sich folglich keine Kovariation zwischen den Veränderungen in der funktionellen Konnektivität und dem Anstieg im momentanen Grübeln. Aufgrund dieses Befundes schlussfolgerten wir, dass es sich bei dem Einfluss von momentanem Grübeln auf die funktionelle Konnektivität lediglich um einen indirekten Effekt handeln könne.

In der allgemeinen Diskussion dieser Arbeit wird ein Modell eines indirekten Grübeleffekts auf eine verlängerte Stressreaktion vorgeschlagen, welcher zu permanenten Änderungen der funktionellen Konnektivität führt. Dieses Modell könnte die beobachteten Effekte der Studien erklären und stimmt mit Forschungsbefunden zur funktionalen Veränderungen kortikaler Netzwerksynchronisation durch chronischen Stress überein. Weiterhin wird ausgeführt, inwiefern die Ergebnisse dieser Studie und die Erforschung der neurobiologischen Grundlagen psychischer Störungen zu einer Weiterentwicklung von vorhandenen Theorien psychischer Störungen und Behandlungsoptionen beitragen können.

1. General Introduction

Depression is one of the leading causes of global burden of disease in terms of disability adjusted life years (DAILYs) and the most common mental disease with 121 million affected people worldwide (Reddy, 2010). With a life-time prevalence between 6 to 21%, it is very likely that any reader of this work will know at least one person that suffered from this disabling disorder. The first time I saw depression was when I was 16 years old and my grandmother had a stroke. When she returned from the hospital, not only her speech and memory were impaired, also her mood was depressed and her affective expression became blunted. While having a stroke is not a necessary prerequisite for developing a depression, the example of my grandmother illustrates clearly that our brain and psychological functioning are highly entangled. As I will outline in the work at hand, *major depressive disorder* is accompanied by a variety of changes in brain functioning, structure and network integration even without neurological medical conditions like in a *post-stroke depression*. Within these neurobiological abnormalities lies the potential for the generation of new therapeutic options that may improve the treatment of the disorder.

1.1 Topic overview and structure of the present work

The topic of this work falls into two scientific areas: Clinical Psychology and Neuroscience. From the clinical-psychological perspective, this dissertation deals with the mental disease of Depression, from a neuroscientific perspective the topics of brain functioning and functional connectivity (FC) are addressed. In detail, this dissertation deals with aberrant activity in and synchronicity between brain areas in Major Depressive Disorder (MDD) and the underling cognitive processes, that may lead to these changes in brain functioning.

In the following section, the central constructs and concepts in the psychopathology and physiology of depression shall be explained. In detail, current models of MDD and relevant cognitive processes will be introduced, as well as models of functional connectivity and network organization. By doing so, the reasons and promises of studying the neurophysiological basis of MDD will be outlined.

Subsequently, the current research on brain activation and functional connectivity in MDD is reviewed and the rationale of the presented projects is given. Following of an overview of the four studies that are the subject of the present work, the studies will be outlined in detail. Finally, the gathered evidence will be summed up and discussed in light of the existing literature in the field.

It must be noted that depressive episodes due to other medical conditions, bipolar disorder or Cyclothymia are not subject of this work and shall not be outlined here. The same applies to the DSM-V diagnoses “Disruptive Mood Dysregulation Disorder” and “Premenstrual Dysphoric Disorder” which are assigned to the chapter “Depressive Disorders”. On a methodological level, the subject of “dynamic functional connectivity“, is also not subject of this dissertation, since accurate and reliable computation techniques are not yet available.

1.2 Symptomatology, Epidemiology and Etiology of MDD

Depression is one of the most common and disabling mental diseases, with a high mortality due to suicide (Zheng et al., 1997). The life-time prevalence of MDD ranges worldwide between 6.5% and 21% (Kessler & Bromet, 2013) and the annual incidence between 2.4% and 3.8% (Ferrari et al., 2013), with a peak risk period for an onset between the middle late adolescence and the early 40s (Kessler & Bromet, 2013). The sex-ratio (f:m) for depressed patients is 2:1, indicating a twofold increased risk for women. Also single (OR = 2.3) or divorced individuals (OR = 1.4), as well as unemployed (OR = 2.2), poor (OR = 3.8) or less educated (OR = 1.9) have a significantly higher risk for depression (Kessler et al., 2003). With respect to comorbidities, it becomes clear that depression is often accompanied by other mental disorders: 72% of MDD patients also meet the criteria of other diagnoses. On a life-time scale, MDD mostly co-occurs with Anxiety disorders (59%), Impulse Control Disorders (30%) and Substance Use Disorders (24%) (Hasin, Goodwin, Stinson, & Grant, 2005; Kessler et al., 2003). As for all mental disorders, certain personality traits such as Neuroticism are positively correlated with depression (American

Psychiatric Association, 2013). Suffering from MDD results in wide-ranging and serious consequences which is why the World Health Organization (WHO) stated that depression is the leading cause of disease burden in middle- and high-income countries (Mathers, Fat, Boerma, & World Health Organization, 2008).

According to the International Statistical Classification of Diseases and related Health Problems (ICD-10) Depression is characterized by three cardinal symptoms:

1) Depressed mood,
2) Loss of interest and enjoyment, and
3) Increased fatigability.

Additionally, secondary symptoms comprise (a) loss of confidence or self-esteem, (b) unreasonable feelings of self-reproach or guilt (c) suicidality (d) complaints or evidence of diminished ability to think or concentrate, (e) psychomotor agitation or retardation, (f) sleep problems and (g) change in appetite with weight change. To fulfill the criteria of a (mild) MDD, at least two major symptoms and two secondary symptoms have to be present during most of the days of two weeks (Dilling, Freyberger, Cooper, & Weltgesundheitsorganisation, 2016). Additionally, there must be an exclusion of manic and hypomanic episodes in the past and the symptoms must not be a consequence of substance abuse or organic disorder. In the ICD-10, a MDD diagnosis can be classified as mild, moderate or severe, as a single or recurrent episode and with our without psychotic symptoms.

Beside the ICD-10, the American Psychiatric Association defined Major Depressive Disorder nearly the same way in their Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-V), despite the definition of only two cardinal symptoms – depressed mood (1) and loss if interest (2) – are defined. To meet criteria for a MDD, five or more symptoms have to be met, of which at least one must be a cardinal symptom. Secondary symptoms are (3) weight loss/gain or change in appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of

worthlessness or excessive or inappropriate guilt, (8) diminished ability to think or concentrate, or indecisiveness and (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Symptoms have to be present during a two-week period nearly every day and must cause clinical significant distress or impairment in social, occupational or other important areas of functioning. Also, symptoms must not be caused by substances, physiological effects or medical conditions. However, depression due to medical conditions or substance abuse may be coded in a separate diagnosis. For differential diagnosis, schizoaffective disorders, schizophrenia, schizophreniform disorders, delusional disorders or other specified and unspecified psychotic or schizophrenia spectrum disorders have to be excluded as well as manic or hypomanic episodes. However, psychotic features can be present during a Depressive Disorder and must be specified.

About 40% to 60% of individuals who experience a first episode of MDD will have at least a second episode in their future; in fact, the likelihood for multiple episodes and chronic courses of the disease increases with every episode up to 90% after the third episode (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015; Eaton et al., 2008; Solomon, 2000). In a clinical sense, it is quite important to distinguish between patients with chronic or multiple MDD episodes and those with only single and current symptoms, since the chronicity of the disease correlates with underlying personality traits, substance abuse and anxiety, which makes a (full and fast) recovery less likely (American Psychiatric Association, 2013). Both diagnostic guidelines – DSM-V and ICD-10 – have a separate diagnosis for a more chronic form of depression: “Persistent Depressive Disorder” (PDD) or “Dysthymia” in which depressive symptoms must be present during a 2-year period on most of the days. However, the diagnosis of both a PDD and an MDD, also known as a “double depression”, is only possible according to the DSM-V, because an MDD must be excluded in the ICD-10 criteria for Dysthymia.

From a developmental standpoint, depression – as any other phenotype or behavior – can be seen as an interaction between personal (e.g., genotypes)

and environmental (e.g., social situation) factors. As these factors can be manifold, modern etiological models such the bio-psycho-social model (Engel, 1977; Zachariae, 2009) assume that the development of MDD is influenced by a variety of factors, that also might interact. Such factors include genes, DNA methylation, telomere length, inflammatory processes, changes in brain structure and functioning on the biological level (Heim & Binder, 2012; Price, Kao, Burgers, Carpenter, & Tyrka, 2013; Ripke et al., 2013) and early life-stress, cognitive schemata, core-beliefs, habits and temperament on a psychological and social level (Dozois & Rnic, 2015; Hammen, 2015; Hankin, 2015).

The risk for depression starts as early as the “life” of an individual, with the formation of its genetic code. Depression has been shown to have a heritability of 40% to 50%, as indicated by twin-studies, and to be common within families, with a twofold to threefold higher lifetime-risk for depression among first-degree relatives (Lohoff, 2010). The most studied candidate genes are those that influence the serotonin transporter, such as the promoter region of the serotonin transporter gene (5-HTTLPR), or the stress response system, e.g., the corticotrophin receptor 1 (CRHR1). Despite the existence of promising primary studies, meta- and mega-analyses of genome wide associations revealed no significant results (Ripke et al., 2013; Wray et al., 2012), indicating small effects of single genes or more complex interactions. Such interactions could include cases, in which a certain genotype (e.g., short allele carriers of the 5-HTTLPR) must be exposed to certain environments (e.g., stressful life-events) to develop depression. Additionally, these interactions might be restricted to certain time-points in life, when influences are most powerful, i.e. sensitive periods (Heim & Binder, 2012; Karg, Burmeister, Shedden, & Sen, 2011), as it is the case with epigenetic changes (Zannas, Wiechmann, Gassen, & Binder, 2016). Interestingly, with respect to mental health, a dose-response relationship was found between maltreatment in childhood and mental health problems in adulthood in general (Edwards, Holden, Felitti, & Anda, 2003), and between adverse childhood experiences and depression in particular (Chapman et al., 2004). These adverse experiences and stressors like emotional abuse (e.g.

insults through an adult, behavior that frightens the child), physical abuse (physical violence) and sexual abuse (covered fondling, attempted intercourse, intercourse) raise the risk for depression in adulthood by an OR from 1.7 to 2.7 with highest scores for emotional abuse. Also, interpersonal stress seems to be more strongly related to depression than non-interpersonal stress (Rudolph et al., 2000a). To date, the exact mediating mechanisms that lead from stressful life-experiences to MDD are not fully understood. One possibility is that such (chronic) experiences change the course of neuronal development and lead to aberrant functioning in a variety of body systems such as the “Stress Response System” or neuronal systems of emotion regulation.

Indeed, in the last decade changes in the stress system, namely the hypothalamic-pituitary-adrenal axis (HPA axis), have been extensively studied in depressed subjects (American Psychiatric Association, 2013) and first meta-analytic data exist. The response of the HPA system can be distinguished into three phases: (1) a baseline reflecting basal activity, (2) stress reactivity and (3) stress recovery. The HPA system is activated through stressors that are processed through the central nervous system, which activates the sympathetic system and the release of epinephrine and norepinephrine, the actual primary stress response. Through this stimulation, the respiration rate and cardiac tone are raised. Also – as a secondary stress response – the hypothalamus is stimulated and corticotrophin releasing hormone (CRH) is released which in turn causes the anterior pituitary to release adrenal corticotropic hormone (ACTH). In turn, glucocorticoids like cortisol are released from the adrenal cortex. In normal functioning, rising cortisol levels innervate a negative feedback-loop through the hippocampus, which inhibits the HPA system and leads to the “recovery phase” in which cortisol levels decrease (Deppermann, Storchak, Fallgatter, & Ehlis, 2014). Following the distinction of the three stress phases, depression has been shown to be associated with (1) lower baseline cortisol levels in the morning, higher baseline cortisol levels in the afternoon, (2) higher stress reactivity of MDD patients in the afternoon, an overall blunted stress response in MDD patients which gets stronger with age, and (3) reduced recovery of cortisol levels after stress (Burke, Davis, Otte, & Mohr, 2005). Since

chronic stress affects the immune system (Segerstrom & Miller, 2004) related to these HPA axis dysregulations, changes in the immune response system (IRS) regarding tumor necrosis factor (TNF)- α and interleukin (IL)-6 have been reported on a meta-analytic level (Dowlati et al., 2010) showing higher concentrations of TNF- α and IL-6 in depressed subjects. These changes likely develop due to adverse effects of prolonged chronic stress. While the stress response is primarily adaptive by supplying energy for the coping with acute stressors (by increasing cardiovascular tone, higher respiratory rate, inhibition of other energy consuming systems like the immune system and digestion), in the long run, chronic stress has pathological allostatic effects involving bodily as well as psychological processes. Most relevant for depression and overlapping with depressive symptoms, chronic stress leads to fatigue, myopathy, reduced digestion and changes in the brain, particularly reductions in the neurogenesis of neurons in the hippocampus, dendritic retraction in the cortex and expansion of dendrites in the amygdala (Brady & Sinha, 2007; Lupien, McEwen, Gunnar, & Heim, 2009). As the hippocampus is directly involved in the negative feedback loop of the HPA axis, these changes may represent a potential mechanism for a vicious circle. Changes in the dendrites of the cortex may be accompanied by cognitive dysfunction and higher amygdala volume may result in enhanced fear responses. Both effects are known to be common in depressed subjects: On the one hand, various meta-analyses of MRI studies on depressed subjects revealed reduced brain volume in the frontal cortex, orbitofrontal cortex, cingulate cortex, hippocampus and striatum (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012a; Sexton, Mackay, & Ebmeier, 2013). On the other hand, on the basis of meta-analyses depression has been shown to be related to reduced processing speed and executive functioning, with components such as updating information from working memory, shifting between tasks, and inhibiting pre-potent responses (Snyder, 2013).

However, despite this association of depression and stress (particularly in early life), it is important to note that not every subject that experiences stressful events develop depression. Part of this variability is due to genetic and epigenetic changes (Zannas et al., 2016), but also to a great extent to cognitive

factors. In fact, psychological factors such as cognitive schemata and coping styles influence the subjective controllability of a situation and may even differentiate between subjects that are stressed by a certain activity (e.g. base jumping or climbing free solo) and individuals that feel pleasure by such activities. From a psychological point of view, which might be just "the other side of the same medal" of a biological functional level, personal schemata and/or core-beliefs[1] are shaped through (stressful) life events and socialization. The concept of schemata refers "to cognitive structures of organized prior knowledge, abstracted from experience with specific instances; schemata guide the processing of new information and the retrieval of stored information" (S. T. Fiske & Linville, 1980). However, as any internal concept, this definition is open and adapted in different ways by different authors. Once such a schema is built, it will influence the processing and interpretation of any information that will be processed in future situations that are similar to the situation that led to the formation of the scheme. In this way, future situations – including internal stimuli like sensations or perceptions – will act as triggers that activate a certain schema. As a result, they influence how a person will react in later situations, e.g. through different appraisals. The contents of a schema are manifold and vary (as its definition) depending on its conceptualization. One of these conceptualizations proposes three levels of a cognitive schema (Sachse & Fasbender, 2010). As an organization of prior knowledge, cognitive self-schemata contain (1) assumptions, or core beliefs, about the self (e.g. "I am bad at football") as well as (2) assumptions about contingencies with regards to the core beliefs (e.g. "If you are bad at football, you won't find friends at school") and (3) appraisals regarding the assumptions with relevant affects (e.g. "having no friends is awful, because you're a loner. You must avoid to be a loner, or you will fail"). In depression, these contents are more generalized (e.g. "I am a silly person/ a loser/ bad mother") and extended, because they were built through the consolidation and interpretation of many different situations. In the example of early life-stress experiences, emotional abuse may lead to cognitive schemata with assumptions as "I am not worthy of being loved", "I am a

[1] core-beliefs themselves can be seen as cognitive schemata, depending on the definition of such internal constructs

deficient person" or "You can't count on other persons". In the *Cognitive Theory of Depression* (Beck & Hautzinger, 2010), these core-beliefs build the ground on which depressive processing develops, leading to the cognitive Triad (a negative interpretation of the self, the environment and the future), automatic negative cognitions and cognitive errors (e.g. overgeneralization). These schemata influence the processing and organization of future experiences e.g. through appraisals, once they are activated by a certain (stressful) situation.

With regards to stress, the Transactional Stress Modell from Lazarus postulates that the stress response is dependent on environmental threats and personal (cognitive) factors, namely appraisals (Lazarus, 1990). The theory states that two appraisals – a primary and a secondary one – occur when an individual is confronted with a stressor. The primary appraisal concerns the question "what is at stake", namely the interpretation of a situation as a threat, challenge, or loss and is followed by the congruent affective reaction. Followed by this primary appraisal, a secondary appraisal regarding the potential coping strategies is performed: either problem-focused or emotion-focused, which includes social support and is accompanied by physiological changes. In a third step, a reappraisal evaluates the effects of the chosen coping-strategy to adapt it if necessary. On an empirical basis, primary (Gaab, Rohleder, Nater, & Ehlert, 2005; Zureck, Altstötter-Gleich, Wolf, & Brand, 2014) as well as secondary appraisals (Slattery, Grieve, Ames, Armstrong, & Essex, 2013) have been found to be related to cortisol and cytokine increases during social stress tasks (Wirtz et al., 2006, 2007). Also, primary and secondary appraisals have been shown to differentiate between depressed and non-depressed subjects, with higher threat appraisals, higher confrontation, self-control, avoidance and felt responsibility in depressed subjects (Chang, 1998; Folkman & Lazarus, 1986). This data is in line with literature from emotion-regulation strategies (secondary appraisals) in depression (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Garnefski & Kraaij, 2006) indicating a higher use of regulation strategies that lead to negative affect (maladaptive strategies like avoidance, suppression and catastrophizing) in depressed subjects. One of these perservative cognitive strategies is rumination, which shall be outlined in detail in the following.

1.3 Rumination

Rumination can be defined as a recursive and persistent process of thinking that is related to past events. It is characterized by a highly self-referential, pessimistic and abstract style of thinking about problems, with little or no goal and change-orientation (Teismann, 2012a). The reference to past events differentiates the process of rumination from the cognitive process of worrying, however, some authors argue, that the overlap between both constructs is so large, that they may represent the same cognitive process, e.g. as perservative cognition (Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; Ed Watkins, Moulds, & Mackintosh, 2005). The process of rumination is often characterized by problem specific questions like “Why did this happen to me?”, “Why can’t I feel in another way”, or “What am I doing wrong, that I feel this way?” and is common in depressed subjects and other mental disorders (S. Nolen-Hoeksema, 2000; Ed Watkins & Baracaia, 2001a). Although, everyone has probably already experienced some kind of repetitive thinking – like worry and rumination – these thinking processes are more common in patients in terms of duration of ruminating per day and the controllability with regards to its termination. In the following, two questions shall be answered before different models of depressive rumination are outlined: (1) If depressive rumination is adverse, why do depressive patients ruminate? And: (2) What are the consequences of depressive rumination?

1.3.1 The causes and consequences of depressive rumination

Why do depressive individuals ruminate? At first glance the first and best answer to this question could be: Because they cannot do it differently, as it is a symptom of depression. However, as it has been shown in different studies, how people react in different situations largely depends on their cognitive appraisals regarding a certain (cognitive) reaction (Papageorgiou & Wells, 2001). Such cognitions about the functions and consequences of thinking styles (which are cognitions) are called *Metacognition*. Therefore, rumination cannot only be seen as a symptom of depression – aside from the fact that rumination

is not defined in the ICD-10 or DSM-V – but also as a maladaptive coping stye. In two different qualitative studies, Watkins et al. dealt with this question and revealed that depressed subjects indeed have positive meta-cognitions about the strategy of depressive rumination(Ed Watkins, 2004; Ed Watkins et al., 2011a). The most reported advantages of rumination were understanding/insight (17.9%), problem solving (13.4%) and preventing future mistakes (7.5%), while the most reported disadvantages were losing control (34.5%), worsening depression (13.8%), not understanding problems (10.3%) and being more selfish (10.3%). Therefore the authors concluded that rumination may give patients the sense of control over their problems, which would act as a reinforcement for using the strategy in later situations (Ed Watkins & Baracaia, 2001a). In a second study, the same authors analyzed appraisals and strategies that are associated with rumination and worry. They found that rumination was correlated with the reaction of concerned disapproval to the ruminative thought, efforts to dismiss the ruminative thought and with appraisals about the importance and seriousness of the situation. Rumination was correlated with analyzing and dwelling on the situation and negative control (devaluation of the thought, reprimanding oneself, replacing thoughts by other unpleasant thoughts).

The consequences of rumination are rather widespread: Subjects with higher rumination scores – mostly measured as a trait construct with the Rumination Response Score – have a higher risk of developing depression, with a longer duration of episodes, are more likely to have stronger symptom severity, higher risk for relapse and higher risk for suicide (Eshun, 2000a; Ito, Takenaka, Tomita, & Agari, 2006; Koval, Kuppens, Allen, & Sheeber, 2012; Papageorgiou & Wells, 2004; Smith & Alloy, 2009a; Spasojevic & Alloy, 2001; Teismann, Willutzki, Michalak, & Schulte, 2008). Also, aside from general health and depressed mood, rumination has also been related to worse cognitive functioning (Lyubomirsky, Kasri, & Zehm, 2003), lower problem-solving (Lyubomirsky & Nolen-Hoeksema, 1995a), memory impairments (Hertel, Benbow, & Geraerts, 2012) and worse sleep quality, which itself is related to affective well-being (Basta, Chrousos, Vela-Bueno, & Vgontzas, 2007;

Bouwmans, Bos, Hoenders, Oldehinkel, & de Jonge, 2017; Slavish & Graham-Engeland, 2015). On a physiological level, a recent review and meta-analysis revealed that rumination induction is associated with higher systolic (g = .45) and diastolic (g = .51) blood pressure, higher cortisol (g = .32-.36), heart rate (g = .20-.28) and lower heart-rate variability (g=.15-.27) (Ottaviani et al., 2016a). As with the effects of depression on the cortisol response, a reduced decline of cortisol responses has also been observed in high ruminators (Denson, Fabiansson, Creswell, & Pedersen, 2009; LeMoult & Joormann, 2014). However, this effect might be more strongly related to state rumination as compared to trait rumination (Hilt, Aldao, & Fischer, 2015).

The exact mechanisms and relations between rumination, behavior, affect and cognition are not yet fully clarified. However, studies of momentary assessment suggest that the relationship between daily hassles and negative affect are mediated by state rumination (Genet & Siemer, 2012). Also, experimental designs have brought preliminary evidence for a causal influence of self-focused/state-oriented repetitive thinking on problem solving (Noreen, Whyte, & Dritschel, 2015; Ed Watkins & Baracaia, 2002). These attenuated problem solving skills might be due to a higher negative tone, self-criticism, self-blame and reduced self-confidence and perceived control in high ruminators (Lyubomirsky, Tucker, Caldwell, & Berg, 1999). Additionally, in their problem formulation, high ruminators show reduced concreteness (Ed Watkins & Moulds, 2007), an effect that is known from the process of worrying in generalized anxiety disorder (GAD). In GAD, reduced concreteness (in form of indistinct, cross-situational, unclear, equivocal and aggregated thoughts) is thought to play an important role as an avoidance mechanism which serves as a maintenance factor of worrying. In fact, exposure therapies for GAD explicitly targeted this factor by provoking *in-vivo* exposures of detail vivid imaginations of the worry contents (Ed Watkins & Moulds, 2007). This data showed not only another overlap between worry and rumination, but also a potential cognitive avoidance mechanism that sustains the maladaptive process. Moreover, such abstract thought processes are associated with overgeneralization (Van Lier, Vervliet, Boddez, & Raes, 2015) and cause lower blood pressure and higher

anxiety levels following social stressors (Zoccola, Rabideau, Figueroa, & Woody, 2014). The negative and stress-prolonging effects of perservative cognitions like rumination and worrying have led to the *perservative cognition hypothesis*, which states that perservative cognitions are a mediator between stressful life events and a prolonged stress response which leads to mental and physical pathologies (Brosschot, Gerin, & Thayer, 2006). Under normal circumstances, subjects use adaptive stress regulation strategies that lead to adaptive coping. If the ability to cope with the stressor is threatened – which results in hopelessness – and the stressor is uncontrollable, maladaptive coping in form of perservative cognition is likely to occur. However, perservative cognitions also prolong the stressful experience by holding the representation of the stressor "online" and prevent in the long run that the stress response ends.

Besides the direct affective and cognitive effects of rumination, it seems that rumination is also related to behavioral effects in terms of lower health behavior. For example Lyobomirsky et al (2006) showed that high ruminators with breast cancer seek later for help than low ruminators by an average of 39 days (Lyubomirsky, Kasri, Chang, & Chung, 2006). This result underlines that the before-mentioned cognitive avoidance of rumination also shows adverse behavioral effects. Also, it might explain why rumination as a mental process is also associated with physical health (Thomsen, Mehlsen, Hokland, et al., 2004; Thomsen, Mehlsen, Olesen, et al., 2004). These findings are further underlined by evidence showing a relation between rumination and other avoidance-related passive emotion regulation strategies such as alcohol consumption (Devynck, Kornacka, Sgard, & Douilliez, 2017; Grynberg et al., 2016). Again, as noted above for the abstract forms of rumination, in the study of Dvynck et al. (2017) abstract-analytic repetitive thinking, but not concrete-experiential thinking, was related to depression and alcohol abuse.

1.3.2 Models of depressive rumination

Depressive rumination is a multi-facetted construct. In the same way, it has been defined in different ways by different authors in more general ways – including rumination as any repetitive thinking style including ruminating about

positive situations – or narrow ways; e.g. by relating rumination only to thinking about depressive symptoms. In the following, three prominent models of rumination shall be outlined: The Response Styles Theory of Susan Nolan-Hoeksema, the self-regulatory executive function (S-REF) model of Adrian Wells and the Disengagement Model of Koster and colleagues.

The Response Styles Theory of Nolan-Hoeksema states that people react in different ways, or rather response styles, that are mostly acquired through learning mechanisms in childhood, to depressive moods. In this framework, rumination is defined as a rather trait-like construct as contemplative thinking about depression and "the causes and consequences of depressive symptoms" (Susan Nolen-Hoeksema, 1991). When subjects respond to depressed mood with rumination, their negative mood state is prolonged and may even get worse. Further, Nolan-Hoeksema argues that depressed mood leads to negative attributions and self-evaluations that together with a negative self-focus, interfere with problem solving and instrumental behavior. In contrast, subjects that respond in other styles like distraction, are thought to cope in a better – problem-focused in comparison to emotion-focused – way and recover faster from negative mood. However, although some predictions of the Response Styles Theory have been confirmed in depressive samples, e.g. the already outlined negative effects of rumination on depression severity and duration of the episodes, some critical point regarding the model have also been raised. Firstly, the model defines rumination in a rather narrow way, by only including ruminations about depressive symptoms and their consequences. While this might be true for some cases, there are also depressed subjects that show repetitive ruminative thinking about other issues, and rumination is also common in other mental disorders. Secondly, the process of rumination is not outlined in the model. Rumination is rather seen as a habitual response style. There are no predictions under what kind of circumstances subjects will start to ruminate, nor why they developed such a style in the first place. The following models of rumination tried to bridge this gap.

While the process of rumination is conceptualized in a rather general form in the Response Styles Theory, Wells and colleagues make some clearer predictions

in the S-REF model. In their conceptualization, rumination is defined as “repetitive thoughts generated by attempts to cope with self-discrepancy that are directed primarily towards processing the content of self-referent information” (Papageorgiou & Wells, 2004). In this framework, rumination is thought of as a subset of worry. The model consists of three levels: (1) lower-level networks, (2) supervisory executive and (3) self-knowledge. The lower-level networks process routine information and are triggered by incoming stimuli. If information is motivationally relevant, it will activate the supervisory executive, which aims to reduce discrepancies between a current state and a desired state. To this end, coping strategies are searched and selected to reduce the discrepancy. The selection of these coping strategies is mostly guided by the third level of self-knowledge which also consists of metacognitive knowledge about these strategies and motives. Rumination is seen as such a coping mechanism which (subjectively) is goal-oriented. Rumination is maintained by the executive control – motivated by positive metacognitive beliefs (e.g. “If I ruminate, I will prevent mistakes in the future”, “At least, I am not a bad mother, when I ruminate about my parenting style”) – which in turn triggers automatic processing at the lower-levels, e.g. through intrusive thoughts or thought suppression. In this way, rumination also interferes with other cognitive activities that a subject performs, which is in line with above reported literature on cognitive impairments through depressive rumination.

In contrast, the Disengagement Model – an information processing model from cognitive science – proposes a different mechanism of rumination. It assumes, that rumination is not a process, but a style of self-referential thinking, and negative cognitions due to rumination are cognitive products (Koster, De Lissnyder, Derakshan, & De Raedt, 2011). In their basic definition, rumination is considered a non-pathological process *per se*, because self-referential processes do guide subjects in finding sense. However, the authors postulate difficulties in disengagement of attention from ruminative topics as a key factor in pathological rumination. As in the S-REF model, internal or external goal-conflicts are considered as triggers for rumination. In search for a reason, self-critical thoughts arise to reflect the responsibility of one’s own behavior. So far,

the process is considered as non-pathological and will be – in healthy individuals – terminated because of internal conflicts between the self-critical thoughts and existing positive self-views. As a result of this conflict, attention will be disengaged and reappraisal strategies will be used. This process can be pathologically interrupted, either by low conflict – when self-views are in line with the self-critical thoughts – or when the attentional control is impaired. Both pathways result in an increased attentional focus on inward rumination, which leads to impairments in adaptive emotion regulation and increased negative affect, which closes the vicious circle by leading to new self-critical thoughts. In this way, ruminative thinking becomes “a habitual mode of thinking” (Koster et al., 2011). In comparison to the S-REF model, the Disengagement Model proposes clear hypotheses why some (healthy) people do ruminate sometimes, but can terminate the process of rumination, while depressed subjects mostly cannot do so. However, one could argue that positive self-views in the disengagement model are represented in the level of self-knowledge in the S-REF model in form of meta-cognitions.

In summary, there are many conceptualizations of rumination in the literature resulting in the rather broad definition given at the beginning of the chapter. While rumination can be conceptualized as a habit as in the Response Styles theory, it can also be seen as a strategy of emotional coping as in the S-REF model or as a process as in the Disengagement Model. It must be noted that there are also conceptualizations as in the perservative cognition hypothesis: These conceptualizations propose that rumination is a result of a lack of alternative reactions in a hopeless situation when subjects cannot cope accurately, rather than a result of a used strategy due to positive meta-beliefs or low internal conflict. Up to date, there is no consensus about the definite process that takes place when subjects ruminate, nor the definition of this style of thinking itself. Nonetheless, the research community agrees in the negative consequences of rumination, and attempts have been made to develop specific interventions to reduce rumination in depressed subjects. In the following section, treatment options for MDD in general and for rumination in particular will be summarized.

1.4 Treatment Options for Depression and Rumination

There exists a variety of treatment options for MDD of which pharmacotherapy and psychotherapy are the most recommended standard interventions accordingly to current guidelines. Additionally, in some cases the use of electroconvulsive therapy, ketamine and sleep deprivation has been shown to have anti-depressive effects. Other treatment options include the use of transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and neurofeedback which are still under exploration for their therapeutic benefit. For the scope of this work, in the following only psychotherapeutic and pharmacotherapeutic interventions shall be outlined briefly.

Pharmacological treatment of depression mostly tackles two different neurotransmitter systems that are related to depression: the serotonergic and dopamine system. According to their affecting point in the central nervous system, most antidepressant medication can be classified into selective-serotonin reuptake inhibitors (SSRI), non-selective monoamine reuptake inhibitors (MRI), selective noradrenaline inhibitors, serotonin-noradrenaline reuptake inhibitors (SNRI), selective noradrenaline dopamine reuptake inhibitors (NDRI), noradrenergic and specific serotonergic antidepressants (NASSA) and monoamine oxidase inhibitors (MAOI). Since anti-depressive medication is one of the oldest (including the usage of herbal drugs in the first routes of medicine (Jakubovski, Varigonda, Freemantle, Taylor, & Bloch, 2016; Petrovska, 2012)) and most commonly used interventions against depressive mood, a massive literature on the subject exists. Most meta-analytic data show a clear evidence in favor of anti-depressive medication against placebo with numbers to be treated between 6 (venlafaxine) and 8.5 (tricyclic antidepressants) (MacGillivray et al., 2017). However, there is also data suggesting, that the effects are only due to characteristics of the used placebo medication (Kirsch & Sapirstein, 1998). Newer data suggest that the effects of pharmacotherapy vary as a function of baseline symptom severity with high effects in severed depressed subjects, and low to non-existent effects in low to moderately severe, depressed subjects (Fournier et al., 2010). Also, the effects vary as a function of depression subtype, showing advantages of

pharmacotherapy over psychotherapy in the case of dysthymia, and in general, when compared to non-specific counseling (Cuijpers et al., 2013). However, when not controlled for depression subtype, acute psychotherapeutic and pharmacotherapeutic effect sizes are comparable (Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012) and advantageous over placebo, treatment-as-usual (TAU) and waiting-list. A combination of psychotherapy and anti-depressive medication seems to have slight advantages over each treatment alone with effect sizes around g = .3 to .4 (Cuijpers, Sijbrandij, et al., 2014; Cuijpers, van Straten, Warmerdam, & Andersson, 2009; Guidi, Tomba, & Fava, 2016; Khan et al., 2012; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004).

As for pharmacotherapy, meta-analytic data for the treatment of depression with psychotherapies also exist. These data indicate an advantageous effect of psychotherapies as compared to TAU with symptom reductions 2 to 3 times higher, in subjects treated with psychotherapy. However, with respect to remission, the beneficial effect of psychotherapy amounts for 14 %; with 62% remission in psychotherapy and 48% in TAU (Cuijpers, Karyotaki, et al., 2014). Cognitive Behavioral Therapy (CBT) – as one of the most used psychotherapeutic approaches for the treatment of depression – has been shown to be superior over pharmacotherapy and other psychotherapies in one meta-analysis (Dobson, 1989). However, newer data challenge these results in so far as it shows that CBT is equally effective to behavioral therapy (Butler, Chapman, Forman, & Beck, 2006). With regard to stability of treatment effects, CBT shows better effects than pharmacotherapy (Vittengl, Clark, Dunn, & Jarrett, 2007), but still 29% of patients treated with CBT relapse within one year and 54% within two years. Because of these relapse rates, new treatment approaches have been developed. For instance, Continuation-phase CBT reduced relapse-recurrence by about an additional 29% compared to no-continuation treatment at follow-up, and when compared to active continuation treatment by about 14% at follow-up. As the APA suggests, any kind of residual symptom at the end of therapy increases the risk for relapses in MDD (American Psychiatric Association, 2013). Although rumination is not included in the symptom definition of MDD, the individual habit to ruminate also increases

the likelihood for further episodes (Smith & Alloy, 2009a; Teismann et al., 2008), which is why several approaches tried to tackle this process, e.g. within the CBT framework as rumination-focused CBT (RFCBT), mindfulness-based treatments, behavioral-activation treatments and eclectic manuals (de Jong-Meyer, Parthe, & Projektgruppe, 2009; Eisendrath, Chartier, & McLane, 2011; Querstret & Cropley, 2013; Teismann, 2012a). These manuals usually include rumination-specific psychoeducative elements, diagnostic elements, techniques that foster resistance against habitual reactions – such as attention-training techniques, postponed rumination to defined daytimes, or mindfulness-based mediation – and the development of adaptive coping styles, e.g. problem solving techniques, behavioral activation, and emotion regulation training (Brosschot & Doef, 2006; Teismann, 2012a). In a first randomized controlled trial (RCT), RFCBT showed higher response rates (81% vs. 26%), higher remission (62% vs. 21%) and lower relapse rates within 6 months after treatment (9.5% vs. 53%) than treatment as usual (Ed Watkins et al., 2011b). Moreover, in a pilot study, Jacobs et al. (2016) showed that RFCBT does not only reduce rumination, but also affects FC. In their study, participants in the RFCBT group showed a reduction in FC between the left posterior cingulate cortex (PCC) and frontal regions such as the bilateral inferior frontal gyrus (IFG), orbital frontal cortex and bilateral medial and inferior temporal (ITG) regions. Increases in FC were found between the PCC and postcentral and fusiform gyri (Brodmann Area (BA) 3 and 19). Also, relative changes in rumination were significantly positively correlated to changes in FC between the PCC and right ITG (Jacobs et al., 2016). However, so far, no RCT with an RFCBT vs CBT comparison exists, which relativizes the above reported results, since responder rates up to 80% have also been found in classic CBT for depression.

Taken together, although a variety of intervention methods has been developed for MDD, with anti-depressive medication – based on a neurobiological model – and psychotherapy – based on psychological models – as empirically supported and recommended treatments (Härter & Deutsche Gesellschaft für Psychiatrie, 2010), the responder rate to treatment and the stability of treatment effects

remains unsatisfying: About 60% of patients respond to treatment (Cuijpers, Karyotaki, et al., 2014; DeRubeis, Siegle, & Hollon, 2008) and about 50% to 60% of these responders relapse, which results in a number needed-to-treat of 5.55 (Steinert, Hofmann, Kruse, & Leichsenring, 2014). Neurobiological research may hold the potential for improving these treatment effects, by providing neurobiological underpinnings of MDD that can be directly targeted by pharmacotherapy, psychotherapy or translational treatments.

1.5 Functional Connectivity

As stated in the introduction, this dissertation also includes the field of neuroscience and especially the analysis of FC. In the following section, the development of FC measures and their definition shall be explained, as well as the discovery of different brain networks that are functionally coupled during certain processes.

The term *functional connectivity* has been defined by Karl J. Friston and colleagues in 1993 as "the temporal correlation between neurophysiological (functional) measurements made in different brain areas" (K. J. Friston, Frith, Liddle, & Frackowiak, 1993). In its simplest way, FC is computed by correlation coefficients – e.g. Pearson correlation – of time-series activation data (x and y) of (two) different brain regions as:

$$Corr(x,y) = \frac{\sum_{i=1}^{n}(x_i - \bar{x}) * (y - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2 * \sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

Therefore, FC contains information about the shared covariance between two brain areas (Figure 1) and informs about their (functional) integration and segregation (Karl J. Friston, 1994, 2011). From a historical perspective, the research on the segregation of brain areas evolved early by the analysis of activation of specific brain areas in different tasks. By contrasting the activity during different tasks in comparison to baseline and control conditions, different areas have been identified that are related to certain (e.g., cognitive) processes. In this way, the cognitive control network, the default mode network or the dorsal and ventral attention networks have been identified. However, the

analysis of integration in terms of FC evolved later, mostly due to the much more complex analysis. FC can be analyzed in the above noted way, but also by different metrics such as cross-correlation, coherence, time-frequency analysis, independent component analysis or principal component analysis based measures. Also, effective connectivity – which implies a causal influence of one brain area on another – can by implemented by using regression analysis, e.g. in the analysis of psychophysiological interaction (PPI) or Granger Causality (Karl J. Friston, 2011). These measures allow for quantifying the degree to which brain areas are functionally coupled while processing information.

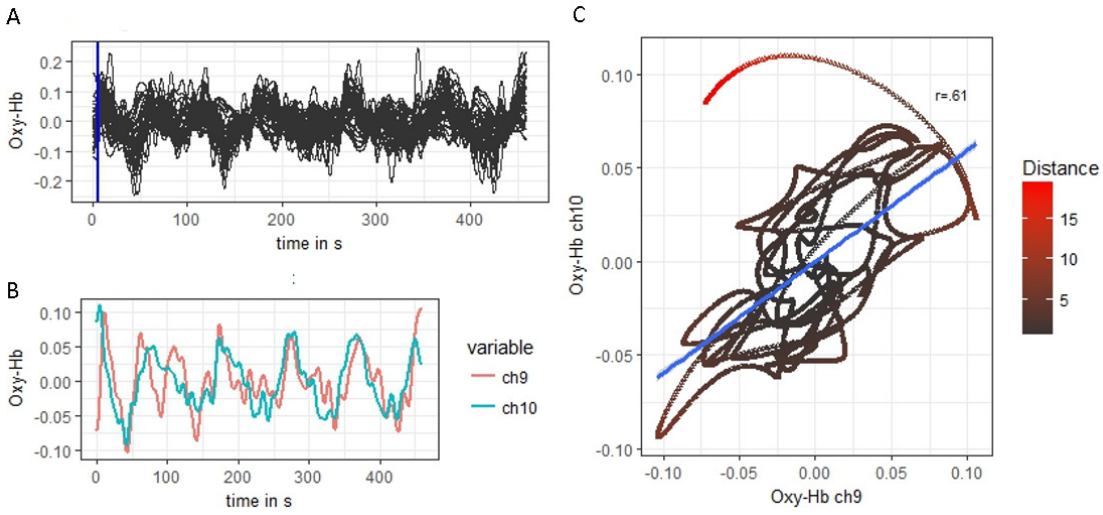

Figure 1. Example of a 7-minute resting-state measurement of a single person with a 46-channel probeset. A) Time-course of the "spontaneous" change in oxy-Hb over the resting-state measurement. B) Time-course of two neighboring example channels of the probeset. C) Covariance of the two example channels during the 7-minute resting state measure. Sample-points are color-coded with respect to their mahalanobis distances. Red points declare outliers that were excluded from the measurement of functional connectivity. Such outliers are present in the example data at the beginning of the measurement, when the phase of the two signals is shifted and the polarity of the channels is inversed. The non-normalized correlation coefficient in the example data is r = .61 (Fisher transformed r = .71). The blue line represents the linear relationship between the activation of the channels. The FC coefficient informs about "the interplay" of the two channels during the time of the resting-state measurement.

Critically, with respect to FC, results largely depend on methodological and design issues. For instance, negative FC may be artificially introduced through a common average reference (it should be noted, that negative activation might

be introduced by that procedure as well). Also, results largely depend on the investigated network and chosen seed regions. One can investigate only FC measures within a certain network (e.g., DMN) or between networks (e.g., DMN and CCN). Within FC research, one might only analyze certain connections between pre-defined nodes, or perform widespread analyses of all possible connections. Some authors only analyze voxel-mirrored homotopic connectivity (VMHC), which is defined as the connectivity between an area and the anatomically corresponding area in the other hemisphere.

The first studies of FC measures during resting-state (rsFC) have been conducted by Bharat Biswal, who was originally interested in the transfer function of the sensorimotor cortex and in noise sources. However, in his experiments he observed that the sensorimotor cortex in one hemisphere showed strong correlations to the corresponding cortex in the contralateral hemisphere during resting conditions, which means in the absence of a task that requires that brain area (B. B. Biswal, 2012a; B. Biswal, Yetkin, Haughton, & Hyde, 1995a). While at first this effect has been thought to possibly be related to an artifact, the reported effects have been found in different datasets with different seed nodes in different conditions. In the following studies, rsFC has been shown to be related to the coupling between cerebral blood flow and brain metabolism (B. B. Biswal, 2012a). Also, at rest, different networks that were previously shown to be related to different states and processes – like the DMN and the task positive network (TPN) – could be identified by using FC parameters. The DMN has been discovered before the analysis of rsFC serendipitously, when researches were searching for perfect baseline conditions. By doing so, they identified brain regions that were more activated during passive viewing tasks than during active tasks (the TPN), including the medial prefrontal cortex, the posterior midline, areas of the lateral temporal cortex, inferior parietal lobule/posterior lateral cortices (Buckner, 2012). For the conceptualization of the DMN related hypothesis and theories, the rsFC data completed the viewpoint that the DMN regions are not only more active in resting-state conditions, but that they are also functionally coupled and therefore might built a coherent brain system. While the primary hypothesis

concerning the DMN was that it is related to the passive processing of internal signals, current hypothesis suggest that DMN activity enables the construction of internal simulations (Buckner, 2012). This hypothesis is grounded on the fact that DMN areas are active during the processing of passive viewing, autobiographical information, thoughts about the future and dilemma decision making (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Mar, & Kim, 2009).

In contrast, the TPN has been related to the processing of external and task-relevant information (Figure 2). In the following years, different networks have been identified that are related to such tasks, such as the CCN, the salience network with the related attention networks (ATN), the affective-frontolimbic network and corticostriatal circuits. The CCN consists of a fronto-parietal circuit that includes the dorsolateral prefrontal cortex (dlPFC), anterior insula/frontal opercularum (aIfO), precuneus, the posterior parietal cortex and the dorsal ACC (dACC) (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; R. Tadayonnejad & Ajilore, 2014a). The regions of the CCN lie in huge parts between the DMN and the dorsal attention network (DAN) that includes parts of the DLPFC, inferior precentral sulcus, frontal eye fields, middle temporal motion complex and superior parietal lobule (Figure 3). As the name implies, the CCN is active during tasks that require cognitive control like planning, working memory tasks, inhibition, task-switching and decision making (Niendam et al., 2012), however, it may also be identified from resting-state measurements (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). The anatomical position between DMN and SN may be due to an interplay role, in which the CCN is co-activated with structures of the dorsal attention network and DMN, if supervisory executive control is needed. Indeed, Spreng and colleagues (2010) found that the DMN is activated during autobiographical planning, whereas the dorsal attention network is activated during visuospatial planning and the CCN is additionally engaged in both tasks (Spreng et al., 2010).

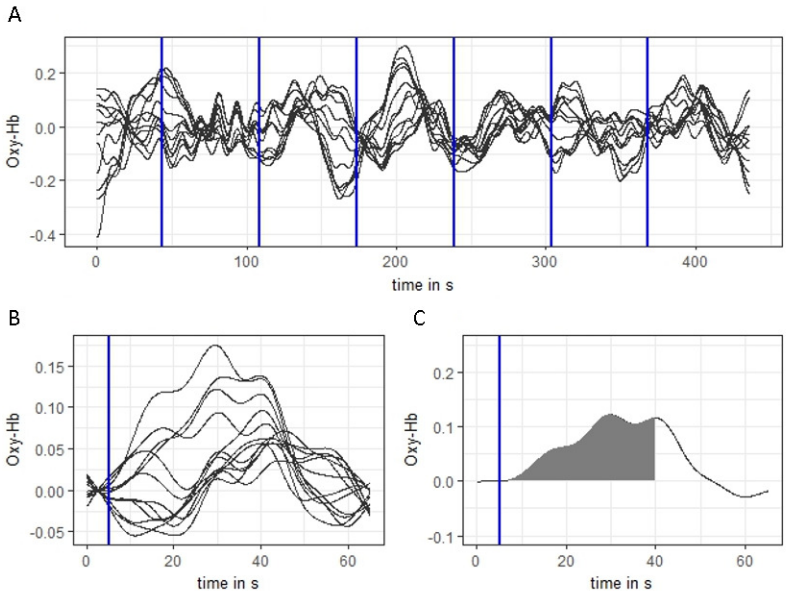

Figure 2. Example of single subject data in an event-related block design. A) Hemodynamic activity of 12 frontal channels (covering mostly areas of the dlPFC and IFG) of a single subject during the completion of an arithmetic task. Blue vertical lines mark the starting point of public computation for 40 s followed by 20 s rest. B) Averaged data of the 12 channels over the 6 task blocks with a 5 s baseline correction. C) Area under the curve (AUC) for a single channel over the 40 s of task performance. The quotient of AUC by time gives the average amplitude, respectively average activity of a certain channel.

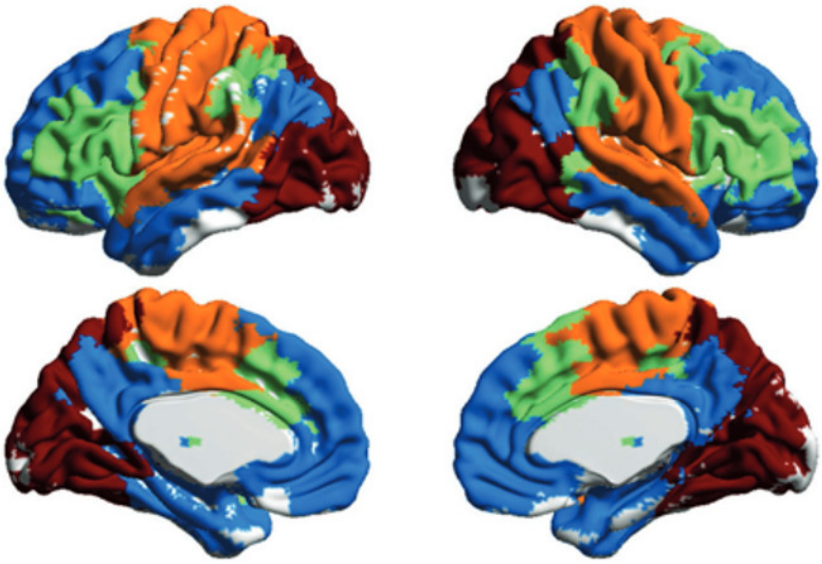

Figure 3. Taken and adapted from (Doucet, Bassett, Yao, Glahn, & Frangou, 2017). By graph-theoretical indices of functionally connectivity derived modules in a healthy group. Modules represent functional integrated subdivisions of a network. The green module represents the CCN, the blue module the DMN, the orange the sensorimotor network and the brown the visual network.

Interestingly, these functional networks have corresponding structural connections (structural connectivity) through nerve bundles in the brain that build the hard wired connection between distinct brain areas (Figure 4 and Figure 5). In their recent work, Jung et al. (2016) describe several pathways that connect the association cortices (Jung, Cloutman, Binney, & Lambon Ralph, 2016). Using graph-theoretical measures, they show that the cortical networks can be distinguished in 5 different modules, clustering areas relevant to the executive control network (module 1), social/semantic processing (module 2), visual "what" pathway (module 3), auditory processing (module 4) and visuomotor control network (module 5). These modules showed a high and graded intra-network structural connectivity and discrete region-specific inter-network connections (only few areas showed long-range connections) indicating that "higher cognitive activities require the synchronized combination of various primary domain-general computations" (Jung, Cloutman, Binney, & Lambon Ralph, 2016, p. 232).

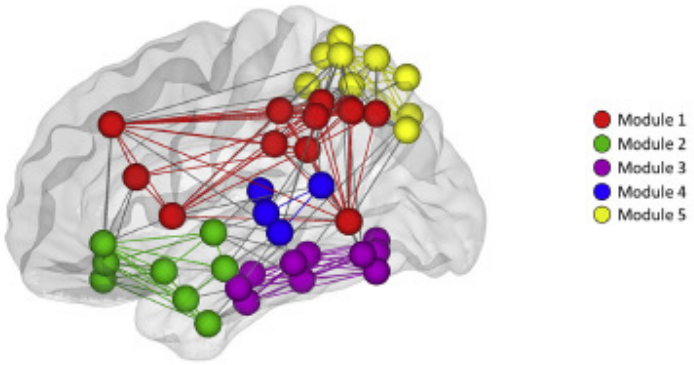

Figure 4. Taken and adapted from Jung et al. (2016). By graph-theoretical indices of structural connectivity derived modules. The red module represents the CCN, the green module the social/semantic processing network, the lilac the visual "what" path, the blue the auditory network and the yellow the visuomotor control network (Jung et al., 2016). Note that most terms are taken from the original article. The naming of modules and networks is mostly due to the functional association of these brain areas to certain cognitive processes and varies from author to author.

Within these networks, the frontal cortex is connected to the temporal lobule through the uncinate fasciculus (UF). The temporal cortex is connected from anterior to posterior through the middle longitudinal fasciculus (MdLF). The dlPFC is connected with the posterior temporal cortex through the arcuate

fasciculus (AF) and with the superior and inferior parietal cortex via the superior longitudinal fasciculus (SLF I/II). With regards to the DMN, fronto-parietal subcortical regions like the middle frontal cortex, ventral ACC and precuneus are connected through the cingulate bundle (CB) (R. Tadayonnejad & Ajilore, 2014a).

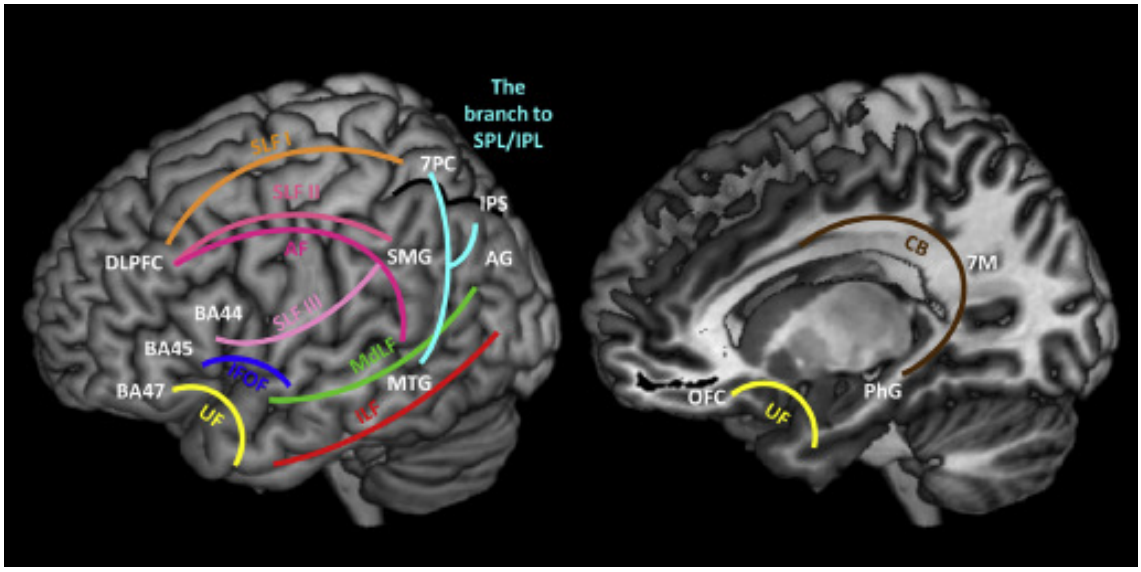

Figure 5. Taken and adapted from Jung et al. (2016). Displayed are white matter tracks that connect separated brain regions. Brain regions are colored in white letters: BA = Brodmann's area, DLPFC = dorsolateral prefrontal cortex, MTG middle temporal gyrus, AG = angular gyrus, SMG = supramarginal gyrus, IPS = intraparietal sulcus, 7PC, 7M = superior parietal cortex, OFC = orbitofrontal cortex, PhG = parahippocampal gyrus. Nerve-bundles are colored non-white: MdLF = middle longitudinal fasciculus, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, UF = uncinated fasciculus, IFOF = inferior fronto-occipital fasciculus, AF = arcuade fasciculus, CB = cingulum bundle. The cyan colored branch is part of the tracks IFOF ILF and MdLF (Jung et al., 2016).

2. Intermediate Summary

In the previous sections, I outlined the definition of MDD and the implied impairments for patients. Further, the process of rumination – which is common in depression and other mental disorders – has been introduced and treatment options have been discussed. Finally, the concept of FC has been explained with the most relevant brain networks for this work.

As we have seen, MDD is a common and severe mental disorder, which is influenced by the perseverative repetitive thinking style of rumination. Although there are various treatment options for MDD, the response and stability of these

interventions is still improvable. The integration of neurobiological and psychological models holds a great potential for the derivation of effective integrative treatment models. In fact, it has been the endeavor of psychotherapy researchers for a long time to unify the multifold models of psychotherapy and psychopathology in a general theory of psychotherapy that is mainly based on neuroscience, which was called “Neuropsychotherapy” by Klaus Grawe (Grawe, 2004). The research on the neuronal underpinnings of rumination in terms of aberrant brain functioning and coupling may hold the potential to give new insights into this psychopathological process, which might result in new interventions, e.g. through FC-based neurofeedback.

3. Background and Rationale for the present projects

In the following, studies regarding the neuronal underpinnings of depression and rumination shall be presented, which provides the background for the presented projects. Since differences in FC depend largely on the network and study sample which is examined, the following section will be ordered in a threefold way: (1) Studies regarding structural brain abnormalities and aberrant functional activation in depression, (2) studies showing increased FC in depression/rumination and (3) studies showing a negative association between FC and depression/rumination.

3.1 Relations of depression, rumination, structural changes and neuronal activation

With the development of structural brain imaging methods, pathological changes in the brain could be investigated. Such differences have been explored in a broad manner in the last three decades in the case of MDD and meta-analytic data is available. A meta-analysis regarding structural changes in MDD by Arnone et al. (2012) which included 101 studies with a total of 4118 patients summarized that MDD is characterized by reduced brain volume within the total frontal cortex, hippocampus, anterior cingulate cortex and caudate nucleus. Enlargements were found within the pituitary gland and also excesses of white matter lesions were observed (Arnone et al., 2012a). In line with this data, meta-analytic data regarding depression in later life indicated that late-life

depression (LLD) is associated with significant volume reductions in the hippocampus, orbitofrontal cortex, putamen and thalamus (Sexton et al., 2013). Importantly, these structural changes were found in brain areas that are important for cognitive control and the regulation of negative affect and stress (e.g. frontal cortex and hippocampus).

In line with these structural changes, functional changes with regard to cortical activation have also been shown. A meta-analysis of fNIRS data showed that MDD is consistently associated with hypo-activation of the frontal cortex during cognitive tasks such as the verbal fluency test (VFT) and 2-back task (Huijun Zhang et al., 2015) which is in line with the executive deficits in MDD (Snyder, 2013). Regarding affective processing, meta-analytic fMRI data suggest that depressed subjects show higher activity for negative material and lower activity for positive stimuli within the amygdala, parahippocampus, striatum, cerebellar, fusiform and anterior cingulate cortex (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). Amygdala reactivity to negative material has also been shown to be prolonged in depressed subject (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). Within cortical regions, hypo-activity within the dlPFC for negative stimuli and hyper-activity for positive material has been found on a meta-analytic level (Groenewold et al., 2013). These results are mostly interpreted in light of a bias for negative emotional content and reduced emotion regulation capacities in depressed subjects.

With respect to resting-state activation, a recent meta-analysis by Zhong and colleagues (2016) found that first-episode depressed subjects showed decreased brain activity in the dlPFC, superior temporal gyrus, posterior cingulate and precuneus, and increased activity in the putamen and anterior precuneus as compared to healthy controls. As these brain areas are part of the fronto-limbic circuit and DMN, they might reflect deficits in cognitive control and affect modulation on the one hand, and autobiographical overgeneralization on the other hand (Zhong, Pu, & Yao, 2016). Consistently, meta-analytic findings of positron emission tomography found decreased metabolism in the bilateral insula, left lentiform nucleus putamen, right caudate and cingulus gyrus, and

higher metabolism in the right thalamus pulvinar, posterior lobe, and anterior lobe (Su et al., 2014).

To sum up, these abnormalities in structural characteristics and functional activation are thought to be related to emotional and cognitive aspects of depression, since these areas are related to the generation and regulation of emotion and higher cognitive functioning. Furthermore, the medial prefrontal cortex is involved in the regulation of autonomic functioning, which might explain why depressed subjects show aberrant autonomic functioning (Drevets, Price, & Furey, 2008).

Since depression and rumination are highly correlated, several similar findings regarding brain functioning have been found in experimental and non-experimental studies with respect to the neuronal correlates of rumination. However, also increased activity in cortical areas has been found in rumination induction experiments. For example, Cooney et al. used a rumination induction task with concrete (“Think about a row of shampoo bottles”) and abstract distraction (“Think about what contributes to team spirit”) conditions and ruminative statements (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010a). Increased activation was found in depressed subjects as compared to healthy controls in the orbitofrontal cortex, subgenual anterior cingulate, and dorsolateral prefrontal cortex as compared to healthy controls during rumination versus concrete distraction. Also, higher activation was found during rumination versus abstract distraction in the amygdala, rostral anterior cingulate, dlPFC, parahippocampus and posterior cingulate in depressed patients as compared to controls. These results are supported by a recent study of Burkhouse et al. (2017) who reported elevated activation in the DMN (PCC, mPFC, IPL and MTG) during a rumination induction vs. distraction. However, elevated activity was also found in the hippocampus and occipital gyrus. Moreover, in the same study, patients with remitted MDD exhibited higher activation during rumination (vs. distraction) than healthy controls in the left precuneus and right IPL (both are parts of the DMN), MTG, amygdala, thalamus and insula (Burkhouse et al., 2017). In line with this, Hamilton et al. (2011) found that DMN dominance over TPN activity is positively correlated with maladaptive depressive rumination and

lower levels of reflective rumination, as most of the above mentioned areas like the medial prefrontal cortex and the posterior cingulate cortex are areas of the DMN (Hamilton et al., 2011). In the same way, Jones and colleagues (2017) found that rumination was negatively correlated to medial frontal gyrus and angular gyrus activity during autobiographical problem solving and positively correlated during negative self-referential processing, which is comparable to maladaptive rumination (Jones, Fournier, & Stone, 2017a). Similarly, self-criticism is associated with activity in the dlPFC and dorsal anterior cingulate, while self-reassurance is associated with activity in the temporal pole and insula (Longe et al., 2010a). Others also reported dissociations within the DMN with increased amplitudes of low-frequency fluctuations in the left dorsal medial PFC and decreased amplitudes in the left parahippocampal gyrus in subjects with MDD (Guo, Liu, Zhang, et al., 2013a). Also activity of other brain areas – like the entorhinal cortex, which is involved in the retrieval of personal memories and self-related information – has been found to be positively correlated to rumination, both at rest and during a cognitive task switching paradigm (Piguet et al., 2014a). Likewise, during autobiographical memory retrieval, subjects with high rumination scores need more time for memory construction and show less detailed and more negative memory content. During memory retrieval, these effects are accompanied by increases in amygdala activation and reduced activity of cortical areas (Schneider & Brassen, 2016a).

Also, neuronal correlates of emotion regulation seem to vary as a function of rumination. In a study of Ray et al. (2015), higher trait rumination was positively associated with activity in the amygdala when subjects were asked to increase their negative affect and with greater decreases in prefrontal regions when subject were asked to decrease their negative affect in response to negative visual stimuli (Ray et al., 2005). In the same way, Vanderhasselt et al. (2013) found, that brooders showed more activity in the posterior dorsal parts of the ACC during the successful inhibition of negative information, suggesting that high ruminating subjects need higher activation in this brain area for successful response inhibition (Vanderhasselt et al., 2013).

To sum up, for the construct of rumination, similar effects are found on a neuronal, cognitive and affective level as for the effects of depression as a diagnostic category. While this isn't surprising, given the high correlation of rumination and depression, it also suggests a convergence or correlation of the two constructs on a neuronal level.

3.2 Studies showing increased FC in depression and rumination

Since activation and functional connectivity contain different information about the represented neuronal process – with activation corresponding to local neuronal metabolism and neuronal firing and FC indicating synchronous activation/deactivation of different brain areas – research findings differ between FC measures and activation studies. In the following, studies that show higher intra- and inter-network FC in depression and rumination shall be outlined.

The most reliable finding with respect to elevated FC in MDD has been shown between sgACC and the DMN. In their review and meta-analysis, Hamilton et al. (2015) argue that higher FC between sgACC and the DMN is the only robust finding in FC depression research (Hamilton, Farmer, Fogelman, & Gotlib, 2015a). In their theory, the authors propose that the sgACC is functionally co-activated with DMN nodes during rumination because of its function in behavioral withdrawal. During rumination, the vmPFC assigns valence to internal stimuli, the DMN applies an egocentric reference frame and the sgPFC causes behavioral withdrawal, that results in a self-focused persistent ruminative state. In line with this theory, others found hyperconnectivity between the DMN and sgPFC, higher connectivity between the CCN and DMN and between the IFG and amygdala in children at risk for depression (Chai et al., 2016). Regarding inter-network connectivity, first meta-analytic data suggests that MDD is related to hyperconnectivity between the CCN and DMN (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Further, others showed elevated FC between the SN and DMN in MDD using ICA based methods (Manoliu et al., 2014) and classical FC measures (Bhaumik et al., 2016). Also, increasing coupling of intrinsic networks in remitted MDD was detected by Jacobs et al. (2014). They found increased FC of posterior cingulate cortex (part of the DMN)

and sgACC seeds to lateral parietal and frontal regions of the CCN. However, these hyper-connections showed a negative correlation with rumination, indicating a compensatory or protective factor (Jacobs et al., 2014a). Similarly, higher FC within the CCN was found in remitted adolescents with MDD; they showed elevated FC between the left dlPFC, left IFG and middle frontal gyri, and the left amygdala and right PCC. Moreover, positive correlations between FC and rumination were found for amygdala to PCC FC and for depression severity and dlPFC to IFG FC (Peters, Burkhouse, Feldhaus, Langenecker, & Jacobs, 2016). Interestingly in one study, treatment with RF-CBT resulted not only in significant reductions in rumination, but also in decreased connectivity between the left PCC, bilateral inferior temporal gyri and right IFG (Jacobs et al., 2016). Moreover, changes in psychopathology were correlated with changes in FC. With respect to local FC, a recent meta-analysis suggests that regional homogeneity shows the highest increase in medial prefrontal cortex FC in depressed subjects compared to controls during resting state and that this effect is higher in un-medicated depressed subjects with multiple episodes (Iwabuchi et al., 2015a). This higher regional homogeneity is interpreted as a pronounced participation of the mPFC in DMN like functions, e.g. rumination, through bottom-up processing in the paralimbic salience system.

3.3 **Studies showing attenuated FC in depression and rumination**

Besides the studies outlined above, some studies also reported reduced FC within and between functional networks. In a recent study, Stange and colleagues (2017) reported attenuated FC within the CCN in a remitted MDD sample with pronounced effects within the dlPFC and right inferior parietal lobule (Stange et al., 2017). In a recent fNIRS investigation, Zhu and colleagues also reported reduced intra-regional and symmetrically interhemispheric FC in the PFC, in the local IFG and bilateral IFG in a depressed sample (H. Zhu et al., 2017). In the same way, FC between the posterior cingulate cortex and the bilateral caudate has been shown to be reduced in MDD (Bluhm et al., 2009) extending the findings regarding the CCN to the DMN. In line with this, others have reported reduced FC in MDD in a network including the left precentral gyrus, left angular gyrus, bilateral rolandic operculum and left IFG (Lai, Wu, &

Hou, 2017) using NBS, and in correlated (posterior DMN) and anti-correlated (including insula, ACC and middle frontal gyrus) networks centered at the PCC using ICA (Yang et al., 2016).

Regarding inter-network connectivity, in the above reported study of Chai et al. (2016) also attenuated FC within the CCN, and between left dlPFC and sgACC has been reported(Chai et al., 2016). Also others reported decreased intra-network FC within the SN and decreased internetwork FC between DMN and CCN (Manoliu et al., 2014), between the CCN and DAN (Kaiser et al., 2015), between dlPFC (CCN) and angular gyrus (DMN) and between mPFC and precuneus (anterior and posterior DMN) in treatment resistant MDD compared to healthy controls and non-treatment resistant MDD (B. P. de Kwaasteniet et al., 2015a).

Mostly robust findings have been found with regards to inter-hemispheric FC measures. Besides the already mentioned fNIRS study by Zhu et al (2017), others reported reduced FC in MDD using voxel-mirrored homotopic connectivity (VMHC) (Hermesdorf et al., 2016; Z. Hou, Sui, Song, & Yuan, 2016; L. Wang et al., 2013; Y. Wang et al., 2015; Xu et al., 2013). However, until today it is not totally clear, in what context theses inter-hemispheric abnormalities of information processing should be interpreted.

In summary, most robustly elevated FC has been found between the sgACC and DMN nodes and reduced FC between inter-hemispheric nodes in MDD compared to healthy controls. The findings regarding other intra- and inter-network connections are inconsistent. The factors that underlie these moderations are to a great extent unknown and may be due to methodological, psychological or physiological factors. One of the factors that might explain some of the variation in FC might be rumination. As outlined in one of the previous chapters, MDD is associated with hypo-activity within cortical areas in cognitive tasks. However, also higher activity within cortical regions is found in the experimental induction of rumination. If such a dissociation would be present in the co-activation of brain areas, rumination might be a factor that

leads to different FC between high ruminating depressed subjects and low ruminating depressed subjects.

As outlined by Hamilton et al. (2015), elevated FC between sgACC and DMN nodes might indeed be related to avoidance-aspects of rumination (Hamilton et al., 2015a). However, since suppression – and likewise also rumination – is associated with difficulties in theory of mind tasks and cognitive executive functioning, areas associated with these cognitive functions (e.g., DMN, CCN) should also show impairments such as reduced FC. On the other hand, rumination per se is also a cognitive process that should be related to activation of and connectivity between process-relevant brain areas. Regarding the factor of rumination, only a few studies exist, including experimental and correlational designs. However, both types of study designs have pros and cons with respect to the generalization of the findings. In the case of experimental designs, a first limitation is the induction method of rumination. Firstly, rumination is mostly an implicit process that might be difficult to induce. In conclusion, explicit instruction to ruminate via autobiographical paradigms or implicit induction via sad mood might differ from the implicit involuntary pathological process in MDD patients outside the lab. Further, rumination induction methods might induce artificial neuronal activity that is not related to rumination per se, but to the induction process (e.g., higher cognitive load). On the other hand, non-experimental correlational approaches mostly use some sort of trait rumination questionnaire like the RRS. This trait-measure is then correlated with a “state” resting-state measure. As noted previously, the RRS might capture other depression related trait-like constructs such as neuroticism or symptom severity when measuring rumination. Finally, the measurement conditions mostly used in neuroscience need to be considered. The majority of studies reported above used fMRI. While fMRI is the gold standard for imaging of hemodynamic changes in the brain, the environment of the scanner itself might disturb the cognitive process of rumination, as will be outlined in the next chapter.

Due to the reported inconsistencies and critical points of the existing research literature, we designed four different studies in which we sought to measure differences between depressed and non-depressed subjects in brain activation

and functional connectivity. Further, we investigated in how far potential differences would be due to the cognitive process of rumination.

4. Aims & Linkage of the studies

In the following, the studies of this dissertation, facing the previously outlined shortcomings of the present research status, shall be outlined briefly. In the presented studies, fNIRS has been used to measure blood oxygenation changes for reasons that will be outlined in the next chapter. In total, four studies have been conducted addressing the questions of aberrant cortical functioning in MDD and whether or not these measures are related to the process of rumination.

In Study 1, we investigated whether or not FC within the CCN can be measured with fNIRS in different states – resting-state vs. cognitive task – (primary aim) and if the reactivity and basal FC within the CCN is different between patients with LLD and healthy controls.

- *Research question 1: Can state-dependent FC within the CCN be measured with fNIRS?*
- *Research question 2: Do depressed subjects show differences in basal FC and FC reactivity within the CCN?*

Since differences in FC due to depression might be mediated by several different cognitive aspects, we developed state-measurements of rumination to investigate in how far the potential physiological differences between patients and controls are due to the psychological construct of rumination.

In Study 2, we focused on FC in a parietal probeset covering parts of the sensorimotor network, DMN and DAN. As in Study 1, we were interested in differences in FC between patients with MDD and healthy controls (primary aim). However, we also investigated, whether or not these differences in FC can be explained by trait- and state-measures of rumination and whether or not these measures differ in their predictive value (secondary aim).

- *Research question 3: Do depressed subjects show differences in FC within the parietal cortex?*
- *Research question 4: Do trait and state measures of rumination explain differences in FC between depressed and non-depressed subjects?*

Although our state-measurements assess momentary rumination by asking the participants for the presence of the process in the moment, so far our studies only investigated single resting-state measurements and are therefore restricted to between-subject comparisons. In order to disentangle state and trait-constructs, the process of rumination has to be induced experimentally (or at least measured at different time points) and has to be correlated on a within-subject level. If such a within-subject correlation was not present, the between-subject differences in brain functioning could also be due to a biological vulnerability factor instead of being a correlate of state rumination per se. Therefore, we sought to induce rumination by a social stress induction method in Study 3.

In Study 3, we investigated if state rumination can be induced by a social stress induction and if hemodynamic responses during the stress induction and parameters of the stress-response vary as a function of trait rumination (primary aim). Further, we investigated if state rumination can be predicted by brain activity during the stress induction (secondary aim).

- *Research question 5: Can state rumination be induced via social stress and do the hemodynamic changes within the CCN vary as a function of trait rumination?*
- *Research question 6: Can state rumination be predicted by cortical reactivity in the CCN due to social stress?*

As measures in brain activity in FC represent different information in brain processing, in Study 4, changes in rsFC due to social stress were investigated in a high- and low trait rumination group in the same sample (primary aim). As a secondary aim, we investigated whether or not changes in rsFC were related to changes in state rumination.

- *Research question 7: Does FC within the CCN vary as a function of social stress and does trait rumination moderate this effect?*
- *Research question 8: Do changes in FC within the CCN predict changes in state rumination?*

4.1 Overview over the present studies

	Study 1	Study 2	Study 3	Study 4
Study aim	Different states in FC between LLD patients and healthy controls	Associations between trait-/ state rumination and FC	Differences between low and high trait ruminators in brain activation during social stress	Differences between low and high trait ruminators in FC before and after the induction of social stress/ state rumination
Paradigm	1) Resting – state 2) Trail Making Test	Resting-state	Trier Social Stress Test	1) Pre- and Post-measurements of resting-state
Sample	LLD and HC	MDD and HC	Student sample: high and low trait ruminators	Student sample: high and low trait ruminators
Investigated Networks	CCN	DAN DMN CCN	CCN DAN	CCN DAN
Main DVs	• rsFC • Reaction time	• rsFC • State rumination (qualitative and quantitative)	• Activity • State rumination (quantitative) • Subjective stress • Cortisol • Heart-rate • Negative affect	• ROI based rsFC • State rumination (qualitative and quantitative)
Analyses (behavioral data)	• t- and F-tests	• t- and F-tests • Qualitative evaluation as suggested by grounded theory	• t- and F-tests	• t- and F-tests • Qualitative evaluation
Analysis (brain imaging data)	• Network Based Statistics	• Network Based Statistics	• Repeated Measurement ANOVA • Multilevel Modelling • Mediation Analysis	• Repeated Measurement ANOVA • Multilevel Modelling

Table 1. The table displays an overview of the four studies that are subject of the work at hand. FC = functional connectivity, LLD = late-life depression, HC = healthy controls, MDD = Major Depressive Disorder/ depressed subjects, CCN = cognitive control network, DAN = dorsal attention network, DMN = default mode network, ROI = region of iInterest, DV = dependent variable

4.2 Choice of brain imaging techniques

Besides the afore-mentioned methodological considerations with respect to the induction and measurement of rumination, some considerations with regards to the used neuroimaging method have to be mentioned. The endeavor of the present work was to measure rumination in depressed subjects while measuring brain activity. Several brain imaging methods exist up to date, with different relative advantages and disadvantages. In the current studies, we used the optical imaging method of functional near-infrared spectroscopy (fNIRS). As we sought to investigate the cognitive process of rumination in depressed subjects, we had to choose an imaging method that enables to measure the subjects in an environment that doesn't disturb the arising cognitions or induces artificial processes, e.g., arousal. While fMRI is still the gold standard in functional brain imaging, the method goes along with several prerequisites such as a lying position of the participants and loud noises of the scanner during the scan. In many subjects, the narrow environment of the scanner itself induces agoraphobic responses together with increases in subjective and physiological stress. In contrast, fNIRS, which has lower spatial resolution and is unable to measure subcortical areas, allows for measurements in nearly every body position in familiar environments with relatively little noise. This high ecological validity of the measurement makes fNIRS especially preferable in clinical populations that are less resilient to stressful environments. Additionally, fNIRS is relatively robust to movement artefacts. Therefore, subjects can be measured while speaking or while performing small movements, e.g. with their arms. Within the presented studies, we measured brain activation during rest, but also during the performance of the Trail Making Test (TMT), where subjects are asked to draw lines between numbered circles, and during the TSST, where participants have to hold a public speech. Both tasks require measurement conditions which are unfeasible in their original form in fMRI. Adaptions of these paradigms exist, but they come along with a loss in ecological validity.

Because of these considerations, we chose fNIRS to measure cortical activation in our studies to allow for an ecologically valid environment that itself allows for the measurement of rumination without severe disturbances.

5. Study 1 – State-dependent altered connectivity in late-life depression: A functional near-infrared spectroscopy study.

The contents of this chapter are published:

Rosenbaum, D., Hagen, K., Deppermann, S., Kroczek, A. M., Haeussinger, F. B., Heinzel, S., Berg, D., Fallgatter, A. J., Metzger, F. G., Ehlis, A.-C. & The TREND Study Consortium (2016). State-dependent altered connectivity in late-life depression: A functional near-infrared spectroscopy study. Neurobiology of Aging, 39, 57-68.

5.1 Abstract

There is a large body of evidence showing a substantial relationship between depression and deficits in cognitive functioning. Especially in late-life depression, cognitive impairments are associated with worse treatment progress and are considered a risk factor for neurodegenerative disorders. However, little is known about the differences in neural processing and coupling during rest and cognitive functions in patients with late-life depression compared to healthy elderly individuals. The study at hand aims to investigate the cognitive control network in late-life depression during a cognitive task and at rest by means of functional near-infrared spectroscopy (fNIRS).

Hemodynamic responses were measured at rest and during the Trail Making Test (TMT) using fNIRS in a matched sample of 49 depressed and 51 non-depressed elderly subjects (age range: 51–83 years; 64.1 ± 6.58 [mean ± SD]). Functional connectivity (FC) and network metrics were derived from the data and analyzed with respect to differences between the subject groups.

Depressed and non-depressed subjects showed significant differences in FC both at rest and during task performance. Depressed subjects showed reduced FC in a left frontopolar cortical network during task performance and increased FC in a left fronto-parietal cortical network at rest.

Depressed elderly subjects showed altered FC and network organization during different mental states. Higher FC at rest may be an indicator of self-referential processes such as rumination that may reduce FC during task performance due to an overtaxed executive control system.

Keywords: Late-life depression, functional connectivity, network analysis, near-infrared spectroscopy, cognitive control network, executive functioning

5.2 Introduction

Although major depressive disorder is one of the most burdening diseases worldwide (Briley & Lépine, 2011), research concerning depression in later life was neglected until its prominent role in the development of neurodegenerative disorders had been explored (Byers & Yaffe, 2011; Diniz, Butters, Albert, Dew, & Reynolds, 2013). Current models of the disease suggest that both early and late-life depression (LLD) have the same phenomenology but may be disorders with different etiology (Alexopoulos, 2005; A. Fiske, Wetherell, & Gatz, 2009; Mackin et al., 2014). Until now, several mechanisms have been proposed to explain the link between depression and neurodegeneration in later life (Taylor, Aizenstein, & Alexopoulos, 2013; Weisenbach & Kumar, 2014). In the same manner, attempts have been made to investigate the underlying neurobiology of LLD. Like depression in early life, LLD seems to be characterized by hypofrontality during cognitive tasks (M. J. Herrmann, Ehlis, & Fallgatter, 2004; Schecklmann et al., 2011; Huijun Zhang et al., 2014), reduced brain volume in a variety of brain regions, e.g. hippocampus, orbitofrontal cortex (OFC), putamen and thalamus (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012b; Sexton, Mackay, & Ebmeier, 2012), and abnormalities in functional/structural connectivity of brain networks (Guo et al., 2014; Guo, Liu, Zhang, et al., 2013b; Korgaonkar, Fornito, Williams, & Grieve, 2014; R. Tadayonnejad & Ajilore, 2014b; Reza Tadayonnejad, Yang, Kumar, & Ajilore, 2014). Furthermore, metrics of network organization have been shown to deviate in LLD (Gong & He, 2015), with higher tendencies to randomized network organization (J. Zhang et al., 2011a) and reduced network resilience (Ajilore et al., 2014) in LLD compared to healthy controls. In addition to corticostriatal networks associated with emotion regulation, fronto-parietal networks associated with cognitive control seem to be especially important in LLD, since patients with LLD and cognitive impairment are at high risk for developing dementia (Alexopoulos, 2005). However, studies which examined the cognitive control network (CCN) in LLD have been inconclusive, showing widespread abnormalities with lower and higher functional connectivity (FC) in LLD depending on the network region under consideration, applied methods (e.g. fMRI, EEG) and measurement

conditions (e.g. resting state vs. task performance). For example, some studies reported reduced FC between the dorsolateral prefrontal cortex (dlPFC) and the dorsal anterior cingulate cortex (dACC) in LLD (Aizenstein et al., 2009; Alexopoulos et al., 2012), but also higher global (Bohr et al., 2013) and local functional connectivity was found in the OFC, middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) (Alexopoulos et al., 2013). To date, the conflicting results of FC in LLD have not been explained satisfactorily and additional evidence is needed. The study at hand aims at advancing our understanding of FC in LLD by systematically investigating FC and network measures of the CCN during performance of a cognitive task and at rest in LLD using functional near-infrared spectroscopy (fNIRS).

fNIRS is an optical imaging method which is based on the principle that light in the near-infrared spectrum is capable of penetrating the human skull and, by doing so, is in part absorbed by the underlying tissue (figure 6). Different tissues (i.e., scalp, muscles, skullcap, cerebrospinal fluid) and oxygenated (O_2HB) and deoxygenated hemoglobin (HHB) absorb near-infrared light to different degrees and at different wavelengths due to different physical characteristics (Florian B. Haeussinger et al., 2011a). Accordingly, it is possible to track changes in cortical O_2HB and HHB patterns in the cortex by sending near-infrared light with a sender-optode (emitter) into the skull and measuring the reflected light with a receiver-optode (detector) at the scalp. Studies using simultaneous fNIRS and fMRI measures estimated the penetration depth of near-infrared light light to be about 2 to 3 cm (Cui, Bray, Bryant, Glover, & Reiss, 2011; Florian B. Haeussinger et al., 2011a).The investigation of brain networks in the elderly presents challenges (e.g. reduced mobility, agitation of subjects) to standard imaging methods (e.g. EEG, fMRI) that may be well addressed by fNIRS. Even though fMRI remains the gold standard in cognitive neuroscience, fNIRS may be favorable in some cases due to its higher time resolution, relative insensitivity to movement-related artifacts and potentially mobile application (Ehlis, Schneider, Dresler, & Fallgatter, 2014a). The validity of the method has been confirmed (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006; Plichta, Heinzel, Ehlis, Pauli, & Fallgatter, 2007) and a good short- and long-term test-

retest reliability was shown (Plichta et al., 2006; Schecklmann, Ehlis, Plichta, & Fallgatter, 2008). Finally, fNIRS is a very practical method with high ecological validity due to short preparation time, low-cost measurements and without contraindications; so many subjects can be examined in a relatively short period of time. These advantages made fNIRS the method of choice for the present study on a subsample of 49 depressed and 51 healthy elderly subjects (selected by propensity score matching) out of a total investigated sample of 1018 elderly participants. Regarding the topics at hand, fNIRS has already been successfully applied to investigate cortical hemodynamic changes in late-onset / LLD (Matsuo et al., 2005; Uemura et al., 2014; Yamagata et al., 2008) as well FC (Niu, Wang, Zhao, Shu, & He, 2012; Sasai et al., 2012a; Sasai, Homae, Watanabe, & Taga, 2011) and network measures (Fekete, Beacher, Cha, Rubin, & Mujica-Parodi, 2014; Niu et al., 2012) in healthy subjects. In the study of LLD, a reduced hemodynamic response has been observed with fNIRS in cognitive tasks such as the Trail Making Test (TMT) and verbal fluency test (VFT). However, to the best of our knowledge hitherto, fNIRS studies of FC have not yet been conducted in a depressed elderly population.

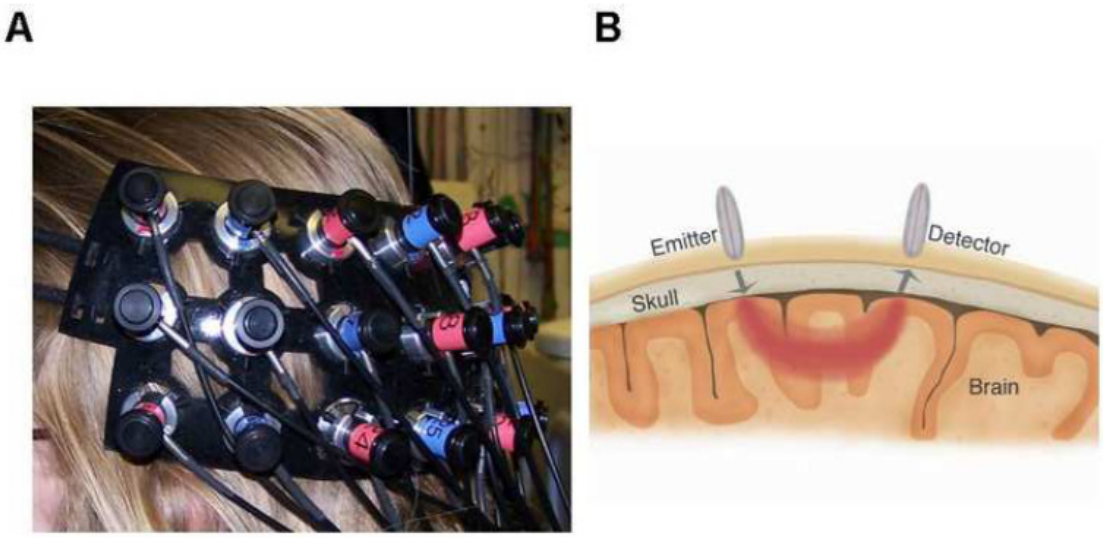

Figure 6. A: Illustration of the fNIRS system on a volunteers head. Red optodes are emitters, blue optodes are detectors. B: Schematic illustration of the fNIRS principle for one emitter and one detector placed on the head surface.

In the present study, patients with LLD were analyzed in terms of their connectivity patterns as compared to healthy controls. Importantly, based on the inconsistency of previous findings (see above), we focused on connectivity patterns during both resting state and task performance. To activate the cognitive control network (CCN) during a cognitive task we employed the TMT. The TMT was chosen for several reasons. First, it is a reliable, valid (Giovagnoli et al., 1996) and easy to use cognitive task, which is frequently used in neuropsychological routine testing but does not produce any speech-related muscle artifacts (in contrast to, e.g., the VFT). Moreover, the TMT-B version has been shown to consistently activate frontal cortices of executive functioning such as the dlPFC, cingulate gyrus and inferior/middle frontal cortices (Hagen et al., 2014; Jacobson et al., 2011; Moll et al., 2002; Zakzanis et al., 2005). The data was analyzed in a twofold manner: First, differing FC in networks were identified with network based statistics (Zalesky, Fornito, & Bullmore, 2010a). Second, network organization characteristics were quantified via graph theoretical measures (Rubinov & Sporns, 2010a; van Wijk, Stam, & Daffertshofer, 2010). Based on previous studies implicating altered FC in depression during earlier age, we predicted that the group of elderly depressed subjects would show changes in FC in parts of the CCN during rest and task performance. Given the special role of cognitive impairments in LLD, we specifically hypothesized that attenuated FC would be found in the fronto-parietal connections of the CCN during performance of a cognitive task.

5.3 Methods and Materials

Participants. Subjects were recruited from the *Tübinger evaluation of risk factors for early detection of neurodegeneration* (TREND)-study database (Heinzel et al., 2014, 2013; Hobert et al., 2011). A depressive sample of 49 patients[1] was selected by the following inclusion criteria: A Beck Depression Inventory (BDI) score higher than 14 and a Geriatric Depression Scale (GDS) score higher than 6. Mean depression scores for the depressive group were 22.24 (SD 7.28, range: 14-42) for the BDI and 8.79 (SD 2.20; range: 6-14) for the GDS. A non-depressive sample was matched to the depressive subgroup

via propensity score matching, controlling for the following variables: age, gender, years of education, learning abilities, visuospatial abilities, and memory performance. Cognitive domains were assessed with the *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD) test battery (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988). Due to the matching procedure, the depressed and non-depressed sample did not differ significantly in any of the matching variables. An overview over the demographic variables and neurocognitive measures in the two samples can be seen in table 2. The matched control group had an average BDI score of 4.75 (SD 3.50 range: 0-12) and a GDS score of 1.16 (SD 1.22; range: 0-5). The whole sample consisted of 68% female participants, had a mean age of 64 years (SD 6.5; range: 53-81) and a mean education of 13.8 (SD 2.5, range: 9-21) years.

26% of the depressed sample and 8% of the non-depressed sample were diagnosed with an anxiety disorder. Furthermore, two participants reported diagnoses of a bipolar disorder and an eating disorder. No person reported a diagnosis of psychosis. In the sample, 54% of participants took some kind of medication, particularly blood pressure medication (34%), antiplatelet drugs (17.2%) and – for the depressive sample – anti-depressive medication (29.3%). Blood pressure medication included beta blockers (18%), angiotensin-converting-enzyme inhibitors (9%), angiotensin II receptor antagonists (11%), calcium channel blockers (12%) and alpha blockers (1%). Antiplatelet drugs involved acetylsalicylic acid (16%), Dipyridamole (1%) and Clopidogrel (1%). Antidepressive medication comprised SSRIs (10%), SNRI (5.1%), NDRI (2%), tricyclic antidepressant (5.1%), tetracyclic antidepressants (5.1%) and MAO inhibitors (2%).

	Non-Depressed		Depressed	
Variable	**mean**	**SD**	**mean**	**SD**
Age (years)	64.16	6.14	64.08	7.06
Female Participants	66%		69%	
Years of education	13.86	2.36	13.74	2.74
BDI score	4.75	3.50	22.24	7.28
GDS score	1.16	1.22	8.79	2.20
Phonemic Verbal Fluency	25.29 (0.25)	6.23 (0.97)	23.88 (0.37)	5.45 (1.05)
Semantic Verbal Fluency	14.76 (0.32)	4.48 (1.17)	15.44 (0.05)	5.18 (0.95)
Boston Naming Test	14.63 (0.45)	.70 (0.75)	14.33 (0.15)	1.04 (0.93)
Mini Mental Status	28.53 (-0.65)	1.40 (1.20)	28.42 (-0.81)	1.41 (1.13)
Word List Learning	22.29 (0.04)	4.04 (1.22)	22.46 (0.05)	4.24 (1.14)
Word List Delayed Recall	7.69 (0.02)	2.31 (1.33)	7.90 (0.09)	1.89 (1.03)
Word List Intrusion	.90 (-0.30)	1.58 (0.99)	.63 (-0.12)	1.14 (0.94)
Savings Wordlist (in %)	88.33 (-0.12)	21.56 (1.34)	91.42 (0.05)	16.28 (1.08)
Figure drawing	10.22 (-0.07)	1.28 (1.21)	10.21 (-0.15)	1.09 (1.22)
Figure recall	9.51 (0.14)	1.76 (1.13)	8.96 (-0.21)	1.95 (1.18)
Savings Figures (in %)	93.37 (0.24)	15.14 (0.94)	88.15 (-0.04)	17.84 (0.94)
Trail Making Test Part A (seconds for completion)	34.00 (0.89)	10.41 (1.11)	35.83 (0.63)	10.33 (0.93)
Trail Making Test Part B (seconds for completion)	92.82 (0.49)	43.63 (0.45)	94.94 (1.53)	53.54 (1.36)
Trail Making Test BA-Ratio	2.82 (-0.34)	1.45 (-0.21)	2.62 (1.14)	1.13 (0.95)

Table 2: Demographic and neurocognitive measures of the samples. Age-stratified standardized z-scores of the neurocognitive parameters are shown in parentheses. BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale

fNIRS. To measure cortical hemodynamic changes, fNIRS was used. Data was assessed during a five-minute resting phase and a subsequent cognitive task. We used a continuous wave, multi-channel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan) with a temporal resolution of 10 Hz. In this study, we used the same optode system (figure S1 supplementary material) as Hagen et al. (Hagen et al., 2014): 38 channels were divided into two frontal (3×3 optodes each: five emitters and four detectors) and two posterior probesets (2×3 optodes each: three emitters and three detectors). Optodes were placed on a plastic cap with reference points at F3/F4 and Fp1/Fp2 for the frontal probe sets and C3/C4 for the posterior probesets, according to the international 10-20 system (Homan, Herman, & Purdy, 1987; Jasper, 1958a). Channel positions for this probeset were described by Hagen et al. (Hagen et al., 2014) using a neuronavigation system (LOCALITE GmbH, St. Augustin, Germany) on a volunteer's head (table 3).

Brain area	Probeset	
	Probeset A: left frontal	Probeset B: right frontal
Dorsolateral prefrontal cortex	4, 7, 9, 10, 11, 12	1, 6, 8, 9, 11, 12
Pars triangularis (Broca's area)	1, 3, 6	2, 4, 7
Pars opercularis (part of Broca's area)	8	5
Frontopolar area	2, 5	3
Pre-motor and supplementary prefrontal cortex		10
	Probeset C: left parietal	Probeset D: right parietal
Primary motor cortex	3, 6	1
Primary somatosensory cortex	1, 4	3
Somatosensory association cortex	2, 5, 7	2, 4, 5, 7
Supramarginal gyrus part of Wernicke's area		6

Table 3: fNIRS channels and assigned brain areas

TMT. During the fNIRS data acquisition, subjects were asked to perform an adapted TMT. The TMT is a cognitive paper-and-pencil task often used in neuropsychological batteries such as the CERAD-Plus test battery. The adapted form used during the fNIRS-experiment consisted of three subtests: TMT-A, TMT-B, and TMT-C. During the TMT-A, subjects were asked to connect encircled numbers in ascending order (1-2-3-4…) which were scattered randomly over a piece of paper (figure 7 B). During the TMT-B, a task switch had to be performed by connecting encircled numbers and letters in an alternating and ascending order (1-A-2-B-3-C…). Moreover, we used a control condition TMT-C in which lines between circles were already drawn and subjects were asked to retrace these lines. In every part of the TMT 25 items were presented. Both the TMT-A and TMT-B require visual search and motor speed abilities, while the TMT-B also stresses set-shifting and working memory functions. In contrast, TMT-C only captures motor speed abilities. The TMT was assessed in an experimental block design with the order A-B-C-A-B-C-A-B. All blocks were separated by 30 s rest periods. The first two blocks consisted of the presentation of the TMT-A and TMT-B as recommended in the CERAD-Plus protocol. First, subjects attended to the TMT-A following an instruction and a brief practice task. After a 30 s pause, participants had a short practice block for the TMT-B before its execution. During the first assessment of the TMT-A and -B subjects had no time limit for test completion (to allow for a standardized analysis of TMT-Behavioral data). In all following blocks, completion-time was restricted to 30 s (in line with typical block-design imaging protocols). After completion of the first two blocks, two repetitions of the experimental 30 s blocks TMT-C, TMT-A, TMT-B were assessed. Including preparation time, the whole task took approximately 25 minutes for completion (figure 7 A). Analysis of the NIRS data included averaging over the repetitions of the three condition blocks. For the conditions TMT-A and -B, averages included the first 30 s of the first presentations and the two time-restricted repetition blocks.

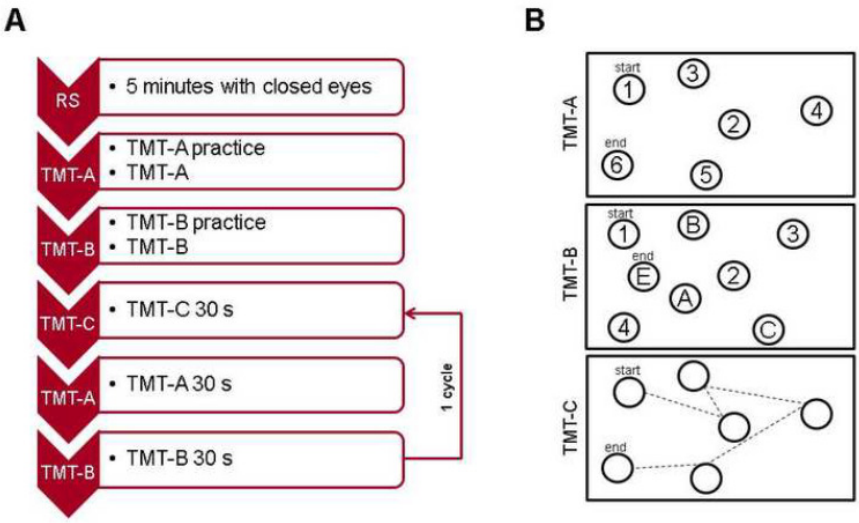

Figure 7. A: Time-flow-chart of the experimental procedure. B: Exemplary illustration of the TMT task. Note that the used task included 25 items which are reduced in the figure for reasons of clarity and comprehensibility.

5.4 Data Analysis

Preprocessing. Data was processed and analyzed using Matlab® R2012a (MathWorks Inc., Natick, USA). Data preprocessing included band-pass filtering (0.001-0.1 Hz), a correlation-based movement correction (Brigadoi et al., 2014; Cui, Bray, & Reiss, 2010), visual inspection of the signal quality and – in case of artifacts – exclusion of data. Band-pass filtering was chosen to minimize artifacts in the very low and high frequency range, which both are not associated with brain activity related hemodynamic change (F.B. Haeussinger et al., 2014; Lu et al., 2010). The correlation-based movement correction algorithm of Cui et al., uses the principle that O_2HB and HHb are correlated negatively to reduce motion induced changes in O_2HB (during motion artefacts O_2HB and HHb are correlated positively). Lastly, a visual inspection of the signal quality was performed to check for massive artifacts that were not removed by the preprocessing, e.g. due to technical problems. For more detailed information of preprocessing steps in fNIRS see the comprehensive methodic work of Brigadoi et al (2014). For the measurement of connectivity during task performance, single blocks of the TMT were averaged with a 5 s baseline correction. The latter step was omitted in the case of resting state data. For the analysis of connectivity, cross-correlations with a zero-time lag between

channels during task performance and at rest were computed for each subject with the *Matlab toolbox for functional connectivity* (Zhou, Thompson, & Siegle, 2009). Afterwards a *Fisher r-to-z-transformation* (Silver & Dunlap, 1987a) was performed. Finally, data was further processed with the *NBS toolbox* (Zalesky et al., 2010a) and the *Matlab toolbox for network analysis* (Bounova & de Weck, 2012; Gergana, 2014).

Network-based statistics (NBS). We analyzed differences in connectivity using NBS (Zalesky et al., 2010a). Briefly, NBS uses massive univariate testing of a contrast on connectivity data and in a second step clusters connections that exceed a significance threshold. The extracted significant cluster is further tested for significance by permutation tests (see supplementary material). Therefore, the procedure accounts for problems of multiple testing. In the present study, we used a statistical threshold of t=2.7 and tested the resulting networks in permutation tests with N=5000 permutations.

After the identification of significantly different networks, graph theoretical measures were computed to characterize individual nodes in the disconnected or hyperconnected networks. We derived measures of nodal centrality to identify hub regions. Therefore, we computed the nodal degree and betweenness centrality of each node in the derived network. The nodal degree is defined as the sum of the connections a node in the network has. Betweenness centrality, on the other hand, is defined as the fraction of shortest paths in the network that are passing through a node (see supplemental material). Both measures are indicators of hub regions that play a crucial role in network integration and resilience (Rubinov & Sporns, 2010a). Hubs in the network were defined by high (more than two standard deviations above the mean) nodal degrees and betweenness centrality.

To test for associations of FC with symptom severity, we correlated FC measures in the derived networks with the BDI and GDS scales by using Spearman correlation coefficients. We computed associations between FC and symptom severity for the whole sample and for the diagnostic groups separately.

5.5 Results

Behavioral Results. Repeated measurement analysis of variance (ANOVAs) revealed significant differences between the conditions TMT-A and TMT-B, regarding time for completion of the first presentation of the TMT-A and -B ($F_{(1,96)}$=177.56, p<.001, η^2=.65) and mean connected targets during the time-restricted presentation of the TMT-A and TMT-B ($F_{(1,96)}$=631.98, p<.001, η^2=.87). Subjects were faster and completed more targets while performing TMT-A in comparison to TMT-B. The depressed and non-depressed groups did not differ in TMT performance (p>.1) (see table 2).

Within-group effects of task condition. Analysis of differences between measurement conditions – resting state, TMT-C, TMT-A, TMT-B – revealed differential changes in connectivity for the depressed and non-depressed subjects (figure 8). A repeated measurement ANOVA of the mean connectivity measures indicated a significant interaction of group by condition ($F_{(3, 288)}$=5.91, p<.001, η^2=.056). Planned comparisons with Helmert contrasts showed that the change in FC from resting state to task performance conditions differed significantly between the depressed and non-depressed subjects ($F_{(1, 96)}$=15.37, p<.001, η^2=.138). Depressed subjects showed a decrease while non-depressed subjects showed an increase in connectivity from resting state to task performance (figure 9). A fine-grained, group-separated NBS analysis of within-group differences revealed a significant increase of connectivity in the non-depressed group from resting state to task performance (p<.05, 10 edges, 11 nodes), from TMT-C to the experimental conditions – TMT-A and TMT-B – (p<.01, 59 edges, 24 nodes) and from TMT-A to TMT-B (p<.01, 53 edges, 32 nodes). Increases in FC were located in inter-hemispheric and fronto-parietal connections with a left hemispheric focus.

In contrast, FC decreased in the depressed group from resting state to task performance globally, with highest drops in frontal inter-hemispheric connections (p<.001, 216 edges, 36 nodes). During task performance, FC increased again in the depressed group during TMT-B in comparison to TMT-A (p<.05, 17 edges, 15 nodes). Comparable to the non-depressed group but with

smaller magnitude, increases in FC from TMT-A to -B were located in an inter-hemispheric and fronto-parietal network with a left hemispheric focus.

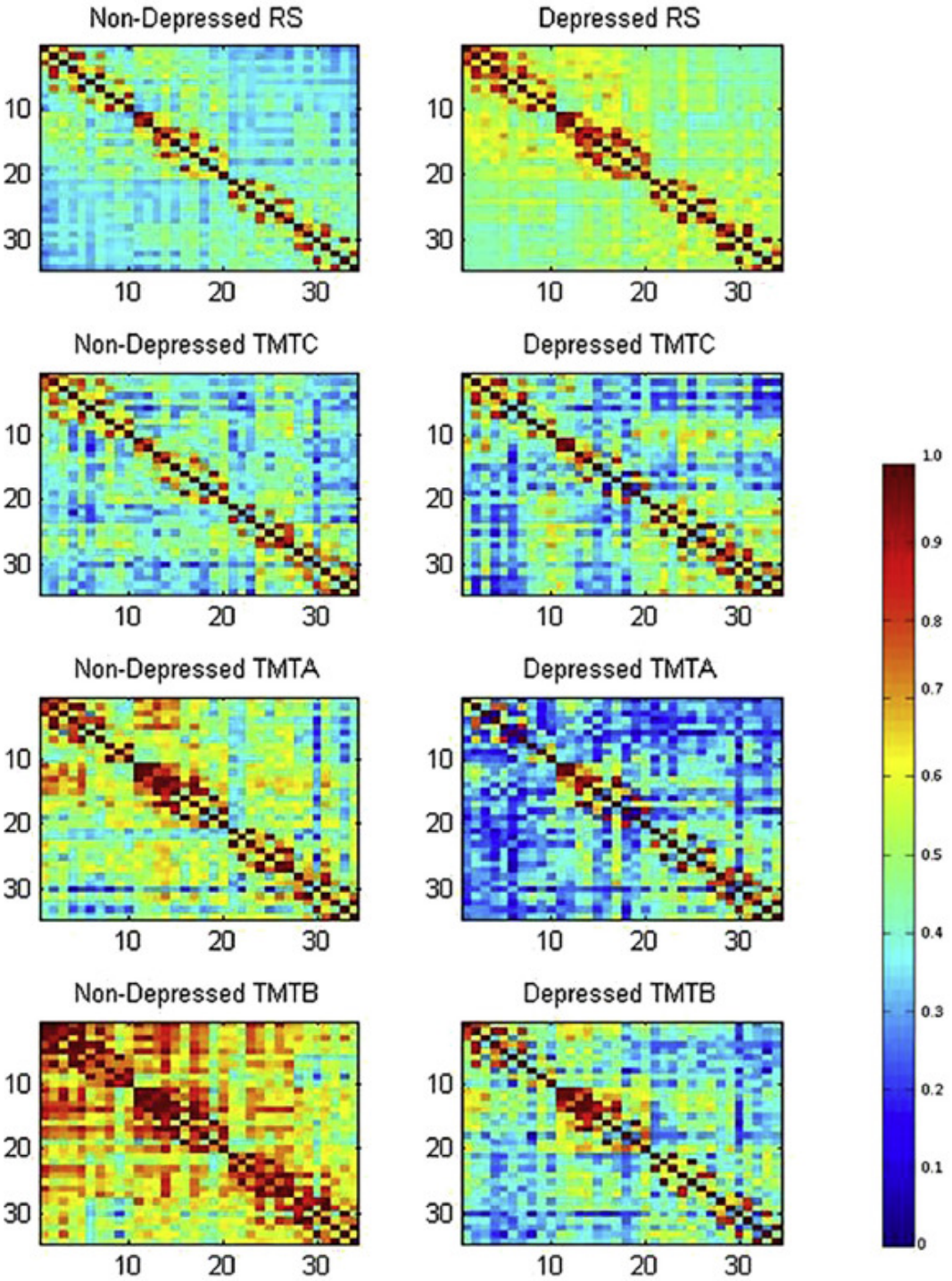

Figure 8. Connectivity matrices for the different measurement conditions for depressed and non-depressed subjects. Bright colors indicate high, dark colors low, correlation coefficients. Axis: Channel 1-12: left frontal probeset, channel 13-24: right frontal probeset, channel 25-31: left parietal probeset, channel 32-38: right parietal probeset. RS = resting state, TMT = Trail Making Test.

Between-group differences during task performance. NBS analysis revealed a disconnected network in the depressed group in comparison to the non-depressed group during the TMT-B (p=.008; ±0.002). No significant differences were found during TMT-A and TMT-C. The TMT-B network was comprised of 26 nodes and 59 connections. The nodes included several executive-control regions (frontopolar area, dlPFC, parietal regions). Within this network, all connections exhibited decreased connectivity in the depressed patients. The highest concentration of affected hub nodes was found in the left frontopolar area, left dlPFC and bilateral IFG (table 4). The disconnected network was bilaterally organized, but had a clear left frontopolar focus as hub regions were located in the left frontal cortex (figure 10). Mean differences in connectivity between depressed and non-depressed subjects for a seed region in Broca's area are depicted in figure 11. Spearman correlation coefficients between the BDI and GDS scales and connectivity measures in the extracted cluster were between rho = -.38 and rho = -.20 ($p<.001$ to $p<.05$). In the depressed group, associations between symptom severity and FC measures ranged between rho = -.33 and rho = .37 ($p<.01$ to $p<.05$). Correlation coefficients were equally distributed in the positive and negative range. In the non-depressed group this relation ranged between rho = -.28 and rho = -.38 ($p<.01$ to $p<.05$).

Ch	Node	k	Betweennes s centrality	Ch	Node	k	Betweennes s centrality
A1	**Broca**	**8**	**108.5**	B1	DLPFC	4	8.2
A2	FP	1	0	B2	**Broca**	**11**	**87.9**
A3	Broca	4	10.2	B3	FP	-	
A4	DLPFC	-		B4	Broca	2	1.7
A5	**FP**	**13**	**171.5**	B5	**Broca**	**9**	**91.8**
A6	Broca	-		B6	DLPFC	1	0
A7	DLPFC	8	60.6	B7	Broca	3	2.5
A8	Broca	1	0	B8	DLPFC	-	
A9	DLPFC	-		B9	DLPFC	3	4.6
A10	**DLPFC**	**8**	**97.7**	B10	DLPFC	4	5.1
A11	DLPFC	-		B11	DLPFC	-	
A12	DLPFC	3	48.8	B12	DLPFC	-	
C1	PSC	1	0	D1	PMC	4	3.7
C2	SAC	-		D2	SAC	1	0
C3	PMC	4	10.5	D3	PSC	4	5.0
C4	PSC	4	2.6	D4	SAC	4	2.6
C5	SAC	-		D5	SAC	-	
C6	PMC	7	66.3	D6	Wernicke	2	1
C7	SAC	4	2.6	D7	SAC	-	

Table 4: Nodal network characteristics for the NBS derived network during task performance. Ch=Channel, k=degree, SAC= somatosensory association cortex, PMC=primary motor cortex, PSC= primary somatosensory cortex, DLPFC= dorsolateral prefrontal cortex, FP=frontopolar cortex

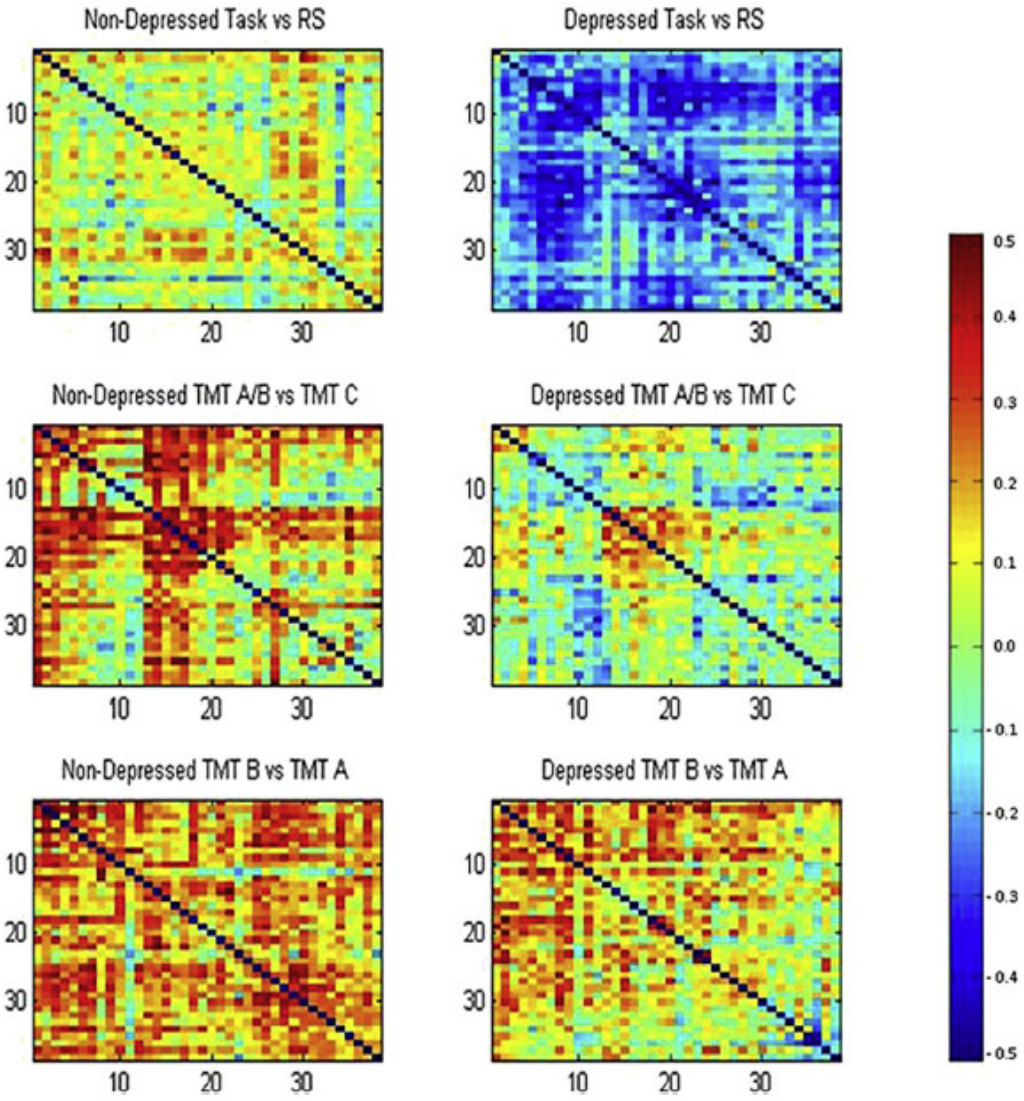

Figure 9. Connectivity matrices for the within-subject effects derived by Helmert contrasts. Bright colors indicate increased, dark colors decreased connectivity. Axis: Channel 1-12: left frontal probeset, channel 13-24: right frontal probeset, channel 25-31: left parietal probeset, channel 32-38: right parietal probeset, RS = resting state, TMT = Trail Making Test.

Between-group differences during resting state. During resting state an altered network was revealed by NBS analysis (p=0.006; ±0.001). In this network, all connections had stronger connectivity in the depressed sample compared to the non-depressed group. The network was comprised of 24 nodes and 41 edges. Hub nodes with high degrees (table 5) were found in left parietal (primary somatosensory cortex, somatosensory association cortex) and frontal (frontopolar area) regions. The derived network was bilaterally organized but had a left parietal focus, i.e. highly connected nodes were localized in the

left parietal probeset (figure 10). Mean differences in connectivity with the left primary somatosensory cortex as seed region are depicted in figure 11. Correlation coefficients between the BDI and GDS scales and connectivity measures in the extracted cluster during resting state were between rho = .37 and rho = .21 ($p<.001$ to $p<.05$). Subgroup analyses revealed that in the depressed group the BDI score was not significantly related to FC measures. However, the association between the GDS and FC ranged between rho = .29 and rho = .34 ($p<.01$ to $p<.05$). In the non-depressed group associations ranged between rho = .28 and rho = .36 ($p<.05$).

Ch	Node	k	Betweennes s centrality	Ch	Node	k	Betweennes s centrality
A1	Broca	-	-	B1	DLPFC	1	0.0
A2	**FP**	**11**	**86.6**	B2	Broca	-	-
A3	Broca	-	-	B3	FP	-	-
A4	DLPFC	3	0.0	B4	Broca	4	13.5
A5	FP	4	3.7	B5	Broca	-	-
A6	Broca	4	9.3	B6	DLPFC	4	8.4
A7	DLPFC	4	9.3	B7	Broca	2	46.0
A8	Broca	2	0.0	B8	DLPFC	-	-
A9	DLPFC	1	0.0	B9	DLPFC	2	0.0
A10	DLPFC	5	21.8	B10	PMPFC	1	0.0
A11	DLPFC	-	-	B11	DLPFC	1	0.0
A12	DLPFC	4	13.5	B12	DLPFC	2	0.0
C1	PSC	3	46.0	D1	PMC	1	0.0
C2	SAC	-	-	D2	SAC	-	-
C3	PMC	-	-	D3	PSC	1	0.0
C4	**PSC**	**15**	**195.9**	D4	SAC	-	-
C5	SAC	-	-	D5	SAC	5	11.2
C6	PMC	4	3.7	D6	Wernicke	-	-
C7	**SAC**	**12**	**144.8**	D7	**SAC**	**8**	**142.3**

Table 5: Nodal network characteristics for the NBS derived network during resting state. Ch=Channel, k=degree, Clocal=local clustering coefficient, SAC= somatosensory association cortex, PMC=primary motor cortex, PSC= primary somatosensory cortex, DLPFC= dorsolateral prefrontal cortex, FP=frontopolar cortex

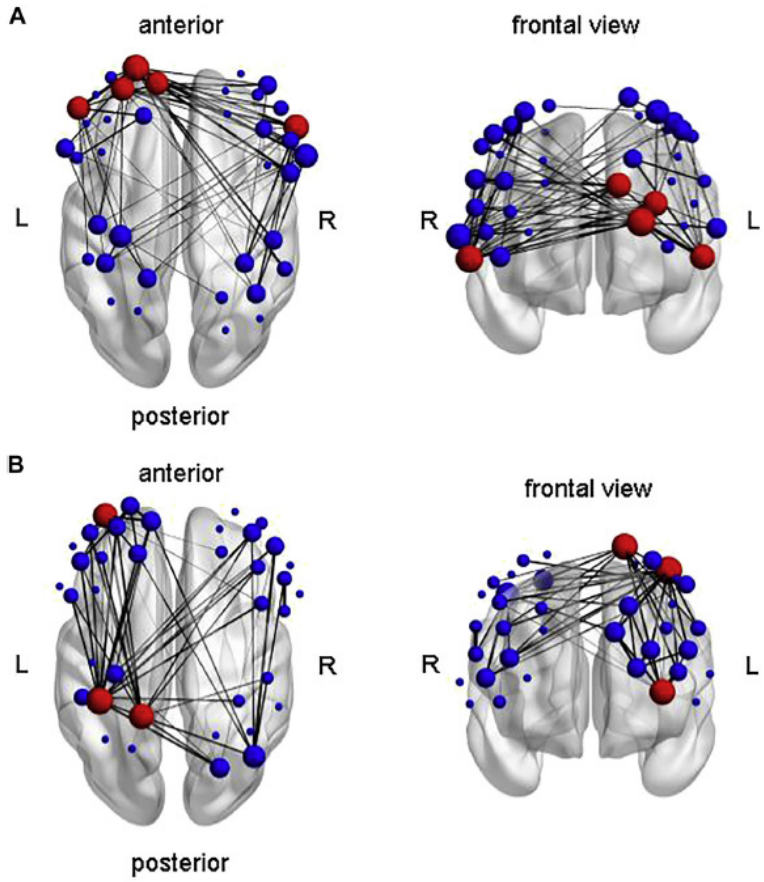

Figure 10: Extracted significant FC network differences between depressed and non-depressed subjects. Size of nodes is dependent on degrees. Line width depends on differences in FC between groups. Main nodes are in red color. Upper Maps: Network differences during task performance. Lower Maps: Network differences during resting state.

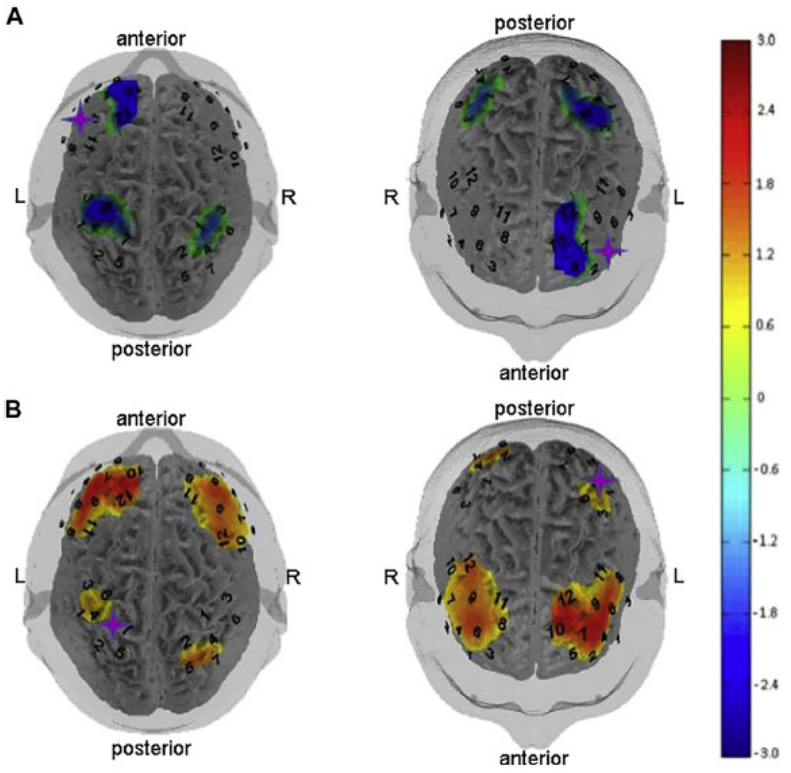

Figure 11: Headmaps of differences in FC between depressed and non-depressed subjects in seed regions (marked by purple star). Light colors indicate increased, dark colors decreased, FC to the seed region in depressed subjects. Differences are scaled in t-scores. Upper maps: FC differences with seed region in the left Broca Area during task performance. Lower maps: FC differences with seed region in the left primary somatosensory cortex during resting state.

Influence of confounding factors. To check for influences of confounding variables on connectivity measures, we reanalyzed our data with the respective cofounders as covariates. We tested our results for the following confounding variables: Comorbid diagnosis of anxiety, sex, neurocognitive functioning – in terms of executive functioning, visuospatial abilities, language-related learning and memory abilities – and medication status.

Memory, language-related learning, executive functioning, sex as well as diagnosis of phobia revealed no significant influence on FC, neither at rest ($p>.1$) nor at task performance ($p>.1$). Accordingly, effects of depression were still significant when controlled for those covariates both at resting state ($p<.01$) and during the TMT ($p<.05$). The factor of visuospatial abilities showed a significant FC network in the resting state condition with a left parietal hub in the somatosensory cortex that showed functional connections to left and right

frontal areas ($p<.032$ ±0.013, 18 edges 18 nodes). Participants with high visuospatial abilities showed lower FC at rest than participants with low visuospatial abilities. Note that the whole network was connected via only one node. However, the depression-related FC network was not influenced when the effect of visuospatial abilities was controlled as a covariate ($p<.05$), probably due to the matching procedure.

Antidepressant medication showed no significant effects on connectivity in the depressed sample. However, blood pressure medication showed significant effects on connectivity data, with lower connectivity for the medicated group. Also, antiplatelet medication influenced FC, with higher FC for the medicated group in the resting state condition. Still, the above reported results remained significant when using blood pressure and antiplatelet medication as a covariate in the analysis, due to equal distributions of medication status in the depressed and non-depressed group.

5.6 Discussion

The study at hand compared connectivity and network organization of depressed and non-depressed elderly during different mental states. Cerebral activity was assessed by functional near-infrared spectroscopy (fNIRS) at rest and during completion of the Trail Making Test (TMT). After data preprocessing, differences in connectivity were analyzed between groups with network-based statistics, and parameters of network organization were derived by graph theoretical measures.

Results showed a dissociation between group membership (depressed vs. non-depressed) and mental state (resting state vs. TMT). Elderly depressed subjects showed higher connectivity strength during resting state measures and lower connectivity strength during the TMT-B. No significant group differences in connectivity strength were found during TMT-A and TMT-C, i.e., for the control conditions. Interestingly, if the task conditions are seen in order of mental effort (resting state, TMT-C, TMT-A, TMT-B), connectivity strength increased in the non-depressed group and decreased in the depressed group from the condition with low mental effort (resting state) to the task conditions

(TMT-C, TMT-A, TMT-B). In the depressed elderly, disconnected regions during performance of the TMT-B were found in left frontal hubs, such as the frontopolar area, the dlPFC and the IFG. Differences in connectivity of these hubs showed widespread disconnections of fronto-parietal and inter-hemispheric connections of the cognitive control network (CCN) in the depressed group. An optimal functional connection is a fundamental premise for optimal information processing and its loss is associated with mental disorders and neurodegenerative processes (Rubinov & Sporns, 2010a; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Wen, He, & Sachdev, 2011). Together, the results of connectivity strength and network organization suggest attenuated information processing in the depressed elderly during conditions of heightened executive demand as shown by lower co-activation and functional segregation of brain areas in the CCN.

Consistent with the above reported results, symptom severity was positively associated with FC measures during resting state and negatively correlated during task performance when computed for the whole sample. However, when computed for the diagnostic groups separately, these associations were only congruent in the non-depressed group and heterogeneous in the depressed sample. From this result one might infer that the above reported results are related more to depression status than to symptom severity per se. This might point to a general process in depression that is not directly related to symptom severity.

In contrast to non-depressed controls, depressed subjects showed a highly connected network during the resting state condition. Hubs of high connection density were located in the left somatosensory association cortex, left primary somatosensory cortex and left frontopolar area. The left hemispheric focus of the derived network is of special interest, since hypoactivation in the left PFC has been proposed to be related to depression as a trait and state construct (Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005; Thibodeau, Jorgensen, & Kim, 2006). The prefrontal cortex is proposed to play a special role in maintaining the representation of personal goals and means to achieve them (Miller & Cohen, 2001), a function that is typically impaired in depression

(Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Although depression status has been shown to be related to impaired left frontopolar cortical functioning, there is first evidence for a positive relation between rumination and left hemispheric activation (Keune, Bostanov, Kotchoubey, & Hautzinger, 2012a). This evidence is in line with the assumption that the function of depressive rumination could be the maintenance of personal goals in the attentional focus (Andrews & Thomson, 2009). Indeed, problem-solving, mistake prevention and increasing self- understanding are counted among the most reported benefits of rumination (Ed Watkins & Baracaia, 2001b). Since rumination is a cognitively demanding activity, one might suggest that it is accompanied by higher neural activity in functionally related brain areas; particularly the PFC. The higher connectivity in the depressed subjects during resting state in our study may be seen as a neural correlate of self-referential processes, such as rumination or heightened inner awareness. This interpretation is supported by studies reporting that depressed subjects show stronger activation in parts of the CCN – such as the orbitofrontal region, medial PFC, dlPFC and posterior cingulate cortex – during rumination tasks (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010b) and affective tasks (Ho et al., 2014). Importantly, our results are in line with those of Sheline et al. (2010) who found that depressed patients showed widespread higher connectivity at rest in portions of the CCN, default mode network (DMN) and affective network via the dorsal nexus(Sheline, Price, Yan, & Mintun, 2010a). In the same manner, others found increased connectivity in parts of the salience network (SN) and CCN in LLD (Yuen et al., 2014a) and in the parietal regions of the DMN before antidepressant treatment, which changed topology to frontal regions of the DMN after treatment (Andreescu et al., 2013). Since the DMN is involved in self-referential processes and in a state of internal focus, it has been hypothesized that increased resting state FC in depression may be related to depressive rumination.

From our results, one might suggest that the high resting state connectivity in the parietal parts of the CCN in depressed subjects may reflect attentional processes which are recruited for rumination. This self-referential process, which is high during resting state in the depressive sample, may conflict with

task relevant processes during TMT performance and may therefore lead to a decrease in connectivity during this executive task. Indeed, it has recently been suggested that, in depressed or dysphoric subjects, rumination might negatively affect executive functioning by interfering with cognitive processes through the "recruitment" of a common processing stage (problem of competing resources) (Philippot & Brutoux, 2008; E Watkins, 2002). Neural findings seem to support such an interpretation since rumination was found to be associated with an increased recruitment of – amongst others – medial and lateral prefrontal cortices in depression, i.e., regions that are directly involved in executive tasks such as the TMT (Cooney et al., 2010b).

On the other hand, an alternative explanation may be derived from evidence showing inverse relations between functional and structural connectivity by the use of diffusion tensor imaging in a depressed sample but not in a non-depressed sample (B. de Kwaasteniet et al., 2013). These results are indicative of two possible explanations. First, increased FC in depressed subjects may occur as a compensatory effect of deficient structural connectivity. Second, altered structural connectivity may be seen as a result of plasticity changes due to prolonged higher FC. In terms of a compensatory effect in FC, higher connectivity in the CCN at rest may reflect compensatory neural activity in the depressed group. This group may invest mental effort to stay calm while staying at rest (e.g. due to intrusive thoughts). During task performance, their executive resources may be overly recruited, which could lead to the disrupted network measures during TMT-B. The lower connectivity in the depressed group during performance of the TMT-B may be of special interest for treatment prediction, since lower CCN connectivity has been found to be related to poorer response to antidepressant medication (Alexopoulos et al., 2012; Dichter, Gibbs, & Smoski, 2015).

Apart from interpretations of compensatory or ruminative processes, the relation between disrupted structural connectivity and enhanced FC may explain the diverging findings of FC in major depressive disorder. In a recent study by Zhang and colleagues (P. Zhang et al., 2014), patients with post ischemic stroke depression showed increased FC in comparison to non-depressed stroke

patients and healthy controls. As hypothesized by Krishnan et al. (2013), depression in later life might be associated with structural brain damages due to aging processes in the ventral and dorsal cerebral systems which may lead to “vascular depression” (Krishnan, 2013). This vascular depression has the same phenotype as depression in early life but has a different etiology. It would be an interesting attempt for future research to distinguish these types of depression, based on their functional brain activity.

Aside from the promising findings discussed above, the following limitations have to be considered. In the current study, we investigated differences in FC between a depressed and non-depressed elderly sample by selecting a depressed subgroup from the TREND study population. Depression status was defined by two clinical assessments, the BDI and GDS. To ensure a sufficient sample size, we used a rather liberal criterion for the definition of the depression status. Accordingly, our depressed group consisted of a heterogeneous sample with mild to severe depression. Also, no structural imaging methods were used to account for possible signs of neurodegeneration, vascular damages and structural connectivity differences between the depressed and non-depressed group. Moreover, even though fNIRS is a method well-suited to obtain physiological data of the cerebral cortex, its depth resolution is restricted to cortical structures. Therefore, it is not possible to completely analyze DMN or fronto-striatal network differences. However, the present study showed that fNIRS is suited to measure the fronto-parietally located CCN.

Conclusions. In conclusion, we found that LLD is characterized by altered FC in the CCN as assessed by fNIRS. To our knowledge this is the first study which examined effects of LLD on connectivity measures with fNIRS (a method with many advantages in the investigation of elderly samples and potentially high practical clinical relevance; (Ehlis et al., 2014a)). Importantly, based on previous contradictory findings, we specifically investigated activation states and functional connectivity during executive functioning vs. resting state conditions. Making such a distinction, depressed elderly showed a pattern of enhanced FC at rest and decreased FC in the CCN during states of increased executive functioning. Also, network organization differed in the depressed sample during

task performance in terms of lower functional segregation during the TMT-B (i.e., the actual executive condition) and higher functional segregation during the TMT-C. Furthermore, spatial differences were identified: The disconnected network in the depressed sample during task performance was primarily located in the left frontal region, while the hyperconnected network at rest had a focus in the left parietal region. Until now, it is not clear which processes may lead to the observed differences in FC. It is therefore necessary to further search for mediators of disease-related processes that explain the observed FC differences.

6. Study 2 – Aberrant functional connectivity in depression as an index of state and trait rumination

The contents of this chapter are published:

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6.1 Abstract

Depression has been shown to be related to a variety of aberrant brain functions and structures. Particularly the investigation of alterations in functional connectivity (FC) in major depressive disorder (MDD) has been a promising endeavor, since a better understanding of pathological brain networks may foster our understanding of the disease. However, the underling mechanisms of aberrant FC in MDD are largely unclear.

Using functional near-infrared spectroscopy (fNIRS) we investigated FC in the cortical parts of the default mode network (DMN) during resting-state in patients with current MDD. Additionally, we used qualitative and quantitative measures of psychological processes (e.g. state/trait rumination, mind-wandering) to investigate their contribution to differences in FC between depressed and non-depressed subjects.

Our results indicate that 40% of the patients report spontaneous rumination during resting-state. Depressed subjects showed reduced FC in parts of the DMN compared to healthy controls. This finding was linked to the process of state/trait rumination. While rumination was negatively correlated with FC in the cortical parts of the DMN, mind-wandering showed positive associations.

Keywords: functional connectivity, depression, rumination, resting-state, functional near-infrared spectroscopy (fNIRS), Network Based Statistics (NBS)

6.2 Introduction

In the last decade, the study of aberrant functional and structural connectivity in depression has become a promising endeavor for the understanding of maladaptive processes underlying its psychopathology. Functional connectivity (FC) is defined by the functional co-activation of spatially distributed brain regions (R. Tadayonnejad & Ajilore, 2014a). The analysis of FC in resting-state and task conditions has revealed aberrant function in various brain networks in Major Depressive Disorder (MDD), both in early life as well as in late-life depression (LLD) (Alexopoulos et al., 2012; Kenny et al., 2010; Sheline et al., 2010a). However, until today the corresponding psychopathological processes that are associated with aberrant FC in MDD are unexplained. The present study aimed at clarifying the processes that are related to alterations in FC in MDD.

Higher FC in MDD and LLD in parts of the Cognitive Control Network (CCN) and the Default Mode Network (DMN) have often been interpreted as manifestations of depression-specific processes (Lan et al., 2016; Rosenbaum et al., 2016a). Especially the DMN – which anatomically consists of the precuneus, adjacent posterior cingulate/retrospinal cortex, the inferior parietal lobe/AngG (angular gyrus) and the medial prefrontal cortex (Horn, Ostwald, Reisert, & Blankenburg, 2014) – has been proposed to play a role in depressive rumination, due to its importance for self-referential processes.

Although there is no unifying definition of depressive rumination (Smith & Alloy, 2009b) it can roughly be defined as a repetitive, rather abstract style of thinking that is focused on the past or shortcomings of oneself. The interpretation of abnormal FC in MDD as a neural correlate of rumination is rather appealing, since rumination is associated with the severity of MDD in regards to duration, symptom severity, risk for suicide, risk for relapse and cognitive functioning(Eshun, 2000b; Lyubomirsky, Kasri, & Zehm, n.d.; Lyubomirsky & Nolen-Hoeksema, 1995b; Philippot & Brutoux, 2008; Smith & Alloy, 2009b).

However, the evidence that altered FC in MDD reflects depressive rumination is heterogeneous(M. G. Berman et al., 2011; Marc G. Berman et al., 2014a; Connolly et al., 2013; Jacobs et al., 2014b). Also, studies vary in their FC measurement, including measurements of “spontaneous” and “induced” rumination.

Regarding induced rumination, there are some limitations that make it difficult to compare or generalize effects. First, the induction of rumination (e.g., via recall of autobiographical information) may induce artificial or confounding neural activation unrelated to rumination per se, but to other aspects of the induction process, e.g. increased cognitive load. Another limitation pertains to the assessment of rumination. Most studies use trait-questionnaires, that measure rumination as a habitual reaction to sad mood. Thus, rumination is measured as a trait-construct and is correlated to a (state-) resting-state measurement of FC. This leaves the possibility that patients with high trait rumination actually are not ruminating during the resting state measurement. The reported correlation between rumination and FC could then be attributed to a trait construct of depression (e.g. neuroticism) rather than to the state process of rumination.

Therefore, the main goal of this study was to investigate state and trait contributions of rumination to altered FC measures in depressed patients and healthy controls using functional near-infrared spectroscopy (fNIRS). To explore the unconstrained flow of ruminative thought we used a quasi-experimental approach that combined qualitative and quantitative measures. To assess trait- and state-aspects of rumination, we used the rumination response scale (RRS) and visual analogue scales (VAS) after the resting-state measurements respectively (Susan Nolen-Hoeksema & Morrow, 1991). Additionally, subjects were asked to describe their inner experiences during the resting-state measurement in detail on a blank page – the self-report form. We hypothesized that depressed subjects would report more ruminative thinking and less mind-wandering during resting-state, and show a higher level of trait rumination than non-depressed subjects. Regarding FC measurements, we expected both state and trait rumination to be anti-correlated with FC in regions of the parietal cortex.

6.3 Materials and Methods

Participants. Subjects were recruited from participants in the WikiD-study (clinical trial: NCT02375308) conducted at the Clinic for Psychotherapy and Psychiatry at the University Hospital of Tübingen. All used methods and procedures in this study were in accordance to the current guidelines of the World Medical Associations Declaration of Helsinki. This study was approved by the ethics committee at the University Hospital and University of Tübingen. All subjects written informed consent. 89 subjects participated in the study. Five subjects were excluded from data analysis due to an insufficient signal quality (fNIRS data). The sample comprised 60 patients with current MDD diagnosed by clinicians based on the structured clinical interview for DSM IV (SCID) (Wittchen H.-U., Wunderlich, U., Gruschwitz, S., & Zaudig, M., 1997). 32% of the depressive sample were treated with anti-depressive medication (for at least 3 months). The mean score of the Patient Health Questionnaire (PHQ-9) was 14.53 (SD=3.84, range: 6-23) which can be interpreted as a moderate to severe average symptom severity (Spitzer, Kroenke, & Williams, 1999). The mean score on the Montgomery–Åsberg Depression Rating Scale (MADRS) based on clinical ratings was 21.1 (SD=5.97, range: 6-34) which corresponds to a moderate symptom severity (Montgomery & Asberg, 1979). In the depressed group, 16.66% of the sample showed a comorbid diagnosis of Persistent Depressive Disorder, 10% had a Specific Phobia, 8.33% had the diagnosis of a Personality Disorder, 5% Social Phobia and 3.33% were diagnosed with a comorbid Panic Disorder. 3.3% of the depressed sample had a main school degree, 16.7% a middle school degree, 46.7% a high-school diploma (German *Abitur*) and 33.3% had a university degree.

Twenty-four healthy controls were additionally recruited. 4.2% of the non-depressed sample had a main school degree, 8.3% a middle school degree, 16.7% a high-school diploma, 12.5% a university of applied science degree and 50% had a university degree. None of the control subjects took anti-depressive medication or reported a life-time diagnosis during the SCID interview. The depressed and non-depressed sample did not diverge in the sex-ratio. However, the control subjects were significantly younger (33 years) than the

depressed subjects (40 years). As expected, the two groups differed in their symptom severity measured with the PHQ-9 and MADRS (table 6), but did not differ with respect to their educational level ($p>.1$, $\chi^2(1)=1.68$). 66.7% and 80% of the non-depressed and depressed group, respectively, had a high educational level (high-school diploma or higher).

	Non-Depressed (n=24)		**Depressed (n=60)**			
Variable	**mean**	**SD**	**mean**	**SD**	**t/χ^2**	**p**
Age (years)	33	11.45	40	14.79	t = 2.19	p<.05
Sex ratio (f/m)	68%		72%		$\chi^2_{(1)}$ = .09	p>.1
Antidepressive Medication (%)	0%		32%		$\chi^2_{(1)}$ = 10.02	p<.001
MADRS	1.43	1.42	21.1	5.97	t(82) = 15.9	p<.001
PHQ-9	2.20	1.77	14.53	3.84	t(82) = 15.0	p<.001
RRS	1.79	.37	2.56	.39	$t_{(82)}$= 8.4	p<.001
Reported Rumination	8.3%	-	40%	-	$\chi^2_{(1)}$ = 8.0	p<.01
Reported Mind-wandering	87.5%	-	48.3%	-	$\chi^2_{(1)}$ = 10.9	p<.001
Reported FAF	29.2%	-	41.7%	-	$\chi^2_{(1)}$ = 1.1	p>.1
Reported Focus on Body Sensation	29.2%	-	8.3%		$\chi^2_{(1)}$ = 6.0	p < .05

Table 6. Demographic variables of the depressed and non-depressed group. MADRS = the Montgomery–Åsberg Depression Rating Scale, PHQ-9= Patient Health Questionnaire, RRS = Rumination Response Scale, FAF = Fight Against Fatique

fNIRS. Hemodynamic changes were measured via fNIRS, an optical imaging method using light in the near-infrared spectrum to measure concentration changes of oxygenated and deoxygenated hemoglobin. The penetration depth

and therefore spatial measurement depth of fNIRS is approximately 2-3 cm (F. Haeussinger et al., 2014; Florian B. Haeussinger et al., 2011b). Advantages of this method comprise a relatively high temporal resolution, mobile application, insensitivity to movement artefacts, low costs and easy assessment(Ehlis, Schneider, Dresler, & Fallgatter, 2014b). Importantly, fNIRS has been shown to be a useful and reliable device to measure FC(Deppermann et al., 2016; Lu et al., 2010; Mesquita, Franceschini, & Boas, 2010; Han Zhang et al., 2010). We used a continuous wave, multichannel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co.,Japan) with a temporal resolution of 10 Hz. To measure parts of the DMN, we placed the probeset over parietal areas covering the precuneus (Horn et al., 2014) with reference points Pz, T3 and T4, according to the 10-20 system (Jasper, 1958b). The system consisted of 52 channels. Channel positions were located using a neuro-navigation system on a volunteer's head (table 7).

Brain area	Channels
Somatosensory Association Cortex	4, 5, 6, 7, 15, 16, 17, 25, 26, 27, 28, 35, 36, 37
Supramarginal gyrus (part of Wernicke's area)	2, 3, 8, 9, 12, 13, 18, 19, 23, 30
Angular gyrus (part of Wernicke's area)	14, 24, 29, 34, 39, 40, 45, 50
Superior Temporal Gyrus	11, 21, 22, 31, 33, 41
V3	38, 46, 47, 48, 49
Fusiform gyrus	43, 44, 51, 52
Middle Temporal gyrus	32, 42
Primary Somatosensory Cortex	1, 20
Subcentral area	10

Table 7. fNIRS channels and related brain areas (estimated based on a neuro-navigational measurement in an exemplary volunteer)

Resting-State Measurement. Data was assessed during a 7-minute resting phase in which participants were asked to sit still with eyes closed and let their thoughts flow. After completion of the resting-state measurement, subjects

documented what they had done during that time and completed visual analogue scales (VAS) regarding the amount of time they had spent with different processes. Subjects were asked to approximately rate on a scale from 0 to 100% how much time they had spent with a specific process (e.g. being relaxed) during the resting-state measurement (see supplemental material). Four main processes were analyzed: state rumination, mind-wandering, fight against fatigue and focus on sensations. Trait rumination was assessed with the Rumination Response Scale(Susan Nolen-Hoeksema & Morrow, 1991). Additionally, subjects were asked to describe their inner experiences during the resting-state measurement in detail on a blank page – the self-report form. The texts were screened and categorized by two independent raters to assess qualitative measures of processes during resting-state according to qualitative methods: First, self-report forms were analyzed and categories were built and defined until saturation was reached. Second, the most common categories were used to categorize self-report forms by two independent psychologists.

6.4 Data Analysis

Preprocessing. Data were processed and analyzed using MATLAB R2015b (MathWorks Inc, Natick, USA). After preprocessing, the matlab NBS toolbox (Zalesky, Fornito, & Bullmore, 2010b), Wavelab850 toolbox (http://statweb.stanford.edu/~wavelab/) and BrainNetViewer toolbox (Xia, Wang, & He, 2013a) (http://www.nitrc.org/projects/bnv/) were used for analyzing and plotting results. Furthermore, PASW (Version 22) was used for data analysis. Data preprocessing included: bandpass filtering (.1-.01 Hz) to minimize high- and low-frequency noise, movement artefact reduction by the algorithm of Cui et al. (Brigadoi et al., 2014; Cui et al., 2010), as well as wavelet-based correction of extreme values (Molavi & Dumont, 2012) to reduce high amplitude artefacts, with the following settings: Mother wavelet ‘Vaidyanathan', support=10, threshold=.0001, alpha=.1 (Molavi & Dumont, 2012). Afterwards, all signals were visually inspected revealing local artefacts after the described pre-processing in 50% of the subjects. In these cases, channels were interpolated from surrounding channels. If more than 10% of the

channels had to be interpolated, subjects were excluded from further analysis (n=4). Since FC can be significantly influenced by global signal changes (Mesquita et al., 2010), a global signal reduction was performed with a spatial gaussian kernel filter (X. Zhang, Noah, & Hirsch, 2016) with a standard deviation of σ=50. After preprocessing, FC-coefficients were computed and transformed via Fishers r-to-z-transformation(Silver & Dunlap, 1987b).

Network-Based Statistics (NBS). Subsequent FC-differences between the diagnostic groups were investigated with Network-Based Statistics(Zalesky et al., 2010b). NBS is a statistical method that uses massive univariate testing of a contrast on connectivity matrices and clusters connections that exceed a significance threshold using a breadth first search. The size of the extracted cluster is then tested on significance using permutation tests. Settings for NBS were set as follows: statistical threshold for massive univariate testing t=2.7, t=3.0 and t=3.4, significance level for permutation tests α=.05, permutations=5000, component size = “intensity”. We estimated confidence intervals for the computed p-values of the permutation tests parametrically following Zalesky et al. (2010):

Eq.1 $2 \times \sqrt{\frac{p(1-p)}{M}}$ with M=number of permutations.

After using NBS, significant network differences between depressed and non-depressed subjects were searched for hub nodes. To identify these regions two indices were used: The degree of the nodes and the strength of the FC difference in the connections of these nodes between the diagnostic groups (assessed by different statistical thresholds). The degree of a node is defined as the number of connections of that node with other nodes in the network(Rubinov & Sporns, 2010b). Figure 12 shows an overview over the analytical steps.

6.5 Results

The following analysis was performed on the data: After the computation of FC measures, network-based statistics (NBS) were used to identify network-differences in FC between depressed and non-depressed subjects. Afterwards

the effects of state- and trait rumination on these differences were assessed by using these variables as covariates in the NBS-model. For further illustration of the effects of rumination, hub nodes of the depression-related network were used as seed regions for further analysis: First, correlations between the FC to these hubs and the rumination scores were computed and plotted for the whole sample. Since depression status and rumination may be confounded and the correlation between rumination and FC in the whole sample might be spurious (because of between-group differences in both of these variables), we also performed a subgroup analysis by separating the depressed subjects into a high rumination and low rumination group as defined by median split of the rumination scales. Differences in FC in the hub nodes between these two sub-groups were assessed via permutation tests using maximal statistic (Camargo, Azuaje, Wang, & Zheng, 2008; Nichols & Holmes, 2002). Finally, the main effects of state and trait rumination on FC were analyzed by deriving network differences via NBS for high and low ruminators for the whole sample. This analysis step was used for an exploratory investigation of the network organization of low and high ruminators to better understand the overlap between the effects of depressive status and rumination. Figure 12 shows an overview over the analytical steps.

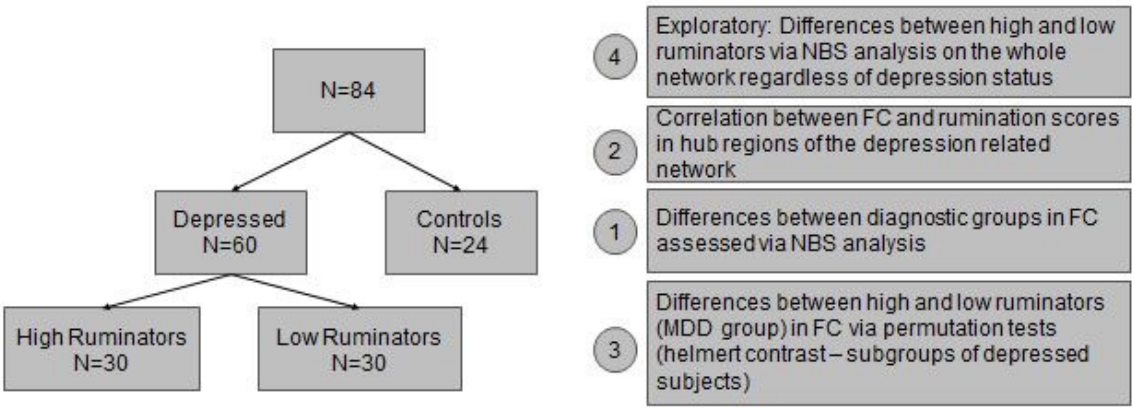

Figure 12.: Analysis scheme: Analysis steps 1, 2 and 4 were performed on the whole sample. In the third analysis step only the depressed subjects were investigated.

Qualitative. 80 subjects (95%) listed at least one of the following categories in their self-report form: mind-wandering (59.5%), future things to do/making plans

(40.5%), fighting against fatigue (38.1%), rumination (31%), thinking about the measurement itself and the instructions (20.2%), suppressing inner experiences (16.7%), thinking about the duration of the measurement (16.7%), doing active relaxation – e.g. mindful focus (15.5%), feeling body sensations (14.3%), hearing sounds, e.g. the NIRS machine (8.3%), feeling bored (4.8%). The healthy controls (HC) described significantly more focus on body sensations (29.2% of HC vs. 8.3% of the patients; $\chi^2_{(1)}$=6.076, p<.05, OR=0.221), more focus on external sounds (33.3% vs. 8.3%; $\chi^2_{(1)}$=8.191, p<.01, OR=0.182), more mind wandering (87.5% vs. 48.3%; $\chi^2_{(1)}$=10.915, p<.001, OR=0.134) and less rumination (8.3% vs. 40%; $\chi^2_{(1)}$=8.044, p<.01, OR=7.33).

On the resting-state scales, depressed subjects showed higher levels of state rumination ($t_{(82)}$=3.64, p<.001, d=.83), lower levels of mind-wandering ($t_{(82)}$=2.445, p<.05, d=0.58) and lower levels of focus on sensations ($t_{(82)}$=2.831, p<.01, d=0.72). The groups also differed in their trait rumination ($t_{(82)}$=8.406, p<.001, d=2.0). Trait rumination was negatively correlated with mind-wandering ($r_{(82)}$=-.42, p<.001) and positively correlated with state rumination ($r_{(82)}$=.32, p<.001). State rumination was negatively correlated with mind-wandering ($r_{(82)}$=-.50, p<.001) and focus on sensations ($r_{(82)}$=-.37, p<.001) (table 8).

	RRS	Scale Rumination-state	Scale FAF	Scale Mind-Wandering	Scale Body
RRS	1				
Scale Rumination-state	**.32****	1			
Scale FAF	.18	-.10	1		
Scale Mind-Wandering	**-.42****	**-.50****	**-.40****	1	
Scale Body	-.02	**-.37****	**-.28***	**-.22***	1

Table 8. Pearson correlations between the resting-state scales and trait rumination. N=84, * p<.05, **p<.001

Differences between HC and patients. The NBS analysis of differences in FC between depressed patients and HC revealed significant network disconnection in the depressed group at all statistical thresholds (Table 9). Depending on the statistical threshold (t(82)=2.7 to t(82)=3.4), the derived disconnected network consisted of 36 to 8 nodes with 72 to 8 edges (p=.003±0.0015 to p=0.016±0.0035). The disconnected network was bilaterally organized within regions of the DMN and consisted mainly of interhemispheric FC differences. In the same way, hub nodes were consistently localized within cortical regions of the DMN: the middle somatosensory association cortex (SAC), left supramarginal gyrus (SupG) and right AnG (Figure 13). Effect sizes in the three seed regions ranged between d=.90 to .47 in the left SupG, d=0.81 to .39 in the middle SAC and d=.81 to .64 in the right AnG. Note that, when placing seeds, some regions with higher FC appeared for the depressed group, lying outside the cortical parts of the DMN and not being part of the NBS cluster solution.

Channel	Region	Depressed vs. Non-Depressed t=2.7 degree	t=3.0 degree	t=3.4 Degree
2	SupG	4	2	1
3	SupG	6	**5**	**3**
4	**SAC**	**10**	**5**	**2**
5	SAC	6	**5**	-
6	SAC	7	4	-
7	SAC	3	2	-
8	SupG	3	2	-
10	SA	2	1	-
12	SupG	1	1	-
13	**SupG**	**9**	**6**	**2**
14	AngG	3	1	-
15	SAC	8	3	-
16	SAC	5	3	-
17	SAC	2	2	-
18	SupG	5	2	2
19	SupG	3	2	-
20	PSC	1	-	-
21	STG	3	1	-
23	SupG	1	-	-
24	AngG	1	1	-
25	SAC	1	-	-
26	SAC	1	-	-
28	SAC	2	2	-
29	**AngG**	**9**	**5**	**3**
30	SupG	1	1	-
35	SAC	2	1	1
36	SAC	5	4	-
38	V3	7	5	-
39	AngG	1	-	-
40	AngG	7	**7**	**2**
45	AngG	1	-	-
46	V3	7	3	-
47	V3	6	**5**	-
48	V3	2	1	-
49	V3	8	4	-
50	AngG	1	-	-
nodes		36	29	8
edges		72	43	8
p-value		.003 ± .0015	.003 ± .0015	0.016± .0035

Table 9. Degrees of the significant network differences between Depressed and Non-Depressed subjects at t(82)=2.7, t(82)=3.0 and t(82)=3.4. Only channels of the significant network are presented. SAC = somatosensory association cortex, SupG = supramarginal gyrus, AngG = angular gyrus, STG = superior temporal gyrus, FusG = fusiform gyrus, MTG = middle temporal gyrus, PSC = primary somatosensory cortex, SC = subcentral area. Bold numbers are hub nodes.

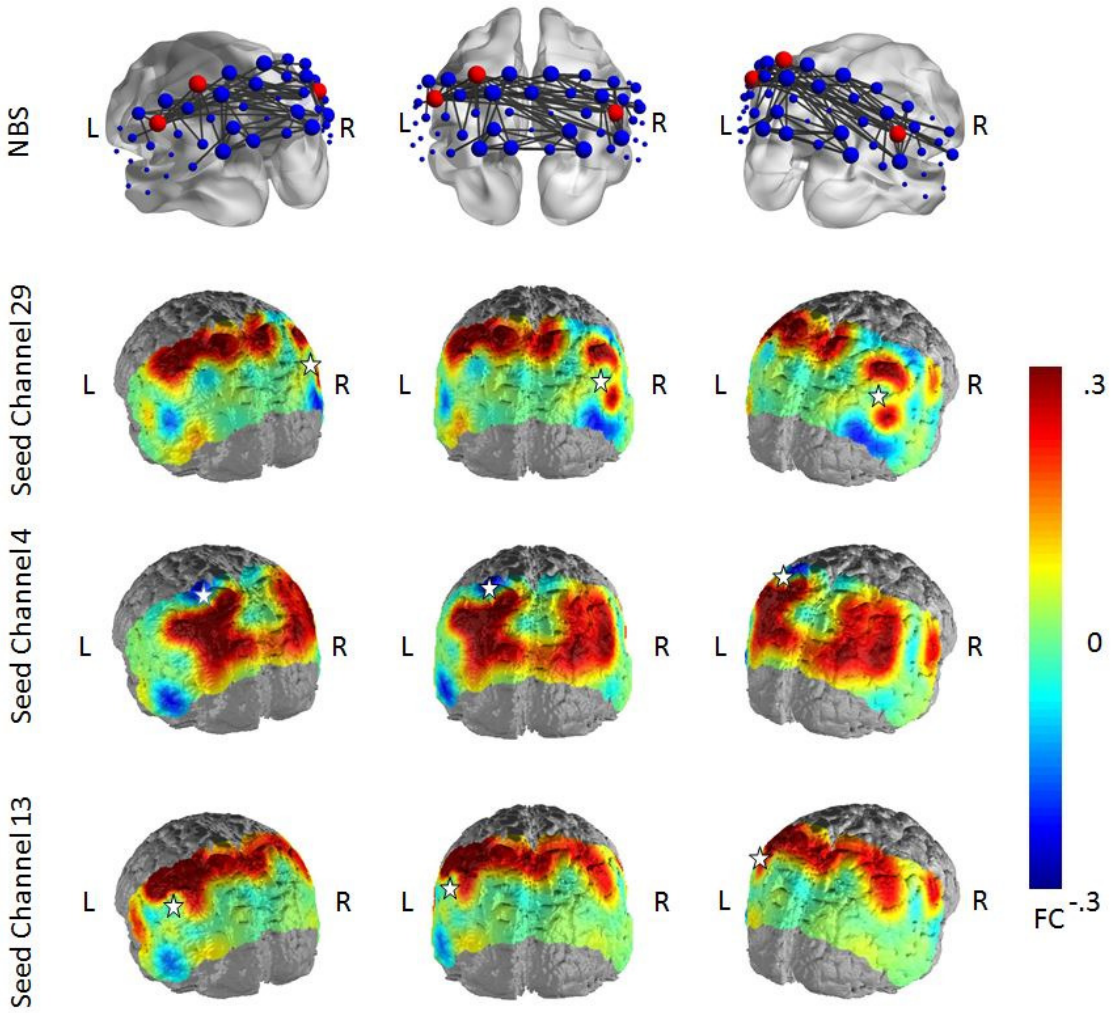

Figure 13: Differences between non-depressed and depressed subjects in FC in the NBS analysis at t=2.7 and in selected seed regions (red nodes in the network maps). Warm colours indicate higher FC in the non-depressed subjects. Seed regions are marked by a white star.

Differences between HC and patients when controlled for rumination. When controlling for state rumination, the significant network differences between depressed and non-depressed subjects were reduced at all statistical thresholds ($t_{(81)}$=2.7, p=0.010, nodes=29, edges=50; reduced by 7 nodes and 43 edges; $t_{(81)}$=3.0, p=.034, nodes=11, edges=12; reduced by 18 nodes and 31 edges; $t_{(81)}$=3.4, p=.041, nodes=7, edges=6; reduced by 1 node and 2 edges). Over all three thresholds, FC was reduced due to the covariate mostly in the middle SAC (Channel 4,5,6,16) and in V3 (Channel 38,46,49).

At all statistical thresholds, the network differences between depressed and non-depressed subjects did not reach significance when controlled for trait

rumination. Remarkably, this means that no significant variance in FC could be explained by depression status when controlled for trait rumination.

Correlations of rumination and FC in the depression-related network. When correlating the scores of trait and state rumination with the FC-scores to the defined seed regions of the depression-related network, we observed for both variables a negative relationship with FC (Figure 14&15). The association between trait rumination and FC was higher and more wide-spread over the whole posterior probeset in all three hub nodes, ranging from -.36 to -.22 ($p<.001$ to $p<.05$) for the seed region in the right AnG, from -.36 to -.21 ($p<.001$ to $p<.05$) in the SAC and from -.42 to -.23 ($p<.001$ to $p<.05$) in the left SupG. From these only correlations with an size >.31 survived correction for multiple comparison. The correlations between state rumination and FC were also negative but weaker and more focused in their distribution ranging between -.29 to -.22 ($p<.01$ to $p<.05$) for the seed region in the left SupG and between -.28 and -.25 in the middle SAC ($p<.01$ to $p<.05$). However, none of the correlations remained significant after controlling for multiple comparisons. For the right AnG, only the FC to the middle SAC showed a negative relationship to state rumination (rho=.-26, $p<.01$). For the two remaining seed regions, associations between state rumination and FC were mainly restricted to this area and the left SupG and AnG. As for the FC differences between depressed and non-depressed subjects, spurious positive correlations between trait rumination and FC from the seed regions to regions outside the DMN were observed.

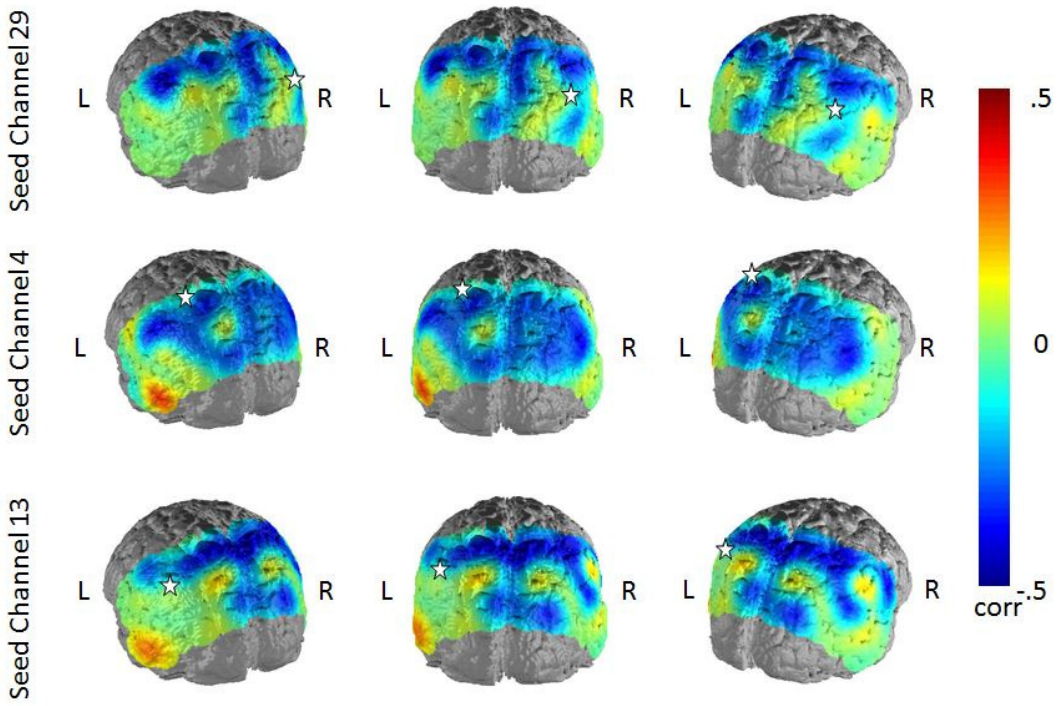

Figure 14. Correlations between trait rumination and FC in the three seed regions of the depression-related network. Seed regions are marked by a white star.

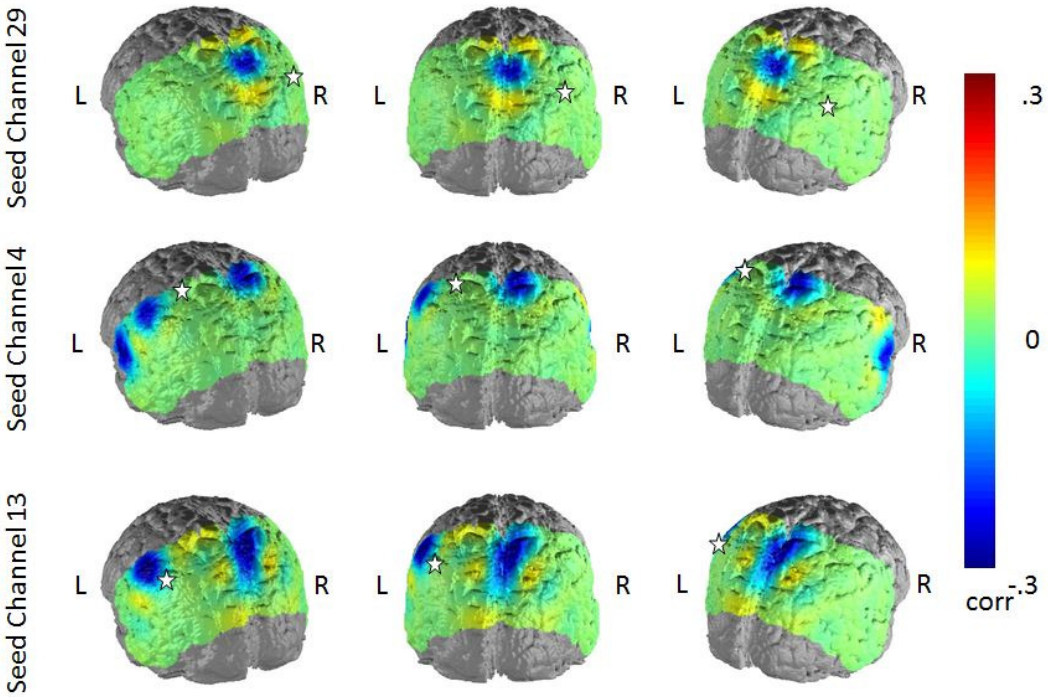

Figure 15. Correlations between state rumination and FC in the three seed regions of the depression-related network. Seed regions are marked by a white star.

Depressed Ruminators vs. Depressed Non-Ruminators. To investigate whether the results in the previous section were only due to differences between diagnostic groups on both FC and rumination variables, we performed a subgroup analysis for “depressed high ruminators” and “depressed low ruminators”. Following a median split for state and trait rumination in the depressed sample, we compared the FC in the depression-related network to the three seed regions for the subgroups by performing permutation tests. Like in the correlation analysis of the whole sample, again trait rumination showed a stronger association with FC than state rumination. ”Depressed high trait ruminators” showed reduced FC compared to the “depressed low trait ruminators” comparing all three seed regions (Figure 16). Effect sizes ranged between d=-.39 to -.66 for the seed region in the SAC, d=-.40 to -.90 in the left SupG and was d=-.60 in the seed region of the AngG regarding the FC to the middle SAC and V3. In contrast to the correlation analysis, significant differences ($p<.05$) in FC between these rumination groups were focused to regions in the middle SAC and left SupG.

Differences between “depressed high state ruminators” and “depressed low state ruminators” were only significant ($p<.05$) in the seed regions of the left SupG and middle SAC. Significant differences in FC were also located in the middle SAC and left SupG (Figure 17). Effect sizes for the seed region of the middle SAC ranged between d=-.34 and -.68 and were d=-.40 for the seed region in the left SupG. In the latter seed regions, higher FC was also observed in the left middle temporal gyrus (d=.41) and right primary somatosensory cortex (d=.46) for the “depressed high-state ruminators”, which was consistent with the correlation analysis of trait rumination and the NBS analysis of depressed and non-depressed subjects.

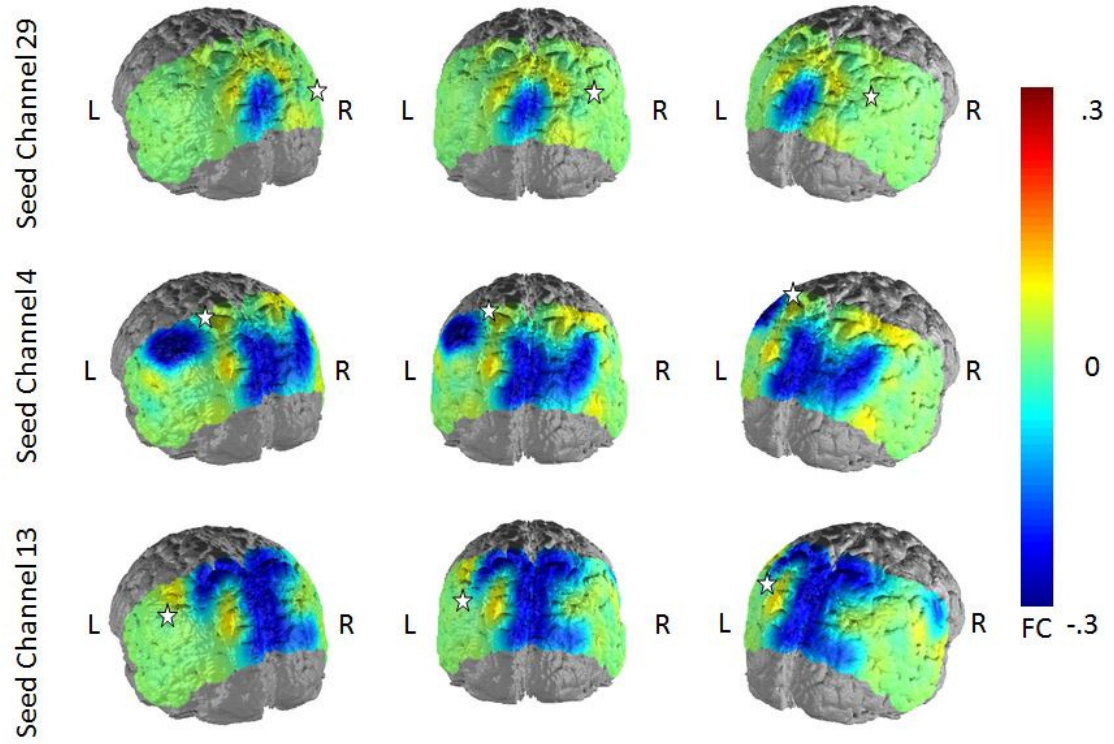

Figure 16: Differences between “depressed low trait ruminators” and “depressed high trait ruminators”. Cold colors indicate lower FC in high-ruminators compared to low-ruminators.

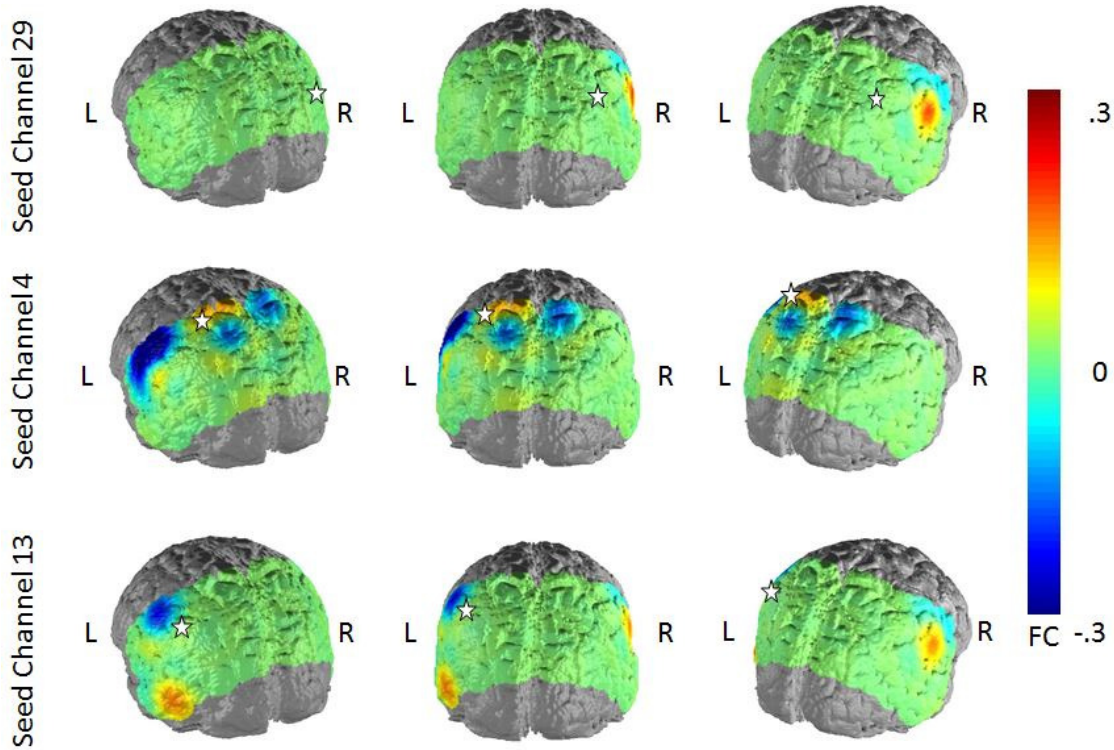

Figure 17. Differences between “depressed low state ruminators” and “depressed high state ruminators”. Cold colors indicate lower FC in high-ruminators compared to low-ruminators.

Main effects of rumination. For a better interpretation of the results reported above, we also ran an exploratory analysis via NBS for the main effects of state and trait rumination regardless of the depression status to reveal differences in FC outside the depression-related network. Both, state and trait rumination revealed a significantly disconnected network for “high ruminators”. The disconnected network for trait rumination consisted of 37 nodes and 87 edges (p=0.002±0.0013) with hub nodes in the middle SAC and V3. The network showed a bilateral organization with dense disconnections in the regions of the DMN – namely the middle SAC and the left and right SupG and AngG (Figure S5). Effect sizes for the seed region in the middle SAC (Channel 16) ranged between d=-.38 to d=-.79.

The state rumination related disconnected network comprised 21 nodes and 29 edges (p=0.022±0.0041) with hub nodes in the middle SAC and the left SupG (Figure S6). The network showed a left hemispheric focus with dense disconnections between the middle SAC and the left SupG and left AngG. Effect sizes for the seed region in the middle SAC ranged between d=-.33 to d=-.81.

6.6 Discussion

The aim of this study was to investigate the impact of state and trait rumination on differences in FC between depressed and non-depressed subjects. Our qualitative measurements revealed that depressed subjects ruminated more than non-depressed subjects. However, only 40% of the depressive sample reported ruminative content, and state and trait rumination were only moderately correlated, suggesting independent constructs. Both state and trait rumination showed strong anti-correlations with the process of mind-wandering – one of the hypothesized core processes behind the DMN.

As expected from our previous findings (Rosenbaum et al., 2016a) and the observed anti-correlation between CCN and DMN (Gao & Lin, 2012), we found reduced FC within regions of the DMN in the depressed sample compared to

the non-depressed sample. These findings are in line with other studies that found disrupted FC in MDD between posterior and temporal areas (Yang et al., 2016), posterior cortex and bilateral caudate (Bluhm et al., 2009), in inter-hemispheric FC (Guo, Liu, Dai, et al., 2013), in the salience network (Manoliu et al., 2014) and between functional connectivity networks (B. P. de Kwaasteniet et al., 2015b). In our study, FC to seed regions in the depression-related network were anti-correlated to state and trait rumination. These effects stayed stable when running a subgroup analysis of “high state/trait ruminators” vs. “low state/trait ruminators” within the depressed sample only. The effects of trait rumination on FC in the seed regions were stronger and more widespread than the effects of state rumination. A possible explanation for this variation in the strength and (spatial) extent of effects might lie in the constructs themselves: while state rumination is a rather narrow process and construct, trait rumination is a much more broadly defined concept that might be linked to other constructs such as neuroticism or distractibility which in turn might influence FC (Smith & Alloy, 2009b). However, both state and trait rumination showed associations to FC differences in the depression-related network and may therefore explain differences in FC between depressed and non-depressed subjects.

When examining the main effects of state rumination on FC in the whole probeset (and not only in the depression-related network), it became clear that the disconnected network for the “high state ruminators“ had a left-hemispheric focus with hub nodes in the left SupG und middle SAC. Interestingly, the left hemispheric focus of the effects of state rumination on FC is consistent with our previous findings (Rosenbaum et al., 2016a). This effect might be due to specialization of the hemispheres (Keune, Bostanov, Kotchoubey, & Hautzinger, 2012b). In contrast, the effects of trait rumination showed a much broader distribution over the cortical DMN as indicated by a bilaterally organized network with dense connections between the DMN nodes. However, both state and trait rumination showed effects similar in size and consistent in the middle SAC and left SupG and AnG.

As another implication, our results also indicate an anti-correlation between rumination and the process of mind-wandering. At this point, the question arises

if the association between state rumination and FC is solely explained by this anti-correlation between state rumination and mind-wandering. From our point of view, the processes of mind-wandering and rumination are two sides of the same medal: Mind-wandering – as measured by our resting-state questionnaire – is defined as being in a relaxed state, in which a person's thoughts flow in an unconstrained way without any focus on a particular subject. State rumination on the other hand is defined as a repetitive stressing style of thinking about unfinished concerns that leads to the urge of suppressing the inner experience. From this point, it becomes clear that a person cannot be in the process of mind-wandering and the process of rumination at the same time. This antagonistic relationship is reflected by the anti-correlation of the processes and the FC differences between the (high mind-wandering) non-depressed and the (high ruminating) depressed subjects. It would be an interesting attempt for future research to categorize and entangle these different "styles of thinking".

Regarding previous findings on FC in depression and rumination, our results are in line with studies reporting a negative association between FC in parietal parts of the DMN and rumination and disrupted network organization in MDD (Marc G. Berman et al., 2014a; Chen, Wang, Zhu, Tan, & Zhong, 2015; Connolly et al., 2013; B. P. de Kwaasteniet et al., 2015b; Guo, Liu, Dai, et al., 2013; Jacobs et al., 2014b; J. Zhang et al., 2011b). For example, Jacobs et al. (2014) found a negative association between a factor analysis derived factor in the PCC and trait rumination. In line with this, Berman et al. (2014) reported reduced global FC for depressed subjects, compared to healthy controls. However, in the same study elevated levels of FC were reported during induced rumination in MDD patients. Other studies also show a positive association between FC in the DMN and depression and rumination (M. G. Berman et al., 2011; Cooney et al., 2010b; Hamilton et al., 2011; Ho et al., 2015; Yuen et al., 2014b). For example, Cooney et al. (2010) found that rumination is associated with enhanced activity in OFC, DLPFC, rostral anterior cingulate, posterior cingulate and parahippocampus(Cooney et al., 2010b). Also, increased FC in the DMN is found during stages of induced rumination(Burkhouse et al., 2016). Since positive associations between FC and rumination in the DMN are also

found during phases of spontaneous rumination, these effects cannot be fully attributed to artificially induced activation by induction tasks.

Here, our results seem to be in conflict with previous research. Interestingly, most studies that reported higher FC in depressed subjects found higher FC between sgACC and the PCC. Similarly, in our previous own work we identified enhanced FC between anterior and posterior regions of the CCN (Rosenbaum et al., 2016a). In their review of the fMRI literature regarding rumination and FC, Hamilton and colleagues (2015) argue that the often found positive correlation between sgPFC and the DMN reflects “a functional integration of properties of the sgPFC and DMN”. These functions include “imbuing of internal stimuli with valence” (DMN) and “affectively laden behavioral withdrawal” supported by the sgPFC (Hamilton et al., 2015a). Since rumination and its immanent withdrawal aspect are rather attention demanding processes, one might suggest that they are associated with enhanced FC between areas in the fronto-parietal networks supporting higher cognitive processes. Our results of reduced FC in MDD in the parietal cortex – including cortical parts of the DMN – might be just in line with this hypothesis and data. The parietal cortex plays a central role in the integration of sensory information. In the same way, the DMN is thought to play a central role in the integration of egocentric information. If a subject is in a mental state that uses such functions – such as mind-wandering – the parietal cortex and the cortical parts of the DMN show higher functional integration. However, if attention demanding states are present – such as during rumination – this functional integration of the parietal cortex should be interrupted. Instead, these cortex areas might then be demanded in other processes and show a high functional integration with anterior regions (like the DLPFC, sgPFC, ACC). The latter assumption is supported by a recent meta-analysis, showing hyper-connectivity between the fronto-parietal CCN and the DMN during resting-state(Kaiser et al., 2015).

A second aspect concerns the bilateral organization of the derived network differences between depressed and non-depressed subjects and low and high trait ruminators. Most of the network differences in our study between these groups comprised inter-hemispheric differences. So far, there are several

studies that show decreased inter-hemispheric FC in MDD (Hermesdorf et al., 2016; Z. Hou et al., 2016; L. Wang et al., 2013; Y. Wang et al., 2015; Xu et al., 2013). However, the biological background of inter-hemispheric FC abnormalities is not fully understood, although studies from split brain patients suggest that a disruption of inter-hemispheric FC affects the information processing and functioning of the brain (O'Reilly et al., 2013; Ridley et al., 2016). In light of this work one might argue that most of the cortical DMN differences in FC we found could be due to the reduced inter-hemispheric FC found in the MDD population. However, this interpretation does not account for the medial temporal disconnections and the left hemispheric focus of the state rumination network.

Aside from the promising and mostly conclusive findings reported above, some limitations have to be considered: Although fNIRS is a well-suited method to obtain neurophysiological data of hemodynamic changes in the cortex, its depth resolution is restricted to cortical structures and the covered area is restricted to the size of the used probeset. Therefore, with this method it is not possible to cover the DMN completely. However, we as others showed that fNIRS is suited to measure the cortical structures of the DMN. Moreover, Sasai et al. (2012) showed in a combined fNIRS/fMRI study that cortically measured fNIRS signals correlated not only with cortical fMRI signals, but also with subcortical parts of the brain networks(Sasai et al., 2012b). However, as long as there is no co-registered fMRI measure, such subcortical projections can only be hypothesized from the imputation of fNIRS results. Although fMRI keeps the golden standard in tracking hemodynamic changes in the brain, fNIRS may be the advantageous method in some cases due to its high time resolution, easy assessment in natural environments, relative robustness against movement artifacts and low operating costs.

Another limitation concerns the difference in age between the groups. The depressed subjects are 7 years older than the non-depressed control group on average. However, the range of the sample is restricted to the ages 20 to 65. A systematic influence of age in this period of live on the effects between the patient groups is unlikely.

It is also important to note that we used a quasi-experimental design, because we wanted to analyze “spontaneous” rumination to prevent induction of experimental artefacts. Therefore, all associations between state and trait rumination and FC are based on between-subject differences. Neither rumination nor depression were induced experimentally and therefore are not controlled and no causality of the effects can be claimed.

To the best of our knowledge, this is the first study comparing the effects of state and trait rumination on the differences in functional connectivity (FC) between depressed and non-depressed subjects. We found that only a subsample of depressed subjects report “spontaneous” rumination during resting-state. FC in the DMN is decreased in depressed subjects compared to non-depressed subjects – an effect that is partly associated with the process of mind-wandering and state/trait rumination. In future studies on the neurophysiological correlates of depressive rumination, the latter should be assessed as a trait- as well as a state-construct, as well as spontaneous and induced rumination.

7. Study 3 – Stress-related dysfunction of the right inferior frontal cortex in high ruminators: An fNIRS Study

The contents of this chapter are published:

Rosenbaum, D., Thomas, M., Hilsendegen, P., Metzger, F. G., Haeussinger, F. B., Nuerk, H.-C., Fallgatter, A. J., Nieratschker, V. & Ehlis, A.-C. (2018). Stress-related dysfunction of the right inferior frontal cortex in high ruminators: An fNIRS study.Neuroimage: Clinical, 18, 510-517.

7.1 Abstract:

Repetitive thinking styles such as rumination are considered to be a key factor in the development and maintenance of mental disorders. Different situational triggers (e.g., social stressors) have been shown to elicit rumination in subjects exhibiting such habitual thinking styles. At the same time, the process of rumination influences the adaption to stressful situations. The study at hand aims to investigate the effect of trait rumination on neuronal activation patterns during the Trier Social Stress Test (TSST) as well as the physiological and affective adaptation to this high-stress situation.

Methods: A sample of 23 high and 22 low ruminators underwent the TSST and two control conditions while their cortical hemodynamic reactions were measured with functional near-infrared spectroscopy (fNIRS). Additional behavioral, physiological and endocrinological measures of the stress response were assessed.

Results: Subjects showed a linear increase from non-stressful to stressful conditions in cortical activity of the cognitive control network (CCN) and dorsal attention network (DAN), comprising the bilateral dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG) and superior parietal cortex/somatosensory association cortex (SAC). High ruminators showed attenuated cortical activity in the right IFG, whereby deficits in IFG activation mediated group differences in post-stress state rumination and negative affect.

Conclusions: Aberrant activation of the CCN and DAN during social stress likely reflects deficits in inhibition and attention with corresponding negative emotional and cognitive consequences. The results shed light on possible neuronal underpinnings by which high trait rumination may act as a risk factor for the development of clinical syndromes.

7.2 Introduction

Rumination is an enduring self-referential pessimistic repetitive thinking style about problems with little or no goal and change-orientation (Teismann, 2012a). The process is considered to be an important factor in the development and maintenance of major depression since it is related to the onset, severity and treatment stability of the disorder (Smith & Alloy, 2009a). Ruminative tendencies elevate the risk for depression even in the absence of other acute symptoms in healthy individuals (Eshun, 2000a; Ito et al., 2006; Koval et al., 2012; Michalak, Hölz, & Teismann, 2011; Smith & Alloy, 2009a; Teismann et al., 2008). However, also other mental disorders – such as anxiety disorders – and physical health – such as immune system and fitness – are affected by high levels of rumination (Mellings & Alden, 2000; Thomsen, Mehlsen, Hokland, et al., 2004; Thomsen, Mehlsen, Olesen, et al., 2004).

On a neuronal level, rumination is associated with aberrant functional activity within several brain areas. Studies showed that activity in the subgenual prefrontal cortex is associated with higher levels of rumination (Bratman, Hamilton, Hahn, Daily, & Gross, 2015), and that activity in this area and parts of the default mode network (DMN) (e.g., posterior cingulate) and cognitive control network (CCN) (e.g., dorsolateral prefrontal cortex (dlPFC)) can be elicited by a rumination induction (Cooney et al., 2010a). However, in comparison to task positive network activity, relative DMN dominance has been associated with rumination (Hamilton et al., 2011). Also, in depressed subjects – a sample that is known to show elevated levels of rumination – meta-analytic data showed decreased activity within the frontal parts of the CCN (Zhong et al., 2016). Moreover, stimulation of the right prefrontal cortex with transcranial direct current stimulation (tDCS) led to higher state rumination after an anger induction (Kelley, Hortensius, & Harmon-Jones, 2013). In this framework, the midline structures of the cortex – mostly belonging to the DMN – are thought to play an important role in self-referential processing, while the lateral parts of the cortex – mostly corresponding to the CCN and attention network – are involved in cognitive control and attention processes (Nejad, Fossati, & Lemogne, 2013).

Usually, rumination is directly induced in experimental designs by instructing participants to think in a certain way, or by using autobiographical paradigms (Marc G. Berman et al., 2014b; Ottaviani et al., 2016a). Since rumination is thought to be elicited by stressful life events (Smith & Alloy, 2009a), stress induction methods (Skoluda et al., 2015) have also been used to induce rumination. While some did not find effects of stress on the induction of rumination (Young & Nolen-Hoeksema, 2001), others found that state rumination can be elicited by stress (Gianferante et al., 2014; Hilt et al., 2015; Shull et al., 2016). However, the stress response itself is also affected by rumination as indicated by a reduced decline of cortisol in high ruminators (Denson et al., 2009; Hilt et al., 2015; LeMoult & Joormann, 2014; Shull et al., 2016). Indeed, meta-analytic data suggests that rumination is associated with higher heart rate, systolic and diastolic blood pressure and cortisol levels in experimental designs (Ottaviani et al., 2016a). Yet, the neural links between rumination, cortical activation and the stress response are still unclear.

In the following work, we sought to investigate how far rumination can be induced through social stress in low and high trait ruminators. Further, we aimed to assess the neural underpinnings of the stress response in these individuals by using functional near-infrared spectroscopy (fNIRS), an optical imaging method that has proven to be compatible with the standard procedure of the Trier Social Stress Test (TSST) (Rosenbaum, Hilsendegen, et al., submitted). We hypothesized that stress-induced increases in state rumination would be stronger in high trait-ruminating individuals. Further, we predicted that the stress response in terms of heart rate, cortisol reactivity and subjective stress would be higher in high trait ruminators and would correlate with the increases in state rumination. On a neural level, we hypothesized that high trait-ruminators would show lower hemodynamic responses in parts of the CCN in comparison to low trait-ruminators during the TSST.

7.3 Materials and Methods

Participants. This study was approved by the ethics committee at the University Hospital and University of Tübingen. All participants gave their written

informed consent. A total of 45 subjects were recruited at the University of Tübingen according to their total Rumination Response Scale (RRS) (Susan Nolen-Hoeksema, 1991) score out of a sample of 400 subjects that completed the online assessment. To maximize differences in trait rumination, only subjects with high (PR>65) and low (PR<27) RRS scores were recruited. RRS score means for high (n=23) ruminators were m=2.59 (SD=.17, range: 2.36–3.04) and for low (n=22) ruminators m=1.53 (SD=.21 range: 1.09–1.86). The average age was 22 (SD=3 years) and 83% of the sample were female. Low and high ruminators did not differ in terms of these variables (see Table 1). High ruminators had a mean Beck Depression Inventory (BDI) score of 8.5 (SD=5.79, range: 0–23) and low ruminators of 1.9 (SD=2.2, range: 0–9) (Beck, Steer, & Hautzinger, 1994). No participant fulfilled full criteria for clinical depression. As expected, high ruminators reported to spend more time per day ruminating than low ruminators ($t_{(43)}$=-2.105, $p<.05$, d=.63). All subjects were right-handed, none took medication (except for contraceptive medication) and no subjects had medical conditions that influence the stress response. High and low ruminators did not differ on their general intelligence as assessed with the Mehrfachwahl-Wortschatz-Intelligenztest ($t_{(43)}$=-0.5, $p>.1$) (Lehrl, 2005).

	Low-Ruminators (n=22)		High-Ruminators (n=23)			
Variable	**mean**	**SD**	**mean**	**SD**	**t/χ^2**	**P**
Age (years)	22.3	3.88	21.69	2.68	$t_{(43)}<1$	p>.1
Percent of female participants	86%		79%		$\chi^2_{(1)}=.5$	p>.1
BDI	1.9	2.25	8.5	5.80	$t_{(43)}=4.99$	p<.001
RRS	1.5	0.21	2.6	0.17	$t_{(43)}=19.32$	p<.001
Time spent ruminating per day (hours?)	0.25	0.38	0.55	0.55	$t_{(43)}=-2.105$	p<.05
Mean Errors (control task)	0.6	0.27	0.6	0.41	$t_{(43)}<1$	p>.1
Mean Calculations (control task)	8.0	2.88	8.5	3.00	$t_{(43)}<1$	p>.1
Mean Errors TSST	1.5	0.64	1.5	0.61	$t_{(43)}<1$	p>.1
Mean Calculations TSST	9.6	3.80	9.7	3.50	$t_{(43)}<1$	p>.1

Table 10. Demographic and performance variables of the high and low ruminators. BDI = Beck Depression Inventory, RRS = Rumination Response Scale, TSST = Trier Social Stress Test.

Procedures. Subjects were screened via online assessment of the RRS score. After inclusion into the study, subjects completed the baseline assessment including demographic variables and a 10-minute interview about rumination symptoms. Afterwards, a 7-minute, eyes-open resting-state measurement was conducted using fNIRS. After the resting-state measurement, state rumination was assessed (see supplementary material). Two control tasks were completed afterwards including a number reading task (CTL1) and an arithmetic task

(CTL2) without social stress, i.e., without judges or videotaping. Both tasks consisted of 6 blocks with 40 s task performance and 20 s pausing. During CTL1, subjects had to read decreasing numbers from 1023 in steps of 13 (i.e., 1023, 1010, 997 and so on). During CTL2, subjects had to subtract the number 13 from 6 different starting points between 1026 and 1014. For the control tasks, subjects were instructed by a friendly study nurse. If errors occurred, the study nurse said: “Ok, please go on from …” and gave the correct answer. Afterwards, the TSST was performed. The TSST committee – comprising a female and male judge – entered the laboratory and sat down in front of the participants. According to the TSST standard protocol, subjects had a 5 min preparation phase before performing a 5 min mock job interview about their personal strengths and qualifications during which they stood in front of the TSST committee and were videotaped. Then a 6 min arithmetic stress challenge followed. Again, subjects had to subtract the number 13 from different starting points between 1026 and 1014 in 6 task blocks. If subjects made an error, one committee member interrupted them saying: “Stop! Please start again from…”. Different starting points were chosen for CTL2 and the arithmetic stress condition. The TSST committee was non-verbally neutral and emotionally non-responsive throughout the TSST. After the completion of the TSST, the committee left the room without any comment. Directly after the TSST, subjects completed a second resting-state measurement. During all experimental conditions, subjects gave subjective stress ratings and heart rate was measured. Cortisol samples were taken after the first resting-state measure, after the TSST and in 15 minute steps up to 60 minutes following the completion of the TSST. After the resting-state measurements, state rumination was assessed. Further, positive and negative affect was measured with the Positive and Negative Affect Schedule (PANAS) following the control conditions, the TSST and before the last salivary sample was taken (Watson, Clark, & Tellegen, 1988) (see Figure 18 and supplementary material).

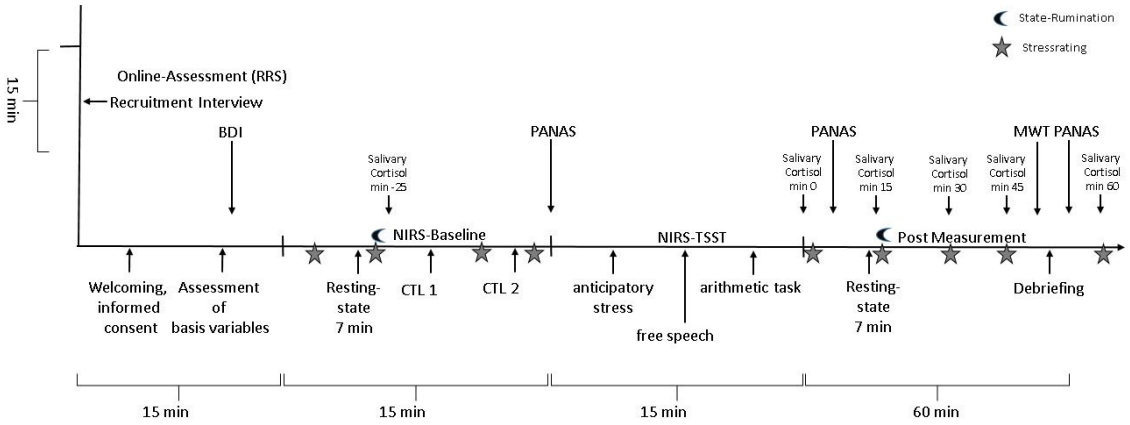

Figure 18: Design and measurements of the experiment

Cortisol Sampling and Assays. Saliva was collected in salivettes (Sarstedt AG & Co., REF 51.1534.500) and was further stored at -20°C. For analysis of cortisol levels, salivettes were thawed and centrifuged for 2 min at 1000g to collect saliva. Further analysis was performed with enzyme immunoassay (IBL International, Cortisol ELISA, REF RE52611) according to the manufacturer's instructions. Average cortisol levels were taken from duplicate runs if intra-assay variation was below 10%. Finally, daytime was regressed out of cortisol coefficients to account for circadian rhythm fluctuations that are not related to the TSST and values were log-transformed. Participants were instructed not to drink alcohol the day before the measurement, to sleep as long as they usually do and to perform no physical activities at the day of the measurement. Also subjects were told not to drink or eat 30 minutes before the measurement started.

Heart rate. The heart rate was recorded with a one channel electro cardiogram (ECG). For ECG recordings, two standard Ag/AgCl EEG ring electrodes of 8 mm diameter were attached to the abraded skin above the left and right collar bone. FPz according to the 10/20 system was taken as a reference. Signal recordings were done with a BrainAmp ExG amplifier and Brain Vision recorder software (Brain Products, Munich, Germany) at 1000 Hz sampling rate. Data was further preprocessed and analyzed using MATLAB R2017a routines (MathWorks Inc, Natick, USA). Preprocessing steps were as follows: Band-pass filtering (0.25–50 Hz) and (for one subject) 50 Hz notch filtering. Afterwards

intervals between R complexes and the average beats per minute were calculated.

fNIRS. Cortical activation was measured with a continuous wave, multichannel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co.,Japan) with a temporal resolution of 10 Hz. The measurement array consisted of two frontal and one parietal probeset (see Table 2). Optodes were positioned on a combined electrode Easycap with sponge rings for additional fixation. The system consisted of three probesets, two frontal probesets (reference points F3 and F4 according to the international 10-20 System (Jasper, 1958c)) with 9 optodes each and one parietal probeset (reference point Pz) with 15 optodes, resulting in a total of 46 channels (see Table 1, supplementary Figure S9 and S10). The combined electrode caps were positioned at reference point Cz according to the international 10-20-system on each participants head. Corresponding brain areas of each channel were extrapolated from reference points based on the Colin 27 template (Cutini, Scatturin, & Zorzi, 2011; Tsuzuki & Dan, 2014).

After the assessment, data was further analyzed using MATLAB R2017a (MathWorks Inc, Natick, USA). Data was first bandpass filtered (.1-.001 Hz) before the movement artefact reduction by the algorithm of Cui et al. (Brigadoi et al., 2014; Cui et al., 2010) was performed and a first interpolation of single artefact-loaded channels was done. As we used the correlation-based signal correction of Cui et al. (2010), we further only analyzed the data of the oxygenated signal (which was corrected for correlation with the deoxygenated signal). The oxygenated signal was further selected due to its higher signal-to-noise ratio, higher variability and excitability. Afterwards, an ICA based reduction of clenching artefacts was done and a second bandpass filtering (.1-.01 Hz) was performed before a global signal reduction was done with a spatial gaussian kernel filter (X. Zhang et al., 2016) with a standard deviation of $\sigma=50$. Finally, data was averaged over the 6 task blocks with a 5 s baseline correction for the total 40 s of task performance.

Brain area	Probeset A: (left frontal)	Probeset B: (right frontal)
Retrosubicular area	1	14, 16
Dorsolateral Prefrontal Cortex	5, 10, 11,12	15, 20, 23,24
Temporopolar Area	2	13
Subcentral Area	3	17
Pre-Motor and Supplementary	8	22
Pars Opercularis	6	19
Pars Triangularis	4, 7, 9	18, 21
	Probeset C: (parietal)	
Somatosensory Association	25, 26, 27, 28, 30, 31, 32, 34, 35, 36, 37	
V3	38, 39, 40, 41, 43, 44, 45, 46	
Angular Gyrus	42	
Supramarginal Gyrus	29, 33	

Table 11. Channels of the used fNIRS probeset and corresponding brain areas

Data Analysis. The different datasets – behavioral, physiological, endocrinological and cortical activation data – were analyzed with respect to the hypothesized group (low vs. high ruminators) by condition interaction. For all measures, repeated measurement ANOVAs were performed with IBM SPSS Statistics Version 24. We hypothesized that high ruminators would have higher stress-ratings, heart rates, state rumination, negative affect and cortisol levels in the post TSST phase than non-ruminators. Due to different path lengths of the near-infrared light, group (high ruminators vs. low ruminators) by condition (CTL1 vs. CTL2 vs. TSST) repeated measures ANOVAs were performed for five ROI (bilateral dlPFC, IFG and SAC) separately (see supplementary figure S10). We hypothesized a linear relationship between blood oxygenation and stress-loading of the task (CTL1<CTL2<TSST) in the low ruminators and that this relationship would be disturbed in the high ruminators (Zhong et al., 2016). Finally, we tested in how far effects of group on behavioral measures were

mediated by changes in cortical activation from CTL1 to the TSST by using regression analysis and Sobel's-Z-test for mediation (Sobel, 1982, 1986). In the paper at hand, only the experimental effects on the hemodynamic response during the control conditions and the TSST are reported. Resting-state measurements were analyzed separately with respect to functional connectivity (FC) differences and will be reported elsewhere since both measures – FC and activity – have differential and independent informational content.

7.4 Results

Behavioral, endocrinological and sympathetic changes. As indicated by repeated measurement ANOVA (group*condition), both the number of arithmetical computations ($F_{(1, 43)=}$37.051, p<.001, η^2=.46) and errors ($F_{(1, 43)=}$114.621, p<.001, η^2=.72) increased from CTL2 to TSST. However, no significant differences were found between high- and low-ruminators. Regarding negative (NA) and positive affect (PA), we found a significant group (high vs. low ruminators) by time (pre TSST vs. 5 min post TSST vs. 50 min post TSST) interaction for negative affect ($F_{(2, 82)}$=6.092, p<.01, η^2=.13). Results indicated a generally higher NA level for high ruminating subjects – reflected by a main effect of group ($F_{(1, 42)}$=11.649, p<.001, η^2=.22) – and higher negative affective reactivity in the high ruminators due to the stress-induction in terms of a quadratic significant interaction ($F_{(1, 41)}$=7.394, p<.01, η^2=.15) (see Figure 19A). In the same way, we found a group (high vs. low ruminators) by time (pre vs. post TSST) interaction for state rumination ($F_{(1, 43)}$=4.49, p<.05, η^2=.095), reflecting higher overall state rumination ($F_{(1,43)}$=27.47, p<.001, η^2=.39) and higher increases in state rumination during the experiment for the high ruminators ($t_{(43)}$=2.12, p<.05, d=.64).

Subjective stress ratings showed a significant main effect for time ($F_{(1, 43)}$=94.703, p<.001, η^2=.68). While there was no significant interaction between time and group, planned comparisons indicated that the subjective stress rating was significantly higher in the high ruminators at 30 minutes post TSST ($t_{(43)}$=2.12, $p_{one\text{-}sided}$<.05, d= .63) and 45 minutes post TSST ($t_{(43)}$=1.93, $p_{one\text{-}sided}$<.05, d= .57) (see Figure 19B).

Regarding sympathetic activation, heart rate measurements indicated a significant variation over conditions (resting-state pre TSST vs. CTL1 vs. CTL2 vs. TSST anticipation vs. TSST free speech vs. TSST arithmetic task vs. resting-state post TSST; $F_{(6, 252)}$=90.610, p<.001, η^2=.68) and a marginally significant difference for the main effect of group ($F_{(1, 42)}$=3.9, p<.1, η^2=.086), showing a trend towards lower heart rates in the high ruminators. Heart rates increased in the whole group from the resting-state measure to CTL1 ($t_{(43)}$=12.75, p>.001, d=1.9), from CTL1 to CTL2 ($t_{(43)}$=2.74, p>.01, d=.41) and decreased from CTL2 to the anticipation phase of the TSST ($t_{(43)}$=3.71, p>.001, d=.56). During the free speech heart rates increased significantly ($t_{(43)}$=11.35, p>.001, d=1.7) and decreased again during the post resting-state measurement ($t_{(43)}$=14.23, p>.001, d=2.1). Importantly, heart rate was significantly elevated during the TSST arithmetic task in comparison to CTL1 ($t_{(43)}$=5.7, p>.001, d=.86) and CTL2 ($t_{(43)}$=5.4, p>.001, d=.81) (see Figure 19C).

In line with this, cortisol levels showed a significant increase through the stress induction ($F_{(1, 43)}$=24.203, p<.001, η^2=.36; see Figure 19D). However, no significant differences in cortisol levels were found between the groups.

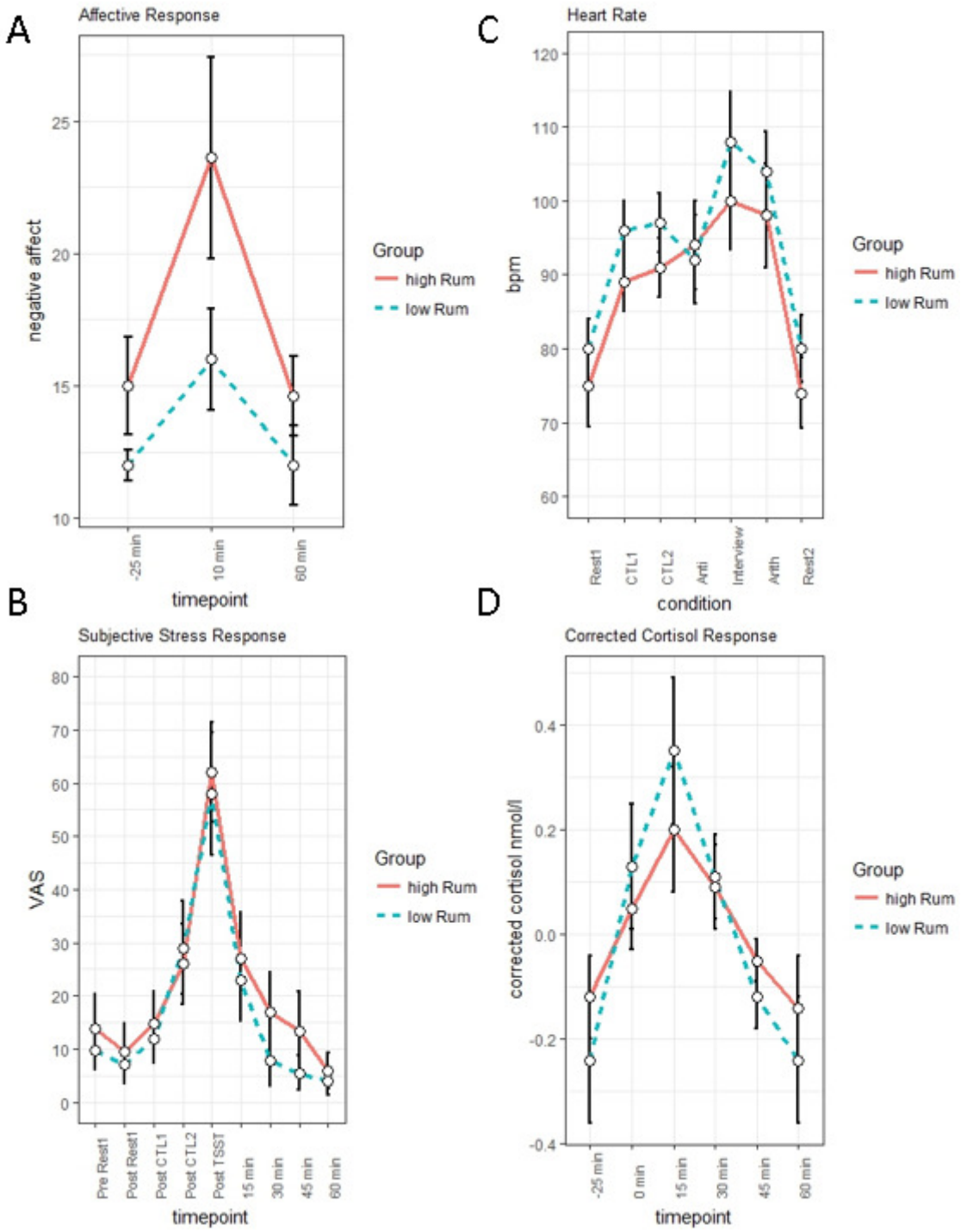

Figure 19. Responses in negative affect (A), subjective stress ratings (B), heart rate (C) and salivary cortisol (D). Timepoints are centered at post TSST (0 min).

Cortical Activation. As indicated by repeated measurement ANOVA with the factors group (high vs. low ruminators) and condition (CTL1 vs. CTL2 vs. TSST arithmetic challenge), we found significant main effects for condition in the ROIs

of the left dlPFC ($F_{(2, 86)}$=4.79, p<.05, η^2=.10), left IFG ($F_{(2, 86)}$=4.19, p<.05, η^2=.09), right dlPFC ($F_{(2, 86)}$=5.10, p<.01, η^2=.11) and SAC ($F_{(2, 86)}$=6.6, p<.01, η^2=.13). Post-hoc tests revealed a significant increase from CTL1 to CTL2 in all of these ROI ($t_{(43)}$=3.22 to 4.23, p<.001, d =.48 to .59). Increases from CTL2 to TSST were found in the left IFG ($t_{(43)}$=1.73, p<.05, d =.26) and SAC ($t_{(43)}$=1.89, p<.05, d =.28). Also, planned comparisons for the right dlPFC showed a significant linear group by condition contrast ($F_{(1, 43)}$=4.75, p<.05, η^2=.10) indicating a higher increase in cortical activation from the non-stressful to stressful conditions in the low ruminators than in the high ruminators (see Figure 20).

A significant group by condition interaction was found for the right IFG ($F_{(2, 86)}$=4.3, p<.05, η^2=.09). As for the right dlPFC, the linear contrast indicated a higher increase in cortical activation for the low ruminators from the control conditions to the TSST ($F_{(1,43)}$=7.19, p<.01, η^2=.14). Post-hoc tests revealed that low ruminators had higher activity within the right IFG during the CTL2 ($t_{(43)}$=2.87, p<.01, d=.85) and TSST ($t_{(43)}$=2.38, p<.05, d=.70) than high ruminators, but not during CTL1 (see supplementary Figure S11). Further post-hoc comparisons revealed that a significant increase in IFG activity from CTL1 to TSST occurred only in low ruminators ($t_{(21)}$=3.6, p>.01, d=.77) (see Figure 21).

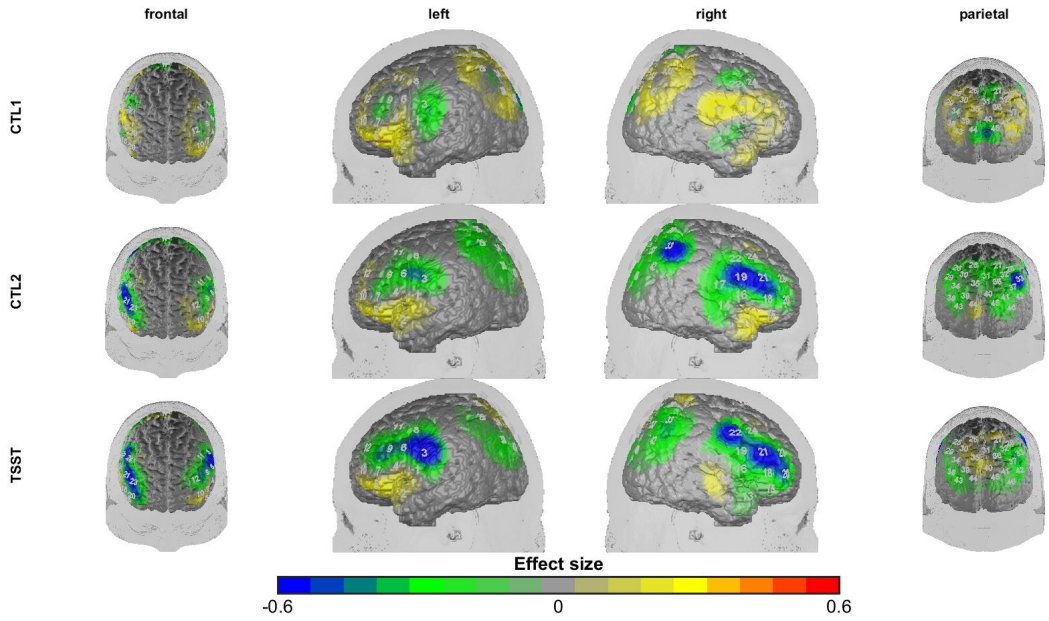

Figure 20: Differences in cortical activation between high and low ruminators in the experimental conditions. Cold colors indicate higher activation in the low ruminators.

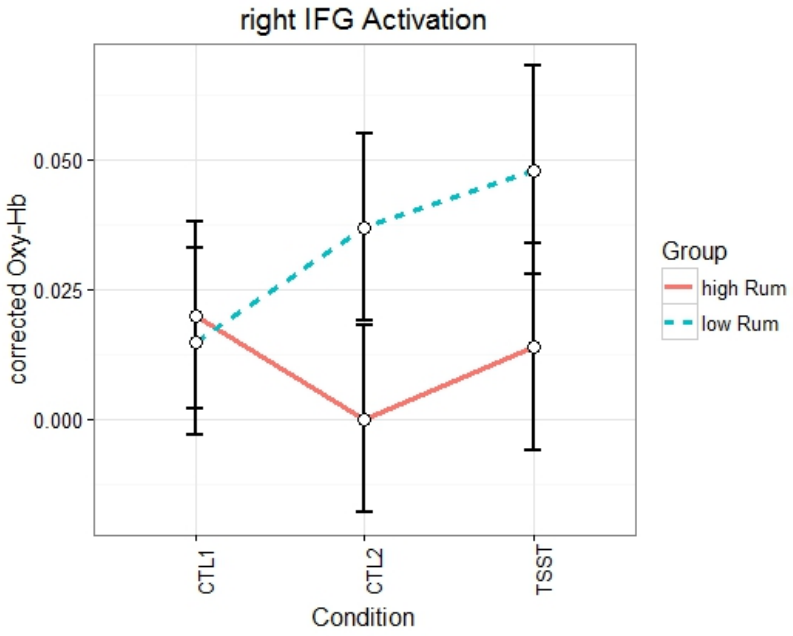

Figure 21: Interaction of condition by group-membership in the right IFG in cortical activation.

Mediation analysis. As indicated by Sobels Z-Test, we found a full mediation of the group effect on negative affect at the end of the experiment (B=2.275 (1.104), $t_{(42)}$=-2.18, p<.05, R^2=.10), by the increase of cortical activation from CTL1 to the TSST in the right IFG (B=-26.279 (9.85), $t_{(42)}$=-2.66, p<.05, R^2=.145; Z=2.697, p<.05). The mediation indicates that the high ruminators had a lower increase in right IFG activation that lead to higher negative affect at the end of the experiment.

Further, the group effect on stress-induced changes in state rumination (B=1.008 (.245), $t_{(42)}$=-4.12, p<.001, R^2=.28) was partially mediated by the increase in right IFG activation (B=-5.42 (.295), $t_{(42)}$=-2.03, p<.05, R^2=.09; Z=3.25, p<.05). As for negative affect, our results indicate that the reduced IFG activation during the TSST in the high ruminators lead to higher state rumination after the experiment. No such mediation effects were found for the effects on subjective stress.

7.5 Discussion

The aim of this study was to explore the effects of rumination on the stress response. We hypothesized that stress would induce ruminative processes (state rumination) and that this effect would be higher in high-trait ruminators. Further, we assumed that high ruminators would show a distinct pattern in subjective stress, sympathetic activity, the endocrinological stress response and cortical activation during and/or following the TSST.

Firstly, as expected, we found significant increases in behavioral, physiological and endocrinological stress indices during the stress induction of the TSST as compared to two control conditions. These were accompanied by elevated cortical activity in regions of cognitive and attentional control, namely the dorsolateral prefrontal cortex, inferior prefrontal cortex and superior parietal lobule/somatosensory association cortex. Additionally, the TSST condition led to further increases in activity of the left IFG and SAC in comparison to the CTL2. These main effects of within-subject comparisons reflect a successful induction of psychosocial stress and their cortical correlates.

With regards to our primary research hypothesis, our results showed that high ruminators showed a higher reactivity in negative affect and state rumination through the stress induction. No differences were found with regards to heart rate and cortisol responses. In line with our hypotheses, we found reduced cortical activity in the right IFG in this group. Finally, a mediation analysis showed that the group effects on negative affect and state rumination were mediated by cortical activation in the right IFG.

The found difference between high and low ruminators in the right IFG fits well with the present literature on the function of the IFG which has been reported to be central to inhibition during cognitive tasks and during physiological and psychological stress paradigms (Aron, Robbins, & Poldrack, 2004; Depue, Curran, & Banich, 2007; Kogler et al., 2015; J. Wang et al., 2005). For example, previous data suggest its involvement during response inhibition in Go-NoGo tasks (Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Rubia, Smith, Brammer, & Taylor, 2003), task switching paradigms (Aron, Monsell, Sahakian, & Robbins, 2004), cold pressure tests and arithmetic stress challenges (Kogler et al., 2015). Also, rumination has been related to deficits in cognitive control and inhibition (Smith & Alloy, 2009a). From our data, we would suggest that the lower activation of the right IFG during CTL2 and TSST conditions in high ruminators reflects such inhibitory deficits. Moreover, these inhibitory deficits during social stress situations led to higher negative affect and higher state rumination in the post TSST phase. These findings indicate – in terms of a more general interpretation – that inhibition deficits in high ruminators might lead to a reduced resilience to adverse events and impaired psychological (and physiological) health (Joormann, 2005, 2006). Interestingly, also data of lesion studies suggests that IFG damage is associated with problems in “directed forgetting”, which means that subjects with IFG damage have problems to suppress or exclude material from memory retrieval (Conway & Fthenaki, 2003). This is in line with some characteristics of rumination, in which subjects can’t stop ruminating after stressful events and have problems to stop thinking about their past failures. Herein lies a potential explanation for the found mediation of group membership

effects on state rumination and negative affect by right IFG activation: The high ruminators were not able to sufficiently activate their right IFG during the stress tasks, which might reflect insufficient inhibition of stress-related emotional and cognitive responses during the TSST. In the aftermath, these inhibitory deficits resulted in elevated levels of state rumination and negative emotionality. In line with this suggestion, Hermann et al. (2016) found reduced stress responses in a threat task after stimulation of the right IFG with transcranial direct current stimulation (Martin J. Herrmann, Beier, Simons, & Polak, 2016). However, with respect to our data it is unclear in how far the reduced IFG activation during the TSST may already be a correlate of intrusive negative thoughts while performing the arithmetic task.

Interestingly, differences between the high and low ruminators in right IFG activation were already found during the second control task. However, also subjective stress levels and heart rate measures were significantly increased during this control task, when compared to CTL1 and resting-state measurements. From this point, one could argue that the arithmetic control task (CTL2) already induced moderate levels of stress that were accompanied by reduced cortical activation in the right IFG in the high ruminators. Indeed, arithmetic tasks – even without explicit social stressors as in the TSST (camera and judges) – have been shown to elicit stress in individuals (Beilock, 2008; Noto, Sato, Kudo, Kurata, & Hirota, 2005).

Planned comparisons by a linear contrast showed a significant group by condition effect in the right dlPFC. The direction of this effect was in line with the reported results of the right IFG, showing attenuated cortical reactivity in the high ruminators. Both areas – IFG and dlPFC – are part of the CCN and have strong functional and structural connections. The adaption during the TSST demands several cognitive functions comprising – besides inhibitory control – also attentional processes, which is likely reflected by an increase in dlPFC activation. Indeed, inhibition and attentional control are both cognitive processes that are deeply entangled and sometimes even interchanged. It has been shown previously that depression and rumination are associated with deficits in tasks that require attention switching (Koster, De Lissnyder, & De

Raedt, 2013; Whitmer & Banich, 2007), cognitive and attentional control (Ottowitz, Dougherty, & Savage, 2002) with attentional biases towards negative information (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005). It is thus very likely that such deficits in high ruminators are also relevant in the TSST in which subjects have to refocus their attention after miscalculations or distractions by emotional non-reactivity of the reviewer board.

Although effects of rumination on heart rate and cortisol levels are reported on a meta-analytic level (Ottaviani et al., 2016a), we did not find group differences in these variables, although they showed an expected reactivity pattern through the stress induction. One possible explanation may lie in the found meta-analytic effect sizes for heart rate (g=.20 to .28) and cortisol (g=.32 to 36), which are small to medium, and the power in our sample, which requires medium to high effect sizes.

Despite these conclusive findings, some limitations have to be noted. Firstly, through the fNIRS method's depth resolution, our results are restricted to the upper 2-3 cm of the cortical parts of the brain (Florian B. Haeussinger et al., 2011c). Potential effects in other areas of the brain could not be measured in the study at hand. Another limitation concerns the study sample. We used a non-clinical sample to prevent the influence of therapeutic interventions on the results. As previous studies have shown, the habit to ruminate is also a predictor for mental and physical health in non-clinical populations and might be considered a risk factor(Michalak et al., 2011; Teismann et al., 2008). Since the mental process per se is likely similar in clinical and non-clinical populations (and might only differ in the amount of time spent ruminating and its controllability), the results of this study should mostly be generalizable to clinical populations. In fact, the trait rumination – as measured with the RRS – of the high ruminators in this sample (m=2.6, SD=.17) were comparable to those of depressed patients in our clinic (N=24, m=2.6, SD= .56). Nonetheless, in future studies, the reported effects should be replicated in clinical populations, with additional consideration of potential effects of medication status. Also, the results of the mediation analysis have to be interpreted with caution due to the relatively small sample size. In future studies, the reported results should be

replicated in clinical samples with larger sample sizes. Further, a classification system of behavioral reactions of participants during the TSST that could be videotaped could give further insight into the specific processes that lead to cortical differences between subject groups.

In conclusion, we found reduced stress-related cortical activation in the right IFG in high ruminators, an effect that is likely related to inhibitory deficits and led to heightened negative affect and ruminative thinking following the stress task. The fNIRS method was shown to be usable in subclinical subjects in the original TSST setting, which might also be valuable for the investigation of depression and other stress-related clinical disorders. Overall, the present findings provide insight into possible mechanisms by which high trait rumination may act as a risk factor for the development of clinical syndromes and maladaptive stress responses.

8. Study 4 – Disrupted prefrontal functional connectivity during post-stress adaption in high ruminators: An indicator of state rumination?

The contents of this chapter are published:

Rosenbaum, D., Hilsendegen, P., Thomas, M., Häußinger, F. B., Nürk, H.-C., Fallgatter, A.J., Nieratschker, V., Ehlis, A.-C., Metzger, F.G. (2018). Disrupted prefrontal functional connectivity during post-stress adaption in high ruminators. Scientific Reports, 8:15588.

8.1 Abstract:

Rumination is a repetitive, persistent and pessimistic thinking style that is associated with adverse mental and physical health. Stressful life situations have been considered as a trigger for this kind of thinking. Until today, there are mixed findings with respect to the relations of functional connectivity (FC) and rumination. The study at hand aimed to investigate, in how far high and low trait ruminators would show elevated levels of state rumination after a stress induction and if these changes would show corresponding changes in FC in the cognitive control network (CCN).

23 high and 22 low trait ruminators underwent resting-state measurements before and after a stress induction with the Trier Social Stress Test (TSST). Changes in FC during resting-state through the TSST were measured with functional near-infrared spectroscopy within and between regions of the CCN.

High trait ruminators showed elevated FC within the CCN before the stress induction, but showed an attenuated increase in FC following the TSST. Increases in FC within the CCN correlated negatively with state rumination.

A lack of FC reactivity within the CCN in high trait ruminators might reflect reduced network integration between brain regions necessary for emotion regulation and cognitive control, particularly in response to high-stress situations.

8.2 Introduction

The tendency to ruminate about negative thought content has been shown to be related to a variety of adverse consequences (Smith & Alloy, 2009a). Rumination can be defined as self-referential persistent repetitive and rather pessimistic thinking style about the past, ones mistakes or shortcomings, with little or no change and goal-orientation (Teismann, 2012b). In the case of mental disorders, rumination is related to the onset, duration and reoccurrence of depressive episodes (Smith & Alloy, 2009a) and to the maintenance of social phobia (Mellings & Alden, 2000). On a neural level, rumination has been shown to be related to various functional alterations in different networks, both regarding activation patterns (Hamilton et al., 2011; Jones, Fournier, & Stone, 2017b; Longe et al., 2010b; Piguet et al., 2014b; Schneider & Brassen, 2016b; Zhong et al., 2016) and functional connectivity (FC) (Hamilton, Farmer, Fogelman, & Gotlib, 2015b; Iwabuchi et al., 2015b; Kaiser et al., 2015). Regarding the default mode network (DMN), rumination has been linked to elevated FC between the subgenual anterior cingulate cortex and parts of the DMN, including parts of the posterior cingulate cortex(Hamilton et al., 2011). Furthermore, hypo-connectivity within frontoparietal control networks, within the dorsal attention network (DAN) and hyper-connectivity between the cognitive control network (CCN) and the DMN have been observed (Kaiser et al., 2015; Rosenbaum et al., 2017; H. Zhu et al., 2017). However, some studies also showed higher FC within the CCN (Peters et al., 2016; Rosenbaum et al., 2016b), and reduced FC in inter-hemispheric FC indices (Hermesdorf et al., 2016; L. Wang et al., 2013; Y. Wang et al., 2015; Xu et al., 2013). So far, most resting-state studies that tried to assess the relationship between FC and rumination used either non-inductive measurements, by correlating the rumination response scale (RRS) with FC during resting-state, or by inducing rumination through biographical induction tasks (Marc G. Berman et al., 2014b). Since the RRS is a trait-like measure, recently certain attempts have been made to develop state rumination questionnaires (de Jong-Meyer et al., 2009; Rosenbaum et al., 2017). In contrast to trait measures, state rumination questionnaires aim to assess the current state of the construct (which only

correlates moderate with the trait), e.g. during a neurophysiological resting state measurement. Also, beside biographical induction methods, indirect induction methods through negative mood inductions have been used (Blagden & Craske, 1996; Broderick, 2005; Rood, Roelofs, Bögels, & Arntz, 2012). Since some theories propose a special role for stressful life events as rumination-eliciting situations (Smith & Alloy, 2009a), attempts have also been made to induce rumination via stress induction techniques (Gianferante et al., 2014; Hilt et al., 2015; Shull et al., 2016; Young & Nolen-Hoeksema, 2001) and to measure the influence of rumination on the stress response (Aldao, McLaughlin, Hatzenbuehler, & Sheridan, 2014; Shull et al., 2016). Indeed, in different studies state rumination has been induced through social stress(Gianferante et al., 2014; Hilt et al., 2015; Shull et al., 2016) and rumination clearly has an effect on the stress response. Recent review and meta-analytic data on the physiological effects of rumination showed that rumination is associated with higher systolic (g = .45) and diastolic (g = .51) blood pressure, higher cortisol (g = .32-.36), heart rate (g = .20-.28) and lower heart-rate variability (g=.15-.27) (Ottaviani et al., 2016a). Following stress induction, rumination has effects on the cortisol response in terms of a reduced decline (Denson et al., 2009; LeMoult & Joormann, 2014). This effect might be more strongly related to state rumination as compared to trait rumination (Hilt et al., 2015).

There is a large body of literature on the issue of stress effects on brain activity(Qin, Hermans, Marle, Luo, & Fernández, 2009) and connectivity (e.g., see the review by van Oort (2017) (van Oort et al., 2017)). With respect to the effects of stress on resting state FC directly after the stress-induction four studies exist (Maron-Katz, Vaisvaser, Lin, Hendler, & Shamir, 2016a; Quaedflieg et al., 2015; Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernández, 2010). In three of these studies a seed based approach has been used, which consistently yielded the result of increased FC between the amygdala and DMN related brain areas as the hippocampus and parahippocampal gyrus(Quaedflieg et al., 2015; Vaisvaser et al., 2013; van Marle et al., 2010; van Oort et al., 2017). Furthermore, the study of Meron-Katz (2016) used a large scale network approach which investigated FC changes

through stress between different brain areas. Following stress, the authors reported increased absolute resting state FC and more concretely increased thalamo-cortical FC, including the frontal, temporal and parietal lobes (Maron-Katz et al., 2016a). However, also decreased FC between cross-hemispherical temporo-parietal areas has been reported in this study.

In the current study, we sought to investigate changes in resting-state FC in low and high ruminators following a stress induction via the Trier Social Stress Test (TSST). Additionally, we assessed quantitative rumination state-variables to investigate in how far social stress elevates ruminative responses following the stress induction. In our primary analysis of the same sample, we already showed that high ruminators show reduced cortical activation during the performance of the TSST in comparison to low ruminators (Rosenbaum et al., 2018). Additionally, cortical reactivity through the TSST mediated group differences in negative affect and state rumination following the TSST procedure. Since measures of functional connectivity give additional information about regional integration and segregation during information processing, in the present work, we investigated changes in resting-state FC through the TSST in high and low ruminators.

We hypothesized that the stress induction would lead to higher FC within the CCN and the DAN and that these changes would still be present in a resting-state measure following the TSST (hypothesis 1). From our previous investigations, we expected that high ruminators in contrast to low ruminators would show higher FC in the CCN before the TSST (hypothesis 2).

Further, from prior data on differences in FC reactivity between depressed and non-depressed subjects (Kaiser et al., 2015), we hypothesized that the high ruminators would show attenuated FC in the Cognitive Control Network (CCN) and DAN following the TSST (hypothesis 3). We further explored the correlations between state rumination, negative affect and increases in FC.

8.3 Materials and Methods

Participants. This study was approved by the ethics committee at the University Hospital and University of Tübingen. 45 subjects – 23 high and 22 low ruminators – were recruited at the University of Tübingen according to their total RRS score. High ruminators had to have a mean RRS score higher than 2.36 (PR > 65) and low ruminators had to have an RRS score lower than 1.9 (PR < 27). Low ruminators were on average age 22 years old (86% female). Their mean BDI-II score was 1.9 which implies the absence of depressive symptoms. The high rumination group was 79% female and was on average 22 years of age. The mean BDI was 8.5, which also implies the absence of clinically-relevant symptoms. However, both groups differed significantly with respect to their BDI scores, indicating subclinical symptoms in the high ruminators (see table 12).

The pre-experimental assessment of ruminative behavior via interview (see supplementary material) indicated significant differences between the groups in the following dimensions: more dwelling thoughts ($\chi^2_{(2)}$=5.8, p<.05), higher persistence ($\chi^2_{(3)}$=5.8, p<.001), higher rumination-associated guilt ($\chi^2_{(1)}$=7.9, p<.01) and shame ($\chi^2_{(2)}$=7.9, p<.05), higher rumination-associated hopelessness ($\chi^2_{(2)}$=14.96, p<.001), more dwelling on “why-questions” ($\chi^2_{(3)}$=9.67, p<.05) and higher subjective impairment though rumination ($\chi^2_{(2)}$=18.18, p<.001) in the high ruminators.

	Low Ruminators (n=22)		High Ruminators (n=23)			
Variable	**mean**	**SD**	**Mean**	**SD**	**t/χ²**	**P**
Age (years)	22.3	3.88	21.69	2.68	$t_{(43)}<1$	p>.1
Percent of female participants	86%		79%		$\chi^2_{(1)}=.5$	p>.1
BDI score	1.9	2.25	8.5	5.80	$t_{(43)}=4.99$	p<.001
RRS score	1.5	0.21	2.6	0.17	$t_{(43)}=19.32$	p<.001
hours spent ruminating per day	0.25	0.38	0.55	0.55	$t_{(43)}=-2.105$	p<.05
State rumination post TSST	1.44	0.43	2.45	1.07	$t_{(43)}=4.12$	p<.001
NA post TSST	16.81	5.377	23.61	9.03	$t_{(43)}=3.05$	p<.01
Qualitatively reported rumination during post-stress resting-state	2.05	2.13	4.0	3.12	$t_{(43)}=-2.42$	p<.05
Rumination score (Interview)	7.50	3.0	10.2	2.95	$t_{(43)}=-2.96$	p<.01

Table 12. Demographic variables of the high and low rumiantion group. BDI= Beck Depression Inventory, RRS = Rumination Response Scale, NA = negative affect from the Positive and Negative Affect Schedule.

Procedures. At the day of the measurement, all subjects gave written informed consent and completed an interview in which basic (demographic) variables and rumination-related behavior were assessed. Afterwards, subjects were brought to the NIRS laboratory were they underwent a 7 minute resting-state measurement with open eyes. Then participants performed two control tasks (reading numbers and counting) with 12 minutes duration before completing the TSST with approximatly 16 minutes duration. During the TSST the committee (a female and male judge) entered the room and took place in front of the

subjects. According to the TSST protocol (Kirschbaum, Pirke, & Hellhammer, 1993) the participants were told that they applied for an job and had a 5 min preparation phase (anticipatory stress phase) before performing a 5 min free speech about their personal strengths and qualifications. During the free speech, the subjects stood in front of the non-verbal neutral and emotional non-responsive TSST committee and were videotaped. In a third phase, subjects were asked to perform a 6 min arithmetic task (arithmetic stress challenge). Again, subjects had to do subtractions (subtracting the number 13 from different starting points between 1026 and 1014) but were interrupted by a committee member if they made an error. Further subjects were asked to perform better and faster from time to time (see (Rosenbaum et al., 2018)). After completion of the TSST, a second resting-state measurement was performed. Directly following each resting-state measurement, subjects completed two resting-state questionnaires that were adapted from the Amsterdam Resting-State Questionnaire (Diaz et al., 2013) to assess state rumination. After the second resting-state, qualitative self-report forms were used to assess cognitive reactions (e.g., rumination) after the stress induction. The self-report forms were quantified by the procedure used by Shull et al. (2016) in which each sentence is rated with respect to ruminative content (Shull et al., 2016).

Cortisol-samples were taken before the experimental procedure and up to one hour after completion of the TSST. Additionally, subjective stress ratings and heart rate measures were assessed during the different parts of the experimental procedure (see figure 22).

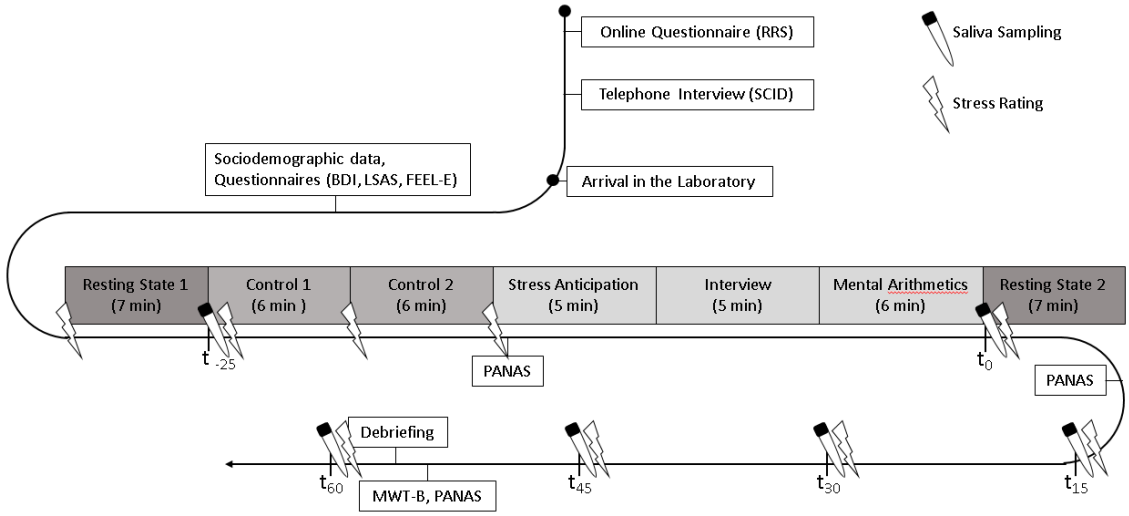

Figure 22. Experimental procedures of the whole experiment.

Functional near-infrared spectroscopy (fNIRS). Hemodynamic fluctuations were assessed with a continuous wave, multichannel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co.,Japan) with a temporal resolution of 10 Hz. In total three probesets were used including two frontal and one parietal measurement array. Optodes were placed on a combined electrode Easycap with sponge rings for additional fixation. The system consisted of 46 channels (see table 13).

Data was analyzed using MATLAB R2017a (MathWorks Inc, Natick, USA). Preprocessing included a first bandpass filter (.1-.001 Hz), movement artefact reduction by the algorithm of Cui et al. (Brigadoi et al., 2014; Cui et al., 2010) and interpolation of single noisy channels. In 16 subjects, channels had to be interpolated. However, no more than three channels were interpolated per measurement in any of the subjects. Afterwards, clenching artefacts were reduced with independent component analysis and a second bandpass filtering (.1-.01 Hz) was performed. To reduce global artefacts, a spatial gaussian kernel filter (X. Zhang et al., 2016) with a standard deviation of σ=50 was used. We used a standard deviation of σ=50 as this yielded the best results in terms of reduction of the global signal without inducing artificial negative activation. FC measures were computed by Fisher's z-transformation of Pearson coefficients

with a zero time-lag. Brain Net figures were plotted with the MATLAB package *BrainNet Viewer* (Xia, Wang, & He, 2013b).

Brain area	Probeset	
	Probeset: left frontal	Probeset: right frontal
Retrosubicular area	1	14, 16
Dorsolateral Prefrontal Cortex	5, 10, 11,12	15, 20, 23,24
Temporopolar Area	2	13
Subcentral Area	3	17
Pre-Motor and Supplementary Motor Cortex	8	22
Pars Opercularis	6	19
Pars Triangularis	4, 7, 9	18, 21
	Probeset: parietal	
Somatosensory Association Cortex	25, 26, 27, 28, 30, 31, 32, 34, 35, 36, 37	
V3	38, 39, 40, 41, 43, 44, 45, 46	
Angular Gyrus	42	
Supramarginal Gyrus	29, 33	

Table 13. Channels of the used probesets and corresponding brain areas

Data Analysis. We analyzed differences between high and low ruminators in their FC changes through the stress induction. Data with respect to hemodynamic responses during the TSST and the control conditions are reported in a separate analysis since the both project parts are independent from each other(Rosenbaum et al., 2018). Briefly, our results concerning the TSST showed that subjects showed higher blood oxygenation during the TSST as compared to the control conditions in ROIs of the CCN. Further, high ruminators showed reduced reactivity in the right IFG during the stressful task conditions. On behavioral subscales the primary analysis showed significant within-between subject interactions of time by group in state rumination and negative affect, indicating higher increases of both parameters in high trait-

ruminators. We observed no difference between high and low ruminators in cortisol responses and heart rate measures. A graphical summary of the results can be seen in the supplementary figures S1 to S5. In the following analysis, we focus on changes (from pre- to post-test) in resting-state FC in high and low ruminators due to the stress induction. In contrast to our primary analysis, this follow-up study informs about the variability due to social stress in network coupling in high and low ruminators during resting-state, while the primary analysis focused on blood oxygenation of predefined ROIs.

To account for the problem of multiple testing, we investigated the average FC differences between and within pre-defined region-specific nodes (see figure 23). As we were interested in the CCN and DAN, we investigated FC between and within the regions of the bilateral dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG) and somatosensory association cortex (SAC). As Zhu et al. (2017), we separated these connections into within-region FC (within each region), short-distance FC (between the ipsilateral IFG and dlPFC) and long-distance FC (between contralateral dlPFC and IFG regions, frontal regions and superior parietal lobule). For each of these connections were performed a mixed repeated measurements ANOVA with the factors group (high vs. low ruminators) and time (pre-stress vs. post-stress). Correction for multiple comparisons was done by the procedure of Armitage-Parmar at an significance level of $\alpha = .05$ (Sankoh, Huque, & Dubey, 1997). All described results are corrected if not stated otherwise.

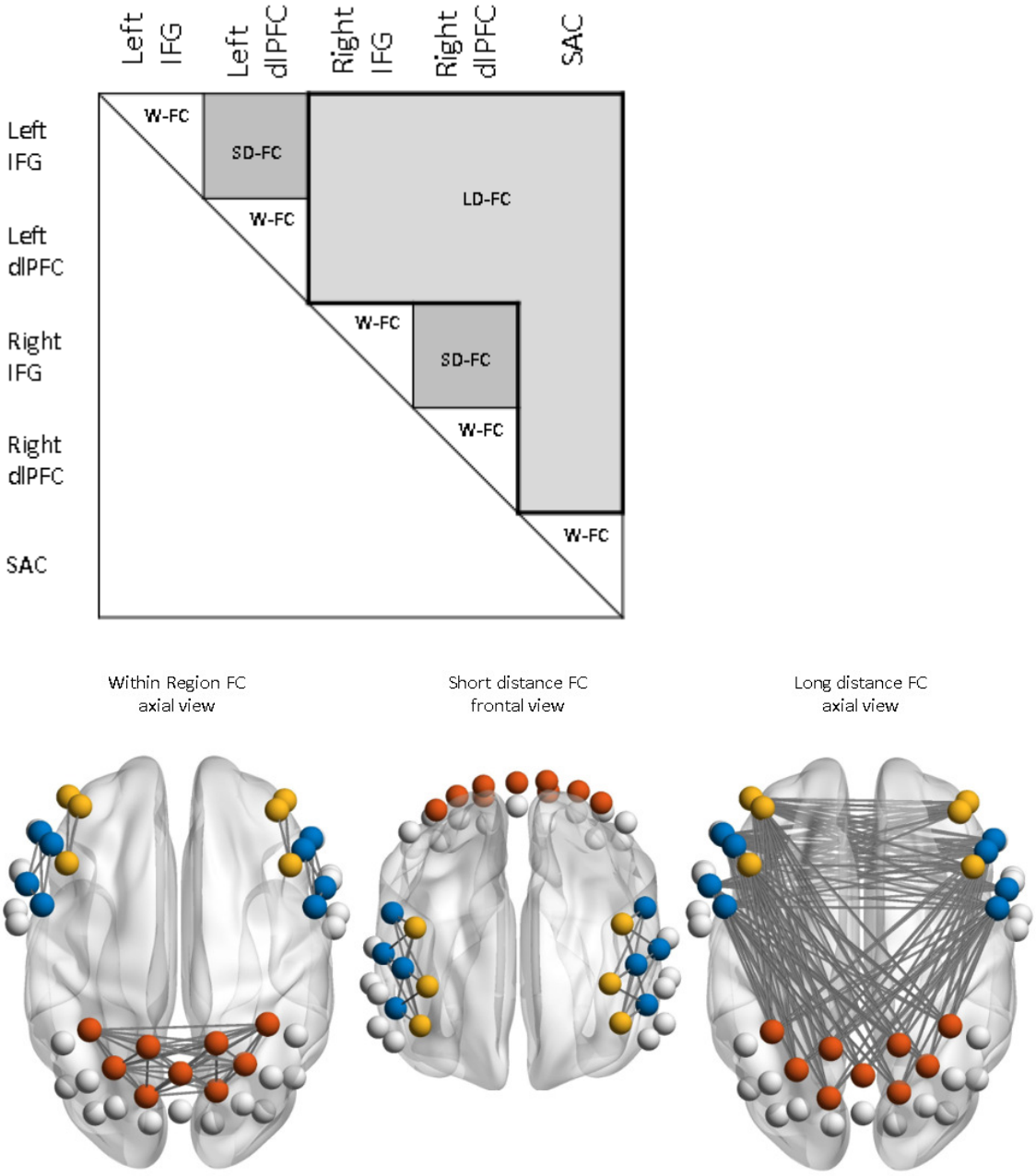

Figure 23. Definition of regions of interest in the analysis and the corresponding within, short-distance and long-distance region connections that were analyzed.

8.4 Results

Behavioral. The quantitative analysis of the qualitative post-stress reports revealed that the high ruminators reported more often ruminative content more often (on average four sentences with ruminative content vs. two) ($t_{(43)}$=2.43, p<.05, d=.72). With respect to different dimensions of rumination, 54% rehearsed their bad performance, 28% speculated about negative causes or

consequences, 39% focused on their negative affect and 59% showed some sort of reflective rumination or cognitive problem solving. Please note that subjects could show more than one dimension in their reports (e.g. first rehearsing bad performance and secondly reflective rumination). Groups differed in the dimension speculating about negative consequences ($\chi^2_{(1)}$=4.87, p<.05), with more subjects in the high ruminators (44%) reporting speculations about negative consequences than in the low ruminators (14%). Further, only four subjects (8.9%) reported aggressive impulses towards the TSST committee, while 15 subjects (33.33%) reported feelings of personal failure. Groups did not differ with respect to these qualitative data.

Also, high ruminators showed higher state rumination in general as indicated by the ARSQ state rumination score ($t_{pre(43)}$=4.91,p<.001, d=1.45; $t_{post(43)}$=4.18,p<.001, d=1.23) and a higher increase in state rumination from pre-TSST to post-TSST resting-state measurements ($t_{(43)}$=2.15,p<.05, d=.82). Changes in heart rate, cortisol and subjective stress ratings were influenced by the stress induction as expected and are reported in our previous article on the topic (Rosenbaum, Thomas, et al., submitteda). Further, with respect to negative affect, we observed a significant higher increase in the high ruminators following the stress induction as compared to the low ruminators(Rosenbaum et al., 2018).

FC. Analysis of within-region FC revealed a significant time by group interaction for the right dlPFC ($F_{(1,43)}$=8.552, p<.01, η^2=.16) and a marginally significant interaction in the right IFG ($F_{(1,43)}$=6.34, p<.1, η^2=.13). Post hoc analysis revealed that this disordinal interaction (see figure 24) was driven by a significantly higher increase through the stress induction in the low ruminators (right dlPFC: $t_{(43)}$=2.924, p<.01, d= .87; right IFG: $t_{(43)}$=2.51, p<.05, d=.74) (hypothesis 1), but a significantly higher FC in the high ruminators within the regions before the stress induction (right dlPFC: $t_{(43)}$=1.962, p<.1, d=.58; right IFG: $t_{(43)}$=2.54, p<.05, d=.75) (hypothesis 2).

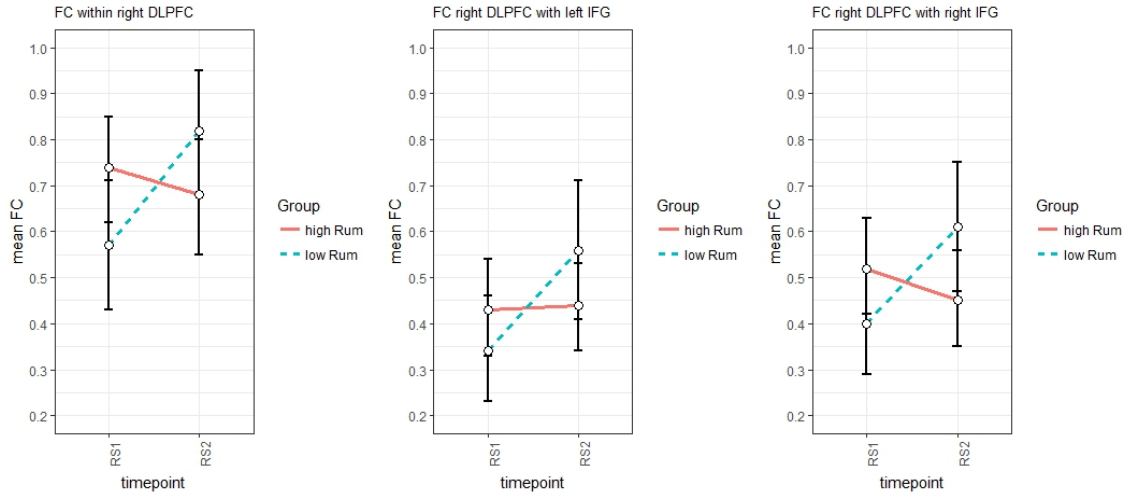

Figure 24. Displaying the disordinal interaction of the time by group effect in three different connections.

Accordingly, we found a time by group interaction for the short-distance FC between right dlPFC and right IFG ($F_{(1,43)}$=12.981, p<.001, η^2=.231). As for within-region FC, post hoc analysis indicated a higher increase in the low ruminators in FC between the right dlPFC and right IFG following the stress induction ($t_{(43)}$=3.59, p<.001, d= 1.07) (see figure 25) (hypothesis 1).

For long-distance FC, we found a significant main effect for time regarding the FC between right dlPFC and SAC ($F_{(1,43)}$=4.26, p<.05, η^2=.09) reflecting a significant increase in FC over the course of the experiment. Also, a significant time by group interaction was found for the coupling of the right dlPFC with the left IFG ($F_{(1,43)}$=6.344, p<.05, η^2=.13). Again, increases in FC were higher for the low trait ruminators ($t_{(43)}$=2.52, p<.05, d=.75) (hypothesis 1).

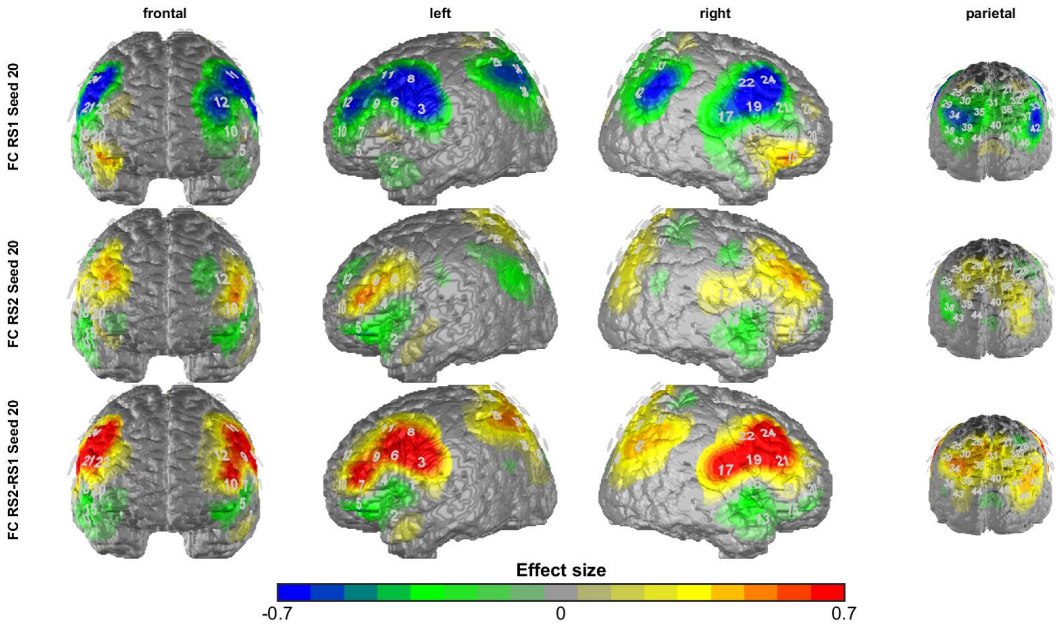

Figure 25. FC differences to a seed region in the right IFG between low and high-ruminators for resting-state pre TSST (upper row), post TSST (middle row) and the increase in FC through the TSST (lower row). Warm colors indicate higher FC values/increases for the low ruminators; cold colors indicate higher FC values/increases for the high ruminators.

In a final explorative analysis we also found correlations between FC measures and behavioral measures. Like in our analysis of cortical activation(Rosenbaum, Thomas, et al., submittedb), we investigated the relationship between negative affect, state rumination and increases in FC through the TSST. Significant (but not corrected for multiple comparisons) negative associations were found in FC increases between the right dlPFC and IFG and post-stress negative affect ($r_{(43)}$=-.30, p<.05) as well as state rumination ($r_{(43)}$=-.29, p<.05), indicating lower post-stress rumination and negative affect in subjects that showed increases in functional integration between the right dlPFC and IFG through the TSST. However, this effect was mainly driven by the group differences in post-stress state rumination and FC increases, since the effect was no longer present when correlations were computed for both groups separately. No correlations between FC measures and state rumination were found at pre-TSST.

8.5 Discussion

The aim of this study was to investigate differences in FC between high and low ruminators in the CCN and DAN before and after stress-induced rumination.

From our previous investigations, we expected that the high ruminators would show a pattern of elevated FC within the CCN before the stress induction. However, with respect to stress-related FC alterations in this network, we expected high ruminators to be less influenced by the stress induction. It remained an open question if these changes would co-vary with changes in state rumination.

Additionally, to the already reported higher reactivity in state rumination and negative affect, we also found higher levels of qualitative reported ruminative contend during the post-stress resting-state measurement. As indicated by the analysis of sub-dimensions of rumination, this effect was mainly driven by the dwelling on negative consequences and causes of the stress task (e.g. “How did I look like during the testing”, “What did the examiner thought about me and my performance”, “Hopefully I do not meet them (the again”, “In the future I could fail again in similar situations”, “I thought about other situations in which I failed”). Interestingly, only a few participants reported feelings of anger in their self-report forms, while most subjects reported feelings associated with personal failure like shame or guilt. Regarding the exact nature of the post-stress rumination, this result suggests that it was particularly induced by self-relevant cognitive processes (e.g. regarding the own performance) and related feelings (e.g. shame), which is in line with research that links rumination to such social emotions (Joireman, 2004; Kim, Thibodeau, & Jorgensen, 2011; Orth, Berking, & Burkhardt, 2006). Although others reported links between rumination and anger(McCullough, Bono, & Root, 2007), we only found few reported aggressions following the TSST. This might be due to the TSST per se, in which the committee stays non-responsive and neutral, which in turn might foster self-related attributions, rather than situational attributions. Further, it might be a result of timing, since the self-report forms were filled out a few minutes after the TSST. In the emotional aftermath of the experiment, anger about the examiners might have occurred after subjects left the institute.

As reported in our previous article, we did not observe differences between the groups in heart rate or cortisol, which is in line with the work of Ali et al. (2017), showing a dissociation of the emotional and affective experience of stress in a

study with dexamethasone suppression(Ali, Nitschke, Cooperman, & Pruessner, 2017).

In line with the analysis of cortical activation in this sample while performing the TSST, time by group interactions of the FC measures were found in relevant prefrontal areas for cognitive and attentional control. Our data suggests that the right dlPFC plays a particularly important role in the networks affected by rumination since the region showed aberrant within- and between-region FC in short- and long-range connections with the bilateral inferior prefrontal gyri. However, all of the results showed disordinal interactions of the time-related changes in FC, indicating higher FC in the high ruminators before the TSST and a reduced increase in functional integration through the stress induction. Out of these FC measures, only reactivity scores showed significant negative correlations with state rumination measures after the TSST.

Interestingly, the increase in FC through the TSST in the low ruminators fits well with the current opinion, that the CCN is especially active in the aftermath but not acute phase) of stress (Hermans, Henckens, Joëls, & Fernández, 2014) and might reflect effective coping. Indeed, Quaedflieg et al. (2015) found higher FC between the left dlPFC and the amygdala in the recovery phase of a stress induction in cortisol non-responders. Additionally, within this study FC between the amygdala and left dlPFC immediately after stress was negatively associated with subjective stress ratings (Quaedflieg et al., 2015).

With respect to the high ruminators, the present findings confirm previous reports of higher FC in the CCN in high ruminators and depressed subjects in non-influenced settings (Peters et al., 2016; Rosenbaum et al., 2016b; Sheline, Price, Yan, & Mintun, 2010b). However, with respect to the attenuated increase in FC in high ruminators the results also question in how far these differences reflect state ruminative processes: While state rumination increased in both groups, but more strongly in the high ruminators, increases in FC were only found in the low ruminators. From the data at hand, it is much more likely that the reduced increases in FC in the high ruminators might reflect a reduced ability to adapt to the stress situation which leads to higher negative affect and

higher state rumination following the TSST, as reflected by a negative correlation of FC reactivity and post-TSST state rumination and affect. Indeed, others reported increased effective connectivity within CCN regions like the DLPFC and inferior parietal lobule, in subjects during forgiveness to imagined social scenarios(Ricciardi et al., 2013). Nonetheless, with respect to our data this reduced capability of adaption might indeed be influenced by rumination. For example, the higher FC in the high ruminators during the first resting-state measurement might be a result of long-lasting allostatic changes due to high rumination and higher chronic stress levels. These elevated levels of baseline FC might result in a ceiling effect, that prevents further increases in FC in the high ruminators. Indeed, in a current study McGirr et al. (2017) found elevated global levels of glutamateric FC within a mouse model of depression after exposure to chronic stress. Additionally these effects were reversed by a treatment with ketamine (McGirr, LeDue, Chan, Xie, & Murphy, 2017).

Further, the main regions that deviated between high and low ruminators – dlPFC and IFG – have previously been shown to be relevant for successful inhibition, attentional control and emotion regulation (Fassbender et al., 2004), which may lead to the observed pattern of higher negative affect in this subject group following the stress induction.

Interestingly, the results of the FC analysis and previous amplitude analysis of this sample (Rosenbaum, Thomas, et al., submitteda) complement each other. In the same sample, we found reduced cortical activation of high ruminators in response to the TSST challenge in the right IFG and right dlPFC. The same regions showed attenuated increases in FC in the high ruminators following the stress induction, which leads to the conclusion that the prefrontal parts of the CCN show reduced cortical reactivity and task-related network integration in high ruminators. On the other hand, low ruminators were not only able to activate frontal cortical areas more strongly during stress, but also showed higher network integration at resting-state following the stress induction. It will be an endeavor of future research to build models that integrate those different measures of cortical functioning.

Some limitations with respect to the article at hand have to be considered. Firstly, we used fNIRS to assess FC. While the method allows to measure cortical hemodynamics in rather natural settings, its resolution in space is restricted to a rather wide area (3 cm) and only cortical parts of the brain can be assessed. Further, due to a limited number of optodes, only parts of the cortex are measured. It is clearly possible that other areas of the cortex – such as the medial prefrontal cortex – may have shown an increase in FC in the high ruminators that could not be measured with the reported measurement setting. Further, with respect to the research design, we were interested in differences between high and low ruminators. For economic reasons, we did not use active control groups that were not stressed. However, from previous data, we would not expect changes in FC between different resting-state measures in such a non-interventional control group(Birn et al., 2013; Grigg & Grady, 2010; Mueller et al., 2015). With respect to the chosen indirect induction of ruminative processes, it has to be mentioned that the stress induction may have also induced stress specific changes in FC that are not related to rumination. Therefore, our FC results may be an entanglement of stress-specific and ruminative processes. On the other hand, the stress induction reliably induced state rumination in both groups and may be an ecologically more valid method for rumination induction than biographical induction methods (e.g. remembering a situation in which a subject ruminated the last time), since rumination usually occurs spontaneously and involuntary following certain internal and external triggers. Also, the used paradigm left the participants blind for the investigated process, which might prevent social desirability biases.

In conclusion, we found higher baseline FC and reduced stress-induced FC reactivity within high ruminators. The FC reactivity was negatively associated with post-stress rumination. To the knowledge of the authors, this is the first study investigating the relationship of FC changes through social stress in high and low ruminators. The stress induction was reliably associated with different measurements of state rumination. The paradigm might be a promising tool to assess FC-related changes in clinical populations that are known to show stress-sensitive effects. In future studies, the passive assessment of state

rumination over multiple FC measurements might give additional information about rumination-specific FC changes.

9. General Discussion

The aim of this dissertation was to investigate in how far differences in functional brain activation and FC between depressed and non-depressed subjects are related to the cognitive process of rumination. To this end, four studies were conducted in which different experimental designs were used to answer eight related research questions. In the following, the presented studies shall be discussed with respect to the research questions formulated in the introduction, before the found effects and gathered evidence will be discussed.

- *Research question 1: Can state-dependent FC be measured with fNIRS within the CCN?*

We already know from the first studies on FC from Biswal that FC of a certain brain region has specific features, such as elevated FC to neighboring brain regions and homologous regions of the contralateral hemisphere (B. B. Biswal, 2012b; B. Biswal, Yetkin, Haughton, & Hyde, 1995b). In addition, it is known that FC within certain networks (e.g. the CCN) is higher than FC between networks (e.g. CCN and DMN), which reflects local integration and global segregation of information processing (Rubinov & Sporns, 2010c). Furthermore, we assumed that tasks including the CCN would lead to higher FC within this network due to an increased functional integration of brain areas necessary for completing the task (Cole, Bassett, Power, Braver, & Petersen, 2014; Cole et al., 2014; Douw, Wakeman, Tanaka, Liu, & Stufflebeam, 2016; Mueller et al., 2013).

As expected, with cortical fNIRS measures of the CCN, we observed a similar pattern as described by Biswal and others: FC of a given channel showed highest FC to neighboring channels and to the hemispheric contralateral channels of the same region. It should also be noted that this central characteristic of FC was observed with the other probesets used in study 2 and study 3/4. Further, we observed – in the non-depressed group – the expected reactivity within the CCN in the challenging task conditions with a steady increase of FC within the CCN from simple to moderate and difficult task

conditions (TMT C < TMT A < TMTB). Based on this evidence, we concluded that fNIRS is suited to measure FC within the CCN.

- *Research question 2: Do depressed subjects show differences in basal FC and FC reactivity within the CCN?*

From studies of cortical activation it is well known that depressed subjects show hypoactivity within frontal regions especially during the performance of cognitive tasks (Huijun Zhang et al., 2014). However, with respect to FC, the focus of research so far has been related to the DMN, and many fMRI studies did not find effects within the CCN with regards to FC. One possible reason why such effects are not found could lie within the small sample sizes, that are usually applied within fMRI research. This is supported by a recent study with more than 1000 participants, where several cortical regions of aberrant FC within depressed subjects could be observed (Drysdale et al., 2017).

As expected from studies of brain activation, we also observed a deviating pattern of FC in subjects with LLD. This pattern reflected a double dissociation with elevated FC within the CCN at baseline levels and reduced FC during task conditions in the depressed subjects as compared to healthy controls. As we did not assess potential psychological covariates, many possible explanations for the resulting effects could be provided. From our perspective, the most likely explanations were that either some pathological process in the depressed subjects would influence CCN activity such as rumination, or that the elevated FC at baseline would reflect some kind of compensation. In a response to this open question, we developed a resting-state questionnaire to measure potential psychological constructs that could be related to the FC differences between depressed and non-depressed subjects in subsequent studies.

- *Research question 3: Do depressed subjects show differences in FC within the parietal cortex?*

The first possibility to test the applicability of these resting-state questionnaires was to implement them in an ongoing study in depressed individuals, the Wiki-D study. Within this study, a parietal probeset was used, covering a large part of

the somatosensory association cortex, including areas that are thought to be part of the DMN, DAN and CCN. Since we used a different probeset in this study – due to other primary research questions – we were not sure if the resulting fronto-parietal differences between depressed and non-depressed subjects would be present in this probeset, as well. As already outlined above, at the time, most fMRI studies had not found cortical differences.

To our surprise, the effects of resting-state FC were in the opposite direction within this parietal probeset: Depressed subjects showed a widespread bilaterally decoupled network during resting-state in parts of the DMN and the DAN, an effect that was replicated a year later in a large sample fMRI study (Drysdale et al., 2017). Moreover, most interestingly, the resulting differences were in part explainable by measured psychological covariates of the resting-state measurement (see also below).

- *Research question 4: Do trait and state measures of rumination explain differences in FC between depressed and non-depressed subjects?*

From the results of our first study, we assumed that the differences between depressed and non-depressed subjects in rsFC would be to some extent due to psychopathological processes such as rumination. As we measured rumination as a state and trait measure, it was an open question to us if these measures would have a different predictive value.

As reported in study 2, we indeed found correlations within and outside the depression-related network differences for state and trait rumination. Especially, the effects of trait rumination were so strong that including this covariate extinguished any further significant difference between depressed and non-depressed subjects. However, the effects of state rumination seemed to be more focused and smaller in spatial extent, which could be due to a narrower definition of this scale in comparison to the RRS.

So far, we expected that rumination indeed could be responsible for the differences in FC between depressed and non-depressed subjects. However, since we did not investigate within-subject differences in FC and rumination –

which would be necessary to assume a causal relationship – we could not be sure, if this conclusion was valid.

- *Research question 5: Can state rumination be induced via social stress and do the hemodynamic changes within the CCN vary as a function of trait rumination?*

To investigate this question, we conducted a final study, in which we analyzed in how far functional brain activity, coupling and measures of rumination, would vary as a function of social stress in a non-clinical sample of high and low trait ruminators. As assumed from prior studies (Gianferante et al., 2014; Hilt et al., 2015; Shull et al., 2016; Young & Nolen-Hoeksema, 2001), we found increases in state rumination through the TSST. Also, this induced effect was higher in the high trait ruminators than in the low trait ruminators. However, it has to be emphasized that the between-group differences in state rumination measures were higher than the within-subject increases, which was indicated by already higher state rumination in the trait ruminators at baseline. Also hemodynamic reactivity through the TSST was moderated by trait rumination in the right IFG, an area that has previously been described as important for cognitive control during stress situations (Kogler et al., 2015).

- *Research question 6: Can state rumination be predicted by cortical reactivity in the CCN due to social stress?*

With respect to our sixth research hypothesis, we found a mediation effect of the group differences on post-stress state rumination by the cortical reactivity during the TSST. However, no correlation between differences in state rumination and differences in cortical activation were observed. Partly, this effect could be due to the small reliability of difference scores *per se*, which will be outlined in the following chapters.

- *Research question 7: Does FC within the CCN vary as a function of social stress and does trait rumination moderate this effect?*

As for cortical activation, we also confirmed our seventh research question, since we found elevated FC baseline levels and reduced FC reactivity in the

high ruminators. Although we used a non-clinical population, the effects found in Study 1 were replicated within the sample of high ruminators, with respect to the observed baseline differences. However, while the low trait ruminators showed a significant increase in FC in the CCN following the stress induction, the high trait ruminators did not, which challenges to some extent the assumption that within-subject variations of FC would covary with within-subject changes in state rumination.

- *Research question 8: Do changes in FC within the CCN predict changes in state rumination?*

The above doubt was further supported, since our final research question did not hold true. While FC correlated with state rumination after the TSST, these effects were only due to the group differences. This effect and the lack of correlations between change scores made it difficult to argue that the aberrant FC in depressed subjects would be a direct effect of state rumination. However, based on the effects of trait rumination it is important to bear in mind that indirect effects of trait rumination on rsFC can't be ruled out.

9.1 Summary and Conclusions

The aim of this dissertation was to shed light on the differences in FC and brain activation in MDD and possible relations to the cognitive process of rumination. Consistently, we found elevated levels of rsFC in depressed subjects (study 1) and high ruminators (study 4) in the CCN. Also consistently, in comparison to healthy controls and low ruminators, depressed subjects (study 1) and high ruminators (study 4) showed reduced neuronal coupling of the CCN during cognitively demanding states, in terms of FC increases during the TMT and TSST. While all of these results are based on between-subject associations, we did not find significant relationships on a within-subject level, e.g. between changes in FC-change scores and state rumination change scores (study 4). With respect to the DMN and DAN, negative associations between state and trait rumination within the DMN and DAN were found.

Interestingly, our findings showed a network-specific distinction between high and low ruminators, with elevated FC within the CCN and reduced FC within the DAN during resting-state. This data is in line with a resent investigation about rsFC biotypes of depression (Drysdale et al., 2017). The authors identified four different biotypes of depression with different rsFC abnormalities within a total sample of N = 1188 subjects. These biotypes were mainly different with regards to their limbic and fronto-striatal FC patterns and showed different behavioral symptoms of depression. Interestingly, while biotypes 1 and 2 showed mainly hypoconnectivity within nodes of the orbitofrontal cortex, dorsomedial prefrontal cortex and limbic areas, biotypes 3 and 4 showed hyperconnectivity in parts of the dlPFC, ventrolateral PFC and subcortical areas, and hypoconnectivity within somatosensory areas. Both effects were found in the studies of this dissertation (study 1, 2 and 4). Both biotypes 3 and 4 were characterized by higher anhedonia, insomnia, felt guilt and anxiety, while biotypes 1 and 2 had higher inertia /fatigue (Drysdale et al., 2017). Interestingly, in a sample of patients with general anxiety disorder – with the cardinal symptom of worry which is comparable to rumination – 59% of the patients were assigned to biotype 4. Also, the GAD sample showed heightened FC within prefrontal areas and within subcortical areas. Importantly, the biotypes differed with respect to their treatment response to rTMS of the dorsomedial PFC, with higher response rates in biotypes 1 and 3 (82% and 61%) when compared to biotypes 2 and 4 (25% and 29%) (Drysdale et al., 2017).

With respect to brain activity, in line with the existing research literature, we found global, reduced activity of the PFC in depressed subjects (study 1, supplementary material) and reduced activity within the right IFG in high ruminators during stress inductive conditions (study 3). Furthermore, lack of IFG activity during task performance mediated group differences in negative affect and state rumination at later stages (study 4).

While we first assumed that heightened FC in the CCN in depressed subject might reflect rumination – a process that is very common in depressed subjects – the lack of within-subject correlations of both variables somehow questioned a direct relationship between FC within the CCN and state rumination. If there

was such a direct relationship, the induction of rumination through social stress should lead to an increase in FC, especially in the high ruminators. Such an association was not found. Especially, since (behaviorally measured) state rumination increases were higher in the high trait ruminators, ceiling effects are rather unlikely. Although it might be possible that the effect of higher state rumination at baseline in the high trait ruminators resulted in ceiling effects of elevated FC on a neurophysiological level. Unfortunately, trait rumination can't be easily (and ethically) induced in an experimental design, which makes it impossible to assume causal effects for this factor. However, since high state- and trait rumination were associated with FC on a between-subject level, there might be an indirect effect, in which rumination might lead to the resulting differences in FC via proxy variables. In the final chapter of this dissertation, a potential framework of the resulting effects that incorporated the concept of rumination into the existing literature on the diathesis-stress-model of depression shall be given.

9.2 Aberrant functional connectivity in depression as a potential result of allostatic load

The central idea of the presented explanation for the research results in this dissertation is that if changes in state rumination are not directly associated with changes in FC, they might be instead associated indirect. Such an association could be in the reverse direction that elevated FC within the CCN is instead a neurobiological risk factor – primarily related to other psychological proxy variables – that leads to higher rumination, or that rumination is (causally) associated with another factor that leads to the changes in FC. However, both hypotheses do not exclude each other. Such an indirect effect between rumination and FC could be mediated by stress and related changes in brain functioning. For example, stress itself could lead to changes in FC that are accompanied by a higher risk for ruminative response styles.

In the following, I will outline an integrative bio-psycho-social model that implements the current literature on stress-related changes in FC into the perseverative cognition hypothesis. Grounded on the current data, I will argue

that chronic stressful experiences lead to allostatic changes in brain structure and functioning which is in line with the stress model of depression (Colodro-Conde et al., 2017; Rudolph et al., 2000b; Willner, 1997). Also, I assume that rumination increases the risk to experience such chronic stressful states and that, on the other side, rumination may be a result of weakened frontopolar functioning.

In the introduction of this work, I outlined that risk factors for depression can be found as early as life begins – with the development of the genetic code, i.e. with the fusion of egg and sperm cells – and that life stressors early in life and adolescence play a special role in the formation of depression. Indeed, it has been shown that prenatal, postnatal and adolescent chronic stress alters the stress-response itself by allostatic changes and increased the risk for developing depressive and anxiety disorders as well as learning impairments (Lupien et al., 2009). On a biological level, chronic exposure to stress leads to increases in amygdala volume and neurotoxic effects in the hippocampus and prefrontal cortex (Joëls, Sarabdjitsingh, & Karst, 2012). It is thought that stress has differential effects on development, depending on the developmental window in which the influences took place; e.g. by influencing the brain development in prenatal stages (programming effects), in childhood (differentiation effects) or adolescence (potentiation or incubation effect): The earlier the influence in life, the stronger the impact. Most importantly, Lupien et al. (2009) argue that the time-window might influence the kind of vulnerability for a certain disorder, e.g. that the development of depression is especially increased, if chronic stressors appear during adolescence when the prefrontal cortex develops (see Figure 26).

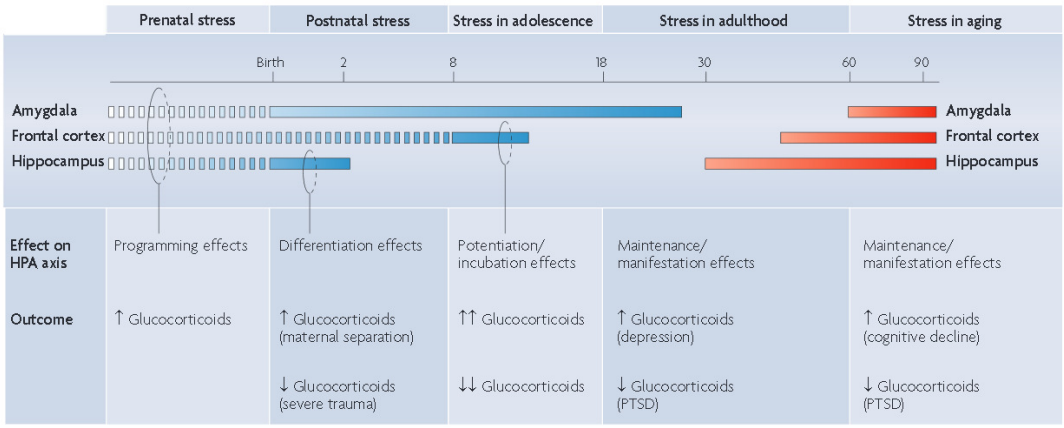

Figure 26. Taken and adapted from (Lupien et al., 2009). Potential effects of stress on the development and allostatic adaption of the stress system during different developmental "windows". Blue bars indicate time windows of growth within a certain area, red bars indicate decline.

Stress itself has time and spatial-dependent effects on the brain (Joëls et al., 2012). During the acute stress response, several monoamines (e.g., noradrenaline, dopamine and serotonin), neuropeptides (e.g., CRH) and steroids (e.g., cortisol) are active, which all influence brain activity through specific receptors, that are spatially differentially distributed within the brain, and have different affinity. Furthermore, at different timescales, the stress response influences synaptic activity itself by changing the excitability through the activation of transcription factors or on a long-ranging time scale through genomic and structural effects (Joëls & Baram, 2009). Within the depression framework, such effects could lead to the measured brain structural (Drevets et al., 2008) and endocrinological differences (Ottaviani et al., 2016b).

With respect to network activity, it is thought that the CCN is relatively deactivated during the acute stress phase, while the salience network is active (Hermans et al., 2014) due to the evolutionary adaptive effect of rapid threat processing. However, Hermans and colleagues assume that the CCN becomes more active in the stress-recovery phase to actively cope with post-stress phenomena (see Figure 27). Indeed, the authors found that noradrenergic activation during stress increased the connectivity between frontoinsular, dorsal ACC and subcortical areas (Hermans et al., 2011). Fittingly, Quaedflieg et al. (2015) reported increased FC between the left dlPFC and the amygdala in the

recovery phase of a stress induction in cortisol non-responders and negative correlations of this FC connection with subjective stress ratings (Quaedflieg et al., 2015).

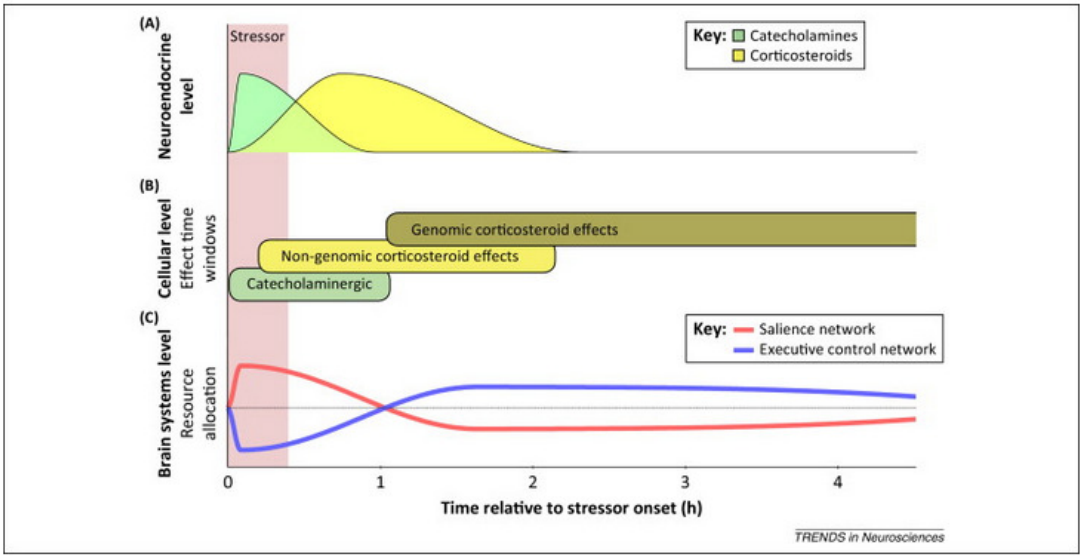

Figure 27. Taken and adapted from (Hermans et al., 2014). A) Time course of different stress hormones after the exposure to a stressor. B) Different stress-affected "levels". C) Time course of stress-affected neuronal systems.

In line with our own results for baseline rsFC deviances in depressed and high-ruminating subjects (study 1 and 2), other authors reported similar effects for the acute stress response; e.g. Maron-Katz and colleagues found reduced parieto-temporal and increased fronto-thalamic FC in response to stress (Maron-Katz, Vaisvaser, Lin, Hendler, & Shamir, 2016b) and Clemens et al. found elevated FC between the SN, IFG and DMN following a cyberball paradigm (Clemens et al., 2017). With respect to the TSST, elevated FC between the amygdala and cortical midline structures was found up to one hour following the completion of the paradigm (Veer et al., 2011). If depression is characterized by a higher sensitivity to stressful experiences and rumination is associated with prolonged stress responses, it may be possible that comparable effects can be observed in such populations. Therefore, one could assume that in some depressed subjects and especially in those with high ruminative tendencies, higher stress levels would lead to comparable effects in the FC of cortical areas.

This idea is further supported by animal models of depression, where symptoms can be directly experimentally induced. In a recent study on transgenetic mice, McGirr et al. shed light on the effects of chronic stress on glutamatergic FC as measured with optogenetic methods (McGirr et al., 2017). In their study, transgenetic mice were exposed to chronic social defeat and showed in the following depressive symptoms as indicated by reduced active swimming in the forced swim test, less social interaction and higher immobility in the trail suspension test. Most importantly, FC as measured by optical imaging showed higher global glutamatergic FC in the mice after chronic stress. A similar pattern was observed in low ruminators after social stress in our study (study 4). While the treatment with ketamine – an anesthetic drug with anti-depressive effects – first show highly increases in FC, these effects were reversed 24 hours following the injection (McGirr et al., 2017). Interestingly, similar effects of ketamine on FC were found in primates, including areas of the cognitive control network like the dlPFC (Gopinath, Maltbie, Urushino, Kempf, & Howell, 2016), and in the DMN and affective network in humans (Scheidegger et al., 2012). With respect to ketamine response, a recent study by Abdallah and colleagues found, that depressed subjects, that responded to an ketamine treatment, showed elevated FC of the lateral PFC with regions lying outside the PFC and reduced FC within the PFC and subcortical regions (Abdallah et al., 2017).

The neurotransmitter of glutamate – which is affected by ketamine – seems to play a central role in the adverse effects of chronic stress, since it is rapidly released during stress, and high concentrations of extracellular glutamate cause neuronal death, degeneration of neurons and excitotoxicity (Musazzi, Racagni, & Popoli, 2011). Importantly, this effect is blocked by antidepressants, which might give a hint for a therapeutic pathway of action (Musazzi et al., 2010). Another hint for the relevance of glutamate comes from the finding that glia cell concentrations are reduced in subjects with mood disorders, since glia cells are relevant for the reuptake of glutamate from the synaptic cleft (Sanacora, Treccani, & Popoli, 2012). Moreover, chronic stress in mice has been shown to reduce cytogenesis of glia in the medial PFC (Czéh et al., 2007). Further, glutamate concentrations in the medial prefrontal cortex as assessed with

magnetic resonance spectroscopy (MRS) have been shown to be positively correlated with FC between the mPFC and subcortical areas like the thalamus (Duncan et al., 2013). Also, positive associations between local glutamate concentrations and FC between the anterior insula (AI) and supramarginal gyrus (Demenescu et al., 2017) and anterior insula and mPFC (As-Sanie et al., 2016) have been reported. In the study of As-Sanie et al. (2016), FC between mPFC and AI further showed positive correlations with clinical anxiety and depression. Interestingly, anodal transcranial direct current stimulation (tDCS) over the right parietal cortex led to elevations in local glutamate concentrations and increases in FC in the sensorimotor network and bilateral inferior parietal network, while ACC FC decreased (Hunter et al., 2015). Also, the BOLD response during a task requiring cognitive control was found to be dependent on resting-state glutamate levels in the dorsal ACC, with high BOLD responses in individuals with low glutamate levels in challenging task conditions and an opposite relationship in subjects with high glutamate levels (Falkenberg, Westerhausen, Specht, & Hugdahl, 2012).

Based on the present data, one could argue that as for changes in brain structure and functioning, chronic stress might also lead to allostatic changes in FC. As high levels of chronic stress are associated with changes in glutamatergic brain-chemistry and associated elevated FC, high-ruminating depressed subjects should show such effects also. Stress occurs any time in life, but may have stronger effects in early life when the brain develops and psychological schemata evolve. From animal studies, it can be extrapolated that chronic stress during childhood leads to stable allostatic changes, while the effects of chronic stress during adulthood seem to be more easily reversed (Lupien et al., 2009). This effect is further supported by cognitive developmental theories stating that cognitive schemata can easily be influenced during childhood and adolescence. Once such a schema exists, it influences the interpretation of following situations. After the development of personality traits during adolescence, our cognitive system becomes more stable and may be less easily influenced. Also, on a biological level, chronic stress will lead to changes in neuroendocrinological functioning, brain volume, activation and

coupling. Due to these psychological and physiological effects that might also have adaptive functions (Andrews & Thomson, 2009), the odds are raised that the individual will react in future stress situations in certain ways, e.g. by using rumination due to reduced resources for adaptive coping or maladaptive meta-beliefs. In this way, chronic stress might influence the occurrence of rumination. Moreover, the state of chronic stress will make memories more accessible from alike situations, when comparable stress levels and emotions were present, which would result in intrusive thoughts (ruminations *sensu lato*) comparable to those in post-traumatic stress disorder. Also, on a behavioral level, perservative cognition such as rumination and worry itself might be seen as adaptive responses to stress as they sought to solve the problem at hand or prevent future problems (Ed Watkins & Baracaia, 2001b). However, since the resources of depressed subjects are often not sufficient for solving the problem at hand, rumination leads to a prolonged stress reaction by holding the cognitive representation of the problem present; which is called the perseverative cognition hypothesis (Brosschot et al., 2006). Such prolonged representations lead to hyperactive states of elevated anxiety and cognitive biases in which overgeneralization takes place and the subject becomes anhedonic through dwelling over problems. In this way, rumination further influences the stress response. Here, an interesting parallel can be seen to the above mentioned biotype 3 and 4 of the Drysdale study, that showed elevated frontostriatal FC (Drysdale et al., 2017). Such chronic stressful situations will lead – as projected by the mouse model – to higher global FC (McGirr et al., 2017), prolonged reactions of the CCN (Hermans et al., 2014) and to genomic changes in neurons. Due to the neurotoxic effects of chronic stress, high ruminators will show less activity within the prefrontal cortex during cognitive tasks due to reduced neuronal resources (study 1 and study 3), which further increases the odds for following ruminative responses. With respect to the transactional stress model, rumination may influence the stress response at four different pathways. Firstly, subjects that ruminate may be biased in their primary perception of stressors and due to their personal characteristics might be more exposed to situations that are stressful through selection processes. Further, due to

pessimism, they will be more likely to appraise situations as personally dangerous (second way) and themselves as less able to cope (third way). Due to their habit to ruminate, the odds for adaptive coping and reappraisal will be reduced and the stressful situation will continue (fourth way).

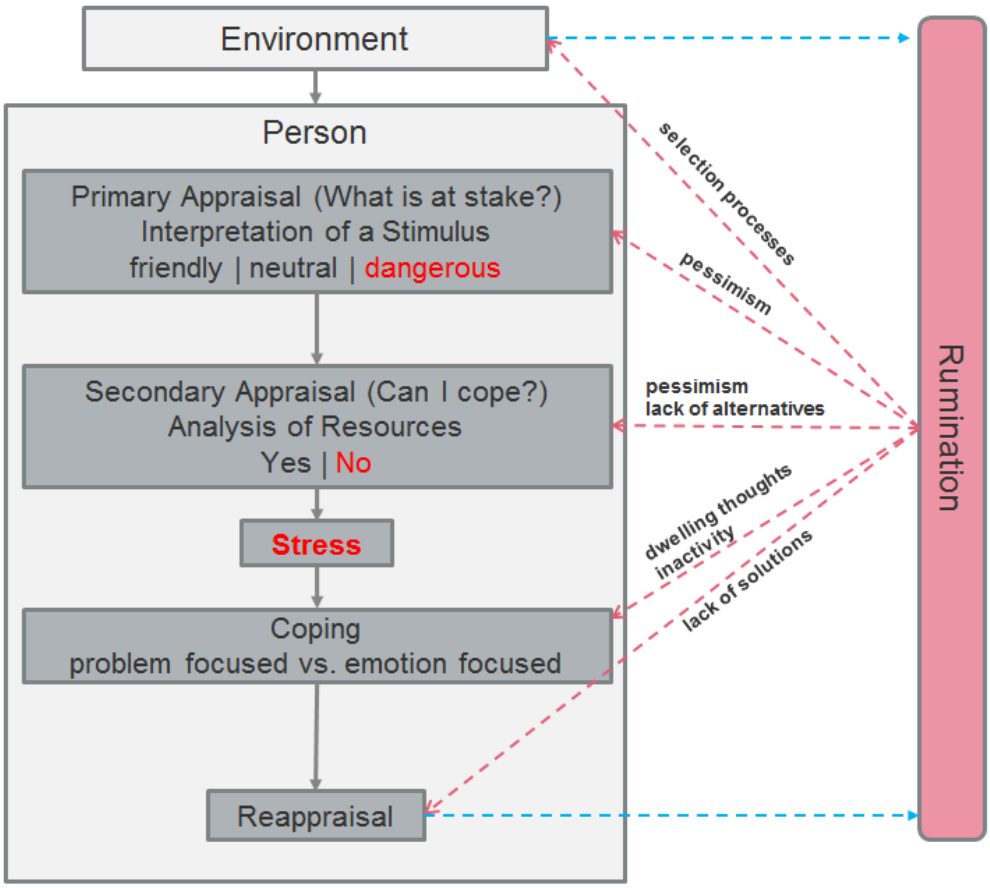

Figure 28. Different ways in which rumination may influence stress in the transactional stress model (grey panel on the left). Red arrows indicate influences of rumination on the environment and the stress response, blue arrows indicate feedback loops: Environmental factors might contribute to the development of a ruminative response style in the first place and negative reappraisals might enforce rumination in negative feedback-loops.

9.3 Specificity: Other mental diseases with alike pathologies and aberrant brain functioning

Although the above outlined theoretic pathway seems to be rather specific, deviations in FC within the PFC are not only common in depressive rumination but also in other mental disorders with related psychopathologies. In fact, depressive rumination as a perseverative cognition has similarities with various other related processes. The largest overlaps might exist with the concept of

worry, since worry also occurs in the absence of specific triggers and is persistent. The only true difference lies in the time focus: While worry is mostly about events that might happen in the future, rumination is – as defined by some authors – mostly focused on past events and personal shortcomings. Therefore, the evolutionary benefit is much clearer for worry than for rumination. While worry might actually lead to the prevention of future mistakes, such a benefit is not clear for rumination, especially since rumination in most cases does not lead to solutions. However, one might argue that rumination also shows in some way such benefits. As I argued before, chronic stress might increase the odds for memory accessibility of past events with alike emotional and physiological states. While in some cases, intrusive thoughts might mark the beginning of rumination, the primary process might indeed be adaptive (Andrews & Thomson, 2009). For instances in cases with effective coping in the past, such intrusions might actually lead to a plausible coping strategy in the present state. Unfortunately, in depressed subjects, past life-events are usually characterized by long periods of social or personal defeat without adaptive coping. In terms of intrusive occurrence of thoughts, rumination shares a common feature with intrusive thoughts in post-traumatic stress disorder (PTSD). Both ruminations in depression and intrusive memories in PTSD are accompanied by anxious feelings, re-actualization of past events and tendencies of suppression and avoidance (E Watkins, 2004; Ed Watkins & Baracaia, 2001b). On the other hand, both constructs can be distinguished as PTSD is mostly restricted to certain (traumatic) experiences that can be triggered by more or less specific stimuli. Rumination, on the other hand, is triggered by – if any – various stimuli. Also in the anxiety spectrum, ruminative thinking is comparable to characteristics of obsessive compulsive disorder (OCD) like obsessive thoughts and obsessive rumination in OCD, in terms of limited controllability and persistence of the thought content. However, in OCD most direct and indirect behaviors (such as thoughts) are related to an avoidance motivation to cope with anxious affect, while rumination is often times accompanied by sadness, shame and guilt.

As the constructs between rumination, worry, intrusive thoughts and obsessive thought overlap, similar abnormalities in FC as found in the present work have been reported for these mental disorders. For OCD, elevated levels of FC have been found within the CCN, between CCN and DMN nodes and between the CCN and the somatosensory/motor network (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), and within the fronto-striatal network (Harrison et al., 2009; J.-M. Hou et al., 2014; Jang et al., 2010; Sakai et al., 2011). Also in PTSD, social anxiety and specific phobia, enhanced FC between the insula and amygdala were observed, an effect that might be due to classical fear conditioning (Etkin & Wager, 2007; Lanius et al., 2005; Rabinak et al., 2011; Sripada et al., 2012). For GAD patients, elevated levels of global FC within areas of the CCN and between prefrontal and subcortical areas have been observed (Drysdale et al., 2017; Makovac et al., 2016; Mohlman, Eldreth, Price, Staples, & Hanson, 2017). Aside from anxiety disorders, for patients with *anorexia nervosa* elevated FC was found within and between the CCN and DMN (Boehm et al., 2014; Cowdrey, Filippini, Park, Smith, & McCabe, 2014) and for alcohol dependence within the left CCN (X. Zhu, Cortes, Mathur, Tomasi, & Momenan, 2017).

While it is not the attempt to argue at this point that these mental disorders are equal to each other in a sense of exchangeability, they might share a great deal in variance and psychopathology, which would result in similar neuronal correlates. Especially the similarities between GAD and MDD are so strong, that the differential diagnosis is difficult. Also, both disorders have a high comorbidity, and depressive symptomatology can be found in nearly every mental disorder. At this point, the question arises what the common factors between these disorders could be. For instance, it may be possible, that early adverse life experiences and chronic stressors that occur in anxiety disorders as well as in mood disorders, lead to brain changes that are alike between the diagnostic entities. Patients with different disorders are alike in some personal characteristics such as neuroticism, which reflects common deficits in emotion regulation, inhibition and/or cognitive control. Also avoidance and an urge for controllability can be observed in many patients that are not restricted to a certain diagnostic category. As shown previously, the areas of the CCN cover

language related areas that are also responsible for inner speech, and these constructs are related to mindwandering (Bastian et al., 2017), cognitive control (Cragg & Nation, 2010), impulsivity (Tullett & Inzlicht, 2010), task-switching (Emerson & Miyake, 2003) and planning (Lidstone, Meins, & Fernyhough, 2010). In the same way, the suppression of unwanted thoughts is associated with activity within the CCN (Anderson et al., 2004). All of these constructs may show a common basis in which patients with various mental disorders show variations from healthy controls, which may underlie the presented differences in FC. The framework of the diathesis-stress model that can be applied to all mental disorders may be well suited as a model in which the effects of aberrant FC can be integrated as outlined above for depressive rumination. It remains an open question under which circumstances an individual develops a mental disorder after exposure to stressful events and what factors modulate which disorder is presented in the phenotype, e.g. depression or anxiety. A potential moderator of these factors could lie within the concept of cognitive schemata that may contribute e.g. to anxious (“The world is a dangerous place and you have to be careful not to be harmed”) or depressive styles (“You have to show perfect performance at work, or you will be a no-one and lose your job”). As the study of Drysdale has shown, even within the diagnostic category of depression, several biotypes can be identified with differential diagnostic and prognostic features. It may be an endeavor of future studies to provide dimensional psychopathological categories that match these biotypes.

9.4 Limitations

Aside from the already mentioned limitations in the presented studies, a final consideration has to be taken. In all of the presented studies it is unclear if the resulting effects in FC are due to a compensatory effect or due to a psychopathological deficit of the depressed subjects and high ruminators. For instance while one interpretation of heightened FC at baseline levels in the high ruminators and depressed subjects could be that these subjects show elevated levels of chronic stress, it could also reflect a higher effort of these subjects in participating in the experimental design. Also, it could reflect cognitive control in

exposure to negative affect or higher impulsivity (X. Zhu et al., 2017) (that is larger at baseline levels). In fact, the presence of psychopathology and attempts of coping with consequences of a disorder are so highly entangled, that it is nearly impossible to develop a research design, in which compensatory and psychopathological effects can be separated. Both effects may also be exchangeable since psychopathologies themselves can be seen as compensatory effects of an organism that adapted to some kind of environmental demand. In an analogy, elevated levels of blood pressure and pulse in adiposities reflect both a biological consequence of the disease and an adaption of the cardiac system to changed demands. It is up to future studies and longitudinal research designs to answer the question of compensatory and deficit effects, e.g. by revealing whether changes in FC occur early in the pathogenesis or at later stages.

A further shortcoming of the presented studies lies in the measurement of state rumination with questionnaires. While this strategy seems plausible at first glance, the assessment of questionnaires comes with different disadvantages, such as tendencies to the mean, tendencies to extreme answers and anchoring effects. These effects make the inter-subject comparison of state rumination to some extent unreliable and may explain the relatively low correlation coefficients between these measures and FC (study 2). Also it may explain, why no correlation between state rumination changes and FC changes could be observed, especially since difference scores have a much lower reliability. Until today, there is no clear behavioral index for rumination as it exists for avoidance, for instance. The development of new scales and measurement strategies to assess state rumination, e.g. with momentary assessments, may improve the estimation of individual levels of state rumination. Within these research designs, statistical models exist that can model the co-variation of two variables (like FC and rumination) over time, e.g. through multilevel modeling or structure models. Unfortunately, our applied research design did not allow for these models, since larger sample sizes and higher measurement repetitions are needed.

9.5 Remaining Questions and future perspectives

While some remaining questions and future directions have already been mentioned in the limitations section, the general remaining research questions derived from the results of this work shall be discussed in the following.

As I argued before, the presented effects of the studies may be due to chronic stress and may also explain why comparable results have been found across diagnostic categories. It will be up to future investigations to explore if this suggestion holds true. Further, it will be an interesting question, whether different patient groups (e.g. with PTSD vs. MDD) react differently to exposure with respect to changes in cortical activation and rsFC. In the same way, it will be challenging to identify the psychological and behavioral dimensions that aggregate the similar effects between diagnostic entities. Herein lies a potential for the usage of neurophysiological assessments and the identification of biotypes. While the phenotypical distinction of mental disorders by the ICD and DSM is to some extent arbitrary, a dimensional classification that is guided by psychological (e.g. impulsiveness, affect regulation) and physiological (e.g. reduced fronto-striatal FC, reduced reactivity within the CCN) dimensions may lead to more reliable diagnoses that directly imply treatment strategies.

Further, the translation of the resulting effects into potential neurophysiologically grounded interventions seems to be a further perspective for future research. It has already been shown that stress-related elevated FC between the sgACC and the amygdala can be reduced through psychotherapeutic interventions such as mindfulness meditation (Taren et al., 2015). Also, it has been shown that neurophysiological interventions such as tDCS and rTMS can influence FC (Hunter et al., 2015). The combination of such treatment approaches may further increase their response rates. For instance, it might be possible to assess cortical activity during a mindfulness-based training and to use the additional information to give feedback strategies to patients that struggle with the intervention. In these individuals, a neurofeedback-enforced mindfulness training might lead to a stronger and faster impact on aberrant network coupling.

Research on pathological changes in brain functioning in terms of activation and coupling of brain areas might further lead to a better understanding of the biological underpinnings of mental disorders. Together with the identification of psychological correlates, a finer graded bio-psycho-social model of depression can be developed which could be the basis of a multidisciplinary intervention (psychological, pharmacological and translational interventions). Further, the aggregation of similarities between diagnostic entities might result in a common etiological model of mental diseases that might unify psychotherapeutic schools in the sense of Klaus Grawe's Neuropsychotherapy.

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11. Supplemental Material

Study 1:

Probeset

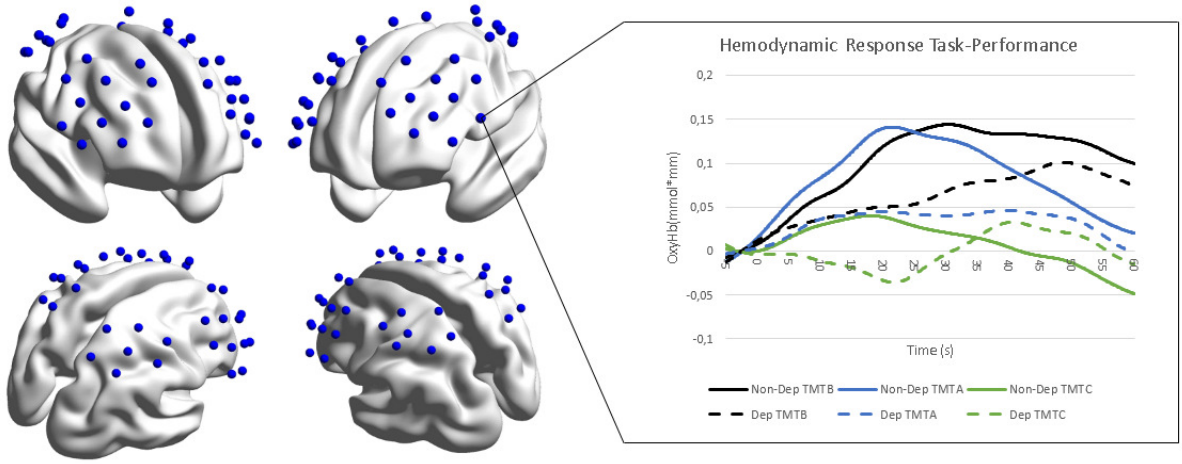

Figure S1. fNIRS probesets used during resting-state and TMT performance. The panel on the right depicts an exemplary hemodynamic response during task performance measured with fNIRS in the broca region (oxygenated hemoglobin; channel #1, averaged for depressed and non-depressed participants). Note that the multivariate analysis of hemodynamic responses revealed a main effect of depression ($F(1,96) = 12.63$, $p > .001$, $\eta^2 = 11.5$), replicating the well known effect of hypofrontality in depression .

Network-based statistics

Network-based statistics (NBS) were developed by Zalesky and colleagues (Zalesky et al., 2010a). NBS is a method to identify large scale connectivity differences between groups or experimental conditions. With NBS it is possible to control for the family wise error rate (FWER) by using clustering methods and permutation tests. During NBS analysis the following steps are performed:

1) To perform NBS analysis, the N x N connectivity matrices were computed as reported in the methods section. Contrary to the analysis of network metrics, there is no need for thresholding/binarizing of the connectivity matrices in NBS analysis.

2) In the next step, a statistical threshold is defined for step 3: massive univariate testing. The statistical threshold is important to define significant suprathreshold connections between groups/conditions that are further analyzed.

3) Massive univariate testing is performed with the significance level defined in step 2. Suprathreshold connections are then clustered. Components are identified by using a breath first search.

4) Afterwards, permutation tests are performed and the size of each extracted component is tested for significance. In our study, we estimated the confidence intervals for each p-value in the manner of Zalesky et al. (Zalesky et al., 2010a) parametrically:

$$2 \times \sqrt{\frac{p(1-p)}{M}}$$ with M=number of permutations

Network metrics

Graph Theory is a mathematical discipline which studies graphs. Graphs are defined as a set of objects (nodes) that have links (edges) between at least some of the objects. In recent years some graph theoretical measures that characterize the organization of the graph have been increasingly used in neuroscience. In functional neuroscience, nodes are mostly given by brain regions – voxels/ROIs in fMRI, electrodes in EEG and channels in fNIRS – and edges are defined by the functional connectivity between these regions.

In our study we used two graph theoretical measures of centrality to identify hub regions in the derived networks: The nodal degree and betweenness centrality. For a more detailed description of these measures and their interpretation see (Rubinov & Sporns, 2010a). The degree (k) is defined as the sum of edges of a node and it is one of the most fundamental elements of most network measures.

$$k_i = \sum_{j \in N} a_{ij}$$

Nodes with a high degree can be seen as hubs in the network, because they have various connections to other nodes in the graph.

Other measures of centrality like the betweenness centrality define hubs by the number of shortest paths that are passing through them. The shortest path between two nodes (i) and (j) is the shortest sequence of the links and nodes between them.

The shortest path length is defined as:

$$d_{ij} = \sum_{auv \in gi \leftrightarrow j} a_{uv}$$

Betweenness centrality on the other hand is defined as:

$$b_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h_{ij} \in N \\ h \neq j, h \neq i, j \neq i}} \frac{p_{hj}(i)}{p_{hj}}$$

with p_{hj} referring to the number of shortest paths between h and j and $p_{hj}(i)$ the number of shortest paths between h and j that pass through i.

Study 2:

Detailed information to the depressed sample

Amongst the most used were Selective Serotonin Reuptake Inhibitors (15% of the sample), Serotonin–Norepinephrine Reuptake Inhibitors (8.3%), Noradrenergic and Specific Serotoneric Antidepressants (5%), Tricyclic Antidepressants (3.4%), Melatonin Agonists (1.7%) and Hypericum perforatum (3.4%). Regarding life-time diagnoses, 8.33% were diagnosed each with PDD and Alcohol Abuse, 6.66% with Panic Disorder, 3.33% each with Social Phobia, Specific Phobia and Bulimia Nervosa and 1.66% had each diagnosis of Obsessive Compulsive Disorder, Posttraumatic Stress Disorder and Anorexia Nervosa.

Additional information on the computation of the state rumination scale

VAS scales for assessing processes during the resting-state comprised the following items:

Mind-wandering:

1) I felt relaxed.
2) I let my mind flow.

Rumination:

3) I ruminated (in the sense of revolving thoughts).
4) I thought about things I have to do/ tried to make plans.
5) I tried to fight certain experiences.
6) I felt stressed.

Focus on sensations:

7) I felt body sensations.
8) I concentrated on things I hear.

Fight against fatigue:

9) I thought about the duration of the measurement.
10) I needed to fight falling asleep.

Additional information on the rating of the self-report form

To validate the used VAS scales and for reasons of additional information on resting-state processes, we also used a qualitative self-report form. On a blank

page subjects were asked to note the experiences they had during the resting-state measurement. The instruction was as follows:

“Please describe in the following what you did during the resting state measurement and how you felt. You may answer the following questions: What did you feel and think during the measurement? How did you react to your thoughts and feelings? What consequences followed your reactions?“

The texts were screened and categorized by two independent raters to assess qualitative measures of processes during resting-state according to qualitative methods: First, self-report forms were analyzed and categories were built and defined until saturation was reached. The following categories were defined:

- Mind-wandering: The subject expressed to be in a relaxed mood and let his mind flow in an unconstrained way without any focus on a particular subject.
  Example: “I relaxed and let my mind flow.”
  Example: “I thought about things that matter to me, but I was not stuck in my thoughts. I liked to let my mind flow.”
- Rumination: The subject expressed a repetitive stressful style of thinking about an unfinished concern that leads to the urge of suppressing the inner experience.
  Examples: “I thought about a stressful meeting I had at work, which made me nervous, so I tried to distract myself from that memory.” “I thought about an argument with my boyfriend and asked myself what I am doing wrong.”
- Focus on body sensations: The subject expressed an attentional focus on their body.
  Examples: “I focused on my breathing.” “I felt my body and my heartbeat.”
- Mindfulness/Relaxation training: The subject expressed to be in a mindful state (detachment from cognition, concentration on breathing with detached mind) or to perform some kind of relaxation technique (e.g. progressive muscle relaxation).

Example: “I focused on my breathing and watched my mind in a detached way.”

- Suppression: The subject expressed withdrawal from or suppression of unpleasant inner experiences.
- Boredom: The subject expressed that the resting-state was boring.
- Unfinished business: The subject expressed thoughts about things they will do.

  Examples: “I thought about what I would eat for dinner and decided to eat pizza.” “I thought about the homework I have to do.”
- Thinking about the measurement: The subject expressed thoughts about the given instructions or how their data might look like.
- Fight against fatigue: The subject expressed feeling sleepy or trying not to fall asleep.
- Thoughts about the duration of the measurement: The subject expressed thoughts about the duration of the measurement or counted the time.

Afterwards, the most common categories were used to categorize self-report forms by two independent psychologists.

Influence of cofounders

Regarding effects of other resting-state process variables, there was no effect for the factors “focus on sensations” and “fighting against fatigue”. One reason for this finding may be that the variance for these scales was smaller, since many participants focused on body sensations and felt sleepy at some point of the resting-state measurement.

In contrast to that, the scale for measuring mind-wandering was positively associated with FC in the DMN, as expected (see supplemental material Figure S2). NBS analysis of the factor revealed a significant ($p=.026\pm0.0045$) network with 28 nodes and 39 edges, reflecting higher FC in participants reporting high mind-wandering (see supplemental material Figure S3 and Table S1).

Medication status had no effect on FC-differences between depressed medicated and depresses non-medicated subjects (p>.1).

FC properties in the probeset

For the whole sample, FC coefficients in the used probeset showed an expected distribution with high connectivity within DMN regions of the middle parietal cortex and the supramarginal gyrus (SupG) and angular gyrus (AngG). These regions showed – as assumed – low to negative FC with the temporal cortex consisting of the superior temporal gyrus, fusiform gyrus and subcentral area (see figure S2). In addition, the self-reported amount of mind-wandering correlated positively with FC measures (see supplemental material Figure S3) and showed significant network differences between subjects reporting high vs. low mind-wandering within the DMN with hub nodes in the middle somatosensory cortex (SAC) and the SupG (see supplemental material: table S1 and Figure S4).

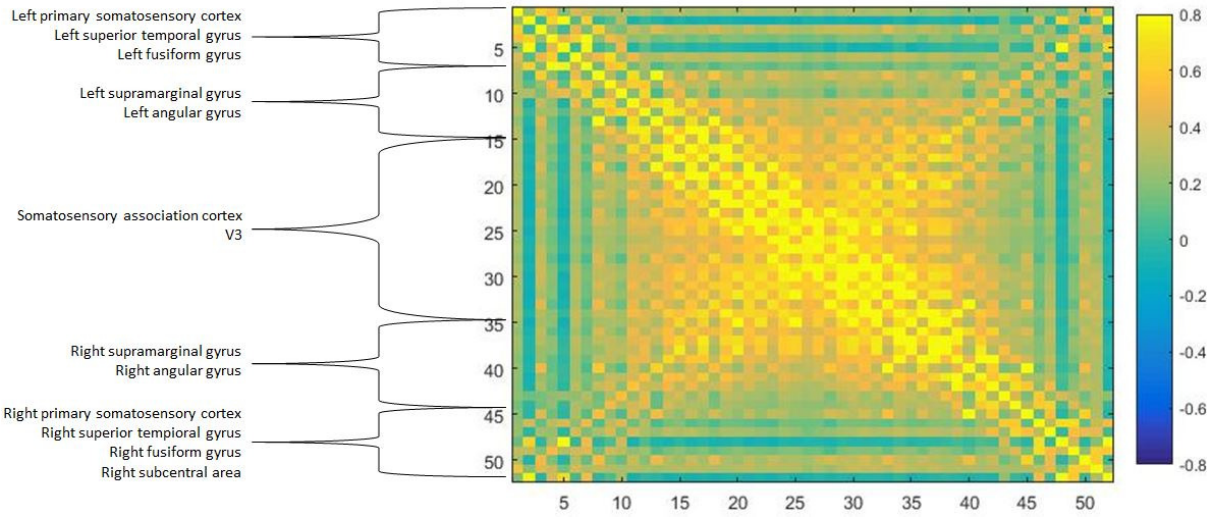

Figure S2. Mean FC of the sample in the different regions of the probeset

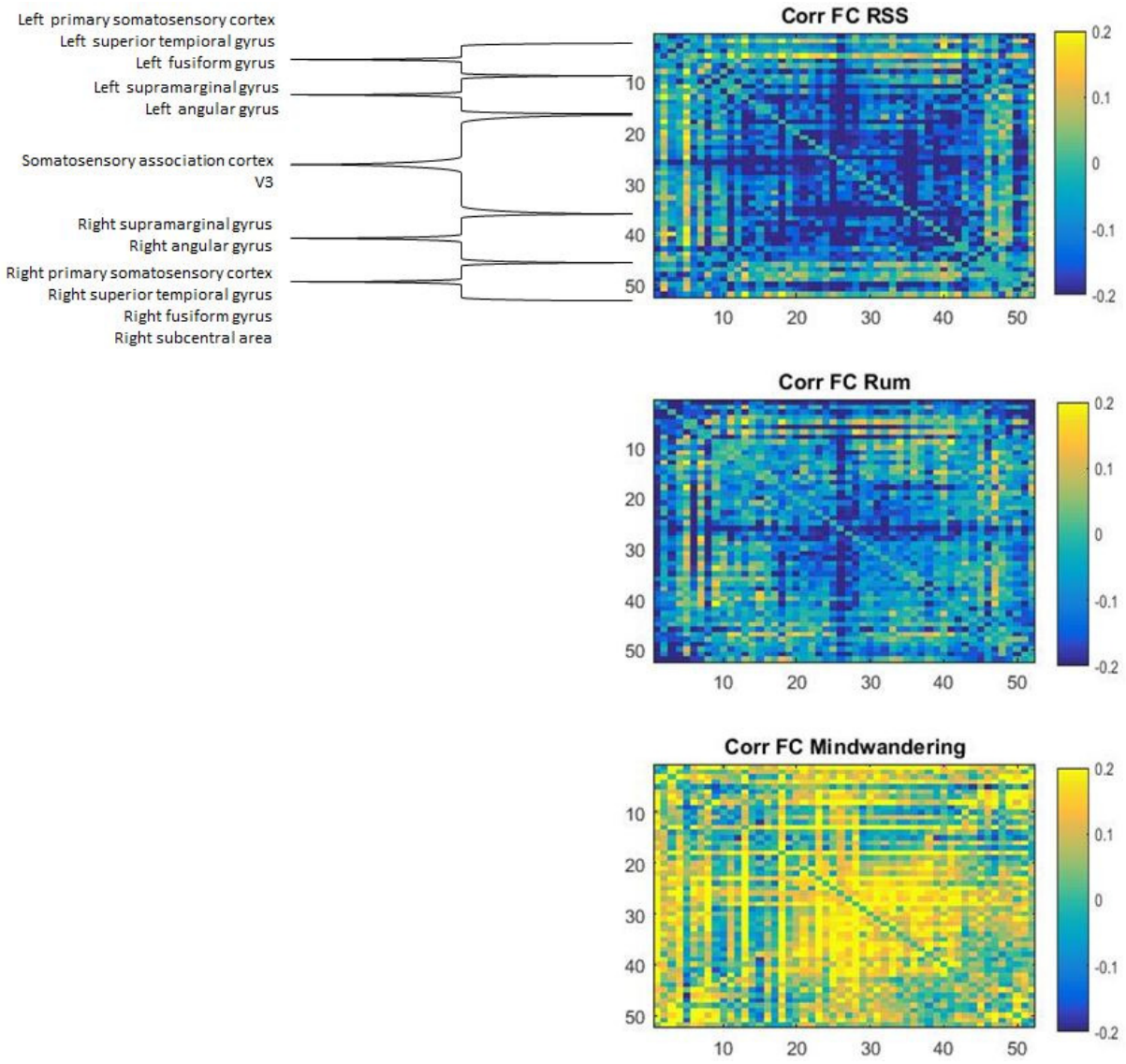

Figure S3. Correlations of trait rumination, state rumination and mind-wanding with FC.

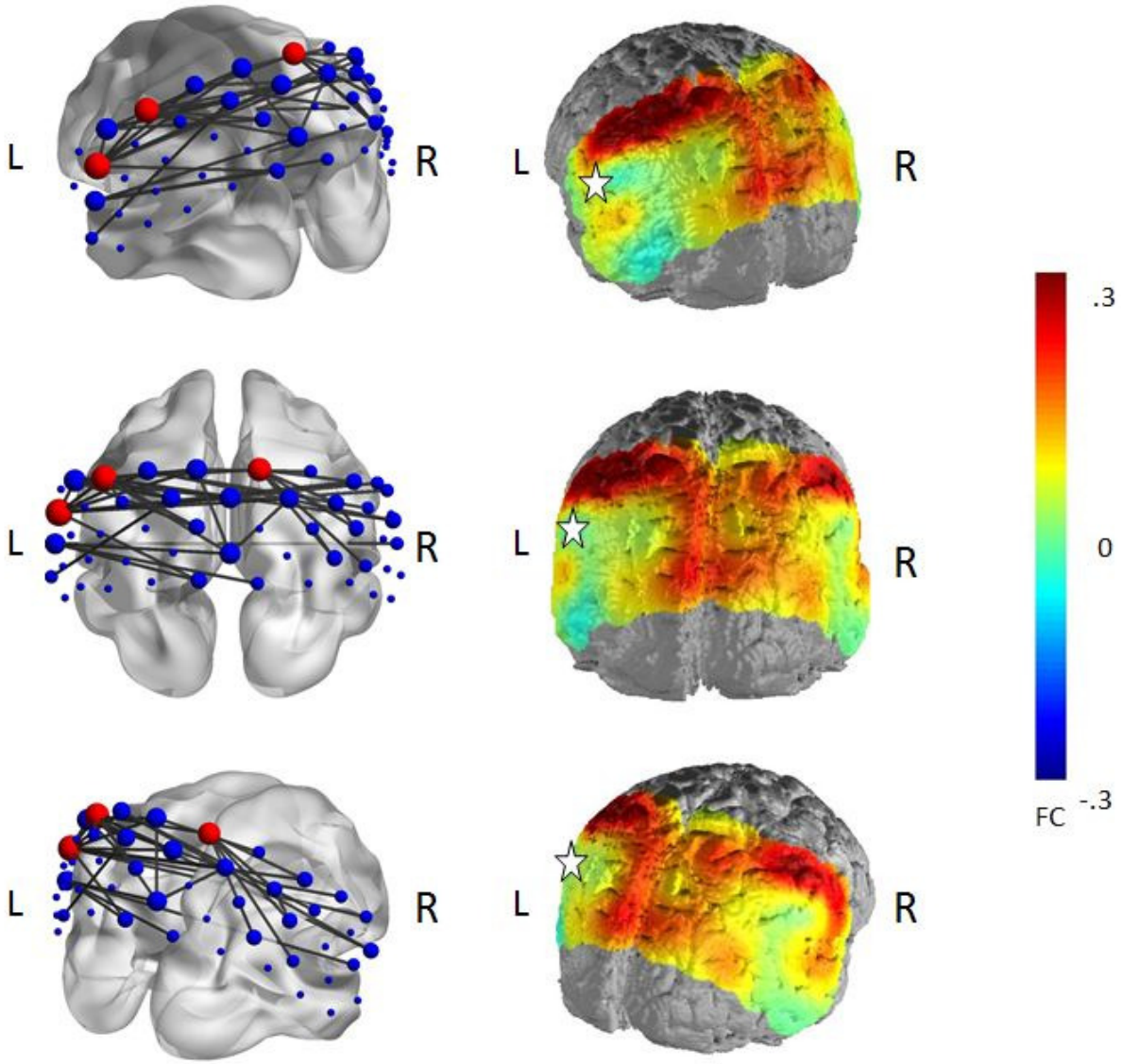

Figure S4. NBS analysis of the main effect for mind-wandering. Left: Significantly hyperconnected network for “high mind-wanderers”. Right: FC maps for the contrast “high vs. low mind-wandering” in the seed region of the left supramarginal cortex. Results of the NBS analysis can be seen in table s1.

Channel	Region	RSS $t_{(82)}$=2.7	Rum $t_{(82)}$=2.8	Mind-wandering $t_{(82)}$=2.9
1	PSC	0	2	0
2	SupG	1	**9**	5
3	SupG	10	0	**8**
4	SAC	10	1	3
5	SAC	6	2	4
6	SAC	10	3	**6**
7	SAC	1	0	1
8	SupG	1	0	2
9	SupG	0	0	1
10	SA	7	0	1
11	STG	1	3	0
12	SupG	2	**13**	**10**
13	SupG	8	1	0
14	AngG	3	0	1
15	SAC	7	0	3
16	SAC	**21**	**6**	4
17	SAC	2	3	3
18	SupG	7	0	2
19	SupG	4	0	1
20	PSC	1	0	0
21	STG	2	0	2
22	STG	0	1	4
24	AngG	2	0	0
26	SAC	3	2	2
27	SAC	3	2	0
28	SAC	2	1	1
29	AngG	3	0	2
30	SupG	1	0	0
31	STG	0	0	1
32	MTG	0	0	1
34	AngG	1	0	0
35	SAC	0	1	0
36	SAC	2	2	0
37	SAC	7	1	4
38	V3	2	2	0
39	AngG	1	0	2
40	AngG	4	0	1
45	AngG	1	0	0
46	V3	2	1	0
47	V3	**18**	1	2
48	V3	3	1	1
49	V3	**12**	0	0
50	AngG	3	0	0
nodes		37	21	28
edges		87	29	39
p-value		.002± .0013	.022± .0041	.023± .0041

Table S1.: Results of the NBS analysis for the main effects of trait rumination (RSS), state rumination (Rum) and mind-wandering. Bold numbers are hub nodes.

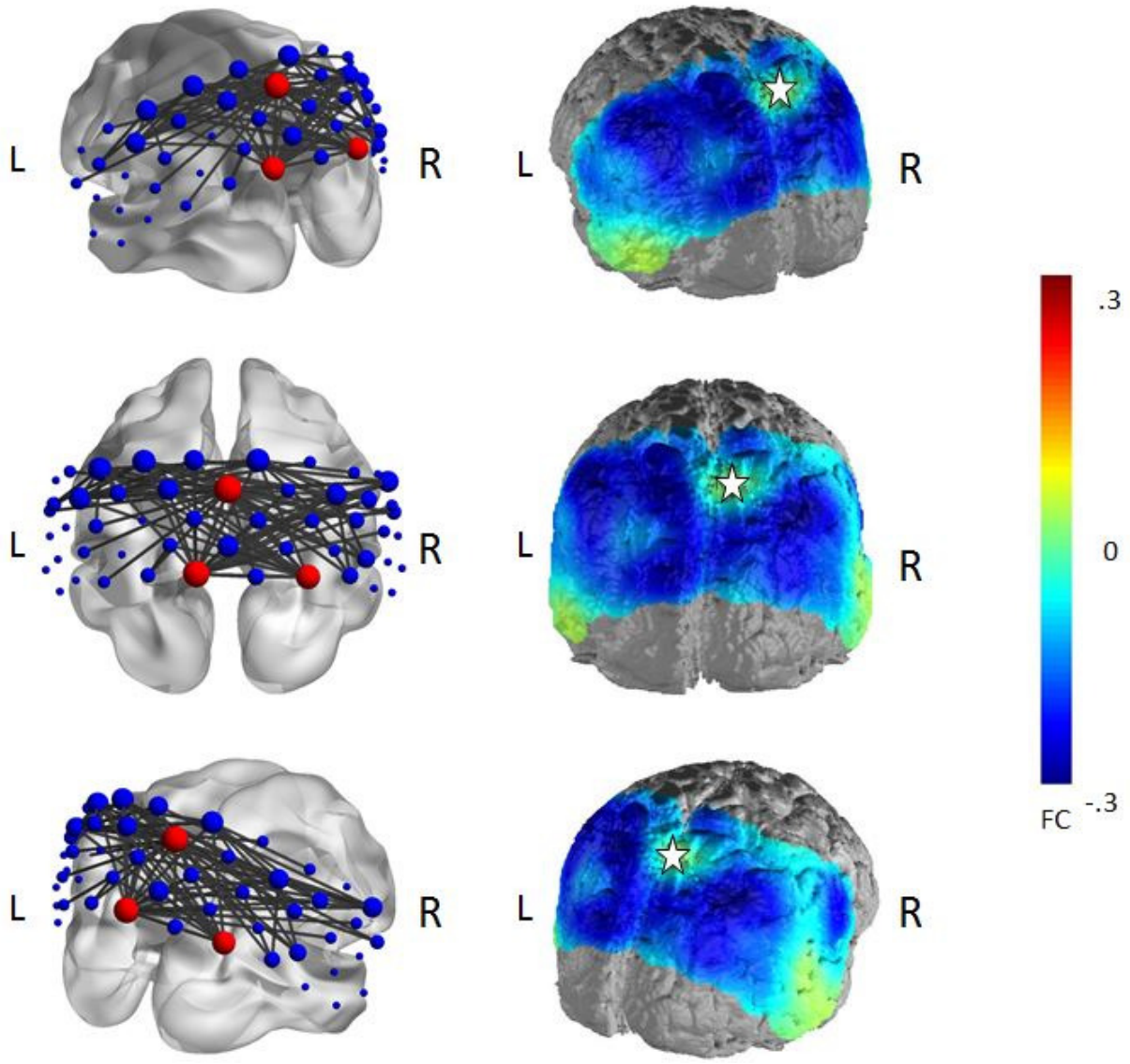

Figure S5. NBS analysis of the main effect for trait rumination. Left: Significantly disconnected network for “high trait ruminators”. Right: FC maps for the contrast “high vs. low trait ruminators” in the seed region of the middle SAC. Cold colours indicate higher FC for the low-rumination group. Results of the NBS analysis can be seen in table s1.

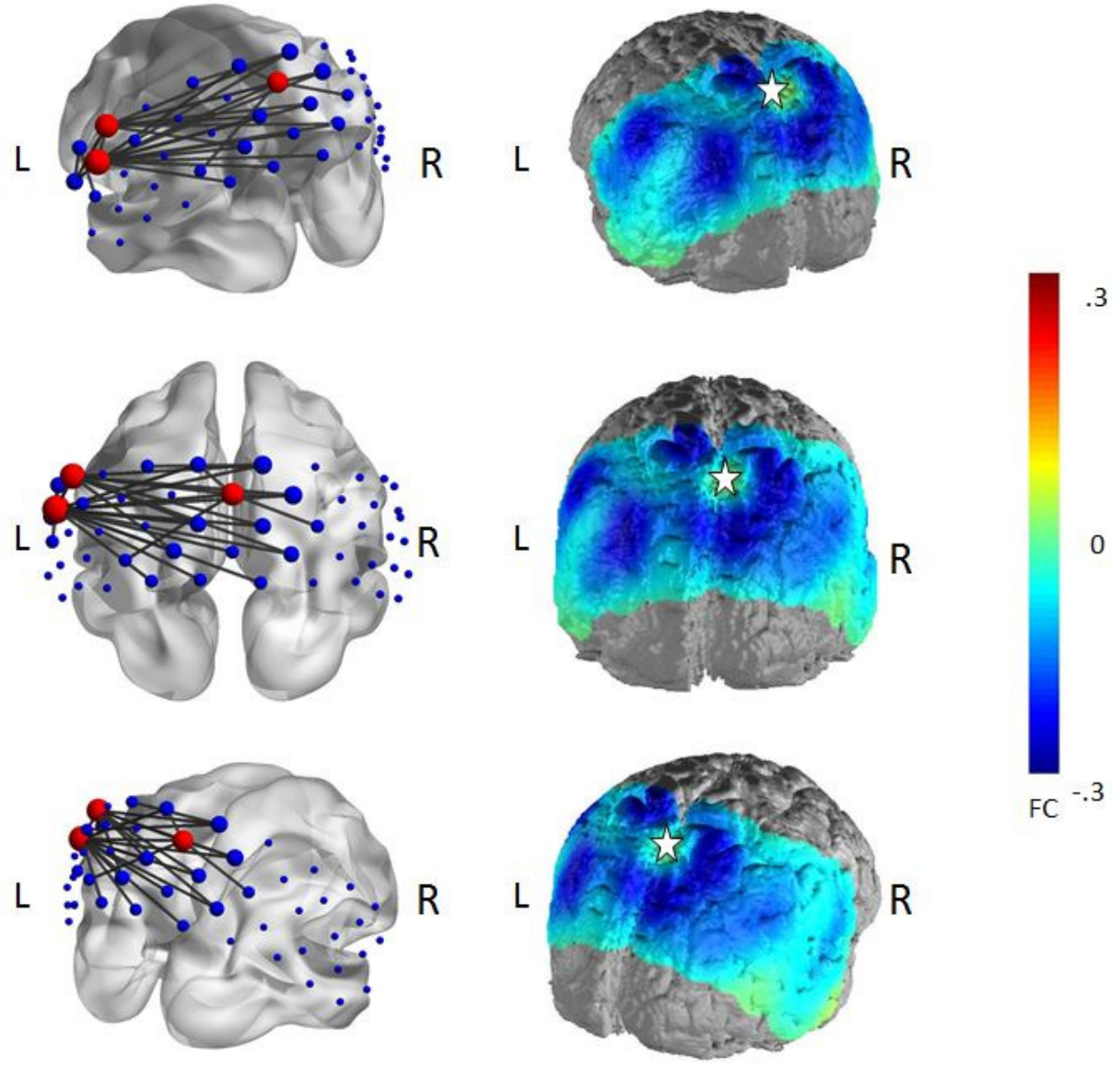

Figure S6. NBS analysis of the main effect for state rumination. Left: Significantly disconnected network for “high state ruminators”. Right: FC maps for the contrast “high vs. low state ruminators” in the seed region of the middle SAC. Cold colours indicate higher FC for the low-rumination group. Results of the NBS analysis can be seen in table s1.

	Seed13				Seed4				Seed29			
	RSS		Rum		RSS		Rum		RSS		Rum	
Ch	rho	p-	rho	p-	rho	p-	rho	p-	rho	p-	rho	p-
1	-0.08	0.469	-0,14	0,197	-0.05	0.653	-0,20	0,062	-0.12	0.258	-0,07	0,530
2	**-0,25**	0,020	**-0,29**	0,008	**-0,31**	0,004	**-0,22**	0,047	**-0,30**	0,006	-0,13	0,244
3	**-0,23**	0,034	-0,17	0,126	**-0,27**	0,014	-0,09	0,429	**-0,29**	0,007	-0,04	0,737
4	**-0,35**	0,001	-0,14	0,191	-	-	-	-	**-0,36**	0,001	-0,17	0,132
5	**-0,40**	0,000	-0,15	0,160	**-0,25**	0,022	-0,06	0,571	**-0,23**	0,033	-0,06	0,601
6	**-0,41**	0,000	**-0,22**	0,040	**-0,28**	0,009	**-0,25**	0,023	**-0,34**	0,002	-0,15	0,170

7	**-0,40**	0,000	-0,14	0,211	**-0,22**	0,041	-0,20	0,066	**-0,25**	0,024	-0,03	0,814
8	**-0,25**	0,022	-0,05	0,648	**-0,26**	0,019	-0,17	0,122	**-0,30**	0,005	-0,04	0,736
9	-0,20	0,065	0,05	0,664	-0,19	0,076	-0,15	0,170	**-0,23**	0,036	0,05	0,637
10	**-0,36**	0,001	-0,17	0,118	-0,14	0,191	-0,10	0,369	**-0,23**	0,037	-0,12	0,257
11	-0,12	0,259	-0,21	0,057	-0,13	0,253	**-0,28**	0,010	-0,08	0,468	-0,11	0,308
12	-0,02	0,830	-0,01	0,964	**-0,27**	0,012	-0,12	0,260	-0,12	0,293	0,05	0,666
13	-	-	-	-	**-0,35**	0,001	-0,14	0,191	**-0,30**	0,006	-0,02	0,836
14	**-0,29**	0,007	-0,08	0,467	**-0,27**	0,012	-0,11	0,303	-0,21	0,052	-0,09	0,397
15	**-0,25**	0,022	-0,11	0,315	**-0,30**	0,006	-0,10	0,371	**-0,22**	0,042	-0,12	0,282
16	**-0,42**	0,000	**-0,29**	0,007	**-0,28**	0,009	-0,08	0,447	**-0,30**	0,005	**-0,26**	0,017
17	**-0,23**	0,034	-0,16	0,134	**-0,28**	0,009	-0,21	0,051	-0,15	0,184	-0,18	0,102
18	**-0,33**	0,002	0,02	0,891	**-0,31**	0,004	-0,11	0,306	**-0,30**	0,006	-0,10	0,383
19	-0,21	0,053	-0,04	0,749	**-0,28**	0,010	-0,09	0,432	-0,19	0,087	-0,09	0,401
20	-0,07	0,500	0,17	0,124	-0,19	0,083	-0,12	0,258	0,00	0,999	0,18	0,105
21	**-0,25**	0,023	-0,04	0,692	-0,15	0,176	**-0,25**	0,021	-0,13	0,243	-0,06	0,581
22	0,01	0,916	0,10	0,365	-0,07	0,534	-0,13	0,236	-0,06	0,617	0,00	0,988
23	-0,10	0,372	-0,02	0,872	-0,07	0,527	0,07	0,548	0,06	0,583	0,10	0,371
24	-0,19	0,087	-0,14	0,212	**-0,25**	0,020	0,01	0,933	-0,11	0,334	-0,08	0,464
25	-0,13	0,240	-0,08	0,496	**-0,24**	0,027	0,01	0,952	-0,15	0,175	-0,07	0,515
26	-0,18	0,111	-0,08	0,453	-0,20	0,068	-0,01	0,904	-0,17	0,114	-0,04	0,717
27	-0,16	0,143	-0,11	0,327	**-0,22**	0,045	-0,05	0,677	-0,25	0,024	-0,05	0,628
28	-0,20	0,064	-0,01	0,923	**-0,28**	0,011	-0,16	0,157	-0,13	0,228	-0,04	0,748
29	**-0,30**	0,006	-0,02	0,836	**-0,36**	0,001	-0,17	0,132	-	-	-	-
30	**-0,22**	0,048	-0,07	0,551	**-0,21**	0,050	-0,02	0,867	-0,09	0,402	-0,12	0,287
31	0,03	0,774	0,07	0,548	-0,03	0,774	-0,06	0,578	0,07	0,504	0,09	0,415
32	**0,23**	0,038	0,05	0,620	0,18	0,097	0,04	0,738	0,04	0,724	-0,11	0,305
33	0,04	0,730	0,12	0,271	0,01	0,958	0,08	0,467	0,12	0,268	0,10	0,342
34	0,02	0,882	0,00	0,987	-0,13	0,235	-0,12	0,283	-0,02	0,883	-0,08	0,470
35	-0,17	0,133	-0,13	0,249	-0,27	0,014	-0,04	0,706	-0,13	0,254	0,00	0,978
36	-0,19	0,080	-0,06	0,618	-0,20	0,067	-0,06	0,580	-0,21	0,057	-0,05	0,663
37	**-0,25**	0,022	**-0,22**	0,047	**-0,28**	0,010	-0,01	0,896	**-0,25**	0,025	-0,10	0,351
38	**-0,20**	0,074	-0,18	0,104	**-0,26**	0,017	-0,17	0,134	-0,12	0,283	-0,10	0,357
39	**-0,21**	0,054	0,00	0,989	**-0,28**	0,011	-0,15	0,163	-0,17	0,120	0,01	0,900
40	-0,23	0,032	0,03	0,792	**-0,34**	0,001	-0,18	0,101	-0,21	0,057	-0,16	0,136
41	-0,02	0,852	-0,13	0,226	0,06	0,608	0,01	0,932	0,06	0,581	-0,07	0,521
42	0,11	0,329	0,08	0,453	0,19	0,089	0,13	0,250	0,05	0,640	0,04	0,728
43	**0,22**	0,046	0,15	0,163	**0,29**	0,007	0,19	0,076	0,20	0,067	-0,02	0,859
44	-0,05	0,640	-0,02	0,826	-0,05	0,670	-0,10	0,363	0,12	0,289	-0,06	0,603
45	-0,07	0,506	-0,03	0,763	-0,19	0,077	-0,14	0,198	-0,05	0,640	0,11	0,339
46	-0,17	0,121	-0,09	0,414	**-0,27**	0,013	-0,09	0,425	-0,13	0,237	-0,05	0,650
47	**-0,29**	0,008	-0,11	0,314	**-0,30**	0,005	0,01	0,948	**-0,22**	0,042	-0,09	0,427
48	**-0,23**	0,038	-0,06	0,581	**-0,23**	0,033	-0,10	0,387	-0,08	0,451	-0,03	0,766
49	**-0,29**	0,008	-0,14	0,217	**-0,31**	0,004	-0,18	0,104	-0,16	0,145	-0,02	0,861
50	-0,20	0,065	-0,12	0,275	**-0,24**	0,026	-0,14	0,195	-0,26	0,018	-0,09	0,399
51	-0,13	0,257	0,00	0,971	-0,14	0,202	-0,10	0,372	-0,10	0,364	-0,06	0,610
52	0,07	0,533	0,07	0,536	0,09	0,430	0,05	0,647	0,02	0,827	-0,02	0,852

Table S2. Korrelations between FC to the seed regions and state- and trait rumination for the whole sample (N=84). P-values are uncorrected, correlations greater .317 are significant after controlling for Type-I errors.

Correlation of resting-state questionnaire scales and VAS Items

		RRS	Scale Rum	Scale FAF	Scale Mind Wandering	Scale Body
RRS	Spearmans Rho	1,000	**,317****	,169	**-,431****	,074
	Sig. (2-seitig)		,003	,125	,000	,502
	N	84	84	84	84	84
Scale Rum	Spearmans Rho	**,317****	1,000	-,063	**-,516****	**-,287****
	Sig. (2-seitig)	,003		,569	,000	,008
	N	84	84	84	84	84
Scale FAF	Spearmans Rho	,169	-,063	1,000	**-,391****	**-,225***
	Sig. (2-seitig)	,125	,569		,000	,039
	N	84	84	84	84	84
Scale Mind Wandering	Spearmans Rho	**-,431****	**-,516****	**-,391****	1,000	**-,249***
	Sig. (2-seitig)	,000	,000	,000		,022
	N	84	84	84	84	84
Scale Body	Spearmans Rho	,074	**-,287****	**-,225***	**-,249***	1,000
	Sig. (2-seitig)	,502	,008	,039	,022	
	N	84	84	84	84	84
Relaxing	Spearmans Rho	**-,400****	**-,546****	-,186	**,726****	-,095
	Sig. (2-seitig)	,000	,000	,091	,000	,388
	N	84	84	84	84	84
Mindflow	Spearmans Rho	**-,221***	-,070	-,180	**,535****	**-,316****
	Sig. (2-seitig)	,044	,528	,100	,000	,003
	N	84	84	84	84	84
ToDo	Spearmans Rho	,105	**,683****	-,048	**-,263***	**-,251***
	Sig. (2-seitig)	,342	,000	,662	,015	,021
	N	84	84	84	84	84
Ruminating	Spearmans Rho	**,313****	**,801****	,125	**-,533****	-,195
	Sig. (2-seitig)	,004	,000	,257	,000	,075
	N	84	84	84	84	84
Body Sensation	Spearmans Rho	,090	-,125	-,136	**-,316****	**,815****
	Sig. (2-seitig)	,415	,256	,218	,003	,000
	N	84	84	84	84	84
Control Myself	Spearmans Rho	**,253***	,071	**,276***	**-,578****	,148
	Sig. (2-seitig)	,020	,519	,011	,000	,179
	N	84	84	84	84	84
Hearing Sounds	Spearmans Rho	,193	-,110	,038	**-,431****	**,718****
	Sig. (2-seitig)	,079	,319	,731	,000	,000
	N	84	84	84	84	84
Supression	Spearmans Rho	**,387****	**,464****	,140	**-,465****	,033
	Sig. (2-seitig)	,000	,000	,205	,000	,765
	N	84	84	84	84	84
Feeling Stressed	Spearmans Rho	**,313****	**,534****	**,250***	**-,649****	-,035
	Sig. (2-seitig)	,004	,000	,022	,000	,749
	N	84	84	84	84	84
Thinking about the duration of the measurement	Spearmans Rho	**,369****	,149	**,692****	**-,582****	,070
	Sig. (2-seitig)	,001	,176	,000	,000	,526
	N	84	84	84	84	84
Fighting with falling asleep	Spearmans Rho	,147	,032	**,864****	**-,382****	**-,217***
	Sig. (2-seitig)	,182	,772	,000	,000	,047
	N	84	84	84	84	84

TableS3. Correlations of the scales and between the scales and the Items of the Resting State Questionnaire.

	Mean		SD		Median		Min		Max	
	HC	MDE	HC	MDE	HC	MDE	HC	MDE	HC	MDE
I felt relaxed	86,46	68,08	11,466	24,171	90,00	70,00	60	5	100	100
I let my mind flow	71,88	71,08	26,777	24,328	80,00	80,00	10	10	100	100
I thought about things I have to do	32,29	38,02	28,589	30,683	27,50	30,00	0	0	90	100
I ruminated	14,33	34,58	17,166	31,211	10,00	22,50	0	0	50	100
I felt sensations of my body	56,67	37,68	31,021	28,132	60,00	30,00	0	0	100	100
I needed to control myself	23,29	33,18	25,506	30,581	15,00	20,00	0	0	80	100
I heard sounds	32,92	25,32	30,321	24,638	22,50	20,00	0	0	100	100
I needed to suppress inner experiences	4,79	19,62	7,442	22,766	0,00	10,00	0	0	30	80
I felt stressed	7,71	16,90	15,250	21,885	0,00	10,00	0	0	60	96
I thought about how long the measurement will last	24,75	36,70	31,489	26,772	10,00	30,00	0	0	100	98
I fought against falling asleep	32,29	42,07	35,201	32,714	20,00	33,50	0	0	100	100

Table S4. Item characteristics of the resting-state VAS scales.

Supplementary Analysis:

As supplementary exploratory analysis we performed three different analysis that were not directly related to the research question:

1) We performed a rumination subgroup analysis as defined by the qualitative rumination rating (based on the self-report form) in the MDD group only. Therefore the 40% of the MDD subjects reporting rumination in the self-report form during resting-state were compared with the 60% which did not report rumination in the self-report form.

2) In the main analysis the RRS total score was used. In a third analysis we also correlated sub-scores of the questionnaire (brooding and reflection) with the FC scores in the whole sample.

Supplementary Analysis of the qualitative rumination rating in the MDD group only.

The analysis of the 40% of the depressed subjects that reported rumination in the self-report form as compared to the 60% of the depressed subjects that did not reported rumination revealed a significant disconnected network (with 36 nodes and 67 edges, $t_{(58)}$=2.7, p=.003).

The network – which showed lower FC in high ruminating subjects – was bilaterally organized and had hubs in the bilateral fusiform gyri and somatosensory association cortex. However inter-hemispheric disconnections were rare and mediated over central hubs. Effect sizes ranged between d=-.44 to d=-96 within FC to the seed channel in the somatosensory association cortex and between d=-.56 to d=-.94 in the right fusiform gyrus.

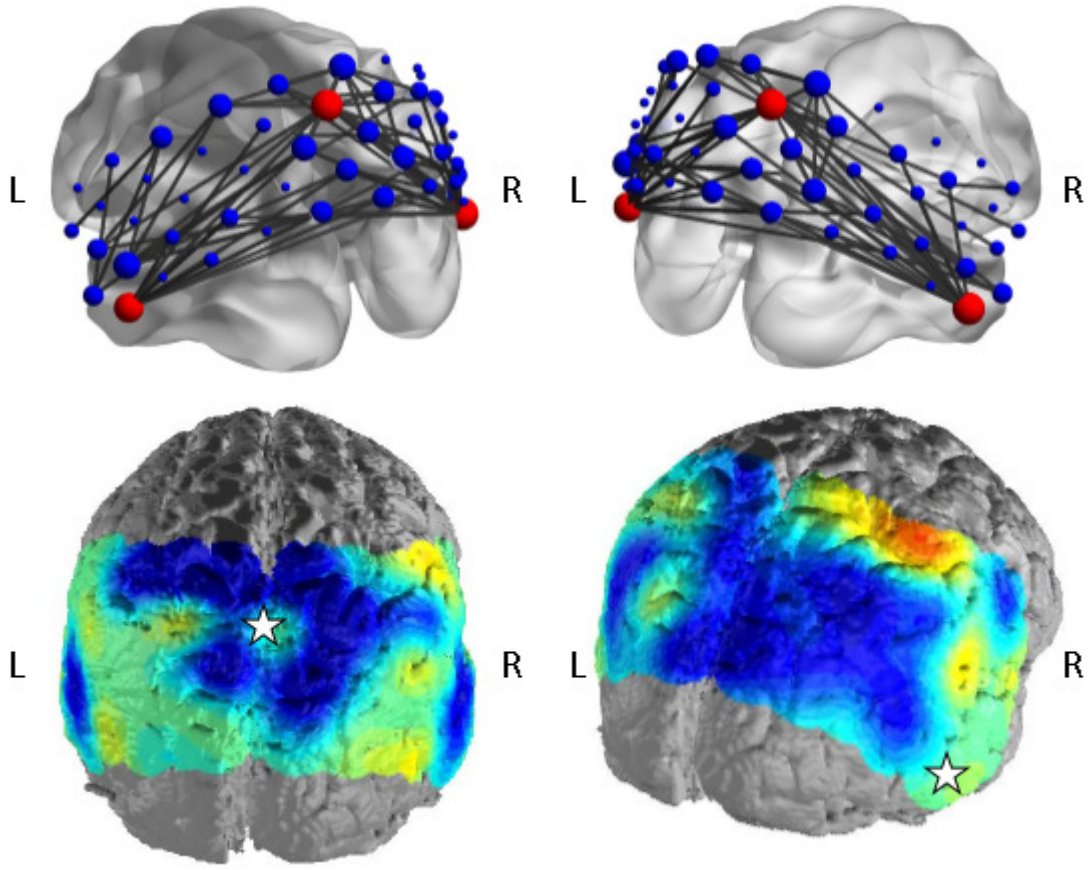

Figure S7. Differences between the subgroup depressed high ruminators and depressed low ruminators according to the qualitative self-report forms. Blue colors indicate reduced FC in high ruminators.

Supplementary Analysis of RRS subscales Rumination and Reflection

As in the analysis of the total RRS score, correlations between FC and the subscale brooding showed negative associations ranging from rho = -.21 to rho = -.36 ($p<.05$ to $p<.001$). The negative relationship between brooding and FC covered areas including the supremarginal gyrus, angular gyrus, somatosensory association cortex, primary somatosensory cortex and the fusiform gyrus. Only the correlation to the right angular gyrus remained significant after controlling for multiple comparisons. On contrary reflection only showed negative correlations with the seed channel 29 and 13. Here correlations were sparse and located in the somatosensory association cortex and the right supramarginal gyrus. No correlation remained significant after controlling for multiple comparison.

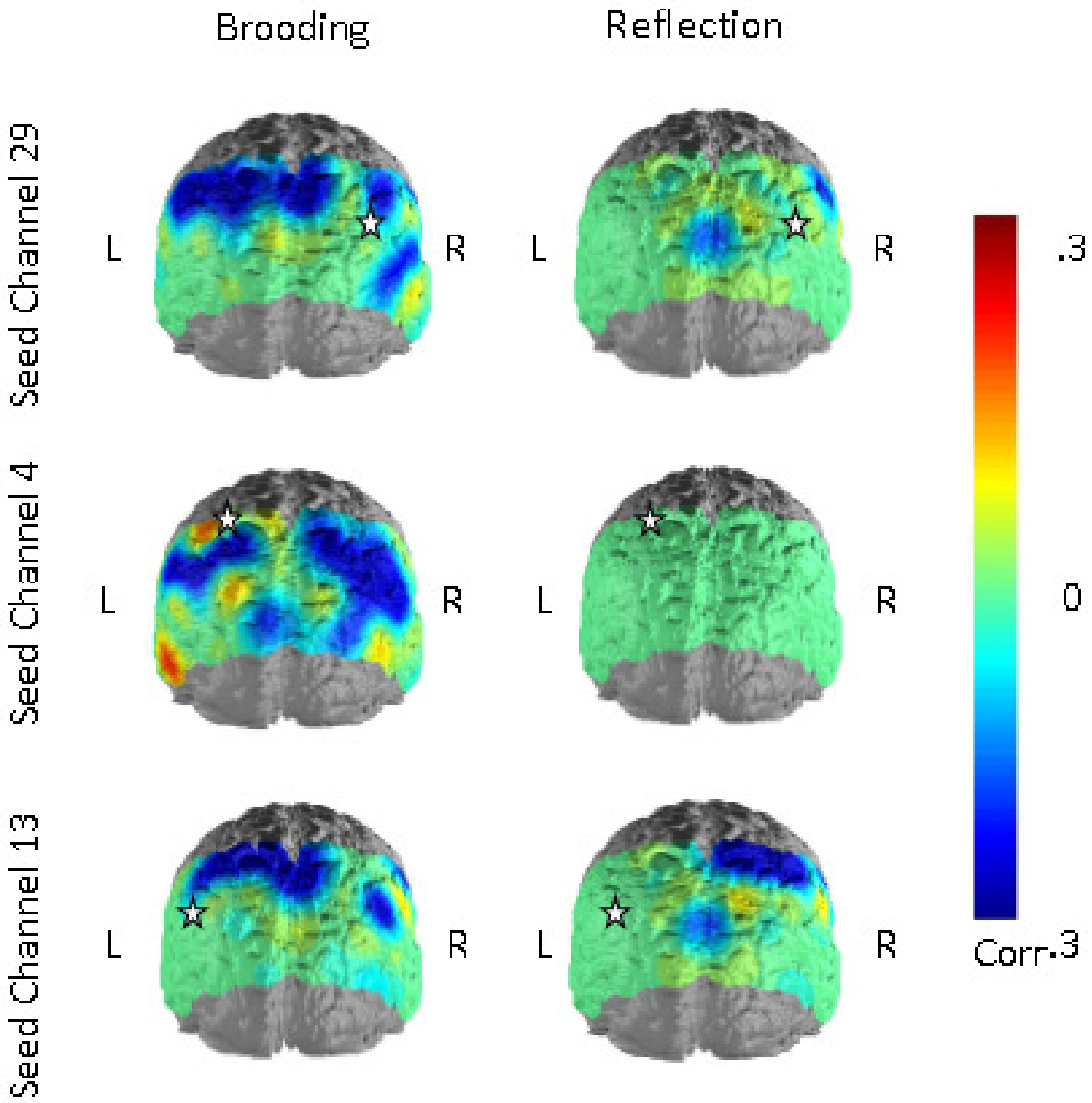

Figure S8. Correlations between seed-channel FC in the depression related network and subscales of the RRS

Study 3:

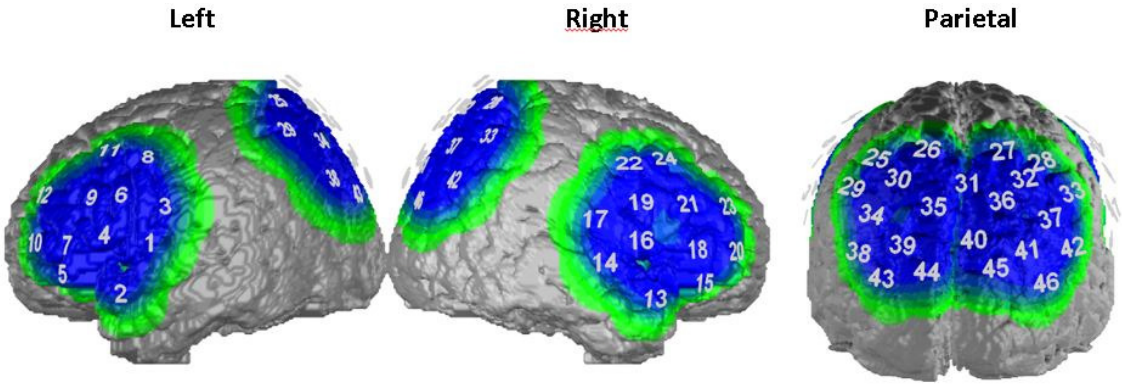

Figure S9. Channel positions of the probesets on the brain.

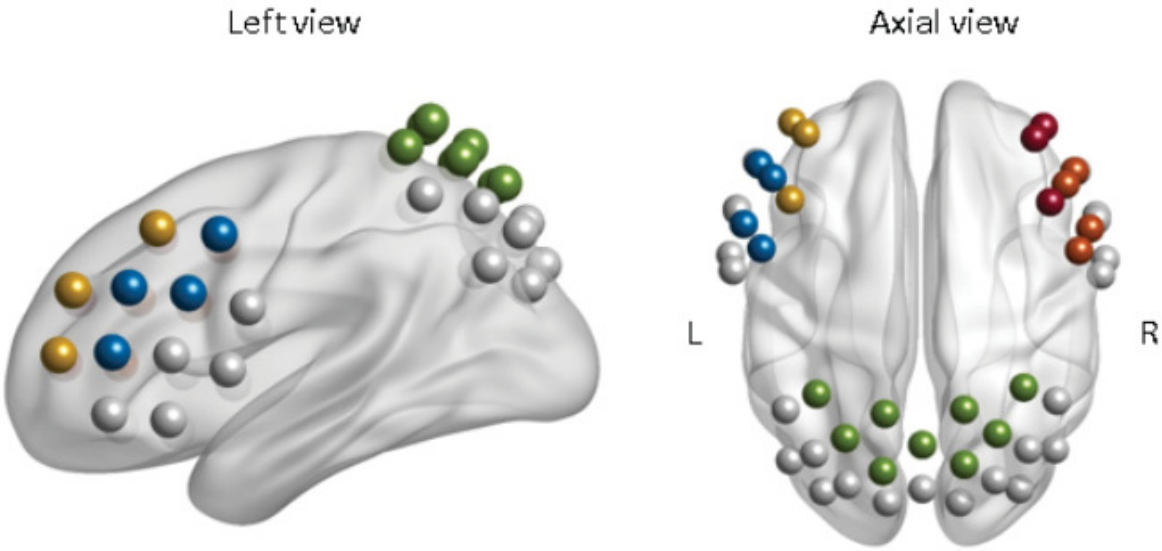

Figure S10. Definition of the 5 ROI within the used Probeset

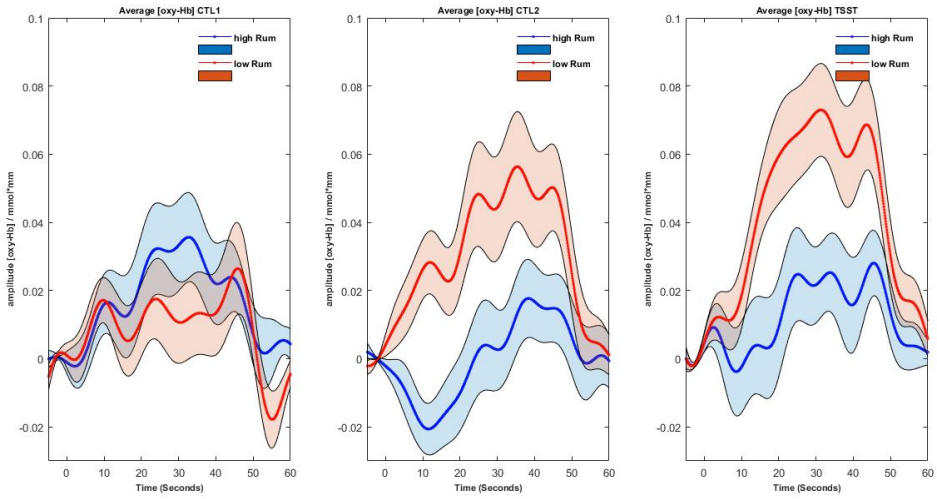

Figure S11. Waveforms of the hemodynamic response (oxy-Hb) averaged over right IFG ROIs for low ruminators (red) and high ruminators (blue) in the three conditions (left: CTL1, middle: CTL2, right: TSST arithmetic).

Study 4:

State rumination was measured with the Amsterdam Resting-State Questionnaire with the following additional items from the RRS:

- I thought about all my shortcomings, failings, faults and mistakes.
- I thought about why I can't handle things better.
- I thought about why I have problems other people don't have.
- I thought about why I misbehaved in certain situations.
- I thought about whereby I deserved my current life situation.
- I couldn't leave my negative thoughts aside.
- I thought about past situations that I regret.
- I thought about all my problems and worries.

Additionally, a semi-structured interview about the ruminative habits has been assessed concerning the following dimensions:

- Presence of dwelling thoughts
- Persistence of ruminative content
- Focus on past events

- High personal relevance of thought content
- Feelings of guilt, sham or sadness
- Perceived hopelessness
- Abstract processing as indicated by
    - Absence of behavioral actions
    - Absence of solutions
    - Non-concrete thought content
    - Why-questions
- Duration of daily rumination
- Felt impairments through rumination

12. List of Abbreviations

5-HTTLPR	Serotonin-transporter-linked polymorphic region
ACC	anterior cingulate cortex
ACTH	adrenal corticotropic hormone
AF	arcuate fasciculus
AG	angular gyrus
AngG	angular gyrus
ANOVA	analysis of variance
APA	American Psychiatric Association
BA	Brodmann’s area
BDI	Beck's depression inventory
CB	cingulate bundle
CBT	Cognitive Behavioral Therapy
CCN	cognitive control network
Ch	Channel
CRH	corticotrophin releasing hormone
CRHR1	corticotrophin receptor 1
CTL	control condition
DAILYs	disability adjusted life years
DAN	dorsal attention network
DMN	default mode network
DNA	deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders,
ECG	electro cardiogram
EEG	Electroencephalography
FAF	Fight Against Fatique
fMRI	functional magnet resonance imaging
fNIRS	functional near-infrared spectroscopy
FP	frontopolar cortex
FusG	fusiform gyrus
GAD	generalized anxiety disorder
GDS	geriatric depression scale
HC	healthy controls
HHB	deoxygenated hemoglobin
HPA	hypothalamic-pituitary-adrenal axis
ICD	International Statistical Classification of Diseases and related Health Problems
IFG	inferior frontal gyrus
IFOF	inferior fronto-occipital fasciculus
IL	Interleukin
IPS	intraparietal sulcus
IRS	immune response system

ITG	inferior temporal gyrus
LLD	late-life depression
MADRS	Montgomery–Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitors
MDD	major depressive disorder
MdLF	middle longitudinal fasciculus
MRI	monoamine reuptake inhibitors
MTG	middle temporal gyrus
NA	negative affect
NASSA	Noradrenergic and specific serotonergic antidepressants
NBS	network based statistics
NDRI	selective noradrenaline dopamine reuptake inhibitors
O_2HB	oxygenated hemoglobin
OFC	orbitofrontal cortex
OR	Odds Ratio
PA	positive affect
PCC	posterior cingulate cortex
PDD	Persistent Depressive Disorder
PFC	prefrontal cortex
PhG	parahippocampal gyrus
PHQ	Patient Health Questionnaire
PMC	primary motor cortex
PPI	psychophysiological interaction
PSC	primary somatosensory cortex
RCT	randomized controlled trial
RFCBT	rumination- focused CBT
ROI	regions of intererest
RRS	ruminative response scale
rsFC	resting-state functional connectivity
SAC	somatosensory association cortex
SC	subcentral area
SCID	standardized clinical interview for DSM
SD	standard deviation
sgACC	subgenual anterior cingulate cortex
SMG	supramarginal gyrus
SN	salience network
S-REF	self-regulatory executive function
SSRI	selective-serotonin reuptake inhibitors
STG	superior temporal gyrus
SupG	supramarginal gyrus
TAU	treatment-as-usual
tDCS	transcranial direct current stimulation

TMS	transcranial magnetic stimulation
TMT	trail-making test
TNF	tumor necrosis factor
TPN	task positive network
TREND	Tübinger evaluation of risk factors for early detection of neurodegeneration
TSST	Trier Social Stress Test
UF	uncinate fasciculus
VAS	visual analogue scales
VFT	Verbal Fluency Test
VMHC	voxel-mirrored homotopic connectivity
WHO	World Health Organization

13. List of Tables

14. List of Figures

15. Organizational Remarks

The work at hand comprises four published publications. According to the guidelines of the publishers – Elsevier and Springer Nature (http://www.nature.com and https://www.elsevier.com) – the original texts and graphics can be used by the author for scholarly, non-commercial purposes as it is the case with this dissertation.

15.1 Contributions of the author

For all included studies in this work the author of this dissertation was the person in charge and therefore involved with regard to the research questions, the programming of the paradigms, the collection, analysis and interpretation of the data as well as the final publication. However, for study one data was used that was already available from the TREND-study and in study two, the measurement of state-processes during resting-state was implemented in the ongoing Wiki-D study. Within the Wiki-D and TREND-study the research questions of this dissertation were implemented in the larger context of the projects. The coauthors supported and contributed at single processing stages, such as study preparation or data analysis.

15.2 Styles and formatting

The APA style in its 6th edition was used throughout this dissertation. The formatting of the published studies was adapted to this style and may differ in the published form. Also, the numbering of headings, footnotes, tables and figures has been altered to give a coherent sequence.

15.3 Eidesstattliche Erklärung

Ich erkläre hiermit, dass ich die zur Promotion eingereichte Arbeit mit dem Titel: “Aberrant brain activation and coupling in Depression – Links between Psychopathology and Neurophysiology” selbstständig verfasst, nur die angegebenen Quellen und Hilfsmittel benutzt und wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe. Ich erkläre, dass die Richtlinien zur Sicherung guter wissenschaftlicher Praxis der Universität Tübingen (Beschluss des Senates vom 25.5.2000) beachtet wurden. Ich versichere an Eides statt, dass diese Angaben wahr sind und dass ich nichts verschwiegen habe. Mit ist bekannt, dass die falsche Abgabe einer Versicherung an Eides statt mit Freiheitsstrafe bis zu drei Jahre oder mit Geldstrafe bestraft wird.

Ort, Datum Unterschrift