The Neural Basis of Stress-Reactive Rumination: Investigating the Modulatory Effects of Theta-Burst Stimulation

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M. Sc. Isabell Int-Veen
aus Friedrichshafen

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1. Berichterstatter/-in: Dr. Ann-Christine Ehlis
2. Berichterstatter/-in: Prof. Dr. Hans-Christoph Nürk
3. Berichterstatter/-in: Prof. Dr. Martin Herrmann

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Abbreviations

ACTH Adrenocorticotropic Hormone

Ag silver

AgCl silver chloride

AIC Akaike Information Criterion

ANS Autonomic Nervous System

ANOVA Analysis of Variance

AP1 first appointment

AP2 second appointment

ARSQ Amsterdam Resting-State Questionnaire

AVP arginine vasopressin

BDI-II Beck's Depression Inventory II

BF01 Bayes Factor

BIC Bayesian Information Criterion

BMI Body-Mass-Index

BOLD blood-oxygen-level-dependent

BPM beats per minute

CBT Cognitive Behavioral Therapy

CEN Central Executive Network

CONSORT Consolidated Standards of Reporting Trials

CRH Corticotropin-Releasing Hormone

CTL1 control task 1

CTL2 control task 2

cTBS continuous Theta Burst Stimulation

DALYs disability-adjusted life-years

DASS-21 Depression, Anxiety and Stress Scale

DBS Deep Brain Stimulation

DLPFC Dorsolateral Prefrontal Cortex

DMN Default Mode Network

DOI Digital Object Identifier

DP patient with depression

DSM-V Diagnostic and Statistical Manual of Mental Disorders

DV dependent variable

ECG electrocardiography

ECT Electroconvulsive Therapy

EEG electroencephalography

EF executive function

EMG electromyogram

ERQ Emotion Regulation Questionnaire

F32.x ICD-10 diagnosis: Depressive episode, unspecified

F33.x ICD-10 diagnosis: Persistent affective disorders, unspecified

F34.1 ICD-10 diagnosis: Recurrent depressive disorder, currently moderate episode

fMRI functional Magnetic Resonance Imaging

fNIRS functional Near-Infrared Spectroscopy

GABA Gamma-aminobutyric acid

GBD Global Burden of Diseases, Injuries, and Risk Factors Study

GSE General Self-Efficacy Scale

HC healthy control

HF-rTMS high-frequency repetitive Transcranial Magnetic Stimulation

HHb deoxygenated hemoglobin

HPA-axis Hypothalamic-Pituitary-Adrenal Axis

HR heart rate

HRV heart rate variability

ICD-10 International Statistical Classification of Diseases and Related Health Problems 10th edition

IFG Inferior Frontal Gyrus

iTBS intermittent Theta Burst Stimulation

LF-rTMS low-frequency repetitive Transcranial Magnetic Stimulation

lDLPFC left Dorsolateral Prefrontal Cortex

lIFG left Inferior Frontal Gyrus

LSAS Liebowitz Social Anxiety Scale

LTD long-term depression

LTP long-term potentiation

MADRS Montgomery-Åsberg Depression Rating Scale

MANOVA Multivariate Analysis of Variance

MDD Major Depressive Disorder

MEG Magnetoencephalography

MEP Motor-Evoked Potential

NIBS Non-Invasive Brain Stimulation

NIRS Near-Infrared Spectroscopy

O_2Hb oxygenated hemoglobin

OCD Obsessive Compulsive Disorder

PANAS Positive and Negative Affect Schedule

PASA Primary and Secondary Appraisal Questionnaire

PET Positron emission tomography

PFC Prefrontal Cortex

PNS Parasympathetic Nervous System

PSQI Pittsburgh Sleep Quality Index

PTQ Perseverative Thinking Questionnaire

RCI Reliable Change Index

RCT Randomized Controlled Trial

rest1 resting-state measurement 1

rest2 resting-state measurement 2

rDLPFC right Dorsolateral Prefrontal Cortex

rIFG right Inferior Frontal Gyrus

rmANOVA repeated measurements Analysis of Variance

rmMANOVA repeated measurements Multivariate Analysis of Variance

RMSSD Root Mean Squared of Successive Differences

ROI Region of Interest

RRS Ruminative Response Scale

RSQ Response Styles Questionnaire

rTMS repetitive Transcranial Magnetic Stimulation

SAC Somatosensory Association Cortex

SAM-axis Sympatho-Adreno-Medullary Axis

SCID Structured Clinical Interview

SECPT Socially-Evaluated Cold Pressor Test

SERI State Emotion Regulation Inventory

SES socioeconomic status

SN Salience Network

SNS Sympathetic Nervous System

SPSS Statistical Package for the Social Sciences

SR state rumination

SRSRQ Stress-Reactive State Rumination Questionnaire

sTBS sham Theta Burst Stimulation

tACS Transcranial Alternating Current Stimulation

TAP Think Aloud Paradigm

TBS Theta Burst Stimulation

tDCS Transcranial Direct Current Stimulation

TDDR Temporal Derivative Distribution Repair

TMS Transcranial Magnetic Stimulation

tES Transcranial Electrical Stimulation

tRNS Transcranial Random Noise Stimulation

TSST Trier Social Stress Test

VAS Visual Analogue Scale

VLPFC Ventrolateral Prefrontal Cortex

Abstract

Ruminative thinking is a transdiagnostic process that plays a crucial role in psychopathology by prolonging the psychological and physiological stress response and exacerbating symptoms of depression and other conditions. Theta Burst Stimulation (TBS) is a Non-Invasive Brain Stimulation (NIBS) technique that has been shown to modulate the affective, emotional and physiological response to stressors and alleviate symptomatology of, for instance, depressive disorders. To date, the underlying neural mechanisms of stress-reactive rumination have not been fully understood. TBS offers a promising tool to investigate the aforementioned processes and gain new insights to potentially improve treatment for mental disorders associated with ruminative thinking in the long term. Especially an aberrant functioning of the left Dorsolateral Prefrontal Cortex (DLPFC) has been repeatedly associated with depressive symptomatology and potentially ruminative thinking; however, it remains inconclusive to what extent the underlying neural correlates are similar or can be disentangled. While the first study of this dissertation examined brain activity to inform TBS research, the subsequent three studies applied TBS to gain deeper insights into the neural basis of stress-reactive rumination.

The first study of this dissertation examines the neural correlates of stress-reactive rumination in patients with depression (DP) compared to healthy controls (HC). Using a fine-grained analysis of functional Near-Infrared Spectroscopy (fNIRS) data, we aimed to replicate commonly observed prefrontal hypoactivation under stress and further distinguish the neural activation patterns associated with rumination and depressive symptomatology in order to identify corresponding stimulation targets. For this, we analyzed the data of 65 HC and 77 DP performing a stress task which has been found to induce ruminative thinking, namely the Trier Social Stress Test (TSST). Throughout the experiment the neural correlates were measured using fNIRS and ruminative thought was assessed in resting-state measurements previous and after the TSST. Depressive symptomatology was associated with blunted increases in cortical oxygenation under stress in the right Inferior Frontal Gyrus (IFG) and bilateral Dorsolateral Prefrontal Cortex (DLPFC). In line with these findings, participants with lower state rumination and no stress-reactive changes also showed the highest increases in cortical oxygenation. Overall, state rumination was associated with a greater number of prefrontal brain regions, and interestingly, these associations remained significant even after correcting for performance during the TSST, in contrast to diagnostic status.

Following the above findings and in line with previous research suggesting the (left) DLPFC to be a promising target in the investigation of the affective and cognitive stress response, **in the second study**, we applied either inhibitory, continuous Theta Burst Stimulation (cTBS), excitatory, intermittent Theta Burst Stimulation (iTBS) or sham Theta Burst Stimulation (sTBS) to the left DLPFC prior to a stress induction using the TSST. We investigated a clinical analogue sample of a total of 127 healthy participants comprising low and high trait ruminators in a between-subjects design. On the one hand, we assessed psychological variables (subjective stress, state rumination, positive and negative affect) and on the other hand the physiological stress response (heart rate (HR), heart rate variability (HRV) and salivary cortisol). Our results indicate that cTBS, as compared to sTBS and iTBS, results in an attenuated stress-induced salivary cortisol response in high compared to low trait ruminators. Further, cTBS showed positive effects on changes in mood, namely no decreases in positive affect and no increases in negative affect following the TSST and TBS, respectively. Additionally, both cTBS and iTBS resulted in an enhanced heart rate recovery following the TSST compared to sTBS. Please note, however, that the latter findings were independent of trait rumination, which was not in line with our initial hypothesis. Lastly, we observed no effect of the stimulation on subjective stress and state rumination as well as HRV.

Using the same study set-up, **the third study** aimed to replicate and extend the findings of the second study by also assessing the neural stress response using fNIRS. Again, we applied either continuous Theta Burst Stimulation (cTBS), intermittent Theta Burst Stimulation (iTBS) or sTBS to the left DLPFC prior to the TSST in a clinical analogue sample of 88 healthy participants comprising low and high trait ruminators. This time, however, we used a within-subjects study design, where participants came to the lab twice and either received active or placebo stimulation, randomized and balanced across stimulation and trait rumination groups. Following the stressor, we observed significantly higher increases in subjective stress and negative affect following iTBS compared to sTBS and cTBS but only in high ruminators. Our results indicated strong habituation effects of the repeated exposure to the TSST. The stimulation had no impact on positive affect, performance in the TSST and heart rate and no clear effects on state rumination. More specifically, here we observed beneficial effects of iTBS but only in low ruminators and only at the second appointment. fNIRS data revealed cortical oxygenation differences during the TSST in the left VLPFC but not left DLPFC. Descriptively, we observed that in high ruminators, cTBS led to higher cortical oxygenation in the left VLPFC compared to sTBS, while in low ruminators, cTBS resulted in lower cortical oxygenation than sTBS. However, this effect only appeared when participants received active stimulation first, suggesting neural habituation effects.

In the fourth study, we used a different stimulation target and applied continuous Theta Burst Stimulation (cTBS), intermittent Theta Burst Stimulation (iTBS) or sTBS to the right Ventrolateral Prefrontal Cortex (VLPFC) in order to modulate cognitive reappraisal circuits rather than focusing on the DLPFC and executive function (EF)-related effects of stressors. We recruited a total of 89 low and high trait ruminators without any mental disorder, who again received active or placebo stimulation, randomized and balanced across stimulation and trait rumination groups. Here, the changes in cortical oxygenation in the right VLPFC were in line with our hypothesis, indicating significantly higher increases in high ruminators following iTBS compared to sTBS. These changes were only observed at the first appointment, which again supports the idea of strong habituation effects of repeated exposure to the TSST. Interestingly, however, we observed significantly higher subjective stress following iTBS and cTBS compared to sTBS during recovery of the TSST but only at the first appointment. No stimulation-dependent effects were found for state rumination, affect and heart rates.

Taken together, these findings have important methodological implications for repeated-measures designs that combine experimental stress induction with TBS. They further highlight the importance of collecting neural data in order to properly interpret TBS-induced changes. In the general discussion, I explore the possibility that the effects of TBS may be too small to influence behavior at the observable level and give future directions regarding the use of TBS in experimental stress research.

Zusammenfassung

Ruminatives Denken (Grübeln) ist ein transdiagnostischer Prozess, der eine entscheidende Rolle in der Psychopathologie spielt, indem er die psychologische und physiologische Stressreaktion verlängert und die Symptome von Depressionen und anderen Erkrankungen verschärft. Theta Burst Stimulation (TBS) ist eine Non-Invasive Hirnstimulations-Technik, die gezeigt hat, dass sie die affektive, emotionale und physiologische Reaktion auf Stressoren modulieren und die Symptomatik von beispielsweise depressiven Störungen lindern kann. Bis heute sind die zugrunde liegenden neuronalen Mechanismen von stressreaktivem Grübeln noch nicht vollständig verstanden. TBS bietet ein vielversprechendes Werkzeug, um die genannten Prozesse zu untersuchen und neue Erkenntnisse zu gewinnen, die potenziell die langfristige Behandlung von psychischen Störungen, die mit ruminativem Denken verbunden sind, verbessern könnten. Insbesondere eine veränderte Funktionsweise des linken Dorsolateralen Präfrontalkortex (DLPFC) wurde wiederholt mit depressiver Symptomatik und potenziell ruminativem Denken in Verbindung gebracht; es bleibt jedoch unklar, inwieweit die zugrunde liegenden neuronalen Korrelate ähnlich sind oder voneinander getrennt werden können. Während die erste Studie dieser Dissertation die Hirnaktivität untersuchte, um die TBS-Forschung zu informieren, setzten die folgenden drei Studien TBS ein, um tiefere Einblicke in die neuronalen Grundlagen der stressreaktiven Rumination zu gewinnen.

Die erste Studie dieser Dissertation untersucht die neuronalen Korrelate des stressreaktiven Grübelns bei Menschen mit Depressionen (DP) im Vergleich zu Menschen ohne Depressionen (HC). Mit Hilfe einer detaillierten Analyse von funktioneller Nah-Infrarotspektroskopie (fNIRS)-Daten wollten wir die oft beobachtete präfrontale Hypoaktivierung unter Stress replizieren und die neuronalen Aktivierungsmuster, die mit Grübeln und depressiver Symptomatik assoziiert sind, unterscheiden, um entsprechende Stimulationsziele zu identifizieren. Dafür analysierten wir die Daten von 65 HC und 77 DP, die eine Stressinduktion unterliefen, die ruminatives Denken auslöst, genauer gesagt den Trier Social Stress Test (TSST). Während des gesamten Experiments wurden die neuronalen Korrelate mittels fNIRS gemessen und ruminatives Denken wurde in Ruhemessungen vor und nach dem TSST erfasst. Die depressive Symptomatik war mit einem abgeschwächten Anstieg der kortikalen Sauerstoffversorgung unter Stress im rechten Inferioren Frontalen Gyrus (IFG) und bilateralen Dorsolateralen Präfrontalkortex (DLPFC) verbunden. In Übereinstimmung mit diesen Ergebnissen zeigten Ver-

suchspersonen mit geringerem stress-reaktiven Grübeln und ohne stressbedingte Veränderungen auch die höchsten Anstiege in kortikaler Oxygenierung. Insgesamt war stressreaktives Grübeln mit einer größeren Anzahl von präfrontalen Hirnregionen verbunden, und interessanterweise blieben diese Assoziationen auch nach der Korrektur für die Leistung während des TSST signifikant, im Gegensatz zum diagnostischen Status.

In Anlehnung an die obigen Ergebnisse und in Übereinstimmung mit vorangegangener Forschung, die den (linken) DLPFC als vielversprechendes Ziel bei der Untersuchung der affektiven und kognitiven Stressreaktion nahelegen, haben wir in der **zweiten Studie** vor einer Stressinduktion mit dem TSST entweder aktivierungssenkende, kontinuierliche Theta Burst Stimulation (cTBS), aktivierungssteigernde, intermittierende Theta Burst Stimulation (iTBS) oder sham Theta Burst Stimulation (sTBS) auf den linken DLPFC angewendet. Wir untersuchten eine klinische Analogstichprobe von insgesamt 127 gesunden Versuchspersonen mit einer eher niedrigen oder eher hohen Neigung zu Grübeln, in einem Zwischensubjektdesign. Wir haben zum einen psychologische Variablen (subjektiver Stress, momentanes Grübeln, positiver und negativer Affekt) und zum anderen die physiologische Stressreaktion (Herzfrequenz, Herzfrequenzvariabilität und Speichelcortisol) untersucht. Unsere Ergebnisse deuten darauf hin, dass cTBS im Vergleich zu sTBS und iTBS bei Menschen, die zum Grübeln neigen, eine abgeschwächte stressinduzierte Speichelcortisolreaktion hervorruft, im Vergleich zu Menschen, welche weniger zum Grübeln neigen. Darüber hinaus zeigte cTBS positive Auswirkungen auf Stimmungsänderungen, nämlich keine Abnahme des positiven Affekts und keine Zunahme des negativen Affekts nach dem TSST bzw. der TBS. Darüber hinaus führten sowohl cTBS als auch iTBS zu einer schnelleren Erholung der Herzfrequenz nach dem TSST im Vergleich zu sTBS. Es ist jedoch anzumerken, dass die letztgenannten Ergebnisse unabhängig von der Grübelneigung waren, was nicht unserer ursprünglichen Hypothese entsprach. Schließlich beobachteten wir keine Auswirkungen der Stimulation auf die subjektiven Stressratings, momentanes Grübeln sowie auf die Herzfrequenzvariabilität.

Mit dem gleichen Studienaufbau sollte die **dritte Studie** die Ergebnisse der zweiten Studie replizieren und erweitern, indem auch die neuronale Stressreaktion mittels fNIRS untersucht wurde. Wieder haben wir entweder cTBS, iTBS oder sTBS vor dem TSST auf den linken DLPFC in einer klinischen Analogstichprobe von 88 gesunden Versuchspersonen mit entweder hoher oder niedriger Grübelneigung angewendet. Diesmal verwendeten wir jedoch ein Studiendesign, bei dem die Teilnehmenden zweimal ins Labor kamen und entweder eine aktive oder eine Placebostimulation erhielten, randomisiert und ausbalanciert nach Stimulations- und Ruminations-Gruppen. Nach dem Stressor beobachteten wir einen signifikant höheren Anstieg des subjektiven Stresses und des negativen Affekts nach iTBS im Vergleich zu sTBS und cTBS, allerdings nur bei Personen, die zum Grübeln neigen. Unsere Ergebnisse deuten auf einen starken Gewöhnungseffekt durch die wiederholte Druchführung des TSST hin. Die Stimulation hatte keinen Einfluss auf den positiven Affekt, die Leistung im TSST und die Herzfrequenz und keine eindeutigen Auswirkungen auf das momentane Grübeln. Unsere fNIRS-Daten zeigten Unterschiede in der kortikalen Oxygenierung während des TSST im linken VLPFC, aber nicht im linken DLPFC. Deskriptiv konnten wir feststellen, dass cTBS bei Personen, die zum Grübeln neigen, zu einer höheren kortikalen Oxygenierung im linken VLPFC im Vergleich zu sTBS führte, während cTBS bei Personen, die eher nicht zum Grübeln neigen, zu einer niedrigeren kortikalen Oxygenierung als sTBS führte. Dieser Effekt trat jedoch nur auf, wenn die Teilnehmenden zuerst die aktive Stimulation erhielten, was auf neuronale Habituationseffekte schließen lässt.

In der vierten Studie verwendeten wir ein anderes Stimulationsziel und applizierten cTBS, iTBS oder sTBS auf den rechten Ventrolateralen Präfrontalkortex (VLPFC), um die neuronalen Netwerke, die mit kognitiver Neubewertung assoziiert sind, zu modulieren, anstatt uns auf die DLPFC- und Effekte von Stressoren auf die Exekutiven Funktionen zu konzentrieren. Wir rekrutierten insgesamt 89 gesunde Versuchspersonen mit einer hohen oder niedrigen Grübelneigung, die ebenfalls eine aktive Stimulation oder eine Placebostimulation erhielten, randomisiert und ausbalanciert zwischen den Stimulations- und Ruminations-Gruppen. Die Veränderungen der kortikalen Oxygenierung im rechten VLPFC stimmten mit unserer Hypothese überein und zeigten einen signifikant höheren Anstieg bei Personen mit Neigung zu Grübeln nach iTBS im Vergleich zu sTBS. Diese Veränderungen wurden nur beim ersten Termin beobachtet, was wiederum die Idee eines starken Gewöhnungseffekts bei wiederholter TSST-Exposition unterstützt. Interessanterweise beobachteten wir jedoch einen signifikant höheren subjektiven Stress nach iTBS und cTBS im Vergleich zu sTBS während der Erholung vom TSST, aber nur beim ersten Termin. Es wurden keine stimulationsabhängigen Effekte für momentanes Grübeln, Affekt und die Herzfrequenz gefunden.

Zusammengefasst haben diese Ergebnisse wichtige methodische Implikationen für Designs mit wiederholten Messungen, die experimentelle Stressinduktion mit TBS kombinieren. Sie unterstreichen außerdem die Bedeutung der Erfassung neuronaler Daten, um TBS-induzierte Veränderungen richtig interpretieren zu können. In der allgemeinen Diskussion gehe ich auf die Möglichkeit ein, dass die Effekte von TBS zu gering sein könnten, um das Verhalten auf der beobachtbaren Ebene zu beeinflussen, und gebe Hinweise für die Verwendung von TBS in der experimentellen Stressforschung.

Chapter 1

General introduction

Mental disorders are characterized both by subjectively experienced symptoms and altered brain functioning. With recent advances in neuroimaging and a growing understanding of neural alterations in psychopathology, there is an increasing effort to conceptualize mental disorders as brain disorders, rooted in underlying brain circuits, genetics, behavior, and cognitive functions (see e.g. Insel et al., 2010). However, despite growing neuroscientific insights into mechanisms underlying psychopathology, diagnoses still rely on clinical interviews and patients' subjective self-reports, based on criteria from diagnostic manuals as diagnostics with brain imaging techniques are so far not reliable and sensitive enough for the diagnostic process. While these insights have yet to be incorporated into diagnostic frameworks, they increasingly inform treatment approaches, such as Non-Invasive Brain Stimulation (NIBS).

1.1 Depressive disorders

Depressive disorders comprise a group of mental health conditions characterized by persistent sadness, loss of interest or pleasure in activities, and a range of cognitive, emotional, and physical symptoms that significantly impair daily functioning.

According to the DSM-V, a diagnosis of Major Depressive Disorder (MDD) requires the presence of five or more of the following symptoms during the same two-week period, with at least one symptom being depressed mood or loss of interest/pleasure (anhedonia): depressed mood, markedly diminished interest or pleasure, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive/ inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death, recurrent suicidal ideation or suicide attempt. These symptoms must cause significant distress or functional impairment and cannot be better explained by other medical conditions. Analogously, in the ICD-10, depressive episodes are based on the presence of at least two of the three core symptoms, namely depressed mood, loss of interest and enjoyment and reduced energy and diminished activity. Additionally, at least two or more additional symptoms must be present, including: reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide, disturbed sleep and diminished appetite. Here, the severity is classified as mild, moderate, or severe, depending on the number and intensity of symptoms.

1.1.1 On the importance of studying depressive disorders

Depressive disorders pose an immense psychosocial burden on not only individuals but also society as a whole, particularly in terms of economic costs and strain on healthcare systems: The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) aims to quantify these factors and simulate their impact in the future. Currently and by the year 2050, depressive disorders are among the leading 20 causes of global disability-adjusted life-years (DALYs) and crucially, the highest-ranked mental health condition (Mettananda & Mettananda, 2024). DALYs is a measure combining years of life lost due to premature death and years lived with disability/illness. These findings highlights the significant impact of depression on global health and the need for effective treatments.

This is further underscored by the epidemiology of depressive disorders, as evidenced, for example, by lifetime prevalence rates. These vary from 21 % in countries with higher income (here: France) to 6.5 % in countries with lower income (here: People's Republic of China) (Kessler & Bromet, 2013, page 122). The authors argue that the variation in the prevalence estimates is likely influenced by a combination of substantive factors, measurement differences, and study design elements (Kessler & Bromet, 2013). This means that, even though these are only estimates and not all variations can be attributed to actual differences in prevalence rates, depressive disorders not only place a significant burden on society but also affect an immense number of people. More specifically, one in four individuals in industrialized countries meet the diagnostic criteria for depression at some point in their life.

Moreover, the relative risk of excess mortality in depressed compared with non-depressed individuals is on average 1.5 (Cuijpers et al., 2014). In other words, patients with depression have a 50 % higher risk of dying within the studied period (or even higher considering shorter time periods: 1.83 in the case of ≤ 1 year compared to 1.29 for $>$ 10 years) compared to non-depressed individuals. Taken together, these findings underscore the urgent need for effective interventions to ensure fast and adequate treatment.

1.1.2 Current forms of treatment for depressive disorders

Currently, there are three main treatment options, which will be briefly introduced in the following. These comprise psychotherapy, pharmacotherapy, and neurostimulation, including Non-Invasive Brain Stimulation (NIBS), Electroconvulsive Therapy (ECT) and Deep Brain Stimulation (DBS). All of these methods aim to achieve the same goal through different mechanisms: The general therapeutic objective in the treatment of mental disorders is to ideally achieve remission. Remission is typically defined as reduction of symptoms, or more precisely as a reduction below a threshold score of symptoms (symptomatic recovery) but does not primarily focus on psychosocial functioning (functional recovery). While all symptoms are equally weighted, the absence or reduction of certain symptoms — particularly concentration deficits, sad mood, and fatigue — has been shown to be more crucial for normal functioning in daily life (Fried & Nesse, 2014). This also explains why some patients achieve symptom remission but not functional recovery (IsHak, Greenberg, & Cohen, 2013), which in turn poses ongoing burden on the individual and society.

Psychotherapy aims to achieve remission by targeting maladaptive thought patterns and behaviors while fostering the use of adaptive emotion regulation strategies. There are different variants of therapies (e.g. Cognitive Behavioral Therapy (CBT), third-wave therapies, psychodynamic therapy) with unique foci and interventions (e.g. homework or exposition in CBT and free association or dream interpretation in psychodynamic therapy). Comparing treatment outcomes of different approaches on a meta-analytic level, "CBT was significantly more effective than other psychotherapies, but the difference was small (g = 0.06; 95 % CI: 0-0.12)" (Cuijpers et al., 2023, page 105). Please note, however, that CBT is also the most investigated in terms of the number of studies investigating efficacy, which might impact these results. More specifically, Cuijpers et al. (2023) found response rates of approximately 40 % and remission rates of approximately 36 % in CBT.

Pharmacotherapy aims to achieve remission by modulating neurotransmitter imbalances, such as deficiencies in serotonin, noradrenaline, and dopamine (monoamines). Common antidepressants are, for instance, Selective Serotonin Reuptake Inhibitors which increase serotonin levels or Monoamine Oxidase Inhibitors which prevent the breakdown of several monoamines. In their meta-analysis, Cuijpers et al. (2023) found comparable response and remission rates of pharmacotherapy compared to CBT, however the latter may be more effective at the longer term, while combined treatment is most effective.

Non-Invasive Brain Stimulation (NIBS) aims to improve symptoms by directly influencing neural activity in brain regions associated with depression (for an overview over the neural alterations, see section 1.1.4). As the name suggests, NIBS modulates brain activation through the intact skull bone (for an introduction to NIBS see section 1.4). I will introduce studies on NIBS in the treatment of depressive disorders at a later point (see section 1.4.3), however, generally, NIBS has been found to be effective in reducing depressive symptoms especially by using high-frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS) applied to the left Dorsolateral Prefrontal Cortex (DLPFC) (Lefaucheur et al., 2014). In their meta-analysis, Berlim et al. (2014) found response rates of 30 % and remission rates of 20 %. Please note, that there are also newer variants of rTMS protocols like Theta Burst Stimulation (TBS) but research using these protocols is not yet that extensive. There are, however, first promising results. For instance, specifically focusing on treatment-resistant depression, Duprat et al. (2016) observed 30-40 % response and 30 % remission rates to accelerated intermittent Theta Burst Stimulation (iTBS) applied to the left DLPFC. Combining psychotherapy with NIBS might be a promising approach compared to monotherapy, however corresponding studies are lacking (Tatti et al., 2022).

Another form of neurostimulation that is used primarily in treatment-resistant depression is Electroconvulsive Therapy (ECT). In ECT, a controlled seizure is caused by an electrical charge under brief general anesthesia (Espinoza & Kellner, 2022). There are studies finding that on average, 60-80 % of patients with treatment-resistant depression experience a positive response to the treatment, and 50-60 % achieve remission (Haq et al., 2015; Van Diermen et al., 2018). Interestingly, however, about 40 % of patients relapse within the following 6 months, with as well as without continuation of ECT (Jelovac, Kolshus, & McLoughlin, 2013). Further, there are various side effects like short-term memory loss, headaches or nausea and the underlying mechanisms of ECT are not yet fully understood.

The mechanisms of action of Deep Brain Stimulation (DBS) also remain elusive up to date. It is hypothesized that it "acts through multifactorial mechanisms, including immediate neuromodulatory effects, synaptic plasticity, and long-term neuronal reorganization" (Ashkan, Rogers, Bergman, & Ughratdar, 2017, page 549). In DBS, a stimulation electrode is intracranially implantated using stereotaxic surgery. The electrodes are permanently connected to a neurostimulator delivering electrical impulses. Implicated brain regions have been e.g. the subgenual cingulate cortex, ventral striatum, nucleus accumbens or medial forebrain bundle. A part of the symptom improvement occurs within seconds after the deep brain stimulation electrodes are turned on (Ashkan et al., 2017). In their meta-analysis, Zhou et al. (2018) found that over a period of 1 to 12 months of DBS, the pooled response rates were 40–50 %, while the pooled remission rates were 10–30 % in treatment-resistant depression.

Non-responsiveness to treatment is observed in approximately one-third of patients with depressive disorders, with some studies reporting rates as high as 55 %, depending on the definition of non-responding (McIntyre et al., 2023). Generally, there are diverse methodological issues in all of the above-mentioned studies and meta-analyses on treatment efficacy. These methodological issues are caused by considerable heterogeneity in the investigated patient populations (e.g. symptom severity, diagnoses, comorbid disorders), outcome measures (e.g. use of different questionnaires, number of measures, follow-up time frames), applied treatments (standardization of the intervention, generalizability for different subgroups of patients) and the chosen comparison group (e.g. treatment as usual, active comparator, waiting list), just to name a few. What is important to note is that although the aforementioned treatment options focus on different approaches to achieve remission, they all aim to address certain aberrant processes within the complex system of depression, which are highly interrelated. This understanding forms the foundation for combining interventions that address different mechanisms — an approach reflected in the state-of-the-art treatment of depressive disorders, which integrates psychotherapy and antidepressant medication as well as in some cases ECT (see e.g. Gelenberg et al., 2010).

Please note that in my summary, I have focused solely on remission as a marker of treatment success, and unfortunately, only unsatisfactory remission rates are achieved by current treatment options. Even if satisfactory remission rates were achieved, one could also critique the efficiency of current treatments, including the speed at which improvements occur (e.g. in psychotherapy), and, in terms of effectiveness, the high relapse rates and treatment resistance or side effects. In sum, treatment of depressive disorders is still a current focus of psychiatric research.

1.1.3 Etiological models

To improve the treatment of depressive disorders, it is crucial to first understand and investigate the underlying mechanisms, to then develop targeted interventions. Over time, several etiological models of depression have evolved. Some of them primarily focus on one aspect of the disorder, such as cognitive models explaining depressive symptoms by learned helplessness (hopelessness model by Abramson, Metalsky, & Alloy, 1989), schemas (Beck's cognitive content-specificity hypothesis; Beck, 1979) or the recently integrated combined cognitive bias hypothesis (Everaert, Koster, & Derakshan, 2012). Other models primarily focus on biological aspects like the neurotrophic hypothesis of depression (Duman, Heninger, & Nestler, 1997; Duman & Monteggia, 2006) or the neurotransmitter imbalance/ deficit (biogenic amine hypothesis; Garver & Davis, 1979). Contrary to the models only focusing on one aspect, a commonly known and investigated model is the bio-psycho-social model which traces back to Engel (1977). This model claims that there is a complex interaction between genetic, biological, psychological and social factors in the development of diseases, posing an interdisciplinary approach. Like this, various findings on genetic predispositions, biological alterations like neurotransmitter-imbalances, as well as cognitive, affective and social findings can be considered and integrated. An extension of the bio-psycho-social model is the diathesis-stress model, also known as the vulnerability-stress model (see e.g., Schotte, Van Den Bossche, De Doncker, Claes, & Cosyns, 2006). This model proposes additional dynamic processes based on two factors: A certain vulnerability that varies from person to person, i.e. the predisposition to develop a certain disease, and, as a second factor, stressors that people encounter (for an illustration see figure 1.1). Several factors contribute to a person's vulnerability, like biological, genetic, social and psychological risk factors (rumination as a psychological risk factor is particularly important in the context of this dissertation) but also respective protective factors. This model explains that despite exposure to the same stressors, some people develop a disease while others do not, because interestingly, "[...] most episodes of major depression are preceded by stressful life events (although most people do not become depressed even if they experience a negative life event)" (Hammen, 2005, page 295). An imaginary threshold of symptom development or disease onset is used, which is crossed in some cases and not crossed in others. This threshold is dynamically influenced by abovementioned risk and protective factors (for a theoretical review see Schotte et al., 2006).

In general, distal (stressors in the past, e.g. early adversity) and proximal stressors (those present immediately before disorder onset, e.g. divorce) are differentiated. However, not only major life events and acute stress are associated with depression but especially long-term exposure in the form of chronic stress (stress ongoing for >12 months) (Hammen, 2005; McEwen, 2017).

Analogous to the way in which diagnoses of mental illness are made using the ICD-10 or DSM-V, the diathesis-stress model implies a cut-off above which symptoms are considered clinically relevant. One point of criticism of this approach is the arbitrary definition of a categorical division into healthy and mentally ill or not in need of help and qualified for treatment.

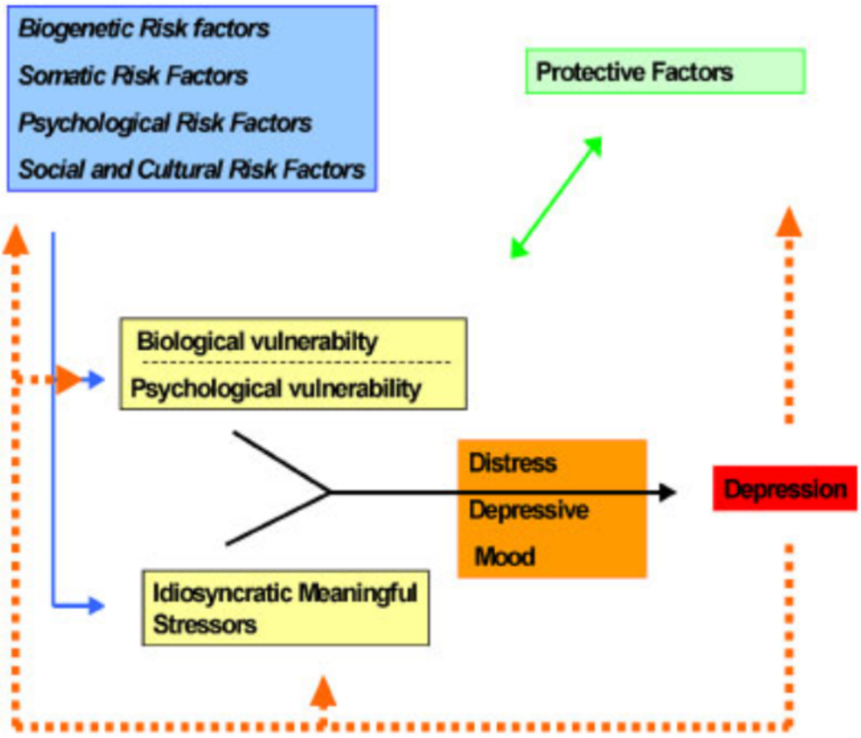


Figure 1.1
Schematic illustration of the diathesis–stress model of depression. The dotted line indicates feedback effects in recurrent depression. Taken from "A biopsychosocial model as a guide for psychoeducation and treatment of depression" (Schotte et al., 2006, page 319). Copyright 2006 by Wiley-Liss, Inc.

1.1.4 From psychopathology to pathophysiology

In line with the basic rationale of the studies in this dissertation, I would like to focus in particular on the integration of cognitive and affective symptoms and processes in depressive disorders, as well as neuronal changes at the level of functional networks. Crucially, (neuro-)physiological findings and altered functioning on a cognitive or affective level have been predominantly investigated on their own rather than all findings being integrated into one coherent model of the psychopathology and pathophysiology of depression (Belzung, Willner, & Philippot, 2015). I will start off by shortly introducing the triple network model of psychopathology by Menon (2011), which proposes a complex interplay of predominantly three networks, the Salience Network (SN), Default Mode Network (DMN) and Central Executive Network (CEN) (see figure 1.2) (for a recent review of the brain's structural and functional changes in MDD, see also Dai, Zhou, Xu, & Zuo, 2019). Then, I will integrate psychopathological findings on a cognitive or affective level. Note, however, that there are inconsistencies in the literature and ongoing research regarding which regions are (mutually exclusive) implicated in which brain network (for an exemplary discussion in the context of brain networks associated with executive function, see Witt, van Ettinger-Veenstra, Salo, Riedel, & Laird, 2021).

One of these networks constitutes the Salience Network (SN), which is, as the name suggests, involved in the identification and evaluation of salient internal or external stimuli such as threat. It allocates attention towards these stimuli and is generally involved in emotional processing. Brain regions associated with the SN are especially the dorsal anterior cingulate cortex, anterior insula (orbital frontoinsula), amygdala and temporal poles, among others (Goulden et al., 2014; Hermans, Henckens, Joëls, & Fernández, 2014; Seeley et al., 2007; Van Oort et al., 2017). The second brain network to mention here is the Default Mode Network (DMN), which is associated with spontaneous and self-generated thought and therefore also associated with ruminative thinking. Regions which are most commonly named in this context are the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and precuneus (Buckner, Andrews-Hanna, & Schacter, 2008; Goulden et al., 2014; Van Oort et al., 2017). The third network of the triple network model of psychopathology by Menon (2011) is the Central Executive Network (CEN), which is activated during higher-order cognitive functions like, for instance, attention, working memory and decision-making. The CEN comprises brain regions such as the dorsomedial prefrontal cortex, the Dorsolateral Prefrontal Cortex (DLPFC) and the posterior parietal cortex (Goulden et al., 2014; Hermans et al., 2014; Seeley et al., 2007; Van Oort et al., 2017).

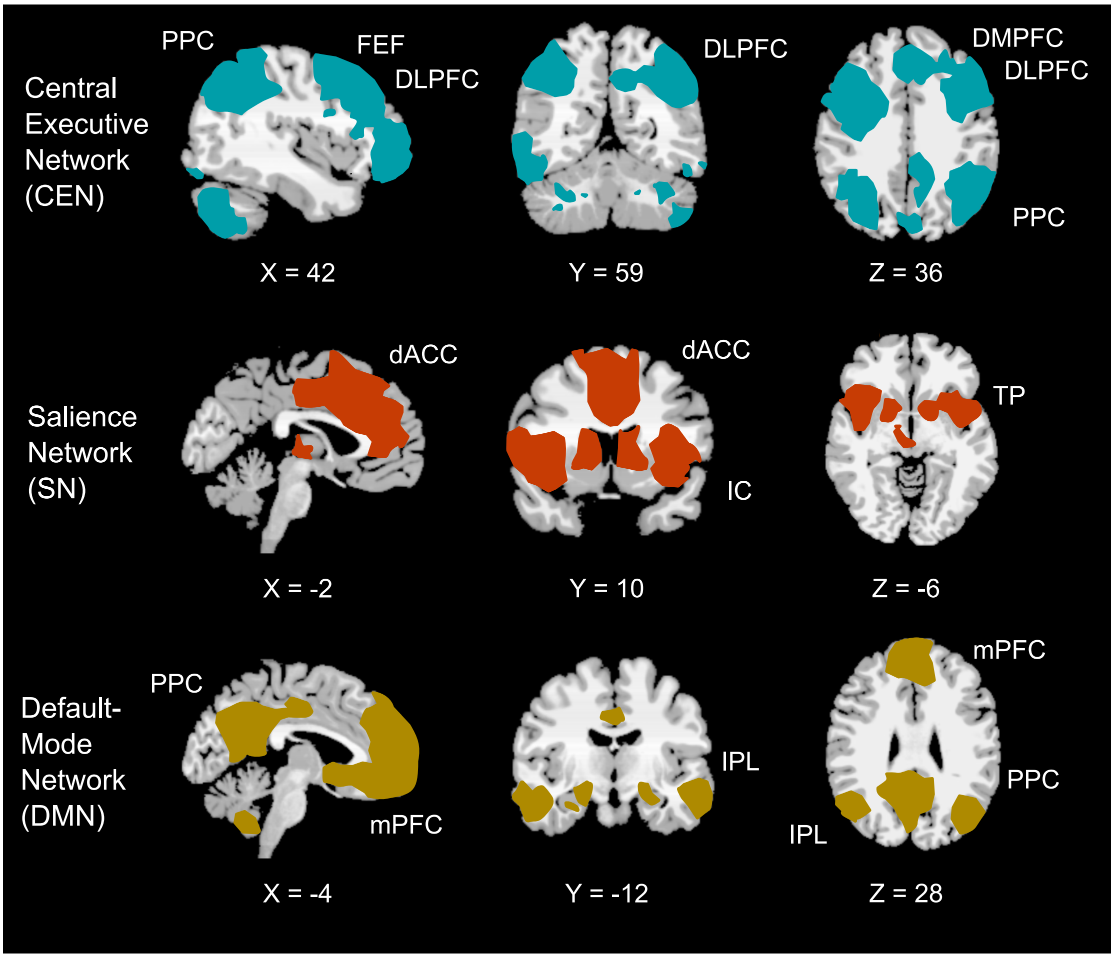


Figure 1.2
Illustration of the Triple Network Model comprising the Default Mode Network (DMN), Salience Network (SN) and Central Executive Network (CEN). The CEN, depicted in blue, is anchored in the Dorsolateral Prefrontal Cortex (DLPFC) and the posterior parietal cortex (PPC). The SN, depicted in red, is anchored in the insular cortex (IC) and dorsal anterior cingulate cortex (dACC). The DMN, depicted in yellow, is anchored in the posterior parietal cortex (PPC) and medial prefrontal cortex (MPFC). TP = temporal pole, FEF = frontal eye fields, IPL = inferior parietal lobule. Adapted from "Large-scale brain networks and psychopathology: A unifying triple network model" (Menon, 2011, page 494), with modifications. Copyright 2011 by Elsevier Ltd.

In depression, an increased activation and connectivity within regions of the DMN have been repeatedly observed (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Hamilton et al., 2011; Nejad, Fossati, & Lemogne, 2013). These findings have been associated with and therefore hypothesized to contribute to excessive self-focus, inattention, and ruminative thinking (Belzung et al., 2015; de Quevedo, Carvalho, & Zarate, 2019; Hamilton et al., 2011; Nejad et al., 2013; Zhu et al., 2012) (for the neural correlates of rumination, see section 1.2.6). Moreover, hyperconnectivity of the DMN with the SN (Hamilton et al., 2011; Manoliu et al., 2014) and altered intrinsic functional connectivity of the DMN with the CEN have been found in patients with depression (Jiang et al., 2017; Manoliu et al., 2014). Generally, findings regarding the CEN are less consist concerning hypo- or hyper-activation, which is most probably due to different underlying processes: "[...] although the DLPFC has been found to be over-activated in reward-related processes (likely to compensate for hypoactive striatal responses to reward cues), the same region has shown hypo-activation in affective and cognitive tasks requiring emotional or stress regulation, cognitive control, and/or shifting attention to external task demands" (Pizzagalli & Roberts, 2022, page 246) (for a summary, see de Quevedo et al., 2019).

Particularly the observed prefrontal hypoactivation (Pizzagalli & Roberts, 2022) is considered a promising target for NIBS intervention (see also section 1.4.3). As most of the aforementioned alterations in brain activation reverse with symptom remission, the idea is to somewhat "normalize" brain functioning and recover it past the repeated stimulation periods via mechanisms of neuroplasticity. Coming back to the idea of depression as a multifaceted phenomenon of different involved levels and processes, psychotherapy has also been associated with neural changes. A recent meta-analysis on the effects of psychotherapy for depressive (and anxiety) disorders found decreased activation, post- compared to pre-therapy in prefrontal regions such as the Inferior Frontal Gyrus (IFG), along with significant decreases in activity in the anterior cingulate/paracingulate gyrus and the insula (Marwood, Wise, Perkins, & Cleare, 2018).

Potentially, in the future, interventions could be personalized by targeting the specific cognitive, affective and (neuro-)physiological alterations apparent in a patient. Revisiting the initial findings that treatment success is often only considered as a symptomatic and not necessarily functional recovery, targeted interventions may help to reduce symptoms that have been shown to be crucial for normal functioning in daily life like concentration deficits, sad mood, and fatigue (Fried & Nesse, 2014).

1.2 Rumination

1.2.1 What do we mean by rumination?

One of the first and most research-generating theories of rumination is the Response Styles Theory by Nolen-Hoeksema (1991), which posits that individual differences in how people respond to negative mood can influence depressive symptoms. This theory defines rumination as "behaviors and thoughts that focus one's attention on one's depressive symptoms and on the implication of these symptoms" (Nolen-Hoeksema, 1991, page 569). That means that ruminators habitually think about their symptoms, e.g., how they experience depressed mood, hopelessness and concentration problems, the causes and the (negative) consequences of these symptoms, e.g., reduced quality of life, social problems, consequences at work. This very early theory characterizes ruminative thinking as a cognitive vulnerability to develop depressive disorders and defined it rather as a trait-like construct, which is consequently not situation-specific ("trait rumination"). However, other researchers also observed situation-specific state-like ruminative processes that have been found to be elicited in response to stress ("stress-reactive rumination" or "state rumination") (Alloy et al., 2000; Hilt, Aldao, & Fischer, 2015; Robinson & Alloy, 2003; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018; Shull et al., 2016). Robinson and Alloy (2003), for example, found a distinct predictive value of state rumination but not trait rumination in terms of the prospective onset, number, and duration of major depressive episodes. They argue, that stress-reactive rumination precedes depression whereas ruminative thinking as proposed by the Response Styles Theory might occur in response to depression. Following these findings, several studies found that rumination can be induced using for instance rumination inductions (explicit instructions using prompts) or experimental stress paradigms (e.g. the Trier Social Stress Test; TSST) (see e.g. Hilt et al., 2015; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018; Shull et al., 2016). Today, there are a number of theories, all with different foci (e.g. rumination on sadness, rumination following social interactions) and assuming different temporal stability (state vs. trait rumination) (for a review see Smith & Alloy, 2009). Although originally defined in the context of depression, rumination has also been observed in patients with anxiety disorders (McLaughlin & Nolen-Hoeksema, 2011; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013; Nolen-Hoeksema, 2000; Smith & Alloy, 2009), eating disorders (Naumann, Tuschen-Caffier, Voderholzer, & Svaldi, 2016; Nolen-Hoeksema, Stice, Wade, & Bohon, 2007), personality disorders (Meaney, Hasking, & Reupert, 2016) as well as substance use disorders (Nolen-Hoeksema et al., 2007), among others. Nowadays, rumination is regarded as transdiagnostic, i.e. it is apparent across psychopathology and, whereas the process is the same, the content of thought is disorder–specific (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Watkins & Roberts, 2020).

Following this transdiagnostic notion, Watkins and Roberts (2020) published an extensive review that aimed to summarize research on ruminative thinking in different branches of research. They synthesized their findings into one model explaining the underlying mechanisms driving state and trait rumination, the so-called H-EX-A-GO-N model (**H**abit development, **EX**ecutive control, **A**bstract processing, **GO**al discrepancies, **N**egative bias) (Watkins & Roberts, 2020). The model "hypothesizes that each of the five mechanisms outlined contributes to the onset and maintenance of rumination in an additive and synergistic way: with each additional mechanism present, the greater the likelihood that an individual develops a propensity towards trait rumination." (Watkins & Roberts, 2020, page 14). That means, that components are assumed to interact with each other rather than only acting independently. Let's have a closer look at the proposed mechanisms. The H-EX-A-GO-N model assumes that "the core mechanism for the development of pathological rumination is the formation of unhelpful repetitive thinking as a mental habit (**H**)" (Watkins & Roberts, 2020, page 12). This could on the one hand be shaped by parenting style. More specifically, parents may experience ruminative thinking and children "are learning from the model", which is further in line with the Response Styles Theory (Nolen-Hoeksema, 1991). Habit formation (**H**) can also be explained by mere repetition. Initially, rumination may have served a goal-directed purpose (e.g., analyzing past "mistakes in social situations" to avoid repeating them in the future). However, through repeated rumination and its association with a lowered mood, a habit develops and over time, negative mood itself becomes the trigger for rumination, leading to a shift from deliberate reflection to automatic behavior, reinforced by an automatic association. Therefore, habit formation is closely linked to the factor "goal discrepancies" (**GO**) which refers to differences between an individuals current situation (e.g. I had an argument with my best friend Julia and now we are not talking anymore) and their desired outcome (e.g. I would like to be friends again). Interestingly, "[t]his goal-habit approach can explain how state rumination can both be triggered by specific circumstances in all people and how trait rumination can develop in some individuals who have experienced the relevant setting and learning conditions." (Watkins & Roberts, 2020, page 11). In line with the proposed interaction of the different components of the model, a negative information-processing bias (**N**) is likely to increase the attention to unsatisfactory goal process or goal discrepancies. Individuals with such a bias exhibit "tendencies to preferentially attend to negative information, show delayed disengagement from negative content, interpret ambiguous information negatively, and recall more negative information" (Watkins & Roberts, 2020, page 13). In our example this would correspond to the fact that individuals with ruminative thinking might be replaying the argument with their best friend in their mind rather than recalling the times their best friend told them how much they mean to them. Closely related is abstract processing (**A**) which "involves general, superordinate, and decontextualized mental representations that convey the essential meaning, causes, and implications of goals and events (the “why” aspects of an action [e.g. “Why did this happen to me?“]). In contrast, there is a more adaptive processing style which is more concrete and that involves a focus on the direct, specific, and contextualized experience of an event. This processing mode addresses the details of goals, events, and actions that denote the feasibility, mechanics, and means of “how” to do the action ["How can I be friends with Julia again?"] (Watkins, 2008)." (Watkins & Roberts, 2020, page 12). The last component of the H-EX-A-GO-N model is executive control (**EX**) or rather deficits in executive control in individuals with ruminative tendencies. "Executive functions can be fractioned into three major components: shifting, updating and monitoring of representations within working memory (updating), and inhibition (Miyake et al., 2000)." (Watkins & Roberts, 2020, page 11). With deficits in executive functioning (**EX**), negative contents of the working memory (see also **N**) are more difficult to be updated to task-relevant information, which, in turn, might hinder goal-directed behavior (**GO**). Many pathways through which the components of the H-EX-A-GO-N model influence one another are well-documented (for a review see Watkins & Roberts, 2020), while others are still under investigation, making this model a valuable source for generating further research.

1.2.2 What do we not mean by rumination?

Along with the appropriate assessment of ruminative thinking comes the conceptual delimitation of it from other constructs. In the following I would like to distinguish rumination from related terms (e.g. self-reflection, problem-solving, worry).

In everyday psychology, rumination is also often associated in a positive way (Papageorgiou & Wells, 2001). For example by thinking intensively about certain problems or about one's own behavior and past situations, the term is often associated with self-reflection and problem-solving. Both types of behaviors are perceived as adaptive in a sense that "a solution" is found or some form of implication for the future follows (e.g. the next time I am in a similar situation, I now know what I have to do). Adaptive in this context illustrates precisely the crucial aspect of differentiation: While problem-solving and self-reflection are most probably adaptive in the sense of adapting/adaptable, which means as a result, they adjust to a specific situation. Ruminative thinking, on the contrary, has little to no goal-orientation (Watkins & Nolen-Hoeksema, 2014) and is actually negatively related to problem-solving (e.g., Lyubomirsky, Tucker, Caldwell, & Berg, 1999). Furthermore, rumination is perceived as uncontrollable, whereas adaptive thinking can be intentionally interrupted. Revisiting the H-EX-A-GO-N model (Watkins & Roberts, 2020) and especially the **H** (Habit formation), ruminative thinking may have once been adaptive, but over time, due to habit formation and the development of habitual tendencies, it no longer supports goal-directed behavior (**GO**).
Concerning self-reflection and rumination, both indeed involve heightened self-attention, however the latter is associated with perceived threats, losses, or injustices and considered more passive, automatic and therefore uncontrollable (Trapnell & Campbell, 1999) compared to self-reflection being more active, generating new insights and "motivated by curiosity or epistemic interest in the self" (Trapnell & Campbell, 1999, page 297).

Another related construct is "worry" which, along with "rumination", is often grouped under the broader categories of perseverative thought or repetitive negative thinking. As the name suggests, repetitive negative thinking is defined as though processes that occur repetitively, are passive and/or relatively uncontrollable and further focused on negative content (Ehring & Watkins, 2008). Up to date, there is an ongoing debate on the exact differentiation or unity of (components of) rumination and worry. Among studies that investigate their differences and similarities, results indicate high correlations of self-report measures and further associations with symptoms of depressive and anxiety disorders to a similar extent (e.g., Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; Segerstrom, Tsao, Alden, & Craske, 2000; Siegle, Moore, & Thase, 2004). In their meta-analysis regarding the structure and differentiability of common emotion regulation strategies, Naragon et al. (2017) find that worry and rumination load onto a factor along with other maladaptive strategies. On the contrary, focusing specifically on the differentiation of worry and rumination, Stade and Ruscio (2023) find in their meta-analysis that both reflect closely related but non-redundant constructs. Traditionally, worry is associated with anxiety and is more future-oriented whereas rumination is associated with depression and more past-oriented. With these findings, it remains inconclusive whether differences that have been found are actually differences in the content (e.g. depression-specific or anxiety-specific) and/or differences in the process itself, respectively. It also remains unclear whether the distinction is clinically relevant and individuals with symptoms of these related constructs benefit from the same treatment due to a similar underlying cognitive process, making the distinction merely a construct of the literature (see e.g., Joubert et al., 2023; Querstret & Cropley, 2013).

In order to move away from specific constructs to gain a more general overview, I would like to shortly introduce the work of Christoff et al. (2016) which is originally focused on spontaneous thought and mind-wandering. They argue that mental states can be generally distinguished (and constrained) regarding the content and the transitions between them (see figure 1.3). Compared to spontaneous thought, there are stronger automatic constraints in rumination and obsessive thoughts. This is reflected by feelings of uncontrollability and high degrees of automation, which is typically reported by ruminators. In other words, there is a spontaneous progression of thoughts and they transition automatically. On the other hand, the content of mental states can be constrained to varying degrees, ranging from weak to strong. Strong, deliberate constraints are evident in goal-directed thinking, where only task- or goal-relevant content is the focus with cognitive control actively employed. In contrast, spontaneous thought is associated with less deliberate control, with constraints gradually diminishing from creative thinking — which still involves some form of guidance — to mind-wandering, and ultimately to dreaming, where deliberate constraints are minimal. Christoff et al. (2016) place rumination and obsessive thoughts along this continuum, ranging from weak to strong deliberate constraints (see figure 1.3). This means that, although there are no strict constraints on the content of thoughts, during rumination (and obsessive thinking), thoughts tend to remain focused on a single theme or topic. There are indeed studies showing positive associations with ruminative thinking and the unacceptable thoughts/neutralizing domain of Obsessive Compulsive Disorder (OCD) (Raines, Vidaurri, Portero, & Schmidt, 2017), or general severity of OCD symptoms (Wahl, Ertle, Bohne, Zurowski, & Kordon, 2011). This further highlights the role of ruminative processes as a transdiagnostic factor in psychopathology, underscoring their broad relevance across different mental health conditions.

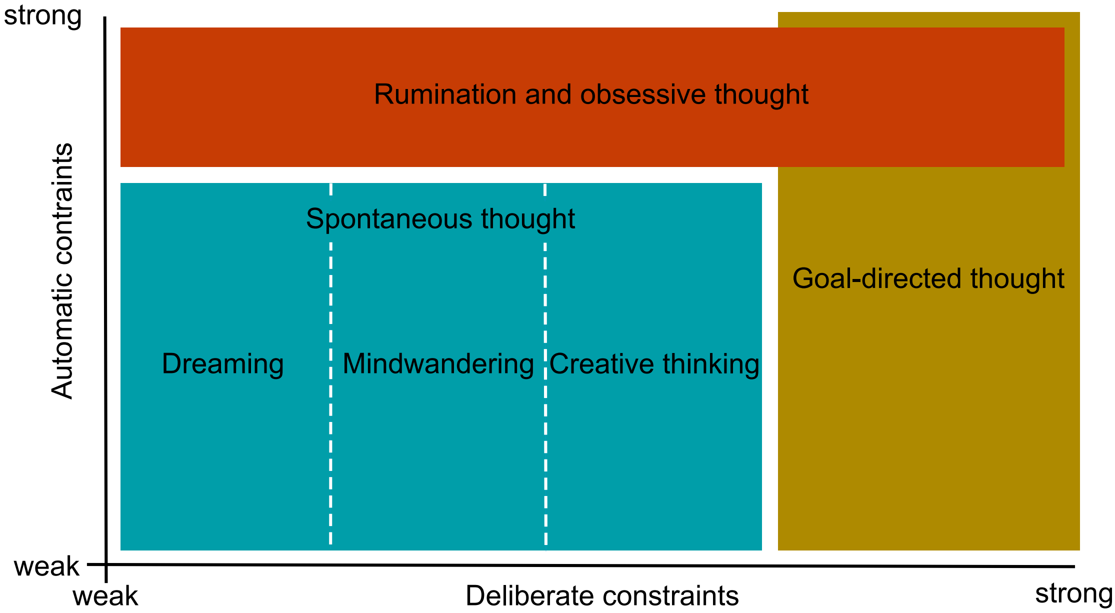


Figure 1.3
Schematic representation of the conceptual space defining different types of thought. Deliberate and automatic constraints limit thought contents and their changes over time. Adapted from "Mind-wandering as spontaneous thought: A dynamic framework" (Christoff et al., 2016, page 2). Copyright 2016 by Macmillan Publishers Limited, part of Springer Nature.

1.2.3 How can we assess ruminative thinking?

Due to the different underlying theories or rather research fields, there are various questionnaires that claim to capture rumination (for a review, see Smith & Alloy, 2009). In particular, however, trait questionnaires that measure a basic tendency to ruminate are often used. Based on the Response Styles Theory (Nolen-Hoeksema, 1991), Nolen-Hoeksema and Morrow (1991) developed the Response Styles Questionnaire (RSQ) with the Ruminative Response Scale (RRS) being a subscale of this questionnaire. The RRS, both in its original (Nolen-Hoeksema & Morrow, 1991) and revised version (Treynor & Gonzalez, 2003), remains widely used today. Notably, Treynor and Gonzalez (2003) revised the version by Nolen-Hoeksema and Morrow (1991) because the original items significantly overlapped with measures of depressive symptomatology.

Another questionnaire used to asses trait rumination is the Perseverative Thinking Questionnaire (PTQ) which was developed by Ehring et al. (2011). The PTQ aims to provide a content-independent, i.e. not depression-specific measure of rumination. The items further focus substantially more on the "process" of ruminative thinking, e.g. assessing the repetitiveness, intrusiveness as well as disengagement-difficulties.

Generally, trait measures are assumed to have a negligible amount of situation-specific variance, which manifests the difference to state measures. Assessing stress-reactive, situational rumination remains a challenge to this day. In some cases, trait measures are also used that are to be answered at a specific time (e.g. at the current moment, during the last resting-state measurement). However, questionnaires have also been developed specifically for the assessment of state rumination, e.g. the Stress-Reactive Rumination Scale (Robinson & Alloy, 2003), the Brief State Rumination Inventory (Marchetti, Mor, Chiorri, & Koster, 2018) or the Stress-Reactive State Rumination Questionnaire (SRSRQ) (Int-Veen, Laicher, Ehlis, Fallgatter, & Rosenbaum, n.d.).

A general problem inherent in trait questionnaires is the assumption that individuals answering the items have the "ability to introspectively assess their own habitual tendencies regarding their whole lifetime and the comparability of this introspection across everyone else" (Int-Veen, Ehlis, Fallgatter, & Rosenbaum, 2024, page 11). Furthermore, we intrinsically assume that the given answers, are valid. That means, the instructions and items are correctly understood and answered truthfully. Researchers do not always keep these underlying assumptions in mind, which can have detrimental consequences as I report in a recent publication regarding data using the RRS (Int-Veen et al., 2024).

One promising way to overcome some of the aforementioned problems and increase ecological validity could be to capture ruminative thinking in the form of a "behavioral assessment". This is the idea of the Think Aloud Paradigm (TAP), that goes back to verbalization think aloud trials by Ericsson and Simon (1980) where individuals verbalize their thoughts as they are still available in short-term memory. First studies concerning the application in the context of ruminative thinking deem promising (Int-Veen, Fallgatter, Ehlis, & Rosenbaum, n.d.; Raffaelli et al., 2021).

1.2.4 Psychological consequences of rumination

Regarding the psychological consequences of ruminative thinking, there are two very influential and extensive reviews summarizing the literature until then. The first review by Nolen-Hoeksema and colleagues (2008) primarily focuses on the empirical support for the Response Styles Theory (Nolen-Hoeksema, 1991), which is, as already mentioned, originally proposed limited to the context of depressive rumination. Studies, indeed, support most aspects of the theory, like enhanced depressed/negative mood due to ruminative thinking, enhanced negative thinking as well as interference with effective problem-solving and instrumental behavior. Like this, "rumination exacerbates and prolongs distress, particularly depression" (Nolen-Hoeksema et al., 2008, page 401). These findings are further supported by the review of Watkins and Roberts (2020) which states that "[a] key finding across experimental and prospective studies is that rumination can exacerbate psychopathology in at least four ways: (a) it magnifies and prolongs existing negative mood states [namely sadness, anger, anxiety and depression] and associated negative thinking; (b) it interferes with effective problem-solving; (c) it interferes with active instrumental behaviour; (d) it reduces sensitivity to changing contingencies and context" (Watkins & Roberts, 2020, page 2).

Consequently, ruminative thinking perpetuates a vicious cycle of negative affect and negative cognition, increasing the likelihood that initial symptoms of a corresponding (subclinical) mental disorder will worsen and, for instance, develop into episodes of major depression. This is in line with the finding that rumination predicts the onset of depressive disorders rather than the duration of corresponding episodes (Nolen-Hoeksema et al., 2008), which contradicts the original assumption of the Response Styles Theory (Nolen-Hoeksema, 1991).

1.2.5 Physiological consequences of rumination

Effects on the cardiovascular system. One very influential hypothesis also focusing on these physiological consequences of repetitive negative thinking is the perseverative cognition hypothesis by Brosschot et al. (2006). After reviewing studies regarding the association of repetitive negative thinking with cardiovascular, endocrinological, immunological, and neurovisceral activity, the authors state "[...] that perseverative cognition moderates the health consequences of stressors because it can prolong stress-related affective and physiological activation, both in advance of and following stressors" (Brosschot et al., 2006, page 113). This hypothesis has its primary focus on the delayed physiological recovery, that means the duration of the stress response and the prolonged activation of the cardiovascular system (for a review, see Brosschot et al., 2006; Brosschot, Pieper, & Thayer, 2005). Another important aspect is the increased reactivity to stress as indicated by the magnitude of the physiological response. A recent meta-analysis of a total of 43 studies (Busch, Possel, & Valentine, 2017) observed large effects of rumination on cardiovascular responses, more specifically, exaggerated heart rates, diastolic and systolic blood pressure.

Interestingly, investigating the differential effects of state and trait rumination on blood pressure and heart rate variability (HRV) recovery, Key and colleagues (2008) found no significantly impaired cardiovascular recovery due to higher state rumination in high trait ruminators but only low ruminators. These findings stress the importance of differentiating temporal aspects of rumination and an appropriate assessment.

In their meta-analysis of 60 studies, Ottaviani et al. (2016) replicated the above findings of the association of repetitive negative thinking and cardiovascular alterations: They observed increased systolic (g = .45) and diastolic blood pressure (g = .51) in experimental studies, increased heart rates (g = .28 and g = .20) and lower heart rate variability (g = .15 and g = .27) in experimental and correlational studies, respectively. According to the conventional standard of Cohen (1988), the effects on blood pressure can be interpreted as medium to large while effects on heart rate and heart rate variability are generally categorized as small.

Taking together these findings, ruminative thinking does not only affect mental health, but over time and repetition, rumination potentially increases susceptibility to cardiovascular disease.

Effects on the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis). An adjacent research branch focuses on the effects of rumination or repetitive negative thinking on the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis) and most frequently reported cortisol responses. In their review of 15 studies investigating the association of rumination and cortisol, Zoccola and Dickerson (2012) were faced with more heterogeneous findings compared to the impact of rumination on the cardiovascular response. Nevertheless, they observed that higher state rumination was linked to increased cortisol levels. They further distinguished between stress-reactive rumination (e.g., in response to social-evaluative threats or laboratory stressors), which was generally associated with heightened cortisol reactivity or delayed recovery, and depression-related rumination (measured with instruments such as the Response Styles Questionnaire (RSQ)/Ruminative Response Scale (RRS), which, as noted, overlap with depressive symptoms), which was linked to lower cortisol responses or showed no significant deviations.

These findings were further replicated and extended by the meta-analyis of Ottaviani et al. (2016) that found increased cortisol levels (g = .36 and g = .32) in experimental and correlational studies, respectively. Based on conventional standards these can be interpreted as small to medium.

Closing this section I would like to emphasize two further studies. In the first, Gianferante et al. (2014) investigated the impact of repeated exposure to a stressor, namely the Trier Social Stress Test (TSST), which 27 healthy participants underwent twice on two consecutive afternoons. Stress-reactive ruminative thinking predicted non-habituation of HPA-axis responses as assessed using salivary cortisol samples. This finding, together with the study of Zoccola and Dickerson (2015) who extended the sampling period of salivary cortisol to the evening after stressor-exposure, suggests that there might be a very prolonged, long-lasting effect of ruminative thinking. Zoccola and Dickerson (2015) further argued that one factor contributing to heterogeneous results in studies investigating rumination might be that several study procedures inherently hinder ruminative thinking (e.g. by completing questionnaires and too short resting phases). Please note, however, that in the first study (Gianferante et al., 2014) the effect was driven by state rumination, independently of trait rumination, while in the second study (Zoccola & Dickerson, 2015), findings were based on trait rumination. Further research is needed to clarify the exact mechanisms; however, it is clear that ruminative thinking has a significant impact on physiological stress responses.

1.2.6 Neural correlates of rumination

I would like to close the section on ruminative thinking by summarizing the neural correlates associated with rumination. These findings, in particular, lay the foundation for the idea of influencing rumination with Non-Invasive Brain Stimulation (NIBS) and thus potentially treating it in a clinical context in the future.

In an fMRI study investigating 7 patients with depression and 10 healthy individuals, Siegle et al. (2002) presented positive, negative and neutral words and participants were asked to indicate the emotionality by pushing a corresponding button. They observed greater bilateral sustained amygdala activity to negative compared to positive words in patients compared to healthy controls. They further used several different questionnaires to assess rumination and observed in some correlations with the difference in activity. However, there is only low power due to the limited sample size.

Ray et al. (2005) conducted an fMRI study with 24 females who viewed negative or neutral photos and were instructed to increase or decrease negative affect by using cognitive reappraisal or to just look at the picture and "respond naturally without using reappraisal" (Ray et al., 2005, page 158). Again, using three different rumination scales, the authors found that "[i]ndividual differences in rumination correlated with increases in amygdala response when participants were increasing negative affect and with greater decreases in prefrontal regions implicated in self-focused thought when participants were decreasing negative affect" (Ray et al., 2005, page 156).

These first studies both only correlated rumination scores with the magnitude of activation in specified brain regions, but did not incorporate an experimental manipulation of ruminative thinking. They suggest that amygdala activation, which is associated with arousal of negative affect, is important in the context of rumination. Further, decreases in prefrontal regions, namely the left Ventrolateral Prefrontal Cortex (VLPFC), suggest that ruminators "chronically recruit brain regions associated with updating the affective salience of stimuli, even when not instructed to regulate their affect" (Nolen-Hoeksema et al., 2008, page 413).

Later studies like the fMRI study by Cooney et al. (2010) that investigated 14 patients diagnosed with Major Depressive Disorder (MDD) and 14 healthy individuals also included experimental rumination inductions. The authors used an enhanced version of the rumination induction originally developed by Nolen-Hoeksema and Morrow (1993): Participants read statements of three conditions, namely "rumination (RUM; “Think about what people notice about your personality”), abstract distraction (ABS; “Think about what contributes to team spirit”), and concrete distraction (CON; “Think about a row of shampoo bottles on display”)" (Cooney et al., 2010, page 471). They found that "[d]epressed participants exhibited increased activation in the orbitofrontal cortex, subgenual anterior cingulate, and dorsolateral prefrontal cortex as compared with healthy controls during rumination versus concrete distraction. Neural activity during rumination versus abstract distraction was greater for depressed than for control participants in the amygdala, rostral anterior cingulate/medial prefrontal cortex, dorsolateral prefrontal cortex, posterior cingulate, and parahippocampus. These findings indicate that ruminative self-focus is associated with enhanced recruitment of limbic and medial and dorsolateral prefrontal regions in depression" (Cooney et al., 2010, page 470). Please note that using rumination induction tasks, however, could alter the neural activation observed as these tasks to some degree might exhibit demand character and lack ecological validity.

As mentioned earlier, ruminative thinking can also be induced through experimental stress paradigms. The advantage of such an indirect method is that it elicits less demand characteristics and may potentially be more ecologically valid. Investigating the neural correlates using functional Near-Infrared Spectroscopy (fNIRS), recent studies employing the TSST further revealed hypo-activation in the bilateral Dorsolateral Prefrontal Cortex (DLPFC) in depressed patients and individuals with high trait rumination under stress (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018). In all three studies, both clinical analog samples and patient with depression (DP) underwent the TSST and converging findings with regard to selectively increased state rumination and frontal hypo-activation in high trait ruminators and DP, compared to HC were observed. Specifically, these results indicated that the stress-rumination link was mediated by reduced activation in the DLPFC and IFG during social stress exposure.

Up to date, there are multiple neuroimaging studies investigating ruminative thinking, or more broadly, self-generated thought. In patients with depression but also non-clinical populations, studies find mostly greater activation and connectivity within the amygdala, medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and precuneus, which are associated with the Default Mode Network (DMN) (e.g. Berman et al., 2011; Cooney et al., 2010; Hamilton, Farmer, Fogelman, & Gotlib, 2015; Hamilton et al., 2011;

Jacob et al., 2020; Jones, Fournier, & Stone, 2017; Mandell, Siegle, Shutt, Feldmiller, & Thase, 2014; Murphy, Barch, Pagliaccio, Luby, & Belden, 2016; Nejad et al., 2019; Philippi et al., 2018; Ray et al., 2005; Siegle et al., 2002) (for reviews see Fox et al., 2018; Nejad et al., 2013; Watkins & Roberts, 2020). While ruminative thinking — which is characterized by increased self-focus and high automaticity — is intuitively linked to the DMN, it is also associated with deficits in executive control, as described in the H-EX-A-GO-N model by Watkins and Roberts (2020). Surprisingly, however, there is much less research on the neural correlates of rumination in relation to deficits in executive control and corresponding neural changes in the Central Executive Network (CEN). One very recently published study by Wei et al. (2024) aimed to disentangle the neural correlates of trait and state rumination using connectome-based predictive modeling, a data-driven approach using functional connectivity data to predict state and trait rumination. Their results yielded on the one hand shared neural mechanisms; however, broader and stronger functional connectivity in trait compared to state measures. Trait rumination involved functional connectivity within the DMN, of course, as well as within the dorsal attention network. Functional connectivity between the DMN and Central Executive Network (CEN) was predictive of state as well as trait rumination. Lastly, trait rumination only was associated with functional connectivity between the dorsal attention network and the Salience Network (SN).

Please note, however, that the direction of causality in ruminative thinking and the associated brain activation patterns is not yet established. This is well summarized by Nolen-Hoeksema et al. (2008): "Certain [...] changes in neural activity may be both causes and consequences of rumination" (Nolen-Hoeksema et al., 2008, page 411).

An important point to consider in this context, as mentioned earlier in this section, is that certain questionnaires designed to assess ruminative thinking show a high overlap with measures of current depressive symptoms (see, e.g., Treynor & Gonzalez, 2003). Consequently, the exact differentiation of neural alterations due to depressive symptomatology and ruminative thinking, respectively, remains inconclusive. Moreover, appropriately validated psychometric measures of state rumination have only been available for a few years (see section 1.2.3).

Together with the few studies conducted to date, further studies are desperately needed. The extent to which state and trait aspects can be differentiated, as well as a comprehensive neural model that summarizes all findings, remains to be established.

1.3 Stress

1.3.1 Definition and models of stress

The first recognition of the concept of stress in the research literature, although in a more biological sense, is often attributed to Hans Selye (1936). This is, even though "[John W.] Mason [, a physician at the Walter Reed Army Institute of Research, Washington,] pointed to earlier usage of the term and parallel formulations of the links between emotional stress and disease" (Jackson, Ramsden, Cantor, & others, 2014, page 22).

Nevertheless, Selye's report of a nonspecific bodily response to "acute non-specific nocuous agents" (Selye, 1936, page 32) undeniably marked a pivotal contribution in the history of stress (Jackson et al., 2014).

Decades later, Lazarus shaped a more cognitive or psychological view on the topic of stress by introducing the Transactional Model of Stress and Coping (Lazarus, 1966; Lazarus & Folkman, 1984). According to this theory, stress is elicited by a situation depending on an individual's cognitive appraisal, or more generally speaking, psychological context. Lazarus and Folkman (1984) define cognitive appraisal as "an evaluative process that determines why and to what extent a particular transaction or series of transactions between the person and the environment is stressful" (Lazarus & Folkman, 1984, page 19). They further distinguish between two types of cognitive appraisal: Primary and secondary appraisal. Primary appraisal is focused on the personal relevance of a situation. Specifically, they suggest that situations can be appraised in one of three ways: Irrelevant, benign-positive, or stressful, whereas stressful is equivalent to threatening, challenging or harmful. Secondary appraisal, on the other hand, is concerned with evaluating "what might and can be done" (Lazarus & Folkman, 1984, page 35). As a combination of both appraisal forms, stress is experienced, for instance, when a situation is perceived as more threatening to the individual (primary appraisal) compared to the resources they have available (secondary appraisal).

Following the emphasis on psychological factors in perceiving stress, McEwen (1993) proposed the Allostatic Load Model, which led to a more holistic view on stress. The model emphasizes the balance between adaptive stress responses, the so-called allostasis, and the damaging effects of chronic stress ("allostatic overload"). "Allostasis refers to the active process of adapting and maintaining stability (or homeostasis) through the production of mediators, like cortisol, that promote adaptation" (McEwen & Akil, 2020, page 12). On the other hand, "[a]llostatic load refers to the price the body pays for being forced to adapt to adverse psychosocial or physical situations” (McEwen, 2000, page 110f). Consequently, this model incorporates on the one hand the protective effects of (acute) stress but also the damaging effects of repeated, chronic exposure to stress. Importantly, McEwen (1993) argues, that on the one hand, physical stressors like heat, cold, trauma, infection and inflammation can cause stress but also psychological factors like fear, anxiety, social defeat, disappointment or humiliation, among others.

Perceived stress elicits a range of responses across physiological, psychological, neural, and behavioral domains to adapt to and overcome the stressor, collectively referred to as the "stress response". In the following sections, I will take a closer look at the physiological stress response as well as the neuronal correlates of stress.

1.3.2 HPA-axis and SAM-axis

Two of the most commonly investigated systems of physiological stress are on the one hand the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis) and on the other hand the Sympatho-Adreno-Medullary Axis (SAM-axis) and more specifically, the Sympathetic Nervous System (SNS) as part of the Autonomic Nervous System (ANS). Together, they are the "primary systems for maintaining or reinstating homeostasis during stress" (Ulrich-Lai & Herman, 2009, page 398).

When the HPA-axis is activated, hypophysiotrophic neurons in the paraventricular nucleus of the hypothalamus secrete Corticotropin-Releasing Hormone (CRH) and arginine vasopressin (AVP). Both hormones act on the anterior pituitary gland (also "adenohypophysis") located ventral to the hypothalamus and initiate Adrenocorticotropic Hormone (ACTH) secretion. ACTH, in turn, acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones like cortisol. Cortisol ultimately acts on nearly all organs of the body, like the liver by stimulating gluconeogenesis for energy supply, the cardiovascular system by increasing blood pressure, bones by inhibiting bone formation, the immune system by suppressing inflammation, et cetera. Lastly, in terms of a negative feedback-loop, cortisol inhibits the production of CRH and ACTH (for an illustration see figure 1.4). Interestingly, the adrenal cortex is also directly innervated by the Sympathetic Nervous System (SNS).

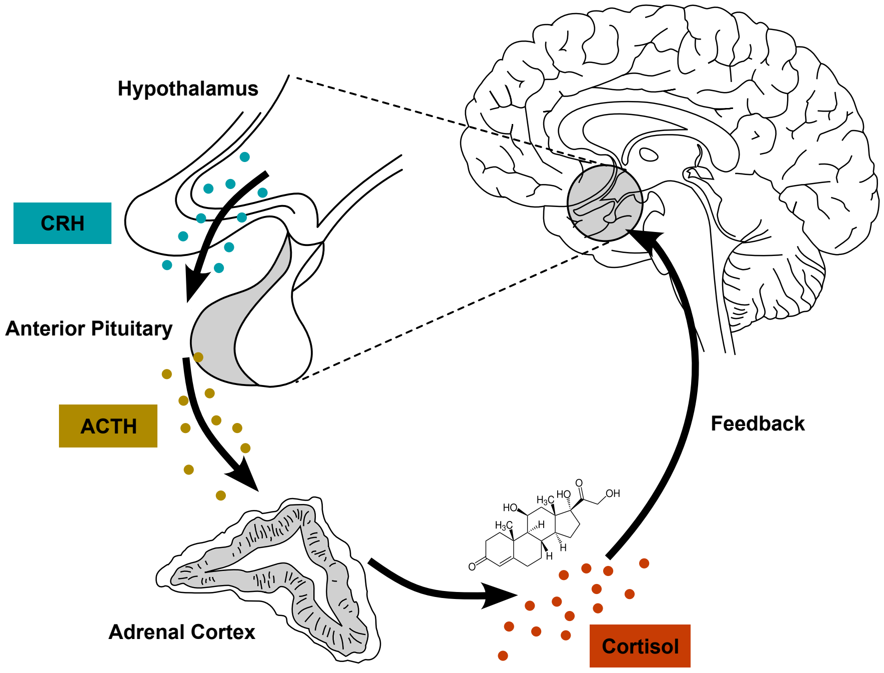


Figure 1.4
Illustration of the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis). Adapted from "Hypothalamic-Pituitary-Adrenal Axis" by Kim, Y. (2024) BioRender. Retrieved from https://app.biorender.com/biorender-templates/t-65fc5afb9970e99daa4b45f5-hypothalamic-pituitary-adrenal-hpa-axis.

The SNS, which is associated with the classic "fight or flight" response, is innervated by the Sympatho-Adreno-Medullary Axis (SAM-axis): Stressors activate preganglionic sympathetic neurons in the spinal cord, which project to pre- or paravertebral ganglia that project to end organs and to chromaffin cells of the adrenal medulla. Consequently, catecholamines such as norepinephrine (also: noradrenaline) and epinephrine (also: adrenaline) are released from the adrenal medulla (note, however, that norepinephrine is also released from sympathetic nerves). Primary consequences of SNS activation are increases in heart rate, blood pressure, respiration and increased release of glucose from the liver for energy supply. Conversely, the counterpart of the SNS, the Parasympathetic Nervous System (PNS), which is associated with relaxation, is deactivated. Compared to the very immediate response of the SNS, the HPA-axis hormonal cascade takes minutes to hours (for a comprehensive review, see Ulrich-Lai & Herman, 2009).

Interestingly, each system is assumed to be activated in response to different situational demands and influenced due to different contextual factors. For instance, Dickerson and Kemeny (2004) have found in their review, that the HPA-axis is primarily triggered (in terms of a pronounced and longer-lasting secretion of cortisol and ACTH) if stressors are perceived as uncontrollable and included social-evaluative threat. "Social-evaluative threat occurs when an important aspect of the self-identity is or could be negatively judged by others" (Dickerson & Kemeny, 2004, page 358). On the other hand, increased mental effort only seemed to impact SNS-responses (Peters et al., 1998).

1.3.3 The Trier Social Stress Test

One experimental stress induction combining the two aforementioned predictors of increased HPA-axis and SNS-responses, namely uncontrollability and social-evaluative threat, is the Trier Social Stress Test (TSST) which was developed by Kirschbaum et al. (1993). In the original protocol of the TSST, the participant was first led into a room by an investigator. There, a committee of three people was already sitting at a table. The investigator explained the following task while the participant stood in front of a microphone and a video camera was also set up. The investigator explained that after a preparation phase of 10 min, the participant was to give a free speech of 5 min to convince the committee that they were the best choice for an advertised job position. During the speech, they would be recorded on video and audio. After the instruction, the participant was taken to another room for the preparation phase. There they were allowed to take notes, although these were not to be used later. After the 10 min, the participant was led back in front of the committee and asked to give the speech. If the participant finished the speech before the time had expired, they were prompted in a standardized manner to continue speaking. Following the job interview, a 5 min mental arithmetic task took place, in which participants were required to count backward in steps of 13 from 1022 as quickly and accurately as possible. If a mistake was made, they were instructed in a standardized manner to start over from the beginning. After completing the arithmetic task, the participant was led out of the room.

Please note, that today, the standard TSST paradigm has been slightly adapted (see Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; Kudielka, Hellhammer, & Kirschbaum, 2007). First, the preparation phase is reduced to 3 min and is often performed in the same room as the committee is sitting after participants received standardized written instructions. Only after the preparation, participants are instructed that they are not allowed to use their notes. Further, the committee members wearing white coats are trained to remain unresponsive and neutral in the interaction with the participant. Lastly, the arithmetic task demands participants to subtract 17 from 2023.

With this experimental procedure, the TSST maximizes social-evaluative threat and uncontrollability. Consequently, results reliably indicate increased physiological stress responses (e.g., cortisol, ACTH, adrenaline and noradrenaline, heart rate, blood pressure) as well as increases in subjective stress and negative affect (Allen et al., 2014). This is why nowadays, the TSST is regarded as "the gold standard in human experimental stress research" (Allen et al., 2017, page 115). Up to date, there are several variants of the original protocol like for instance the TSST-G for groups, a virtual reality version of the TSST-VR as well as a variant for children (TSST-C) (Allen et al., 2017). The TSST itself was originally designed without a control condition, however today there is a "friendly TSST" that does not induce negative affect or activate the HPA-axis (Wiemers, Schoofs, & Wolf, 2013).

An interesting point to note regarding the models introduced earlier, which either incorporate psychological aspects (McEwen, 1993) or focus exclusively on them (Lazarus & Folkman, 1984), is that the psychological and physiological experiences of stress correlate only moderately to little. In a review of 49 studies that conducted (variants of the) TSST and examined the association of psychological and physiological stress, Campbell and Ehlert (2012) found that only in about 1/4 of the studies correlations were found, and correlation coefficients mostly ranged between 0.3 and 0.5. Consequently, to get a holistic picture of the multi-faceted stress response, several levels (e.g. subjective, physiological and neuronal changes) should be assessed.

What is particularly interesting in the context of this dissertation are studies finding that stress elicited by the TSST reliably induces ruminative thinking (Gianferante et al., 2014; Hilt et al., 2015; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018; Shull et al., 2016; Zoccola, Dickerson, & Zaldivar, 2008; Zoccola, Figueroa, Rabideau, Woody, & Benencia, 2014) and, as already introduced, that perseverative thought modulates cortisol responses (Ottaviani et al., 2016) (see also section 1.2.5).

1.3.4 Neural networks of the stress response

Apart from specific brain regions involved in coordinating the HPA-axis and synthesizing CRH and AVP, such as the paraventricular nucleus of the hypothalamus, frontal cortex, amygdala, and hippocampus (Shirazi, Friedman, Kaufer, & Sakhai, 2015; Ulrich-Lai & Herman, 2009), exposure to a stressor triggers significant shifts in neural networks as a form of neural adaptation. In the following, I will outline findings on the involvement of specifically the Default Mode Network (DMN), Central Executive Network (CEN) and Salience Network (SN) in the acute stress response (for an introduction on the associated brain regions and assumed tasks, see section 1.1.4). For an illustration of the networks and corresponding changes see figure 1.5.

Summarizing previous findings in their review on the neural responses to acute stress, Hermans et al. (2014) hypothesized that there is a reallocation of resources to the Salience Network (SN) at the cost of Central Executive Network (CEN) functioning. That means, during and closely after the initial exposure phase, the SN is increasingly active while the CEN is deactivated until this relation is reversed in the aftermath of stress (Hermans et al., 2014). Their qualitative review incorporated data from both animal and human studies and found initial support for this hypothesis (Hermans et al., 2014), highlighting working memory dysfunction and impairments in cognitive flexibility tasks under stress (i.e. deactivation of the CEN in response to stress). Additionally, findings indicated increased amygdala activation in response to acute stress, along with correlations between heightened connectivity in the SN and physiological stress responses (i.e. activation of the SN).

A recent systematic review of 35 studies investigating the functional connectivity and functional activity in response to acute stress by van Oort et al. (2017) further supported the idea of an initial increase in activity and connectivity within the SN. Interestingly, however, they observed no changes in the CEN in response to stressors and even studies showing increases in activation. The authors argue that this might be due to the higher cognitive load in the stress compared to the control condition (Van Oort et al., 2017). Potentially, there is an inverse-u-shaped relation between stress and activation in the CEN which might have masked corresponding overall associations. That means, while the CEN in not active during low and high stress, moderate stress indeed increases CEN activation.

Further, van Oort et al. (2017) found an increased activation within the DMN in most studies and across most paradigms in the initial reaction as well as direct aftermath of the stressor. An explanation for this rather surprising finding might be an increased negative self-referential processing which is also initiated by several stress paradigms. As already mentioned, experimental stress induction is highly efficient in case social-evaluative threat incorporated, which is also a trigger for ruminative thinking or generally repetitive negative thought.

An important point to consider when interpreting the findings of their review, is that van Oort et al. (2017) included several types of stressors in their review, namely physiological stressors (e.g. the Cold Pressor Test, where participants are asked to submerge their hand into ice-cold water) as well as psychosocial stressors (e.g. the Trier Social Stress Test (TSST)) and combinations of those (e.g. the imaging Maastricht Acute Stress Task where the Cold Pressor Test is combined with the arithmetic task of the TSST). The authors acknowledge that neural responses where more similar between studies using the same compared to studies using different stress induction paradigms and that this should be taken into account when the neural stress response is studied. Explicitly comparing physiological and psychophysiological stress, Kogler et al. (2015) found in their meta-analysis partly overlapping (e.g. activation in the Inferior Frontal Gyrus (IFG) and insula) but also distinct brain regions to be active dependent on the type of stress, which further supports the idea that inconsistent findings regarding the CEN might be due to non-differentiated stressors.

Further, with respect to the explanation of increased DMN activation in response to stress due to increased negative self-referential processing, Rosenbaum et al. (2021) found differences in the potential to induce rumination using the TSST and an adapted version of the Socially-Evaluated Cold Pressor Test (SECPT) (Schwabe, Haddad, & Schachinger, 2008), which combined the Cold Pressor Test with social-evaluative threat. More specifically, they found quasi no ruminative response to the SECPT in healthy individuals and patients with depression but following the TSST. Interestingly, prefrontal hypoactivation in the bilateral DLPFC and IFG under stress in patients with depression were significant negatively associated with post-stress rumination (Rosenbaum et al., 2021). A similar pattern of reduced brain activity during the TSST was also found in a clinical analogue sample of high vs. low trait ruminators when Rosenbaum et al. (2018) observed hypoactivation in the right IFG and DLPFC during the TSST.

As a summary of their findings, van Oort et al. (2017) introduced the triple network of acute stress based on the triple network model of psychopathology by Menon (2011) (see also section 1.1.4) as it "offers a framework for understanding how aberrations in these same networks can lead to a wide range of psychiatric disorders, in which stress also plays an important role" (Van Oort et al., 2017, page 281). Understanding the neural reactions under stress in healthy individuals and aberrations in patients will potentially lead to a more thorough understanding of the contribution of stress to psychopathology. As we know that the neural responses to stressors differ depending on the stressor type as well as studied population (see e.g. Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Noack, Nolte, Nieratschker, Habel, & Derntl, 2019; J. Wang et al., 2007), it seems to be a good start to investigate the association and causal relation of stress, ruminative thinking and neural activation in healthy individuals first.

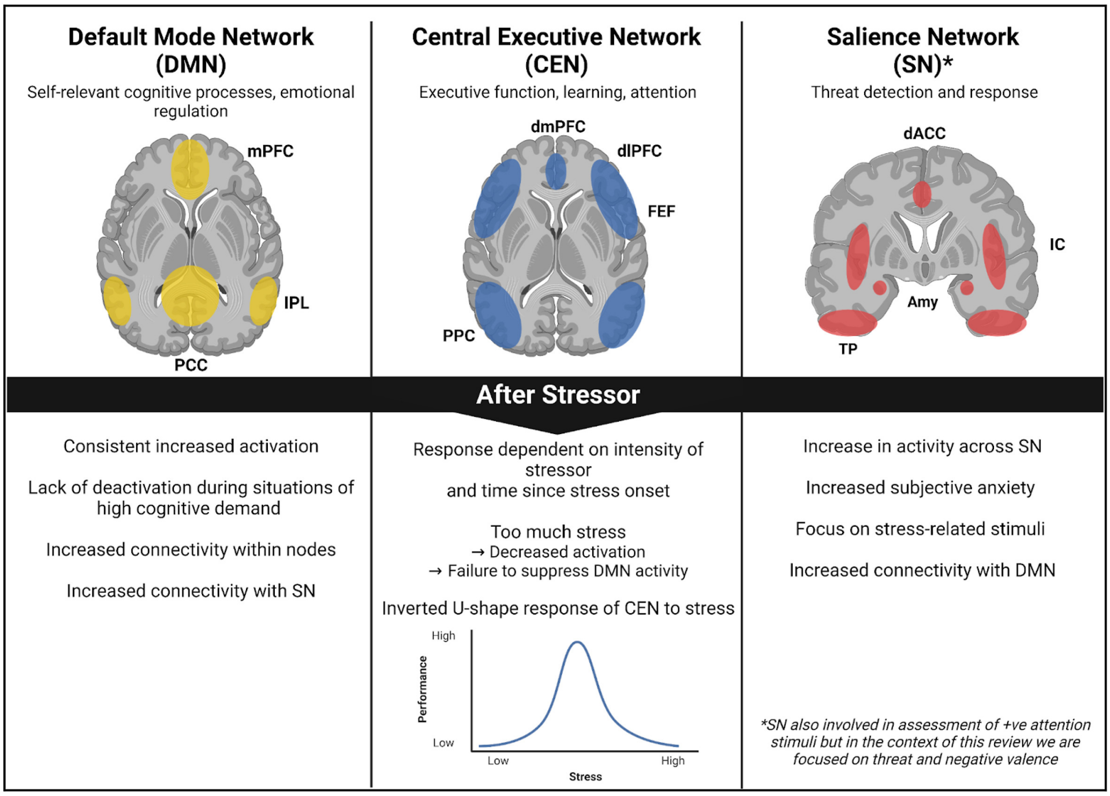


Figure 1.5
Schematic illustration of the roles of the DMN, CEN, and SN at baseline and following psychosocial stress exposure. Abbreviations: mPFC: medial prefrontal cortex, IPL: inferior parietal lobule, PCC: posterior cingulate cortex, dmPFC: dorsomedial prefrontal cortex, dlPFC: dorsolateral prefrontal cortex, FEF: frontal eye fields, PPC: posterior parietal cortex, dACC: dorsal anterior cingulate cortex, IC: insular cortex Amy: amygdala, TP: temporal pole.
Taken from "Effects of neuromodulation on cognitive and emotional responses to psychosocial stressors in healthy humans" (Moses, Gray, Mischel, & Greenwald, 2023, page 5), under a CC BY-NC-ND license.

1.4 Non-Invasive Brain Stimulation (NIBS)

After introducing the content-related constructs, the methodological aspects will be outlined. This section briefly covers Non-Invasive Brain Stimulation (NIBS), followed by an explanation of the physical and physiological principles of Transcranial Magnetic Stimulation (TMS). Finally, TMS application in depression treatment and its role in stress and ruminative thinking are discussed.

1.4.1 What is Non-Invasive Brain Stimulation (NIBS)?

Non-Invasive Brain Stimulation (NIBS) is an umbrella term for non-invasive techniques used to modulate neural activation. That means, in contrast to Deep Brain Stimulation (DBS), where an electrode is implanted in the brain, stimulation is applied through the intact skull bone. There are three main categories of NIBS defined according to their mode of stimulation (Bhattacharya et al., 2022): Transcranial Electrical Stimulation (tES), Transcranial Magnetic Stimulation (TMS) and Transcranial Ultrasound. In addition to the established NIBS methods, there is another very recently proposed approach — photobiomodulation — which used near-infrared light (Waight, Arias, Jiménez-García, & Martini, 2024), though research on this application remains limited, which is why it is not further evaluated in the following.

In tES, a current flow is induced between electrodes applied to the scalp, which causes excitation in the neuronal tissue of the underlying cortex. Depending on the type of current applied, tES includes for instance Transcranial Direct Current Stimulation (tDCS), Transcranial Alternating Current Stimulation (tACS) and Transcranial Random Noise Stimulation (tRNS) (Bhattacharya et al., 2022; Siebner & Ziemann, 2007). For TMS, on the other hand, a coil is placed on the scalp inducing a time-varying magnetic field, which consequently induces an electric field. Forms of TMS are for instance single-pulse, paired-pulse or repetitive Transcranial Magnetic Stimulation (rTMS). Lastly, Transcranial Ultrasound uses high-frequency sound waves to modulate brain activation. This relatively new method provides the opportunity to target deeper structures, though the underlying mechanisms still require exploration (Polanía, Nitsche, & Ruff, 2018).

Generally, NIBS generate electric fields that span relatively large areas of tissue (see figure 1.6), which is also why claims about spatial focality of induced effects have to be interpreted with caution (Polanía et al., 2018). Regarding the direct comparison of different NIBS modalities, literature is relatively sparse (Bhattacharya et al., 2022). For instance, Inukai et al. (2016) compared three tES methods for increasing cortical excitability and found tRNS to be most effective. Techniques of different modality, like for instance tDCS and rTMS, are often compared within a specific area of application, like the treatment of different mental disorders. Focusing on depression, Hejzlar et al. (2021) assessed the efficacy of low-frequency rTMS applied to the right DLPFC and left-sided anodal tDCS (anode over the left DLPFC, cathode over the right DLPFC) in 117 patients with (non-)treatment-resistant depression. As indicated by a changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) scores, Hejzlar et al. (2021) found comparable efficacy of rTMS and tDCS. Please note, however, that the variety of targets (e.g. distance to the skull), stimulation parameters (e.g. duration, number of pulses) and experimental set-ups (devices, electrode size, coils) pose a difficulty regarding the comparability, which is why (other) studies may come to other conclusions. Further, effects are rarely quantified using functional neuroimaging techniques like electroencephalography (EEG), functional Magnetic Resonance Imaging (fMRI) or functional Near-Infrared Spectroscopy (fNIRS), which could generate more insights. In conclusion, so far, "there is no strict recommendation about which of the two techniques [rTMS and tDCS] is better for specific uses" (Priori, Hallett, & Rothwell, 2009, page 244) and "[b]oth rTMS and tDCS are generally safe if used properly" (Priori et al., 2009, page 244). Nevertheless, Bhattacharya et al. (2022) conclude that TMS is the "most established and the only approved modality for treatment of brain disorders" (Bhattacharya et al., 2022, p. 488), which is why, I will specifically focus on TMS as I chose this technique for the studies in this dissertation.

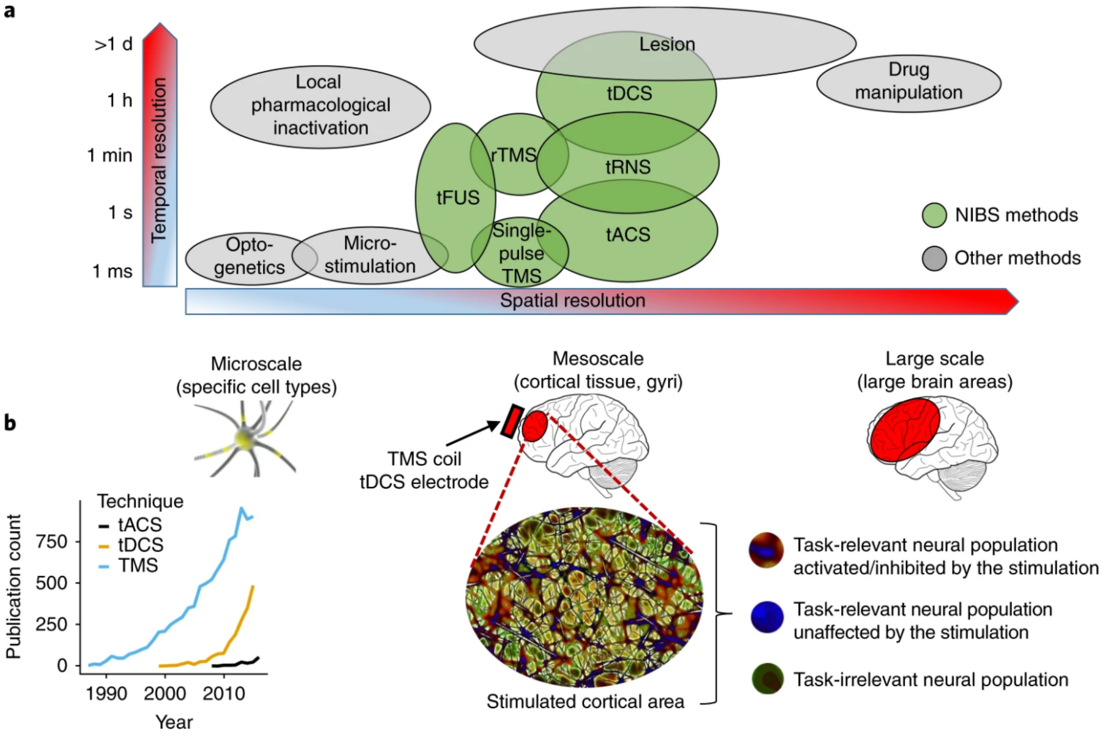


Figure 1.6
Illustration of the temporal and spatial resolution of different causal brain interventions. Taken from "Studying and modifying brain function with non-invasive brain stimulation" (Polanía et al., 2018, page 174). Copyright by Nature America Inc., part of Springer Nature.

1.4.2 The physical and physiological mechanisms of TMS

Transcranial Magnetic Stimulation (TMS) is a Non-Invasive Brain Stimulation (NIBS) technique modulating neural activity through magnetic stimulation. A coil placed on the scalp generates a time-varying magnetic field, which, according to Faraday's law of induction induces an electric field, influencing cortical excitability (Siebner & Ziemann, 2007). According to Ampère's law, the electric current flowing through the coil produces the magnetic field necessary for this induction. The electric field is always perpendicular to the magnetic field, so a tangentially placed coil induces a parallel electric field in the brain tissue (see figure 1.7).

Brain tissue has relatively low electrical conductivity, meaning that induced electric currents do not flow easily. Using shorter magnetic pulses (<100 μs) increases the strength of the induced electric field in the brain (Siebner & Ziemann, 2007). Depending on the used protocol, corresponding magnetic pulses are applied in different patterns and timing: Single-pulse TMS applies isolated pulses, in comparison to paired-pulse TMS and repetitive Transcranial Magnetic Stimulation (rTMS), where magnetic pulses are repetitively applied at a constant frequency (Siebner & Ziemann, 2007). Important to note is that the latter has been found to produce longer-lasting effects (Oberman, 2014) and high-frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS) ($\geq$ 5 Hz) has been found to have an excitatory effect, while low-frequency repetitive Transcranial Magnetic Stimulation (LF-rTMS) ($\leq$ 1 Hz) is has been found to produce an inhibitory effect by reducing neuronal excitability (Oberman, 2014).

A specific variant of rTMS is Theta Burst Stimulation (TBS) whose name is derived from the description of the employed protocol. TBS involves bursts of typically three pulses at 50 Hz, delivered at a 'theta frequency' (5 Hz). The term 'theta' comes from EEG studies that identified theta oscillations (approximately 4-7 Hz) in the hippocampus, which occur naturally in the brain. TBS has gained popularity especially due to similar outcomes to rTMS but a reduced stimulation duration (Blumberger et al., 2018; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

Huang and colleagues (2005) were the first investigating the effect of TBS on Motor-Evoked Potentials (MEPs). A MEP is the electrical response recorded from muscles following stimulation of the primary motor cortex (M1). More specifically, the stimulation using for instance TMS activates corticospinal neurons (pyramidal cells in M1), which subsequently travel down the corticospinal tract, leading to a measurable response in the corresponding muscles like the abductor pollicis brevis (Rothwell et al., 1999).

Crucially, Huang and colleagues (2005) were able to show that in comparison to MEP amplitudes evoked by single-pulse TMS, a protocol of continuous Theta Burst Stimulation (cTBS) resulted in inhibition of the primary motor hand area and on the contrary, intermittent Theta Burst Stimulation (iTBS) resulted in an increase of the cortical excitability for approximately 20 min. Interestingly, they also employed different durations of cTBS protocols, namely 300 or 600 pulses, and observed reduced MEP amplitudes for about 20 min for the shorter protocol and reductions for about 60 min in the longer protocol (Huang et al., 2005).

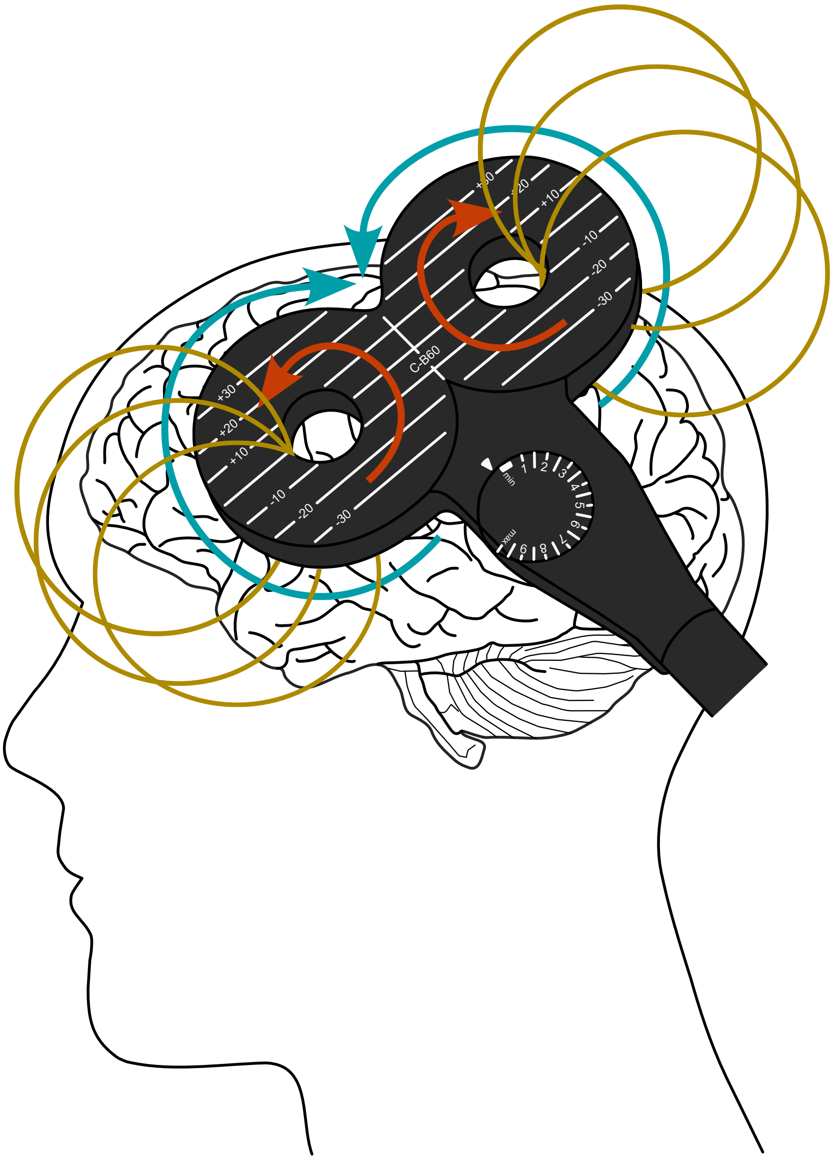


Figure 1.7
Schematic illustration of Transcranial Magnetic Stimulation (TMS) applied to M1 (motor cortex). The red lines represent the electric field in the coil, the blue lines indicate the induced electric current in the cortex, and the yellow lines depict the magnetic field.

In the following years, a controversy regarding the duration and direction of effects dependent on the stimulation duration and/or protocol sparked as some researchers found revered effects of cTBS dependent on prior motor activity (Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008) or reversed effects compared to the findings of Huang et al., (2005) in case prolonged cTBS and iTBS protocols were used (Gamboa, Antal, Moliadze, & Paulus, 2010). Please note, however, that the latter study only included 14 participants, which limits its generalizability. Following studies found a high degree of intra- and inter-subject variability of effects on MEP amplitudes in response to TBS paradigms (Guerra, López-Alonso, Cheeran, & Suppa, 2020), however a recent review of 64 TBS studies showed a generally excitatory effect of iTBS and generally inhibitory effect of cTBS on the motor cortex through a variety of stimulation intensities, target muscles and durations of effects (Wischnewski & Schutter, 2015). Nevertheless, the exact underlying mechanisms, sources of variability to outcomes and their relative importance are still discussed (Gamboa et al., 2010; Guerra et al., 2020; Jannati, Oberman, Rotenberg, & Pascual-Leone, 2023). Only recently, a large study investigated optimal stimulation parameters found iTBS of a total of 1200 pulses to decrease excitability for up to 50 min and cTBS of a total of 3600 pulses increasing excitability for up to 60 min as optimal parameters (McCalley et al., 2021). Please note, however, that these studies only investigated TBS on the motor cortex.

On a physiological level, electric fields induce local voltage changes in axon membranes, which can lead to neuronal depolarization if a critical threshold is reached. Then, the permeability of depolarizing ion channels (especially sodium channels) increases. This change in the permeability of the ion channels causes an acute influx of Na-ions from extracellular to intracellular and triggers an action potential. These action potentials are transmitted trans-synaptically, which in turn activate networks of connected brain regions. In order for a nerve cell to depolarize, it is not only the strength of the electric field that is relevant, but also its spatial gradient. Please note, however, that from the perspective of a bent axon which are apparent in the cortex, a uniform electric field already exhibits a gradient. Just as a side note, this means that TMS possibly "prefers" bent axons lying parallel to the electric field. Crucially, the cortex has a large number of different neuron populations with different spatial orientation and excitability (Siebner & Ziemann, 2007).

Following these theoretical considerations, the shape of the coil is consequently also important for the induced electric field distribution on the brain surface. With figure-eight (or butterfly) shaped coils, the induced electric fields add up at the point of contact of the two partial coils, generating a relatively focal maximum compared to circular coils (Deng, Lisanby, & Peterchev, 2013). Due to the variety in coil sizes and device manufacturers, it is difficult to make general statements about the penetration depth of TMS. The coil used in the studies of this dissertation (Magventure B-65 coil) has a half-value depth of 1.4 cm (Deng et al., 2013), which means that the intensity of the signal decreases to half (i.e. 50 %) of its original value after penetrating 1.4 cm into the tissue.

As previously mentioned, the effects of rTMS last beyond the stimulation period. In their review, Klomjai et al. (2015) state that "[t]he physiological bases of rTMS after-effects have not yet been clearly identified. Many arguments support the idea that the mechanisms underlying rTMS after-effects resemble long-term potentiation (LTP) and long-term depression (LTD) described in animals" (Klomjai et al., 2015, page 210). LTP and LTD are important mechanisms of synaptic plasticity, more specifically, the formation, strengthening or weakening neural connections dependent on experiences (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). "Long-term potentiation (LTP) is defined as an increase in synaptic strength, whereas long-term depression (LTD) reflects a decrease in synaptic strength" (Klomjai et al., 2015, page 211).

Summing it all up, future research is still pending to clarify the exact underlying mechanisms; however, TMS offers a promising way to investigate the causal involvement of brain regions and potentially offers an effective treatment method.

1.4.3 TMS in the treatment of depression

As previously mentioned, the effectiveness of current psychotherapeutic and pharmacological treatments remains insufficient (see section 1.1.2). Neurobiological treatments such as NIBS are relatively recent developments, yet they offer promising potential for alleviating depressive symptoms by addressing underlying neural aberrations. TMS was first approved as a treatment for Major Depressive Disorder (MDD) in adults who had not achieved sufficient improvement with antidepressant medications in 2008 (Cohen, Bikson, Badran, & George, 2021). Since then, its use has expanded, and it is now also approved for conditions such as Obsessive Compulsive Disorder (OCD) and smoking cessation (Cohen et al., 2021). Nowadays, there are multiple devices and protocols approved for clinical use (for an up-to-date overview over the current landscape of TMS devices see Gutiérrez-Muto et al., 2023). In line with the current state of research regarding the neural underpinnings of depression (see section 1.1.4), experts concluded an antidepressant effect of HF-rTMS applied to the left DLPFC (Lefaucheur et al., 2014). Regarding the use of newly developed TBS, unfortunately there are not as many studies, yet. Summarizing the data of five Randomized Controlled Trials (RCTs) applying active (either iTBS or cTBS) or sham TBS to the left or right DLPFC, Berlim et al. (2017) observed significant reductions of depressive symptoms in response to active vs. sham treatment. These findings could be replicated and extended by Voigt and colleagues (2021) who further observed statistically non-significant differences in reductions of depressive symptoms between TBS compared to standard HF-rTMS. Please note, however, that only one RCT comparing TBS and HF-rTMS was included in the aforementioned meta-analysis.

As previously mentioned, up to date, the exact mechanisms of TMS and especially TBS are still investigated. Berlim et al. (2017), attempt to summarize the complexity of the findings to date as follows: "Based on current preliminary data, TBS seems to exert its clinical effects in [Major Depressive Disorder (MDD)] through a number of complementary mechanisms including, e.g., the modulation of both local and broader functional neural networks (Hubl et al., 2008; Iwabuchi et al., 2017), direct and indirect neurochemical effects such as reductions in GABA/glutamate concentrations (Iwabuchi et al., 2017; Stagg et al., 2009), as well as changes in oscillatory brain activity (Noh, Fuggetta, Manganotti, & Fiaschi, 2012)" (Berlim et al., 2017, page 107). I conclude that TMS, and due to its higher efficacy especially TBS, are promising and research-generating approaches to improve treatment of depressive disorders, among others. To enhance the clinical effectiveness and potential of TMS, a deeper understanding of its fundamental mechanisms is essential. This includes refining methodological aspects such as optimal stimulation parameters and precise targeting, as well as identifying which patient subgroups are most likely to benefit from TBS and which may not. As part of the investigation of the basic mechanisms, the research on stress and rumination using TMS should be mentioned in the context of this dissertation.

In their systematic review, Vignaud et al. (2023) summarized that HF-rTMS and anodal tDCS applied to the left DLPFC seem efficient in reducing cortisol responses to acute stress. There were, however, only three studies that could be considered in their review, which is why they are separately reported in the following.

Pulopulos and colleagues (2019) were the first to apply iTBS on the left DLPFC in a total of 35 healthy participants. Participants first underwent the TSST, followed by two consecutive stimulation sessions — either two rounds of active iTBS or two rounds of sham iTBS. Stimulation was delivered to the left DLPFC, with the stimulation site precisely determined via neuronavigation. Cortisol levels were measured at 7 time points previous to the TSST, after the TSST and after the stimulation. Pulopulos et al. (2019) observed no general impact of the stimulation on mood or cortisol responses.

These findings were replicated by other researchers of the same research group with a similar study setup and a total of 40 healthy participants (De Witte et al., 2020). Again, participants underwent the TSST previous to two consecutive stimulation sessions of active or sham iTBS over the left DLPFC. Here, cortisol levels were measured at 5 time points throughout the experimental session and De Witte et al. (2020) also observed no general impact of the stimulation on mood or cortisol. Interestingly, the authors also investigated the impact of the iTBS and trait rumination (brooding subscale of the RRS) on changes in ruminative thinking as assessed using the 2-item Ruminative Self-Focus scale (Moberly & Watkins, 2008) and cortisol. In these moderations, they found that "higher levels of brooding were associated with marginally significant higher ruminative thoughts in the sham, but not in the active condition (i.e., rumination increases with increasing brooding levels in the sham, but not in the active condition)" (De Witte et al., 2020, page 6) and furthermore "higher levels of brooding were associated with a significant decrease in cortisol secretion in the active, but not in the sham condition" (De Witte et al., 2020, page 6). This data suggests a complex interaction of stress, ru-

minative thinking and the impact of TBS. Potentially, iTBS applied to the left DLPFC might be able to disrupt the link between brooding and stress-reactive increases in rumination and therefore may help regulate the stress response.
Lastly, Era and colleagues (2021) applied cTBS to either the left DLPFC, the left ventral-premotor cortex as an active control condition or sham TBS. A sample of 32 participants underwent the 20 s cTBS previous to a rumination induction. For this, they should recall a personal experience "that made them sad, angry, anxious or worried and about which they happened to think without intentionally wanting to (perseverative cognition induction). When such an event was identified, participants were instructed to tell the experimenter about it until instructed to stop (3 min)" (Era et al., 2021, page 2). After the rumination induction, participants rested for 5 min and during the last 3 min of this phase, participants were asked to think about the same episode they had reported earlier for 3 min (perseverative cognition prompts). This rumination induction was used to elicit psychophysiological stress. Then, they performed a tracking task for 15 min "by following with the cursor a white dot slowly moving on a black background on the screen. The task was made very easy as to facilitate (off-task) perseverative cognition" (Era et al., 2021, page 3). This process was repeated three times as each participant received each stimulation at the same day approximately 40 min after the last stimulation. The stimulation sites were determined via neuronavigation. Please note that only two salivary samples were assessed to measure cortisol levels (once at baseline and once after the stimulation and task). They observed increased HR and cortisol responses and reduced heart rate variability (HRV) when cTBS was applied over the left DLPFC as compared to ventral-premotor cortex and sham.

The three studies reported above show, on one hand, that there is currently insufficient research on the effects of TBS on the stress response. Further findings, particularly those that also capture neural changes, are important to investigate the complex underlying mechanisms. It may be beneficial to examine both cTBS and iTBS in a single study, especially by using a larger sample size to detect small effect sizes of the TBS. Given the findings related to neural changes due to rumination and its impact on the stress response I reported earlier, it seems promising to include both state and trait rumination as variables in future studies. Please note that, in line with the research on NIBS in the treatment of depression (see section 1.4.3), all of the three studies above used the left DLPFC as a stimulation target. This is also supported by a recent review of Moses and colleagues (2023) on the effects of different NIBS techniques on cognitive and emotional responses to acute experimental stressors in healthy participants: The authors come to the conclusion that "[b]ased on current evidence, the DLPFC — a key structure within the CEN — appears to be the best-supported target for addressing EF-related effects of stressors. In contrast, the VLPFC — a key structure in cognitive reappraisal circuits — may be the best-supported target to affect stress modulation of emotional responses" (Moses et al., 2023, page 17).

1.5 Functional Near-Infrared Spectroscopy

In particular, this section aims to justify the choice of functional Near-Infrared Spectroscopy (fNIRS) as functional neuroimaging technology in the studies of this dissertation. Shortly summarized, "[f]unctional Near-Infrared Spectroscopy (fNIRS) is a non-invasive diffuse optical technique that quantifies changes in measured signals from a single or several source-detector pairs over short periods of time (ranging from seconds to hours) in order to detect functional brain activation. Typically, it is assumed that the changes in light intensity during this temporal range reflect changes in absorption only (i.e., scattering is constant during this period). The changes in absorption can then be related to changes in chromophore concentration such as oxy- and deoxy-hemoglobin, water, and cytochrome c oxidase. fNIRS is performed with continuous-wave spectroscopy devices, as well as frequency-domain and time-domain spectroscopy techniques. In the case of frequency-domain and time-domain systems, it is possible to obtain absolute parameters of optical properties and therefore absolute concentration changes, but this is less commonly performed" (Stute et al., n.d.).

There has been a rapid growth of the use of fNIRS technology in recent years (Ferrari, Mottola, & Quaresima, 2004; Pinti et al., 2020), which is likely to be due to the advances in the technology and advantages compared to other functional neuroimaging techniques. Generally, fNIRS is a safe and low-cost technology. "It has been shown that fNIR[S] is reliable and trustworthy for research based on investigating groups of subjects, although reliability in single subjects is not sufficient yet (Kono et al., 2007; Plichta, Heinzel, Ehlis, Pauli, & Fallgatter, 2007; Plichta, Herrmann, et al., 2007; Plichta et al., 2006; Schecklmann, Ehlis, Plichta, & Fallgatter, 2008)" (Scholkmann et al., 2014, page 8). With a spatial resolution of 2-3 cm and temporal resolution of 10 Hz, fNIRS has a higher spatial resolution than EEG and higher temporal resolution than fMRI (for an overview over the main characteristics including differences and similarities between these neuroimaging techniques, see table 1.1). A major limitation of fNIRS is, however, that near-infrared light is only able to penetrate approximately 1.5 cm of the cortex, limiting the brain regions to be investigated. Compared to other methods, however, fNIRS is not too prone for motion artifacts, offering exciting new possibilities for its application, for instance in infants or psychiatric patients. In addition to the aforementioned advantages of fNIRS, the Regions of Interest (ROIs) in each of the studies are cortical areas (in particular the DLPFC and VLPFC), which are easily accessible using fNIRS.

Another important point to consider is the ecological validity of the stress induction using the Trier Social Stress Test (TSST). With fMRI, participants would have to lie still in a scanner due to susceptibility to motion artifacts. In contrast, fNIRS allows participants to stand and gesture naturally while speaking, enhancing the similarity to the original TSST. Compared to not only fMRI but also EEG, fNIRS is far less susceptible to movement artifacts which are likely when considering the tasks of the TSST, namely giving a speech and calculating aloud. Indeed, there are adaptions of the TSST for instance to the fMRI environment, however, there is a higher similarity to the original TSST when fNIRS is employed (Henze et al., 2023).

Regarding the use of fNIRS in the context of TMS, there are several studies using fNIRS to quantify TMS-induced neural changes. In their systematic review, Curtin et al. (2019) have found a total of 53 articles investigating the effects of various TMS protocols on neural activation of particularly M1 and the DLPFC at rest and during various tasks. While the primary output of the review is a vast diversity of experimental setups and lack of standardization, the authors summarize that "fNIRS as a methodology is well-equipped to monitor both transient and prolonged effects of TMS, but as of yet, the available research is limited in its replication and scope" (Curtin et al., 2019, page 21).

	fNIRS	**fMRI**	**EEG/MEG**	**PET**
Signal	O_2Hb, HHb	BOLD (HHb)	Electromagnetic	Cerebral blood flow, Glucose metabolism
Spatial resolution	2–3 cm	0.3 mm voxels	5–9 cm	4 mm
Penetration depth	Brain cortex	Whole head	Brain cortex for EEG/ deep structures for MEG	Whole head
Temporal sampling rates	Up to 10 Hz	1–3 Hz	>1000 Hz	<0.1 Hz
Range of possible tasks	Enormous	Limited	Limited	Limited
Robustness to motion	Very good	Limited	Limited	Limited
Range of possible participants	Everyone	Limited, can be challenging for children/patients	Everyone	Limited
Sounds	Silent	Very noisy	Silent	Silent
Portability	Yes, for portable systems	None	Yes, for portable EEG systems	None
Cost	Low	High	Low for EEG; high for MEG	High

Table 1.1
Comparison of fNIRS with other neuroimaging modalities. Reproduced from "The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience" (Pinti et al., 2020, page 15), under a CC BY 4.0 license.

1.6 Interim summary

In the previous chapter, I provided a brief overview of the five topics covered in this thesis: depressive disorders, rumination, stress, fNIRS, and TMS. In addition to summarizing key findings from current research, I began drawing connections between these topics. Here, I will succinctly reiterate their interrelations in the context of this thesis.

Rumination is a transdiagnostic process that was initially defined and extensively studied in the context of depression. However, research has since identified repetitive thought patterns in various mental disorders, characterized by their automatic and uncontrollable nature, which interferes with goal-directed behavior and psychotherapeutic treatment. Stress is a trigger of rumination, which, in turn, amplifies and prolongs stress responses on a psychological and physiological level. Depression is widely recognized as a stress-related disorder, with stressors — such as critical life events — playing a significant role in its development. Alterations in the stress response on an emotional, cognitive, and (neuro-)physiological level, are not only symptomatic of depression but also contribute to its persistence. Rumination could serve as a moderator, affecting the strength of this relationship, or mediator, as it has been found to impact the stress response and depressive symptomatology.

Preliminary neuroimaging studies have linked rumination to specific neuronal changes in brain regions of functional networks like the DMN and CEN as well as changes in the connectivity between these networks. However, future research has yet to distinguish these findings from general depressive symptomatology as often trait measures of rumination are used which have a high contentual overlap with depressive symptoms.

TMS, a NIBS technique, offers the chance to influence brain activity through the intact skull. Previous studies using TMS and a newer variant, TBS, have been found to alleviate depressive symptoms by stimulating prefrontal areas. In particular, the DLPFC and VLPFC are promising target regions, as modulating their activity is hypothesized to impact emotional and cognitive stress responses. There is further evidence that the stress response is influenced by ruminative thinking and potentially rumination itself can be modulated by TBS.

So far, no study has investigated the effect of TBS on the aforementioned processes while simultaneously assessing neurophysiological data to demonstrate its effects on a neural level.

Functional Near-Infrared Spectroscopy (fNIRS), a functional imaging method, allows for the implementation of stress paradigms such as the TSST — the gold standard in human experimental stress research — due to its reduced susceptibility to motion artifacts. The TSST has been repeatedly found to elicit ruminative thinking. Notably, fNIRS has also demonstrated its ability to assess TBS-induced changes in cortical oxygenation making it perfectly suitable to investigate the neuromodulatory effects of TBS on the stress-rumination link.

Chapter 2

Aims and linkage of the studies

This chapter is dedicated to provide a brief overview of the studies reported in the subsequent chapters. It should be noted that the experimental paradigms and protocols, as well as the methods and analyses used, were kept as consistent as possible across the studies to facilitate comparison of study results and conclusions.

The first study aims to differentiate the stress-related neural correlates of depressive symptomatology, trait rumination, and stress-reactive state rumination in order to inform neurostimulation research. The research questions are summarized as follows:

1. To what extent are the neural correlates under stress in DP, compared to HC (e.g., the frequently replicated prefrontal hypoactivation), associated with depressive symptomatology or rumination? In other words, in how far can brain activation be predicted by depressive symptomatology or trait rumination, which is highly correlated with it, or by stress-reactive state rumination?
2. How do differences in performance under stress influence the neural correlates observed during stress? In other words, how robust are the aforementioned associations when controlling for performance in the TSST?

The second study investigates the impact of neurostimulation using TBS applied to the left DLPFC on the psychological and physiological stress response. Designed as a pilot study, it aimed to assess feasibility of the experimental procedure without incorporating neural data and sought to answer the following questions:

3. Does a single session of iTBS, cTBS, and sTBS affect the psychological and physiological stress response in healthy individuals? More specifically, do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS?
4. Do high trait ruminators benefit more from TBS? Namely, are the effects of the TBS more pronounced in individuals with higher trait rumination?

The third study aimed to replicate and extend the findings of the second study. Again, healthy individuals received TBS applied to the left DLPFC. This time, however, neural activation patterns were assessed together with the psychological and physiological stress response. Further, participants underwent two sessions at the laboratory, during which they received either sTBS or active stimulation (iTBS or cTBS), whereby the order of these stimulation conditions was randomized.

5. Are we able to replicate the findings of different TBS protocols on the stress response from study 2? Namely, do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS using a within-subjects design?
6. Are the aforementioned effects of the TBS more pronounced in individuals with higher trait rumination?
7. Does inhibitory stimulation of the left DLPFC using cTBS exacerbate prefrontal dysfunction in high trait ruminators under stress, compared to sTBS? Conversely, does excitatory stimulation with iTBS "normalize" prefrontal functioning? Are these effects also found in low ruminators who already exhibit higher prefrontal activation under stress?

The fourth study used the exact same study setup as the third study but aimed to investigate the effects of TBS applied to the right VLPFC. The research questions are summarized as follows:

8. Following stimulation applied to the right VLPFC, do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS using a within-subjects design?
9. Again, are the aforementioned effects of the TBS more pronounced in individuals with higher trait rumination?
10. In how far does inhibitory stimulation of the left DLPFC using cTBS exacerbate prefrontal dysfunction in high trait ruminators under stress, compared to sTBS? Conversely, does excitatory stimulation with iTBS "normalize" prefrontal functioning? Are these effects also observed in individuals with low rumination, who already show higher prefrontal activation under stress?

The following table aims to provide a short overview of the similarities and differences between the studies, offering a quick reference to the samples, paradigms, analyses, and aims of the studies.

Category	**Study 1**	**Study 2**	**Study 3**	**Study 4**
Sample	77 depressive patients, 65 healthy subjects	127 healthy subjects (low & high ruminators)	88 healthy subjects (low & high ruminators)	89 healthy subjects (low & high ruminators)
Age Range	18-40 years	18-35 years	18-50 years	18-50 years
Paradigm	TSST	TSST	TSST	TSST
Measures	• Brain activity (fNIRS)	• Subjective stress • Mood • State rumination • Heart rate • HRV • Cortisol	• Subjective stress • Mood • State rumination • Heart rate • Brain activity (fNIRS)	• Subjective stress • Mood • State rumination • Heart rate • Brain activity (fNIRS)
Stimulation	None	TBS: • iTBS • cTBS • sTBS • between-subjects	TBS: • iTBS and sTBS • cTBS and sTBS • within-subjects • randomized order	TBS: • iTBSand sTBS • cTBS and sTBS • within-subjects • randomized order
Stimulation Target	None	left DLPFC (F3)	left DLPFC (F3)	right VLPFC (F8)
Analysis	• rmANOVAs • rmMANOVAs	• (generalized) linear mixed models	• rmANOVAs • rmMANOVAs	• rmANOVAs • rmMANOVAs
Aim	Differentiation of neural activation patterns of trait vs. state rumination to inform neurostimulation studies	Investigation of TBS effects on psycho- and physiological stress response	Investigation of TBS effects on psycho- and (neuro-) physiological stress response	Investigation of TBS effects on psycho- and (neuro-) physiological stress response
DOI	• `10.1038/s41598-023-41403-y`	• `10.1016/j.clinph.2024.03.016`		

Table 2.1
Similarities and differences between the studies. TSST = Trier Social Stress Test, fNIRS = functional Near-Infrared Spectroscopy, HRV = heart rate variability, TBS = Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, sTBS = sham Theta Burst Stimulation, DLPFC = Dorsolateral Prefrontal Cortex, VLPFC = Ventrolateral Prefrontal Cortex, rmANOVA = repeated measurements Analysis of Variance, rmMANOVA = repeated measurements Multivariate Analysis of Variance, DOI = Digital Object Identifier.

Chapter 3

STUDY 1: Prefrontal hypoactivation induced via social stress is more strongly associated with state rumination than depressive symptomatology

The contents of this chapter are published:

Int-Veen, I., Fallgatter, A. J., Ehlis, A.-C., & Rosenbaum, D. (2023). Prefrontal hypoactivation induced via social stress is more strongly associated with state rumination than depressive symptomatology. *Scientific Reports, 13*(1), 15147.

3.1 Abstract

Previous studies have consistently shown a pattern of prefrontal hypoactivation in patients with depression (DP); however, it remains unclear whether this neural correlate is a consequence or concomitant feature of depression and/or whether ruminative thinking might be underlying. Using a sample comprising 65 healthy controls (HC) and 77 DP, we investigated the behavioral and neural correlates in response to stress and their association with depressive symptomatology, trait and state rumination. Fitting repeated-measurement MANOVAs including 21 fNIRS-channels covering the bilateral Inferior Frontal Gyrus (IFG), Dorsolateral Prefrontal Cortex (DLPFC) and Somatosensory Association Cortex (SAC), we investigated the predictive value of diagnostic group (HC vs. DP) and state rumination. In DP, we observed significantly lower increases in cortical oxygenation under stress in channels of the right IFG and bilateral DLPFC. Participants reporting lower state rumination and no increases in state rumination under stress showed higher increases in cortical oxygenation compared to the other groups and in more channels compared to the analysis on diagnostic group. Re-running our fNIRS-analysis while correcting for performance resulted in time-dependent changes dependent on group (DP vs. HC) no longer yielding significance, however for the differentiation of state rumination groups.

3.2 Introduction

Rumination was initially defined as a cognitive vulnerability to develop depressive disorders and is therefore regarded as a trait construct that has been strongly associated with depressive psychopathology (Nolen-Hoeksema et al., 2008). Trait rumination has been traditionally investigated using the Ruminative Response Scale (RRS), a subscale of the Response Style Questionnaire, which was originally developed by Nolen-Hoeksema and Morrow (1991). Approximately 15 years later, Robinson and Alloy (2003) discovered corresponding state rumination processes in a large community sample, which gave rise to the definition of trait and state aspects of ruminative thinking and the need for an appropriate distinction of them using questionnaires. In the same year, Treynor and Gonzalez (2003) further revised the original RRS due to substantial contentual overlap with symptoms of depression in order to assess ruminative thinking without depression-specific content. This was accompanied by the discussion of ruminative thinking as a cognitive vulnerability also being observable in the context of other psychopathologies (Aldao & Nolen-Hoeksema, 2010; Arditte, Shaw, & Timpano, 2016; Gustavson, du Pont, Whisman, & Miyake, 2018; Kaplan et al., 2018; Klemanski, Curtiss, McLaughlin, & Nolen-Hoeksema, 2017; Laicher et al., 2022) which ultimately resulted in rumination being regarded as a transdiagnostic process (Nolen-Hoeksema et al., 2008). From a neurobiological perspective, there are various findings on prefrontal hypoactivation in patients with depression (DP) (e.g. Koenigs & Grafman, 2009; Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003; Rogers et al., 2004) using different experimental settings, methods and subtypes of depression (for a recent review see Pizzagalli & Roberts, 2022).

In short, especially the left Dorsolateral Prefrontal Cortex (DLPFC) has consistently been found to be hypo-activated during “affective and cognitive tasks requiring emotional or stress regulation, cognitive control, and/or shifting attention to external task demands” (Pizzagalli & Roberts, 2022, p. 240). The authors point out that this might be due to reduced recruitment of the DLPFC in general and a cortical PFC inefficiency in DP. This means, most probably dependent on the type and need for resources, at some point healthy controls (HC) and DP might show similar DLPFC-activation but, with an increased need of resources, an aberrant functioning is observed on a neural and behavioral level. Interestingly, in studies including experimental stress inductions by using for instance the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), prefrontal hypoactivation was not only observed in DP (Rosenbaum et al., 2021) but also in HC which were categorized as high trait ruminators according to the RRS (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum, Thomas, et al., 2018). The TSST has not only been shown to be a very potent and ecologically valid stressor (Allen et al., 2014) but also to be capable of eliciting stress-reactive rumination (Allen et al., 2014; Gianferante et al., 2014; Hilt et al., 2015; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018; Shull et al., 2016; Zoccola et al., 2014). Consequently, high trait ruminators as well as DP showed higher increases in state rumination as induced via the TSST compared to low trait ruminators as well as HC (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021). There are only few studies investigating the neural correlates of state rumination, however first investigations also show aberrant DLPFC-functioning in HC during resting-state measurements (Kühn, Vanderhasselt, De Raedt, & Gallinat, 2014). Moreover, other prefrontal areas like the Medial Prefrontal Cortex, left Medial Orbito-Frontal Cortex but also several further regions like Precuneus and the Anterior Cingulate Cortex (Fossati et al., 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Jacob et al., 2020; Kross, Davidson, Weber, & Ochsner, 2009; Nejad et al., 2013; Northoff et al., 2006; Vanderhasselt et al., 2013) might be related to state rumination, but further research is needed to reach conclusive results. Please note that one issue in the literature of the neural correlates of state rumination involves the lack of a psychometrically evaluated and commonly used measure. Often, state rumination is assessed using the RRS which has been, as already mentioned, originally designed to assess trait rumination. This is why we aimed to investigate the neural correlates of state rumination using a questionnaire specifically designed to assess state-processes in two previous studies of our lab (Rosenbaum et al., 2021, n.d.). In both studies, DP and HC underwent the Trier Social Stress Test as well as two resting-state measurements before and after the stress induction while their cortical oxygenation was assessed using functional Near-Infrared Spectroscopy (fNIRS). We observed blunted prefrontal activation increases in DP compared to HC and overall reduced O_2Hb-levels in the cognitive control network in DP; however, analyzing our data using Regions of Interest (bilateral DLPFC, bilateral IFG and SAC), we were not able to perform post-hoc tests between different ROIs because of potential confounds of absolute differences due to different optical path lengths. To the knowledge of the authors, no study has so far investigated the association of prefrontal hypoactivation with depressive symptomatology, trait and state rumination. While the well-known prefrontal hypoactivation for example under stress in DP is proposed to be associated with a reduced recruitment of the DLPFC in general and a cortical PFC inefficiency in DP, interestingly, prefrontal hypoactivation was not only observed in DP (Rosenbaum et al., 2021) but also in HC which were categorized as high trait ruminators (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum, Thomas, et al., 2018) and the influence of group membership on post-stress rumination was partly mediated by the reduced O_2Hb-levels under stress in the left DLPFC (Rosenbaum et al., 2021). This, with first preliminary results on the neural correlates of state rumination, gives rise to the question of whether trait measures (like the diagnostic group) or state measures (state rumination) might be two sides of the same coin and somewhat interchangeable. More specifically, in case depressive symptom severity, trait and state rumination are all not only highly intercorrelated on a psychological and behavioral basis but also associated with the same neural activation pattern, these findings would propose their interchangeability and implicate a discussion of shared and unique variance in a psychometric analysis. In order to disentangle these interrelationships, we merged the samples of two previous functional Near-Infrared Spectroscopy (fNIRS) studies of our lab in order to increase the power to detect effects on a single channel level (Rosenbaum et al., 2021, n.d.). Like this, it is possible to assess a more fine-grained activation pattern which could inform future neuromodulation studies, which might then be used to investigate the aforementioned relationships by a direct modulation of DLPFC-activity (and thus unravel causal relations).

3.3 Methods

3.3.1 Recruitment

Participants merged in this analysis were originally recruited within two distinct studies, which however followed the same recruitment procedure. In the first study we recruited 23 HC and 22 DP, in the second study 42 HC and 55 DP. Exclusion criteria for both studies were any disorder or medical condition affecting the cerebral metabolism, heart rate variability and/or cortisol levels: Diabetes mellitus, kidney insufficiency, hypertension, dysrhythmia, Cushing syndrome, substance abuse, adrenal insufficiency, cortisone medication, pacemaker, craniocerebral trauma as well as any medication except for oral contraceptives (or antidepressants in case of DP). HC were excluded in case they had any acute mental disorder and were additionally screened prior to study inclusion using the Structured Clinical Interview (SCID) (First, Williams, Karg, & Spitzer, 2015) by trained psychologists. For DP, furthermore any other primary mental disorder except ICD-10 diagnosis F32.x, F34.1 and F33.x was excluded in addition to subjects with acute suicidal tendencies, extraordinarily severe depressive symptoms (BDI-II > 50), deficient emotional stability according to the currently treating psychologist and decompensation under social stress in the past. HC were recruited via circular emails; DP were recruited at the University Hospital of Tübingen and via ambulant psychotherapists. All procedures were approved by the ethics committee at the University Hospital and University of Tübingen and are in line with the Declaration of Helsinki in its latest version.

All participants gave their written informed consent prior to data collection.

3.3.2 Procedure

For both studies the experimental procedure was the same (see figure 3.1). At first, baseline questionnaires assessing demographic data, depressive symptoms (Beck's Depression Inventory II (BDI-II); German version by Hautzinger et al., 2009) and trait rumination (Ruminative Response Scale; RRS; (Nolen-Hoeksema & Morrow, 1991)) were assessed. Meanwhile, participants were prepared for the fNIRS-measurement which was assessed pre-stress, during the stress induction and for 7 min post-stress. After the administration of the questionnaires, a 7 min resting-state measurement rest1 was performed where participants were instructed to sit still while letting their mind wander and keeping their eyes open. Following this, two control tasks were performed: For each of the 6 trials of control task 1 (CTL1), participants were given number sequences they had to read out aloud for 40 s which was followed by 20 s rest allowing a recovery of the hemodynamic response. In case they made an error, those were not pointed out and participants did not have to start all over again. In the end, the number of numbers read out aloud and errors per trial were documented. For each of the 6 trials of control task 2 (CTL2), participants were given different numbers from which they had to sequentially subtract 13 for 40 s, followed by 20 s rest. During the control tasks, only a friendly study nurse operating the fNIRS-device was present and participants were instructed to complete the tasks at their own pace. In case they made an error in CTL2, participants had to start all over again from the respective starting point. Afterwards, the number of errors made and the number of calculations per trial were documented. After both control tasks, two experimenters who remained socially non-responsive and were wearing white coats entered the room for the stress-induction using the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993). Participants were instructed to imagine having applied for a job at the University Hospital and part of the job interview was to give a speech about their personal strengths and qualifications. During a 5 min anticipation phase, participants had time to prepare themselves before the experimenters took away their notes, instructed them to stand up and deliver the speech. After 5 min, the experimenters instructed an arithmetic task analogue to CTL2, but this time participants had to calculate as fast and as correctly as possible while holding eye-contact with one of the experimenters. The other experimenter documented the number of performed calculations and errors. Afterwards, the experimenters left the room without any comment and a second resting-state analogue to the first one was conducted. Throughout the experiment, participants rated their subjective stress using Visual Analogue Scales (0–100%) on one page so they could allow for their last rating. After both resting-states, state rumination was assessed using a questionnaire that was already evaluated in other studies (Int-Veen, Laicher, et al., n.d., for the items, see supplementary material S1). Lastly, a post-stress phase of 45 min resting followed in which subjective stress was assessed every 15 min (for further details see (Rosenbaum et al., n.d.)).

3.3.3 Neural correlates

Using an ETG-4000 Optical Topography System with a sampling rate of 10 Hz, we measured cortical blood oxygenation (46-channel continuous wave multichannel fNIRS; Hitachi Medical Co., Japan). Two frontal probesets (with reference positions F3 and F4) and one parietal probeset (with reference positions Pz, P3 and P4) with a fixed 3 cm inter-optode-distance were placed according to the 10–20 reference points (28 light emitters,

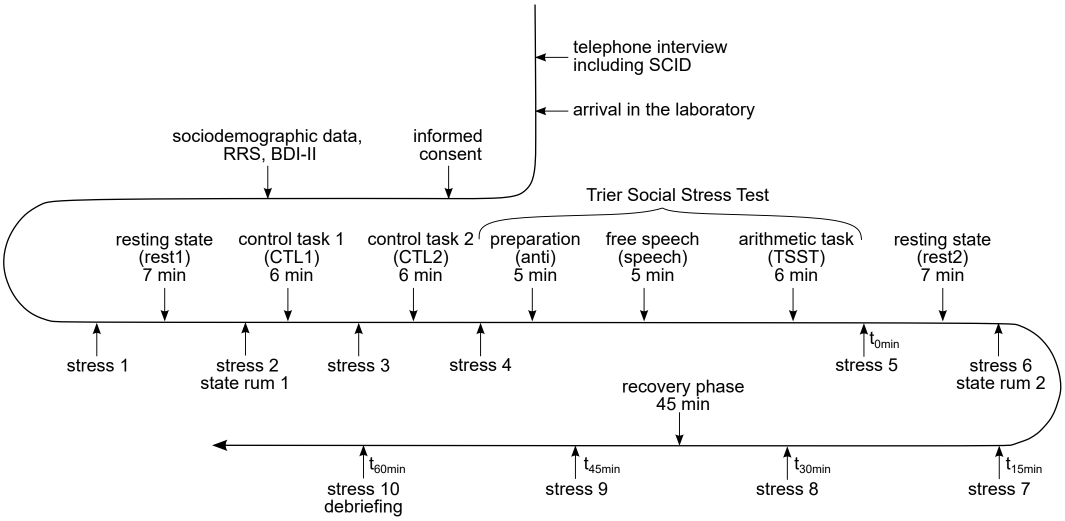


Figure 3.1
Time course of both studies. SCID = Structured Clinical Interview, RRS = Ruminative Response Scale, BDI-II = Beck Depression Inventory II, stress = Visual Analogue Scale assessing subjective stress (0–100%)

i.e. semiconductor lasers and 15 light detectors, i.e. avalanche photodiodes at two wavelengths (695 ± 20 nm and 830 ± 20 nm) with 2.0 ± 0.4 mW for each wavelength at each optode). Relative changes in oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin were computed using self-written MATLAB 2017 scripts by means of a modified Beer-Lambert Law (Sassaroli & Fantini, 2004). Preprocessing included the interpolation of single noisy channels, correction of motion artifacts using Temporal Derivative Distribution Repair (Fishburn, Ludlum, Vaidya, & Medvedev, 2019), Correlation-based signal improvement (Cui, Bray, & Reiss, 2010) and bandpass-filtering to remove low-frequency baseline-drifts (< 0.01 Hz) and high-frequency noise (> 0.1 Hz). In order to remove artifacts due to data correction, another channel interpolation followed and we used a global signal reduction with a spatial gaussian kernel filter ($\sigma = 40$). For data analysis, we calculated event-related averages for each trial including a 5 s baseline correction. For a visualization of the probeset placement see figure 3.2. For an assignment of channels to the Regions of Interest (ROIs), see table 3.1. Lastly, we exported the data for each channel of our ROIs separately: left Inferior Frontal Gyrus (lIFG), right Inferior Frontal Gyrus (rIFG), left Dorsolateral Prefrontal Cortex (lDLPFC), right Dorsolateral Prefrontal Cortex (rDLPFC) and Somatosensory Association Cortex (SAC). Scalp-brain correspondence was estimated based on Okamoto et al. (2004), Okamoto and Dan (2005), as well as Singh et al. (2005).

ROI	Channel
left IFG	7 9 6
left DLPFC	10 12 11
right IFG	18 21 19
right DLPFC	20 23 24
SAC	27 26 25 28 30 31 32 35 36

Table 3.1
Assignment of channels to the defined regions of interest. IFG = Inferior Frontal Gyrus, DLPFC = Dorsolateral Prefrontal Cortex, SAC = Somatosensory Association Cortex.

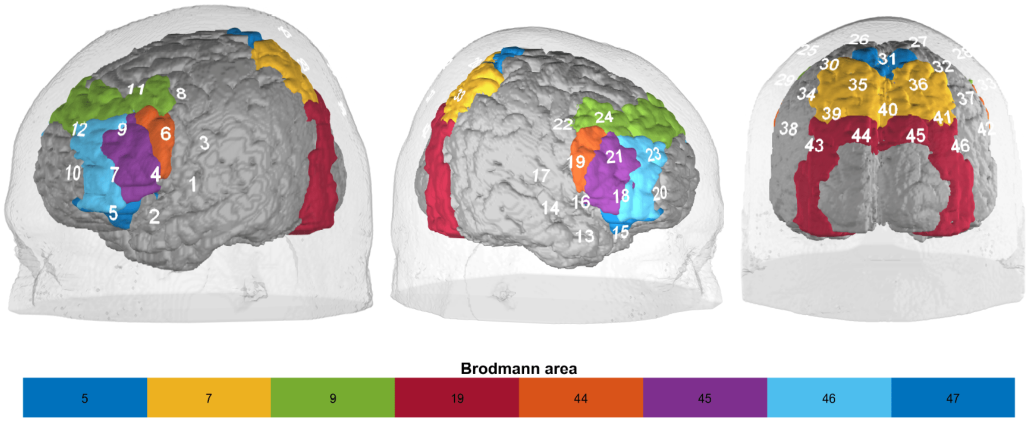


Figure 3.2
Placement of the three probesets. Numbers represent channels (see table 3.1). Please note that the probesets were integrated into EEG-Easycaps with additional sponge rings to ensure optimal placement. Scalp-brain correspondence was estimated based on Okamoto et al. (2004), Okamoto and Dan (2005=, as well as Singh et al. (2005).

3.3.4 Data analysis

Data analysis was done using IBM SPSS Statistics Version 28. Graphics were plotted using RStudio Version 1.4.1717 (RStudio Team, 2021) and R Version 4.0.3 (R Core Team, 2019) using the packages ggplot2 (Wickham, 2009), ggthemes (Arnold, 2024) and ggExtra (Attali & Baker, 2019). As we aimed to investigate the predictive value of state rumination for the hemodynamic changes due to the stress induction and did not only want to consider change scores but also state rumination levels post-stress (we expected more pronounced differences post-stress and we were primarily interested in the neural correlates of stress-induced rumination), we combined both in one variable by using hierarchical clustering. According to the dendrogram we decided for a 4-cluster solution: One cluster of n = 61 participants showing low state rumination levels in general and little to no change in state rumination due to the stress induction (83.1% of the n = 61 were HC), one cluster (n = 20) including participants with low baseline rumination but increases due to the TSST (15.4% of the n = 20 were HC), one cluster (n = 35) including high baseline rumination and increases due to the TSST (1.5% of the n = 35 were HC) and a forth cluster (n = 24) including high baseline rumination but little to no change due to the TSST (0% of the n = 35 were HC) (see figure 3.3, table 3.2). Next, we investigated the effects of trait rumination (RRS score), depressive symptomatology (BDI-II score) and group (DP vs. HC). Please note, however, that RRS and BDI-II were overall highly correlated ($r(137) = 0.786$, $p < 0.001$; disattenuated correlation using the psych-package $r = 0.982$ (Revelle, 2023)), and group membership (DP vs. HC) was strongly associated with BDI-II and RRS scores: Performing a median-split resulted in 84.3% HC in the low RRS group, 91.4% DP in the high RRS group, $\chi(1)^2 = 80.669$, $p < 0.001$, and 90.1% HC in the low BDI-II group and 98.6% DP in the high BDI-II group, $\chi(1)^2 = 110.669$, $p < 0.001$ (for an illustration see figure 3.4), which is why we abstained from fitting separate models for the aforementioned three variables of interest instead only including diagnostic group (DP vs. HC) as a predictor in our models. We firstly investigated state rumination ratings and therefore fitted a repeated measurements Analysis of Variance (rmANOVA) dependent on time and group (HC vs. DP). Next, we investigated the effect of group and state rumination cluster on the performance measures of the TSST (number of solved items and errors). Lastly, in order to investigate the fNIRS-data, we fitted separate multivariate repeated measurements ANOVAs (rmMANOVAs) including time and group (DP vs. HC) or state rumination cluster (SR-cluster) as a between-subjects factor, respectively. In order to correct fNIRS-data for potential effects of the number of calculations (e.g. higher increases in cortical oxygenation due to an increased recruitment of corresponding brain regions), we computed the ratio of a subject's given average O_2Hb-concentration and the average performance in the corresponding task (CTL1, CTL2 and the arithmetic task of the TSST) (Rosenbaum, Blum, et al., 2018). This ratio resulted in the measure "O_2Hb per item solved" [(mmol*mm)/item] which we investigated with the same rmMANOVA as previously described. Please note that univariate post-hoc tests as well as pairwise comparisons were corrected using the Benjamini–Hochberg procedure whereas due to the complexity of the fNIRS analysis, pairwise comparisons of the main effect of time are to be found in supplementary material S2. In case sphericity assumptions were violated, we corrected using Greenhouse Geisser estimates (in all cases, $\epsilon > 0.75$). We further excluded two participants whose state rumination ratings were identified as multivariate outliers ($p < 0.01$) according to their Mahalanobis distances. In the following, we will report the results of all channels of our ROIs; however, plots of all significant results of all channels except for the left DLPFC are to be found in the supplementary material S3.

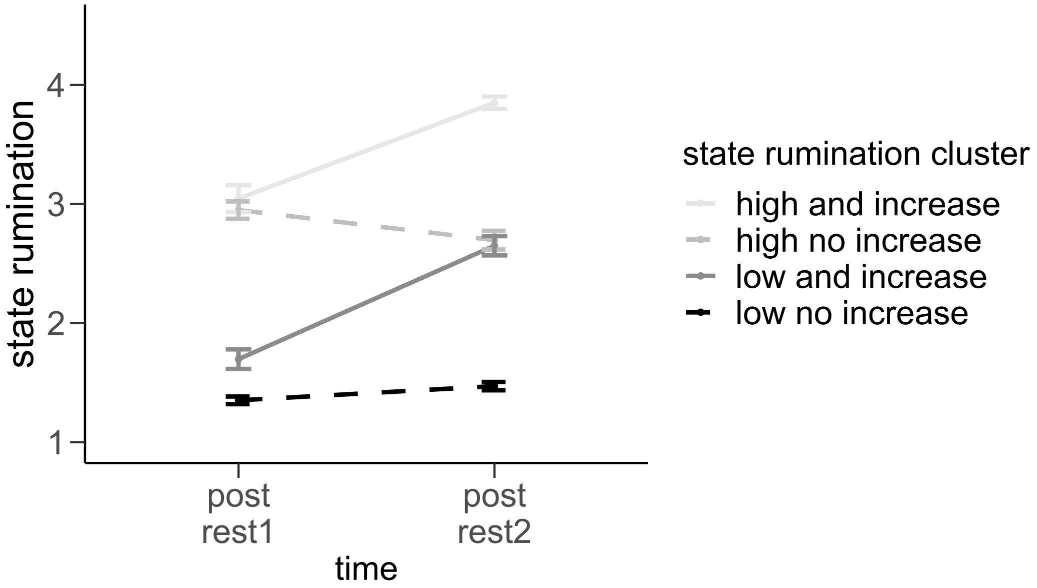


Figure 3.3
Illustration of state rumination ratings dependent on state rumination clusters. Post rest1 = prior to the stress induction; post rest2 = after the stress induction. Error bars indicate standard errors (+/- 1 SE).

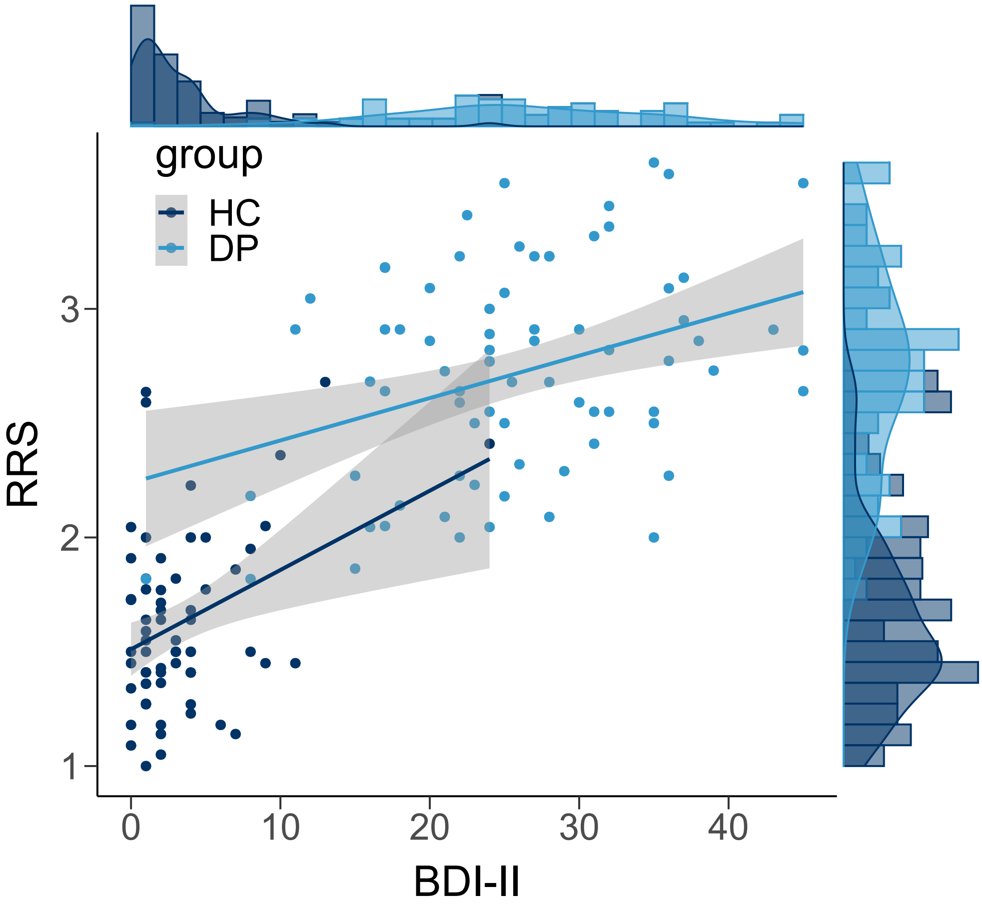


Figure 3.4
Scatterplot with marginal histograms and density plots of RRS and BDI-II scores dependent on group (HC = healthy controls, DP = depressed patients).

Table 3.2
Crosstable investigating the distribution of group (DP = depressed patients, HC = healthy controls) dependent on state rumination cluster (SR-cluster).

			SR-cluster				
			SR-cluster 1 (high and increase)	SR-cluster 2 (high and no increase)	SR-cluster 3 (low and increase)	SR-cluster 4 (low and little to no increase)	total
Group	DP	*n*	35	23	10	7	75
		% within group	46.7%	30.7%	13.3%	9.3%	100%
		% within SR-cluster	100%	95.8%	50.0%	11.5%	53.6%
		% of total	25.0%	16.4%	7.1%	5.0%	53.6%
	HC	*n*	0	1	10	54	65
		% within group	0.0%	1.5%	15.4%	83.1%	100%
		% within SR-cluster	0.0%	4.2%	50.0%	88.5%	46.5%
		% of total	0.0%	0.7%	7.1%	38.6%	46.4%
Total		*n*	35	24	20	61	140
		% within group	25.0%	17.1%	14.3%	43.6%	100%
		% within SR-cluster	100%	100%	100%	100%	100%
		% of total	25.0%	17.1%	14.3%	43.6%	100%

3.3.5 Participants

Before merging both study samples, we performed independent samples *t*-tests comparing the demographic variables of the overall samples as well as the subsamples (HC and DP). Concerning the overall samples, we found no significant differences in depressive symptoms as assessed using the BDI-II, $t(140) = -1.643$, $p = 0.103$, $d = -0.296$, trait rumination levels as assessed using the RRS, $t(139) = -0.789$, $p = 0.432$, $d = -0.142$, or the sex distribution, $\chi(1)^2 = 0.341$, $p = 0.559$. However, we did find the sample of study 1 to be on average 4 years younger compared to the sample of study 2, $t(135.34) = -2.908$, $p < 0.01$, $d = -0.431$. Comparing the HC subsamples, we found no differences concerning age, $t(63) = -0.899$, $p = 0.372$, $d = -0.233$, RRS, $t(63) = 1.651$, $p = 0.104$, $d = 0.428$, or the percentage of female participants, $\chi(1)^2 = 0.001$, $p = 0.977$. However, we found HC in study 1 to rate their depressive symptoms as significantly lower compared to HC in study 2, $t(60.43) = -2.232$, $p < 0.05$, $d = -0.471$. Concerning DP, we found patients of study 1 to be comparable regarding their BDI-II, $t(27.58) = -0.915$, $p = 0.368$, $d = -0.282$, and RRS, $t(74) = -1.645$, $p = 0.104$, $d = -0.416$, and sex distribution, $\chi(1)^2 = 0.515$, $p = 0.473$, but DP of study 1 were significantly younger than DP of study 2, $t(67.17) = -2.743$, $p < 0.01$, $d = -0.282$. For means and standard deviations please see table 3.3. The final total sample comprised $n = 77$ DP and $n = 65$ HC. 74.65% of the sample was female with a mean age of 29.01 (*SD* = 9.62) years, mean BDI-II of 15.56 (*SD* = 13.30) and mean RRS of 2.23 (*SD* = 0.69) (see table 3.3). Not surprisingly, we found BDI-II and RRS to be highly correlated ($r(142) = 0.784$, $p < 0.001$) (see 3.4). The diagnoses in the patient sample included recurrent Major Depressive Disorder (MDD) ($n = 52$), first episode MDD ($n = 21$) as well as $n = 1$ patient with an adjustment disorder and $n = 3$ patients with problems related to life management difficulties. All DP were currently in a depressed state according to their BDI-II score ($M = 25.91$, $SD = 8.82$). 51.3% were currently receiving psychotherapy and 41.6% antidepressant medication.

Table 3.3

Demographic data dependent on the subsamples and the merged total sample.

study	variable	group	*M*	*SD*	test-statistic comparing DP and HC	*p*-value	Cohen´s *d*
1	age	DP (*n* = 22)	27.14	6.15	*t*(43) = 1.008	0.319	.301
		HC (*n* = 23)	25.35	5.75			
	BDI-II	DP (*n* = 22)	24.14	11.85	*t*(22.10) = 8.596	.001	2.619
		HC (*n* = 23)	2.13	1.96			
	RRS	DP (*n* = 22)	2.59	0.50	*t*(43) = 6.447	.001	1.923
		HC (*n* = 23)	1.73	0.39			
	% female	DP (*n* = 22)	77.27 %		$\chi(1)^2$= .006	.936	
		HC (*n* = 23)	78.26 %				
2	age	DP (*n* = 55)	32.60	11.12	*t*(93.985) = 2.548	.01	.510
		HC (*n* = 42)	27.29	9.39			
	BDI-II	DP (*n* = 55)	26.62	7.29	*t*(91.919) = 18.727	.001	3.619
		HC (*n* = 42)	3.95	4.58			
	RRS	DP (*n* = 55)	2.78	0.44	*t*(94) = 14.415	.001	2.966
		HC (*n* = 42)	1.57	0.37			
	% female	DP (*n* = 55)	69.09 %		$\chi(1)^2$= 1.091	.296	
		HC (*n* = 42)	78.57 %				
total	age	DP (*n* = 77)	31.04	10.22	*t*(139.795) = 2.856	. 01	.473
		HC (*n* = 65)	26.60	8.29			
	BDI-II	DP (*n* = 77)	25.91	8.82	*t*(108.946) = 20.218	.001	3.217
		HC (*n* = 65)	3.31	3.94			
	RRS	DP (*n* = 77)	2.72	0.46	*t*(139) = 15.270	.001	2.580
		HC (*n* = 65)	1.63	0.38			
	% female	DP (*n* = 77)	71.43 %		$\chi(1)^2$= .921	.334	
		HC (*n* = 65)	78.47 %				

Note. study 1 = (Rosenbaum et al., 2021); study 2 = (Rosenbaum et al., n.d.), BDI-II = Beck Depression Inventory II (Beck, Steer, & Hautzinger, 1994; Hautzinger et al., 2009); RRS = Ruminative Response Scale (Nolen-Hoeksema & Morrow, 1991), DP = depressed patients, HC = healthy controls.

3.4 Results

3.4.1 State rumination

Investigating subjective state rumination ratings, we fitted a repeated measurements Analysis of Variance (rmANOVA) dependent on time (post rest1 vs. post rest2) and group (DP vs. HC) and found a significant main effect of time, $F(1, 138) = 46.163$, $p < 0.001$, $\eta_p^2 = 0.251$, indicating an increase in state rumination due to the stress induction. We further observed a significant main effect of group, $F(1, 138) = 250.633$, $p < 0.001$, $\eta_p^2 = 0.645$, reflecting higher state rumination in general in the case of DP compared to HC, as well as a significant interaction of time and group, $F(1, 138) = 4.388$, $p < 0.05$, $\eta_p^2 = 0.031$, reflecting higher increases in the case of DP (see figure 3.5).

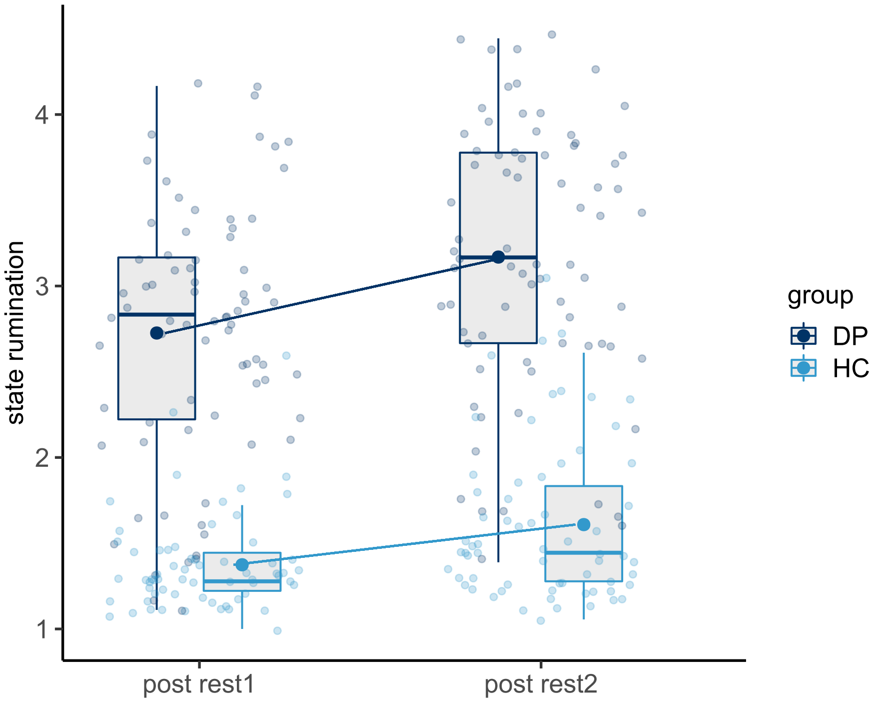


Figure 3.5
*Line and boxplots of state rumination ratings. Transparent dots and Boxplots indicate the raw data. The lower and upper hinges of the boxplot correspond to the first and third quartiles. Whiskers extend from the hinge to the largest value no further than 1.5*Interquartile-Range. Bold dots and lines indicate the estimated marginal mean of the fitted models. DP = depressed patients, HC = healthy controls, post rest1 = assessment of state rumination after resting state measurement 1 (baseline), post rest2 = assessment of state rumination after resting state measurement 2 (post stress).*

3.4.2 *Performance under stress*

Investigating the performance of mental arithmetics, we fitted a rmANOVA on the mean number of items solved dependent on group (DP vs. HC) and time (control task 1 (CTL1) vs. control task 2 (CTL2) vs. arithmetic task of the TSST). We observed a significant main effect of time, $F(1.252, 171.549) = 992.468$, $p < 0.001$, $\eta_p^2 = 0.879$. In general, HC solved on average 1.5 more items compared to DP, which was reflected by a significant main effect of group, $F(1, 137) = 6.148$, $p < 0.05$, $\eta_p^2 = 0.043$. Post-hoc tests of the main effect of time revealed that participants performed significantly ($p < 0.05$) less calculations (CTL2 and TSST) compared to reading numbers (CTL1) and in case they were instructed to calculate as fast and as correctly as possible (TSST) significantly more compared to CTL2. When analyzing the number of errors, we did not observe any differences dependent on group but again a significant main effect of time, $F(1.442, 197.593) = 167.689$, $p < 0.001$, $\eta_p^2 = 0.550$. Pairwise comparisons indicated significantly more errors during CTL2 as well as the TSST compared to CTL1 and during the TSST compared to CTL2 (see figure 3.6).

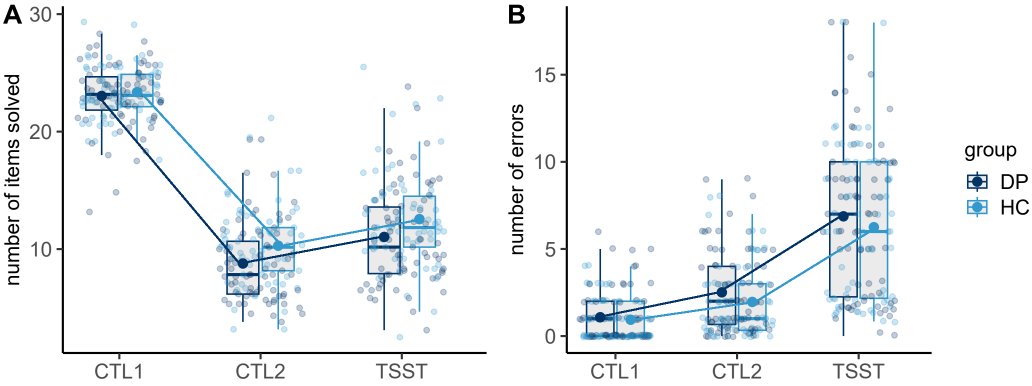


Figure 3.6
Line graphs of the mean number of items solved (A) and total number of errors (B) dependent on the state rumination cluster. CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress), TSST = arithmetic task of the TSST (performing calculations under social stress).

Fitting the same rmANOVA dependent on the state rumination cluster variable (SR-cluster, see methods section), we observed a significant main effect of time, $F(1.258, 169.852) = 910.201$, $p < 0.001$, $\eta_p^2 = 0.871$, a significant main effect of SR-cluster, $F(3, 135) = 6.669$, $p < 0.001$, $\eta_p^2 = 0.129$, as well as a significant interaction of time and SR-cluster, $F(3.774, 169.852) = 2.507$, $p < 0.05$, $\eta_p^2 = 0.053$. Benjamini-Hochberg-corrected post-hoc tests of the interaction of time and SR-cluster indicated an overall significantly ($p < 0.05$) higher number of solved items in the case of cluster 4 (low state rumination and little to no increase in state rumination due to the stress induction) when compared to cluster 3 (low state rumination and increase in state rumination due to the stress induction) and cluster 1 (high state rumination and increase in state rumination due to the stress induction) whereas cluster 4 and 3 only differed during the arithmetic task of the TSST and cluster 4 and 1 differed at CTL2 as well as the arithmetic task of the TSST. Concerning the number of errors, we observed a significant main effect of time, $F(1.461, 197.249) = 173.345$, $p < 0.001$, $\eta_p^2 = 0.562$, as well as a significant interaction effect of SR-cluster and time, $F(4.383, 197.249) = 2.373$, $p < 0.05$, $\eta_p^2 = 0.050$. Benjamini-Hochberg-corrected pairwise comparisons revealed significant increases in errors over time (CTL1 vs. CTL2 vs. TSST). Investigating the interaction effect of time and SR-cluster, Benjamini-Hochberg-corrected post-hoc tests indicated no significant differences between the 4 groups during CTL2 nor during the TSST (uncorrected pairwise comparisons indicated a significant difference between cluster 3 and 4 in the case of the arithmetic task of the TSST) but significant increases ($p < 0.05$) in each of the 4 groups from CTL1 to CTL2 to the TSST (see figure 3.7).

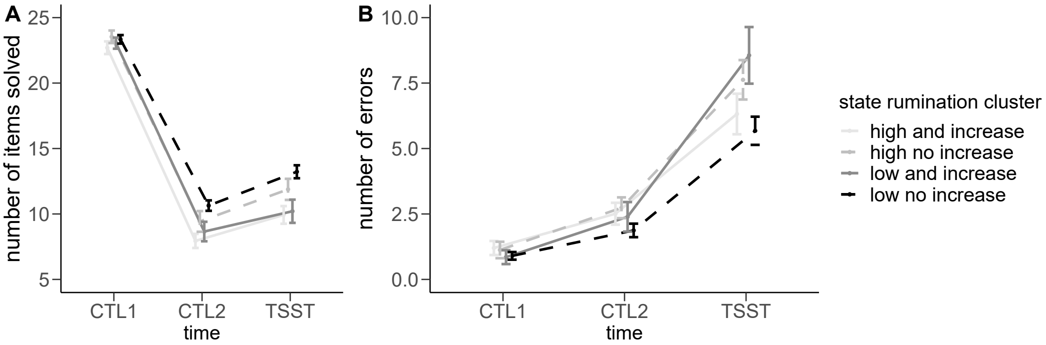


Figure 3.7
*Line and boxplots of the mean number of items solved (A) and total number of errors (B) dependent on group (DP vs. HC). Transparent dots indicate the raw data. Bold dots indicate the estimated marginal mean of the fitted models. The lower and upper hinges of the boxplot correspond to the first and third quartiles. Whiskers extend from the hinge to the largest value no further than 1.5*Interquartile-Range. DP = depressed patients, HC = healthy controls, CTL1 = control task 1 (reading numbers aloud), CTL2 = control task 2 (performing calculations without social stress), TSST = arithmetic task of the TSST (performing calculations under social stress).*

3.4.3 Neural correlates

Next, we fitted a rmMANOVA dependent on time (control task 1 (CTL1), control task 2 (CTL2) and arithmetic task of the TSST) and group (DP vs. HC). This rmMANOVA resulted in a significant main effect of time, $F(42, 512) = 2.987$, $p < 0.001$, wilks $\lambda = 0.645$, $\eta_p^2 = 0.197$, as well as a significant interaction of time and group, $F(42, 512) = 1.681$, $p < 0.01$, wilks $\lambda = 0.772$, $\eta_p^2 = 0.121$. We firstly investigated the univariate tests of the main effect of time. Consequently, time yielded a significant predictor ($p < 0.05$) in all channels except for channel 19 and 21 (both right IFG). The interaction of time and group yielded significance in the case of two out of three channels of the left DLPFC (channel 11, 12), two out of three channels of the right DLPFC (channel 20, 23), one out of three channels of the right IFG (channel 21) as well as two out of nine channels of the SAC (channel 35, 36). Investigating the pairwise comparisons of the interaction of time and group, we observed significant differences between HC and DP during CTL2 in the case of channel 20 (right DLPFC) and significant differences between HC and DP during the arithmetic task of the TSST in the case of two channels of the left DLPFC (channel 11, 12), one channel of the right IFG (channel 21) and one channel of the right DLPFC (channel 23). We further observed significant increases between CTL1 and the TSST — but only in HC — in the case of all the aforementioned IFG and DLPFC channels (channel 11, 12, 21, 23), two channels of the SAC (channel 35, 36) and another channel of the right DLPFC (channel 20). A subgroup of those further showed significant increases from CTL2 to TSST in the case of HC (channel 11, 12, 21, 36) and in the case of DP one channel of the right DLPFC (channel 20) (see table 3.4). For an illustrative comparison of cortical oxygenation dependent on channel and group (DP vs. HC) see supplementary Material S4. Lastly, we fitted a rmMANOVA dependent on time and state rumination cluster and observed a significant main effect of time, $F(42, 504) = 2.395$, $p < 0.001$, wilks $\lambda = 0.695$, $\eta_p^2 = 0.166$, and a significant interaction effect of time and state rumination cluster, $F(126, 1468.91) = 1.437$, $p < 0.01$, wilks $\lambda = 0.510$, $\eta_p^2 = 0.106$. Univariate tests yielded a significant ($p < 0.05$) main effect of time in one channel of the right DLPFC (channel 20), two channels of the left IFG (channel 7, 9) and two SAC-channels (channel 25, 32). Univariate tests of the time by SR-cluster interaction yielded significance in the case of all three channels of the left DLPFC (channel 10, 11, 12), two channels of the right DLPFC (channel 20, 24), one channel out of three of the left (channel 6) and right IFG (channel 21) as well as two out of the nine SAC-channels (channel 26 and 36) (for a summary of the channels in which the interaction of time and SR-cluster yielded significance in the univariate tests, please see table 3.4). We investigated the pairwise comparisons of the significant interaction of time and SR-cluster and observed significant differences at CTL2 between cluster 1 and 4 in the case of channel 20. Further, significant differences during the arithmetic task of the TSST have been observed between cluster 1 (high state rumination and increase) and 4 (low state rumination and little to no increase) in all channels covering the left DLPFC, one channel of the right IFG (channel 21), two channels of the right DLPFC (channel 20, 24) and two out of nine channels of the SAC (channel 26, 36). Significant differences during the arithmetic task of the TSST were observed between cluster 2 (high state rumination with little to no increase) and cluster 4 (low state rumination and little to no increase) in the case of three channels (one left DLPFC (channel 12), one right DLPFC (channel 24), one SAC (channel 36)). Significant differences during the arithmetic task of the TSST were also found between cluster 3 (low state rumination and increase) and 4 (low state rumination and little to no increase) in the case of six channels (two left DLPFC (channel 10, 12), two right DLPFC (channel 20, 24), one right IFG (channel 21), one SAC (channel 26)). With respect to changes between the different tasks, only cluster 4 (low state rumination and little to no increase) showed significant increases in cortical oxygenation between CTL1 and TSST in the case of all channels of the left DLPFC, one channel of the left IFG (channel 6), two channels of the right DLPFC (channel 20, 24), one channel of the right IFG (channel 21) and two channels of the SAC (channel 26, 36). Increases between CTL2 and the TSST were observable in all of the aforementioned channels but one channel of the right DLPFC (channel 24). For an illustration of the previously reported effects, see figures 3.8 and 3.9.

3.4.4 Performance-corrected fNIRS-data

In order to account for the differences in performance in calculations during the TSST arithmetic task, we fitted a rmMANOVA dependent on time (control task 1, control task 2 and arithmetic task of the TSST) and group (DP vs. HC) using our fNIRS-data corrected for the number of items solved. This rmMANOVA again resulted in a significant main effect of time, $F(42, 508) = 4.525$, $p < 0.001$, wilks $\lambda = 0.530$, $\eta_p^2 = 0.22$; however, the interaction effect of time and group did no longer yield significance, $F(42, 508) = 1.245$, p = 0.145, wilks $\lambda = 0.822$, $\eta_p^2 = 0.093$. Univariate ANOVAs yielded time to be a significant predictor ($p < 0.05$) in the case of all channels except for channel 7, 18 and 21. Fitting the same rmMANOVA using the corrected fNIRS-data dependent on time and state rumination cluster, we observed similar results as without correcting for performance, namely a significant main effect of time, $F(42, 500) = 4.225$, $p < 0.001$, wilks $\lambda = 0.545$, $\eta_p^2 = 0.262$, and a significant interaction of time and SR-cluster, $F(126, 1457.309) = 1.245$, $p < 0.05$, wilks $\lambda = 0.530$, $\eta_p^2 = 0.094$. Investigating the univariate tests, we found time to yield a significant predictor in the case of all channels of the right DLPFC, one channel of the left DLPFC (channel 10), seven out of nine channels of the SAC (channel 25, 26, 27, 28, 30, 32, 35) as well as one channel of the left (channel 6) and right IFG (channel 19), respectively. Investigating the significant interaction of time and SR-cluster, univariate tests revealed that it was a significant predictor only in channel 21 (right IFG). Pairwise comparisons revealed significant increases in cortical oxygenation in channel 21 from CTL1 to the TSST only in the case of cluster 4 (low state rumination and little to no increase in state rumination due to the stress induction). During the TSST, cluster 4 (low state rumination and little to no increase) showed significantly higher cortical oxygenation compared to cluster 3 (low state rumination and increase) and cluster 1 (high state rumination and increase). For an illustration see figure 3.10.

ROI	left IFG			left DLPFC			right IFG			right DLPFC			SAC								
channel	6	7	9	10	11	12	18	19	21	20	23	24	25	26	27	28	30	31	32	35	36
group					+	+			+	+	+									+	+
SR-cluster	+			+	+	+			+	+		+		+							+

Table 3.4
*Illustration of the significant Benjamini-Hochberg-corrected time*group interactions (depicted as +) of the repeated measurements Multivariate Analyses of Variance (rmMANOVAs) investigating fNIRS cortical oxygenation (group = depressed patients vs. healthy controls, SR-cluster = state rumination cluster). IFG = Inferior Frontal Gyrus, DLPFC = Dorsolateral Prefrontal Cortex, SAC = Somatosensory Association Cortex.*

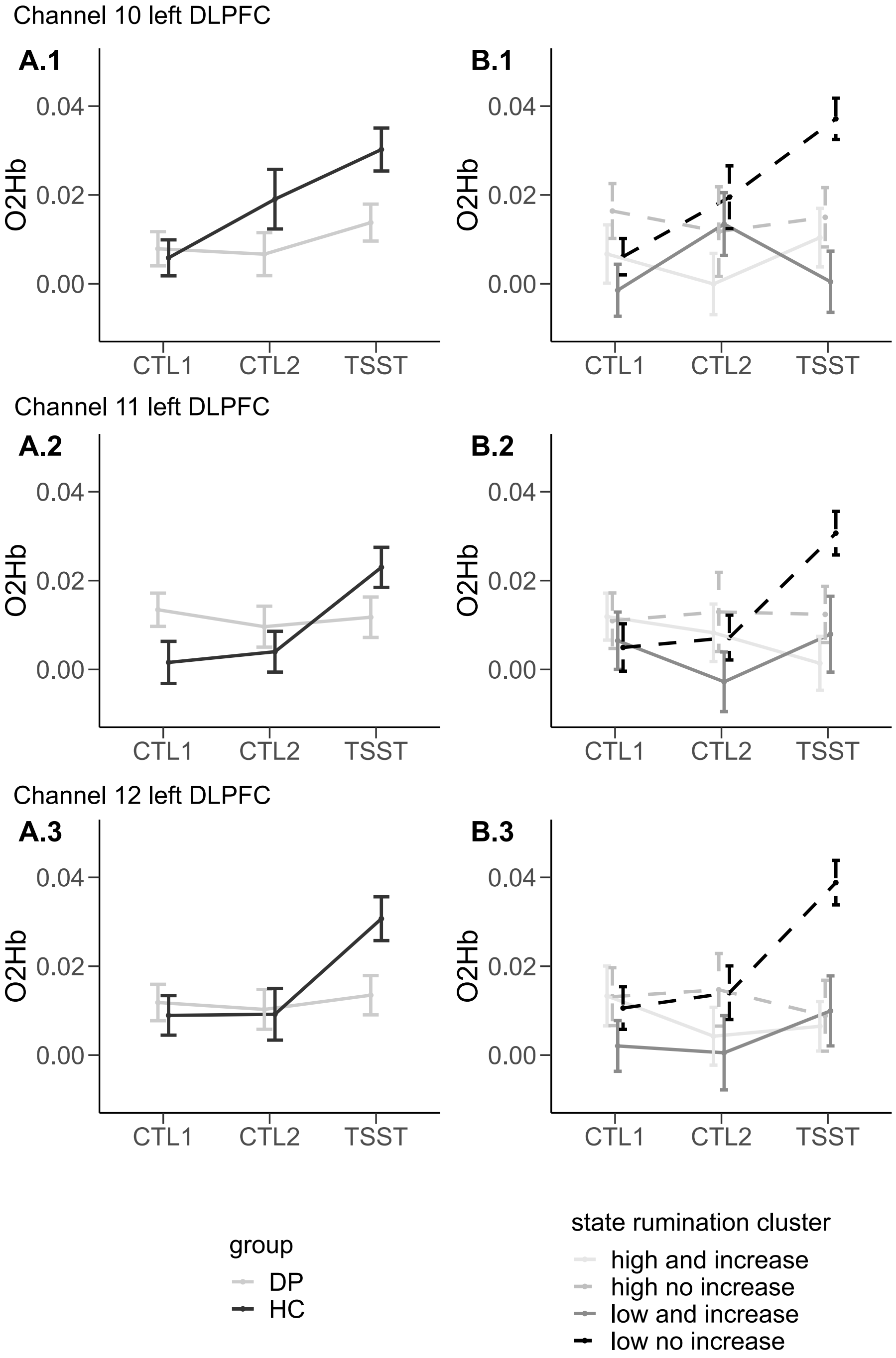


Figure 3.8
Illustration of the results of the repeated measures fNIRS-MANOVAs for each channel of the left DLPFC and group (A = patients with depression (DP) vs. healthy controls (HC); B = state rumination cluster). For an illustration of the probeset where the channels are exactly located, we refer to 3.2. CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress), TSST = arithmetic task of the TSST (performing calculations under social stress). Please note that the interaction effect of time and group was significant in all channels of the left DLPFC besides channel 10 in the case of DP vs. HC. We depicted it either way for completeness. Error bars indicate +/- 1 SE.

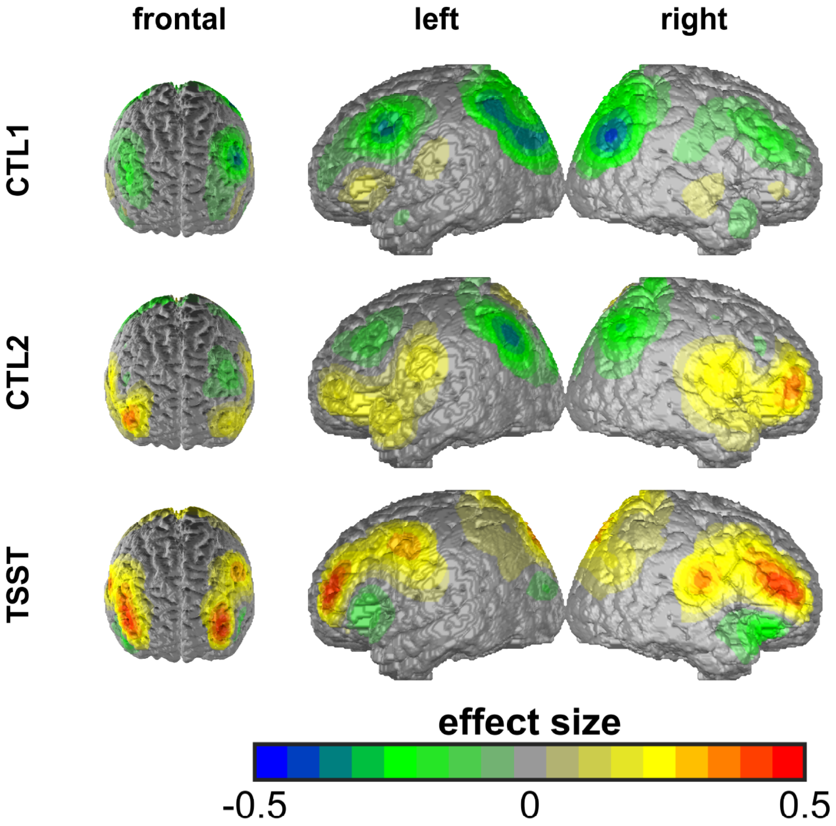


Figure 3.9
Differences in O_2Hb-levels (not corrected for performance) dependent on group (DP vs. HC) during control task 1 (CTL1 = reading numbers), control task 2 (CTL2 = performing calculations without social stress) and TSST (performing calculations under social stress). Warm colors indicate higher O_2Hb-levels in the HC compared to the DP; cool colors vice versa. Differences are depicted in Cohen's d.

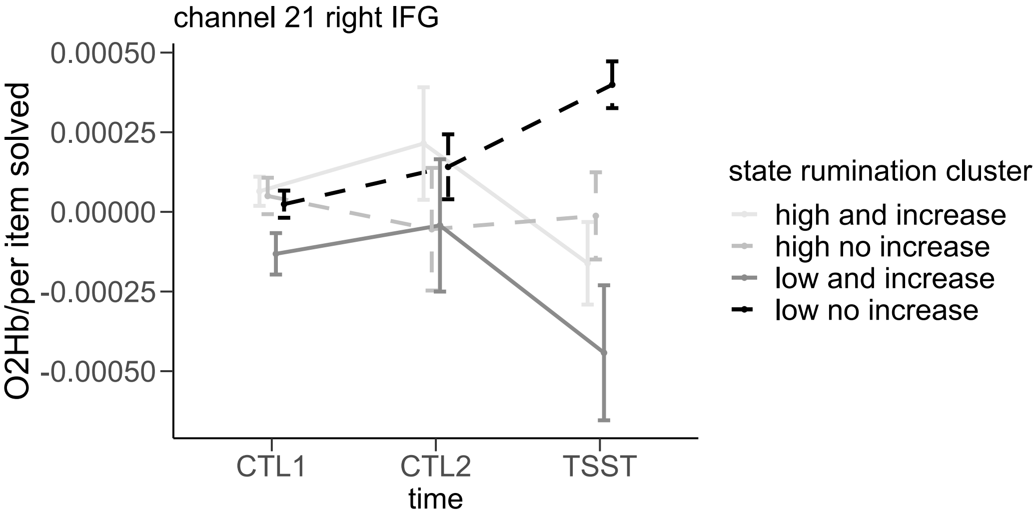


Figure 3.10
Illustration of the results of the repeated measures fNIRS-MANOVA using the performance-corrected fNIRS data in the case of channel 21.

3.5 Discussion

Prefrontal hypoactivation is an intensely studied phenomenon in the context of depression. With the use of several neuroimaging techniques, this neural correlate has been repetitively replicated and is now regarded to be a robust finding across different samples (for a review see Pizzagalli & Roberts, 2022). As a major vulnerability to develop depressive episodes, rumination has also been found to be linked to prefrontal hypoactivation. Interestingly, however, rumination is not only apparent in DP but also in HC and first studies on state rumination also show aberrant DLPFC-functioning in HC (Kühn et al., 2014). Due to a rather scarce literature, it remains unclear whether the aforementioned neural correlates might be a concomitant feature of symptoms of depression, or whether trait or state rumination might (also) account for this characteristic neural activation pattern. As ruminative thinking is assumed to be a transdiagnostic factor and part of the psychopathological abnormalities in various disorders (Aldao & Nolen-Hoeksema, 2010; Arditte et al., 2016; Gustavson et al., 2018; Kaplan et al., 2018; Klemanski et al., 2017), this might have crucial implications for a more coherent model of neural pathways assumed to be involved in these disorders and consequently also in the respective treatment. To investigate these associations, we merged the samples of two of our previous studies on rumination investigating the cortical hemodynamic changes using fNIRS and behavioral alterations of HC and DP when stress is induced using the TSST. Merging these two studies with an equivalent experimental set-up resulted in a total sample of N = 142, which increased the power to detect even smaller effect sizes. Intuitively, high levels of trait rumination are nearly in all cases simultaneously present with increased symptoms of depression and therefore more often apparent in DP. These issues of multicollinearity do pose major problems in the differentiation of the effects which is why we only investigated “trait measures” (BDI-II, RRS) and diagnostic group (DP vs. HC) and state rumination in separate models. Statistical models including corresponding other variables as covariates would result in interpretations of the predictor “in case the other variable is held constant”. This, in fact, would pose a rather artificial situation and potentially lead to biased estimates, which is why we opted for the aforementioned analysis. We are, as a consequence, not able to estimate the amount of shared and unique variance of the trait variables as well as state and trait measures, nor estimate whether one model might be a significantly better fit for the data; however, we are able to compare trait and state aspects in their predictive value of behavioral and neural responses due to the stress induction. We firstly investigated the behavioral stress response including state rumination and performance in control tasks and the TSST. Intuitively and as shown in the previous analysis of the subsamples of this data, DP showed higher increases in state rumination after social stress compared to HC, and the latter further performed generally better. Better performance was reflected by more items solved in the control tasks and the TSST, whereas we did not observe less errors in HC compared to DP. In order to investigate the effect of state rumination while considering change scores and post-stress state rumination, we combined both in one variable: In SPSS, we used hierarchical clustering (average linkage between-groups) and extracted 2–5 clusters and according to the dendrogram, four "state rumination clusters" emerged: One group of participants showing generally high levels of state rumination and increases due to the stress induction (cluster 1), one group with high levels of state rumination but little to no increase (cluster 2), one group with generally low levels of state rumination and increases due to stress (cluster 3) as well as a group with low state rumination with little to no increases (cluster 4). Please note that cluster 4 primarily comprised HC, cluster 1 and 2 comprised primarily DP and cluster 3 both. This differentiation on a behavioral level was of major interest concerning potentially distinct neural response patterns to stress. That is, as state rumination is apparent in HC and DP, we were interested in whether prefrontal hypoactivation in distinct channels would be associated with only, for instance, both clusters with state rumination increases which would question the more general categorization of HC vs. DP in case of the investigation of prefrontal hypoactivation. Concerning the performance during the TSST, state rumination clusters reflected more or less the same but more fine-grained results as the analysis of "trait"-group (DP vs. HC): We observed cluster 4 (low state rumination and little to no increase $\sim$ HC) to perform better compared to cluster 3 (low state rumination and increase) as well as cluster 1 (high state rumination and increase). That means, participants showing increases in state rumination due to the stress induction performed worse compared to groups with little to no increase. This is well in line with the idea of a less efficient recruitment of the prefrontal areas plus cortical inefficiency in DP in the case of "affective and cognitive tasks requiring emotional or stress regulation, cognitive control, and/or shifting attention to external task demands" (Pizzagalli & Roberts, 2022, p. 240), which is ultimately reflected by a worse performance on a behavioral level. However, on the other hand, this might also be a concomitant feature of lower motivation and other factors inducing malperformance as a recent meta-analysis found that worse performance of depressed patients in neuropsychological tests might be overestimated (Moritz et al., 2017, 2023) and it is reasonable to assume that the neuronal correlates could then also be exaggerated. However, to the knowledge of the authors, there is no analogous investigation concerning neural data of depressed patients, so far. When analyzing fNIRS-data dependent on group (DP vs. HC) using a repeated measures MANOVA, we observed significant increases in cortical oxygenation in nearly all channels due to the stress induction as well as time-dependent differences between HC and DP: In DP we observed prefrontal hypoactivation under stress in the case of two out of three channels of the left and right DLPFC, respectively, as well as one channel of the right IFG. Following the extensive review concerning prefrontal cortex alterations in depression by Pizzagalli and Roberts (2022), especially the results of aberrant functioning in the left DLPFC being associated with depression are well in line with an extensive body of literature. While there is a clear focus on the left DLPFC in the literature, recent meta-analyses of randomized controlled trials using repetitive transcranial magnetic stimulation over the right DLPFC also evaluated them as successful in the treatment of DP (Cao, Deng, Su, & Guo, 2018; Chen, Rapee, & Abbott, 2013). Future studies are needed to evaluate and integrate these findings and extend the literature on the exact underlying neural pathways. When we investigated the neural correlates dependent on state rumination clusters, we firstly found nearly the same channels being associated with time-dependent changes as in our previous analyses using “trait”-groups, but crucially more channels: For instance, we now observed significantly lower activation in all channels of the left DLPFC in the case of cluster 1 (high state rumination and increase) when compared to cluster 4 (low state rumination and little to no increase $\sim$ HC). This translates to a specific sub-group of DP showing a prefrontal activation pattern significantly differing from HC, which is identified through their respective pattern of state rumination-reactivity. This finding suggests that the mere differentiation of diagnostic groups (clinical vs. nonclinical, i.e. meeting a predefined number of symptom categories or not) might not comprehensively explain state-dependent brain activity. Again, due to problems of multicollinearity and the current sample size, we are not able to investigate shared and unique variance to trait or state measures; however, this data suggests this might be an interesting endeavor. This is even clearer when we recap the results of the same rmMANOVA using performance-corrected fNIRS-data. As previously reported, we observed significant differences of both, DP vs. HC as well as the different SR-clusters, in the performance during (the non-stressful control tasks and) the arithmetic task of the TSST. In this rmMANOVA, the interaction-effect of time and group (DP vs. HC) and the corresponding prefrontal hypoactivation in DP vanished in the case of our “trait”-analysis. This was, however, not the case for SR-cluster. Here, the interaction effect of time and SR-cluster remained significant. Using Benjamini–Hochberg-corrected post-hoc tests, we observed significant increases in cortical oxygenation in channel 21 (right IFG) from CTL1 to the TSST only in the case of cluster 4 (low state rumination and little to no increase). Please note that this was the result after correction of multiple testing as we analyzed a total of 21 channels to be able to tell where exactly differences were present. Most probably, a larger sample size with balanced groups would be beneficial in evaluating this effect. Generally speaking, however, state measures do pose an important predictor when investigating stress-induced prefrontal hypoactivation and future studies should consider state measures in group differentiation rather than—or in addition to—trait measures. One limitation concerning the interpretation of the aforementioned results concerns the penetration depth of fNIRS, which is estimated to 3 cm. While the cortex can be captured, deeper brain structures cannot be assessed. In this case, further studies using other neuroimaging techniques are needed to investigate the neural correlates of state rumination as regions like the Anterior Cingulate Cortex are also discussed to be involved (Kross et al., 2009; Vanderhasselt et al., 2013). A combined fMRI- and fNIRS-study using neuro-navigation software would be able to quantify between-subjects as well as within-subjects (over the course of the experiment) variability of channel placement and also assess deeper underlying brain regions. Nevertheless, in order to ensure high ecological validity, the merged studies used fNIRS as it is less prone to motion artifacts (Pinti et al., 2020) and participants are able to stand in front of the jury members as in the original TSST (Kirschbaum et al., 1993). The findings presented in our analyses add to a very scarce literature on the neural correlates of ruminative processes as well as the differentiation of state and trait aspects in these neural aberrations. Aforementioned results might be used in experimental studies investigating the causal link between neural activity and rumination using neuromodulation to gain insights into the underlying mechanisms. Repetitive Transcranial Magnetic Stimulation (rTMS) for instance has been proposed as a noninvasive approach to alter brain excitability (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). It is nowadays regarded as a useful adjunct to the treatment of depression complementary to antidepressant medication and psychotherapy. rTMS, and especially Theta Burst Stimulation (TBS) has been found to result in longer lasting effects, which were already found to be effective in the treatment of depression (Chistyakov, Rubicsek, Kaplan, Zaaroor, & Klein, 2010; Fitzgerald et al., 2006; Holzer & Padberg, 2010; Plewnia et al., 2014); however, the exact underlying mechanism and especially the interplay of depressive symptoms and rumination is so far not well understood. One pioneer study by De Witte et al. (2020) applied intermittent (i.e., facilitating) TBS (iTBS) to the left DLPFC and observed a—although only marginally significant—buffering effect of iTBS on increases in state rumination in high trait ruminators. Following their idea, we recently conducted a study using continuous (i.e., inhibiting) TBS (cTBS) and iTBS in a sample of low and high trait ruminators (De Smet et al., n.d.). After investigating behavioral effects on state rumination, we also plan on conducting a TBS-fNIRS-study in order to assess the direct neural correlates of the stimulation. In the long run, these findings might lead to insights that could form the basis for better treatments of depression and other mental disorders associated with rumination.

3.6 Supplementary Material Study 1

S1 Items of the state rumination questionnaire

Items of the state rumination questionnaire including adapted items from the Ruminative Response Scale (Nolen-Hoeksema & Morrow, 1991), Amsterdam Resting-State Questionnaire (Diaz et al., 2013) and the Perseverative Thinking Questionnaire (Ehring et al., 2011). Subjects were instructed to rate if the items were in line with their mental state during the last resting-state measurement.

German translation	**English translation**
Ich dachte immer wieder an meine Probleme.	I repeatedly thought about my problems.
Ich verharrte im Denken an Dinge, die mich beunruhigen.	I kept thinking about things that bother me.
Meine Gedanken wiederholten sich, ohne dass ich zu einer Lösung kam.	I dwelled on my thoughts without coming to a solution.
Ich verlor mich in meinen negativen Gedanken.	I got lost in my negative thoughts.
Ich konnte meine Gedanken nur mühsam festhalten.	I had difficulties holding on to my thoughts.
Ich konnte mich nicht von meinen negativen Gedanken lösen.	I could not let go of my negative thoughts.
Ich war bei der Sache.	I was present.
Ich dachte darüber nach, warum ich mich in bestimmten Situationen falsch verhalten habe.	I thought about why I acted wrong in certain situations.
Ich fragte mich, warum ich Probleme habe, die andere nicht haben.	I thought why I have problems other people don´t have.
Ich fragte mich, womit ich meine momentane Lebenssituation verdient habe.	I thought about whereby I deserved my current life situation.
Ich dachte darüber nach, warum ich die Dinge nicht besser in den Griff bekomme.	I thought why I can´t handle things better.
Ich dachte an all meine Defizite und Misserfolge, Macken und Fehler.	I thought about all my shortcomings, failings, faults, mistakes.
Ich konnte flexibel zwischen meinen Gedanken hin und her schalten.	I could switch between my thoughts flexibly.
Ich dachte an vergangene Situationen, die ich bereue.	I thought about past situations that I regret.
Ich machte mir Selbstvorwürfe.	I blamed myself.
Ich verlor mich in Gedanken an Vergangenes.	I got lost in thoughts about the past.
Ich war von meinen Problemen und Sorgen stark vereinnahmt.	I was consumed by my problems and worries.
Meine negativen Gedanken ließen mich nicht los.	I couldn´t let go of my negative thoughts.

S2 Results of Benjamini-Hochberg-corrected pairwise comparisons main effect of time of the NIRS-analysis

NIRS dependent on group (DP vs. HC): Benjamini-Hochberg-corrected post-hoc pairwise comparisons of the main effect of time (CTL1 vs. TSST and CTL2 vs. TSST for significant channels) indicated significant increases from CTL1 to the TSST in the case of all three channels of the left IFG, left DLPFC, right DLPFC, all nine channels of the SAC as well as one of three channels of the right IFG (channel 18) respectively. Significant increases from CTL2 to TSST were observed in the case of all three channels of the left DLPFC, two out three channels of the left IFG (channel 6, 9), two out of three channels of the right DLPFC (channel 20, 24) and two out of nine channels of the SAC (channel 27, 31).

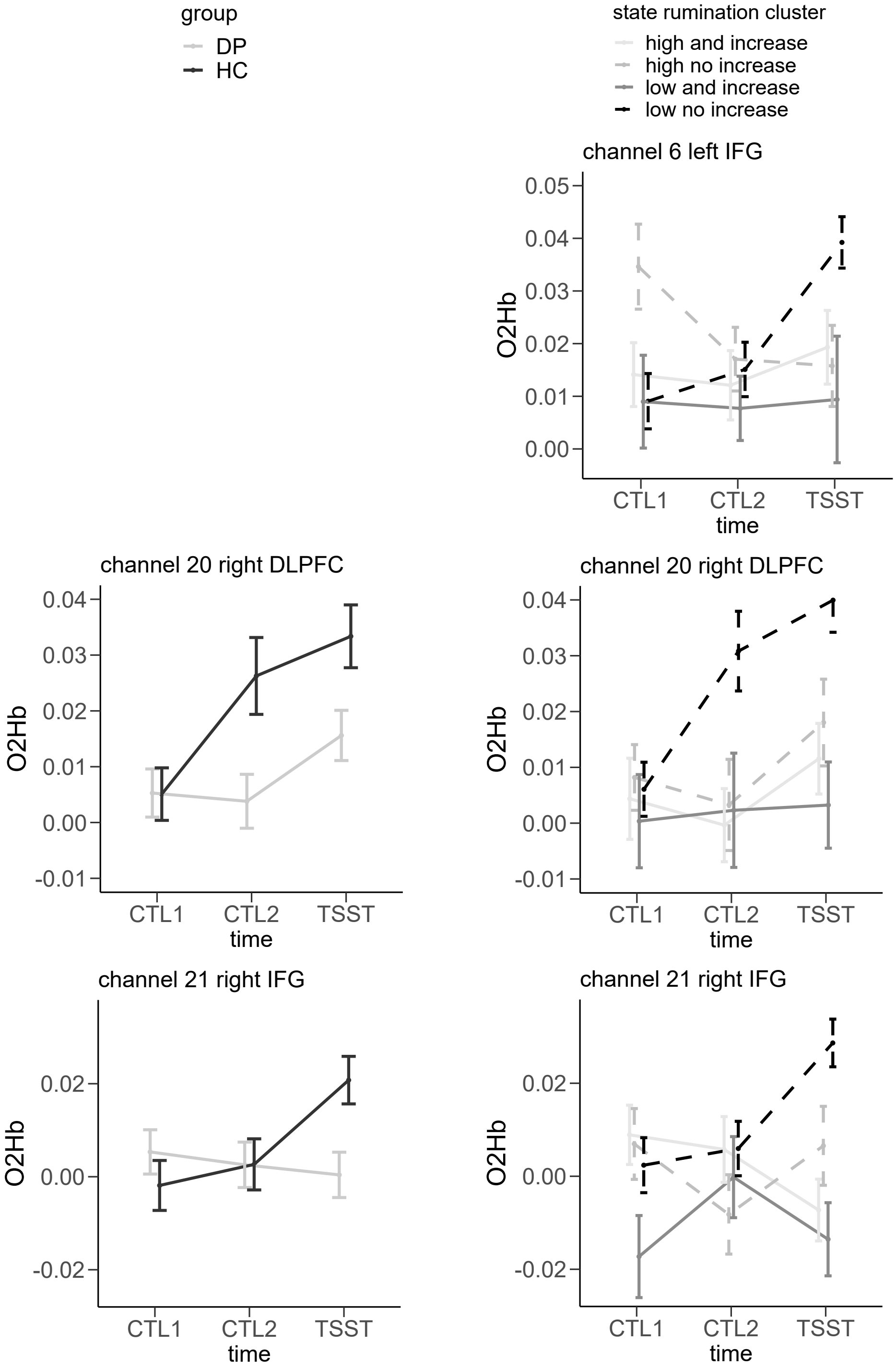
NIRS dependent on SR-cluster: We investigated the Benjamini-Hochberg-corrected pairwise comparisons of the main effect of time and observed significant increases from CTL1 to the TSST in the case of two channels of the left IFG (channel 7, 9), one channel of the right DLPFC (channel 20), and two channels covering the SAC (channel 25, 32). We further observed significant increases from CTL2 to the TSST in the case of a subset of the aforementioned channels, namely channel 9 and 20.

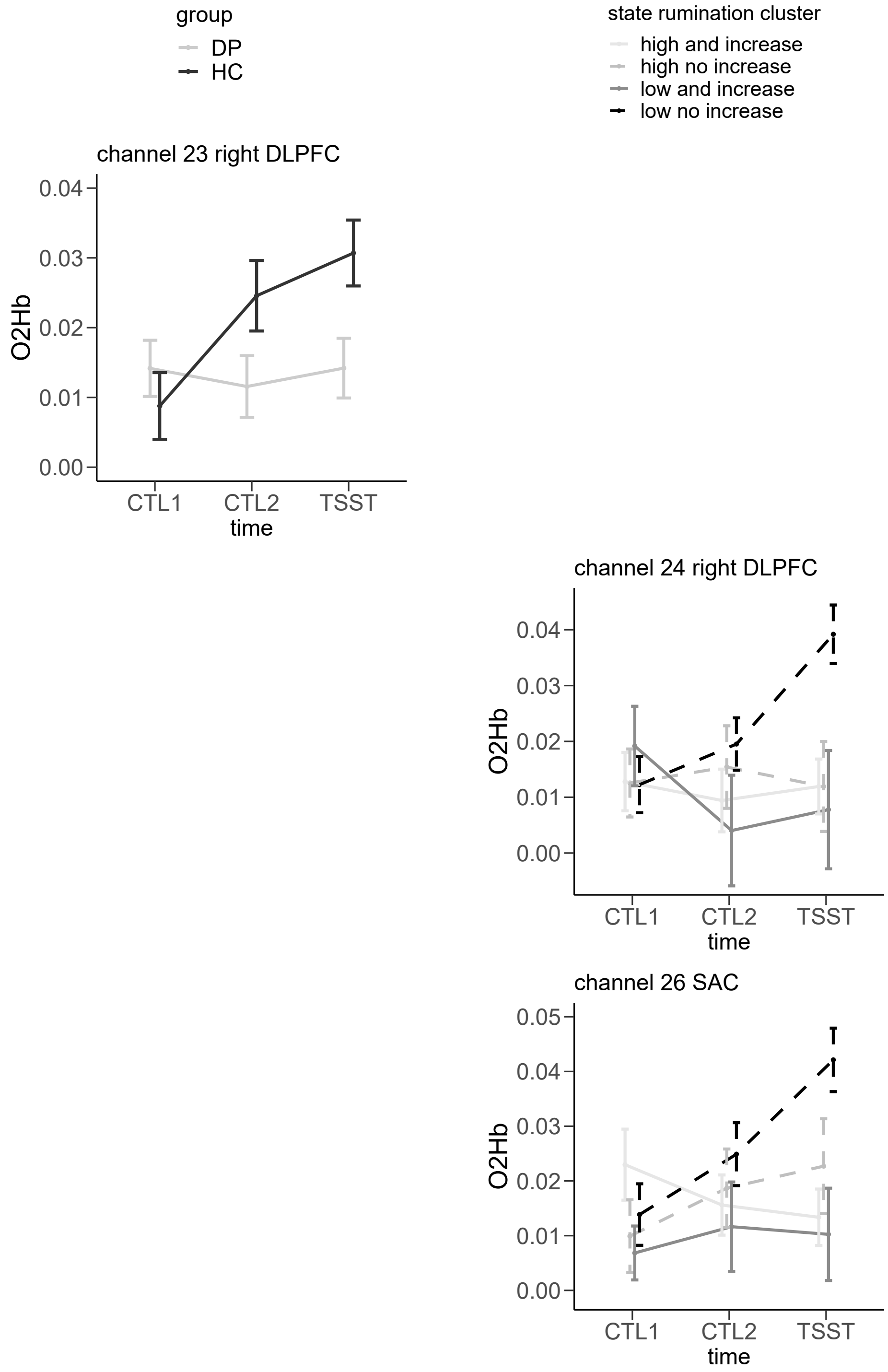
Performance-corrected NIRS dependent on group (DP vs. HC): Pairwise comparisons of the time effect in the case of these channels yielded significant differences between CTL1 and TSST in the case of all channels of the left and right DLPFC, all channels of the SAC as well as two out of three channels of the left IFG (channel 6, 9). We further observed significant differences between CTL2 and TSST in the case of all channels of the left DLPFC, two out of three channels of the right DLPFC (channel 20. 24), a subset of two channels of the SAC (channel 27, 31) as well as the same channels of the left IFG (channel 6, 9).

Performance-corrected NIRS dependent on SR-cluster: Pairwise comparisons of the time effect in these channels yielded significant increases between CTL1 and TSST in the case of all channels of the right DLPFC, one channel of the left DLPFC (channel 10), seven out of nine channels of the SAC (channel 25, 26, 27, 28, 30, 32, 35) and one channel of the left IFG (channel 6). We further observed significant increases between CTL2 and TSST in the case of three channels of the SAC (25, 28, 32).

S3 Illustration of the results of the fNIRS-MANOVAs

Please note that only channels with significant group*time interactions are depicted. Error bars indicate +/- 1 *SE*




group
DP
HC
state rumination cluster
high and increase
high no increase
low and increase
low no increase
channel 23 right DLPFC
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0.04
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0.00
CTL1
CTL2
TSST
time
channel 24 right DLPFC
O2Hb
0.04
0.03
0.02
0.01
0.00
CTL1
CTL2
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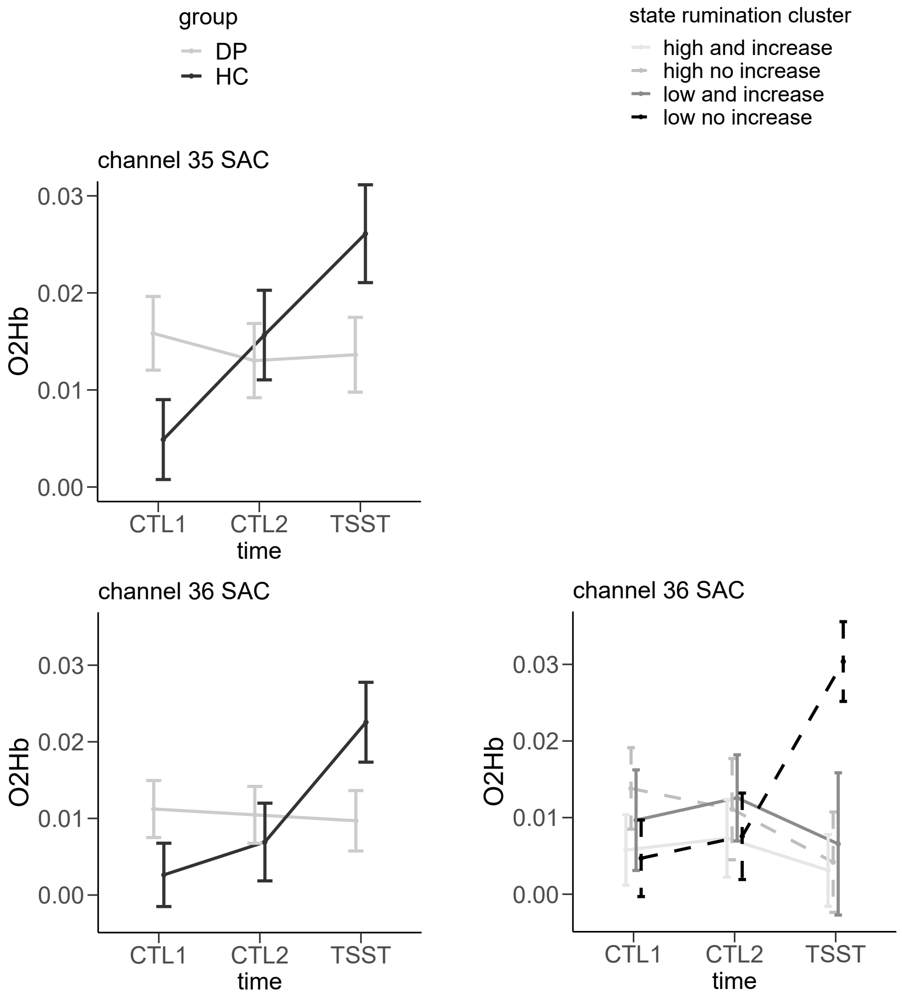
group
DP
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high and increase
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channel 35 SAC
O2Hb
0.03
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CTL1
CTL2
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S4 t-tests investigating differences in cortical oxygenation dependent on group

t-tests investigating the differences in NIRS cortical oxygenation dependent on group (DP = depressed patients vs. HC = healthy controls). Please note that this is for illustrative purposes only and therefore not corrected for multiple comparisons. Note: p-value of one-sided t-tests

	group	*N*	*M*	*SD*	*t*	df	*p*	95% CI	effect size *d*
CTL1 Ch6	HC	65	0.008	0.040	-1.853	138	0.033	[-0.026; 0.001]	-0.314
	DP	75	0.020	0.039					
	total sample	140	0.015	0.040					
CTL1 Ch7	HC	65	-0.006	0.034	0.540	138	0.295	[-0.008; 0.015]	0.092
	DP	75	-0.009	0.035					
	total sample	140	-0.008	0.034					
CTL1 Ch9	HC	65	-0.008	0.037	-1.441	124.59	0.076	[-0.020; 0.003]	-0.248
	DP	75	0.000	0.030					
	total sample	140	-0.003	0.033					
CTL1 Ch10	HC	65	0.006	0.033	-0.365	138	0.358	[-0.013; 0.009]	-0.062
	DP	75	0.008	0.033					
	total sample	140	0.007	0.033					
CTL1 Ch11	HC	65	0.002	0.038	-1.986	138	0.024	[-0.024; 0.000]	-0.337
	DP	75	0.013	0.032					
	total sample	140	0.008	0.036					
CTL1 Ch12	HC	65	0.009	0.036	-0.480	138	0.316	[-0.015; 0.009]	-0.081
	DP	75	0.012	0.036					
	total sample	140	0.010	0.036					
CTL1 Ch18	HC	65	-0.009	0.029	0.123	138	0.451	[-0.011; 0.012]	0.021
	DP	75	-0.010	0.038					
	total sample	140	-0.010	0.034					
CTL1 Ch19	HC	65	0.018	0.038	0.033	138	0.487	[-0.014; 0.014]	0.006
	DP	75	0.018	0.046					
	total sample	140	0.018	0.042					
CTL1 Ch20	HC	65	0.005	0.038	-0.030	138	0.488	[-0.013; 0.012]	-0.005
	DP	75	0.005	0.037					
	total sample	140	0.005	0.037					
CTL1 Ch21	HC	65	-0.002	0.043	-1.008	138	0.158	[-0.021; 0.007]	-0.171
	DP	75	0.005	0.041					
	total sample	140	0.002	0.042					
CTL1 Ch23	HC	65	0.009	0.039	-0.869	138	0.193	[-0.018; 0.007]	-0.147
	DP	75	0.014	0.035					
	total sample	140	0.012	0.037					
CTL1 Ch24	HC	65	0.010	0.033	-0.963	138	0.169	[-0.017; 0.006]	-0.163
	DP	75	0.016	0.036					
	total sample	140	0.013	0.035					
CTL1 Ch25	HC	65	0.012	0.037	-1.472	138	0.072	[-0.022; 0.003]	-0.249
	DP	75	0.021	0.037					
	total sample	140	0.017	0.037					
CTL1 Ch26	HC	65	0.010	0.036	-1.295	138	0.099	[-0.021; 0.004]	-0.219
	DP	75	0.018	0.040					
	total sample	140	0.014	0.038					
CTL1 Ch27	HC	65	0.011	0.033	-0.550	138	0.292	[-0.015; 0.008]	-0.093
	DP	75	0.014	0.036					
	total sample	140	0.013	0.034					

	group	*N*	*M*	*SD*	*t*	df	*p*	95% CI	effect size *d*
CTL1 Ch28	HC	65	0.014	0.038	-1.215	138	0.113	[-0.020; 0.005]	-0.206
	DP	75	0.022	0.036					
	total sample	140	0.018	0.037					
CTL1 Ch30	HC	65	0.011	0.043	-1.854	138	0.033	[-0.027; 0.001]	-0.314
	DP	75	0.024	0.040					
	total sample	140	0.018	0.041					
CTL1 Ch31	HC	65	0.004	0.035	-1.583	138	0.058	[-0.020; 0.002]	-0.268
	DP	75	0.013	0.031					
	total sample	140	0.009	0.033					
CTL1 Ch32	HC	65	0.008	0.034	-1.721	138	0.044	[-0.022; 0.002]	-0.292
	DP	75	0.018	0.037					
	total sample	140	0.014	0.036					
CTL1 Ch35	HC	65	0.005	0.033	-1.956	138	0.026	[-0.022; 0.000]	-0.332
	DP	75	0.016	0.033					
	total sample	140	0.011	0.033					
CTL1 Ch36	HC	65	0.003	0.033	-1.550	138	0.062	[-0.020; 0.002]	-0.263
	DP	75	0.011	0.032					
	total sample	140	0.007	0.033					
CTL2 Ch6	HC	65	0.014	0.041	0.004	138	0.498	[-0.012; 0.012]	0.001
	DP	75	0.014	0.033					
	total sample	140	0.014	0.036					
CTL2 Ch7	HC	65	0.011	0.045	1.045	138	0.149	[-0.007; 0.022]	0.177
	DP	75	0.003	0.040					
	total sample	140	0.007	0.042					
CTL2 Ch9	HC	65	-0.007	0.045	-0.542	138	0.294	[-0.018; 0.010]	-0.092
	DP	75	-0.003	0.039					
	total sample	140	-0.005	0.041					
CTL2 Ch10	HC	65	0.019	0.054	1.524	138	0.065	[-0.004; 0.028]	0.258
	DP	75	0.007	0.042					
	total sample	140	0.012	0.048					
CTL2 Ch11	HC	65	0.004	0.037	-0.862	138	0.195	[-0.019; 0.007]	-0.146
	DP	75	0.010	0.040					
	total sample	140	0.007	0.039					
CTL2 Ch12	HC	65	0.009	0.047	-0.151	138	0.440	[-0.015; 0.013]	-0.026
	DP	75	0.010	0.039					
	total sample	140	0.010	0.043					
CTL2 Ch18	HC	65	0.006	0.045	1.835	138	0.034	[-0.001; 0.030]	0.311
	DP	75	-0.008	0.047					
	total sample	140	-0.002	0.046					
CTL2 Ch19	HC	65	0.023	0.041	1.715	138	0.044	[-0.002; 0.025]	0.291
	DP	75	0.011	0.039					
	total sample	140	0.017	0.040					
CTL2 Ch20	HC	65	0.026	0.056	2.723	138	0.004	[0.006; 0.039]	0.462
	DP	75	0.004	0.042					
	total sample	140	0.014	0.050					
CTL2 Ch21	HC	65	0.003	0.044	0.013	138	0.495	[-0.014; 0.015]	0.002
	DP	75	0.003	0.042					
	total sample	140	0.003	0.043					
CTL2 Ch23	HC	65	0.025	0.041	1.945	138	0.027	[0.000; 0.026]	0.330
	DP	75	0.012	0.038					
	total sample	140	0.018	0.040					

	group	*N*	*M*	*SD*	*t*	df	*p*	95% CI	effect size *d*
CTL2 Ch24	HC	65	0.014	0.037	-0.125	138	0.450	[-0.013; 0.012]	-0.021
	DP	75	0.014	0.037					
	total sample	140	0.014	0.037					
CTL2 Ch25	HC	65	0.030	0.044	-0.358	138	0.361	[-0.017; 0.012]	-0.061
	DP	75	0.033	0.040					
	total sample	140	0.032	0.042					
CTL2 Ch26	HC	65	0.021	0.040	0.307	138	0.380	[-0.011; 0.015]	0.052
	DP	75	0.019	0.039					
	total sample	140	0.020	0.039					
CTL2 Ch27	HC	65	0.014	0.037	-1.165	138	0.123	[-0.020; 0.005]	-0.197
	DP	75	0.022	0.038					
	total sample	140	0.018	0.037					
CTL2 Ch28	HC	65	0.028	0.040	-0.841	138	0.201	[-0.019; 0.008]	-0.142
	DP	75	0.034	0.041					
	total sample	140	0.032	0.041					
CTL2 Ch30	HC	65	0.030	0.046	0.815	138	0.208	[-0.009; 0.021]	0.138
	DP	75	0.024	0.042					
	total sample	140	0.027	0.044					
CTL2 Ch31	HC	65	0.012	0.047	1.135	110.74	0.129	[-0.006; 0.021]	0.197
	DP	75	0.004	0.032					
	total sample	140	0.008	0.039					
CTL2 Ch32	HC	65	0.024	0.048	-0.779	138	0.219	[-0.020; 0.009]	-0.132
	DP	75	0.030	0.038					
	total sample	140	0.027	0.043					
CTL2 Ch35	HC	65	0.016	0.037	0.443	138	0.329	[-0.009; 0.014]	0.075
	DP	75	0.013	0.033					
	total sample	140	0.014	0.035					
CTL2 Ch36	HC	65	0.007	0.041	-0.564	120.92	0.287	[-0.016; 0.009]	-0.097
	DP	75	0.010	0.032					
	total sample	140	0.009	0.036					
TSST Ch6	HC	65	0.029	0.039	0.789	138	0.216	[-0.009; 0.020]	0.134
	DP	75	0.023	0.046					
	total sample	140	0.026	0.043					
TSST Ch7	HC	65	0.013	0.046	-0.358	138	0.361	[-0.023; 0.016]	-0.061
	DP	75	0.017	0.066					
	total sample	140	0.015	0.058					
TSST Ch9	HC	65	0.013	0.035	0.763	138	0.223	[-0.008; 0.018]	0.129
	DP	75	0.008	0.042					
	total sample	140	0.011	0.039					
TSST Ch10	HC	65	0.030	0.039	2.595	138	0.005	[0.004; 0.029]	0.440
	DP	75	0.014	0.036					
	total sample	140	0.021	0.038					
TSST Ch11	HC	65	0.023	0.036	1.744	138	0.042	[-0.002; 0.024]	0.296
	DP	75	0.012	0.039					
	total sample	140	0.017	0.038					
TSST Ch12	HC	65	0.031	0.040	2.605	138	0.005	[0.004; 0.030]	0.442
	DP	75	0.013	0.038					
	total sample	140	0.021	0.040					
TSST Ch18	HC	65	0.009	0.045	1.394	138	0.083	[-0.004; 0.024]	0.236
	DP	75	-0.001	0.040					
	total sample	140	0.003	0.042					

	group	*N*	*M*	*SD*	*t*	df	*p*	95% CI	effect size *d*
TSST Ch19	HC	65	0.029	0.036	1.699	138	0.046	[-0.002; 0.024]	0.288
	DP	75	0.018	0.041					
	total sample	140	0.023	0.039					
TSST Ch20	HC	65	0.033	0.045	2.492	138	0.007	[0.004; 0.032]	0.422
	DP	75	0.016	0.039					
	total sample	140	0.024	0.043					
TSST Ch21	HC	65	0.021	0.041	2.878	138	0.002	[0.006; 0.034]	0.488
	DP	75	0.000	0.042					
	total sample	140	0.010	0.043					
TSST Ch23	HC	65	0.031	0.038	2.593	138	0.005	[0.004; 0.029]	0.439
	DP	75	0.014	0.037					
	total sample	140	0.022	0.038					
TSST Ch24	HC	65	0.030	0.042	1.879	138	0.031	[-0.001; 0.027]	0.318
	DP	75	0.017	0.040					
	total sample	140	0.023	0.041					
TSST Ch25	HC	65	0.032	0.037	0.482	138	0.315	[-0.009; 0.015]	0.082
	DP	75	0.029	0.036					
	total sample	140	0.030	0.037					
TSST Ch26	HC	65	0.034	0.043	1.712	138	0.045	[-0.002; 0.026]	0.290
	DP	75	0.021	0.041					
	total sample	140	0.027	0.042					
TSST Ch27	HC	65	0.030	0.039	1.270	138	0.103	[-0.005; 0.021]	0.215
	DP	75	0.022	0.037					
	total sample	140	0.025	0.038					
TSST Ch28	HC	65	0.031	0.040	0.551	138	0.291	[-0.010; 0.017]	0.093
	DP	75	0.028	0.041					
	total sample	140	0.029	0.041					
TSST Ch30	HC	65	0.034	0.043	0.840	138	0.201	[-0.008; 0.020]	0.0142
	DP	75	0.028	0.040					
	total sample	140	0.030	0.042					
TSST Ch31	HC	65	0.025	0.045	1.793	138	0.038	[-0.001; 0.027]	0.304
	DP	75	0.012	0.039					
	total sample	140	0.018	0.042					
TSST Ch32	HC	65	0.034	0.053	0.895	138	0.186	[-0.009; 0.023]	0.152
	DP	75	0.027	0.040					
	total sample	140	0.030	0.046					
TSST Ch35	HC	65	0.026	0.041	1.994	138	0.024	[0.000; 0.025]	0.338
	DP	75	0.014	0.033					
	total sample	140	0.019	0.037					
TSST Ch36	HC	65	0.023	0.042	1.997	138	0.024	[0.000; 0.026]	0.338
	DP	75	0.010	0.034					
	total sample	140	0.016	0.038					

Chapter 4

STUDY 2: Trait-dependent effects of theta burst stimulation after psychosocial stress: a sham-controlled study in healthy individuals

The contents of this chapter are published:

De Smet, S.*, **Int-Veen, I.***, Vanhollebeke, G., Pulopulos, M. M., Barth, B., Pasche, S., ... & Rosenbaum, D. (2024). Trait-dependent effects of theta burst stimulation after psychosocial stress: a sham-controlled study in healthy individuals. *Clinical Neurophysiology*, *162*, 235-247.

* Shared first authorship

4.1 Abstract

Objective: Previous studies suggest that Theta Burst Stimulation (TBS), a form of repetitive Transcranial Magnetic Stimulation (rTMS), applied to the left Dorsolateral Prefrontal Cortex (DLPFC) might be a promising approach to modulate stress-reactive rumination and the associated psychophysiological stress response. Crucially, individuals showing higher levels of trait rumination might benefit more from prefrontal stimulation. **Methods:** In this sham-controlled study, 127 healthy individuals, with varying ruminative tendencies, received a single-session of intermittent TBS (iTBS), continuous TBS (cTBS) or sham TBS (sTBS) over the left DLPFC before being confronted with a Trier Social Stress Test. **Results:** Results showed significant TBS effects on salivary cortisol as a function of trait rumination. cTBS, as compared to sTBS and iTBS, resulted in an attenuated stress-induced cortisol response in high compared to low trait ruminators. Although independent of trait rumination levels, cTBS showed positive effects on stress-related changes in mood and, both cTBS and iTBS (versus sham) presented an enhanced heart rate recovery following the stressor. We found no evidence for (trait rumination-dependent) TBS effects on stress-reactive rumination, negative affect, subjective stress or heart rate variability. **Conclusions:** cTBS shows beneficial effects on certain measures of stress, especially in high trait ruminators. **Significance:** These findings highlight the importance of accounting for individual differences when examining TBS effects.

4.2 Introduction

Rumination is a perseverative cognitive process that is characterized by repetitive negative thinking about self-relevant topics without any goal-orientation (Watkins & Roberts, 2020). It is often triggered by stressful events (Brosschot et al., 2006, 2005) and has been shown to predict depressive symptoms (Connolly & Alloy, 2017). Importantly, rumination may prolong and worsen the psychophysiological stress response (Michl et al., 2013; Verkuil, Brosschot, Gebhardt, & Thayer, 2010; Vrshek-Schallhorn, Velkoff, & Zinbarg, 2019). These responses entail heightened emotional and cardiovascular reactivity, reduced heart rate variability (HRV) and disrupted stress-induced cortisol stress responses (Hilt et al., 2015; LeMoult & Joormann, 2014; Ottaviani et al., 2016; Shull et al., 2016; Watkins & Roberts, 2020; Zoccola & Dickerson, 2012). Therefore, the persistent psychophysiological activation resulting from stress-reactive rumination may form a pathogenic path linking chronic stress to long term negative mental and physical health outcomes (Ottaviani et al., 2016).

Rumination has been functionally linked to various brain regions including the dorsolateral prefrontal cortex (DLPFC; Zhou et al., 2020). The DLPFC plays a crucial role in inhibiting physiological and psychosocial stress reactivity, potentially resulting in reduced rumination (Arnsten, 2009, 2015). Poor stress regulation (resulting in higher cortisol levels, heart rates, and lower HRV) is linked to increased limbic activity and decreased DLPFC functioning (Arnsten 2009; although see Cooney et al. 2010; Henze et al. 2023). As a result, this may cause an inability to exert inhibitory control over negative perseverative processes, such as rumination, leading to sustained negative affect (De Raedt & Koster, 2010). Neuroimaging studies further support this, showing decreased activity of the left DLPFC in high, compared to low, ruminators (Ferdek, van Rijn, & Wyczesany, 2016). Hence, investigating the modulation of brain regions involved in stress-reactive rumination and the psychophysiological stress response, such as the DLPFC, in healthy individuals can provide crucial information for conducting clinical trials with depressive patients. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive approach to modulate brain activity by altering the excitability of targeted brain areas (Maeda et al., 2000). Besides its (adjunctive) use in depression treatment (Baeken et al., 2019; Sathappan, Luber, & Lisanby, 2019), rTMS is a useful tool for directly manipulating prefrontal cortical excitability to study its effects on rumination and the psychophysiological stress response (e.g. Baeken et al., 2014; De Smet et al., 2021; Pulopulos et al., 2020; Remue et al., 2016). Theta Burst Stimulation (TBS), a patterned variant of rTMS, has gained popularity due to similar outcomes with reduced stimulation duration and intensity compared to conventional rTMS protocols (Blumberger et al., 2018; Huang et al., 2005). TBS involves three gamma frequency pulses repeated every 200 milliseconds, and its effects can induce long-term potentiation (LTP) or long-term depression (LTD) based on the delivery method and stimulation duration (Huang & Rothwell, 2007; McCalley et al., 2021; Suppa et al., 2016). The left DLPFC is often targeted in TBS protocols (Fitzgerald, 2021) and is considered the most suitable region for modulating psychophysiological stress reactivity (Moses et al., 2023; Vignaud et al., 2023). Therefore, applying TBS to the left DLPFC might be a promising approach to modulate stress-reactive rumination and psychophysiological activation. Despite its scientific and clinical relevance, few studies have examined the effects of TBS on psychological and physiological changes following acute stress in healthy individuals, yielding mixed results. For instance, Era and colleagues (2021) reported that cTBS of the left DLPFC before a rumination induction led to a sustained physiological stress response, indicated by increased heart rate and cortisol levels, and reduced vagally-mediated HRV. However, no TBS-induced changes were found on behavioral and self-report measures. De Witte and colleagues (2020) reported no direct effects of two consecutive iTBS sessions (versus sham) after psychosocial stress on cortisol recovery. Nevertheless, higher levels of depressive brooding, a subform of rumination, were associated with a reduction in cortisol secretion during stress recovery. Although the data suggested a buffering effect of active iTBS on increases in state rumination in high trait ruminators (De Witte et al., 2020), the relatively small sample size, mainly consisting of low trait ruminators, might have limited the power to detect (rumination-dependent) TBS effects on stress-reactive rumination (De Witte et al., 2020). Moreover, a systematic review indicated that applying stimulation before exposure to a stressful event, rather than after, is more effective in decreasing psychophysiological stress responses (Vignaud et al., 2023). These findings underscore the complexity of TBS effects on psychophysiological stress measures, and indicate that individual differences in trait rumination might have a crucial role in TBS outcomes on stress measures. Notably, previous research has shown that individuals with higher ruminative tendencies have aberrant mechanisms of prefrontal control (e.g., De Raedt & Koster, 2010; Vanderhasselt et al., 2017), implying that prefrontal stimulation might be particularly beneficial for this population. Consequently, studies investigating the effects of TBS on stress-reactive rumination and the psychophysiological stress response should account for individual differences in rumination. This informs us about the working mechanisms of TBS on stress for individuals with varying ruminative tendencies and how to reduce variability in stimulation outcomes. Building upon these prior findings (De Witte et al., 2020; Era et al., 2021), this well-powered randomized sham-controlled study aimed to evaluate the effects of a single session of TBS (iTBS versus cTBS versus sham TBS) on stress-reactive state rumination and the psychophysiological stress response in healthy individuals. To ensure a comprehensive representation of the population, we recruited a stratified sample based on the Ruminative Response Scale (RRS), which included individuals with varying levels of rumination tendencies. Focusing on the left DLPFC as the target region for stimulation due to its crucial role in stress regulation and rumination, we hypothesized that iTBS of the left DLPFC would would lead to reduced stress-reactive rumination and psychophysiological stress response (lower negative affect and higher positive affect, lower subjective stress, lower mean heart rate and cortisol levels, and higher heart rate variability) compared to cTBS and sham. Conversely, we hypothesized that cTBS would result in heightened stress-reactive rumination and stress response (higher negative affect and lower positive affect, higher subjective stress, higher mean heart rate and cortisol levels, and lower heart rate variability) compared to iTBS and sham. Additionally, we expected the effects of iTBS and cTBS to be more pronounced in individuals with higher levels of trait rumination. By addressing the role of individual trait rumination in TBS outcomes, this study seeks to contribute valuable insights to the existing literature, enhancing the understanding of prefrontal stimulation's potential for stress management and therapeutic applications.

4.3 Methods

This study was part of a multicenter research trial in healthy participants conducted at the University Hospital of Ghent (UZGent) and the University Hospital of Tuebingen (UKT). All procedures were approved by the local ethics committees (UZGent: B67Q2021000115, UKT: 673/2019BO1) and are in line with the Declaration of Helsinki in its latest version.

4.3.1 Study sample

At both study sites, right-handed healthy volunteers aged 18 to 35 years were recruited via posts spread across the university hospital and social media platforms. All volunteers were asked to fill in an online screening to assess their eligibility to participate in the study. To ensure a proportional number of low, medium and high ruminators, a stratified random sampling method was used based on participants' scores on the Ruminative Response Scale (RRS, i.e., low trait ruminators: mean RRS score < 1.82, medium trait ruminators: mean RRS score $\geq$ 1.82 and < 2.55, high trait ruminators: mean RRS score $\geq$ 2.55, cut-offs based on the combined data of 715 participants from prior studies from our group; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al. 2018; Rosenbaum et al. 2021; Rosenbaum, Thomas, et al. 2018; Treynor and Gonzalez 2003). For an overview of all inclusion criteria, we refer to the supplementary materials. All eligible volunteers received an invitation to participate in the study. Based on a priori power calculations (see data plan), 138 participants were recruited for the study. However, for a variety of reasons (see supplementary materials), eleven participants (3 in Ghent, 8 in Tuebingen) were excluded from the final sample, resulting in a total study sample of 127 participants (62.2% female, mean age = 22.21, *SD* = 2.99). Participants were randomly assigned to one of three stimulation conditions: intermittent TBS (iTBS, n = 39), continuous TBS (cTBS, n = 43) or sham TBS (sTBS, n = 45), resulting in a between-subjects study design. We refer to the supplementary materials for an overview of the sample characteristics and description of the baseline questionnaires that were assessed.

4.3.2 Procedure

After an eligibility screening, participants were invited for the experimental session which took place in a well-controlled laboratory environment at the university hospital of Ghent or Tuebingen. To control for the circadian rhythm of cortisol, the sessions started at 12:30, 13:30, 16:00 or 17:00 (counterbalanced, there were no significant differences in starting times between conditions, $\chi^2(6, N = 127) = 2.82, p = 0.831, \phi = 0.15$). Participants were asked to sleep sufficiently and restrain from alcohol and intense physical activity 24 hours prior to the experimental session (Labuschagne, Grace, Rendell, Terrett, & Heinrichs, 2019). Moreover, they were asked to abstain from any caffeinated beverages, food or nicotine 2 hours prior to their appointment (Kudielka, Hellhammer, & Wüst, 2009; Labuschagne et al., 2019; Lovallo, Al'Absi, Blick, Whitsett, & Wilson, 1996). At the start of the session, participants gave written informed consent, and their resting motor threshold was determined (see neurostimulation section). Afterwards, participants were seated and all lab equipment was set-up (i.e., for the physiological measurements, see also figure 4.1). With exception of the period during stimulation and the stress task, participants remained seated on a chair positioning their knees at a 90-degree angle. During a 10-minute habituation period, participants were instructed to relax and remain quiet. Participants were allowed to read garden magazines during this period and, in the meanwhile, the stimulation target (i.e., the left DLPFC) was marked using a water-soluble pencil. Following the habituation, the magazines were taken away and a 10-minute resting-state (i.e., baseline) measurement was assessed during which participants were instructed to let their mind wander but keep their eyes open. Afterwards, a baseline assessment of mood, state rumination and subjective stress followed and a first salivary sample (approximately 25-30 minutes before the Trier Social Stress Test i.e., the TSST, T1) was taken. Next, depending on the stimulation condition, participants received iTBS, cTBS or sham stimulation in another room. After another mood, state rumination and subjective stress assessment, participants were guided to another room for the stress induction. Please note that in Ghent there were three rooms (one for the habituation and recovery period, one for the stimulation and one for the TSST), whereas in Tuebingen, due to practical limitations, there were only two rooms as the TSST was performed in the same room where the habituation and recovery period took place. After reading the instructions of the TSST, participants filled out the primary and secondary appraisal PASA scale to assess stress appraisal (for a description and results of the PASA, we refer to the supplementary materials). Then, participants had 3 minutes to prepare the speech and take notes (i.e., in combination with reading the instructions and filling in the PASA, this resulted in a 5-minute stress anticipation or preparation phase). Following the speech part of the TSST, participants rated their subjective stress before the jury members instructed them to perform the arithmetic task. After another stress rating, mood assessment and salivary sample (directly after the TSST, T2) another 10 min resting-state measurement analogue to the first one was performed. Following this, participants completed another stress rating, state rumination and State Emotion Regulation Inventory (SERI) (for a description and results of the SERI, we refer to the supplementary materials). During the recovery period, salivary cortisol samples were taken every 15 min (T3-6) while subjective stress was assessed. One hour post TSST, a last assessment of mood, state rumination and subjective stress as well as potential side effects of the stimulation followed. Importantly, all participants were naive to the stimulation condition and purpose of the study. As a manipulation check, we asked participants about their beliefs of the stimulation condition they were in at the end of the experimental session. Thereafter, participants were debriefed and received monetary compensation or course credit for participation.

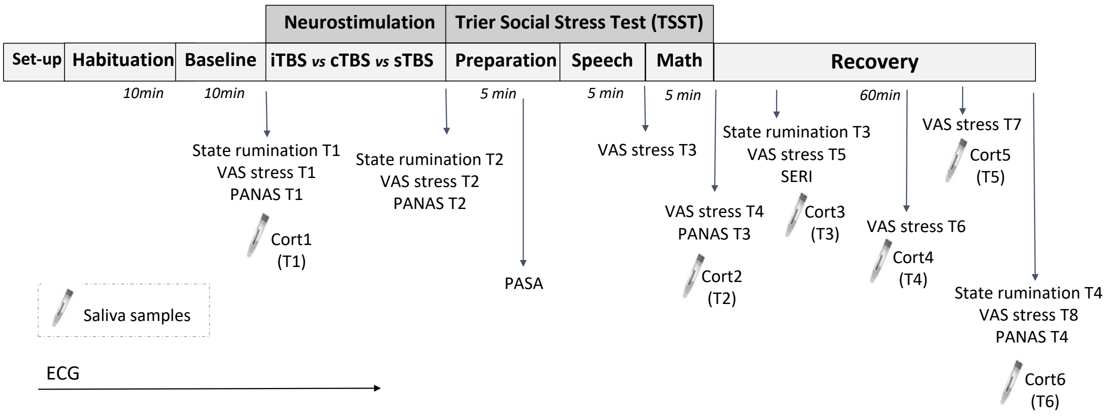

Figure 4.1
Overview of the experimental procedure. Cardiac activity was measured, using an electrocardiogram, throughout the session. Cortisol samples were taken 25 to 30 minutes before the end of the TSST (T1), directly post TSST (T2), 15 min post TSST (T3), 30 min post TSST (T4), 45 min post TSST (T5) and 60 min post TSST (T6). Abbrev.: Cort, cortisol; cTBS, continuous theta burst stimulation; ECG, electrocardiogram; iTBS, intermittent theta burst stimulation; PANAS, Positive and Negative Affect Schedule; PASA, Primary Appraisal Secondary Appraisal Scale; SERI, State Emotion Regulation Inventory; sTBS, sham theta burst stimulation; TSST, Trier Social Stress Test; VAS, Visual Analogue Scales.

4.3.3 Neurostimulation

All participants received a single session of TBS applied to the left DLPFC. To obtain optimal coil positioning, the left DLPFC was localized using the Beam F3 localization method (Beam, Borckardt, Reeves, & George, 2009; Mir-Moghtadaei et al., 2015). To obtain the individual protocol intensity, each participant's resting motor threshold was operationalized as the minimum TMS intensity necessary to yield a motor response in the right abductor pollicis brevis in 5 out of 10 successive attempts (Rothwell et al., 1999). The stimulation intensity was set at 80% of the resting motor threshold (Huang et al., 2005). There were no significant differences in stimulation intensity between the cTBS (M = 39.40, SD = 7.45), iTBS(M = 39.58, SD = 8.93) and sTBS (M = 38.73, SD = 7.28) condition, $F(2,122) = 0.14$, $p = 0.872$, $\eta_p^2 < 0.001$. However, the overall mean stimulation intensity was significantly higher in Ghent (M = 43.95, SD = 7.13) as compared to Tuebingen (M = 34.56, SD = 5.25), $F(2,119) = 69.53$, $p < 0.001$, $\eta_p^2 = 0.37$. For differences between the study sites (e.g., in coils and devices), we refer to the supplementary materials. For both sites, the stimulation parameters included a total of 1200 pulses at a frequency of 50 Hz and burst frequency 5 Hz, during cTBS there was an 80 s train of uninterrupted TBS including 400 bursts of 3 pulses, and the iTBS protocol consisted of 40 cycles of 2 s theta burst trains (10 bursts of 3 pulses each) followed by 8 seconds of rest (i.e., a total of 390 s, McCalley et al. 2021). Please note that the duration and end of both stimulations, cTBS and iTBS, were aligned as a waiting period was inserted prior to the cTBS. Sham TBS was applied with a coil that mimics the active stimulation. Stimulation was applied while participants were seated in a TMS chair in Fowler's position. All participants were naive to the stimulation condition, were blindfolded and asked to wear ear protection during the stimulation. To ensure double blinding, the stimulation was applied by a study nurse not further involved in the experiment. Possible side effects of the stimulation protocol were systematically evaluated following the recommendations of Rossi and colleagues (2009; 2011). Specifically, participants were asked to rate on a five-point likert-like scale if they had any of the following experiences during or after the stimulation: transient feelings of hyperactivity, impulsivity or irritability, headache, local pain, neck pain, tooth pain, tingling sensations, changes in hearing, cognitive or neuropsychological changes and irritation at the stimulation site (responses ranging from "1 = not at all" to "5 = very much").

4.3.4 The stress task

The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was used to induce psychosocial stress in the participants (Allen et al., 2014, 2017). Specifically, participants were instructed to imagine having applied for a job and part of the job interview is to prepare for a speech about their personal strengths and qualifications. After a short preparation period, participants had to give the speech in front of two jury members (i.e., two experimenters) wearing white physician coats who were unresponsive to any signs of social interaction of the participants. Each interview lasted 5 minutes and if the participants' speech ended before this predetermined time limit, a standardized response was given by one of the jury members to encourage them to continue. Following the speech, participants were confronted with a surprise arithmetic task during which they had to count aloud backwards in steps of 13 from 2081 for 5 minutes. To maximize social evaluative threat, participants were instructed to keep eye contact with one of the jury members and calculate as fast and accurately as possible. If a mistake was made, participants were instructed to stop and restart from the starting number. Independent of their performance, participants were asked to improve their speed and accuracy during the task. Additionally, participants were informed that a video camera was recording their performance throughout the TSST, and that this data was going to be used for further analysis by behavioral experts. To maximize feelings of uncontrollability, participants were not informed of the total duration of the interview and arithmetic task.

4.3.5 Psychophysiological assessments

Psychological measures

Mood Participants were repeatedly asked to rate their current mood using the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) for adjectives of positive and negative affect, respectively. Responses were made on 5-point Likert scales ranging from "1 = very slightly" to "5 = extremely". Total scores were calculated by summing all items per subscale, with higher scores representing higher levels of negative and positive affect, respectively. The PANAS has acceptable reliability and internal consistency (Krohne, Egloff, Kohlmann, and Tausch 2016; negative affect subscale Cronbach's α = 0.86, positive affect subscale Cronbach's α = 0.84).

Subjective stress Throughout the session, participants were repeatedly asked to rate their current subjective stress level using Visual Analogue Scales (VAS). Each scale consisted of a 100-millimeter straight line ranging from 0% (i.e., "not stressed at all") to 100% (i.e., "very stressed"), where steps of 10% were marked at steps of 10 millimeters. Higher scores indicate higher levels of subjective stress.

State rumination To assess state rumination during the session, a questionnaire validated by Rosenbaum and colleagues (2018; 2021; 2018) was used, showing excellent internal consistency (Cronbach's α current study = 0.93). Participants rated the extent to which they agreed on 18 statements referring to thoughts that might have occurred during the past rest period. Responses were given on a 5-point Likert scale ranging from "1 = not at all" to "5 = very often". The questionnaire comprises items of the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011), the Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991), the Amsterdam Resting-State Questionnaire (ARSQ; Diaz et al., 2013) and a questionnaire by de Jong-Meyer and colleagues 2009. We refer to table S1 of the supplementary materials for an overview of all items. Total scores were calculated by summing all items (items 7 and 13 reversed), with higher scores reflecting higher levels of state rumination.

Physiological measures

Heart rate and heart rate variability Heart rate was measured with a one-channel electrocardiography (ECG). In Tuebingen, three Ag/AgCl ring electrodes with a diameter of 8 mm were attached to the participants' skin above the right collar bone, below the left costal arch and below the neck (i.e., for reference). The signal was recorded with a BrainAmp MR plus amplifier and Brain Vision recorder software (Brain Products, Munich, Germany) at a 1000 Hz sampling rate. In Ghent, two Ag/AgCl electrodes (42x24 mm) were attached under the left and right clavicle, and one ground electrode under the ribs (i.e., for reference). The signal was recorded with a Biopac MP160 system using a ECG100D smart amplifier, at a sampling rate of 1000 Hz, and the Biopac Acqknowledge software 5.5 (Biopac Systems Inc., USA). All ECG data were manually checked for artifacts and analyzed with Kubios HRV Premium version 3.5.0 (Lipponen & Tarvainen, 2019; Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014). Medium correction was applied to ensure the detection of erroneous (e.g., ectopic) beats, using cubic spline interpolation to replace misidentified or missing values (Tarvainen et al., 2014). HRV was assessed by calculating the Root Mean Squared of Successive Differences (RMSSD, in milliseconds) which, compared to other HRV indices, is less sensitive to movement artifacts and respiratory influences (Laborde, Mosley, & Thayer, 2017; Penttilä et al., 2001). As recommended (Malik et al., 1996), RMSSD was calculated for time epochs of 5 minutes resulting in a total of 16 epochs. Consistent with RMSSD, the mean heart rate (beats/minute) was also calculated in 5-minute epochs. Given our interest in cardiac changes over the different phases of the experiment (e.g., stress reactivity and recovery), the RMSSD and mean HR epochs during the baseline and recovery were averaged resulting in one measure per phase per participant (see also De Smet et al., 2021, 2023). For instance, the baseline phase resulted in 2 epochs of 5 minutes that were averaged resulting in one mean value per baseline. For the recovery, each three (or two for the last phase) consecutive 5-minute epochs were averaged into one mean value resulting in 4 recovery phase values, i.e., one for 0–15 min post TSST, 15–30 min post TSST, 30–45 min post TSST and 45–55 min post TSST.

Salivary cortisol Salivary cortisol (nmol/L) was assessed six times during the experiment using salivettes (Sarstedt AG and Co., REF 51.1534.500). Samples were collected according to the manufacturer's instructions by placing the swab in the mouth of the participants for 2 minutes. After being stored at -20 °C the samples were thawed and centrifuged for 4 minutes at 1000g before enzyme immunoassays (IBL International, Cortisol ELISA, REF RE52611) were performed in duplicate according to the manufacturer's instructions. Intra and inter-assay variation coefficients were below 10%.

4.3.6 Data plan

Past studies have shown moderate to high effect sizes in clinical samples for the increase in state rumination after the TSST (Rosenbaum et al. 2021; and a small effect size in healthy participants following TBS, see De Witte et al. 2020). Sensitivity analysis using G*Power 3.1 software (Faul, Erdfelder, Buchner, & Lang, 2009) resulted in a required sample size of $N = 120$ to detect small differences between stimulation conditions between $d = 0.2$ (assuming $r = 0.8$) to $d = 0.3$ (assuming $r = 0.5$; within-between interaction of repeated measurements: $\alpha = 0.05$, power of 0.80, groups = 3, measurements = 3, non-sphericity criterion $\epsilon = 0.6$). Considering possible losses and a dropout rate of 15%, 138 participants were recruited. The final study sample consisted of 127 participants. Due to technical issues during the session, there was less data for the analyses of the cardiac measures ($n = 120$). All statistical analyses were performed with R version 4.1.2 in the R studio environment (RStudio Team, 2021). To fit models within the linear mixed effects framework, the 'lmerTest' (Kuznetsova, Brockhoff, & Christensen, 2017) and 'lme4' (Bates, Mächler, Bolker, & Walker, 2015) packages were used. Model contrasts were set using sum (i.e., effect) coding schemes. For each repeated measure, model selection was conducted by comparing the Akaike Information Criterion (AIC) for different distributions (i.e., normal, gamma, inverse-gaussian). For all (generalized) linear models, intercepts were allowed to vary randomly across participants and trait rumination (i.e., measured using the RRS) was mean centered and entered as a continuous predictor in all models. Given the results did not change when entering the study site (i.e., Ghent or Tuebingen) as a covariate in the model, and to ensure the use of parsimonious models, this term was not included in the final models. Hence, all reported models were built as follows: values of the dependent variable $\sim$ time*condition*RRS + (1 | participant). The p-values of the mixed effects models were reported using type III Wald chi-squared statistics. Post-hoc tests for interaction effects consisted of pairwise comparisons of the estimated marginal means or pairwise comparisons of the estimated marginal means of linear trends using the “emmeans” and “emtrends” functions of the ‘emmeans’ package (Lenth & others, 2022), respectively. The Tukey method was used to correct for multiple comparisons. Effect sizes were described using the partial eta squared (η_p^2) and phi (ϕ) for F and $\chi 2$ test statistics, and Cohen’s d was used for t and z tests, respectively. The significance level was set at 0.05 for all statistical tests. First, one-way ANOVAs (type III sum of squares), $\chi 2$ and F exact tests were used to examine differences between the three stimulation conditions in sample characteristics (e.g., baseline questionnaire), self-reported side effects to the stimulation protocol and task performance during the TSST (i.e., number of errors). To evaluate the effects of the different stimulation conditions on the psychological and physiological measures, and whether these effects were dependent on individual trait rumination levels, (generalized) linear mixed effects models were fitted for the repeated measures. Specifically, for mood (i.e., positive and negative affect), 4 (time: baseline, post stimulation, directly post TSST, 60 min post TSST) by 3 (condition: cTBS, iTBS, sTBS) generalized linear models were conducted. Whereas the positive affect data was best represented by a gamma distribution with an identity link function, the negative affect data showed a better fit with a gamma distribution with log link function. For subjective stress, an 8 (time: baseline, post stimulation, post speech, post math, 15 min post TSST, 30 min post TSST, 45 min post TSST, 60 min post TSST) by 3 (condition: cTBS, iTBS, sTBS) linear mixed effect model with gaussian error distribution was fit. For state rumination, a 4 (time: baseline, post stimulation, 15 min post TSST, 60 min post TSST) by 3 (condition: cTBS, iTBS, sTBS) generalized model was conducted with a gamma distribution and log link function. The cardiac data (i.e., mean heart rate and heart rate variability) was best represented by an 8 (time: baseline, preparation, speech, math, 0–15 min post TSST, 15–30 min post TSST, 30–45 min post TSST, 45–55 min post TSST) by 3 (condition: cTBS, iTBS, sTBS) generalized linear model with a log link function and gamma distribution. For cortisol, a 6 (time: baseline, directly post TSST, 15 min post TSST, 30 min post TSST, 45 min post TSST, 60 min post TSST) by 3 (condition: cTBS, iTBS, sTBS) generalized linear model with gamma distribution and log link function was fit. Additionally, a cortisol reactivity index was used to examine the change in cortisol from baseline to the maximum cortisol secretion after the TSST. As such, a 2 (time: baseline, max cortisol peak) by 3 (condition: cTBS, iTBS, sTBS) generalized model was fit with gamma distribution and log link function. Lastly, for the different indices of the PASA (i.e., primary appraisal, secondary appraisal and the stress index), one-way ANOVAs were performed (type III sum of squares) and for the subscales of the SERI (i.e., reappraisal, distraction, brooding and acceptance), a MANOVA was performed using Pillai's trace test statistic (including condition and trait rumination as independent variables). Non-significant interactions between time, condition and trait rumination and, non-significant interactions between time and condition, were further examined using Bayesian statistics. The Bayes Factor (BF01) was estimated to provide evidence for the lack of interaction effects and compared the likelihood of the data under the null hypothesis compared to the alternative hypothesis. The structure of the null model excluded the interaction term of interest but followed the structure of the corresponding alternative model for all other terms. The BF01 was computed based on the Bayesian Information Criterion (BIC) of the null and alternative model (for the formula see Wagenmakers 2007), with larger values indicating more evidence in favor of the null hypothesis and reported according to Jeffreys (1961). For an overview of the results of the Bayesian analyses, we refer to table S5 of the supplementary materials.

4.4 Results

4.4.1 Descriptive statistics

Importantly, no differences between the cTBS, iTBS and sham TBS groups were observed in trait rumination (p = 0.859) or other study sample characteristics (all p´s > 0.081). An overview of the sample characteristics, and accompanying comparative statistics, can be found in table S2 of the supplementary materials. An exact binomial test showed that the overall success probability of participants guessing the correct stimulation condition was significantly different from chance level (64% correct, p = 0.002). In addition, the success probability was different between study sites, with the exact binomial test indicating successful blinding in Ghent (56% correct, p = 0.374) but not in Tübingen (72% correct, p < 0.001). Additional tests showed that, in Tübingen, participants in the cTBS condition guessed, above chance level, that the stimulation was active (versus sham), p < 0.001. Crucially, participants were unable to identify sham from real stimulation as correct guesses in the sham condition were not significantly different from chance in both study sites (57% correct $sTBS_{Ghent}$, p = 0.664 and 54% correct $sTBS_{Tuebingen}$, p = 0.839).

4.4.2 Adverse effects

There was a marginally significant difference between conditions in self-reported irritation at the site of stimulation (i.e., left DLPFC), F(2,122) = 3.19, p = 0.045, η_p^2 = 0.05. Specifically, participants in the cTBS condition (M = 1.90, SD = 1.62) reported significantly more irritation at the stimulation site as compared to participants in the sham condition (M = 1.22, SD = 1.29), t(78.48) = 2.16, p = 0.048, d = 0.47. There were no other significant differences in self-reported adverse effects between the three types of stimulation (cTBS vs iTBS vs sTBS), all F's < 2.66 and p's > 0.074. For an overview of the mean responses to each of the self-report items assessing side effects to the different stimulation protocols, and comparative statistics between conditions, we refer to table S3 of the supplementary materials.

4.4.3 Task performance

For the task performance during the TSST, results revealed no significant interaction between condition and trait rumination, F(2, 120) = 0.43, p = 0.651, η_p^2 < 0.01, nor a significant main effect of condition, F(2, 120) = 0.51, p = 0.599, η_p^2‘s < 0.01, or trait rumination, F(1, 120) = 0.09, p = 0.770, η_p^2 < 0.01.

4.4.4 Psychological measures

Mood

The results for the generalized linear model with positive affect revealed no significant interaction between time, condition and trait rumination, $\chi^2(6, N = 127) = 8.04$, $p = 0.235$, $\phi = 0.25$. There was a significant interaction between time and condition (see figure 4.2A, $\chi^2(6, N = 127) = 13.92$, $p = 0.031$, $\phi = 0.33$. Post-hoc analyses showed significantly lower levels of positive affect directly after the TSST as compared to baseline in the iTBS, $z = 2.82$, $p = 0.025$, $d = 1.46$, and sTBS condition, $z = 2.87$, $p = 0.020$, $d = 1.30$, but not in the cTBS condition, $z = 0.87$, $p = 0.820$, $d = 0.44$. In all conditions, the level of positive affect 60 min post TSST was significantly lower as compared to baseline (all z's > 3.08, p's < 0.011, d's > 1.38). In addition, results showed a significant interaction between time and trait rumination, $\chi^2(3, N = 127) = 7.89$, $p = 0.048$, $\phi = 0.25$, with a negative association between trait rumination and positive affect directly after the TSST compared to baseline ($z = 2.74$, $p = 0.031$, $d = 0.78$) and, 60 min post TSST compared to baseline ($z = 6.37$, $p < 0.001$, $d = 1.71$) and compared to directly post TSST ($z = 3.56$, $p = 0.002$, $d = 0.93$). Besides a (lower order) significant main effect of time, $\chi^2(3, N = 127) = 43.02$, $p < 0.001$, $\phi = 0.58$, no other significant effects were found, all χ^2's < 3.05, p's > 0.218, ϕ's < 0.15.

In line with the results of positive affect, the analysis revealed no significant interaction between time, condition and trait rumination, $\chi^2(6, N = 127) = 7.30$, $p = 0.294$, $\phi = 0.24$, for the generalized linear model with negative affect. There was a significant interaction between time and condition (see figure 4.2B), $\chi^2(6, N = 127) = 17.68$, $p = 0.007$, $\phi = 0.37$. Post-hoc analyses showed that although there was no significant difference in the level of negative affect between baseline and post stimulation for the cTBS and sTBS condition (cTBS: $z = 0.91$, $p = 0.801$, $d = 0.17$; sTBS: $z = 0.75$, $p = 0.876$, $d = 0.14$), participants in the iTBS condition reported significantly higher negative affect following stimulation compared to baseline, $z = 2.81$, $p = 0.026$, $d = 0.55$. In all conditions, there was a significant increase in negative affect directly after the TSST (versus baseline, all z's > 12.02, p's < 0.001, d's > 2.23), followed by a significant decrease 60 min post TSST (all z's > 11.64, p's < 0.001, d's > 2.19). Overall, the level of negative affect 60 min post TSST was not significantly different as compared to baseline ($z = 1.58$, $p = 0.391$, $d = 0.30$). Results also showed a significant main effect of trait rumination, χ^2(1,

N = 127) = 11.32, p = 0.001, ϕ = 0.30, with an overall positive association between trait rumination and negative affect, and a significant (lower order) effect of time, χ^2(3, N = 127) = 677.84, p < 0.001, ϕ = 2.31. No other significant effects were found, all χ^2's < 4.79, p's > 0.188, ϕ's < 0.19.

Subjective stress

For the linear mixed effects model with self-reported subjective stress, results showed no significant interaction between time, condition and trait rumination, χ^2(14, N = 127) = 13.41, p = 0.495, ϕ = 0.32, nor a significant interaction between time and condition (see figure 4.2C), χ^2(14, N = 127) = 23.01, p = 0.060, ϕ = 0.43. Results showed a significant main effect of trait rumination, χ^2(1, N = 127) = 12.64, p < 0.001, ϕ = 0.32, with an overall positive association between trait rumination and subjective stress, and a significant main effect of time, χ^2(7, N = 127) = 1746.62, p < 0.001, ϕ = 3.71. Overall, there was a significant increase in subjective stress after the speech, t(846) = 21.70, p < 0.001, d = 2.73, and math part of the TSST, t(846) = 21.84, p < 0.001, d = 2.75, as compared to baseline, followed by a decrease in subjective stress up to 60 min post TSST, t(846) = 27.99, p < 0.001, d = 3.52. No other significant effects were found, all χ^2's < 12.53, p's > 0.085, ϕ's < 0.31.

State rumination

The results of the analysis for the generalized linear model with state rumination as outcome measure revealed no significant interaction between time, condition and trait rumination, χ^2(6, N = 127) = 8.14, p = 0.228, ϕ = 0.25, nor a significant interaction between time and condition (see figure 4.2D), χ^2(6, N = 127) = 3.90, p = 0.690, ϕ = 0.18. There was a significant main effect of trait rumination, with an overall positive association between participants' trait rumination and state rumination during the session, χ^2(1, N = 127) = 34.30, p < 0.001, ϕ = 0.52. The results also showed a significant main effect of time, χ^2(3, N = 127) = 188.17, p < 0.001, ϕ = 1.22. Post-hoc tests revealed an overall significant decrease in ruminative thinking following TBS (z = 6.15, p < 0.001, d = 0.66) and a significant increase 15 min post TSST (z = 6.98, p < 0.001, d = 0.75), as compared to baseline. Furthermore, 60 min post TSST, ruminative thinking was significantly decreased compared to 15 min post TSST (z = 9.92, p < 0.001, d = 1.07) and compared to baseline (z = 2.94, p = 0.017, d = 0.32). There were no other significant effects, all χ^2's < 3.97, p's > 0.265, ϕ's < 0.18.

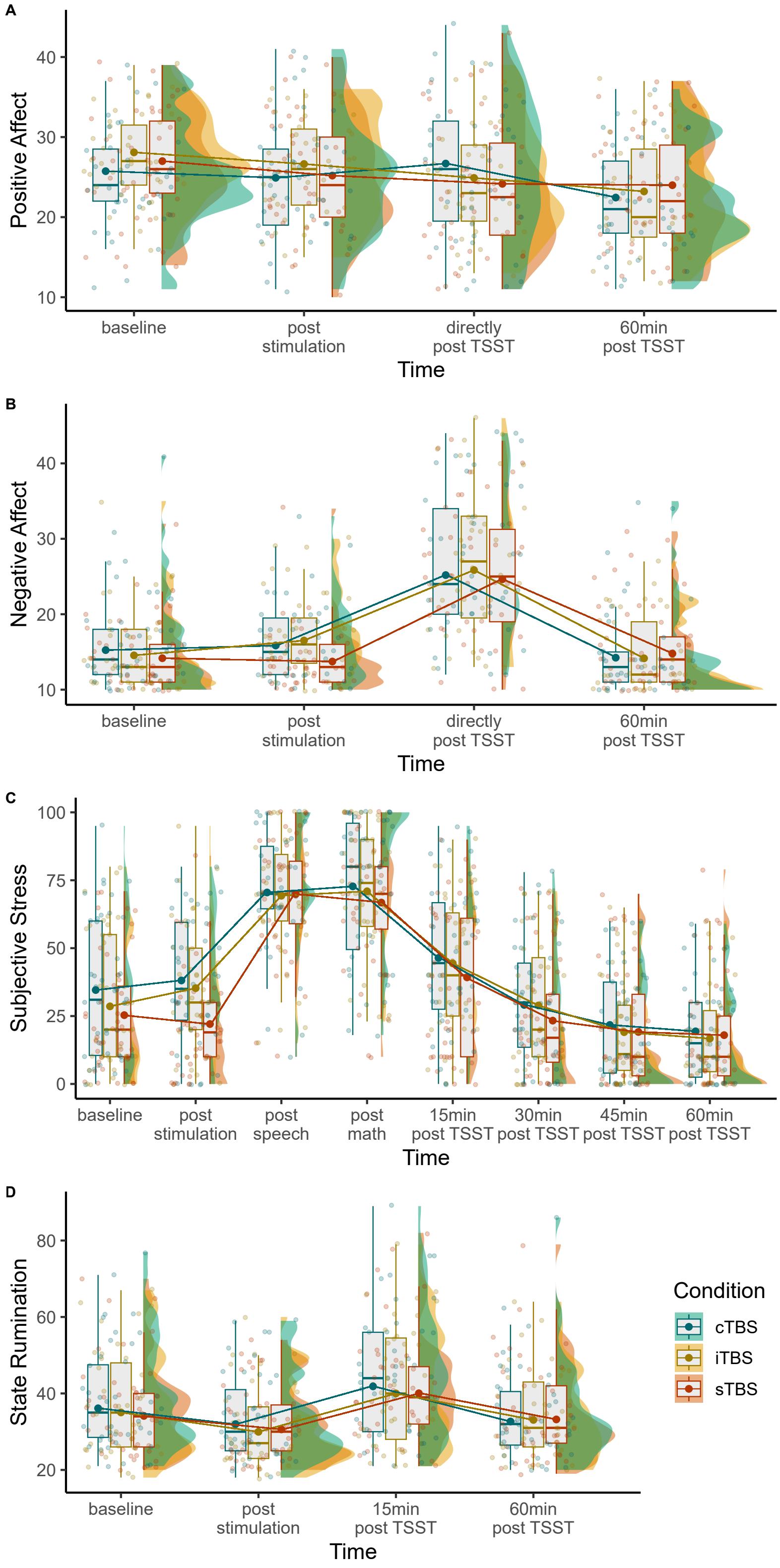

Figure 4.2

Raincloud plots for (A) positive affect, (B) negative affect, (C) subjective stress and (D) state rumination. Individual jittered raw data is represented by dots. Data distributions are depicted by split-half violin plots (on the right side of each series of boxplots). Each boxplot displays the stimulation condition median alongside the interquartile ranges (horizontal lines). Bold dots in the boxplots represent the estimated marginal mean of the fitted models. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; min, minutes; sTBS, sham theta burst stimulation; TSST, Trier Social Stress Test.

4.4.5 Physiological measures

Heart rate

The results of the analysis revealed no significant interaction between time, condition and trait rumination for the generalized linear model with mean heart rate, $\chi^2(14, N = 120) = 13.80$, $p = 0.465$, $\phi = 0.34$. Results did show a significant interaction effect between time and condition (see figure 4.3A), $\chi^2(14, N = 120) = 24.48$, $p = 0.040$, $\phi = 0.45$. Post-hoc tests revealed that in the cTBS condition mean heart rate was significantly lower 15–30 min post TSST ($z = 3.70$, $p = 0.005$, $d = 0.67$), 30–45 min post TSST ($z = 3.47$, $p = 0.012$, $d = 0.62$) and 45–55 min post TSST ($z = 4.53$, $p < 0.001$, $d = 0.82$), compared to baseline. For iTBS, mean heart rate was significantly lower than baseline only 45–55 min post TSST, $z = 3.10$, $p = 0.041$, $d = 0.61$, but not 15–30 min and 30–45 min post TSST, z's < 2.86, p's > 0.081, d's < 0.56. For sTBS, there was no significant difference between the mean heart rate at baseline and the different recovery phases (i.e., 15–30 min, 30–45 min or 45–55 min post TSST), all z's < 2.17, p's > 0.368, d's < 0.41. In all conditions, there was a significant increase in mean heart rate during the math and speech part of the TSST compared to baseline and the preparation, all z's > 17.01, p's < 0.001, d's > 2.74, and a significant decrease 0–15 min post TSST compared to during the math task, all z's > 18.80, p's < 0.001, d's > 3.72. Besides a (lower order) significant main effect time, $\chi^2(7, N = 120) = 3528.27$, $p < 0.001$ $\phi = 5.42$, no other significant effects were found, all χ^2's < 0.54, p's > 0.762, ϕ's < 0.07.

Heart rate variability

The results of the analysis for the generalized linear model with HRV revealed no significant interaction between time, condition and trait rumination, $\chi^2(14, N = 120) = 11.56$, $p = 0.641$, $\phi = 0.31$, nor a significant interaction between time and condition (see figure 4.3B), $\chi^2(14, N = 120) = 16.11$, $p = 0.307$, $\phi = 0.37$. There was a significant interaction between time and trait rumination, $\chi^2(7, N = 120) = 22.73$, $p = 0.002$, $\phi = 0.44$. Specifically, a positive association between trait rumination and HRV was found during the acute stress phase (i.e., higher HRV values during math and speech compared to baseline for higher levels of trait rumination) and a negative association during the recovery phases (i.e., lower HRV during e.g., 0–15 min post TSST compared to baseline for higher trait ruminators), all z's > 3.90, p's < 0.002, d's > 0.43. In addition, results revealed a significant main effect of time, $\chi^2(7, N = 120) = 1250.27$, $p < 0.001$, $\phi =$

3.23. Post-hoc tests showed significant decreases in HRV during the TSST compared to baseline (baseline-speech: $z = 14.29$, $p < 0.001$, $d = 1.67$; baseline-math: $z = 17.82$, $p < 0.001$, $d = 2.09$), and a significant increase 0–15 min post TSST compared to the math task, $z = 22.27$, $p < 0.001$, $d = 2.63$. The level of HRV did not differ between the different phases of the recovery (i.e., 0–15 min vs 15–30 min vs 30–45 min vs 45–55 min post TSST; all z's < 0.705, p's > 0.997, d's < 0.08), but all remained significantly higher than baseline, all z's > 4.59, p's < 0.001, d's > 0.53. No other significant effects were found, all χ^2's < 1.01, p's > 0.603, ϕ's < 0.9.

Salivary cortisol

The results of the analysis revealed a significant interaction between time, condition and trait rumination for the generalized linear model with cortisol (see figure 4.4), $\chi^2(10, N = 127) = 19.53$, $p = 0.034$, $\phi = 0.39$. Specifically, there was a significant interaction between time and trait rumination for the cTBS, $\chi^2(5, N = 127) = 25.57$, $p < 0.001$, $\phi = 0.77$, but not the iTBS nor sTBS condition, χ^2's < 8.65, p's > 0.124, ϕ's < 0.47. Post-hoc tests showed a negative association between trait rumination and the cortisol secretion 15 min post TSST as compared to baseline, $z = 6.05$, $p < 0.001$, $d = 1.18$, and as compared to directly post TSST, $z = 6.61$, $p < 0.001$, $d = 1.28$, indicating a lower stress-induced cortisol response for individuals with higher levels of trait rumination following cTBS (see also figure 4.4). Although not present in comparison to baseline or directly post TSST, for the cortisol secretion 30 min to 60 min post TSST (i.e., T2 to T4) compared to 15 min post TSST (i.e., T1), there was a positive association with trait rumination, all z's > 4.88, p's < 0.001, d's > 0.95, with smaller decreases during the recovery period for higher levels of trait rumination. In addition, there was a lower-order significant interaction effect between time and condition (see figure 4.3C), $\chi^2(10, N = 127) = 20.02$, $p = 0.029$, $\phi = 0.40$, and between time and trait rumination, $\chi^2(5, N = 127) = 14.71$, $p = 0.012$, $\phi = 0.34$, and a lower-order main effect of time, $\chi^2(5, N = 127) = 217.41$, $p < 0.001$, $\phi = 1.31$. Regarding the analysis of the cortisol reactivity index, the interaction between time, condition and trait rumination was not significant, $\chi^2(2, N = 127) = 4.94$, $p = 0.085$, $\phi = 0.20$. During the TSST, 73.23% of the participants showed an increase in cortisol and 52.76% showed an increase higher than 1.25 nmol/L (Miller & Plessow, 2013). For an overview of the raw (mean) cortisol levels for each of the stimulation conditions during the session, we refer to table S4 of the supplementary materials.

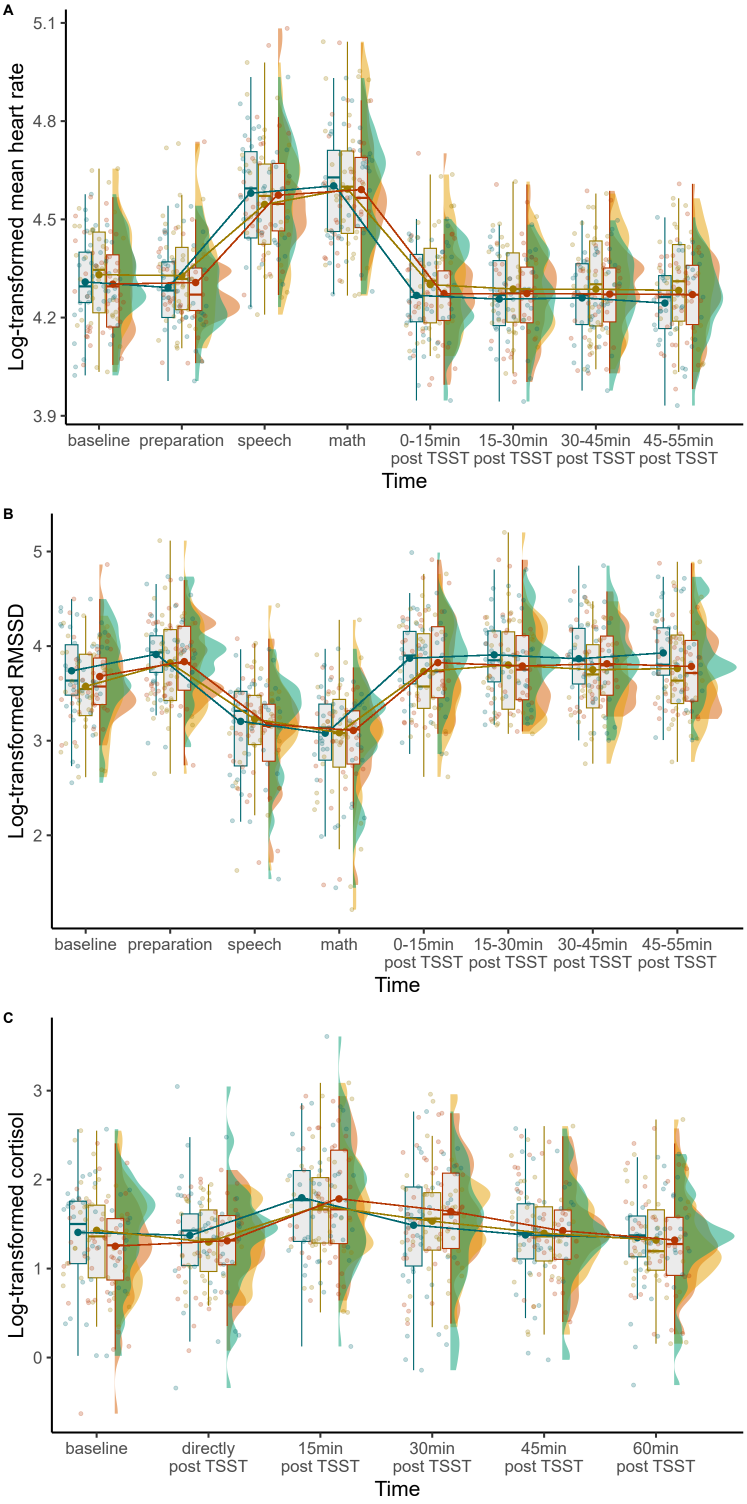

Figure 4.3
Raincloud plots for (A) mean heart rate, (B) heart rate variability and (C) salivary cortisol. Individual jittered raw data is represented by dots. Data distributions are depicted by split-half violin plots (on the right side of each series of boxplots). Each boxplot displays the stimulation condition median alongside the interquartile ranges (horizontal lines). Bold dots in the boxplots represent the estimated marginal mean of the fitted models. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; min, minutes; RMSSD, root mean square of successive differences; sTBS, sham theta burst stimulation; TSST, Trier Social Stress Test.

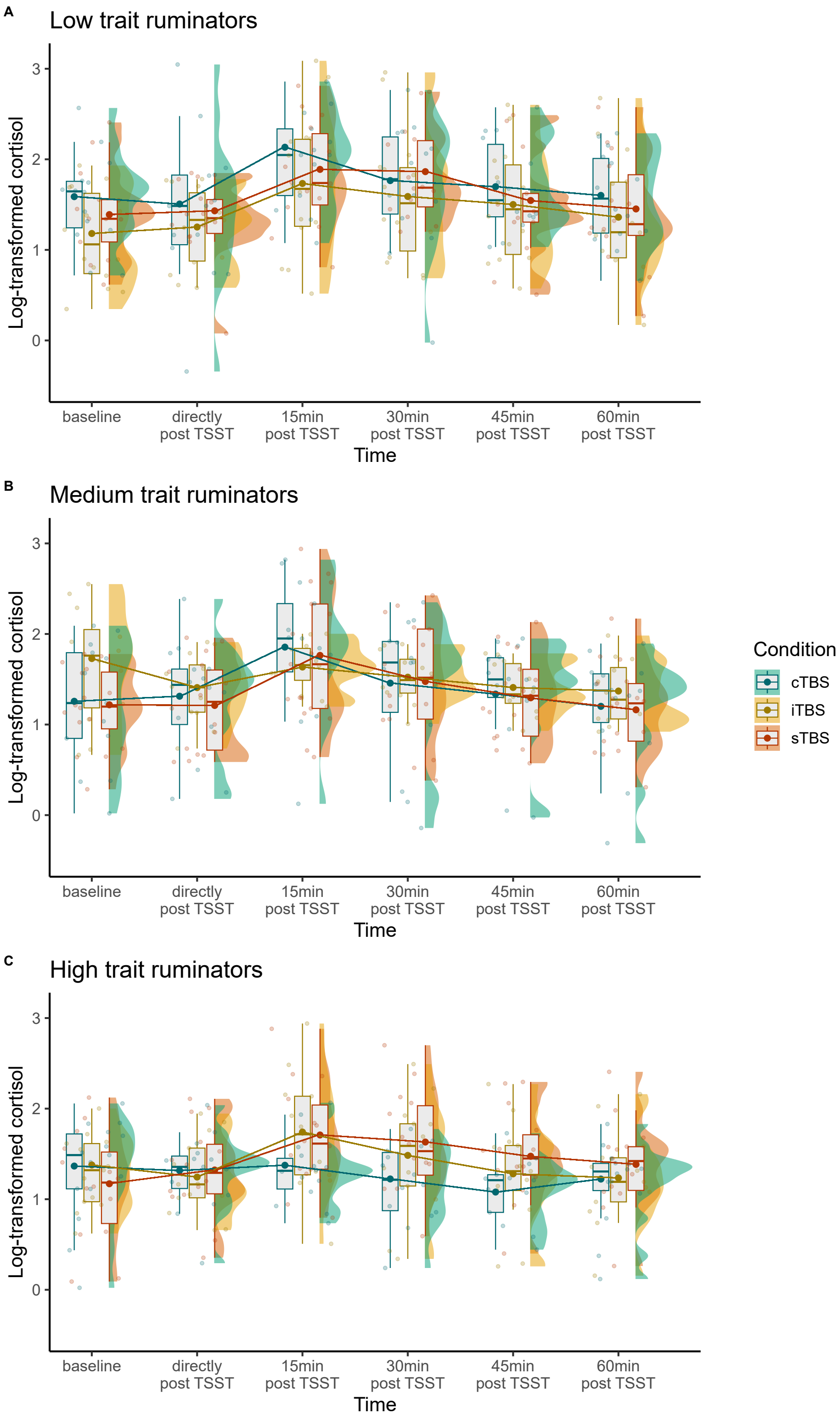

Figure 4.4
Raincloud plots for cortisol secretion during the session for (A) low trait ruminators, (B) medium trait ruminators and (C) high trait ruminators. Individual jittered raw data is represented by dots. Data distributions are depicted by split-half violin plots (on the right side of each series of boxplots). Each boxplot displays the stimulation condition median alongside the interquartile ranges (horizontal lines). Bold dots in the boxplots represent the estimated marginal mean of the fitted models. Centered trait rumination scores were entered as a continuous predictor in the model. However, for visualization purposes, trait rumination is here presented as a factor. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; min, minutes; sTBS, sham theta burst stimulation; TSST, Trier Social Stress Test.

4.5 Discussion

The aim of this randomized, sham-controlled study was to investigate the effects of TBS of the left DLPFC on stress-reactive rumination and the psychophysiological stress response, considering individual trait rumination levels. The stress task elicited robust psychological and physiological changes, including increased subjective stress, negative affect, salivary cortisol, and heart rate, along with decreased heart rate variability, consistent with prior work (Allen et al., 2014, 2017). We also successfully replicated a significant increase in state rumination following the TSST (De Witte et al., 2020; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al., 2018). Regarding trait rumination, the study found that cTBS (compared to sTBS and iTBS) led to a reduced stress-induced cortisol response in high trait ruminators compared to low trait ruminators. However, there were no trait rumination-dependent effects of TBS on stress-reactive rumination and other psychophysiological measures of stress, contrary to the initial hypotheses. Regardless of individual trait rumination levels, cTBS showed a positive effect on buffering positive affect, indicating that positive emotions were less diminished following the stressor. Both cTBS and iTBS (versus sham) resulted in an enhanced heart rate recovery. However, no significant TBS effects were observed for other measures of interest. Non-significant findings were further corroborated by Bayesian analyses. The study results for physiological measures showed mixed findings. High (versus low) ruminators showed increased HRV during the acute stress phase but worse HRV recovery, although Bayesian analyses did not support any (rumination-dependent) TBS effects. This differs from meta-analytical evidence showing increased HRV following rTMS (Makovac, Thayer, & Ottaviani, 2017). Notably, only one of the included rTMS studies used a stress induction (Remue et al., 2016), and the intensity of our stressor might have masked group differences. In line with prior work (Makovac et al., 2017), both cTBS and iTBS (compared to sham stimulation) had positive effects on cardiac recovery, but within different temporal windows. Participants in the cTBS condition showed enhanced cardiac recovery within 15 minutes after the stressor, while for iTBS, the improvement was present 45 minutes post TSST. These findings suggest that different TBS modalities have different temporal effects on stress-induced changes in heart rate and may have specific impacts on the sympathetic nervous system. Crucially, we found trait rumination dependent TBS effects on stress-induced cortisol secretion. Contrary to our expectations, cTBS resulted in an attenuated stress-induced cortisol response in high trait ruminators compared to low trait ruminators, while no such effects were observed for the iTBS or sTBS condition. These cortisol findings align with the enhanced heart rate recovery and buffering effects on positive affect observed with cTBS. Our initial hypothesis that cTBS would mainly lead to inhibitory neural effects and heightened psychophysiological stress responses is most probably an oversimplification. The excitatory or inhibitory nature of TBS depends on various factors, including stimulation parameters (McCalley et al., 2021), baseline neural activity, cognitive factors such as attention (Nicolo, Ptak, & Guggisberg, 2015), and affective states preceding or during stimulation (Schutter, Smits, & Klaus, 2023). Our findings emphasize the complexity of TBS effects and highlight the potential of exploring trait-dependent effects of TBS treatments in future research. For the psychological measures, we replicated the well-known reactivity pattern of high trait ruminators, showing higher levels of negative affect, subjective stress and state rumination, along with greater decreases in positive affect during the acute stress and recovery phases (Aldao, Jazaieri, Goldin, & Gross, 2014; Nolen-Hoeksema et al., 2008; Watkins & Roberts, 2020). However, contrary to our expectations, Bayesian analyses showed extreme evidence against any trait rumination dependent modulation of TBS on mood (i.e., positive and negative affect) and subjective stress. It is essential to note that the effects of trait rumination were medium to strong, but overall time-dependent changes due to the stress induction showed even larger effects. The intensity of the stressor might have masked existing group differences and any relatively small TBS-induced changes. Nevertheless, regardless of trait rumination, we observed a significant interaction between time and stimulation condition for positive affect. Specifically, positive affect significantly decreased after the TSST (versus baseline) in both iTBS and sTBS conditions, but no significant changes were found in the cTBS condition. This suggests that cTBS had a buffering effect on the detrimental impact of stress on positive affect, rather than leading to a heightened psychological stress response. On the other hand, we found no TBS effects on stress-induced changes in negative affect and subjective stress, with Bayesian analyses strongly favoring the null hypothesis. These findings align with previous studies indicating a lack of rTMS effects on self-report measures of mood or subjective stress (e.g., Pulopulos et al., 2020). Moreover, meta-analytic evidence suggests that a single session of rTMS might not be sufficient to induce robust, clinically relevant effects on stress-related emotional reactivity (Smits, Schutter, van Honk, and Geuze 2020; see also Moses et al. 2023). Regarding self-reported stress-reactive rumination, we did not find any significant TBS effects dependent on trait rumination. Bayesian analyses provided extreme evidence supporting the absence of TBS effects. Overall, consistent with previous research (De Witte et al., 2020; Era et al., 2021), our results indicate that TBS does not significantly influence self-reported stress-reactive rumination. While there were some discrepancies with the findings from De Witte and colleagues (2020), their trending results could potentially be attributed to the low number of high trait ruminators in their sample and the potential priming effects of administering the TSST before stimulation (Jackson et al. 2016; although see Vignaud et al. 2023). In contrast, our well-powered study sample, which included a balanced representation of low, medium and high trait ruminators, found no evidence supporting TBS effects on stress-reactive rumination. The complexity of TBS-stress interaction warrants further investigation, and future research should take into account the nuances in experimental designs and sample characteristics. Although our study did not observe significant TBS effects on stress-reactive rumination, it is important to recognize that the influence of TBS on these stress-induced changes in rumination is likely multifaceted and context-dependent. Understanding these nuances will be crucial in advancing the potential therapeutic use of TBS for stress and rumination-related disorders. This study has several strengths, including its rigorous design, a well-powered sample size, and the use of a stratified sample based on trait rumination levels. However, some limitations need to be underscored. First, blinding was insufficient, as 64% of participants correctly guessed the stimulation they received (active vs sham). Notably, this was mainly driven by participants from Tübingen who received cTBS, correctly identifying the active stimulation. The difference in blinding success between the two study sites may be attributed to the use of different TBS devices, known to impact blinding effectiveness due to variations in E-field strengths and distributions in the brain for the coils used (Smith & Peterchev, 2018). Despite recruiting participants naive to rTMS, blinding was still less effective in Tübingen, and the reasons for this remain unclear. Importantly, the study findings were not driven by placebo effects, as only two high ruminators in the cTBS condition believed their performance improved due to stimulation. Additionally, a similar number of low and medium trait ruminators in the cTBS condition report the same expectations. Nevertheless, given the differences in blinding between study sites, it remains important to recognize the potential impact of participants' beliefs regarding the received stimulation and the possibility of bias in the results. Crucially, despite this observation, additional analysis of the (in)correct guesses as a moderator did not reveal significant influence on the study results. Second, this study is limited in the causal inferences it is able to draw. Due to the scarcity of literature on TBS in the context of state rumination, this study did not include neuroimaging assessments. Investigating neural correlates could shed light on whether the lack of effects is due inadequate neuromodulation of the underlying brain areas and network. Future research with neuroimaging assessments may further illuminate the neural mechanisms underlying these effects. In conclusion, contrary to our a priori expectations, cTBS over the left DLPFC (versus iTBS and versus sham) demonstrated beneficial effects on certain psychological (i.e., positive affect) and physiological (i.e., mean heart rate and cortisol) measures of stress. One potential explanation for these findings is that cTBS may exert its beneficial effects by suppressing specific brain regions or circuits responsible for self-monitoring of stress, leading to an improved stress regulation and a potential positive emotional buffer. However, it is important to note that further research is required to fully explore the underlying working mechanisms of cTBS in this context. Notably, individuals with higher trait rumination appeared to benefit more from the cTBS effects in terms of the stress-induced cortisol response, highlighting the importance of considering individual differences in rumination when examining the effects of stimulation. To gain a comprehensive understanding of the link between TBS and stress, further research is needed to investigate the underlying neural mechanisms and the specific brain regions involved in mediating TBS effects on stress and emotional responses. Additionally, studying the effects of TBS in various stress-related conditions and populations may help identify its potential as a therapeutic tool for stress management and related disorders.

4.6 Supplementary Material Study 2

S1 Methods

2.1 Study sample

Inclusion criteria included: 1) age between 18 and 35 years old, 2) right-handed, 3) no history or current psychiatric or neurological disorders, 4) no cardiovascular diseases, 5) no drugs or medication use that affects mood, cognitive functioning or cardiovascular activity including antidepressant drugs, benzodiazepines and Z-drugs, 6) smoking no more than 10 cigarettes a day, 7) normal or corrected to normal vision, 8) no history of serious head injuries, brain surgery or epileptic seizures, 9) no metal implants or fragments in the head, 10) no cochlear implants or pacemaker, 11) no pregnancy, 12) no contraindications for theta burst stimulation (TBS, see also Rossi et al. 2009, 2011) and 13) naive to any form of Transcranial Magnetic Stimulation (TMS). Moreover, given the influence of sex hormones on heart rate variability (e.g., Schmalenberger et al., 2020), only females taking hormonal contraceptives were included. Eleven participants (3 in Ghent, 8 in Tuebingen) were excluded from the final sample. In Ghent, one participant was excluded because of his familiarity with the Trier Social Stress Test (TSST) and two female participants were excluded as they were not using hormonal contraceptives at the time of the experimental session. In Tuebingen, three participants were absent from their appointment of the experimental session, two participants were excluded due to technical issues during the session, two participants were dropouts due to painful experiences during the stimulation and one participant due to the stress induction being too overwhelming.

2.3 Neurostimulation

In Ghent, TBS was employed using a figure-eight shaped coil (Magstim 70 mm double air film coil) connected to a Magstim Rapid² Plus¹ magnetic stimulator (Magstim Company Limited, Wales, UK). For the sham TBS, a placebo variant of the Magstim figure-eight coil was used that mimics the somatosensory sensations of active TBS without causing any after-effects. In Tuebingen, a MagVenture MagPro X100 Stimulator (MagVenture, Farum, Denmark) was used and a MagVenture Cool-B65 Active/Placebo coil, a figure-eight shaped coil specifically designed for double-blind stimulation by automatically changing between active or sham mode by coil flipping according to the device instructions. In addition, two pre-gelled surface electrodes (28x20mm) were placed around the stimulation area applying a low current for a superficial sensation in case of the sham TBS as well as active TBS. For sham TBS, there was a fixed sham duration equivalent to the duration of the iTBS (i.e., 390s) in Ghent whereas in Tuebingen, the duration was either equivalent to the duration of the cTBS (i.e., 80s) or iTBS (i.e., 390s) and was balanced between participants. Crucially, participants were unable to identify sham from real stimulation as correct guesses in the sham condition were not significantly different from chance, for both study sites (57% correct $sTBS_{Ghent}$, p = 0.664 and 54% correct $sTBS_{Tuebingen}$, p = 0.839) and different sham durations (55% correct $sTBS_{390s}$, p = 0.728 and 58% correct $sTBS_{80s}$, p = 0.774).

2.5 Psychophysiological assessments

2.5.1. Psychological measures

2.5.1.3. State rumination

An overview of the 18 items of the state rumination questionnaire validated by Rosenbaum and colleagues (2018; 2020; 2018). Responses are given on a 5-point Likert scale ranging from “1 = not at all” to “5 = very often”. Item scores on items 7 and 13 need to be reversed.

2.5.1.4. Stress appraisal

Participants’ stress appraisal was measured using the Primary Appraisal Secondary Appraisal Scale (PASA; Gaab, Rohleder, Nater, & Ehlert, 2005), a self-report questionnaire that was designed to assess cognitive stress appraisal in response to the TSST. Participants rated 16 self-report items on a 6-point Likert-like scale ranging from “1 = totally disagree” to “6 = totally agree”. The PASA contains four primary stress appraisal scales, namely “Threat”, “Challenge”, “Self-Concept of Own Abilities” and “Control Expectancy”. Two secondary scales assess primary appraisal and secondary appraisal, by linking the “Threat” and “Challenge” scales and the “Self-Concept of Own Abilities” and “Control Expectancy” scales, respectively. Each secondary scale consists of 8 items and total scores were derived by calculating the mean of the combined scales (e.g., primary appraisal score = (threat + challenge)/2; Gaab 2009). The tertiary scale, also referred to as the stress index, was computed by subtracting the secondary appraisal score from the primary appraisal score (Gaab, 2009), with a higher stress index indicating a more negative anticipatory stress appraisal. Psychometric properties of the PASA scales have been demonstrated to be satisfying to good (Cronbach´s α = 0.6-0.8; Gaab et al. 2005).

Table S1
Items of the state rumination scale

Item	Statement
1	I repeatedly thought about my problems.
2	I kept thinking about things that bother me.
3	I dwelled on my thoughts without coming to a solution.
4	I got lost in my negative thoughts.
5	I had difficulties holding on to my thoughts.
6	I could not let go of my negative thoughts.
7	I was present.
8	I thought about why I acted wrong in certain situations.
9	I thought why I have problems other people don´t have.
10	I thought about whereby I deserved my current life situation.
11	I thought why I can´t handle things better.
12	I thought about all my shortcomings, failings, faults, mistakes.
13	I could switch between my thoughts flexibly.
14	I thought about past situations that I regret.
15	I blamed myself.
16	I got lost in thoughts about the past.
17	I was consumed by my problems and worries.
18	I couldn´t let go of my negative thoughts.

2.5.1.5. State emotion regulation

To assess which cognitive strategies participants used to regulate their emotions following the stress task, the State Emotion Regulation Inventory (SERI, Katz, Lustig, Assis, and Yovel 2017) was used. The SERI consists of 16 self-report items measuring momentary use of reappraisal, distraction, brooding and acceptance. Responses were made on a 7-point Likert-like scale ranging from “1 = strongly disagree” to “7 = strongly agree”. For each subscale (i.e., cognitive strategy), a total score was computed by taking the mean of all item scores. Higher scores indicate more deployment of the cognitive strategy. An acceptable reliability and internal consistency have been reported for the different subscales (Katz et al. 2017; Cronbach´s α = 0.82-0.91).

2.5.3. Baseline questionnaires

To ensure that there were no baseline differences between stimulation conditions, self-report questionnaires assessing symptoms of depression, anxiety and stress (Depression, Anxiety and Stress Scale, DASS-21; Lovibond and Lovibond 1995), social anxiety

(Liebowitz Social Anxiety Scale, LSAS; Liebowitz 1987), general self-efficacy (General Self-Efficacy Scale, GSE; Schwarzer and Jerusalem 1995) and trait emotion regulation (Emotion Regulation Questionnaire, ERQ; Gross and John 2003) were assessed via an online survey, together with questions assessing participants' demographics and lifestyle (e.g., exercise and sleep habits).

S2 Results

2.1 Descriptive statistics

	cTBS (n = 43)	iTBS (n = 39)	sTBS (n = 45)	Statistics
Age	22.14 (2.72)	21.97 (2.70)	22.49 (3.48)	$F(2,124) = 0.33, p = 0.723, \eta_p^2 < 0.01$
Sex	62.8% female	66.7% female	57.8% female	$\chi^2(2, 127) = 0.71, p = 0.701, \phi = 0.07$
BMI	22.53 (3.48)	21.68 (2.89)	23.11 (3.67)	$F(2,122) = 1.86, p = 0.160, \eta_p^2 = 0.03$
Education level	college = 2 middle school = 26 university = 14	college = 2 middle school = 26 university = 11	college = 5 middle school = 28 university = 11	Fisher's Exact Test, two-tailed: $p = 0.736$
SES	5.29 (1.61)	5.97 (1.27)	5.68 (1.22)	$F(2,122) = 2.56, p = 0.081, \eta_p^2 = 0.04$
Smokers	4	4	4	Fisher's Exact Test, two-tailed: $p = 1$
Alcohol intake	never = 4 <1/month = 5 <4/month = 17 >4/week = 0 <3/week = 16	never = 1 <1/month = 7 <4/month = 24 >4/week = 0 <3/week = 7	never = 4 <1/month = 9 <4/month = 18 >4/week = 1 <3/week = 12	Fisher's Exact Test, two-tailed: $p = 0.244$
Diet	none = 27 flexitarian = 1 vegetarian = 7 vegan = 7 other = 0	none = 23 flexitarian = 6 vegetarian = 8 vegan = 1 other = 1	none = 31 flexitarian = 4 vegetarian = 5 vegan = 2 other = 2	Fisher's Exact Test, two-tailed: $p = 0.104$
Exercise habits	daily = 9 weekly = 20 monthly = 9 yearly = 3 never = 1	daily = 5 weekly = 24 monthly = 8 yearly = 1 never = 1	daily = 10 weekly = 28 monthly = 5 yearly = 1 never = 0	Fisher's Exact Test, two-tailed: $p = 0.558$
PSQI	5.60 (2.71)	5.00 (2.64)	5.36 (2.48)	$F(2,122) = 0.53, p = 0.588, \eta_p^2 < 0.01$
RRS	2.21 (0.62)	2.16 (0.63)	2.14 (0.54)	$F(2,124) = 0.15, p = 0.859, \eta_p^2 < 0.01$
DASS-21 depression	5.00 (3.77)	4.51 (3.97)	5.14 (4.43)	$F(2,122) = 0.26, p = 0.770, \eta_p^2 < 0.01$
DASS-21 anxiety	4.52 (3.92)	4.31 (4.05)	4.23 (3.89)	$F(2,122) = 0.06, p = 0.938, \eta_p^2 < 0.01$
DASS-21 stress	5.33 (3.61)	5.03 (4.09)	4.93 (3.97)	$F(2,122) = 0.12, p = 0.884, \eta_p^2 < 0.01$
LSAS	44.07 (22.43)	39.31 (21.02)	39.16 (25.87)	$F(2,122) = 0.60, p = 0.549, \eta_p^2 < 0.01$
GSE	28.57 (4.82)	27.67 (4.38)	29.20 (4.20)	$F(2,122) = 1.23, p = 0.297, \eta_p^2 = 0.02$
ERQ suppression	15.31 (4.86)	13.31 (5.69)	14.61 (4.43)	$F(2,122) = 1.67, p = 0.193, \eta_p^2 = 0.03$
ERQ reappraisal	28.14 (6.36)	27.00 (5.68)	26.80 (4.00)	$F(2,122) = 0.76, p = 0.469, \eta_p^2 = 0.01$

Table S2

Characteristics of the study sample. Mean (SD i.e., standard deviation) for age, Body-Mass-Index (BMI), Subjective Socio-economic Status (SES; measured using the nine-rung 'social ladder', cf., Adler, Epel, Castellazzo, and Ickovics 2000), scores on the Pittsburgh Sleep Quality Index (PSQI), Ruminative Response Scale (RRS), depression, anxiety and stress subscales of the Depression, Anxiety and Stress Scale (DASS-21), Liebowitz Social Anxiety Scale (LSAS), General Self-Efficacy Scale (GSE) and the suppression and reappraisal subscales of the Emotion Regulation Questionnaire (ERQ). Sex is described as the percentage of females in each stimulation condition. Education level was defined as the highest level of education degree the participant completed. Smokers are presented in absolute numbers. Alcohol intake was operationalized by the number of glasses of alcohol the participant consumed on average. All participants were asked if they followed a particular diet, and their exercise habits were described by how often they engaged in sports or physical activity. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; sTBS, sham theta burst stimulation.

	cTBS (n = 43)	iTBS (n = 39)	sTBS (n = 45)	Statistics
Transient feelings of hyperactivity, impulsivity or irritability	1.48 (1.25)	1.34 (1.05)	1.13 (0.97)	$F(2{,}122) = 1.09$, $p = 0.341$, $\eta_p^2 = 0.02$
Headache	1.81 (1.40)	1.55 (1.16)	1.20 (1.14)	$F(2{,}122) = 2.66$, $p = 0.074$, $\eta_p^2 = 0.04$
Local pain	1.71 (1.38)	1.45 (1.16)	1.31 (1.31)	$F(2{,}122) = 0.98$, $p = 0.379$, $\eta_p^2 = 0.02$
Neck pain	0.86 (1.00)	0.92 (1.19)	0.93 (0.94)	$F(2{,}122) = 0.07$, $p = 0.937$, $\eta_p^2 < 0.01$
Tooth pain	0.71 (0.77)	0.66 (0.81)	0.53 (0.50)	$F(2{,}122) = 0.76$, $p = 0.472$, $\eta_p^2 = 0.01$
Tingling sensations	1.79 (1.26)	1.74 (1.45)	1.71 (1.47)	$F(2{,}122) = 0.03$, $p = 0.969$, $\eta_p^2 < 0.01$
Hearing changes	0.88 (1.09)	0.74 (0.76)	0.71 (0.82)	$F(2{,}122) = 0.44$, $p = 0.647$, $\eta_p^2 < 0.01$
Cognitive or neuro-psychological changes	1.12 (0.92)	1.13 (1.07)	1.07 (0.94)	$F(2{,}122) = 0.05$, $p = 0.948$, $\eta_p^2 < 0.01$
Irritation stimulation site	1.90 (1.62)	1.34 (0.97)	1.22 (1.29)	$F(2{,}122) = 3.19$, $p = 0.045$, $\eta_p^2 = 0.05$

Table S3
Self-reported side effects to the stimulation protocol. Mean (SD i.e., standard deviation) for each of the items examining possible side effects to the different stimulation conditions. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; sTBS, sham theta burst stimulation.

3.4 Psychological measures

3.3.4. Stress appraisal

For all stress appraisal indices (i.e., primary appraisal, secondary appraisal and stress index), results revealed no significant interaction between condition and trait rumination, all F's < 0.19, p's > 0.827, η_p^2's < 0.01, nor a significant main effect of condition (see figure S1 of the supplementary materials), all F's < 1.58, p's > 0.209, η_p^2's < 0.03, or trait rumination, all F's < 0.90, p's > 0.346, η_p^2's < 0.01. These results were corroborated by Bayesian analyses showing extreme evidence against main or interaction effects with condition and trait rumination for all three indices (all BF01's > 100).

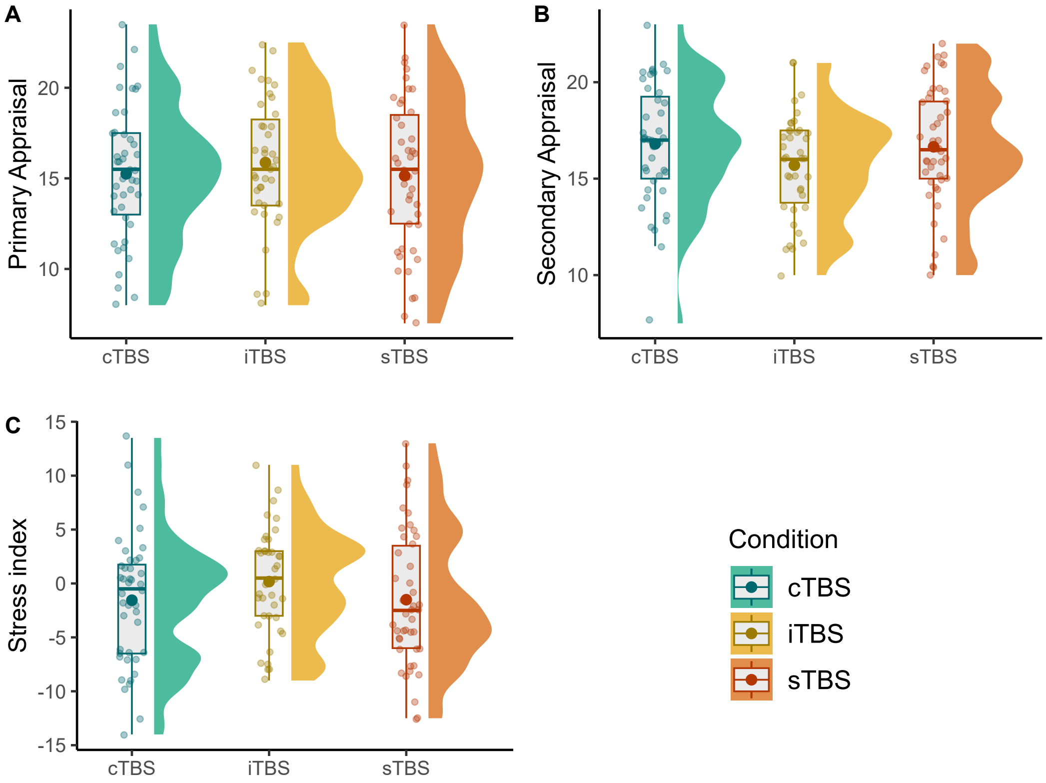

Figure S1
Raincloud plots for (A) primary appraisal, (B) secondary appraisal and (C) stress index of the Primary and Secondary Appraisal Questionnaire (PASA). Individual jittered raw data is represented by dots. Data distributions are depicted by split-half violin plots (on the right side of each series of boxplots). Each boxplot displays the stimulation condition median alongside the interquartile ranges (horizontal lines). Bold dots in the boxplots represent the estimated marginal mean of the fitted models. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; sTBS, sham theta burst stimulation.

3.3.5. State emotion regulation

Results of the MANOVA revealed no significant interaction between condition and trait rumination, $F(8, 121) = 0.07$, $p = 0.372$, nor a significant main effect of condition (see figure S2 of the supplementary materials), $F(8, 121) = 0.03$, $p = 0.921$, or trait rumination, $F(4, 121) = 0.07$, $p = 0.083$. For all subscales (i.e., distraction, reappraisal, acceptance and brooding), Bayesian analyses provided extreme evidence against the alternative hypotheses, all BF01's > 100.

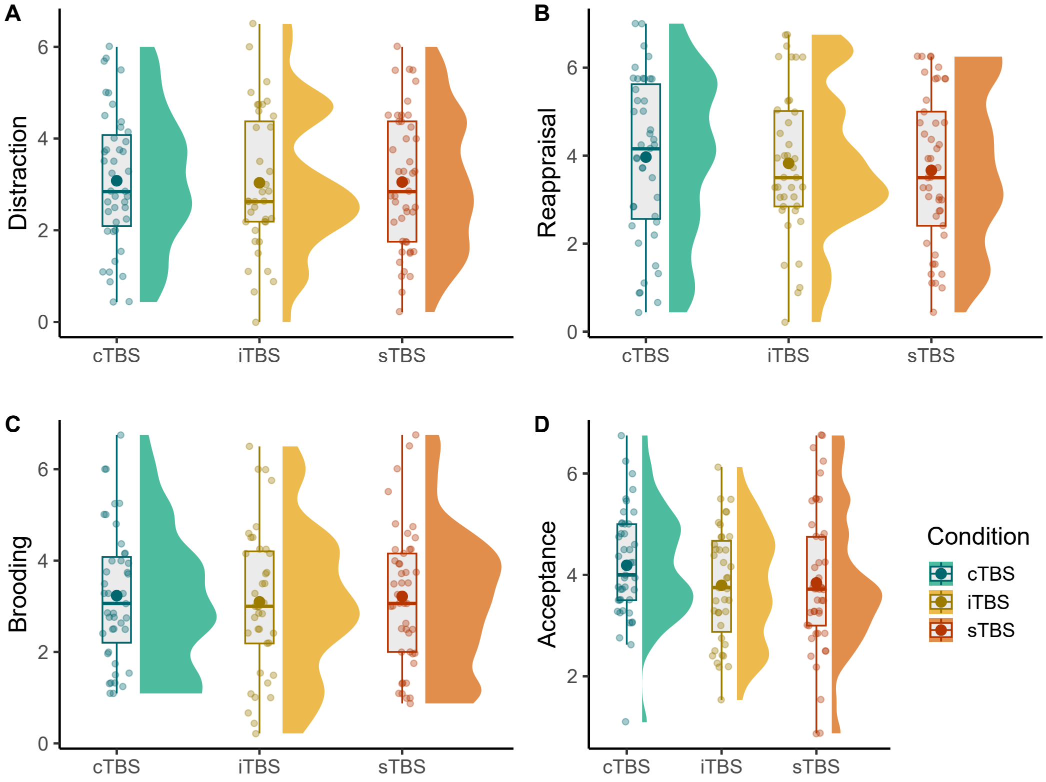

Figure S2
Raincloud plots for the (A) distraction, (B) reappraisal, (C) brooding and (D) acceptance subscales of the State Emotion Regulation Inventory (SERI). Individual jittered raw data is represented by dots. Data distributions are depicted by split-half violin plots (on the right side of each series of boxplots). Each boxplot displays the stimulation condition median alongside the interquartile ranges (horizontal lines). Bold dots in the boxplots represent the estimated marginal mean of the fitted models. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; sTBS, sham theta burst stimulation.

3.5 Psychological measures

3.5.3. Salivary cortisol

	Baseline	Directly post TSST	15min post TSST	30min post TSST	45min post TSST	60min post TSST
cTBS	4.58 (2.45)	4.62 (3.14)	7.42 (6.30)	5.17 (3.18)	4.62 (2.56)	4.26 (2.11)
iTBS	4.50 (2.66)	3.93 (1.57)	6.48 (4.55)	5.47 (3.78)	4.61 (2.61)	4.30 (2.64)
sTBS	3.87 (2.14)	4.02 (1.77)	6.98 (4.52)	6.06 (3.59)	4.72 (2.61)	4.29 (2.53)

Table S4
Raw cortisol levels. Mean (SD) for cortisol levels (nmol/L) during the session. Abbrev.: cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; min, minutes; sTBS, sham theta burst stimulation; TSST, Trier Social Stress Test.

3.6 Bayesian analyses

	Effect	BF01	Note
Mood	Time*condition*RRS	> 100	Extreme evidence against H_A
Subjective Stress	Time*condition*RRS	> 100	Extreme evidence against H_A
Subjective Stress	Time*condition	> 100	Extreme evidence against H_A
State rumination	Time*condition*RRS	> 100	Extreme evidence against H_A
State rumination	Time*condition	> 100	Extreme evidence against H_A
Mean heart rate	Time*condition*RRS	> 100	Extreme evidence against H_A
Heart rate variability	Time*condition*RRS	> 100	Extreme evidence against H_A
Heart rate variability	Time*condition	> 100	Extreme evidence against H_A

Table S5
Bayesian statistics for non-significant findings. References values to interpret the Bayes Factor (BF01) as evidence in favor of the null hypothesis (H_0), as opposed to the alternative hypothesis (H_A): weak = 1-3; substantial/moderate = 3-10; strong = 10-30; very strong = 30-100, extreme > 100 *(Jeffreys, 1961).*

Chapter 5

STUDY 3: Investigating the neural and behavioral correlates of the stress-rumination link in healthy humans by modulating the left Dorsolateral Prefrontal Cortex using Theta Burst Stimulation

The contents of this chapter are published:

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* Shared last authorship

5.1 Abstract

Theta Burst Stimulation (TBS) offers a noninvasive way to modulate neural activation patterns, helping explore the causal role of brain regions in psychiatric symptoms. Prefrontal hypoactivation is commonly observed in high ruminators and patients with depression during stress. However, the impact of modulating Dorsolateral Prefrontal Cortex (DLPFC) activity via excitatory and inhibitory TBS during stress remains unexplored. We studied 88 healthy participants (44 low, 44 high ruminators), each attending two appointments that included stress induction using the Trier Social Stress Test (TSST) and cortical oxygenation assessment with functional Near-Infrared Spectroscopy (fNIRS). Participants received either intermittent TBS (iTBS) or continuous TBS (cTBS) applied to the left DLPFC, with sessions randomized between active and sham stimulation. While TBS had no impact on positive affect, TSST performance, or heart rate, we observed effects on stress, state rumination, negative affect, and cortical oxygenation. We observed higher stress and higher negative affect during and after the TSST in high ruminators receiving iTBS compared to sham TBS (sTBS). Low ruminators showed reduced state rumination increases after iTBS compared to sTBS at their

second appointment. fNIRS data revealed cortical oxygenation differences during the TSST, although only without multiple comparison corrections. Descriptively, we observed higher activation in the left Ventrolateral Prefrontal Cortex (VLPFC) following cTBS compared to sTBS in high ruminators but lower cortical oxygenation following cTBS compared to sTBS in low ruminators but only when participants received active stimulation first. This suggests stimulation sequence affects repeated-measures TMS-studies in stress contexts. Findings highlight expectancy effects and suggest a potential reduction in TBS impact due to strong hemodynamic responses during stress.

5.2 Introduction

With Non-Invasive Brain Stimulation (NIBS), the investigation of brain functioning in mental disorders has gained a highly promising tool to evaluate the involvement of brain regions in altered physiological and psychological mechanisms. Using, for instance, Transcranial Magnetic Stimulation (TMS), it is possible to produce very focal electric field patterns (Deng et al., 2013) and therefore explicitly stimulate a circumscribed target region. This is particularly helpful in research fields where certain brain areas (as parts of respective brain networks) have repeatedly been found to show aberrant functioning in patients.

There are for instance various findings on prefrontal hypoactivation in patients with depression (DP) within the left Dorsolateral Prefrontal Cortex (DLPFC) during "affective and cognitive tasks requiring emotional or stress regulation, cognitive control, and/or shifting attention to external task demands" (Pizzagalli & Roberts, 2022, page 246). This is currently thought to be due to reduced recruitment of the DLPFC in general, as well as cortical inefficiency in DP. Cortical inefficiency in this context refers to the idea that the DLPFC, even when recruited, fails to engage effectively when needed. This could mean that greater neural activity is required to achieve the same level of cognitive or emotional regulation as in healthy controls. Consequently, whereas healthy controls and DP show similar DLPFC activation at some point, an increased need for resources (e.g. in case of higher stress) leads to aberrant functioning both on a neural as well as behavioral level in DP. What is particularly interesting, is that studies including experimental stress inductions such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which is a very potent and ecologically valid stressor (Allen et al., 2017; Henze et al., 2023, 2017; Kudielka et al., 2007), have found that prefrontal hypoactivation under stress was not only observed in DP (Rosenbaum et al., 2021) but also in healthy controls with an increased tendency to ruminate (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al., 2018; Rosenbaum, Thomas, et al., 2018). This gives rise to the question to what extent ruminative thinking, which has been found to be induced using stress inductions, such as the TSST, might be associated with a somewhat inefficient recruitment of brain regions involved in cognitive control (e.g., the DLPFC as part of the Central Executive Network) and therefore result in insufficient inhibition of negative, self-focused and nongoal-oriented thoughts.

“Rumination is repetitive, prolonged, and recurrent negative thinking about one’s self, feelings, personal concerns and upsetting experiences” (Watkins & Roberts, 2020, page 1). Ruminative thinking is also apparent in healthy controls but has been recognized as a significant risk factor for the onset of mood disorders, including depression and anxiety, as well as other mental health conditions. As such, it is regarded as a transdiagnostic cognitive vulnerability (Nolen-Hoeksema et al., 2008). Ruminative thinking is associated with increased and prolonged negative affect, stress and has been shown to interfere with effective problem-solving, because it has little to no goal orientation (for comprehensive reviews, see e.g. Nolen-Hoeksema et al., 2008; Watkins & Roberts, 2020). However, rumination affects not only the psychological but also the physiological stress response, as a meta-analysis has shown its association with elevated blood pressure, increased heart rate, reduced heart rate variability, and higher cortisol levels (Ottaviani et al., 2016).

First investigations regarding the neural underpinnings of rumination have found primarily greater activation and connectivity within regions of the Default Mode Network, which is associated with increased self-referential thinking (e.g., amygdala, medial prefrontal cortex, posterior cingulate cortex and precuneus) (Berman et al., 2011; Cooney et al., 2010; Hamilton et al., 2015, 2011; Jacob et al., 2020; Jones et al., 2017; Mandell et al., 2014; Murphy et al., 2016; Nejad et al., 2013; Philippi et al., 2018; Ray et al., 2005; Siegle et al., 2002). Moreover, prefrontal regions such as the DLPFC and VLPFC, have consistently been shown to exhibit altered functioning in response to ruminative thinking (Cooney et al., 2010; Kühn et al., 2014; Ray et al., 2005; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018).

In this context, TMS is capable of inducing excitability changes in the cortex and investigating the causal involvement of the corresponding brain networks. There are various forms of TMS, such as single-pulse, paired pulse, or repetitive TMS (rTMS). The latter is found to produce longer-lasting effects, persisting past the period of stimulation (Oberman, 2014). Recently, rTMS has been intensely studied, for instance, in the context of the treatment of depression by modulating activation of the left DLPFC (Gaynes et al., 2014; Sathappan et al., 2019; Schutter, 2009). In experimental settings, rTMS has also been found to be capable of examining effects on rumination and also the psychophysiological stress response (Baeken et al., 2014; De Smet et al., 2021; Pulopulos et al., 2020; Remue et al., 2016). A relatively newer variant of rTMS, Theta Burst Stimulation (TBS), in which high-frequency TMS is applied in the form of bursts simulating the theta-rhythms of the hippocampus (Huang et al., 2005), offers particularly interesting possibilities. Specifically, depending on the interpulse interval and intertrain interval, TBS is capable of eliciting excitatory effects that are assumed to resemble long-term potentiation (intermittent Theta Burst Stimulation; iTBS) or inhibitory effects resembling long-term depression of neural excitability (continuous Theta Burst Stimulation; cTBS) (Huang, Rothwell, Chen, Lu, & Chuang, 2011). So far, only three studies employed TBS in the context of stress: Pulopulos et al. (2019) were the first to investigate iTBS on the left DLPFC and found no general impact on mood or cortisol responses. This was replicated by De Witte et al. (2020), who also found no significant effect of iTBS on mood or cortisol. However, they observed that trait rumination was linked to increased rumination only in the sham condition, suggesting that iTBS may disrupt the relationship between brooding and stress-reactive rumination, potentially regulating the stress response. Era et al. (2021) applied cTBS to the left DLPFC and found that it induced increased heart rate and cortisol responses, indicating a detrimental, stress-reactive effect. Overall, these studies point to the complexity of the relationship between TBS, stress, and rumination, suggesting a need for further research, particularly with larger samples and neural data. Including both state and trait rumination as variables could be promising for understanding these effects.

In combination with the finding that the left DLPFC is considered the most appropriate target region for manipulating stress reactivity using NIBS (Moses et al., 2023), the aim of the current study was to evaluate the effects of cTBS and iTBS versus sTBS on the neural correlates of stress-reactive rumination and the psychophysiological stress response. The neural correlates were investigated using functional Near-Infrared Spectroscopy (fNIRS) which has been found capable of assessing TBS-induced changes in cortical oxygenation in the DLPFC in previous studies (Curtin et al., 2019).

We hypothesized that inhibiting the left DLPFC with cTBS would exacerbate prefrontal dysfunction under stress in high ruminators, while excitatory stimulation (iTBS) would "normalize" cortical oxygenation in the left DLPFC, leading to higher oxygenation. For low ruminators, we expected inhibitory stimulation to decrease cortical oxygenation, while excitatory stimulation would increase it, although the effect would likely be smaller, as low ruminators are thought to already have higher prefrontal activity under stress. For the fNIRS data, we anticipated higher cortical oxygenation in the left

DLPFC following iTBS compared to sTBS and lower oxygenation after cTBS compared to sTBS during the stress induction (i.e. the arithmetic task of the TSST). We predicted that iTBS would reduce subjective stress, negative affect, and stress-reactive rumination, while cTBS would increase these measures. However, the effects of iTBS in low ruminators were expected to be modest due to their already high prefrontal functioning and low rumination. We expected the TBS effects to last at least through the TSST (about 20 min post TBS) and the second resting-state measurement (about 30 min post TBS).

5.3 Methods

5.3.1 Participants

Interested volunteers were made aware of the study by means of circular emails via the university mailing list. Initially, an eligibility screening using an online questionnaire was completed, in which demographic and clinical variables as well as the Ruminative Response Scale (RRS; Treynor & Gonzalez, 2003) were assessed (for a list of inclusion and exclusion criteria see supplementary material S1). According to an a priori power analysis (see supplementary material S2), we aimed to recruit a stratified sample of 44 low and 44 high trait ruminators (low trait ruminators: mean RRS ≤ 1.82 (*PR* 25); high trait ruminators: mean RRS ≥ 2.36 (*PR* 64). Please note that these corresponding cut-offs are based on the combined data of 983 participants from prior studies (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018). Following the a priori power analysis, we recruited participants until this target was reached, which resulted in the final sample size matching the planned number. All eligible volunteers received an invitation to participate in the study. After inclusion in the study, a total of 22 participants declined to participate (n = 15 owing to loss of interest in participation prior to the first appointment, n = 2 owing to discomfort with the TBS, n = 2 owing to circulatory problems during the measurement, n = 2 without giving a reason, and n = 1 owing to discomfort of the stress induction), A total of seven participants were excluded as their mean RRS substantially changed between the online screening and a second assessment (second online screening 1 week prior to the lab appointment or at the first lab appointment) either by changing the category or falling between the cutoffs and being closer to the corresponding other category[1] (please find the CONSORT-diagram in supplementary material S3). In total, the final sample comprised 88 right-handed healthy volunteers aged 18 to 50 years (44 low and 44 high trait ruminators). After inclusion, participants were randomly assigned to one of two stimulation conditions: iTBS (n = 44; 22 low ruminators, 22 high ruminators) or cTBS (n = 44; 22 low ruminators, 22 high ruminators). Each participant completed two laboratory sessions (AP1 and AP2), during which they received either an active (iTBS or cTBS) or a sham (sTBS) stimulation. The sham condition was matched in duration to

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[1] Please note that we observed these issues only halfway through recruiting. Consequently, thereafter participants had to complete another online RRS 1 week prior to their first appointment where we again checked whether participants completed the RRS as a trait measure, which should remain moderately stable, and excluded participants even at their first appointment in case their RRS score deviated substantially from the initial online screening. For an analysis of this issue we refer to Int-Veen et al. (2024).

its corresponding active stimulation (i.e., participants receiving active cTBS underwent sTBS of the same duration as cTBS, and those receiving active iTBS underwent sTBS of the same duration as iTBS). The order of stimulation (active vs. sham) was randomized and counterbalanced across participants and stimulation groups (for an illustration of the allocation of experimental groups see figure 5.1A).

5.3.2 Procedure

After inclusion in the study, participants underwent two appointments at the laboratory. At their first appointment, participants gave written informed consent. Afterwards, at each appointment, the participants' resting motor threshold was determined using the visual observation of muscle twitch with the relative frequency method (Rothwell et al., 1999). While participants were prepared for the electrocardiogram (ECG)- and fNIRS-measurement, they completed several questionnaires assessing demographic data, symptoms of depression (Beck's Depression Inventory II: BDI-II; Beck, Steer, Brown, & others, 1996) and trait rumination (Ruminative Response Scale: RRS; Treynor & Gonzalez, 2003) and a Visual Analogue Scale assessing subjective stress levels on a scale ranging from 0 % to 100 %. We do not anticipate any significant influence of the preparation process on the questionnaire responses, as participants were only briefly interrupted during the completion of the questionnaires and were not under direct observation. Then, a 7 min resting-state measurement followed (rest1), where participants were instructed to let their mind wander but keep their eyes open. Following this, participants gave another stress rating and completed a questionnaire assessing their current affect (Positive and Negative Affect Schedule: PANAS; Watson et al., 1988, please note that we used an adapted version with two additional items, namely "happy" and "sad") and an assessment of state rumination using the Stress-Reactive State Rumination Questionnaire (SRSRQ; Int-Veen, Laicher, et al., n.d., for a full list of items see supplementary material S4). Following this, participants completed two control tasks as in Rosenbaum et al. (2018; 2021; 2018) including reading numbers aloud (control task 1; ctl1) and performing mental arithmetic without time or social pressure (control task 2; ctl2). Both tasks consisted of 6 trials of 40 s duration and 20 s rest, and subjective stress ratings were assessed following each task. Then participants were guided to another room where the neurostimulation followed (see the section on Theta Burst Stimulation). After the TBS and another stress rating, as well as an assessment of the PANAS and SRSRQ, participants underwent the stress induction (see section Trier Social Stress Test). Following the

TSST (0 min post TSST), participants again rated their current stress and completed another PANAS prior to another 7 min resting-state measurement (rest2). Finally, subjective stress and another SRSRQ were assessed. For the last part of the study, participants were again guided to the room where the TBS took place where they were seated until 60 min post TSST and instructed to let their mind wander, while another stress rating was assessed every 15 min. At 60 min post TSST, participants additionally completed a PANAS, SRSRQ and a questionnaire about potential side effects of the TBS. Lastly, as a manipulation check, we asked participants about their beliefs regarding the stimulation condition they were in (sham vs. active), and how confident they were in answering the question. After completion of both appointments, participants were debriefed and received 100 € as monetary compensation or 6 hours of course credit (for an overview over the study procedure, see figure 5.1B). The two appointments (AP1 and AP2) at the laboratory were scheduled approximately 5 weeks apart (M = 41.48 days, SD = 8.45 days). This study was approved by the ethics committee at the University Hospital and University of Tübingen (673/2019BO1).

5.3.3 Theta Burst Stimulation

The motor threshold determination and stimulation were performed by a study nurse who was no further involved in the study. We used a MagVenture MagPro X100 Stimulator (MagVenture, Farum, Denmark) as well as a figure-eight shaped coil without cooling for motor threshold determination (MagVenture C-B60 coil) and another figure-eight shaped coil with active cooling (MagVenture Cool-B65 Active/Placebo coil), specifically designed for double-blind stimulation by automatically changing between active or sham TBS via coil flipping according to the device instructions. A total of 88 pairs of randomization codes were created, with each participant assigned one pair. One code in the pair triggered active stimulation, and the other triggered sham stimulation in the TBS device. The order of stimulation (active → sham or sham → active) was balanced across participants. The first code in the pair was used for appointment 1 (AP1), and the second code for appointment 2 (AP2). The randomization was conducted using Excel prior to the study. Randomization pairs were assigned in the order of participant recruitment. To ensure balanced randomization across the RRS-groups (low and high ruminators), numbers 1 to 4 representing the four conditions were listed 11 times each and then randomly shuffled. The four conditions were: "cTBS-arm: active → sham", "cTBS-arm: sham → active", "iTBS-arm: active → sham" and "iTBS-arm: sham → active". TBS over

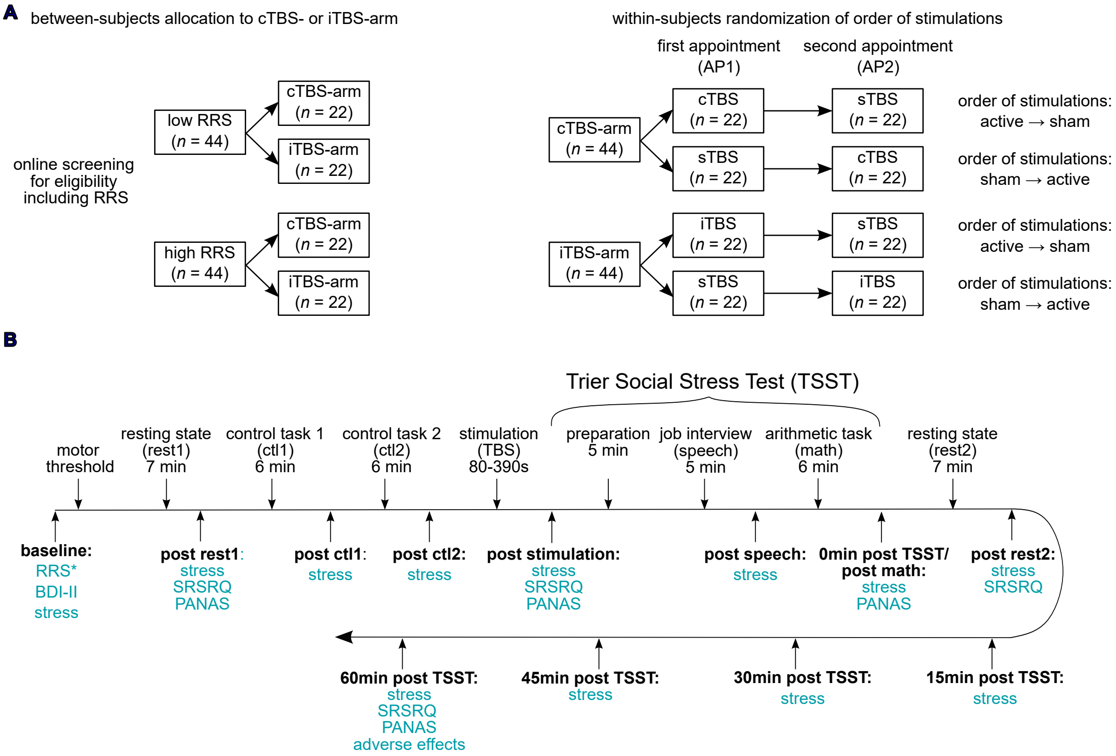


Figure 5.1
*Illustration of the allocation of experimental groups (A) and overview of the experimental procedure (B). Above the line, the respective tasks and experimental phases are shown. Below the line, the time points of questionnaire assessments are displayed in bold, with the names of the corresponding questionnaires highlighted in blue. RRS = Ruminative Response Scale, TBS = Theta Burst Stimulation, BDI-II = Beck's Depression Inventory II, PANAS = Positive and Negative Affect Schedule; SRSRQ = Stress-Reactive State Rumination Questionnaire; stress = subjective stress assessed via a Visual Analogue Scale (0-100 %); * = only assessed at the first appointment (AP1).*

the left DLPFC was applied at 80 % of the resting motor threshold (Huang et al., 2005). The coil was positioned according to the 10-20 electrode position F3 (Jasper, 1958), which corresponded to one channel of the left frontal fNIRS probeset (for an illustration of the TBS-induced electric field, see supplementary material S5). Please note that the coil was placed directly on the scalp, as the fNIRS device did not permit simultaneous acquisition of fNIRS data and TBS. To mask the active stimulation and ensure better blinding in the case of sTBS, two pre-gelled surface electrodes (28x20mm) were placed 1 cm around the stimulation site applying a low current for a superficial sensation during the TBS. The sham side of the coil is shielded, preventing the transmission of magnetic pulses to the brain. As a result, while participants still experience the typical auditory effects of stimulation, they do not perceive any tactile sensation. The additional surface electrodes were introduced to ensure a more effective blinding procedure by providing a superficial sensory experience during sTBS. However, the applied current is minimal and did not penetrate the brain, nor did it stimulate peripheral nerves (Smith & Peterchev, 2018). We opted for this method to enhance blinding and minimize potential differences in subjective experience between active and sham stimulation, thereby reducing the risk of unblinding effects that could influence neural and behavioral responses. Participants were randomly assigned to receive cTBS (80 s train of uninterrupted TBS including 400 bursts of 3 pulses at a frequency of 50 Hz and burst frequency of 5 Hz) or iTBS (40 cycles of 2 s theta burst trains (10 bursts of 3 pulses each) followed by 8 seconds of rest (i.e., total of 390 s). Consequently, the stimulation parameters included a total of 1200 pulses for both paradigms.

5.3.4 Trier Social Stress Test

To reliably induce psychosocial stress following the TBS, we used an adapted version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). After the participants had been guided back to the measurement room and were prepared for the ECG- and fNIRS-measurement, they were told that two other people were going to join. Two experimenters wearing white physician coats entered and took a seat in front of the participant's table. They instructed the participant to imagine having applied for a job at the university hospital, with part of the recruitment procedure involving a speech about their personal strengths and qualification for the corresponding position. Participants had 5 min time to prepare for this speech by taking notes, which were then collected. Standing up in front of the two experimenters, who remained unresponsive to any social interaction signs, participants were urged to talk for 5 min without this time limit being known beforehand. During this, participants were video recorded in order to maximize social threat. After the 5 min speech, participants completed a subjective stress rating receiving instructions about the next task. For the mental arithmetic task, participants were instructed to calculate aloud as quickly and accurately as possible from various starting points (e.g., 1013). Additionally, participants were instructed to maintain eye contact with one experimenter while the other experimenter asked them to start over if they made an error. Similar to the control tasks, participants completed 6 trials of 40 s each, with 20 s pauses in order for the hemodynamic response to recover. After the final trial, the experimenters stopped the video recording and left the room without any comment.

5.3.5 Electrocardiogram

Throughout the experimental session (rest1 until rest2), heart rate was assessed using three Ag/AgCl ring electrodes with a diameter of 8 mm, which were attached to the participants' skin above the right collar bone, below the left costal arch and below the neck (reference). The signal was recorded with a BrainAmp ExG amplifier and Brain Vision recorder software (Brain Products, Munich, Germany) at a sampling rate of 1000 Hz. Data was preprocessed and analyzed using Brain Vision Analyzer 2.1 and MATLAB 2024. Preprocessing included band-pass filtering (1-30 Hz; slope: 48 db/Oct, time constant 0.1591549 s) and applying a notch filter at 50 Hz in order to eliminate power line artifacts. Lastly, we calculated the mean interval between subsequent R-peaks for each recorded condition in beats per minute (BPM).

5.3.6 Functional Near-Infrared Spectroscopy

Throughout the experimental session (rest1 until rest2), cortical oxygenation was measured using an ETG-4000 Optical Topography System with a sampling rate of 10 Hz (46-channel continuous wave multichannel fNIRS; Hitachi Medical Co., Japan). Two frontal and one parietal probeset with a fixed 3 cm inter-optode distance (28 light emitters, i.e. semiconductor lasers and 15 light detectors, i.e. avalanche photodiodes at two wavelengths (695 ± 20 and 830 ± 20 nm) with 2.0 ± 0.4 mW for each wavelength at each optode) were placed according to the 10-20 reference points Fpz and Cz. Relative changes in oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin were computed using custom MATLAB 2024a scripts by means of the modified Beer-Lambert Law (Sassaroli & Fantini, 2004). Preprocessing included interpolation of single noisy channels, correction of motion artifacts using Temporal Derivative Distribution Repair (Fishburn et al., 2019), Correlation-based signal improvement (Cui et al., 2010) and bandpass filtering to remove low-frequency baseline drifts (< 0.01 Hz) and high-frequency noise (> 0.1 Hz). To remove artifacts due to data correction, additional channel interpolation was performed, followed by a global signal reduction with a spatial gaussian kernel filter ($\sigma = 40$) and z-standardization of the signal. Note that in the following, O_2Hb data refers to the correlation-based improved O_2Hb signal. For data analysis, we calculated event-related averages including a 5 s baseline correction. For a visualization of the probeset placement and respective Regions of Interest (ROIs), we refer to supplementary material S6 and S7. Lastly, data was exported as an average for each ROI as well as each channel separately: left and right Ventrolateral Prefrontal Cortex (VLPFC), left and right Dorsolateral Prefrontal Cortex (DLPFC), and Somatosensory Association Cortex (SAC). Scalp-brain correspondence was estimated based on Okamoto et al. (2004), Okamoto and Dan (2005) and Singh et al. (2005). Please note that channel 12 of the left frontal probeset, which corresponds to electrode position F3 of the 10-20 system (Jasper, 1958), was the stimulated site.

5.3.7 Data analysis

Data analysis was conducted using SPSS (Version 28, IBM Corp., 2021). To analyze the effects of TBS, we applied three complementary analytical approaches for all dependent variables (DV): subjective stress, state rumination, positive and negative affect, math performance, heart rate, and cortical oxygenation (to reduce the article's length, results on positive affect, math performance, and heart rate are included in supplementary material S8). First, following standard procedures for within-subject designs, we conducted contrast analyses comparing active stimulation (iTBS/ cTBS) to sham stimulation. For this, we calculated contrasts for each DV by subtracting sham stimulation values from active stimulation values at each time point. These contrasts were then entered into repeated measures ANOVAs (rmANOVAs), including a four-way interaction of time, stimulation condition (iTBS vs. cTBS), group (low RRS vs. high RRS), and order of stimulation conditions (active → sham vs. sham → active). Please note that "time" refers to the number of repeated assessments of the corresponding DVs (12 times for subjective stress, 4 times for state rumination, 4 times for positive and negative affect, 3 times for math performance, 7 times for heart rate, and 3 times for cortical oxygenation). We identified strong habituation effects in nearly all DVs, which is in line with previous findings of habituation effects on the HPA-axis response with repeated exposure to the TSST (Allen et al., 2017; Kudielka et al., 2007; Schommer, Hellhammer, & Kirschbaum, 2003). Most probably owing to the novelty of the situation, stress responses were stronger during the initial exposure, which might cause the small TBS effects to be masked. After an initial a priori planned analysis of the rmANOVAs without the factor “order of stimulation conditions” yielding predominantly null results, we decided to include the factor in the rmANOVA, because incorporating the order of stimulation conditions as a factor enables a more precise understanding of how habituation interacts with the effects of the stimulation on stress reactivity. If the highest interaction involved the order of stimulation conditions, separate rmANOVAs were performed based on the order, excluding lower-order effects to streamline the results.

In addition to the contrast analysis, we reported the raw data to provide a clearer overview of the observed effects. More specifically, we fitted rmANOVAs including a three-way interaction of time, stimulation condition (iTBS vs. cTBS vs. sTBS), group (low RRS vs. high RRS) for each appointment, separately. Finally, we conducted planned contrasts to examine specific time points at which TBS effects were expected to be most pronounced. This approach provided a more targeted hypothesis test while increasing statistical power.

For each analysis, multivariate outliers were identified using Mahalanobis distances separately for each DV. Please note that there were no significant baseline differences between the stimulation conditions.

For fNIRS data specifically, we further performed a manipulation check in the form of paired *t*-tests to compare the cortical oxygenation in each channel during the arithmetic task of the TSST, contrasting the levels after active stimulation with those following sham stimulation (active vs. sham) within subjects across all participants. Then, a repeated measures MANOVA (rmMANOVA) was conducted based on five ROIs (left VLPFC, left DLPFC, right VLPFC, right DLPFC, and SAC), including the aforementioned four-way interaction. Lastly, we calculated Reliable Change Indices (RCIs) for state rumination ratings to determine how many participants exhibited reliable changes in their ratings between post rest1 and post rest2. We calculated RCI to assess whether the TSST has led to significant changes at the individual level, complementing group-level statistical analyses (for further reading, see Blampied, 2022).

Significant effects were followed by post-hoc tests corrected for multiple comparisons using the Benjamini-Hochberg procedure. Nonsignificant post-hoc tests and those related to lower-order effects involved in significant higher-order interactions are not reported. Polynomial contrasts (linear and quadratic) were provided for interpretative purposes. Please note that we also investigated quadratic contrasts because this approach captures potential nonlinear changes, such as an increase or decrease during stress induction followed by a return toward baseline in the post-stress phase.

As an exploratory analysis, we also examined the influence of expectancy effects on the previously described analyses. For this purpose, we included the item "Do you believe that the stimulation made you perform better or worse on the task? (better vs. worse vs. no effect)" as a covariate.

All significant effects, including lower-order ones, are reported, and marginally significant effects are noted if $p < .1$. Violations of sphericity (Mauchly test $p < .05$) were corrected using Greenhouse-Geisser estimates if $\epsilon < 0.75$, and Huynh-Feldt estimates if $\epsilon > 0.75$. Data visualization was conducted using MATLAB 2024, RStudio Version 2022.02.3+492 (RStudio Team, 2022), R Version 4.3.1 (R Core Team, 2023), and the ggplot2 package (Wickham, 2009).

5.4 Results

5.4.1 Sample characteristics

Overall, the average age of the sample was 24.22 years (*SD* = 4.85 years), and 79.55% of the participants were female. On average, participants had a mean RRS score of 1.99 (*SD* = 0.64) and a BDI-II total score of 7.22 (*SD* = 7.19), indicating "no depression" according to the BDI-II cutoff scores (Hautzinger et al., 2009). There were no significant differences in demographic variables between the cTBS- and iTBS study arm (see table 5.1).

	cTBS-arm	iTBS-arm	Test statistic	Total sample
Age	24.05 (2.91)	24.50 (6.30)	$F(1, 86) = 0.255, p = .615, \eta_p^2 = .003$	24.22 (4.85)
Percent female	77.27%	81.82%	$\chi^2(1) = 0.070, p = .792$	79.55%
BDI-II	6.91 (7.04)	7.53 (7.91)	$F(1, 86) = 0.153, p = .697, \eta_p^2 = .002$	7.22 (7.19)
RRS	2.04 (0.68)	1.93 (0.60)	$F(1, 86) = 0.723, p = .398, \eta_p^2 = .008$	1.99 (0.64)

Table 5.1
Demographic variables of the sample by study arm.BDI-II = Beck Depression Inventory II, RRS = Rumination Response Scale. Test statistic = comparison of the cTBS- and iTBS-arm.

5.4.2 Manipulation check and blinding

A binomial test showed that participants could not distinguish between sham and active stimulation, as correct guesses in all stimulation conditions were not significantly different from chance (all *p*'s > .101, see table 5.2). Additionally, there were no significant differences in stimulation intensity among the cTBS (*M* = 42.34, *SD* = 6.10), iTBS (*M* = 41.11, *SD* = 7.05) and sTBS conditions (*M* = 41.83, *SD* = 6.24), $F(2, 173) = 0.408$, $p = .666$, $\eta_p^2 = .005$.

	percent	95 % CI	p-value
correct identification of sTBS as sham (AP1)	56.10%	[39.75; 71.53]	.533
correct identification of iTBS as active (AP1)	50.00%	[27.20; 72.80]	.999
correct identification of cTBS as active (AP1)	38.10%	[18.11; 61.57]	.383
correct identification of sTBS as sham (AP2)	62.79%	[46.73; 77.02]	.126
correct identification of iTBS as active (AP2)	66.67%	[43.03; 85.41]	.189
correct identification of cTBS as active (AP2)	63.64%	[40.66; 82.80]	.286
correct identification of sTBS as sham (overall)	59.52%	[48.25; 70.10]	.101
correct identification of iTBS as active (overall)	58.54%	[42.11; 73.68]	.349
correct identification of cTBS as active (overall)	51.16%	[35.47; 66.69]	.999

Table 5.2
Summary of exact binomial tests assessing the blinding of participants (H_0: $p = .5$). AP1 = first appointment, AP2 = second appointment, sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation.

We examined whether participants believed that stimulation affected their performance (either improving or worsening it) using a logistic regression model. The results showed no significant effect of the stimulation condition, $\chi^2(2) = 2.492$, $p = .288$. Next, we used a linear mixed model to analyze participants' confidence in their responses to a question about the impact of stimulation on their performance. More specifically, we fitted a model with the response to the respective item as DV, stimulation condition as a predictor and separate intercepts per subject. Again, we found no significant main effect of the condition, $\chi^2(2) = 1.946$, $p = .378$. Descriptively, in all three TBS groups, approximately half of the participants felt that stimulation had no impact on their performance, while the other half believed it did (see table 5.3). Additionally, when analyzing the logistic regression and linear mixed models based on the RRS group, there were no significant effects of the group, $\chi^2(1) = 0.980$, $p = .322$ and $\chi^2(1) = 0.629$, $p = .428$, respectively. For both RRS groups, most participants thought that stimulation had no effect (low RRS group: 47.6% no change, 30.5% better, 22.0% worse; high RRS group: 55.2% no change, 25.3% better, 19.5% worse).

			condition			
			sTBS	cTBS	iTBS	total
impact on performance	no change	count	45	17	25	87
		% within impact on performance	51.7%	19.5%	28.7%	100%
		% within condition	52.9%	41.5%	58.1%	51.5%
		% of all data points	26.6%	10.1%	14.8%	51.5%
	better	count	23	15	9	47
		% within impact on performance	48.9%	31.9%	19.1%	100%
		% within condition	27.1%	36.6%	20.9%	27.8%
		% of all data points	13.6%	8.9%	5.3%	27.8%
	worse	count	17	9	9	35
		% within impact on performance	48.6%	25.7%	25.7%	100%
		% within condition	20.0%	22.0%	20.9%	20.7%
		% of all data points	10.1%	5.3%	5.3%	20.7%

Table 5.3
Absolute and relative frequencies of participants' ratings on the impact of stimulation on performance by stimulation condition. sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation. Please note that 7 data points were missing as the item was not answered or not answered unambiguously.

5.4.3 Psychological measures

Subjective stress contrasts. We identified multivariate outliers using Mahalanobis distances ($p < .001$) and excluded the data from 5 participants for the subsequent analysis. When we fitted the rmANOVA of the subjective stress contrasts, we observed a significant four-way interaction between time, group, stimulation condition, and order of stimulation conditions, $F(5.005, 375.371) = 3.338$, $p < .01$, $\eta_p^2 = .043$, as well as significant lower-order interactions: a time and order of stimulation conditions interaction, $F(5.005, 375.371) = 23.818$, $p < .001$, $\eta_p^2 = .241$; a three-way interaction of group, stimulation condition, and order of stimulation conditions, $F(1, 75) = 6.166$, $p < .05$, $\eta_p^2 = 0.076$; an interaction between group and stimulation condition, $F(1, 75) = 4.418$, $p < .05$, $\eta_p^2 = .056$; and a main effect of the order of stimulation conditions, $F(1, 75) = 37.940$, $p < .001$, $\eta_p^2 = .336$. To gain a deeper understanding of the four-way interaction, we performed separate rmANOVAs considering the order of the stimulation conditions. As a result, only for participants who received sham first, we observed a significant three-way interaction of time, group and stimulation condition, $F(4.806, 182.645) = 3.805$, $p < .01$, $\eta_p^2 = .091$. Additionally, there was a significant intercept regardless of the order of stimulation conditions (i.e., a significant main effect of active stimulation vs. sham) (sham → active: $F(1, 38) = 21.698$, $p < .001$, $\eta_p^2 = .363$; active → sham: $F(1, 37) = 17.318$, $p < .001$, $\eta_p^2 = .319$). Polynomial contrasts of the three-way interaction of time, group and stimulation condition revealed a significant quadratic contrast, $F(1, 38) = 12.630$, $p <$

.01, η_p^2 = .249, and post-hoc tests indicated significant differences between stimulation conditions in high ruminators following the job interview of the TSST. Specifically, high ruminators exhibited more negative contrasts following cTBS (*M* = -1.10, *SD* = 24.42) compared to high ruminators following iTBS (*M* = -31.18, *SD* = 15.43), $t(19)$ = 3.410, p < .01, d = 1.490. In both cases, we observed negative contrasts, indicating higher subjective stress following the job interview of the TSST in case of the sham compared to the active appointment (i.e., the first appointment, AP1) but more negative contrasts following iTBS (i.e., more pronounced differences between active and sham stimulation). The raw data shows that high ruminators who received sTBS of the duration of iTBS at AP1 generally reported higher levels of subjective stress (*M* = 80.60, *SD* = 12.14) compared to high ruminators receiving sTBS of the duration of cTBS at AP1 (*M* = 38.73, *SD* = 19.54), $t(18.171)$ = -5.529, p < .001, d = -2.260. At AP2, both groups exhibited significantly lower stress (M_{iTBS} = 47.55, SD_{iTBS} = 16.68; M_{cTBS} = 35.50, SD_{cTBS} = 13.83), whereas the group receiving iTBS exhibited stronger and the cTBS-group non-significant reductions (iTBS-arm: $t(19)$ = 5.144, p < .001, d = 2.248; cTBS-arm: $t(19)$ = 0.433, p = .335, d = 0.189) (see figure 5.2).

Subjective stress raw data. Based on Mahalanobis distances (p < .001), we excluded the data from eight participants: three from the first appointment (AP1) and five from the second appointment (AP2). When we fitted the rmANOVA separately for each appointment on the raw data, we observed a significant main effect of time (AP1: $F(3.458, 273.160)$ = 137.998, p < .001, η_p^2 = .636; AP2: $F(2.985, 229.849)$ = 93.942, p < .001, η_p^2 = .550) with quadratic polynomial contrasts each (AP1: $F(1, 79)$ = 252.274, p < .001, η_p^2 = .762; AP2: $F(1, 77)$ = 149.649, p < .001, η_p^2 = .660), indicating increases in subjective stress due to the TSST and respective decreases post-stress (see figure 5.2C-D). We further observed a significant main effect of group at both appointments, indicating that high ruminators reported significantly higher subjective stress compared to low ruminators (AP1: $F(1, 79)$ = 10.791, p < .01, η_p^2 = .120; AP2: $F(1, 77)$ = 8.315, p < .01, η_p^2 = .097). Lastly, polynomial contrasts indicated a significant linear contrast for the interaction of time and stimulation condition in case of the first appointment, $F(2, 79)$ = 4.079, p < .05, η_p^2 = .094, and a marginally significant quadratic contrast of the interaction of time and group, indicating higher stress-induced increases in high ruminators, $F(1, 77)$ = 3.156, p = .080, η_p^2 = .039.

Subjective stress planned contrasts. When we investigated the differences in subjective stress separately for each appointment and RRS group, we observed significantly higher subjective stress in high ruminators at their first appointment following iTBS compared with high ruminators at their first appointment following sTBS after the second resting-state measurement, *t*(29) = -2.065, *p* < .05, *d* = -0.775 (M_{sTBS} = 24.60, SD_{sTBS} = 19.35, M_{iTBS} = 40.46, SD_{iTBS} = 22.41), 15 min, *t*(29) = -2.575, *p* < .01, *d* = -0.967 (M_{sTBS} = 16.05, SD_{sTBS} = 15.28, M_{iTBS} = 31.91, SD_{iTBS} = 18.37), 30 min, *t*(29) = -1.988, *p* < .05, *d* = -0.746 (M_{sTBS} = 12.75, SD_{sTBS} = 12.21, M_{iTBS} = 22.00, SD_{iTBS} = 12.73), 45 min, *t*(29) = -2.061, *p* < .05, *d* = -0.773 (M_{sTBS} = 10.40, SD_{sTBS} = 11.17, M_{iTBS} = 19.64, SD_{iTBS} = 13.29), and 60 min post TSST, *t*(29) = -2.437, *p* < .05, *d* = -0.915 (M_{sTBS} = 8.05, SD_{sTBS} = 7.51, M_{iTBS} = 16.55, SD_{iTBS} = 11.96). We further observed significantly higher subjective stress in high ruminators at AP2 following iTBS compared with high ruminators at AP2 following sTBS but only after the second resting-state measurement, *t*(29) = -1.743, *p* < .05, *d* = -0.654 (M_{sTBS} = 15.90, SD_{sTBS} = 10.45, M_{iTBS} = 23.82, SD_{iTBS} = 14.74) as well as marginally significantly higher subjective stress in low ruminators at AP2 following iTBS compared with high ruminators at AP2 following sTBS but only 45 min after the TSST, *t*(12.385) = -1.685, *p* = .058, *d* = -0.768 (M_{sTBS} = 2.20, SD_{sTBS} = 3.33, M_{iTBS} = 5.40, SD_{iTBS} = 5.52).

State rumination contrasts. According to Mahalanobis distances (*p* < .001), there were two multivariate outliers and three participants with missing data, which were excluded for the following analysis. Fitting the rmANOVA, we observed a significant three-way interaction of time, group and order of stimulation conditions, *F*(3, 225) = 5.235, *p* < .01, η_p^2 = .065) and a significant lower-order interaction of time and order of stimulation conditions, *F*(3, 225) = 15.850, *p* < .001, η_p^2 = .174. We then conducted separate rmANOVAs based on the order of the stimulation conditions. In case participants received sham stimulation first, we observed a marginally significant interaction between time and group (sham → active: *F*(3, 105) = 2.144, *p* = .099, η_p^2 = .058). In case participants received active stimulation first, we observed a significant interaction between time and group (active → sham: *F*(3, 120) = 4.096, *p* < .01, η_p^2 = .093). Polynomial contrasts of the interaction of time and group revealed a linear contrast but in opposite directions dependent on the order of stimulation conditions (see figure 5.3A and 5.3B). For participants having received active stimulation first, the differences between the active and passive stimulation increase and increase more in high ruminators, *F*(1, 40) =

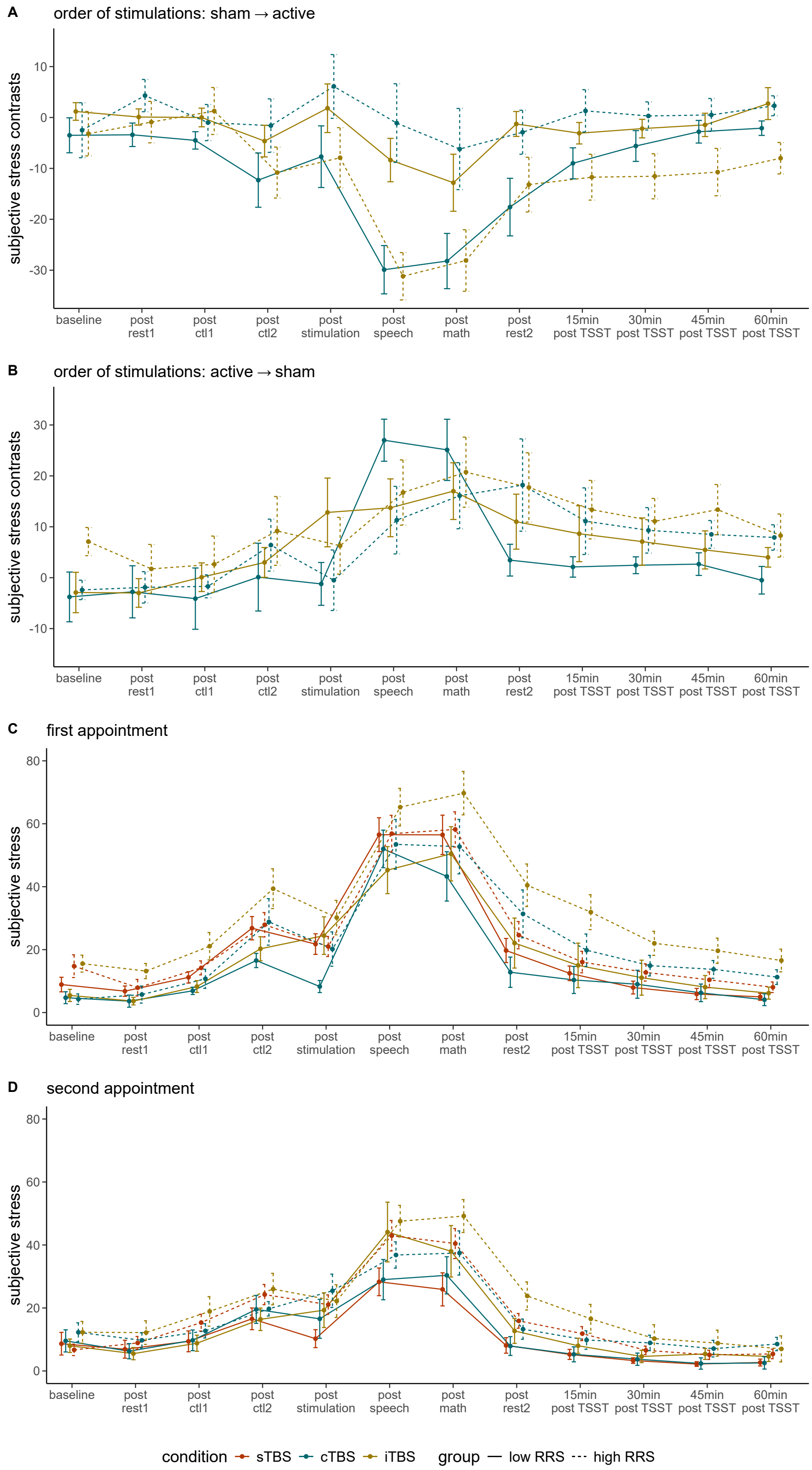


Figure 5.2

Line plot of the contrasts of subjective stress ratings dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of subjective stress ratings dependent on the appointment (C = first appointment; d = second appointment). rest = resting-state measurement, ctl1 = control task 1, ctl2 = control task 2, TSST = Trier Social Stress Test, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, 15 min = 15 min after the TSST, RRS = Ruminative Response Scale. Please note that the effect of the order of stimulation conditions is visually depicted within the plots of the different appointments (first appointment: sTBS = participants with order of stimulation conditions sham → active; iTBS and cTBS = participants with order of stimulation conditions active → sham; second appointment: vice versa). Error bars indicate 1 standard error of the mean.

7.235, $p < .05$, $\eta_p^2 = .153$. The opposite was true for participants having received sham stimulation first: Differences between the active and passive stimulation decrease and decrease more for high ruminators, $F(1, 35) = 3.880$, $p = .057$, $\eta_p^2 = .100$. However, after adjusting for multiple comparisons, Benjamini-Hochberg-corrected post-hoc tests showed no significant differences between low and high ruminators at any time point.

State rumination raw data. After checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded four data points and three due to missing data, specifically two participants' data from the first and five participants' data from the second appointment, for the following analysis. Fitting the rmANOVA on the raw data, we observed a significant interaction of time and RRS group (AP1: $F(2.762, 220.970) = 6.559$, $p < .001$, $\eta_p^2 = .076$; AP2: $F(3, 231) = 8.288$, $p < .001$, $\eta_p^2 = .097$) with quadratic polynomial contrasts, each indicating higher increases in state rumination in high ruminators (AP1: $F(1, 80) = 4.093$, $p < .05$, $\eta_p^2 = .049$; AP2: $F(1, 77) = 6.870$, $p < .05$, $\eta_p^2 = .082$). Benjamini-Hochberg-corrected pairwise comparisons yielded significant differences between low and high ruminators at any given time point ($p < .05$) (see figure 5.3C-F).

State rumination planned contrasts. We observed no significant differences in state rumination ratings after the second resting-state (i.e., following the stress induction) between sTBS and cTBS, neither for low nor high ruminators during appointment 1 or 2 (all p's > .117). When comparing sTBS and iTBS, we observed significantly higher state rumination following sTBS ($M = 1.40$, $SD = 0.35$) compared to iTBS ($M = 1.21$, $SD = 0.12$) for low ruminators at their second appointment, $t(27.069) = 2.305$, $p < .05$, $d = 0.661$ and marginally significant differences for low ruminators at their first appointment, $t(13.232) = -1.480$, $p = .081$, $d = -0.657$, this time, however, higher state rumination following iTBS ($M = 1.66$, $SD = 0.58$) compared to sTBS ($M = 1.38$, $SD = 0.32$).

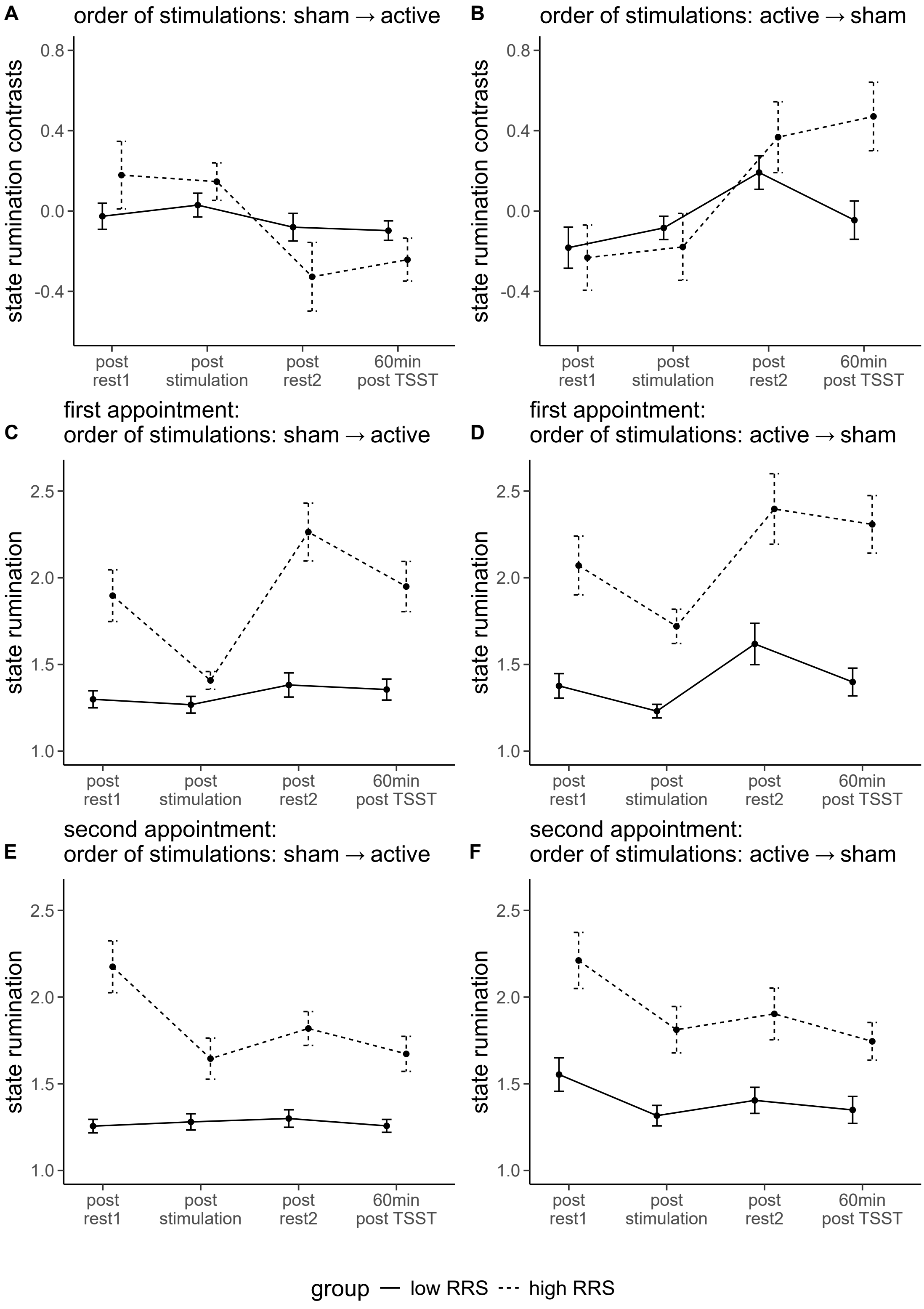


Figure 5.3
Line plot of the contrasts of state rumination ratings dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of state rumination ratings dependent on order of conditions and appointment (C = first appointment sham stimulation; d = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). rest = resting-state measurement, 60min post TSST = 60min after the Trier Social Stress Test, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.

State rumination reliable change. Finally, we calculated Reliable Change Indices (RCIs) by comparing state rumination ratings from before the stress induction (rest1) to after the stress induction (rest2), separately for each appointment and RRS group. In case of both appointments, most participants exhibited no reliable change in state rumination (see table 5.4). Interestingly, about 43 % of high ruminators showed reliable increases at the first appointment and only 2 % at the second appointment. The same pattern was observed for low ruminators. Further, while only three low ruminators and five high ruminators showed significant decreases in state rumination ratings due to the stress induction at the first appointment, at appointment 2, this was the case in three low and 16 high ruminators (for an illustration of RCI see supplementary material S9).

	low ruminators (n = 44)	high ruminators (n = 44)	test-statistic
appointment 1:			$\chi^2(2) = 6.433, p < .05$
reliable decrease	3 (6.98%)	5 (11.37%)	
no reliable change	31 (72.09%)	20 (45.45%)	
reliable increase	9 (20.93%)	19 (43.18%)	
appointment 2:			$\chi^2(2) = 11.410, p < .001$
reliable decrease	3 (6.81%)	16 (36.37%)	
no reliable change	39 (88.64%)	27 (61.36%)	
reliable increase	2 (4.55%)	1 (2.27%)	

Table 5.4
Absolute and relative frequencies of reliable change. Percentages refer to the relative frequencies in the corresponding subsample (low or high ruminators) and the test-statistic indicated χ^2*-tests comparing the distribution of RCI-categories in low and high ruminators at the respective appointment. Please note that the data of one low ruminator at the first appointment was missing.*

Negative affect contrasts. According to their Mahalanobis distances ($p < .001$), we excluded four multivariate outliers and nine due to missing data. Fitting the rmANOVA, we observed a significant interaction of time and order of stimulation conditions, $F(2.750, 184.249) = 21.689$, $p < .001$, $\eta_p^2 = .245$, and a significant main effect of order of stimulation conditions, $F(1, 67) = 10.054$, $p < .01$, $\eta_p^2 = .130$. Consequently, we fitted the rmANOVA separately for the different stimulation conditions and observed a marginally significant three-way interaction of time, group and stimulation condition for participants having received active stimulation first, $F(3, 99) = 2.194$, $p = .093$, $\eta_p^2 = .062$ (see figure 5.4B). Regardless of order of stimulations, we observed a significant main effect of time (sham → active: $F(2.401, 81.643) = 8.893$, $p < .001$, $\eta_p^2 = .207$; active → sham: $F(3, 99) = 19.085$, $p < .001$, $\eta_p^2 = .366$) as well as a (marginally) significant main effect of the intercept (i.e., a significant difference between active vs. passive stimulation; sham → active: $F(1, 34) = 3.293$, $p = .078$, $\eta_p^2 = .088$; active → sham: $F(1, 33) = 7.293$, $p < .05$, $\eta_p^2 = .181$). Further investigating the main effect of time using polynomial contrasts revealed a linear time course in case participants received sham first (see figure 5.4A), $F(1, 34) = 11.498$, $p < .01$, $\eta_p^2 = .253$, which was reflected by comparable negative affect prior to the TBS and more pronounced decreases in negative affect in case of sham stimulation compared to active stimulation afterwards. We further observed a quadratic time course in case participants received active stimulation first (see figure 5.4B), $F(1, 33) = 10.656$, $p < .01$, $\eta_p^2 = .244$, which was reflected by comparable negative affect prior to the TBS and more pronounced decreases in negative affect in case of the active stimulation compared to sham stimulation afterwards.

Negative affect raw data. After checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded nine data points and nine due to missing data, specifically ten participants' data from the first and eight participants' data from the second appointment, for the following analysis. Investigating the raw data, we observed a significant interaction between time and RRS group, but this was only evident in the second appointment, $F(2.268, 167.838) = 3.638$, $p < .05$, $\eta_p^2 = .047$, with a linear polynomial contrast, $F(1, 74) = 8.963$, $p < .01$, $\eta_p^2 = .108$. Benjamini-Hochberg-corrected pairwise comparisons yielded significant differences between low and high ruminators at any given time point ($p < .05$). In both rmANOVAs, the interaction of RRS group and stimulation condition yielded (marginal) significance (AP1: $F(2, 72) = 2.386$, $p = .099$, $\eta_p^2 = .062$; AP2: $F(2, 76) = 3.991$, $p < .05$, $\eta_p^2 = .095$). Benjamini-Hochberg-corrected pairwise comparisons yielded significantly lower negative affect following sTBS (*M* = 15.34, *SE* = 0.62) compared with iTBS (*M* = 18.93, *SE* = 0.88) in high ruminators at AP2 ($p < .05$). We further observed significant (lower-order) main effects of RRS group (AP1: $F(1, 72) = 22.213$, $p < .001$, $\eta_p^2 = .236$; AP2: $F(1, 74) = 34.981$, $p < .001$, $\eta_p^2 = .321$) and time (AP1: $F(1.887, 135.853) = 52.728$, $p < .001$, $\eta_p^2 = .423$; AP2: $F(2.269, 167.838) = 33.000$, $p < .001$, $\eta_p^2 = .308$). Polynomial contrasts yielded quadratic time courses (AP1: $F(1, 72) = 51.589$, $p < .091$, $\eta_p^2 = .417$; AP2: $F(1, 74) = 44.573$, $p < .001$, $\eta_p^2 = .376$).

Negative affect planned contrasts. Investigating the planned contrasts of negative affect directly after the TSST, we observed significantly higher negative affect ratings following iTBS (*M* = 2.15, *SD* = 0.73) compared with sTBS (*M* = 1.63, *SD* = 0.44) but only in high ruminators at their second appointment, $t(28) = -2.463$, $p < .05$, $d = -0.954$.

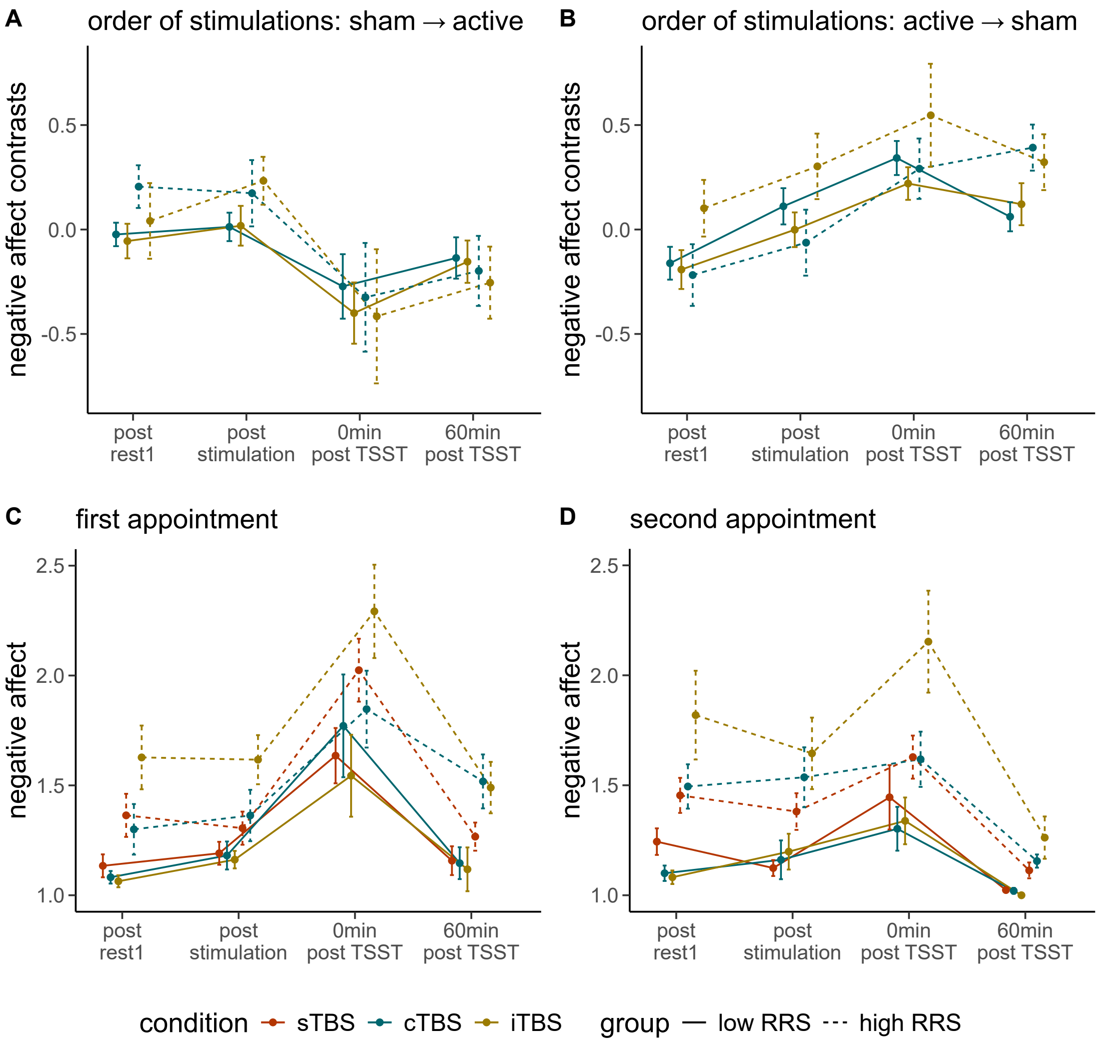


Figure 5.4
Line plot of the contrasts of negative affect ratings dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of negative affect ratings dependent on the appointment (C = first appointment; d = second appointment). rest = resting-state measurement, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, 0min post TSST = 0min after the Trier Social Stress Test, RRS = Ruminative Response Scale. Please note that the effect of the order of stimulation conditions is visually depicted within the plots of the different appointments (first appointment: sTBS = participants with order of stimulation conditions sham → active; iTBS and cTBS = participants with order of stimulation conditions active → sham; second appointment: vice versa). Error bars indicate 1 standard error of the mean.

5.4.4 Physiological measures

Cortical oxygenation overall t-tests. We first performed paired t-tests to compare cortical oxygenation in each channel during the arithmetic task of the TSST, contrasting the levels after active stimulation with those following sham stimulation (active vs. sham) within subjects across all participants. Significant channels in the cTBS condition are channel 9 (left VLPFC), 22, 34, 36 (SAC), 41 and 42. Significant channels in the iTBS condition are channel 7 (left VLPFC), 33 and 34 (see figure 5.5).

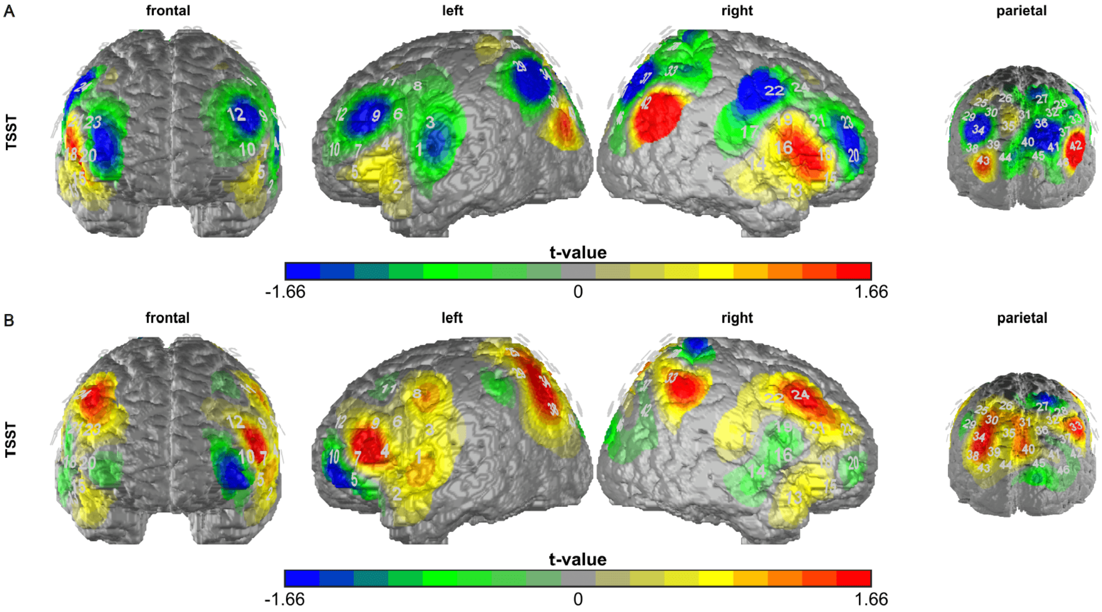


Figure 5.5
Plots of the t-values of the paired t-tests in each channel testing the active stimulation condition against the sham stimulation in each channel dependent on the stimulation condition A = cTBS, B = iTBS, TSST = arithmetic task of the TSST. The figure legend was scaled so that channels showing a significant t-value are displayed in blue (≤-1.66) or red (≥1.66). Significant channels in the cTBS condition are channel 9 (left VLPFC), 22, 34, 36 (SAC), 41 and 42. Significant channels in the iTBS condition are channel 7 (left VLPFC), 33 and 34.

Cortical oxygenation contrasts single channel. According to Mahalanobis distances ($p < .001$), there were no multivariate outliers but three participants with missing data. Fitting the rmANOVA on the single channel level where the TBS was applied (channel 12/ electrode position F3), we observed no significant effects ($p > .112$), only a significant quadratic polynomial contrast of the interaction of time and group, $F(1, 77) = 4.670$, $p < .05$, $\eta_p^2 = .057$. Descriptively, contrasts during control task 1 and the arithmetic task were comparable between low and high ruminators, while during control task 2, the low ruminators exhibited positive contrasts (i.e., higher activation during the appointment with active stimulation) compared to negative contrasts in high ruminators (i.e., higher activation during the appointment with sham stimulation).

Cortical oxygenation contrasts ROIs. According to Mahalanobis distances (p < .001), there were no multivariate outliers but three participants with missing data. Fitting the rmMANOVA using the ROIs (left and right DLPFC, left and right VLPFC and SAC) as DVs, we observed a significant four-way interaction of time, group, stimulation condition and order of stimulation conditions, F(10, 302) = 3.160, Pillai's trace = 0.189, p < .001, η_p^2 = .095.

We then fitted separate rmMANOVAs dependent on the order of stimulation conditions. This resulted in a significant three-way interaction of time, group and stimulation condition but only in the case participants received active stimulation first, F(10, 146) = 2.733, Pillai's trace = 0.315, p < .01, η_p^2 = .158 (for brainmaps see supplementary material S10). Benjamini-Hochberg-corrected univariate tests of this three-way interaction of time, group and stimulation condition yielded significance (p < .05) only in the left VLPFC, F(2, 76) = 7.327, p < .01, η_p^2 = .162.

Polynomial contrasts of the three-way interaction of time, group and stimulation condition revealed a linear contrast in the left VLPFC, F(1, 38) = 13.615, p < .001, η_p^2 = .264. This was reflected by linear increases in high ruminators following cTBS and low ruminators following iTBS and decreases in high ruminators following iTBS and low ruminators following cTBS.

Benjamini-Hochberg-corrected pairwise comparisons of the three-way interaction of time, group and stimulation condition in the left VLPFC yielded no significant differences in the contrasts (p < .05) between low or high ruminators at any time point, nor between the stimulation conditions at any time point. Without correction, we observed significantly lower contrasts for low ruminators (M = -0.43, SD = 0.50) compared to high ruminators after having received cTBS (M = 0.25, SD = 0.66) during the arithmetic task of the TSST, t(19) = -2.700, p < .01, d = -1.18.

Without correction, we further observed significantly lower contrasts during the arithmetic task of the TSST for low ruminators having received cTBS (M = -0.43, SD = 0.50) compared to low ruminators having received iTBS (M = 0.34, SD = 0.83), t(20) = -2.647, p < .01, d = -1.129, as well as marginally significantly higher contrasts during control task 1 for low ruminators having received cTBS (M = 0.25, SD = 0.73) compared with low ruminators having received iTBS (M = -0.34, SD = 0.68), t(20) = 1.963, p < .05, d = 0.837.

When we only investigated polynomial contrasts, we further observed a significant three-way interaction of time, group and stimulation condition for participants having received active stimulation first in the left DLPFC (quadratic contrast: $F(1, 38) = 4.274$, $p < .05$, $\eta_p^2 = .101$) as well as the right DLPFC (linear contrast: $F(1, 38) = 5.404$, $p < .05$, $\eta_p^2 = .124$).

In case of the left DLPFC, this effect seemed to be primarily driven by differences between low and high ruminators (positive contrasts in low and negative contrasts in high ruminators) following iTBS, as well as between the stimulation conditions (positive contrasts in case of iTBS and negative contrasts in case of cTBS) but only in low ruminators during control task 2, i.e., before the stimulation.

In the right DLPFC, on the other hand, the effect seemed to be driven by differences during the arithmetic task of the TSST, i.e., after the TBS. More specifically, we observed positive contrasts in high ruminators and negative contrasts in low ruminators following cTBS. We further observed positive contrasts during the arithmetic task following iTBS compared to negative contrasts following cTBS but only in the case of low ruminators.

Interestingly, we further observed a significant three-way interaction of time, group and stimulation condition for participants having received sham stimulation first in the right DLPFC (linear contrast: $F(1, 39) = 7.529$, $p < .01$, $\eta_p^2 = .162$) and the right VLPFC (linear contrast: $F(1, 39) = 4.195$, $p < .05$, $\eta_p^2 = .097$). In the right DLPFC during the arithmetic task of the TSST, we observed positive contrasts in low and negative contrasts in high ruminators following cTBS. In the right VLPFC during the arithmetic task of the TSST, we observed positive contrasts following cTBS and negative contrasts following iTBS but only in low ruminators.

Cortical oxygenation raw data ROIs. According to Mahalanobis distances ($p < .001$), there was one multivariate outlier and three participants with missing data (2 of AP1 and 1 of AP2). Fitting the rmMANOVA separately for each appointment on the raw data, we observed a significant main effect of time for the first and second appointment (AP1: $F(10, 314) = 5.984$, Pillai's trace = 0.320, $p < .001$, $\eta_p^2 = .160$; AP2: $F(10, 314) = 6.373$, Pillai's trace = 0.337, $p < .001$, $\eta_p^2 = .169$).

Benjamini-Hochberg-corrected univariate tests revealed a significant main effect of time for all ROIs at the first appointment, and for the bilateral DLPFC, left VLPFC, and SAC at the second appointment ($p < .05$). Polynomial contrasts revealed a linear time course during AP1 in the case of the left DLPFC, $F(1, 80) = 24.880$, $p < .001$, $\eta_p^2 = .237$, left

VLPFC, $F(1, 80) = 9.605, p < .01, \eta_p^2 = .107$, right DLPFC, $F(1, 80) = 18.125, p < .001$, $\eta_p^2 = .185$, and SAC, $F(1, 80) = 57.247, p < .001, \eta_p^2 = .417$, and a quadratic time course in case of the right VLPFC, $F(1, 80) = 6.474, p < .05, \eta_p^2 = .075$.

At the second appointment, we observed a linear time course in the left DLPFC, $F(1, 80) = 17.058, p < .001, \eta_p^2 = .176$, left VLPFC, $F(1, 80) = 12.541, p < .001, \eta_p^2 = .136$, SAC, $F(1, 80) = 40.647, p < .001, \eta_p^2 = .337$, and a quadratic time course in the right DLPFC, $F(1, 80) = 11.548, p < .01, \eta_p^2 = .126$.

No significant between-subjects effects were observed.

Investigating the polynomial contrasts, we further found a quadratic contrast of the three-way interaction of time, stimulation condition and RRS group in the case of the left DLPFC at AP1, $F(2, 80) = 3.626, p < .05, \eta_p^2 = 0.83$. Descriptively, this effect was driven by higher cortical oxygenation in low ruminators compared to high ruminators during control task 2 (i.e. previous to the TBS) but comparable activation during control task 1 and the arithmetic task of the TSST. Investigating the polynomial contrasts, we further found a linear contrast of the three-way interaction of time, stimulation condition and RRS group in the case of the right DLPFC at AP2, $F(2, 80) = 4.582, p < .05, \eta_p^2 = .103$. Descriptively, this effect seemed to be driven by differences between low and high ruminators during control task 1 having received cTBS (higher cortical oxygenation in high ruminators) (i.e., previous to the TBS).

Lastly, we observed a significant linear contrast of the interaction of time and RRS group in case of the left VLPFC, $F(1, 80) = 9.014, p < .01, \eta_p^2 = .101$, and right VLPFC at AP2, $F(1, 80) = 4.362, p < .05, \eta_p^2 = .052$. Descriptively, the interaction of time and RRS group in the right VLPFC was reflected by higher cortical oxygenation in case of the high ruminators during control task 1, comparable cortical oxygenation during control task 2 and higher cortical oxygenation during the arithmetic task of the TSST in case of low ruminators. In case of the left VLPFC, this interaction was primarily driven by significantly higher cortical oxygenation in high ruminators during control task 1.

Cortical oxygenation planned contrasts. Lastly, we examined potential differences in cortical oxygenation in the left DLPFC during the arithmetic task of the TSST (i.e., following TBS) based on the stimulation condition, separately for low and high ruminators, and for each appointment. These planned contrasts yielded no significant differences (all p's > .157) (for an illustration of the time series in the left DLPFC; see figure 5.6).

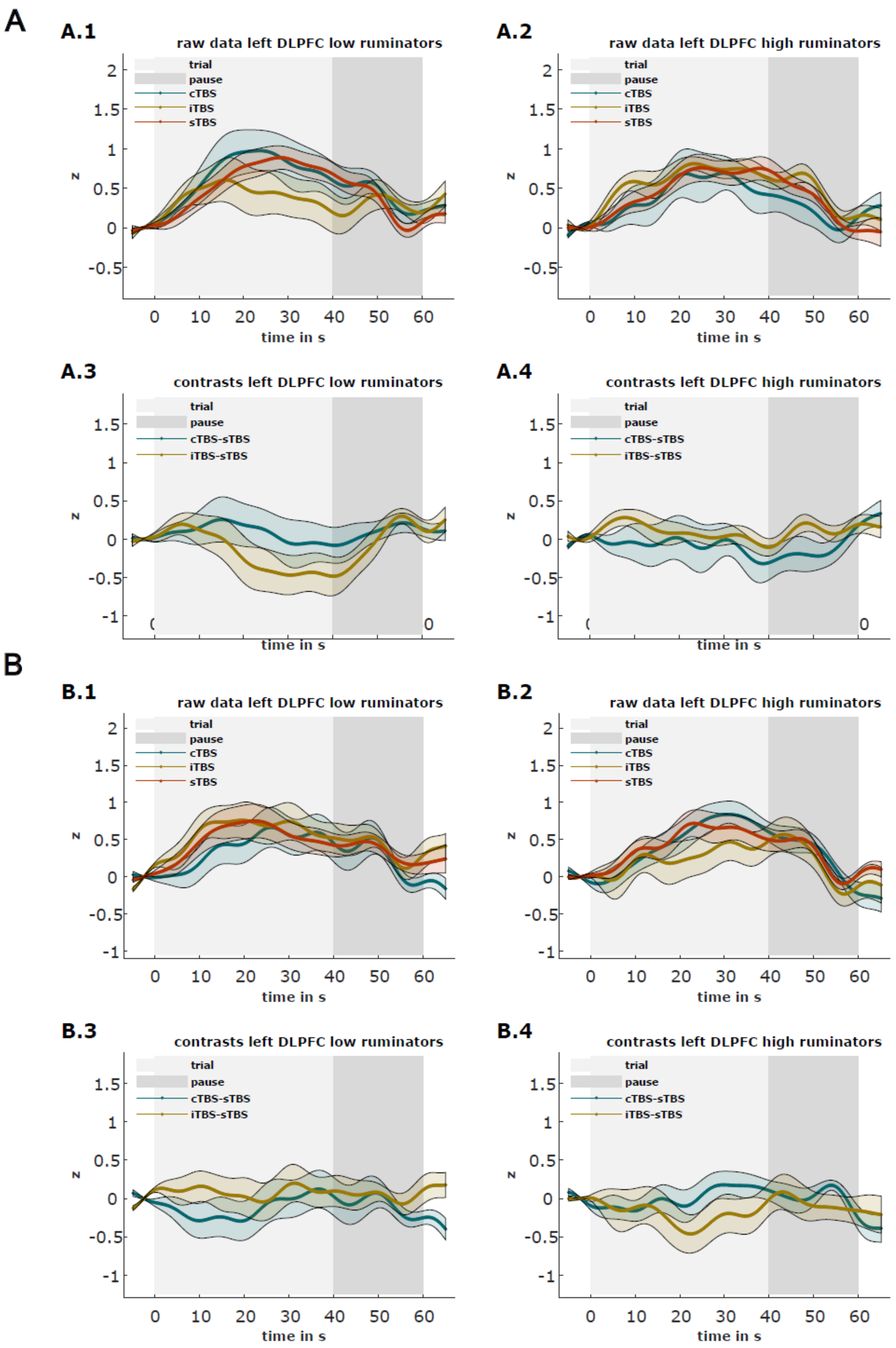


Figure 5.6

Illustration of the z-standardized hemodynamic responses during the arithmetic task of the TSST in the left DLPFC in low and high ruminators depending on the TBS-condition at the first appointment (A) and the second appointment (B). A.1, A.2, B.1, and B.2 illustrate the raw data, while A.3, A.4, B.3 and B.4 illustrate the contrasts (cTBS minus sTBS and iTBS minus sTBS). The light shading marks the 40 s trial and the dark shading the 20 s pause to allow the hemodynamic response to recover. Shadings around the hemodynamic curves reflect standard errors of the mean. The baseline includes the 5 s before each trial; 0 s on the x-axis marks the beginning of the trial. See supplementary material S11 for the time series of the other ROIs.

5.4.5 Exploratory analysis: Impact of expectancy effects

When we investigated the impact of expectancy effects, we observed no significant main effects or interaction with time in the case of subjective stress or cortical oxygenation. For state rumination, there was a significant interaction with time at the first appointment, $F(2.851, 205.272) = 3.129$, $p < .05$, $\eta_p^2 = .042$. In case of negative affect, we observed a marginally significant interaction of expectancy effects and time at the first appointment, $F(1.981, 128.763) = 2.695$, $p = .072$, $\eta_p^2 = .040$, and a significant main effect at the second appointment, $F(1, 75) = 4.757$, $p < .05$, $\eta_p^2 = .060$.

5.5 Discussion

This study aimed to investigate the impact of modulating left DLPFC activity on the stress-rumination link using sham-controlled TBS. For this purpose, a total of 88 healthy participants comprising 44 low and 44 high trait ruminators underwent a neurostimulation prior to a social stress induction using the Trier Social Stress Test (TSST). At one appointment, participants either received cTBS (i.e., inhibitory) or iTBS (i.e., excitatory), and the other one 5 weeks apart sTBS (sham), with the order randomized and balanced between subjects. Throughout the experiment, we assessed cortical oxygenation using fNIRS, heart rate, and psychological measures including subjective stress, state rumination, and positive and negative affect. First, all manipulation checks concerning the blinding, stress induction and stratification were successfully met: All study subsamples were comparable regarding their respective distribution of demographic and clinical variables. Further, the blinding of the TBS seemed to be successful as participants were unable to identify real from sham stimulation. Moreover, the stress induction using the TSST was successful as we observed significant increases in subjective stress, heart rates and negative affect due to the stress induction, at both, the first as well as second appointments, replicating findings of previous studies proposing the TSST as a highly ecologically valid stressor and the "gold-standard" for the investigation of the psychophysiological stress response (Allen et al., 2014).

When examining the effects of TBS on the dependent variables, we observed a highly complex interplay between time-dependent changes, group differences between low and high ruminators, TBS effects, habituation effects, and the order in which stimulation conditions were administered (i.e., whether participants received active stimulation in their first session and sham in their second, or vice versa). We acknowledge that the analyses were relatively complex and that including stimulation order is not common practice. However, given the strong habituation effects observed across nearly all dependent variables, we deemed this factor crucial. Stress responses were most pronounced during the first exposure, likely due to novelty effects, potentially masking small TBS effects. Initial rmANOVAs without stimulation order yielded predominantly null results, leading us to include this factor to better understand how habituation interacts with stimulation effects on stress reactivity. The importance of accounting for stimulation order becomes particularly evident in the analysis of subjective stress responses. For instance, we found a significant three-way interaction of time, group, and stimulation condition, but only in the sham → active sequence. This interaction was primarily driven by high ruminators in the iTBS-arm, who reported higher stress during stress induction when they received sham stimulation at the first session, compared with high ruminators in the cTBS-arm, who reported lower stress when receiving sham at the first session (i.e., sham with the duration of cTBS). At the second appointment, overall stress responses were lower; the iTBS group showed a more pronounced reduction, while the cTBS group exhibited non-significant changes. Planned contrasts comparing post-stress stress levels revealed a significant difference between iTBS and sTBS, although in an unexpected direction: stress levels were higher following iTBS compared to sTBS, particularly at the first appointment and most pronounced in high ruminators. These findings align intuitively with the results of the negative affect analysis. While overall analyses did not reveal significant TBS effects, planned contrasts comparing post-stress negative affect indicated higher negative affect following iTBS compared to sTBS, again in high ruminators but only at the second appointment. These findings suggest that the effects are highly complex, requiring large sample sizes to detect small effects within such intricate experimental designs. Similarly, for state rumination, overall analyses did not indicate a significant TBS effect, but planned contrasts at the second appointment revealed a pattern consistent with our hypotheses: low ruminators in the sTBS condition reported higher state rumination post-stress (rest2) compared to those in the iTBS condition, aligning with the expected excitatory effects of iTBS. Please note, however, that increases in state rumination were generally low and only in case of the first appointment strong increases in state rumination were found in the high ruminators, reflected by reliable change indices. We did not find any impact of the stimulation on heart rate, positive affect and performance during the TSST.

The major advantage of the current study setup compared to the previous studies on the impact of TBS on stress-reactive rumination (De Smet et al., 2024; De Witte et al., 2020) is the additional assessment of brain activation prior to and after the stimulation. Regarding the results of cortical oxygenation, we could replicate the effect of a stress-induced increase in cortical oxygenation in prefrontal areas which might be interpreted as a successful stress induction owing to the need for increased resources. We then initially focused on the single fNIRS channel corresponding to electrode position F3, where TBS was applied. This analysis did not reveal any significant effects of TBS. Expanding the analysis by using the ROI, including the mean signal from the three channels covering the left DLPFC in the repeated-measures MANOVA, we found no overall significant differences in the left DLPFC between stimulation conditions during the TSST — only differences between low and high ruminators previous to the TBS. Additionally, we observed a significant influence of stimulation order: Specifically, a significant three-way interaction of time, group, and stimulation condition emerged in the left VLPFC, but only in participants who received active stimulation at their first appointment and sham at their second. However, given the complexity of this analysis and the small effect sizes, the following results reached significance only without correction for multiple comparisons: Interestingly, in the left VLPFC, we found stimulation-related differences in line with our hypotheses, but exclusively in low ruminators and only when stimulation was administered in the active → sham order. More precisely, we observed negative contrasts in cortical oxygenation following cTBS (i.e., greater activation after sham compared to active stimulation, indicating an inhibitory effect of cTBS) and positive contrasts following iTBS (i.e., lower activation after sham compared to active stimulation, suggesting an excitatory effect of iTBS). A similar pattern was found in the right DLPFC when polynomial contrasts were examined. Interestingly, however, the right VLPFC exhibited the opposite pattern in the sham → active stimulation order —meaning that in low ruminators, cTBS had an excitatory effect, while iTBS had an inhibitory effect during the arithmetic task of the TSST. What is particularly interesting is that we did not observe the well-documented prefrontal hypoactivation under stress in the left DLPFC, which has been repeatedly found for patients with depression (Pizzagalli & Roberts, 2022) and has also been observed to be associated with trait rumination (Int-Veen, Fallgatter, Ehlis, & Rosenbaum, 2023), which is why we expected to replicate these findings in high ruminators at least in the sTBS condition.

One explanation for finding significant effects of the stimulation in some but not all measures may be differences in noise and effect sizes in the corresponding measures. Because of the distinct underlying physiological mechanisms and measurement methods, it seems reasonable to assume diverse measurement errors and reliability. Please keep in mind that these might also be differently affected by the stimulation itself, which is why ultimately a huge variance in actual data, as well as errors, might arise which is not sufficiently explained by the current analysis.

There are several possible interpretations of these inconclusive TBS effects beyond the already mentioned different measurement errors of physiological, neurophysiological and behavioral data. On the one hand, these findings may result from a potential diminishing of the TBS effect in the case of the very pronounced hemodynamic response induced by using an experimental stress induction like the TSST. This is partly due to the TSST being a very potent stressor evoking strong subjective and physiological responses (Allen et al., 2014) and on the other hand due to the block design of the study (the control tasks as well as the arithmetic task of the TSST) where multiple hemodynamic response functions linearly add up. Another interpretation of the absence or inconsistency of TBS effects could be the timing of the stimulation within the experimental procedure. While the duration of TBS effects seems to differ systematically depending on the protocol (Lowe, Manocchio, Safati, & Hall, 2018), we aimed to minimize the time between the end of the TBS and the stress induction. This is also why we did not perform the stimulation before the control tasks. As a consequence, approximately 11 min (*SD* = 6 min) passed between the end of the TBS and the beginning of the TSST. With a duration of approximately 15 min of the TSST, a 7 min resting-state measurement and instructions about the further procedure, the assessment of stress-reactive state rumination was approximately 50 min (*SD* = 8 min) after the end of the TBS. This rather long time passing might also have an impact on the magnitude of the TBS effects and the potential vanishing of significance. Speaking of the timing of the TBS, one further limitation of the current study setup is that we were not able to measure cortical oxygenation during the stimulation itself (Kozel et al., 2009). It should also be noted that the timing of the fNIRS measurement and the functioning of the continuous-wave fNIRS device may have additionally contributed to the inadequate representation of the TBS effects; only relative (as opposed to absolute) changes in hemoglobin concentration over time, relative to a baseline measurement taken at the beginning of each measurement segment, are recorded. It is likely that during the fNIRS measurement conducted during stress induction, the baseline was influenced by the preceding TBS, which may have artificially reset the various TBS conditions to zero. Therefore, only differences between the TBS conditions can become significant if brain activity during the TSST continues to be inhibited or increased. Recent studies with special hardware are nowadays able to assess fNIRS simultaneously with the stimulation which offers the chance for online feedback and as a consequence new insights regarding TBS-induced changes in cortical oxygenation.

Finally, another important point of discussion is coil positioning, which may not have been optimal when using the electrode position F3 instead of a neuronavigation system. However, it is important to note that structural fMRI data were not available for this study, limiting the feasibility of this approach. To account for potential small deviations in coil placement, we reanalyzed the data using both the single-channel covering F3 and a merged signal from the three channels of the left DLPFC. These additional analyses did not yield any systematically different findings. Furthermore, the stimulation location and target of the TBS itself might also be suboptimal as suggested by a recent meta-analysis (Moses et al., 2023) on the effects of neuromodulation of the cognitive and emotional stress response in healthy individuals. Following this meta-analysis the predominant share of studies found no significant effects of NIBS on emotional reactivity and salivary cortisol following a stress induction. Furthermore, although "all of the studies used a between-subjects design, there were no other common design features and the wide-ranging approaches prohibit clear conclusions from these studies about potential optimal targets for modulating the effects of stress on working memory." (Moses et al., 2023, page 17). Surely, the field of NIBS is still evolving and further studies are needed to draw a more conclusive pattern of findings; however, first evidence suggests the VLPFC as a key structure in cognitive reappraisal circuits "may be the best-supported target to affect stress modulation of emotional responses" (Moses et al., 2023, page 16). We plan to conduct a study with the same study setup, but this time however using the right VLPFC as a target for TBS (Int-Veen, Eisenlohr, et al., n.d.). With the knowledge of these findings, eventually, we will be able to gain more trust in any of the aforementioned interpretations of the current results.

In an exploratory analysis, we further investigated the impact of expectancy effects. We first analyzed whether, dependent on the stimulation protocol, participants believed that the stimulation had an impact on their performance (better or worse) or not. Results indicated no significant effect of the stimulation condition: Generally, irrespective of the TBS, about half of all participants thought that the TBS had no impact on their performance, while about 20 % said they thought the stimulation made them worse and 20-30 % thought the stimulation made them better. We then investigated whether participants believed that the stimulation made them better or worse at the task and whether this predicted the outcome variables. While we did not find a significant impact of expectancy effects on subjective stress and cortical oxygenation. State rumination and negative affect seemed to be somewhat influenced by the anticipated effects of TBS on performance during the TSST. Please note that we abstained from a further exploratory analysis, because expectations were not uniformly distributed, were not manipulated, and the sample size would be too small for conclusive interpretation when the analysis is performed separately for each stimulation condition, RRS group and appointment. Nevertheless, the aforementioned results hint at a potentially important association of external or internal attribution and subjective self-assessments which should be considered in future TBS-research. Another point to consider in the context of potential impacts on expectancy effects, is that we did observe a significant impact of the order of stimulation conditions (active → sham vs. sham → active) in almost all variables. The repeated measures design is likely susceptible to expectancy effects; however, we chose this setup in order to be able to effectively reduce the impact of between-person error and increase statistical power to detect smaller effect sizes. We further noted that with the study design, state rumination increases were generally low after the (TBS and) TSST (AP1: $F(1, 85) = 16.188$, $p < .001$, $\eta_p^2 = .160$; AP2: $F(1, 82) = 15.855$, $p < .001$, $\eta_p^2 = .162$) compared with previous studies with similar study setups but no TBS, which may underscore the role of expectancy effects especially in the development of rumination (see supplementary material S12 for a comparison of state rumination in the current and previous studies). However, the actual underlying causal mechanism remains unclear and has to be evaluated in future studies.

One last limitation should be noted concerning the interpretation of the current findings. After having recruited approximately half of all participants, we noticed substantial changes in the online assessment of the RRS, which was used to recruit a stratified sample of low and high trait ruminators, compared with their respective RRS scores of the paper-pencil version at the first appointment. Because of the suspected careless responses, we changed the recruitment procedure by including a second online assessment of the RRS as well as specific rules for excluding participants with changes in RRS scores (for details and analysis of predictors of changes in RRS scores, see Int-Veen et al., 2024). These results call into question whether the recruited sample truly exhibits the assumed levels of trait rumination. Potentially, this could also explain why no pronounced prefrontal hypoactivation was found in high ruminators (Int-Veen et al., 2023; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018).

In future research, it will be essential to delve deeper into the complex effects of TBS to understand the underlying mechanisms. Specifically, the impact of the order of stimulation conditions and the strong effects of habituation on psychological variables need further investigation.

5.6 Supplementary Material Study 3

S1 Inclusion and exclusion criteria

Inclusion criteria:

- age between 18 and 50 years
- normal vision (or appropriate correction)
- right-handedness
- no metal in the skull / brain
- German as native language or very good knowledge of German

Exclusion criteria:

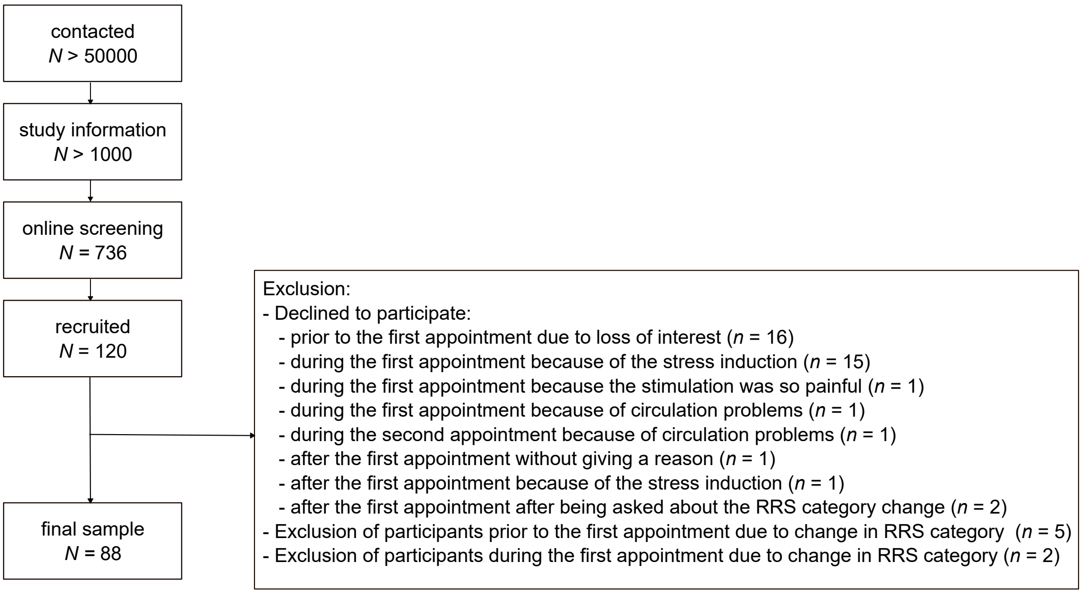
- diabetes mellitus
- renal insufficiency
- untreated hypertension
- history of traumatic brain injury
- cardiac arrhythmia
- acute substance abuse
- adrenal insufficiency
- any acute psychiatric or neurological disorder (including any anomalies in the SCID-Screening (Structured Clinical Interview; First et al., 2015)
- in case of women: pregnancy

S2 Information on the a priori power analysis

Currently, only one study exists that investigated the effects of TBS on state rumination increases through the TSST. In the study of De Witte et al. (2020), N = 40 participants were either stimulated with iTBS or sham TBS after the TSST was applied. Note that the study also used a within-subject design in which all participants received iTBS and sham after the TSST was conducted on two separate days. In their study, the authors found an increase of state rumination through the TSST and a marginally significant interaction between trait rumination and the TBS protocol on increases of state rumination (De Witte et al., 2020). The statistical parameters are given as B = -.32, t(36) = -1.891, p = .067. Thankfully, the authors sent us the data of this study and we therefore were able to compute the effect size of this effect directly from the data, which was η_p^2 = .107 (approx. d = .69, f = .34). However, it is important to note that the study didn't use a stratified sample of trait rumination or clinical participants. As a result, only 8 of 38 subjects fulfilled our previous criteria for high ruminators (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum, Thomas, et al., 2018). As we showed in our previous studies (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021, 2024; Rosenbaum, Thomas, et al., 2018) that state rumination increased in high trait ruminators/patients more than in low trait ruminators/healthy controls, we would assume that in stratified and clinical samples the above-noted buffering effect of the TBS protocol could be even higher, as the general reactivity of these samples in state rumination (under sham stimulation) is stronger than in the study of De Witte et al. (2020).

However, as seen in the study of De Witte et al. (2020), it is important to achieve high power as the effect was only marginally significant. Therefore, we aim to assess N = 80 subjects which allows to detect between-within subject interactions up to f = .15 for the effect of state rumination, as computed with G*Power 3.1.9.2 (with a power of 1-β = .95, α = .05. r = .7; between measurements, assessed on the basis of data from our previous studies). To compensate for data loss and drop-outs, we plan to collect an additional 10 % (n = 8) of participants to the computed sample size, resulting in N = 88 participants.

S3 Consort diagram



Exclusion:

- Declined to participate:
  - prior to the first appointment due to loss of interest (*n* = 16)
  - during the first appointment because of the stress induction (*n* = 15)
  - during the first appointment because the stimulation was so painful (*n* = 1)
  - during the first appointment because of circulation problems (*n* = 1)
  - during the second appointment because of circulation problems (*n* = 1)
  - after the first appointment without giving a reason (*n* = 1)
  - after the first appointment because of the stress induction (*n* = 1)
  - after the first appointment after being asked about the RRS category change (*n* = 2)
- Exclusion of participants prior to the first appointment due to change in RRS category (*n* = 5)
- Exclusion of participants during the first appointment due to change in RRS category (*n* = 2)

S4 Items of the state rumination questionnaire

Items of the state rumination questionnaire including adapted items from the Ruminative Response Scale (Nolen-Hoeksema & Morrow, 1991), Amsterdam Resting-State Questionnaire (Diaz et al., 2013) and the Perseverative Thinking Questionnaire (Ehring et al., 2011). Subjects were instructed to rate if the items were in line with their mental state during the last resting-state measurement.

item	German translation	English translation
1	Ich dachte immer wieder an meine Probleme.	I repeatedly thought about my problems.
2	Ich verharrte im Denken an Dinge, die mich beunruhigen.	I kept thinking about things that bother me.
3	Meine Gedanken wiederholten sich, ohne dass ich zu einer Lösung kam.	I dwelled on my thoughts without coming to a solution.
4	Ich verlor mich in meinen negativen Gedanken.	I got lost in my negative thoughts.
5	Ich konnte meine Gedanken nur mühsam festhalten.	I had difficulties holding on to my thoughts.
6	Ich konnte mich nicht von meinen negativen Gedanken lösen.	I could not let go of my negative thoughts.
7	Ich war bei der Sache.	I was present.
8	Ich dachte darüber nach, warum ich mich in bestimmten Situationen falsch verhalten habe.	I thought about why I acted wrong in certain situations.
9	Ich fragte mich, warum ich Probleme habe, die andere nicht haben.	I thought why I have problems other people don´t have.
10	Ich fragte mich, womit ich meine momentane Lebenssituation verdient habe.	I thought about whereby I deserved my current life situation.
11	Ich dachte darüber nach, warum ich die Dinge nicht besser in den Griff bekomme.	I thought why I can´t handle things better.
12	Ich dachte an all meine Defizite und Misserfolge, Macken und Fehler.	I thought about all my shortcomings, failings, faults, mistakes.
13	Ich konnte flexibel zwischen meinen Gedanken hin und her schalten.	I could switch between my thoughts flexibly.
14	Ich dachte an vergangene Situationen, die ich bereue.	I thought about past situations that I regret.
15	Ich machte mir Selbstvorwürfe.	I blamed myself.
16	Ich verlor mich in Gedanken an Vergangenes.	I got lost in thoughts about the past.
17	Ich war von meinen Problemen und Sorgen stark vereinnahmt.	I was consumed by my problems and worries.
18	Meine negativen Gedanken ließen mich nicht los.	I couldn´t let go of my negative thoughts.

S5 Illustration of the approximation of the TBS-induced electric field

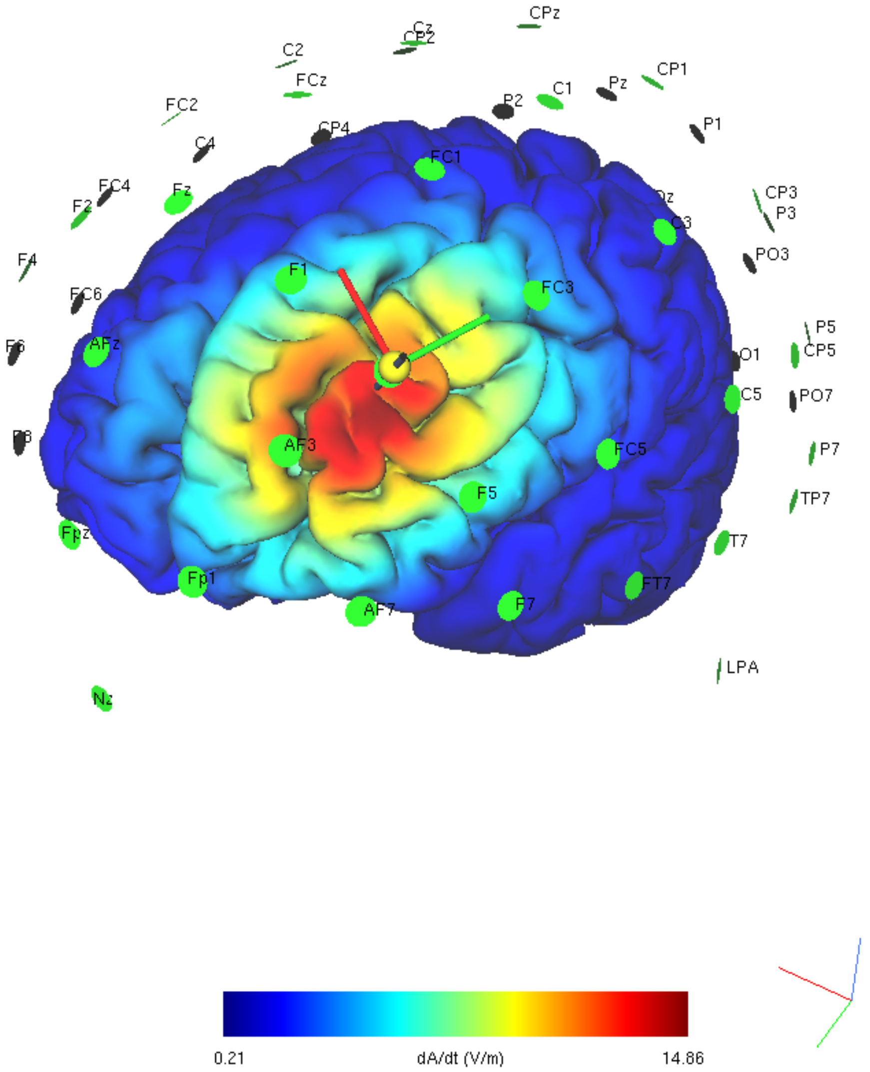
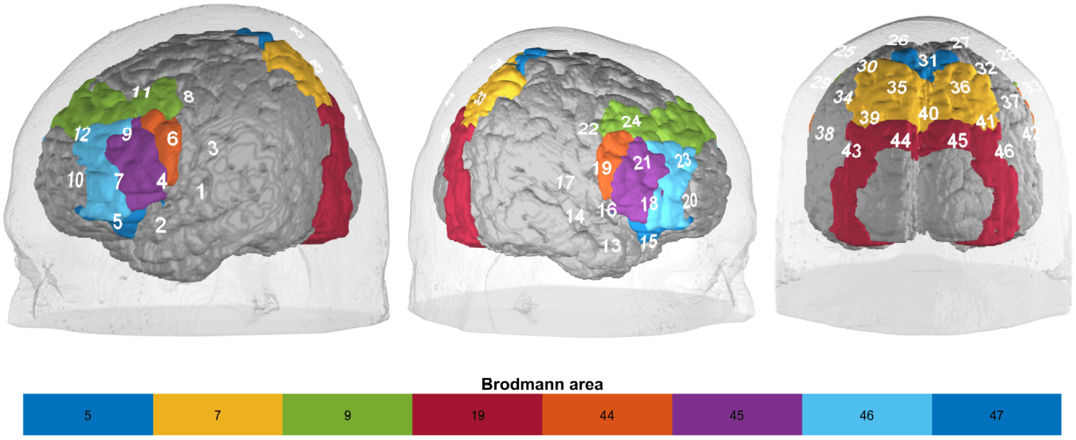


Figure S4

Approximation of the TBS-induced electric field. The coil (MagVenture Cool-B65 Active/Placebo coil) was positioned over the left DLPFC, corresponding to the F3 electrode according to the 10–20 EEG system. The color red indicates the strongest electric field. The y-axis in green indicates the direction of the coil handle. This plot was created using SimNIBS 4.1.0. (Thielscher, Antunes, & Saturnino, 2015).

S6 Placement of the three probesets



Please note that the corresponding numbers represent the channels (located midway between emitter and detector).

S7 Definition of Regions of Interest

ROI	channel
left VLPFC	7 9 6
right VLPFC	18 21 19
left DLPFC	10 12 11
right DLPFC	20 23 24
SAC	27 26 25 28 30 31 32 35 36

Note. VLPFC = Ventrolateral Prefrontal Cortex, DLPFC = Dorsolateral Prefrontal Cortex, SAC = Somatosensory Association Cortex. Please note that the TBS was applied over channel 12 which corresponds to F3.

S8 Results of positive affect, math performance and heart rate

Positive affect contrasts According to Mahalanobis distances (p < .001), there were no multivariate outliers for positive affect ratings but 9 participants with missing data. Fitting the rmANOVA, we observed a significant interaction of time and order of stimulation conditions, $F(3, 213) = 10.566$, $p < .001$, $\eta_p^2 = .130$, and a marginally significant interaction of time and group, $F(3, 213) = 2.156$, $p = .094$, $\eta_p^2 = .029$. We then fitted separate rmANOVAs dependent on the order of stimulation conditions. As a result, we observed only a significant main effect of time (sham $\rightarrow$ active: $F(2.577, 92.767) = 5.887$, $p < .01$, $\eta_p^2 = .141$, active $\rightarrow$ sham: $F(3, 105) = 4.764$, $p < .01$, $\eta_p^2 = .120$). Polynomial contrasts revealed a linear relationship in both cases but, again, in different directions depending on the order of stimulation conditions (active $\rightarrow$ sham: $F(1, 35) = 11.211$, $p < .01$, $\eta_p^2 = .243$; sham $\rightarrow$ active: $F(1, 36) = 10.481$, $p < .01$, $\eta_p^2 = .225$). For participants having received sham stimulation first, the differences between active and sham stimulation increased over the course of the experiment while they decreased in case participants received active stimulation first (see figure S7.1).

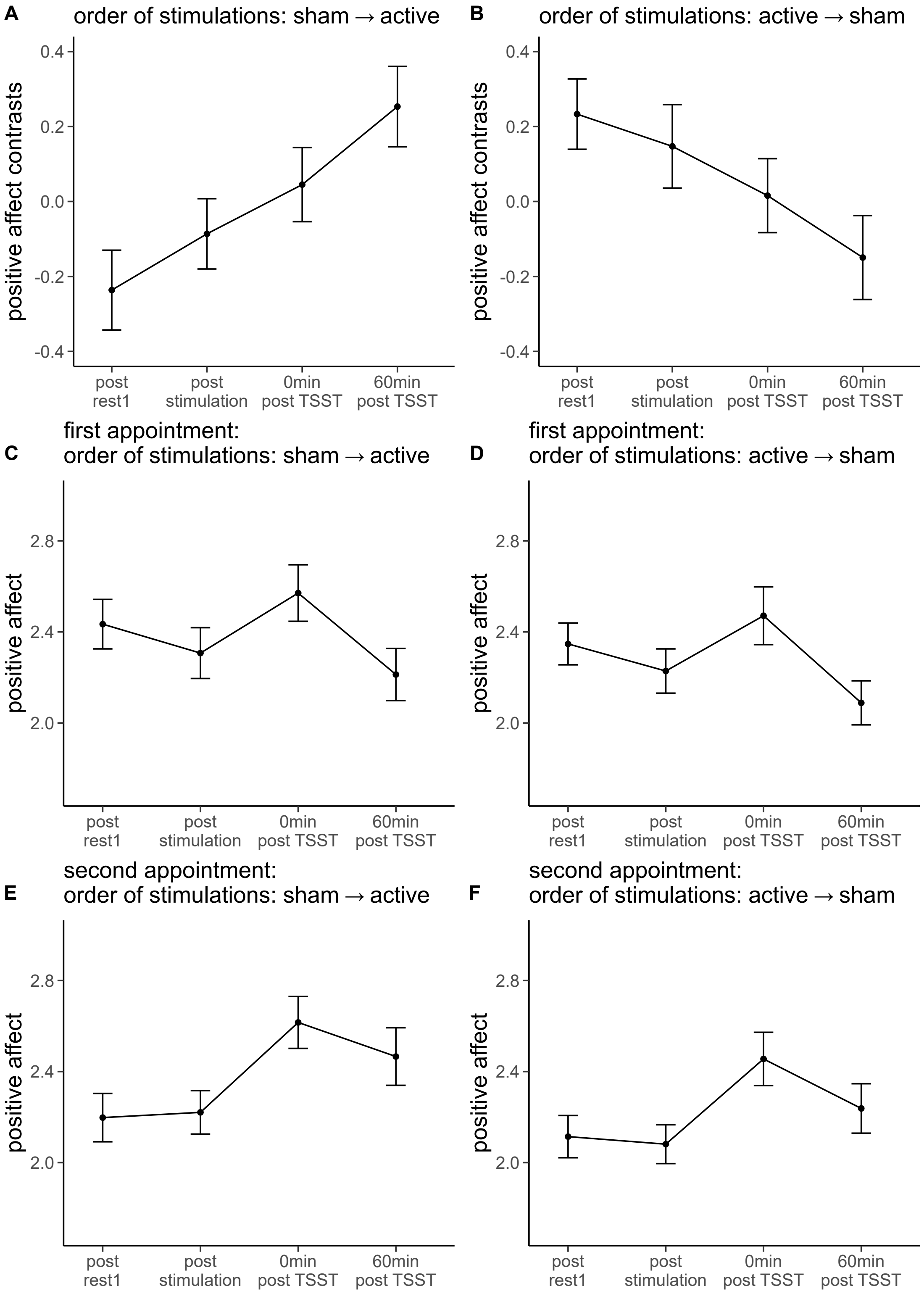


Figure S7.1
Line plot of the contrasts of positive affect ratings dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of positive affect ratings dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). rest = resting-state measurement, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, 0min post TSST = 0min after the Trier Social Stress Test. Error bars indicate 1 standard error of the mean.

Mean number of performed calculations contrasts According to Mahalanobis distances ($p < .001$), there were no multivariate outliers for the number of performed calculations. Fitting the rmANOVA, we observed a significant interaction effect of time and the order of stimulation conditions, $F(1.817, 145.388) = 61.208, p < .001, \eta_p^2 = .433$, as well as a significant lower-order main effect of the order of stimulation conditions, $F(1, 80) = 118.729, p < .001, \eta_p^2 = .597$. We further found a marginally significant interaction of group and order of stimulation conditions, $F(1, 80) = 3.900, p = .052, \eta_p^2 = .046$, and a marginally significant main effect of stimulation condition, $F(1, 80) = 3.023, p = .086, \eta_p^2 = .036$. We then fitted separate rmANOVAs dependent on the order of stimulation conditions. As a result, we observed a significant main effect of time (sham $\rightarrow$ active: $F(1.764, 70.573) = 30.964$, $p < .001$, $\eta_p^2 = .436$; active $\rightarrow$ sham: $F(1.895, 75.811) = 30.990$, $p < .001$, $\eta_p^2 = .437$) as well as a significant intercept (sham $\rightarrow$ active: $F(1, 40) = 77.755$, $p < .001$, $\eta_p^2 = .660$; active $\rightarrow$ sham: $F(1, 40) = 48.773$, $p < .001$, $\eta_p^2 = .549$) as well as a marginally significant main effect of stimulation condition but only in case participants received active stimulation first, $F(1, 40) = 3.133, p = .084, \eta_p^2 = .073$. Polynomial contrasts of the main effect of time indicated a quadratic time course of the contrasts but in opposing directions depending on the order of stimulation conditions (active $\rightarrow$ sham: $F(1, 40) = 21.297$, $p < .001$, $\eta_p^2 = .347$; sham $\rightarrow$ active: $F(1, 40) = 46.159$, $p < .001$, $\eta_p^2 = .536$). Initially, the mean number of read-out numbers (control task 1) was comparable between active and sham stimulation, regardless of the order of stimulation conditions. For participants having received sham stimulation first, we observed positive contrasts during control task 2 and the arithmetic task of the TSST. That means, participants performed more calculations following the active stimulation compared to the sham stimulation. The opposite was true for participants having received active stimulation first (see figure S7.2).

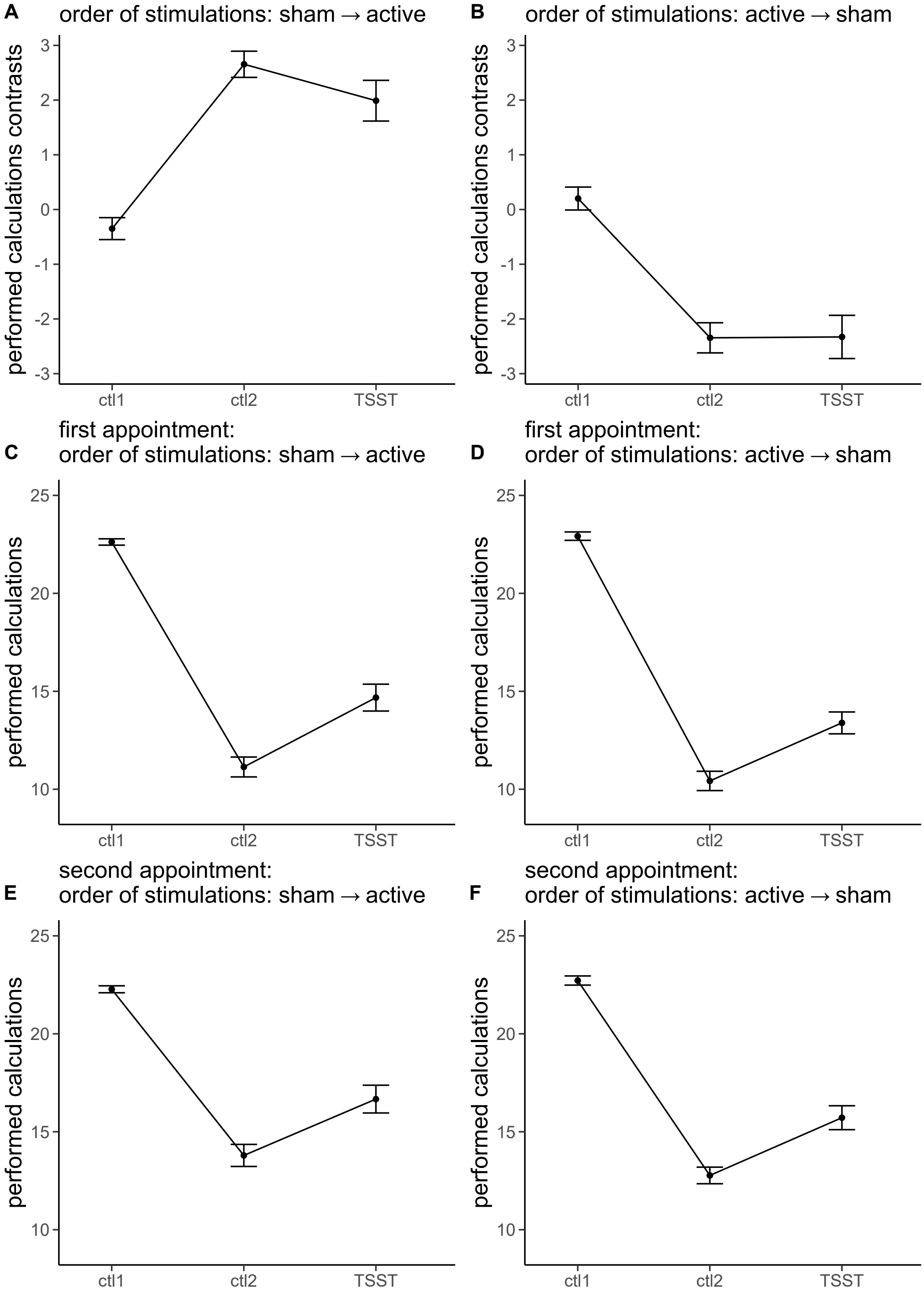


Figure S7.2
Line plot of the contrasts of the number of performed calculations dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of performed calculations dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). RRS = Ruminative Response Scale, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, CTL1 = control task1, CTL2 = control task 2, TSST = arithmetic task of the TSST; Error bars indicate 1 standard error of the mean.

Total number of errors contrasts Checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded the data of 2 participants. Fitting the rmANOVA, we observed a significant three-way interaction of time, group and order of stimulation conditions, $F(1.646, 128.426) = 4.174$, $p < .05$, $\eta_p^2 = .051$, a significant lower-order interaction of time and the order of stimulation conditions, $F(1.646, 128.426) = 11.746$, $p < .001$, $\eta_p^2 = .131$, as well as a significant main effect of the order of stimulation conditions, $F(1, 78) = 11.670$, $p < .01$, $\eta_p^2 = .130$. We then fitted the same rmANOVA dependent on order of stimulation conditions. As a result, we observed a significant interaction of time and group in case participants received active stimulation first, $F(1.606, 61.038) = 4.116$, $p < .05$, $\eta_p^2 = .098$ (see figure S7.3B), as well as a marginally significant interaction of time and stimulation condition, $F(1.606, 61.038) = 2.702$, $p = .086$, $\eta_p^2 = .066$. For participants having received sham stimulation first, we only observed a significant main effect of time, $F(1.710, 68.391) = 7.080$, $p < .01$, $\eta_p^2 = .150$ and significant main effect of the constant term, $F(1, 40) = 11.273$, $p < .01$, $\eta_p^2 = .220$. Polynomial contrast of the interaction of time and group indicated linear association, $F(1, 38) = 6.692$, $p < .05$, $\eta_p^2 = .150$: While for both groups, low and high ruminators, the number of errors was comparable between active and sham stimulation during control task 1 and 2, low ruminators made more errors following active stimulation (AP1) and less errors following sham stimulation (AP2) during the arithmetic task of the TSST while the number of errors stayed the same for high ruminators. Benjamini-Hochberg-corrected post-hoc tests indicated no significant differences between the groups at any given time point.

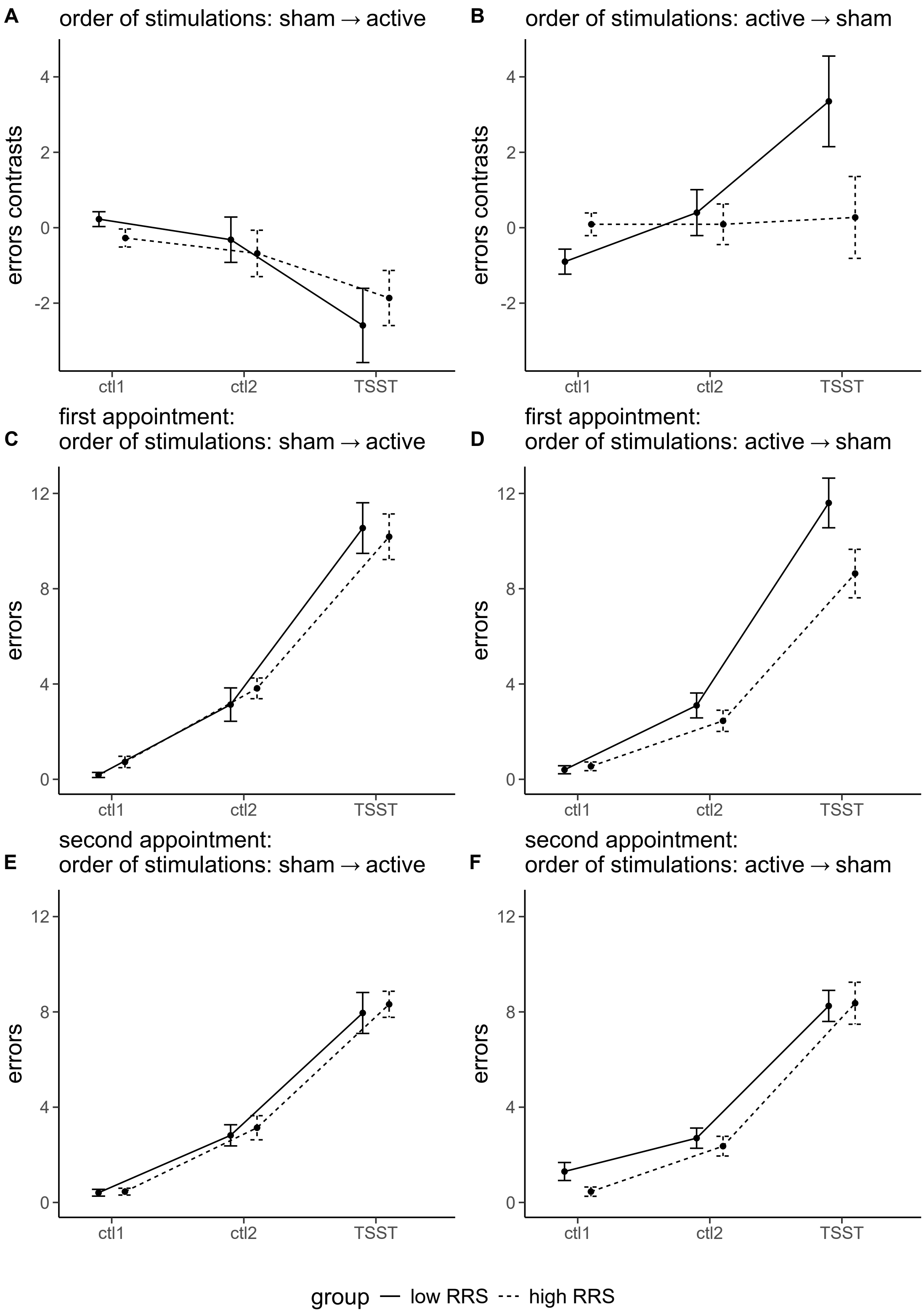
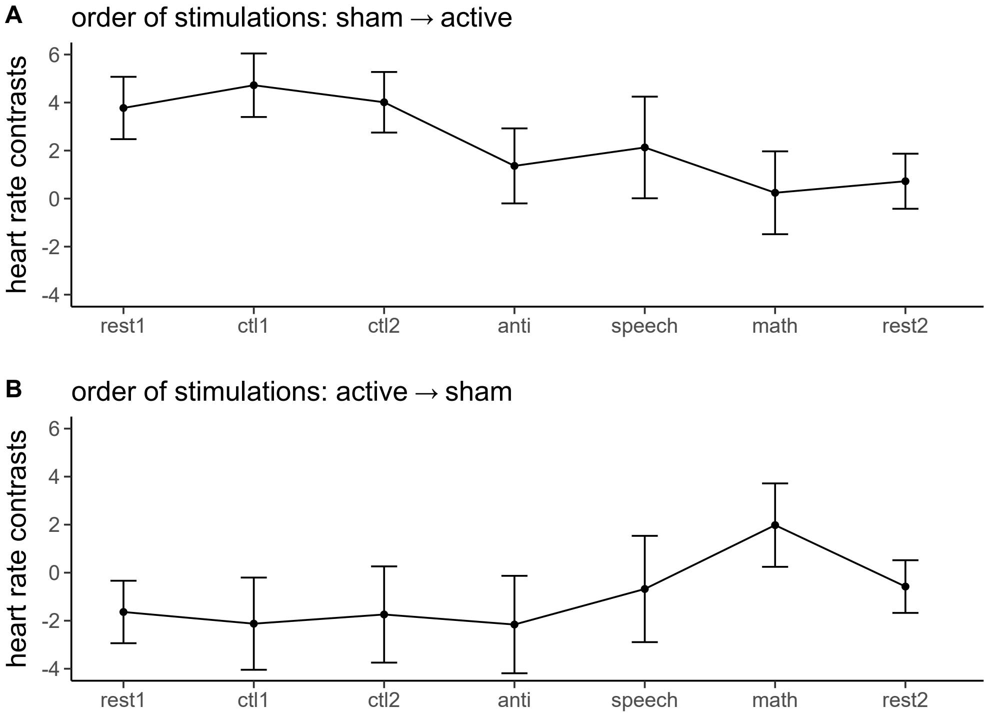
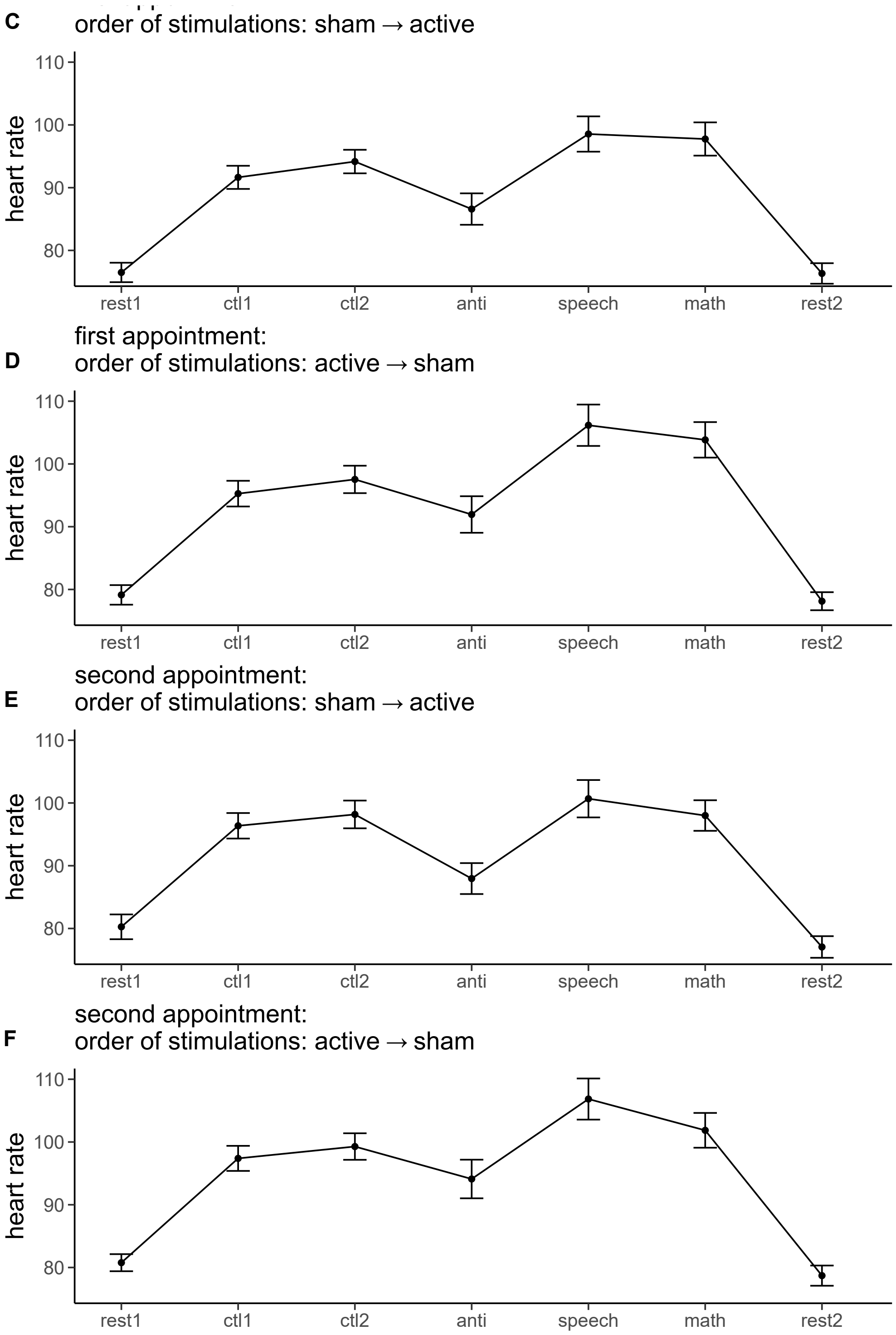


Figure S7.3
Line plot of the contrasts of the number of errors made dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of the number of errors made dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). RRS = Ruminative Response Scale, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, CTL1 = control task1, CTL2 = control task 2, TSST = arithmetic task of the TSST; Error bars indicate 1 standard error of the mean.

Heart rate contrasts Checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded the data of 4 participants and 7 missing data. Fitting a rmANOVA, we observed a significant interaction of time and order of stimulation conditions, $F(3.558, 245.519) = 4.959$, $p < .01$, $\eta_p^2 = .067$, as well as a marginally significant main effect of order of stimulation conditions, $F(1, 69) = 2.855$, $p = .096$, $\eta_p^2 = .040$. Fitting the same rmANOVA separately for participants dependent on order of stimulation conditions yielded a significant main effect of time (sham $\rightarrow$ active: $F(3.075, 101.459) = 3.204$, $p < .05$, $\eta_p^2 = .088$; active $\rightarrow$ sham: $F(3.620, 139.331) = 2.611$, $p < .05$, $\eta_p^2 = .068$), as well as a marginally significant main effect of the intercept but only in case participants received sham first, $F(1, 33) = 3.925$, $p = .056$, $\eta_p^2 = .106$. Investigating the main effect of time using polynomial contrasts, yielded a linear time course in both cases (sham $\rightarrow$ active: $F(1, 40) = 11.446$, $p < .01$, $\eta_p^2 = .222$; active $\rightarrow$ sham: $F(1, 38) = 7.942$, $p < .01$, $\eta_p^2 = .173$) (see figure S7.4).





C order of stimulations: sham → active

D first appointment: order of stimulations: active → sham

E second appointment: order of stimulations: sham → active

F second appointment: order of stimulations: active → sham

Figure S7.4

Line plot of the contrasts of mean heart rates in beats per minute dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of mean heart rates in beats per minute dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). RRS = Ruminative Response Scale, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, rest1 = resting-state measurement 1, CTL1 = control task1, CTL2 = control task 2, anti = anticipation phase of the TSST, speech = job interview of the TSST, math = arithmetic task of the TSST; Error bars indicate 1 standard error of the mean.

S9 Illustration of Reliable Change Indices

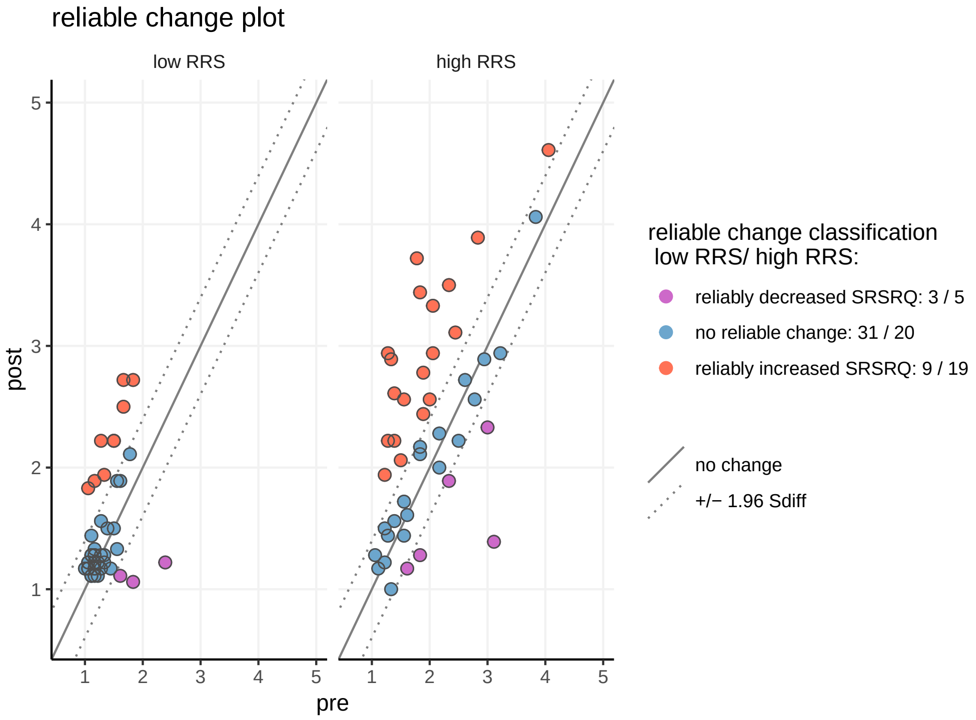


Figure S8.1
Reliable change index plotted for changes in state rumination previous to the stress induction (rest1) to after the stress induction (rest2) for the first appointment dependent on RRS group

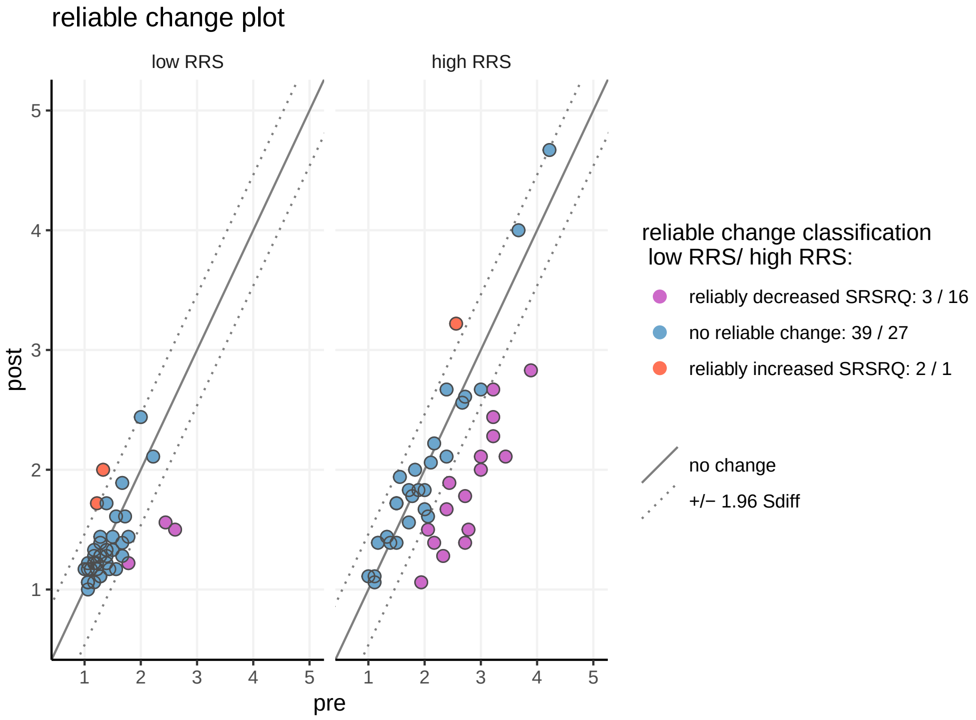


Figure S8.2
Reliable change index plotted for changes in state rumination previous to the stress induction (rest1) to after the stress induction (rest2) for the second appointment dependent on RRS group

S10 Illustration of Brainmaps

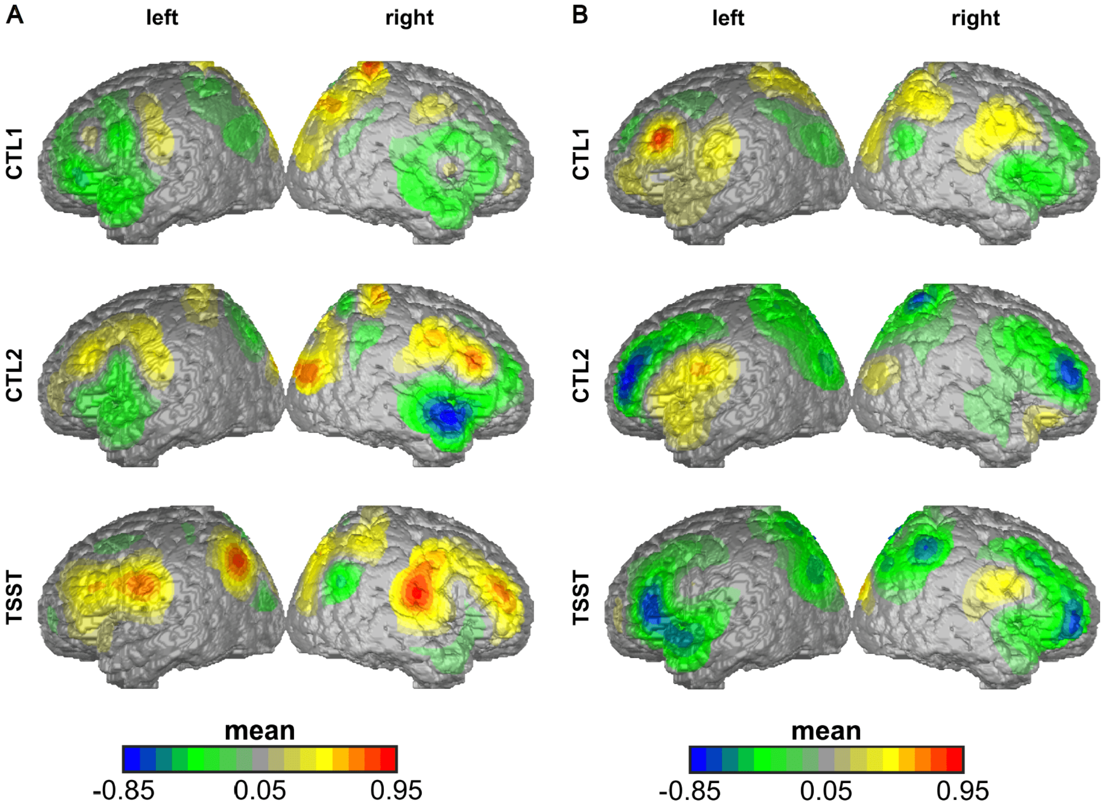


Figure S9.1
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of low ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions active → sham; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

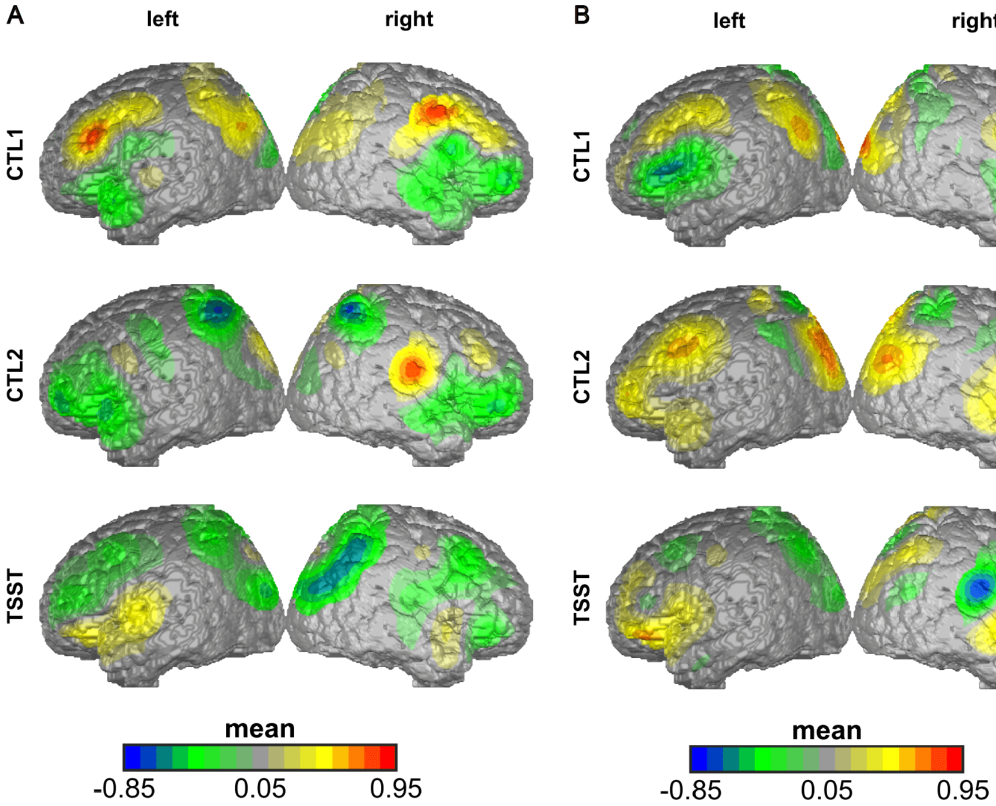
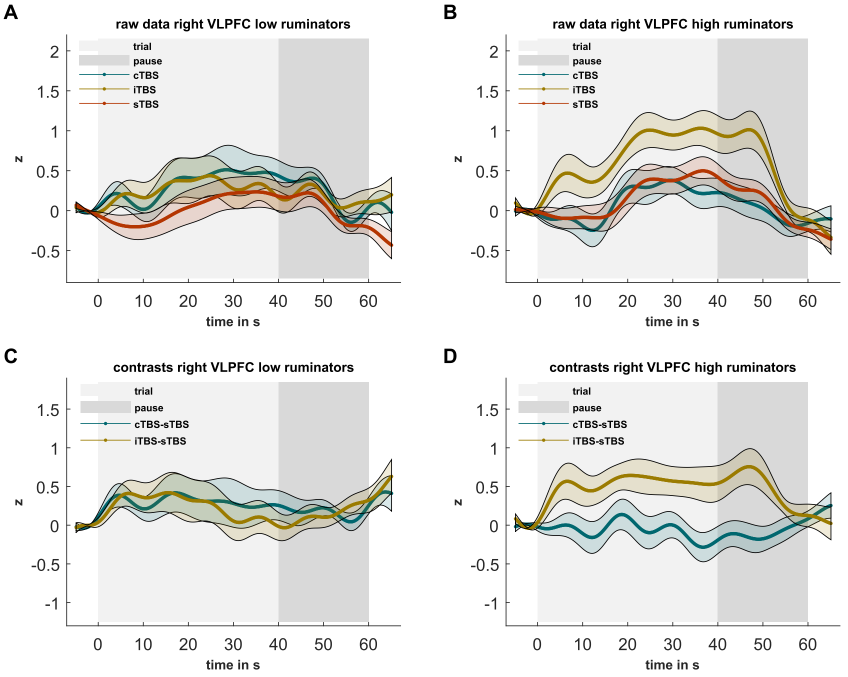


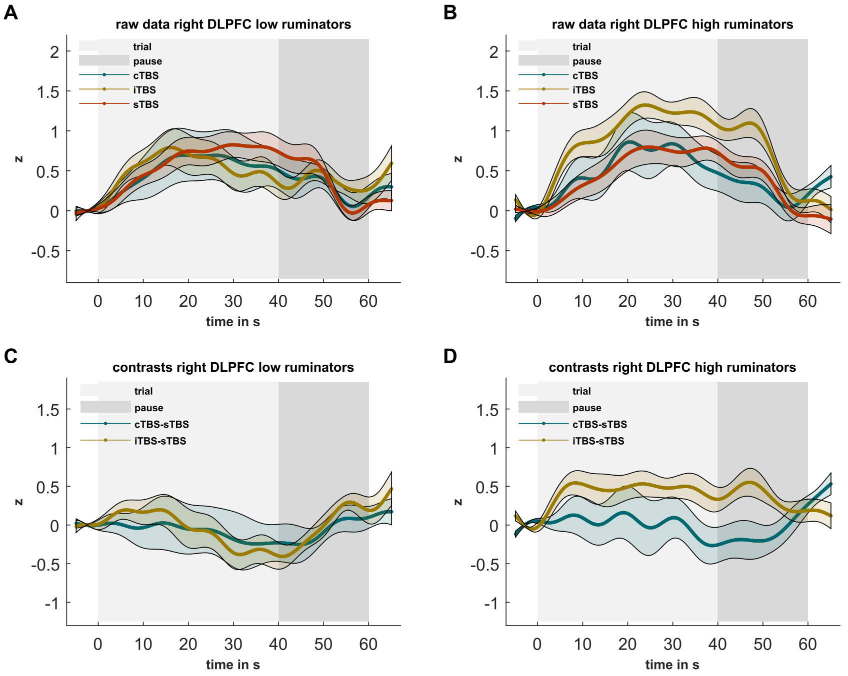
Figure S9.2
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of high ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions active → sham; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

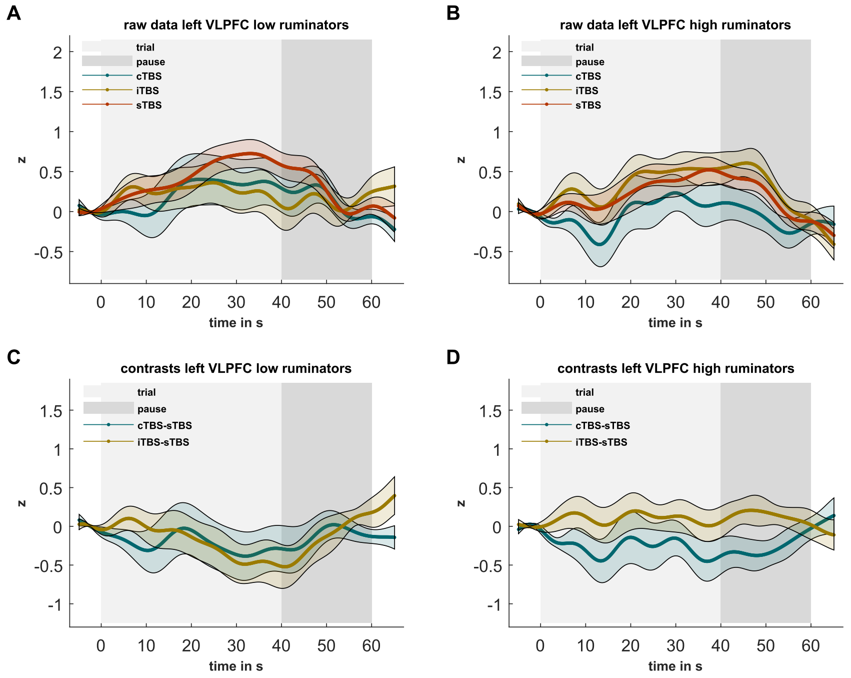
S11 Time series of the hemodynamic responses during the arithmetic task of the TSST

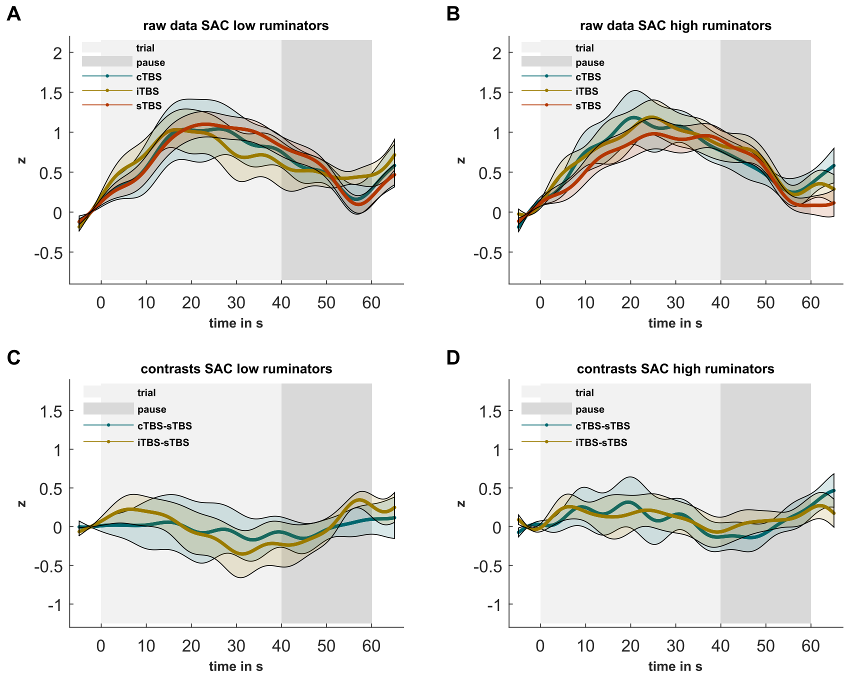
Illustration of the z-standardized hemodynamic responses during the arithmetic task of the TSST in the Regions of Interest in low and high ruminators depending on the TBS-condition. A and B illustrate the raw data, while C and D illustrate the contrasts (cTBS minus sTBS and iTBS minus sTBS). The light shading marks the 40 s trial and the dark shading the 20 s pause to allow the hemodynamic response to recover. Shadings around the hemodynamic curves reflect standard errors of the mean. The baseline includes the 5 s before each trial; 0 s on the x-axis marks the beginning of the trial.

Time series of the first appointment:

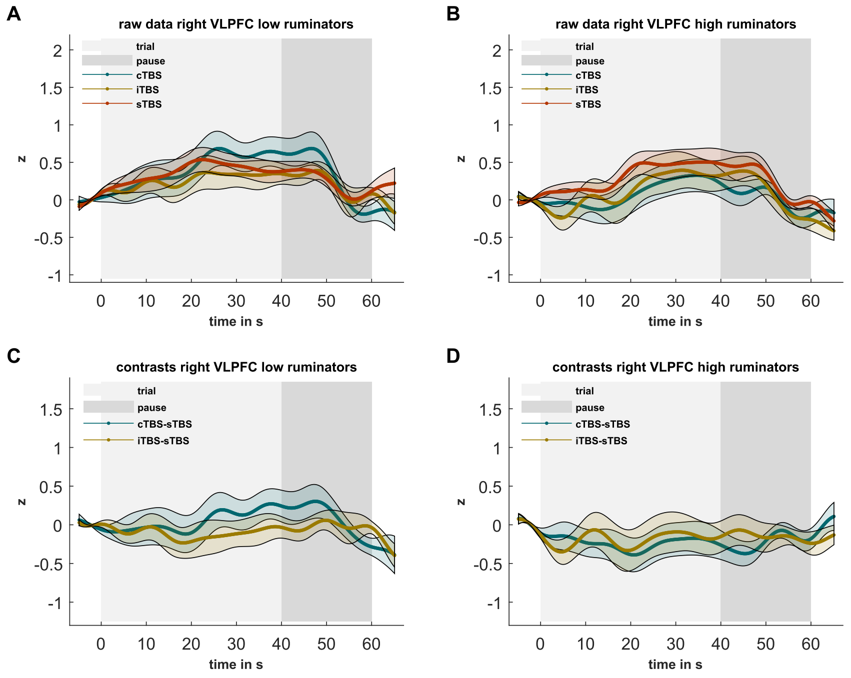


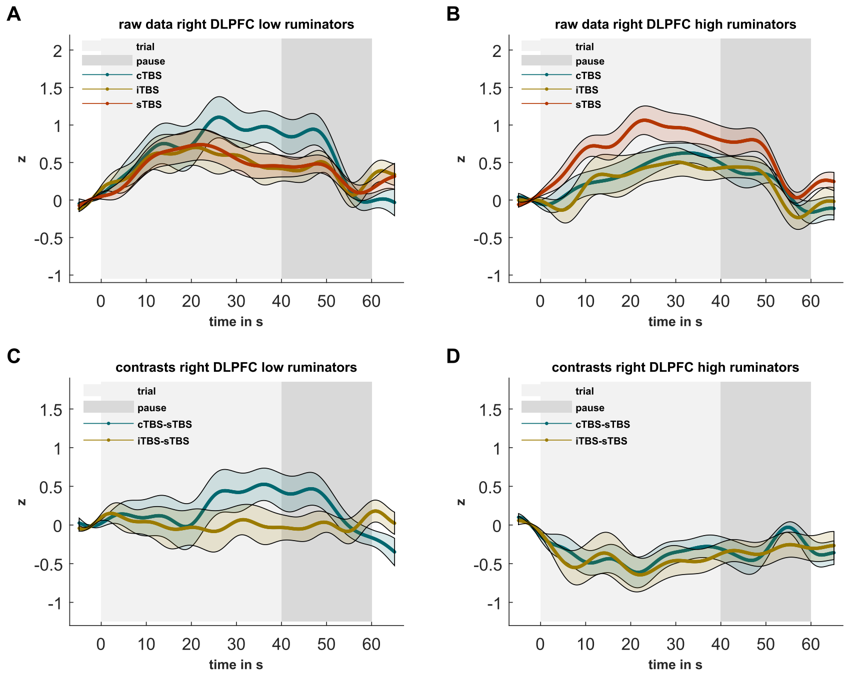


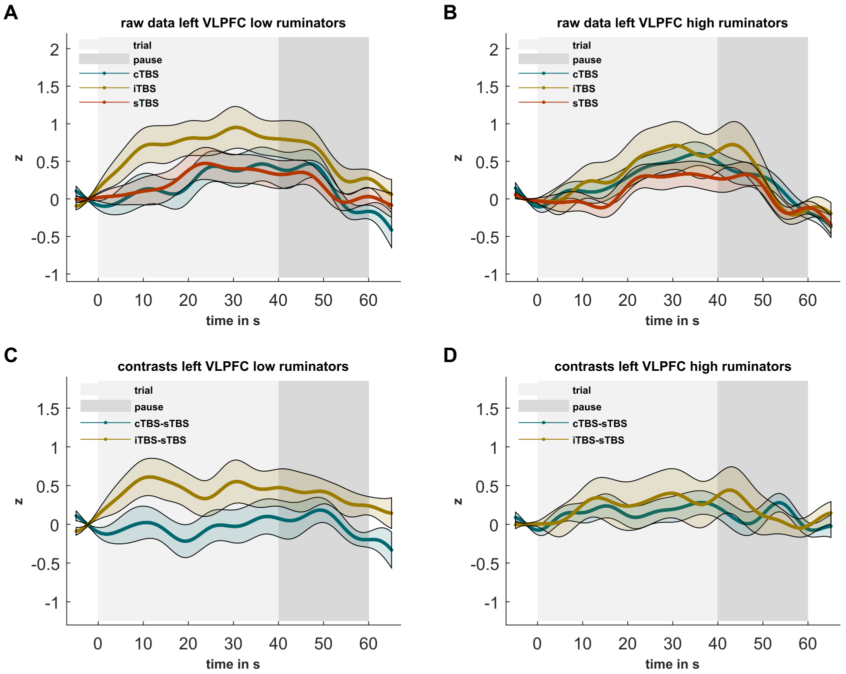

A
raw data left VLPFC low ruminators
B
raw data left VLPFC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
time in s
C
contrasts left VLPFC low ruminators
D
contrasts left VLPFC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
1.5
1
0.5
0
-0.5
-1


A
raw data SAC low ruminators
B
raw data SAC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
time in s
C
contrasts SAC low ruminators
D
contrasts SAC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
1.5
1
0.5
0
-0.5
-1

Time series of the second appointment:






A
raw data left VLPFC low ruminators
B
raw data left VLPFC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
-1
0
10
20
30
40
50
60
time in s
C
contrasts left VLPFC low ruminators
D
contrasts left VLPFC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
z
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-0.5
-1
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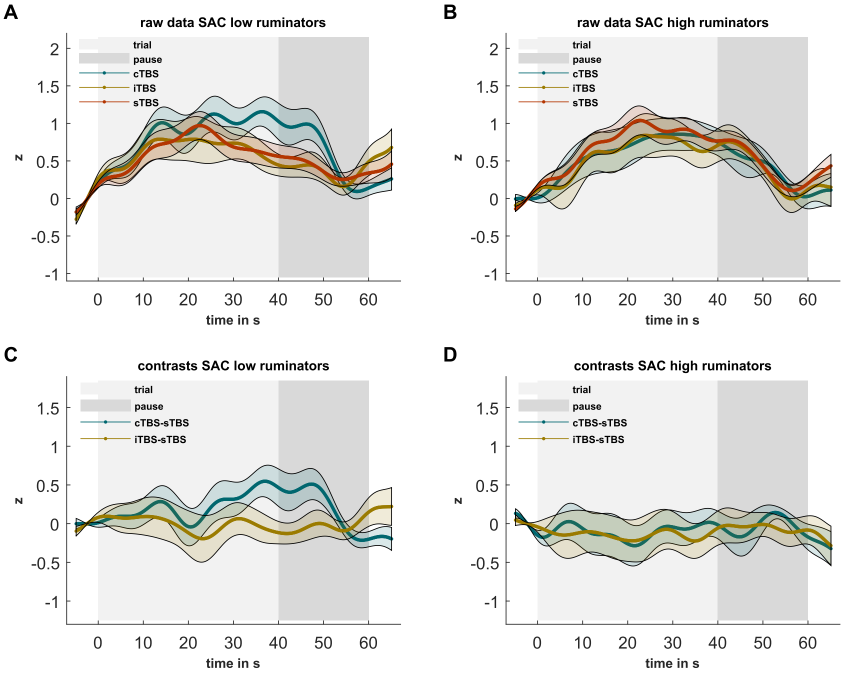
10
20
30
40
50
60
time in s


A
raw data SAC low ruminators
B
raw data SAC high ruminators
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pause
cTBS
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time in s
C
contrasts SAC low ruminators
D
contrasts SAC high ruminators
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cTBS-sTBS
iTBS-sTBS
z
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0.5
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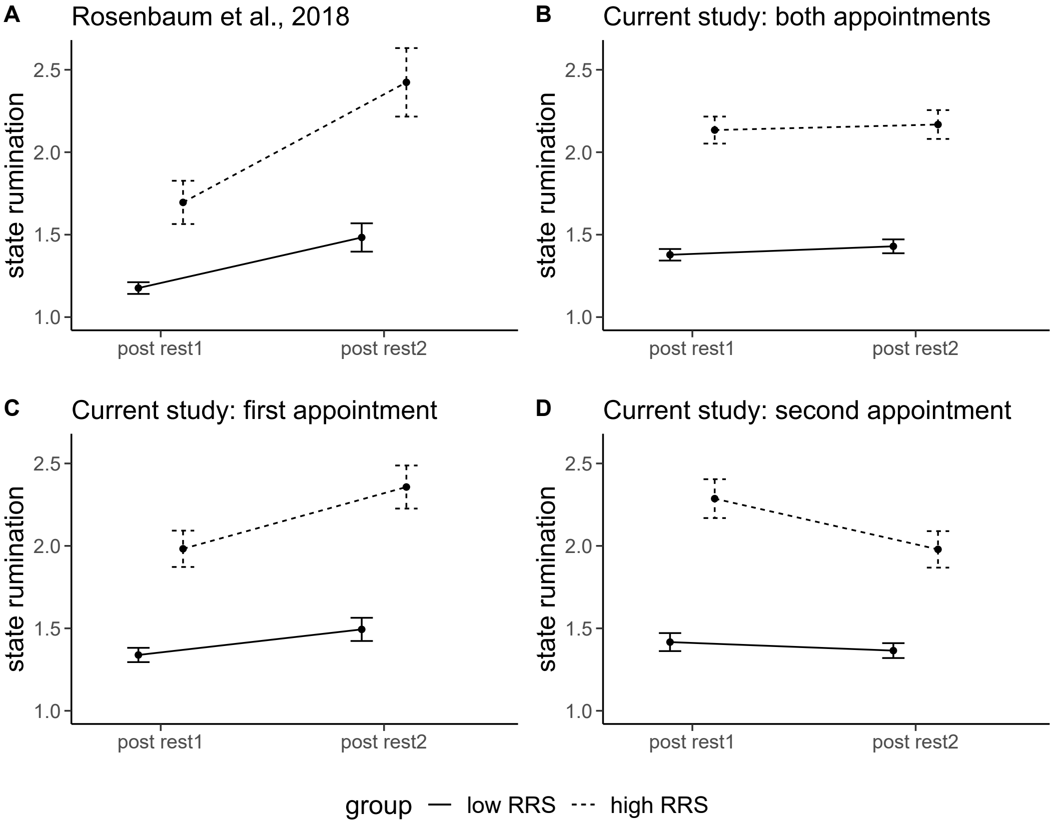
-0.5
-1
0
10
20
30
40
50
60
time in s

S12 Plots comparing state rumination induction in previous studies

Plots of state rumination as assessed in this study and in a previous study of our group: A = State rumination ratings dependent on RRS group in a study with similar set-up (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018) where low and high trait ruminator HC underwent the TSST but without a neurostimulation beforehand. The study consisted of only one appointment at the laboratory; B = State rumination ratings of the current study dependent on RRS group merged for both appointments; C = State rumination ratings of the current study dependent on RRS group only considering the first appointment; D = State rumination ratings of the current study dependent on RRS group only considering the second appointment. Please note that for both studies, the same cutoffs were used to determine RRS groups. RRS = Ruminative Response Scale Please note that state rumination increases were in general low after the (TBS and) TSST (first appointment: $F(1, 85) = 16.188$, $p < .001$, $\eta_p^2 = .160$; second appointment: $F(1, 82) = 15.855$, $p < .001$, $\eta_p^2 = .162$) compared to Rosenbaum et al., (2018): $F(1, 44) = 19.832$, $p < .001$, $\eta_p^2 = .311$.



Chapter 6

STUDY 4: Repeated theta burst stimulation of the right ventrolateral prefrontal cortex reveals strong habituation in the context of stress and rumination

The contents of this chapter are published:

Int-Veen, I., Eisenlohr, C., Täglich, R., Schopp, B., Nuerk, H.-C., Plewnia, C., De Smet, S., Vanderhasselt, M.-A., Kroczek, A., Barth, B., Fallgatter, A. J., Ehlis, A.-C., & Rosenbaum, D. (2025). Repeated theta burst stimulation of the right ventrolateral prefrontal cortex reveals strong habituation in the context of stress and rumination. *Scientific Reports*, 15*(1)*, 31073.

6.1 Abstract

Prefrontal hypoactivation under stress has been consistently observed in individuals with high trait rumination and in patients with depression. However, no study has yet investigated the mechanisms of modulating activity of the Ventrolateral Prefrontal Cortex (VLPFC) by using excitatory and inhibitory Theta Burst Stimulation (TBS) in this context. To address this, we recruited 89 healthy participants (44 low trait ruminators and 45 high trait ruminators) who attended two lab sessions, each including stress induction via the Trier Social Stress Test (TSST). Participants received either excitatory intermittent TBS (iTBS) or inhibitory continuous TBS (cTBS). One session involved active TBS, while the other used sham TBS (sTBS), with the order randomized and balanced across stimulation conditions and groups. In high ruminators, we observed a significant impact of iTBS in the hypothesized direction when considering cortical oxygenation in the right VLPFC. We found higher subjective stress following iTBS and cTBS compared to sTBS during recovery of the TSST but only at the first appointment. No stimulation-dependent effects were found for other measures (state rumination, positive and negative affect, and heart rates). In our discussion, we draw conclusions concerning repeated-measures designs in TBS-studies.

6.2 Introduction

Non-Invasive Brain Stimulation (NIBS) comprises techniques to alter neural activation. One form of NIBS is Transcranial Magnetic Stimulation (TMS), which is capable of inducing excitability changes in the cortex and investigating the causal involvement of brain regions. TMS exists in several forms, such as single-pulse, paired-pulse, and repetitive TMS (rTMS), with rTMS shown to produce effects that last beyond the stimulation period (Oberman, 2014). A newer variant of rTMS, known as Theta Burst Stimulation (TBS), uses high-frequency TMS bursts mimicking the hippocampal theta-rhythms (Huang et al., 2005). Depending on the interpulse and intertrain intervals, TBS can induce excitatory effects, thought to resemble long-term potentiation (intermittent TBS; iTBS), or inhibitory effects, akin to long-term depression (continuous TBS; cTBS) (Huang et al., 2011).

TMS has been extensively investigated, particularly as a potential treatment for depression by modulating the left Dorsolateral Prefrontal Cortex (DLPFC) (Gaynes et al., 2014; Sathappan et al., 2019; Schutter, 2009). This is because prefrontal hypoactivation of the left DLPFC in patients with depression was observed during “affective and cognitive tasks requiring emotional or stress regulation, cognitive control, and/or shifting attention to external task demands” (Pizzagalli & Roberts, 2022, page 246). This means that, while increases in prefrontal brain activity—particularly in regions of the Fronto-Parietal Network (FPN) such as the DLPFC—are generally expected when moving from non-stressful to stressful tasks, individuals with depression consistently show attenuated increases in activation. This has been theorized to result at least in part from rumination, which is defined as “repetitive, prolonged, and recurrent negative thinking about one’s self, feelings, personal concerns and upsetting experiences”(Watkins & Roberts, 2020, page 1). Recently, rTMS has been extensively investigated both as a treatment for depression—particularly via modulation of the left DLPFC—and in experimental contexts for its effects on rumination and the psychophysiological stress response (Baeken et al., 2014; De Witte et al., 2020; Gaynes et al., 2014; Remue et al., 2016; Sathappan et al., 2019; Schutter, 2009). While the left DLPFC is an important brain region involved in emotion regulation, cognitive control and the appropriate response to stressors, the Ventrolateral Prefrontal Cortex (VLPFC)—which is also part of the FPN—is proposed to be responsible for signaling the need to regulate to the DLPFC in the first place (Kohn et al., 2014). More specifically, the VLPFC initiates the appraisal and evaluates salience and indicates the need to regulate (Kohn et al., 2014). This is supported by reviews and meta-analyses of neuroimaging studies of cognitive reappraisal (Buhle et al., 2014; Kalisch, 2009). A review by Moses and colleagues (2023) highlights the importance of the VLPFC for studies using NIBS to investigate cognitive and emotional responses to psychosocial stressors, as "[...] the VLPFC—a key structure in cognitive reappraisal circuits—may be the best-supported target to affect stress modulation of emotional responses".

Although research on the VLPFC remains limited compared to the left DLPFC, existing NIBS studies suggest that stimulation of the VLPFC improves emotion regulation and cognitive reappraisal (Chick, Rolle, Trivedi, Monuszko, & Etkin, 2020; He et al., 2023, 2018, 2020; Li et al., 2022; Marques, Morello, & Boggio, 2018; Vergallito, Riva, Pisoni, & Lauro, 2018; Zhao et al., 2021). This may especially be the case in social situations. Three studies combined the well-established Cyberball paradigm—a virtual ball-toss game where feelings of inclusion or exclusion are manipulated using the number of times participants receive the ball—with tDCS targeting the right VLPFC (Riva, Romero Lauro, DeWall, & Bushman, 2012; Riva, Romero Lauro, DeWall, Chester, & Bushman, 2015; Riva, Romero Lauro, Vergallito, DeWall, & Bushman, 2015) and showed that excitatory anodal tDCS applied to the right VLPFC buffers against social exclusion while the converse effects have been found for cathodal stimulation. Although the aforementioned studies did not include neural measures, their findings suggest that increased activation of the right VLPFC—also in more ecologically valid settings—may reduce emotional distress in socially challenging situations, such as social exclusion, likely by exerting top-down control over limbic regions.

Beyond ostracism and social stress, early findings suggest the Cyberball paradigm also induces ruminative thinking (Fowler, Miernicki, Rudolph, & Telzer, 2017; Wesselmann, Ren, Swim, & Williams, 2013). Originally defined in the context of depression as persistent focus on symptoms and their implications (Nolen-Hoeksema & Morrow, 1991), rumination was considered a stable, situation-unspecific trait. Newer theories conceptualize it as a state-like process triggered by stress, observable even in healthy individuals (Alloy et al., 2000; Robinson & Alloy, 2003; Smith & Alloy, 2009). Some researchers propose rumination functions as an emotion regulation strategy (Garnefski, Kraaij, & Spinhoven, 2001) and rather than being limited to depression, rumination has been shown to contribute to various mental disorders (Aldao & Nolen-Hoeksema, 2010;

Arditte et al., 2016).

Using Cyberball and an emotion regulation task, Fowler et al. (2017) found that amygdala– VLPFC connectivity mediated the link between stress-reactive rumination and depressive symptoms in adolescent girls. Yet, the causal role of the VLPFC in adult stress-reactive rumination remains unclear.

Another widely used stress-induction is the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) which combines public speaking and mental arithmetic in front of an unresponsive panel. The TSST reliably induces stress and is considered the gold standard in human stress research (Allen et al., 2017; Dickerson & Kemeny, 2004). It also elicits rumination in an ecologically valid way (De Smet et al., 2024; Gianferante et al., 2014; Hilt et al., 2015; Int-Veen et al., 2023; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018; Shull et al., 2016; Zoccola et al., 2008) and can be used repeatedly (Federenko, Nagamine, Hellhammer, Wadhwa, & Wüst, 2004; Jönsson et al., 2010; Kudielka et al., 2006; Madison et al., 2025; Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010; Roos, Janson, Sturmbauer, Bennett, & Rohleder, 2019; Schommer et al., 2003; von Känel, Kudielka, Preckel, Hanebuth, & Fischer, 2006; Wüst, Federenko, van Rossum, Koper, & Hellhammer, 2005) though longer intervals (10–16 weeks) are recommended to avoid habituation (Madison et al., 2025; Petrowski et al., 2010). TSST-induced rumination has been linked to reduced prefrontal activity, especially in the DLPFC and Inferior Frontal Gyrus (IFG) (Int-Veen et al., 2023; Rosenbaum, Hilsendegen, Thomas, Haeussinger, Nuerk, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018). So far, NIBS studies in the context of rumination have targeted only the left DLPFC. De Witte et al. (2020) observed interactions with trait rumination, which moderated TBS-effects on the physiological and psychological stress response. Era et al. (2021) observed elevated heart rate and cortisol, and lower HRV when cTBS was applied before a rumination induction.

Using 20-Hz HF-rTMS applied to the left DLPFC after the TSST, Wang et al. (2023) observed reduced stress-induced cortisol increases. De Smet et al. (2024) applied cTBS, iTBS, or sTBS in a between-subjects design and found reduced cortisol responses in high ruminators following cTBS. Active TBS further enhanced heart rate recovery. Further assessing the neural correlates using functional near-infrared spectroscopy (fNIRS) and using a within-subject design (Int-Veen et al., 2025), no impact on heart rates but higher increases in negative affect and perceived stress were observed when high ruminators received iTBS. Overall, strong habituation effects in terms of most pronounced responses to the TSST in case of first-time exposure were observed.

These findings suggest that active TBS may have the potential to reduce rumination following the TSST and to modulate the stress response, highlighting their possible utility in mitigating stress-related cognitive and physiological processes.

In the current study, we aimed to investigate the causal role of the VLPFC. The present study offers a unique contribution to the field by employing a high-powered, sham-controlled, double-blind design to investigate the causal role of the right VLPFC in the stress-rumination-link. To our knowledge, this is the first study to apply both excitatory and inhibitory TBS to the right VLPFC prior to the TSST. Participants attended two laboratory sessions, receiving active stimulation in one session (iTBS or cTBS) and sham stimulation in the other, with the order of conditions randomized between subjects. Following the stimulation, participants underwent stress induction via the TSST. Our primary outcomes were stress, state rumination and negative affect. Moreover, we extended previous work by incorporating neural correlates of stimulation effects using fNIRS, thereby providing a more comprehensive understanding of the neurobiological mechanisms underlying stress-related rumination. Specifically, we assessed cortical oxygenation in our stimulation target, the VLPFC, which is known to play a key role in emotion regulation within social contexts. Additionally, we examined the DLPFC, given its involvement in emotion regulation, cognitive control, and adaptive responses to stressors. Finally, we measured the Somatosensory Association Cortex (SAC) as a proxy for the ventral Posterior Parietal Cortex—a critical component of the Central Executive Network (CEN)—since direct recording from this region was not feasible with our NIRS probe configuration. The SAC was selected as it constitutes the closest accessible cortical area.

We hypothesized that modulation of the VLPFC via TBS would influence prefrontal activation under stress and, in turn, affect emotion regulation such as cognitive reappraisal and state rumination. Specifically, we expected that activation of the VLPFC would facilitate adaptive reappraisal and thereby suppress state rumination. Accordingly, we predicted that inhibitory cTBS of the VLPFC would lead to reduced prefrontal activation under stress, particularly in high ruminators, exacerbating their pre-existing prefrontal dysfunction. In contrast, excitatory iTBS should increase VLPFC-activation, thereby potentially normalizing prefrontal functioning in high ruminators. For low ruminators, we expected a smaller impact of TBS due to their already high prefrontal engagement under stress. Specifically, cTBS was expected to reduce VLPFC-activation, whereas iTBS might lead to slightly increased cortical oxygenation.

Consequently, we hypothesized that iTBS would result in reduced stress, negative affect, and state rumination. Conversely, cTBS was expected to impair emotion regulation, leading to increased stress, negative affect, and rumination, particularly in high ruminators.

6.3 Methods

6.3.1 Participants

Participants were recruited by sending informational emails to mailing lists within the university, reaching over 50000 individuals. Approximately 1000 expressed interest, and 850 completed an online screening assessing the Ruminative Response Scale (RRS) (Treynor & Gonzalez, 2003) as well as demographic and clinical variables. Inclusion and exclusion criteria (see supplementary material S1) were checked again in a structured telephone interview. To determine the required sample size, we conducted an a priori power analysis using G*Power for a 2x2 mixed design (GroupxTime), targeting the detection of a between-within interaction effect (see supplementary material S2). Accordingly, we aimed for a sample size of 88 subjects comprising 44 low and 44 high ruminators based on their scores on the online RRS. Specifically, low ruminators were defined as individuals with a mean RRS score of ≤ 1.82, corresponding to the 25th percentile rank, and high ruminators as individuals with a mean RRS score of ≥ 2.36, corresponding to the 64th percentile rank. These cutoffs were determined based on normative data from a large sample previously assessed by our group (*N* = 983) (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum, Thomas, et al., 2018). We recruited participants until this target was reached. Please note that we accidentally recruited one additional male high ruminator receiving sTBS at his first and iTBS at his second appointment.

In total, 139 individuals were recruited, however 23 declined participation and 27 participants were excluded as their RRS scores, assessed one week prior to or at their first laboratory appointment, no longer clearly qualified them as either high or low trait ruminators (i.e., if they switched groups or scored closer to the opposite group) (for a CONSORT diagram, see supplementary material S3). The final sample consisted of 89 right-handed healthy volunteers aged 18 to 50 years (68.54% female, M_{age} = 23.72 years, SD_{age} = 6.01 years). After inclusion, participants were randomly assigned to either intermittent TBS ("iTBS-arm", *n* = 45; of these, 22 were low ruminators and 23 were high ruminators) or continuous TBS ("cTBS-arm", *n* = 44; of these, 22 were low ruminators and 22 were high ruminators). Each participant attended two laboratory appointments during which they received either active stimulation (iTBS or cTBS) or sham stimulation (sTBS). The order of sham and active stimulation was randomized and balanced across participants and stimulation groups.

6.3.2 Procedure

The two appointments were scheduled approximately 5 weeks apart in order to reduce the memory effects of the experimental procedure and stimulation (*M* = 41.30 days, *SD* = 8.28 days). At the first appointment, subjects gave written informed consent, and completed the RRS again. Afterwards, the participants' individual resting motor threshold was determined. Then, functional near-infrared spectroscopy (fNIRS) and electrocardiography measurements (ECG) were prepared while the subject had to complete several questionnaires assessing socio-demographic data and depressive symptoms using the Beck Depression Inventory II (BDI-II) (Hautzinger et al., 2009). Throughout the entire experiment, subjects rated their subjective stress level at the moment on a Visual Analogue Scale (VAS) ranging from 0 to 100% 12 times (see figure 6.1). After completing the above-mentioned questionnaires, the first stress rating was assessed (VAS 1; baseline). A 7-min resting-state followed (rest1), where participants were instructed to let their mind wander while keeping their eyes open. Then, another stress rating was assessed (VAS 2; post rest1) as well as current mood using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) (PANAS 1; post rest1) (note that an adapted version with 2 additional items was used, namely "happy" and "sad") and state rumination using the Stress-Reactive State Rumination Questionnaire (SRSRQ) (Int-Veen, Laicher, et al., n.d.) (SRSRQ 1; post rest1) (for items see supplementary material S4). Then, two control tasks followed with a similar structure to the arithmetic task of the Trier Social Stress Test (TSST), which were intended as control conditions without social stress and time pressure. For the first control task (ctl1), subjects were given a sheet of paper with number sequences to be read out loud in a total of six trials. During control task 2 (ctl2), also comprising 6 trials, subjects were given different starting numbers from which they should continuously subtract 13 or 17 (depending on the appointment, randomized in order). Each trial consisted of 40 s reading and 20 s inter-trial interval. In case subjects made an error in ctl2, they had to start over again from the respective starting number, while this was not the case for ctl1. After each task, subjective stress ratings were assessed (VAS 3; post ctl1 and VAS 4; post ctl2) and following both control tasks, the fNIRS- and the ECG-assessments were interrupted, and the neurostimulation was performed in a separate room. The fNIRS device did not allow for simultaneous measurement of cortical oxygenation during neurostimulation, as the coil placement would have interfered with the optode positioning on the head. After the stimulation, participants gave another stress rating (VAS 5; post stimulation) and returned to the fNIRS room. Five min after the stimulation, they were asked to complete another PANAS (PANAS 2; post stimulation) and SRSRQ (SRSRQ 2; post stimulation). Meanwhile, the fNIRS and ECG were prepared. Readjusting the probeset, which involved removing the participants' hair from beneath the optodes, took between 5 to 10 min depending on the participant's hair type. Then, the stress induction using the TSST followed (for details see supplementary material S5), consisting of a 5 min anticipation phase where participants were allowed to take notes, a 5 min job interview where they had to give a speech about their strengths and qualifications, and a 5 min arithmetic task. Following both tasks, participants rated their stress (VAS 6; post speech and VAS 7; post math) and directly after the TSST, another PANAS was assessed (PANAS 3; 0 min post TSST). Then, another 7-min resting-state was conducted (rest2) and subjects completed another SRSRQ (SRSRQ 3; post rest2). Subjective stress was assessed every 15 minutes for one hour after the TSST (VAS 8-12), and at 60 min after the TSST subjects additionally completed a fourth SRSRQ (SRSRQ 4; 60 min post TSST) and PANAS (PANAS 4; 60 min post TSST) and adverse effects of the TBS were assessed. Further, we assessed the subjects' expectancy effects using a custom questionnaire. More specifically, they were asked about the stimulation condition they were in (sham vs. active), whether they believed the stimulation made them perform better vs. worse vs. had no impact on their performance during the TSST and the confidence about their respective answers in percent. After completing both appointments, participants were debriefed and received either monetary compensation (100 €) or 6 hours of course credit. This study was approved by the ethics committee at the University Hospital and University of Tübingen (673/2019BO1). All methods were carried out in accordance with relevant guidelines and regulations.

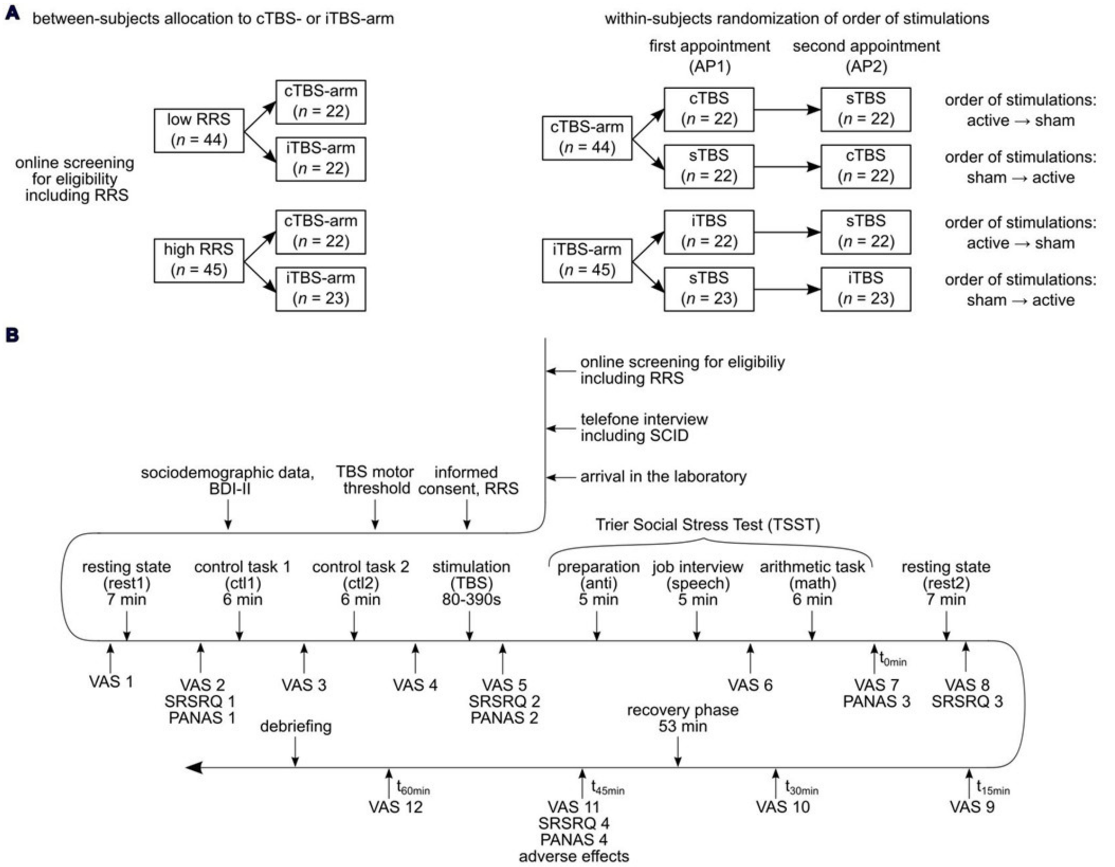


Figure 6.1
Overview over the study design (A) and time course of the experimental procedure (B). RRS = Ruminative Response Scale, SCID = Structured Clinical Interview, TBS = Theta Burst Stimulation, BDI-II = Beck's Depression Inventory II, VAS = Visual Analogue Scale assessing subjective stress, SRSRQ = Stress-Reactive State-rumination Questionnaire, PANAS = Positive and Negative Affect Schedule.

6.3.3 Theta Burst Stimulation (TBS)

A study nurse, not further involved in the study, performed the motor threshold determination and stimulation. We used a MagVenture MagPro X100 Stimulator (MagVenture, Farum, Denmark), a figure-eight shaped coil without cooling for motor threshold determination (MagVenture C-B60 coil) and another figure-eight shaped coil with active cooling (MagVenture Cool-B65 Active/Placebo coil) for the stimulation. This design enables double-blind stimulation by automatically switching between active or sham TBS by coil flipping as per the device instructions. Motor threshold was determined using an electromyogram (EMG) with the 4-channel EMG-EP-System (Schreiber & Tholen Medizintechnik GmbH, Stade) (for details, see supplementary material S6). The TBS over the right VLPFC was applied at 80% of the resting motor threshold (Huang et al., 2005). Stimulation was applied at the 10-20 electrode position F8, which corresponded to the maximum of the induced electric field. The induced electric field is relatively focal, as the Magventure B65 coil used has a half-value depth of 1.4 cm (Deng et al., 2013), meaning the signal intensity decreases by 50% after penetrating 1.4 cm into the tissue. This ensures that the right VLPFC is appropriately targeted (for an illustration of the approximation of the TBS-induced electric field see supplementary material S6). After disinfecting the corresponding skin area, two pre-gelled surface electrodes (28x20 mm) were placed 1 cm around the stimulation site to induce a low current for a superficial sensation during stimulation (active and sham). Three different TBS protocols were utilized in the study: iTBS (40 cycles of 2 s theta burst trains (10 bursts of 3 pulses each) followed by 8 seconds of rest (i.e., total of 390 s), cTBS (80 s train of uninterrupted TBS including 400 bursts of 3 pulses at a frequency of 50 Hz and burst frequency of 5 Hz) and sham stimulation, where the duration was the same as either the iTBS or cTBS protocol. Consequently, the stimulation parameters included a total of 1200 pulses for both paradigms.

6.3.4 Electrocardiogram (ECG)

After disinfecting the corresponding skin areas, three Ag/AgCl ring electrodes with an 8 mm diameter were placed below the left costal arch, above the right collar bone and below the neck (reference). The signal was assessed using a BrainAmp ExG amplifier and Brain Vision recorder software (Brain Products, Munich, Germany) with a sampling rate of 1000 Hz. Preprocessing using Brain Vision Analyzer 2.1 involved band-pass filtering (1-30 Hz; slope: 48 db/Oct, time constant 0.1591549s) and a notch filter at

50 Hz to eliminate power line artifacts. Using MATLAB 2017a, we then computed the mean interval between consecutive R-peaks in beats per minute (BPM) for each experimental condition, respectively.

6.3.5 Near-Infrared Spectroscopy (NIRS)

Cortical oxygenation was assessed using an ETG-4000 Optical Topography System with a sampling rate of 10 Hz (46-channel continuous wave multichannel fNIRS system; Hitachi Medical Co., Japan). Two frontal probesets and one parietal probeset were integrated into EEG-Easycaps, which were placed on the subject's head oriented to the electrode positions Fpz and Cz. Probeset placement and Regions of Interest (ROIs) are illustrated in supplementary material S7. We stimulated electrode position F8 of the 10-20 system (Jasper, 1958), which corresponded to one channel of our right frontal probeset. For details on the preprocessing of the fNIRS-data using custom MATLAB 2024 scripts, we refer to supplementary material S7. For data analysis, event-related averages were computed for each 40 s trial of ctl1, ctl2 and the arithmetic task of the TSST including a 5 s baseline correction. Data was exported separately for the stimulated channel and as an average for each of our ROIs: Left and right VLPFC, left and right DLPFC, and SAC. We chose fNIRS to assess the neural correlates, specifically cortical oxygenation, because it is relatively robust to motion artifacts (see e.g., review by Pinti et al. (2020)), which are common during the TSST (e.g., gestures and facial expressions). Unlike fMRI, where participants must remain still, fNIRS allows participants to move naturally, enhancing ecological validity and ensuring higher similarity to the original TSST when fNIRS is employed (Henze et al., 2023). Additionally, fNIRS has been successfully used in conjunction with TMS to measure TMS-induced neural changes (Curtin et al., 2019).

6.3.6 Data analysis

Data analysis was conducted using SPSS (Version 28, IBM Corp., 2021). Data visualization was carried out using MATLAB 2024, RStudio Version 2022.02.3+492, R Version 4.3.1 and the ggplot2 package. We firstly identified and excluded multivariate outliers were identified using Mahalanobis distances for each of our dependent variables (DV): subjective stress, state rumination, positive and negative affect, math performance, heart rate, and cortical oxygenation (for the number of excluded participants per DV, see supplementary material S8). Then, to analyze the effects of TBS, we fitted repeated measures ANOVAs (rmANOVAs) using contrasts comparing active stimulation (iTBS/cTBS) with sham stimulation before performing planned contrasts (see below). For an analysis of the raw data, we refer to supplementary material S9. Significant effects were followed by post-hoc tests, which were corrected for multiple comparisons using the Benjamini-Hochberg procedure. Non-significant post-hoc tests and those related to lower-order effects in significant higher-order interactions are not reported. Polynomial contrasts (linear and quadratic) were used for interpretative purposes, particularly to capture potential nonlinear changes, such as a peak during stress induction followed by a return to baseline in the post-stress phase. Violations of sphericity (Mauchly test $p < .05$) were corrected using Greenhouse-Geisser estimates if $\epsilon < 0.75$, and Huynh-Feldt estimates if $\epsilon > 0.75$. There were no significant baseline differences between the stimulation conditions.

(1) **Contrast analysis**: For each DV, we calculated contrasts by subtracting the sham stimulation values from the active stimulation values at each time point. These contrasts were then entered into rmANOVAs which included a four-way interaction of time, stimulation condition (iTBS vs. cTBS), group (low vs. high RRS), and the order of stimulation conditions (active → sham vs. sham → active). Time refers to the number of repeated assessments for each DV (12 for subjective stress, 4 for state rumination, 4 for positive and negative affect, 3 for math performance, 7 for heart rate, and 3 for cortical oxygenation). To account for potential habituation effects in stress responses due to repeated exposure to the TSST, we included the factor "order of stimulation conditions" in the rmANOVA. This allowed us to better capture how habituation may interact with the effects of stimulation on stress reactivity. When interactions involving the order of conditions were observed, we conducted separate rmANOVAs to analyze each order individually.

(2) **Planned contrasts**: Finally, based on our previous studies(Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018)—using the same experimental design but without neurostimulation—where we investigated on the one hand high and low trait ruminators and on the other hand depressed patients and healthy controls, we conducted planned contrasts to examine specific time points where TBS effects were anticipated to be most pronounced. These studies consistently showed most pronounced group differences for subjective stress and negative affect immediately following the stress induction, while

state rumination peaked after the second resting state. Furthermore, we consistently observed prefrontal hypoactivation during the arithmetic task in high-ruminators and depressed patients. Therefore, only these specific time points were selected as planned contrasts. This approach enabled more focused hypothesis testing and increased statistical power. Specifically, we investigated subjective stress ratings following the TSST (post-math, post-rest2, 15–60 min post TSST), state rumination ratings after the second resting state, negative affect ratings following the TSST, and cortical oxygenation in the right VLPFC during the arithmetic task of the TSST. We chose the arithmetic task to investigate cortical oxygenation rather than the TSST job interview because, although both are cognitively demanding and we expect similar effects of TBS, the arithmetic task includes non-stressful control conditions (control task 1 and control task 2) with a consistent structure of six trials each that can be averaged. This design allows for within-subject comparisons that are not feasible during the continuous 5-minute job interview. It is important to note that these one-sided t-tests are uncorrected for multiple comparisons and should therefore be interpreted with caution and only in conjunction with the broader pattern of findings. To reduce the article's length, results on positive affect, math performance, and heart rate are included in supplementary material S10-S13.

fNIRS data

For the fNIRS data, we first conducted a manipulation check using paired t-tests to compare cortical oxygenation in each channel during the arithmetic task of the TSST, contrasting active stimulation with sham stimulation (active vs. sham) within subjects across all participants. Next, we conducted a rmANOVA where cortical oxygenation of the single channel, corresponding to the stimulated electrode position F8, was the DV. Then, a repeated measures MANOVA (rmMANOVA) was performed based on five ROIs (left VLPFC, left DLPFC, right VLPFC, right DLPFC, and SAC), incorporating the aforementioned four-way interaction (see (1) Contrast analysis).

Reliable change indices

Additionally, we calculated Reliable Change Indices (RCIs) for state rumination ratings to assess how many participants exhibited statistically meaningful changes between post rest1 and post rest2. We focused the RCI analysis on state rumination, as it represents the primary dependent variable in this study. RCIs are a method used to determine whether an observed change in an individual's score over time exceeds what could be expected due to measurement error or natural variability alone. In this context, calculating the RCI allows us to identify participants whose changes in state rumination following the stressor are not only statistically significant at the group level but also clinically or psychologically meaningful at the individual level. This approach provides a more nuanced understanding of the effects of the TSST by revealing patterns of reliable individual change that may be masked in group-level analyses. For further details on the application and interpretation of RCI, see Blampied (2022).

Exploratory analysis

As an exploratory analysis, we also examined the influence of expectancy effects on the previously described raw data analysis. For this purpose, we included the item “Do you believe that the stimulation made you perform better or worse on the task? (better vs. worse vs. no effect)” as a covariate.

6.4 Results

6.4.1 Sample

Overall, the mean age of the sample was 23.82 years (*SD* = 6.00 years), and a total of 68.54% of the sample were female. Participants scored a mean RRS of 2.01 (*SD* = 0.64) and a BDI-II of 6.07 (*SD* = 5.99) equaling "no depression" according to the cutoff scores (Hautzinger et al., 2009). There were no significant differences concerning demographic variables among the two study arms (see table 6.1).

	cTBS-arm	iTBS-arm	test statistic	total sample
age	23.45 (6.15)	24.18 (5.89)	$F(1, 87) = 0.321$, $p = .572$, $\eta_p^2 = .004$	23.82 (6.00)
percent female	72.7%	64.4%	$\chi^2(1) = 0.376$, $p = .540$	68.54%
BDI-II total score	6.36 (5.73)	6.38 (6.21)	$F(1, 87) = 0.00$, $p = .991$, $\eta_p^2 = .000$	6.07 (5.99)
RRS mean	2.06 (0.62)	1.89 (0.55)	$F(1, 87) = 1.97$, $p = .164$, $\eta_p^2 = .02$	2.01 (0.64)

Table 6.1
Demographic variables of the sample by study arm. BDI-II = Beck Depression Inventory II, RRS = Rumination Response Scale. Test statistic = comparison of the cTBS- and iTBS-arm. Please note that the RRS and BDI-II scores correspond to assessments at the first appointment.

6.4.2 Blinding and comparability of motor thresholds

A binomial test testing whether participants correctly identified whether they received active or sham stimulation (true vs. false; H_0: $p = .5$) showed that participants could not distinguish between sham and active-stimulation during the first, but blinding failed at the second appointment (for details on blinding see supplemental material S14). Note that while we did not specifically recruit participants with no prior experience with TMS/tDCS, only 5 had previously experienced TMS, 3 of whom had also used tDCS, and 5 participants had experience with tDCS but not TMS. There were no differences in motor thresholds between cTBS (*M* = 43.89, *SD* = 6.93), iTBS (*M* = 40.80, *SD* = 5.20) and sTBS (*M* = 42.18, *SD* = 6.06), $F(2, 175) = 2.872$, $p = .059$, $\eta_p^2 = .03$.

6.4.3 *Psychological measures*

Subjective stress: contrasts. We first fitted a rmANOVA for stress contrasts (active minus sham) as a function of time (indicating the 12 repeated assessments of stress over the course of one appointment), RRS-group (low vs. high-ruminators), stimulation condition (cTBS vs. iTBS) and order of stimulation conditions (active → sham vs. sham → active). As a result, we observed a significant interaction of time and order of stimulation conditions, $F(5.617, 432.473) = 14.037, p < .001, \eta_p^2 = .154$, which is why we then fitted separate rmANOVAs dependent on the order of stimulation conditions. In both cases, we only observed a significant main effect of time (active → sham: $F(4.595, 174.603) = 7.703, p < .001, \eta_p^2 = .169$; sham → active: $F(5.059, 197.320) = 16.269, p < .001, \eta_p^2 = .294$) and a main effect of the constant term (i.e. a significant main effect of active stimulation vs. sham) (active → sham: $F(1, 38) = 40.338, p < .001, \eta_p^2 = .515$ (figure 6.2A); sham → active: $F(1, 39) = 14.732, p < .001, \eta_p^2 = .274$ (figure 6.2B)). To evaluate the time course in greater detail, we investigated polynomial contrasts, which revealed a significant quadratic time course illustrating the stress increase due to the TSST and subsequent decrease in the post-stress phase. This effect, however, was inversely dependent on the order of stimulation conditions. When participants received sTBS first, stress ratings were U-shaped, $F(1, 39) = 19.636, p < .001, \eta_p^2 = .335$; when participants received active first, stress was inversely U-shaped, $F(1, 38) = 33.196, p < .001, \eta_p^2 = .466$. That means that stress increases were higher in case of first-time exposure to the TSST. Lastly, only when participants received active stimulation first, we observed a significant main effect of the stimulation, $F(1, 38) = 4.443, p < .05, \eta_p^2 = .105$, which was illustrated by increased differences between active and sham stimulation following iTBS compared to cTBS. This means participants rated their stress overall higher when they received iTBS at the first appointment compared to when they received sTBS at the second appointment, whereas stress was more comparable between the two appointments when participants received cTBS.

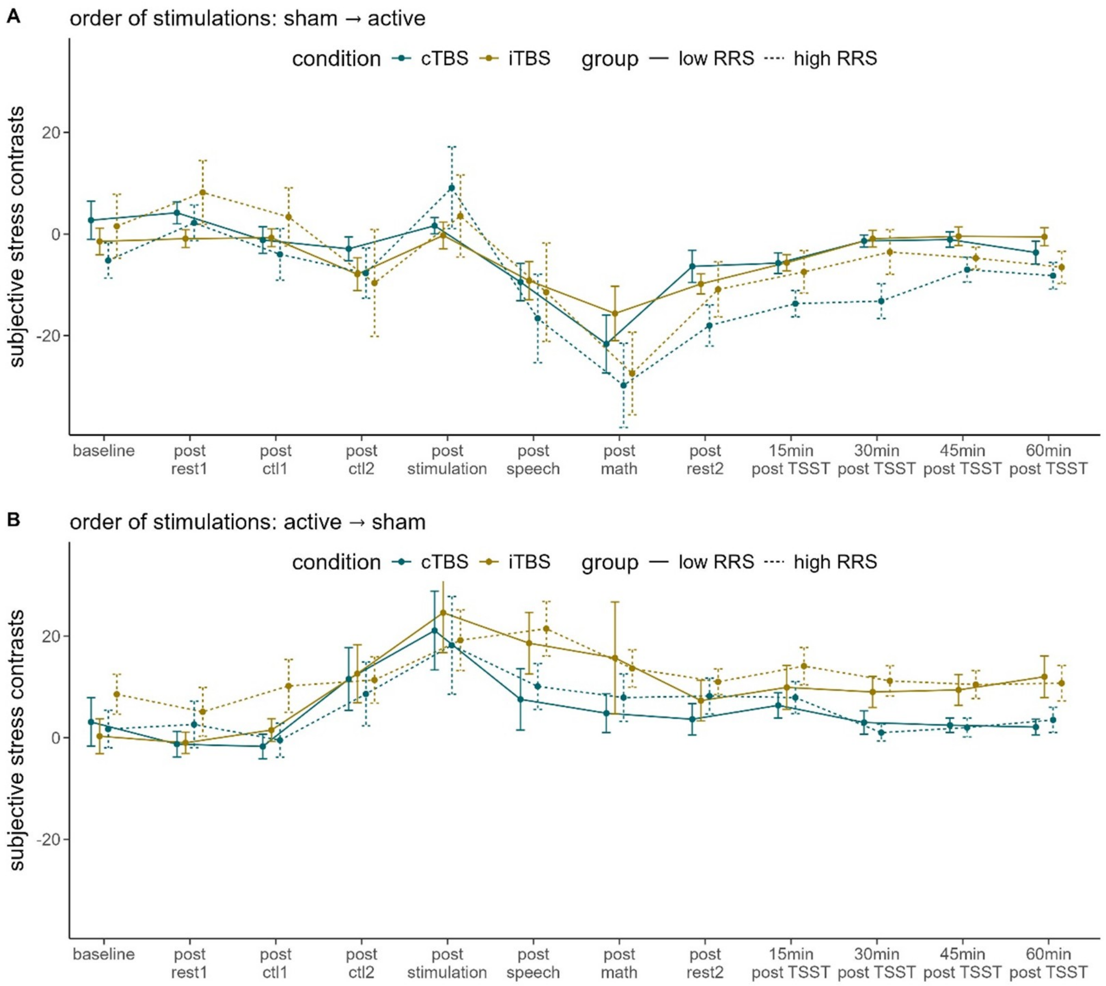


Figure 6.2
*Line plot of the contrasts of subjective stress ratings dependent on order of conditions (**A** sham stimulation at the first appointment, active stimulation at the second appointment; **B** active stimulation at the first appointment, sham stimulation at the second appointment). rest = resting-state measurement, ctl1 = control task 1, ctl2 = control task 2, speech = job interview of the TSST, math = arithmetic task of the TSST, TSST = Trier Social Stress Test, sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation, 15 min = 15 min after the TSST, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.*

Subjective stress: planned contrasts. As planned contrasts, we compared stress between the iTBS and cTBS vs. sTBS conditions at the six time points following the TSST. These comparisons were conducted separately for low and high ruminators across the different appointments. We observed higher stress following iTBS compared to sTBS, but only at the first appointment: Namely, we observed higher stress following iTBS compared to sTBS in low ruminators at 30 min (M_{sTBS} = 7.27, SD_{sTBS} = 9.14; M_{iTBS} = 16.50, SD_{iTBS} = 10.01, $t(30) = -2.571$, $p < .01$, $d = -0.981$), 45 min (M_{sTBS} = 5.73, SD_{sTBS} = 8.10; M_{iTBS} = 18.20, SD_{iTBS} = 12.01, $t(30) = -3.463$, $p < .001$, $d = -1.321$) and 60 min post TSST (M_{sTBS} = 6.68, SD_{sTBS} = 8.71; M_{iTBS} = 16.00, SD_{iTBS} =

10.49, $t(30) = -2.633$, $p < .01$, $d = -1.004$) (figure 6.3A) and in high ruminators at 45 min post TSST ($M_{sTBS} = 11.36$, $SD_{sTBS} = 11.56$; $M_{iTBS} = 20.50$, $SD_{iTBS} = 15.71$, $t(30) = -1.851$, $p < .05$, $d = -0.703$) (figure 6.3B). When comparing cTBS and sTBS, we observed higher stress in high ruminators at the first appointment following sTBS ($M = 62.50$, $SD = 24.25$) compared to cTBS ($M = 42.30$, $SD = 23.13$) directly after the TSST, $t(30) = 2.214$, $p < .05$, $d = 0.845$ (figure 6.3B).

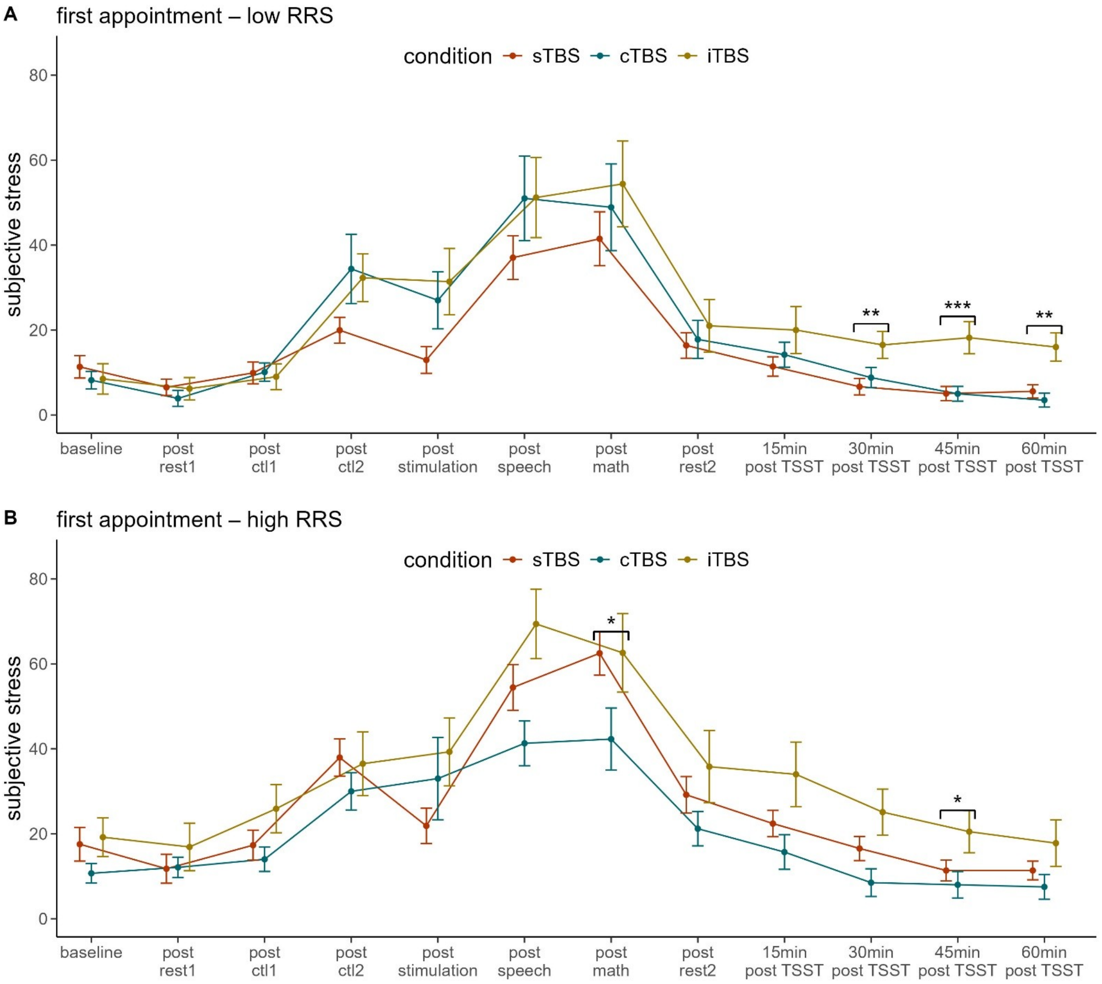


Figure 6.3
*Illustration of the planned contrasts of subjective stress for low ruminators (**A**) and high ruminators (**B**). At the first appointment, we observed significantly higher subjective stress following iTBS compared to sTBS. In low ruminators, this effect was evident at 30 min (p < .01), 45 min (p < .001), and 60 min post TSST (p < .01). In high ruminators, significantly higher stress following iTBS compared to sTBS was observed at 45 min post TSST (p < .05). Additionally, when comparing cTBS and sTBS, high ruminators reported significantly higher subjective stress following sTBS compared to cTBS immediately after the TSST (p < .05). rest = resting-state measurement, ctl1 = control task 1, ctl2 = control task 2, speech = job interview of the TSST, math = arithmetic task of the TSST, TSST = Trier Social Stress Test, sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation, 15 min = 15 min after the TSST, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.*

State rumination: contrasts. Fitting a rmANOVA for state rumination contrasts (active minus sham) as a function of the four-way interaction of time (indicating the 4 repeated assessments of state rumination over the course of one appointment), RRS-group (low vs. high ruminators), stimulation condition (cTBS vs. iTBS) and order of stimulation conditions (active → sham vs. sham → active), we observed a significant interaction of time and the order of stimulation conditions, $F(2.917, 224.632) = 5.251$, $p < .01$, $\eta_p^2 = .064$. We then fitted separate rmANOVAs dependent on the order of stimulation conditions. For participants having received sham stimulation first, we observed a significant main effect of time, $F(3, 114) = 6.975$, $p < .001$, $\eta_p^2 = .155$ and a significant main effect of RRS-group, $F(1, 38) = 7.583$, $p < .01$, $\eta_p^2 = .166$ (see figure 6.4A). Polynomial contrasts of the main effect of time revealed a significant linear contrast, $F(1, 38) = 12.273$, $p < .01$, $\eta_p^2 = .244$. This is reflected in comparable state rumination between active and sham stimulation prior to the stimulation and TSST, with increasing differences observed afterward. Following the TSST, we found negative contrasts, indicating higher state rumination following sham (i.e. their first appointment). The main effect of group was reflected by negative contrasts: High ruminators experienced higher state rumination following sham compared to active stimulation (i.e. their first appointment), whereas low ruminators experienced lower rumination regardless of the type of stimulation. No significant effects were observed in case participants have received active stimulation first (all p's > .396) (see figure 6.4B).

State rumination: planned contrasts. When we investigated state rumination after the second resting-state separately for low and high ruminators on each appointment, we observed no differences (all p's > .056).

State rumination: reliable change. Lastly, we calculated Reliable Change Indices (RCIs) using state rumination prior to the stress induction (rest1) to after the stress induction (rest2) for each appointment and RRS-group separately. In case of both appointments, most participants exhibited no reliable change in state rumination (see table 6.2). Interestingly, about 35 % of high ruminators showed reliable increases at the first appointment and only 13 % at the second appointment. The same pattern was observed for low ruminators. Further, no low ruminator and only 3 high ruminators showed significant decreases at the first appointment; this was the case in 1 low and 12 high ruminators at the second appointment (see supplementary material S15).

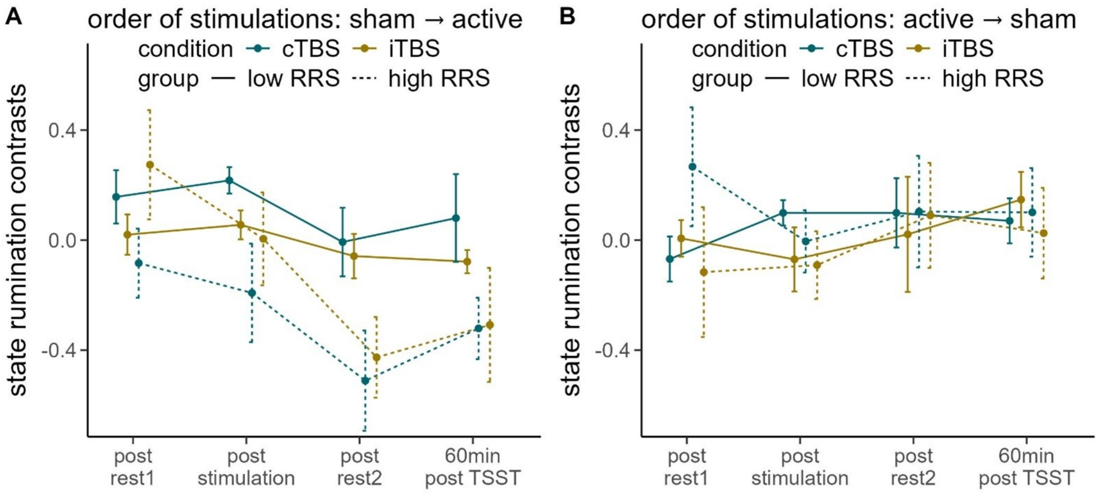


Figure 6.4
*Line plot of the contrasts of state rumination ratings dependent on order of conditions (**A** sham stimulation at the first appointment, active stimulation at the second appointment; **B** active stimulation at the first appointment, sham stimulation at the second appointment). rest = resting-state measurement, TSST = Trier Social Stress Test, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.*

	low ruminators (n = 44)	high ruminators (n = 45)	test-statistic
appointment 1:			$\chi^2(2) = 8.432$, $p < .05$
reliable decrease	0 (0.00%)	3 (6.67%)	
no reliable change	37 (84.09%)	26 (57.78%)	
reliable increase	7 (15.91%)	16 (35.55%)	
appointment 2:			$\chi^2(2) = 14.181$, $p < .001$
reliable decrease	1 (2.27%)	12 (26.67%)	
no reliable change	41 (93.18%)	27 (60.00%)	
reliable increase	2 (4.55%)	6 (13.33%)	

Table 6.2
Absolute and relative frequencies of reliable change. Percentages refer to the relative frequencies in the corresponding subsample (low or high ruminators) and the test-statistic indicated χ^2-tests comparing the distribution of RCI-categories in low and high ruminators at the respective appointment.

Negative affect: contrasts. We conducted a rmANOVA on negative affect contrasts (active minus sham), with time (reflecting the 4 repeated assessments of the PANAS within one appointment), RRS-group (low vs. high ruminators), stimulation condition (cTBS vs. iTBS), and order of stimulation conditions (active → sham vs. sham → active) as factors. We observed a significant interaction of time and order of stimulation conditions, $F(2.503, 192.699) = 9.012, p < .001, \eta_p^2 = .105$. Fitting separate rmANOVAs dependent on the order of stimulation conditions, we observed a significant main effect of the constant term (i.e. a significant main effect of active stimulation vs. sham: sham → active: $F(1, 39) = 13.297, p < .001, \eta_p^2 = .254$) (figure 6.5A); active → sham: $F(1, 38) = 8.505, p < .01, \eta_p^2 = .183$ (figure 6.5B). Only in participants having received sham first, we observed a main effect of time, $F(2.713, 103.079) = 11.566, p < .001, \eta_p^2 = .233$. Investigating the main effect of time using polynomial contrasts, we observed a linear contrast, $F(1, 38) = 8.781, p < .01, \eta_p^2 = .188$, which was reflected by comparable negative affect between active and sham stimulation previous to the TSST and negative contrasts (higher negative affect following sTBS, i.e. the first appointment) afterwards.

Negative affect: planned contrasts. We observed no significant differences in negative affect directly after the TSST (all p's > .063).

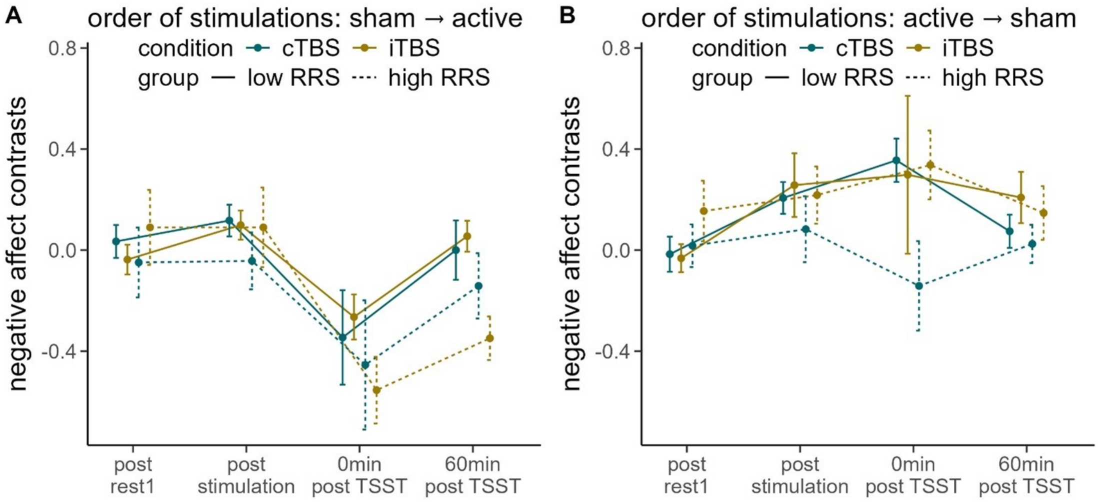


Figure 6.5
*Line plot of the contrasts of negative affect ratings dependent on order of conditions (**A** sham stimulation at the first appointment, active stimulation at the second appointment; **B** active stimulation at the first appointment, sham stimulation at the second appointment). rest = resting-state measurement, TSST = Trier Social Stress Test, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.*

6.4.4 *Physiological measures*

Cortical oxygenation: overall *t*-tests. Paired *t*-tests comparing cortical oxygenation during the arithmetic task of the TSST between active and sham stimulation revealed significant effects in two channels for cTBS (channel 29 and 31; Brodmann area 7) (figure 6.6A), and three in the iTBS condition (channel 1, 22; both Brodmann area 6 and 44; Brodmann area 7) (figure 6.6B). Please note that, although we expected a negative difference after cTBS and a positive difference after iTBS, the results showed the opposite pattern in channel 31 (cTBS) and channel 1 (iTBS), respectively.

Cortical oxygenation: contrasts single channel. We then fitted a rmANOVA with the four-way-interaction of time (reflecting the three tasks during which cortical oxygenation was assessed: control task 1, control task 2, and the arithmetic task of the TSST), RRS-group (low vs. high ruminators), stimulation condition (cTBS vs. iTBS), and order of stimulation conditions (active → sham vs. sham → active) to investigate whether stimulation had a significant effect in the single stimulated channel corresponding to electrode position F8. No significant effects were observed (all *p*'s > .085).

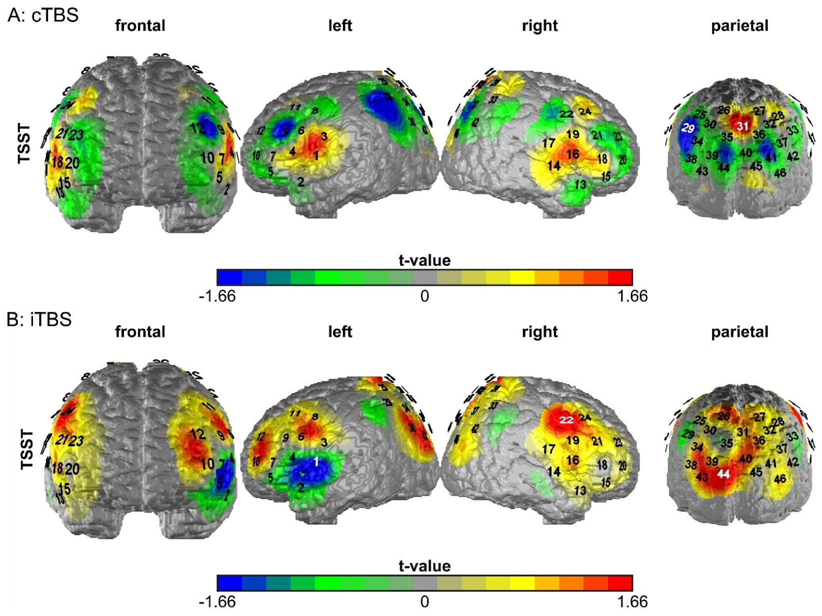


Figure 6.6
Plots of the t-values of the paired t-tests in each channel testing the active stimulation condition against the sham stimulation in each channel dependent on the stimulation condition. A = cTBS, B = iTBS, TSST = arithmetic task of the TSST. The figure legend was scaled so that channels showing a significant t-value are displayed in blue (≤ -1.66) or red (≥ 1.66). Significant channels are displayed in white to make them more easily identifiable. Significant channels in the cTBS condition are channel 29 and 31. Significant channels in the iTBS condition are channel 1, 22 and 44. This plot was generated using custom MATLAB 2024a scripts. Please note that, although we expected a negative difference after cTBS and a positive difference after iTBS, the results showed the opposite pattern in channel 31 (cTBS) and channel 1 (iTBS), respectively.

Cortical oxygenation: contrasts ROIs. Lastly, we fitted a rmMANOVA using our 5 ROIs (bilateral DLPFC, bilateral VLPFC and SAC) dependent on the four-way interaction of time (reflecting the three tasks during which cortical oxygenation was assessed: control task 1, control task 2, and the arithmetic task of the TSST), RRS-group (low vs. high ruminators), stimulation condition (cTBS vs. iTBS) and order of stimulation conditions (active → sham vs. sham → active). We observed a significant interaction of time, RRS-group and stimulation condition, $F(10, 310) = 2.097$ $p < .05$, $\eta_p^2 = .063$. Univariate tests did not yield significance in any ROI. When investigating polynomial contrasts, we observed a significant linear contrast of the four-way interaction of time, RRS-group, stimulation condition and order of stimulation conditions in the left DLPFC, $F(1, 79) = 4.250$, $p < .05$, $\eta_p^2 = .051$. This effect seemed to be driven by group differences previous to the TBS, namely positive contrasts in the low ruminators compared to negative contrasts in the high ruminators during control task 1 but only in case participants received active stimulation first (figure 6.7A).

We further observed a significant linear contrast of the three-way interaction of time, condition and order of stimulation condition in the right DLPFC, $F(1, 79) = 4.607$, $p < .05$, $\eta_p^2 = .055$. This was primarily driven by participants having received sham stimulation at their first and active stimulation at the second appointment: During control task 1, participants having received iTBS and participants having received cTBS exhibited comparable, positive contrasts (higher cortical oxygenation at the second appointment, i.e. during active stimulation). During the arithmetic task of the TSST, this pattern was reversed: Participants having received iTBS showed positive contrasts (higher cortical oxygenation at the second appointment, i.e. during active stimulation), while participants having received cTBS showed negative contrasts (higher cortical oxygenation at the first appointment, i.e. during sham stimulation) (figure 6.7B).

We also observed a quadratic contrast of the three-way interaction of time, group and order of stimulation conditions in the right VLPFC, $F(1, 79) = 5.420$, $p < .05$, $\eta_p^2 = .064$. This was reflected by similar contrasts between low and high ruminators at every given time point and quasi no changes over time in case participants received sham stimulation first. In case they received active stimulation first, low ruminators exhibited positive contrasts (higher cortical oxygenation at the first appointment, i.e. during active stimulation) while high ruminators exhibited negative contrasts (higher cortical oxygenation at the second appointment, i.e. during sham stimulation) during control task 1. During control task 2, this pattern was reversed and during the arithmetic task, both groups exhibited comparable positive contrasts (for brainmaps see supplementary material S16) (figure 6.7C). We observed no significant between-subjects effects.

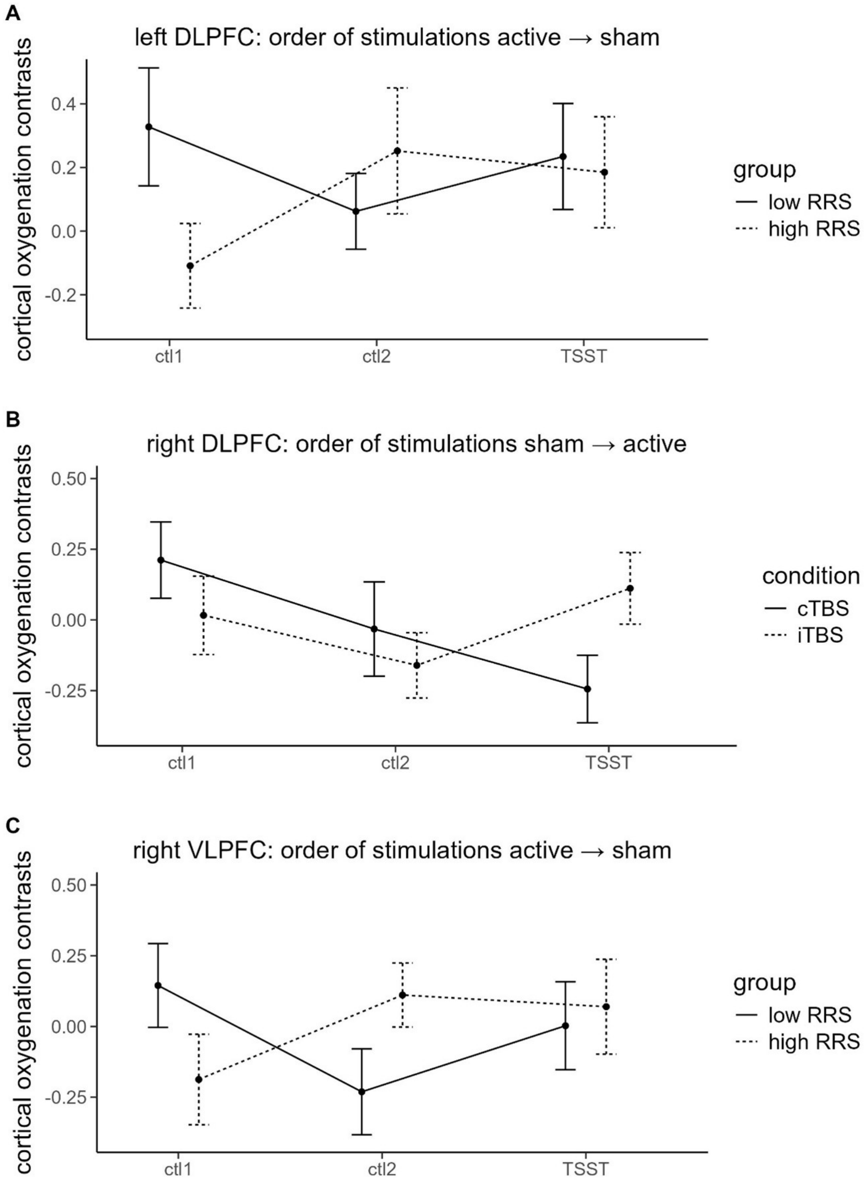


Figure 6.7
Illustration of the polynomial contrasts of the fNIRS analysis: (A) contrasts in the left DLPFC in case participants received active stimulation first; (B) contrasts in the right DLPFC in case participants received sham stimulation first; (C) contrasts in the right VLPFC in case participants received active stimulation first. ctl1 = control task 1 (reading numbers), ctl2 = control task 2 (mental arithmetic without social stress), TSST = arithmetic task of the Trier Social Stress Test (mental arithmetic with social stress). Error bars indicate 1 standard error of the mean.

Cortical oxygenation: planned contrasts. Investigating our planned contrasts, we observed significantly higher cortical oxygenation in the right VLPFC during the arithmetic task following iTBS for the high ruminators at the first appointment (M = 0.83, SD = 0.51) compared to sTBS (M = 0.40, SD = 0.51), $t(32) = -2.268$, $p < .05$, $d = -0.831$ (figure 6.8).

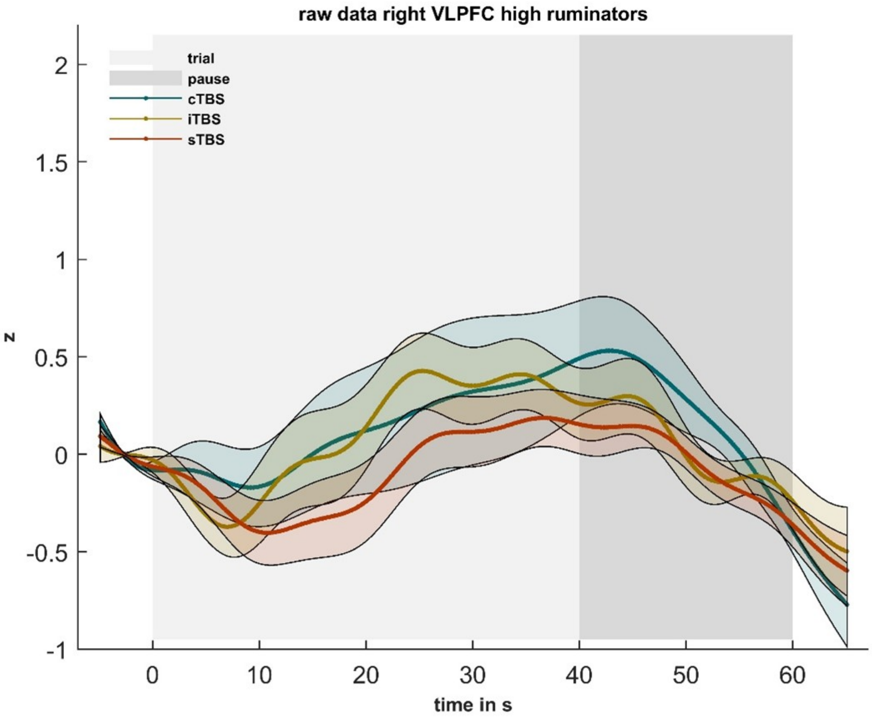


Figure 6.8
Illustration of the z-standardized hemodynamic responses during the arithmetic task of the TSST in the right VLPFC in high ruminators depending on the TBS-condition at the first appointment. The light shading marks the 40 s trial and the dark shading the 20 s pause to allow the hemodynamic response to recover. Shadings around the hemodynamic curves reflect standard errors of the mean. The baseline includes the 5 s before each trial; 0 s on the x-axis marks the beginning of the trial. See supplementary material S17 for the time series of the other ROIs.

6.4.5 Impact of expectancy effects

We observed a main effect of expectancy effects during the first appointment, $F(2, 59) = 5.659$, $p < .01$, $\eta_p^2 = .161$, and the second appointment for stress, $F(2, 62) = 3.212$, $p < .05$, $\eta_p^2 = .094$. We observed a significant interaction of time and expectancy effects during the first appointment for negative affect, $F(1.972, 138.055) = 3.921$, $p < .05$, $\eta_p^2 = .053$. No significant expectancy effect emerged when included in the fNIRS-analysis.

6.5 Discussion

The study at hand aimed to investigate the effects of TBS applied to the right VLPFC on the physiological and behavioral stress response. In general, replicating previous findings (Allen et al., 2017; Kudielka et al., 2007) we observed stronger responses to the TSST in terms of stress, state rumination, and negative affect during first-time exposure to the paradigm. This is most likely due to a reduced feeling of uncontrollability as the experimental stress induction was very similar for both appointments despite different starting points, different calculations and a change in TSST jury members. Nevertheless, the stress induction was also successful in the case of the second exposure to the TSST. For stress, we observed a significant main effect of the stimulation but only in participants receiving active stimulation first: Participants rated their stress overall higher when they received iTBS at the first appointment compared to when they received sTBS at the second appointment. In contrast, stress was more consistent and lower across both appointments when participants received cTBS. When we investigated the post-stress phase, we found higher stress in low and high ruminators having received iTBS compared to participants having received sTBS but only at the first appointment. This is contrary to our initial hypothesis where we expected a positive effect on stress levels due to the suggested excitatory effect on the right VLPFC and therefore facilitation of adaptive emotion regulation. Potentially, the uncomfortableness of the stimulation may have led to higher stress that may be experienced as more intense compared to a smaller effect of facilitated emotion regulation. Further, the rating of stress using a Visual Analogue Scale might not be the optimal form of assessment because several aspects of rating how stressful an experience is are merged in a single number which makes it impossible to evaluate why participants rated their stress the way they did. It is also important to note that many studies investigating the VLPFC so far were conducted using tDCS (He et al., 2018; Marques et al., 2018; Vergallito et al., 2018) which is often perceived as less painful. Especially due to the relative closeness to facial nerves and muscles, future investigations using TBS applied to the VLPFC are desperately needed to disentangle the potentially opposing effects of experienced discomfort and the facilitation of emotion regulation on stress.

With respect to state rumination, our results showed no clear effect of the stimulation conditions, but again an effect of order of stimulation conditions, reflecting habituation effects between the TSST-sessions. Moreover, high ruminators exhibited significantly higher state rumination compared to low ruminators, consistent with prior research (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021; Rosenbaum, Thomas, et al., 2018).

As reflected by reliable change indices, low ruminators showed low or no increases in state rumination while strong increases were found in the high ruminators at the first appointment.

We further observed higher negative affect in high-ruminators and more pronounced increases in case of the first-time exposure, however, no impact of the stimulation. Considering performance measures of the TSST, we again observed no significant impact of the stimulation but of the order of stimulation conditions. Also, heart rates indicated successfully induced stress at both appointments but no differences among stimulation conditions. Please note that analysis of performance measures and heart rates are to be found in the supplementary material.

The absent effect of TBS might be explained by several factors, e.g. the timing of the stimulation and time passing between the TBS and the TSST or potentially suboptimal targeting of the right VLPFC. Indeed, the VLPFC is difficult to target due to the closeness to facial nerves and muscles. However, we observed hypothesis-conform differences in cortical oxygenation in the right VLPFC during the TSST in high ruminators: At the first appointment, we observed higher cortical oxygenation following iTBS compared to sTBS. However, in the rmMANOVA including the other ROIs, we observed no significant impact of the stimulation. This may be due to rather small effects to be detected and potential power problems. Our sample size calculation was based on only one study investigating the effect of TBS on stress-reactive rumination (De Witte et al., 2020). Please note that we focused on the analysis of the arithmetic task of the TSST. It would further be interesting to analyze the speech phase of the TSST, despite our expectation of similar TBS effects as observed during the arithmetic task. While the continuous nature of the speech task poses methodological challenges—such as the lack of discrete trials for within-subject comparisons—it could provide additional insights into the neurophysiological responses to stress.

What is particularly interesting is that, contrary to expectations, we did not observe the well-documented prefrontal hypoactivation under stress (Int-Veen et al., 2023; Pizzagalli & Roberts, 2022). These findings contrast previous studies with the same experimental setup, but without TBS (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021, 2024; Rosenbaum, Thomas, et al., 2018). One potential explanation might be the influence of performance-related expectancy effects. As the prefrontal hypoactivation in the TSST has been found to be linked to performance (Int-Veen et al., 2023) it is plausible that participants who perceived TBS as enhancing their performance—regardless of the actual neurobiological effects of TBS—may have experienced improved cognitive output during the TSST. This could have led to the attenuation or absence of the typical prefrontal hypoactivation. We also suggest that expectancy effects might have an impact on the assessed (psychological) variables because the order of stimulation conditions had a significant impact on most variables and several effects were only observed at the first appointment.

One factor contributing to the observed patterns may be participants' expectations regarding the impact of TBS on their performance. In exploratory analyses, these beliefs appeared to be associated with stress and negative affect, either through interactions with time or as main effects. However, since expectancy was not systematically manipulated in our study design, only investigated in an exploratory analysis, and given that subgroups became very small, these findings should be interpreted with caution.

Further, although we recruited primarily naive participants, 65–85% identified their stimulation condition at the second appointment. Regardless of the potential role of expectancy effects, the main finding of the current investigation is a strong habituation to the TSST in the neural stress response and stress-reactive rumination.

Another possible source of inconsistent findings is the strong hemodynamic response induced by the TSST. The small TBS-effects might have vanished due to the intensity of the stressor. This might also be reflected on a cognitive level as reappraisal as an emotion-regulation strategy is preferred following low-intensity stimuli (Shafir, Schwartz, Blechert, & Sheppes, 2015; Sheppes, Scheibe, Suri, & Gross, 2011). Likewise, TBS-effects on a behavioral level might be obliterated. Note that we did not observe prefrontal hypoactivation in high ruminators which has repeatedly been found in depression (Pizzagalli & Roberts, 2022). This contrasts recent findings that aberrant prefrontal functioning has been observed in high ruminators as trait rumination and depressive symptoms are highly correlated and similar neural activation was observed (Int-Veen et al., 2023).

Unfortunately, the fNIRS-device used does not allow coil placement and concurrent measurement and only records relative hemoglobin concentration changes, based on a baseline measurement taken at the start of each segment. This means that brain activity could not be recorded during stimulation.

Lastly, one likely contributor to the inconsistency of findings is the increasingly questioned assumption that TBS protocols have inherently excitatory or inhibitory effects. This classification, originally derived from studies targeting the motor cortex, may be an oversimplification. This is supported by findings of increased cortical oxygenation following cTBS and decreased oxygenation following iTBS in some channels. A recent meta-analysis by Kirkovski et al. (2023) concluded that both iTBS and cTBS can produce either excitatory or inhibitory effects on neural activity and connectivity, particularly when applied to the prefrontal cortex. In addition to methodological variability (e.g., targeting strategies, coil placement), this heterogeneity likely reflects the complex neural architecture of the frontal cortex and contextual influences, like task demands. Accumulating evidence suggests that individual differences in psychological states may correlate with the magnitude and directionality of effects of NIBS (Schutter et al., 2023) and individual characteristics (age, genetics) have a substantial impact (Corp et al., 2020; Ridding & Ziemann, 2010). This emerging understanding challenges the traditional classification of protocols as purely excitatory or inhibitory and highlights the need for more nuanced models (Hussain & Freedberg, 2025).

Future research should carefully consider within-subject designs, which may introduce habituation and comparability issues across sessions. Systematic investigation of factors influencing variability in TBS effects—such as task demands and cognitive load—is recommended, with an emphasis on standardizing task engagement and avoiding stimulation without concurrent cognitive tasks. Importantly, neural correlates must be measured, as behavioral null results do not imply absent neural effects. Advances in methods enabling neural activity assessment during stimulation should be adopted to enhance mechanistic understanding and interpretability in TBS research.

6.6 Supplementary Material Study 4

S1 Inclusion and exclusion criteria

Inclusion criteria:

- age between 18 and 50 years
- normal vision (or appropriate correction)
- right-handedness
- no metal in the skull / brain
- German as native language or very good knowledge of German

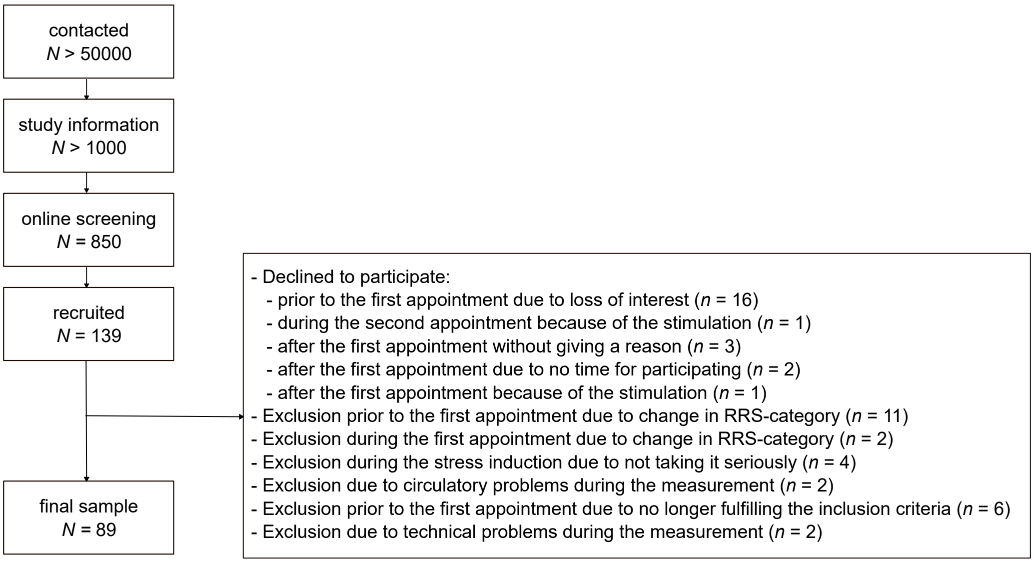
Exclusion criteria:

- diabetes mellitus
- renal insufficiency
- untreated hypertension
- history of traumatic brain injury
- cardiac arrhythmia
- acute substance abuse
- adrenal insufficiency
- any acute psychiatric or neurological disorder (including any anomalies in the SCID-Screening (Structured Clinical Interview; First et al., 2015)
- in case of women: pregnancy

S2 Information on the a priori power analysis

Currently, only one study exists that investigated the effects of TBS on state rumination increases through the TSST. In the study of De Witte et al. (2020), N = 40 participants were either stimulated with iTBS or sham TBS after the TSST was applied. Note that the study also used a within-subject design in which all participants received iTBS and sham after the TSST was conducted on two separate days. In their study, the authors found an increase of state rumination through the TSST and a marginally significant interaction between trait rumination and the TBS protocol on increases of state rumination (De Witte et al., 2020). The statistical parameters are given as B = -.32, $t(36)$ = -1.891, p = .067. Thankfully, the authors sent us the data of this study and we therefore were able to compute the effect size of this effect directly from the data, which was η_p^2 = .107 (approx. d = .69, f = .34). However, it is important to note that the study didn't use a stratified sample of trait rumination or clinical participants. As a result, only 8 of 38 subjects fulfilled our previous criteria for high ruminators (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum, Thomas, et al., 2018). As we showed in our previous studies (Rosenbaum, Hilsendegen, Thomas, Haeussinger, Metzger, et al., 2018; Rosenbaum et al., 2021, 2024; Rosenbaum, Thomas, et al., 2018) that state rumination increased in high trait ruminators/patients more than in low trait ruminators/healthy controls, we would assume that in stratified and clinical samples the above-noted buffering effect of the TBS protocol could be even higher, as the general reactivity of these samples in state rumination (under sham stimulation) is stronger than in the study of De Witte et al. (2020). However, as seen in the study of De Witte et al. (2020), it is important to achieve high power as the effect was only marginally significant. Therefore, we aim to assess N = 80 subjects which allows to detect between-within subject interactions up to f = .15 for the effect of state rumination, as computed with G*Power 3.1.9.2 (with a power of $1 - \beta$ = .95, α = .05. r = .7; between measurements, assessed on the basis of data from our previous studies). To compensate for data loss and drop-outs, we plan to collect an additional 10% (n = 8) of participants to the computed sample size, resulting in N = 88 participants.

S3 Consort diagram



- Declined to participate:
  - prior to the first appointment due to loss of interest (*n* = 16)
  - during the second appointment because of the stimulation (*n* = 1)
  - after the first appointment without giving a reason (*n* = 3)
  - after the first appointment due to no time for participating (*n* = 2)
  - after the first appointment because of the stimulation (*n* = 1)
- Exclusion prior to the first appointment due to change in RRS-category (*n* = 11)
- Exclusion during the first appointment due to change in RRS-category (*n* = 2)
- Exclusion during the stress induction due to not taking it seriously (*n* = 4)
- Exclusion due to circulatory problems during the measurement (*n* = 2)
- Exclusion prior to the first appointment due to no longer fulfilling the inclusion criteria (*n* = 6)
- Exclusion due to technical problems during the measurement (*n* = 2)

Change in RRS-category = Prior to study inclusion, we screened participants online using the Ruminative Response Scale (RRS; Treynor & Gonzalez, 2003) and only recruited low and high ruminators (low trait ruminators: mean RRS $\leq$ 1.82 (PR 25); high trait ruminators: mean RRS$\geq$ 2.36 (PR 64)). One week prior to their appointment at the laboratory, participants completed another online RRS. In case they were now categorized as the corresponding other group (low ruminators now exceeding the cutoff of high ruminators or high ruminators now scoring below the low ruminator cutoff) or their score now was closer to the corresponding other group (low ruminators now scoring a medium RRS but closer to the high ruminator cutoff or high ruminators now scoring a medium RRS but closer to the low ruminator cutoff), participants were excluded. At their first appointment in the laboratory, participants completed the RRS a third time, this time in paper-pencil format. Again, the same exclusion criteria as for the second online RRS were applied.

S4 Items of the state rumination questionnaire

Items of the state rumination questionnaire including adapted items from the Ruminative Response Scale (Nolen-Hoeksema & Morrow, 1991), Amsterdam Resting-State Questionnaire (Diaz et al., 2013) and the Perseverative Thinking Questionnaire (Ehring et al., 2011). Subjects were instructed to rate if the items were in line with their mental state during the last resting-state measurement.

German translation	**English translation**
Ich dachte immer wieder an meine Probleme.	I repeatedly thought about my problems.
Ich verharrte im Denken an Dinge, die mich beunruhigen.	I kept thinking about things that bother me.
Meine Gedanken wiederholten sich, ohne dass ich zu einer Lösung kam.	I dwelled on my thoughts without coming to a solution.
Ich verlor mich in meinen negativen Gedanken.	I got lost in my negative thoughts.
Ich konnte meine Gedanken nur mühsam festhalten.	I had difficulties holding on to my thoughts.
Ich konnte mich nicht von meinen negativen Gedanken lösen.	I could not let go of my negative thoughts.
Ich war bei der Sache.	I was present.
Ich dachte darüber nach, warum ich mich in bestimmten Situationen falsch verhalten habe.	I thought about why I acted wrong in certain situations.
Ich fragte mich, warum ich Probleme habe, die andere nicht haben.	I thought why I have problems other people don´t have.
Ich fragte mich, womit ich meine momentane Lebenssituation verdient habe.	I thought about whereby I deserved my current life situation.
Ich dachte darüber nach, warum ich die Dinge nicht besser in den Griff bekomme.	I thought why I can´t handle things better.
Ich dachte an all meine Defizite und Misserfolge, Macken und Fehler.	I thought about all my shortcomings, failings, faults, mistakes.
Ich konnte flexibel zwischen meinen Gedanken hin und her schalten.	I could switch between my thoughts flexibly.
Ich dachte an vergangene Situationen, die ich bereue.	I thought about past situations that I regret.
Ich machte mir Selbstvorwürfe.	I blamed myself.
Ich verlor mich in Gedanken an Vergangenes.	I got lost in thoughts about the past.
Ich war von meinen Problemen und Sorgen stark vereinnahmt.	I was consumed by my problems and worries.
Meine negativen Gedanken ließen mich nicht los.	I couldn´t let go of my negative thoughts.

S5 Additional information to the conducted Trier Social Stress Test (TSST)

To induce psychosocial stress, an adaptation of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was used. Participants were informed that two additional people would join for the upcoming tasks before two experimenters wearing white physician coats entered the room and sat down in front of the participant. Then participants were instructed to imagine having applied for a job at the university hospital and having 5 minutes time to prepare a speech about their strengths and qualifications for the respective position. During this anticipation phase (anti) participants were allowed to take notes. After 5 minutes, one of the experimenters started a video camera while the participant was helped to stand up to deliver the speech. The experimenters took away the notes and following this remained socially unresponsive to any social interaction cues. If participants paused for more than 20 s, the experimenters instructed them to continue. After the speech, participants gave another subjective stress rating. Then the experimenter introduced the following arithmetic task which has the same structure as control task 2. Participants had to subtract in either 13 or 17 steps (randomized in order between the two different appointments) from different starting points while holding eye-contact with one experimenter. If participants made a mistake, they had to restart with the initial starting number. The participant is instructed to calculate as fast and correctly as possible while holding eye-contact with one of the experimenters. After the arithmetic task of the TSST the experimenters turn off the camera and leave the room without saying a word, and another stress rating is assessed.

S6 Additional information to section Theta Burst Stimulation (TBS)

Previous to the motor threshold determination using a 4-channel EMG-EP-System (Schreiber & Tholen Medizintechnik GmbH, Stade), the corresponding skin areas were sanitized. Then two gold-plated surface cup electrodes of 11 mm diameter were placed on the right abductor pollicis brevis muscle (one thenar and one on the proximal phalanx) and one reference electrode on the inner arm below the wrist. Stimulation intensity was reduced until the amplitude of motor-evoked potentials of 50 μV in less than 50 % of 10 consecutive stimuli was recorded.

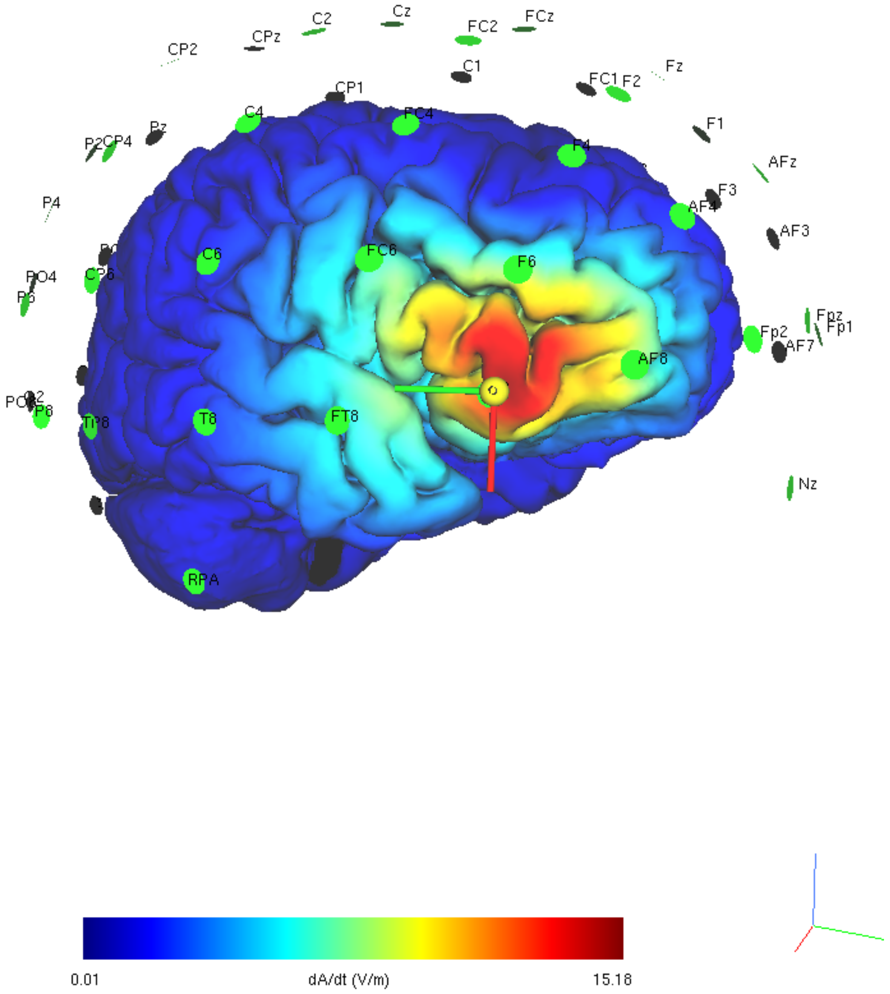
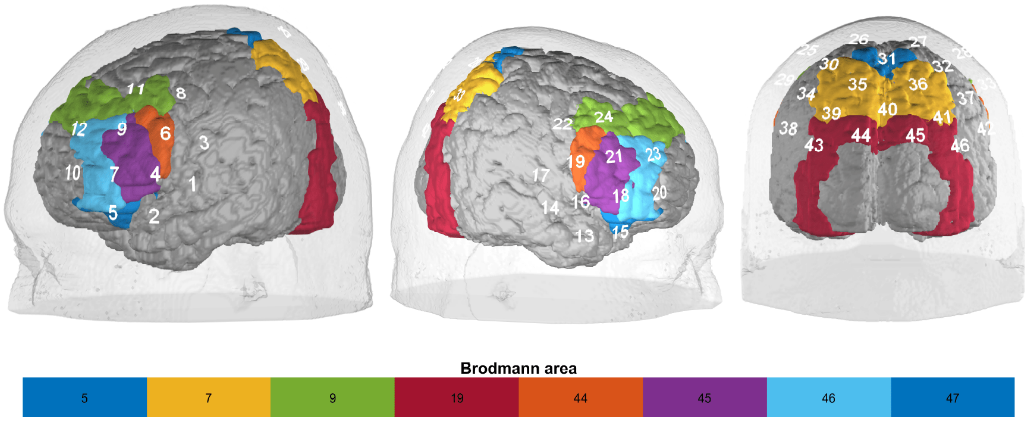


Figure S6
Approximation of the TBS-induced electric field. The coil (MagVenture Cool-B65 Active/Placebo coil) was positioned over the right VLPFC, corresponding to the F8 electrode according to the 10–20 EEG system. The color red indicates the strongest electric field. The y-axis in green indicates the direction of the coil handle. This plot was created using SimNIBS 4.1.0. (Thielscher et al., 2015)

S7 Additional information to section Near-Infrared Spectroscopy (NIRS)

In total, we used 28 light emitters (semiconductor lasers) and 15 light detectors (avalanche photodiodes) with an inter-optode distance of 3 cm, operating at two wavelengths (695 ± 20 nm and 830 ± 20 nm). The power output for each wavelength at every optode was 2.0 ± 0.4 mW. We used customized MATLAB 2024 scripts to calculate relative changes in oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin using the modified Beer-Lambert Law (Sassaroli & Fantini, 2004). Preprocessing steps involved an automatic detection and interpolating of single noisy channels, correcting motion artifacts using Temporal Derivative Distribution Repair (Fishburn et al., 2019), employing Correlation-based signal improvement (Cui et al., 2010), and bandpass-filtering to eliminate low-frequency baseline-drifts (< 0.01 Hz) and high-frequency noise (> 0.1 Hz). Then, another channel interpolation followed, and we performed a global signal reduction using a spatial Gaussian kernel filter ($\sigma = 40$) and a z-standardization. Note that in the following, O_2Hb data refers to the correlation-based improved O_2Hb signal.



Placement of the three probesets. Please note that the corresponding numbers represent the channels (located midway between emitter and detector).

ROI	Channel
left VLPFC	7 9 6 5
right VLPFC	18 21 19 15
left DLPFC	10 12 11
right DLPFC	20 23 24
SAC	27 26 25 28 30 31 32 35 36

Table S7
Definition of the Regions of Interest. VLPFC = Ventrolateral Prefrontal Cortex, DLPFC = Dorsolateral Prefrontal Cortex, SAC = Somatosensory Association Cortex. Please note that the TBS was applied over channel 15 which corresponds to F8.

S8 Details on the number of excluded participants

- **Subjective stress contrasts**: Checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded the data of 4 participants for the following analysis.
- **Subjective stress raw data:** Checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded 12 data points, namely 5 participants' data of the first appointment (AP1) and 7 participants' data of the second appointment (AP2) for the following analysis.
- **State Rumination contrasts:** According to their Mahalanobis distances ($p < .001$), we excluded the data of 2 participants and 2 participants due to missing data from the following analysis.
- **State Rumination raw data:** After checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded 7 data points and 2 due to missing data, specifically 5 participants' data from the first appointment and 4 participants' data from the second appointment, for the following analysis.
- **Negative affect contrasts:** Based on their Mahalanobis distances ($p < .001$), the data of 2 participants, and 2 participants due to missing data, were excluded prior to fitting the rmANOVA.
- **Negative affect raw data:** After checking for multivariate outliers using Mahalanobis distances ($p < .001$), we excluded 3 data points and 2 due to missing data, specifically 3 participants' data from the first appointment and 2 participants' data from the second appointment, for the following analysis.
- **Cortical oxygenation contrasts single channel:** No data was flagged as a multivariate outlier ($p < .001$), however, 2 participants had to be excluded due to missing data.
- **Cortical oxygenation contrasts ROIs:** No data was flagged as a multivariate outlier ($p < .001$), however 2 participants had to be excluded due to missing data.
- **Cortical oxygenation raw data ROIs:** No data was flagged as a multivariate outlier using Mahalanobis distances ($p < .001$), however, we excluded 2 missing data, namely one participant's data of the second appointment and one participant's data of the first appointment for the following analysis.

S9 Results of the analysis of the raw data

In addition to the contrast analysis, we analyze raw data to offer a clearer overview of the observed effects. Specifically, we fitted rmANOVAs with a three-way interaction of time, stimulation condition (iTBS vs. cTBS vs. sTBS), and group (low RRS vs. high RRS) for each appointment separately.

Subjective stress raw data.

We investigated the raw data using a rmANOVA for subjective stress dependent on the three-way interaction of time (indicating the 12 repeated assessments of subjective stress ratings over the course of one appointment), RRS-group (low vs. high ruminators) and stimulation condition (cTBS vs. iTBS vs. sTBS) separately for each appointment. Here, we again only observed significant main effects of time (AP1: $F(3.407, 265.762) = 95.194$, $p < .001$, $\eta_p^2 = .550$; AP2: $F(2.807, 213.362) = 65.757$, $p < .001$, $\eta_p^2 = .464$). Polynomial contrasts revealed a quadratic time course for both appointments, indicating successful stress inductions during both the first and second exposures (AP1: $F(1, 78) = 194.839$, $p < .001$, $\eta_p^2 = .714$; AP2: $F(1, 76) = 102.062$, $p < .001$, $\eta_p^2 = .573$).

At the first appointment, we also observed a significant main effect of RRS-group, $F(1, 78) = 6.076$, $p < .05$, $\eta_p^2 = .072$, indicating overall higher stress in case of high ruminators, as well as a significant main effect of stimulation condition, $F(2, 78) = 3.320$, $p < .05$, $\eta_p^2 = .078$, reflecting overall higher subjective stress in case participants received iTBS.

State rumination raw data.

Next, we investigated the raw data using a rmANOVA for state rumination dependent on the three-way interaction of time (indicating the 4 repeated assessments of state rumination ratings over the course of one appointment), RRS-group (low vs. high ruminators) and stimulation condition (cTBS vs. iTBS vs. sTBS) separately for each appointment. We observed a significant interaction of time and RRS-group but only at the first appointment: $F(3, 234) = 6.271$, $p < .001$, $\eta_p^2 = .074$. Using polynomial contrasts to investigate this interaction, we found a quadratic association, $F(1, 78) = 4.008$, $p < .05$, $\eta_p^2 = .026$, indicating higher increases in state rumination in the case of the high ruminators compared to low ruminators.

At the second appointment, we did not observe a significant interaction but significant main effects of time, $F(2.885, 227.935) = 6.826$, $p < .001$, $\eta_p^2 = .080$, and RRS-group, AP2: $F(1, 79) = 31.092$, $p < .001$, $\eta_p^2 = .282$, indicating overall higher state rumination

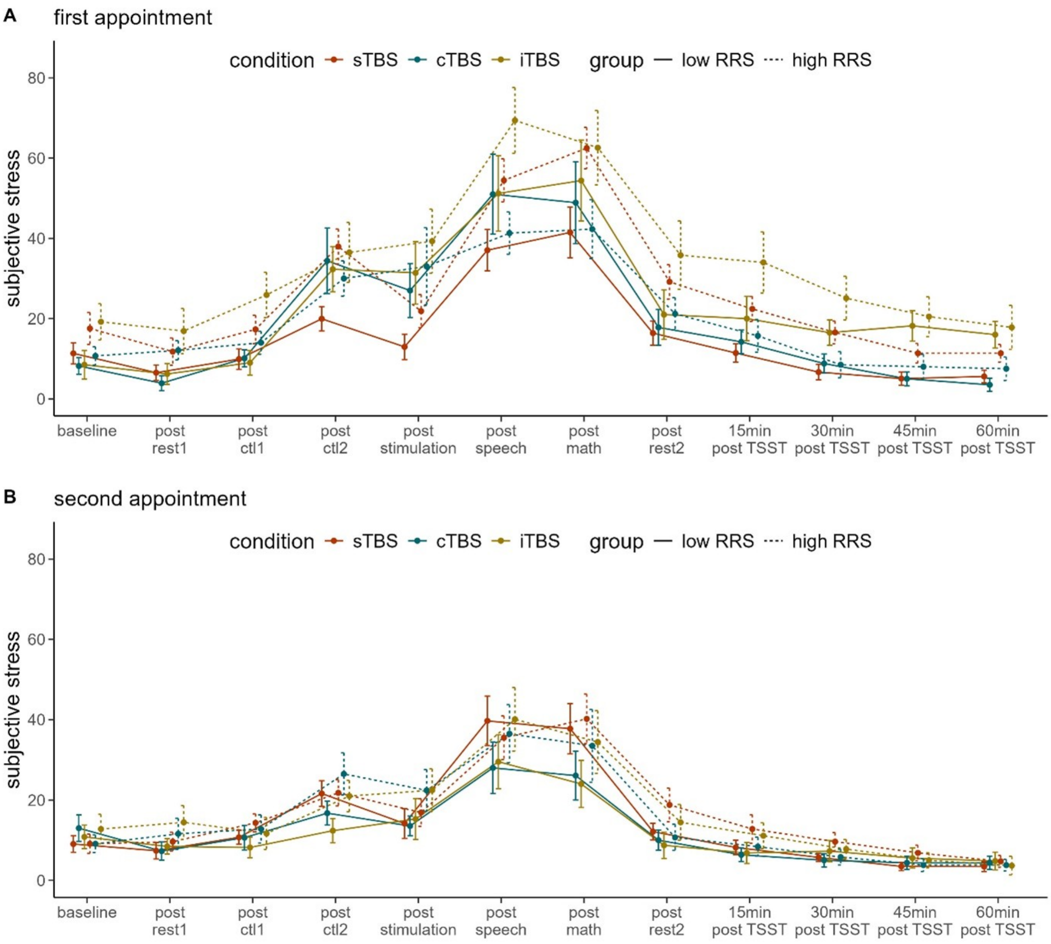


Figure S9.1
Line plot of the raw data of subjective stress ratings dependent on the appointment (A = first appointment; B = second appointment). rest = resting-state measurement, ctl1 = control task 1, ctl2 = control task 2, speech = job interview of the TSST, math = arithmetic task of the TSST, TSST = Trier Social Stress Test, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, 15 min = 15 min after the TSST, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.

in high ruminators compared to low ruminators.

Lastly, only when considering polynomial contrasts, we observed a significant quadratic contrast for the interaction of time, RRS-group and stimulation condition at the first appointment, $F(2, 78) = 3.272$, $p < .05$, $\eta_p^2 = .077$. Interpreting this contrast using plots of the raw data, low ruminators exhibited generally low state rumination ratings and only minimal increases throughout the experimental procedure and regardless of the stimulation condition. Descriptively, high ruminators exhibited steeper decreases in state rumination ratings directly after the stimulation following cTBS but comparable ratings for all other time points. Please note, however, that there were no significant differences between the stimulation conditions before as well as after correction for multiple comparisons.

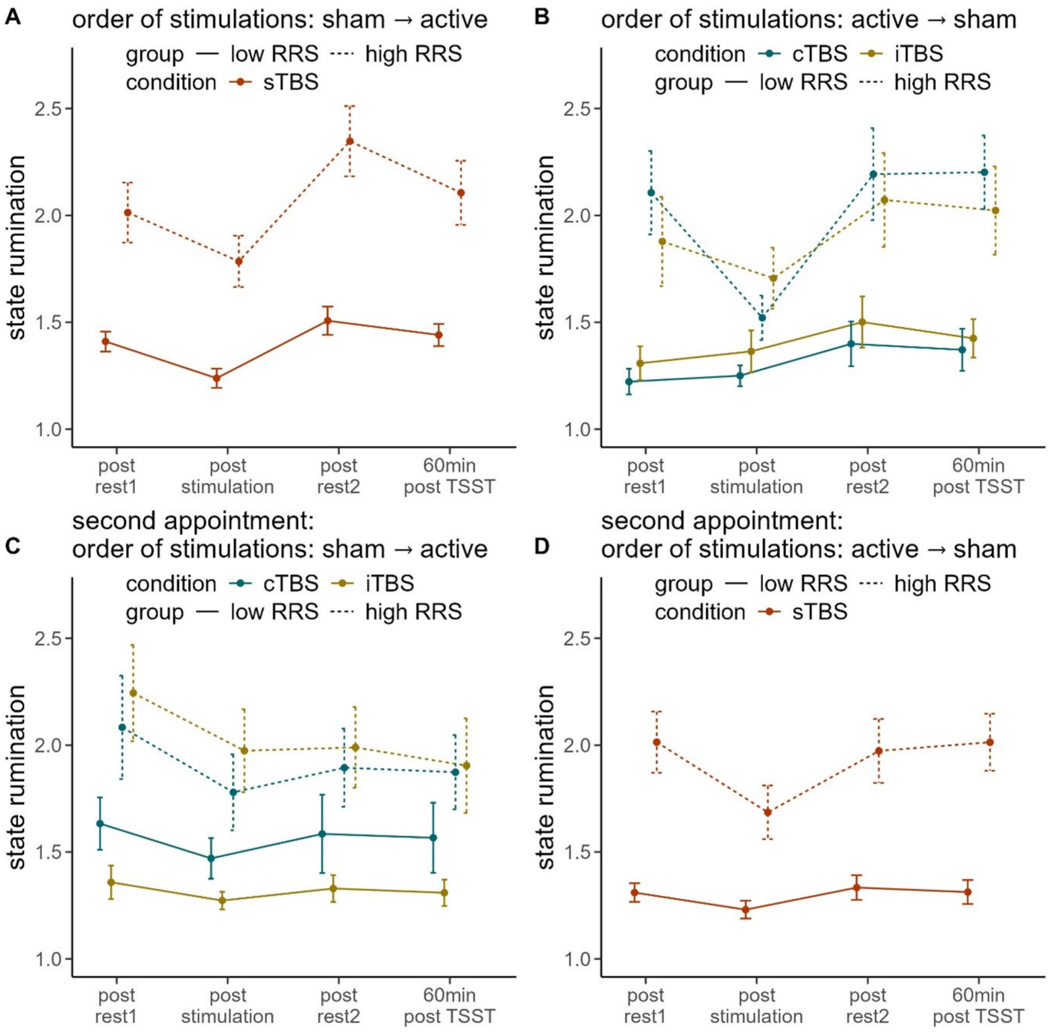


Figure S9.2
Line plot of raw data of state rumination ratings dependent on order of conditions and appointment (A = first appointment sham stimulation; B = first appointment active stimulation; C = second appointment active stimulation; D = second appointment sham stimulation). rest = resting-state measurement, TSST = Trier Social Stress Test, RRS = Ruminative Response Scale. Error bars indicate 1 standard error of the mean.

Negative affect raw data.

Investigating the raw data using a rmANOVA dependent on the three-way interaction of time (indicating the 4 repeated assessments of the PANAS), RRS-group (low vs. high ruminators) and stimulation condition (cTBS vs. iTBS vs. sTBS) dependent on appointment, we observed a significant main effect of time (AP1: $F(2.060, 164.794) = 56.824$, $p < .001$, $\eta_p^2 = .415$; AP2: $F(2.017, 163.383) = 19.439$, $p < .001$, $\eta_p^2 = .194$). In the case of both appointments, we observed quadratic time courses (AP1: $F(1, 80) = 64.606$, $p < .001$, $\eta_p^2 = .447$; AP2: $F(1, 81) = 19.463$, $p < .01$, $\eta_p^2 = .194$), indicating significant increases in negative affect due to the stress induction and decreases again post-stress (see figure 6.5C-F).

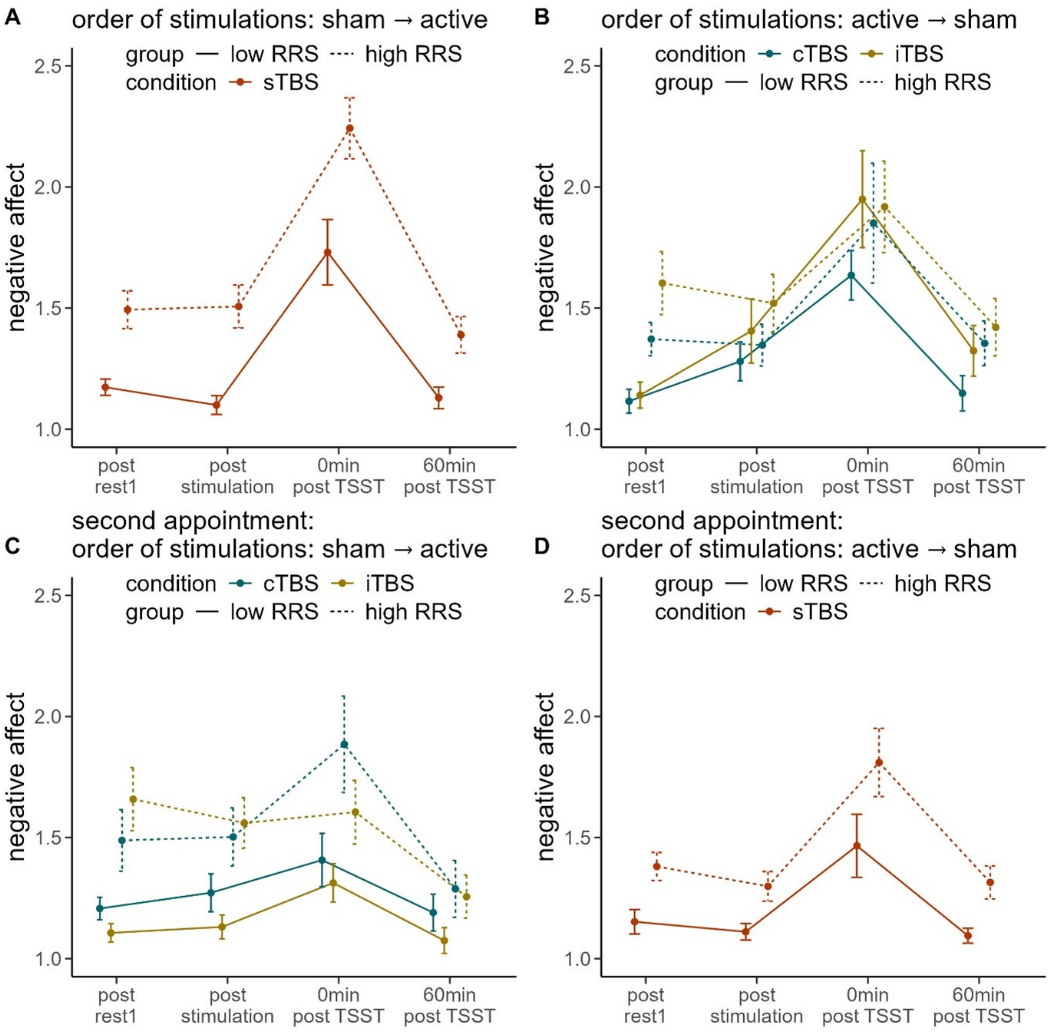


Figure S9.3

Line plot of raw data of negative affect ratings dependent on order of conditions and appointment (A = first appointment sham stimulation; B = first appointment active stimulation; C = second appointment active stimulation; D = second appointment sham stimulation). rest = resting-state measurement, TSST = Trier Social Stress Test. Error bars indicate 1 standard error of the mean.

For both appointments, we also observed a significant main effect of RRS-group, indicating overall higher negative affect in the case of high ruminators (AP1: $F(1, 80) = 13.786$, $p < .001$, $\eta_p^2 = .147$; AP2: $F(1, 81) = 30.127$, $p < .001$, $\eta_p^2 = .271$).

Cortical oxygenation raw data ROIs. Then, we fitted a rmMANOVA using our 5 ROIs (left and right DLPFC, left and right VLPFC and SAC) dependent on the three-way interaction of time (reflecting the three tasks during which cortical oxygenation was assessed: control task 1, control task 2, and the arithmetic task of the TSST), RRS-group (low vs. high ruminators) and stimulation condition (cTBS vs. iTBS vs. sTBS) for each appointment separately. Fitting the rmMANOVA for the data of the first appointment, we only observed a significant main effect of time, $F(10, 322) = 6.150$, Pillai's trace = 0.321,

$p < .001$, $\eta_p^2 = .160$. Benjamini-Hochberg corrected univariate tests indicated a significant main effect of time ($p < .05$) in case of all ROIs except for the bilateral VLPFC. Polynomial contrasts revealed linear time courses in all ROIs except for the left VLPFC where we observed a quadratic time course (left DLPFC: $F(1, 82) = 19.932$, $p < .001$, $\eta_p^2 = .196$, left VLPFC, $F(1, 82) = 6.463$, $p < .05$, $\eta_p^2 = .073$, right DLPFC, $F(1, 82) = 13.092$, $p < .001$, $\eta_p^2 = .138$ and SAC, $F(1, 82) = 44.586$, $p < .001$, $\eta_p^2 = .352$).

Benjamini-Hochberg-corrected between-subjects effects indicated a significant main effect of stimulation condition ($p < .05$) in the left DLPFC at the first appointment. This effect seemed to be driven by generally lower cortical oxygenation following sTBS.

Fitting the rmMANOVA for the data of the second appointment resulted in a significant interaction of time, condition and RRS-group, $F(20, 652) = 1.594$, Pillai's trace = 0.186, $p < .05$, $\eta_p^2 = .047$. However, univariate tests indicated no significant three-way interaction in case of no ROI, neither previous nor after correction for multiple comparisons.

S10 Positive affect contrasts

For positive affect ratings, we observed 2 multivariate outliers and 2 participants with missing data. Fitting a rmANOVA, we observed a significant main effect of time, $F(2.883, 221.963) = 4.306$, $p < .01$, $\eta_p^2 = .053$, and a significant main effect of order of stimulation conditions, $F(1, 77) = 8.738$, $p < .01$, $\eta_p^2 = .102$. Polynomial contrasts of the main effect of time revealed a significant linear contrast, $F(1, 77) = 5.592$, $p < .05$, $\eta_p^2 = .068$. This is reflected by comparable positive ratings between active and sham stimulation previous to the stimulation and stress induction and more increasing differences afterwards. Following the TSST, we observed positive contrasts, that means higher positive affect ratings in case of the active stimulation irrespective of the order of stimulation conditions (see figure S10A and S10B). Investigating the main effect of order of stimulation conditions, we observed overall comparable ratings between active and sham stimulation in case participants received sham stimulation first (see figure S10A) and positive contrasts (i.e. higher positive affect following active vs. sham stimulation) in case participants received active stimulation first (see figure S10B).

S11 Number of performed calculations contrasts

No multivariate outliers ($p < .001$) were apparent for the number of performed calculations but data was missing in one participant. Fitting our rmANOVA, we observed a significant interaction of time and order of stimulation conditions, $F(1.311, 104.887) = 4.127$, $p < .05$, $\eta_p^2 = .049$, as well as a lower-order significant main effect of order of stimulation conditions, $F(1, 80) = 4.340$, $p < .05$, $\eta_p^2 = .051$. Next, we fitted separate rmANOVA dependent on the order of stimulation conditions. As a result, we observed a significant main effect of time, $F(1.303, 50.305) = 4.293$, $p < .05$, $\eta_p^2 = .095$, but only in case participants received sham stimulation first (see figure S11A). Polynomial contrasts revealed a quadratic time course, $F(1, 41) = 11.335$, $p < .01$, $\eta_p^2 = .217$, which is reflected by comparable number of read-out numbers (control task 1) following active and sham stimulation but positive contrasts in the case of control task 2 and the arithmetic task of the TSST (more calculations performed in case of the second appointment, i.e. active stimulation).

S12 Number of errors contrasts

The data of one participant was flagged as an outlier ($p < .001$) and data was missing in one participant. Fitting our rmANOVA, we observed no significant effects (all p's > .100).

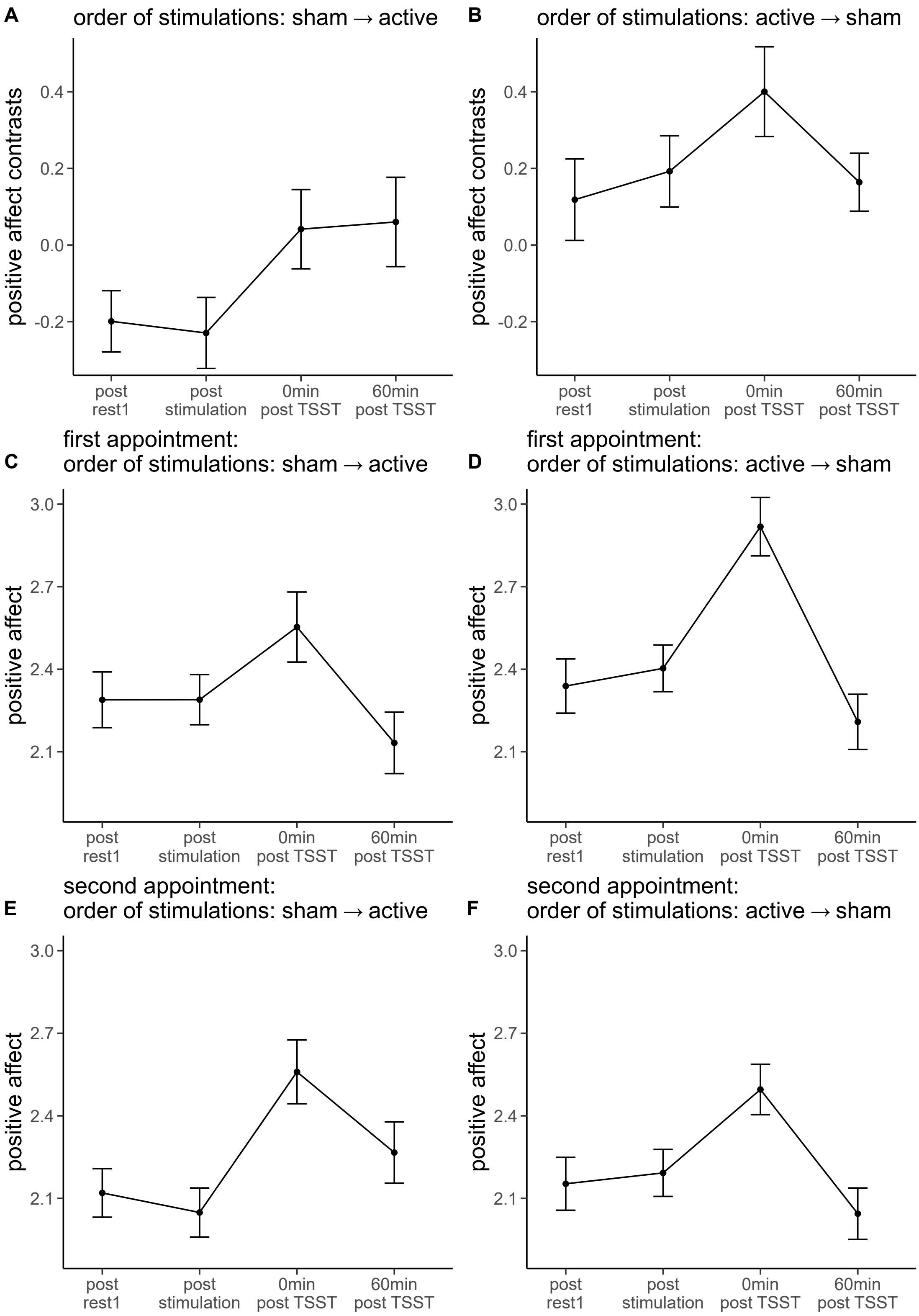


Figure S10
Line plot of the contrasts of positive affect ratings dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of positive affect ratings dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). rest = resting-state measurement, TSST = Trier Social Stress Test. Error bars indicate 1 standard error of the mean.

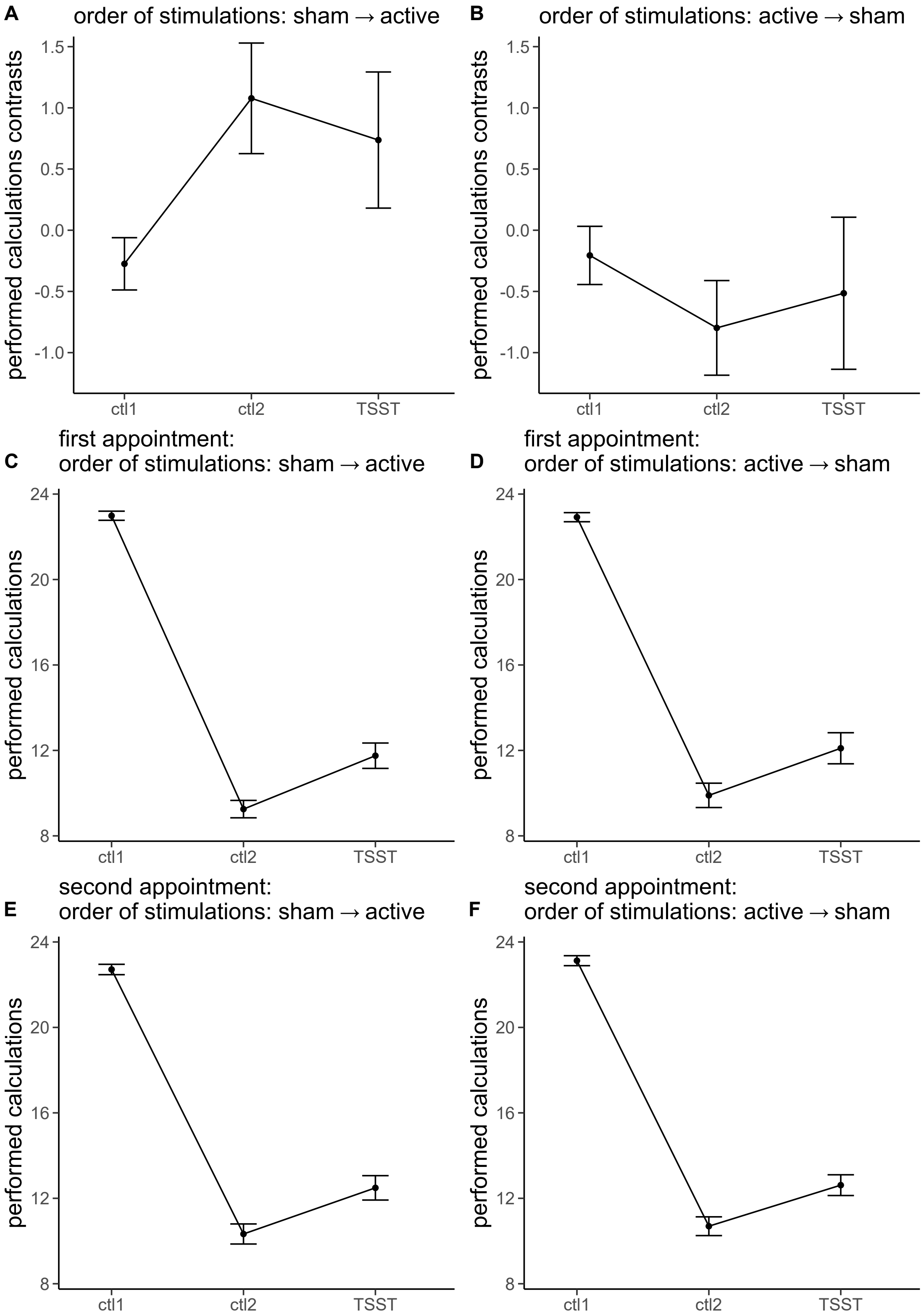
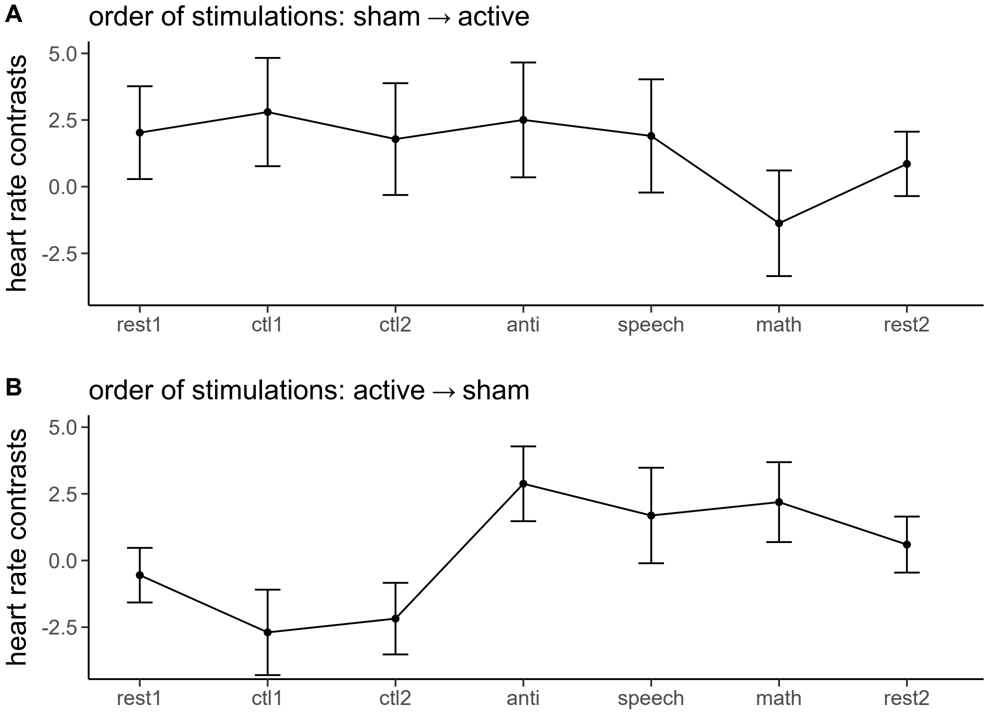


Figure S11

Line plot of the contrasts of the number of performed calculations dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of the number of performed calculations dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). ctl1 = control task 1, ctl2 = control task 2, TSST = arithmetic task of the Trier Social Stress Test, Error bars indicate 1 standard error of the mean.

S13 Heart rate contrasts

One participant was flagged as a multivariate outlier ($p < .001$) and was therefore excluded. Data was missing in 19 participants. As a result of our rmANOVA, we observed a significant interaction of time and order of stimulation conditions, $F(4.537, 276.777) = 4.561$, $p < .001$, $\eta_p^2 = .070$, and a marginally significant lower-order main effect of time, $F(4.537, 276.777) = 2.138$, $p = .068$, $\eta_p^2 = .034$. We then fitted separate rmANOVA dependent on the order of stimulation conditions and found a significant main effect of time but only in participants having received active stimulation first, $F(3.432, 106.395) = 4.762$, $p < .01$, $\eta_p^2 = .133$ (see figure S13B). Polynomial contrasts revealed a linear time course of the contrasts, $F(1, 31) = 8.137$, $p < .01$, $\eta_p^2 = .208$.



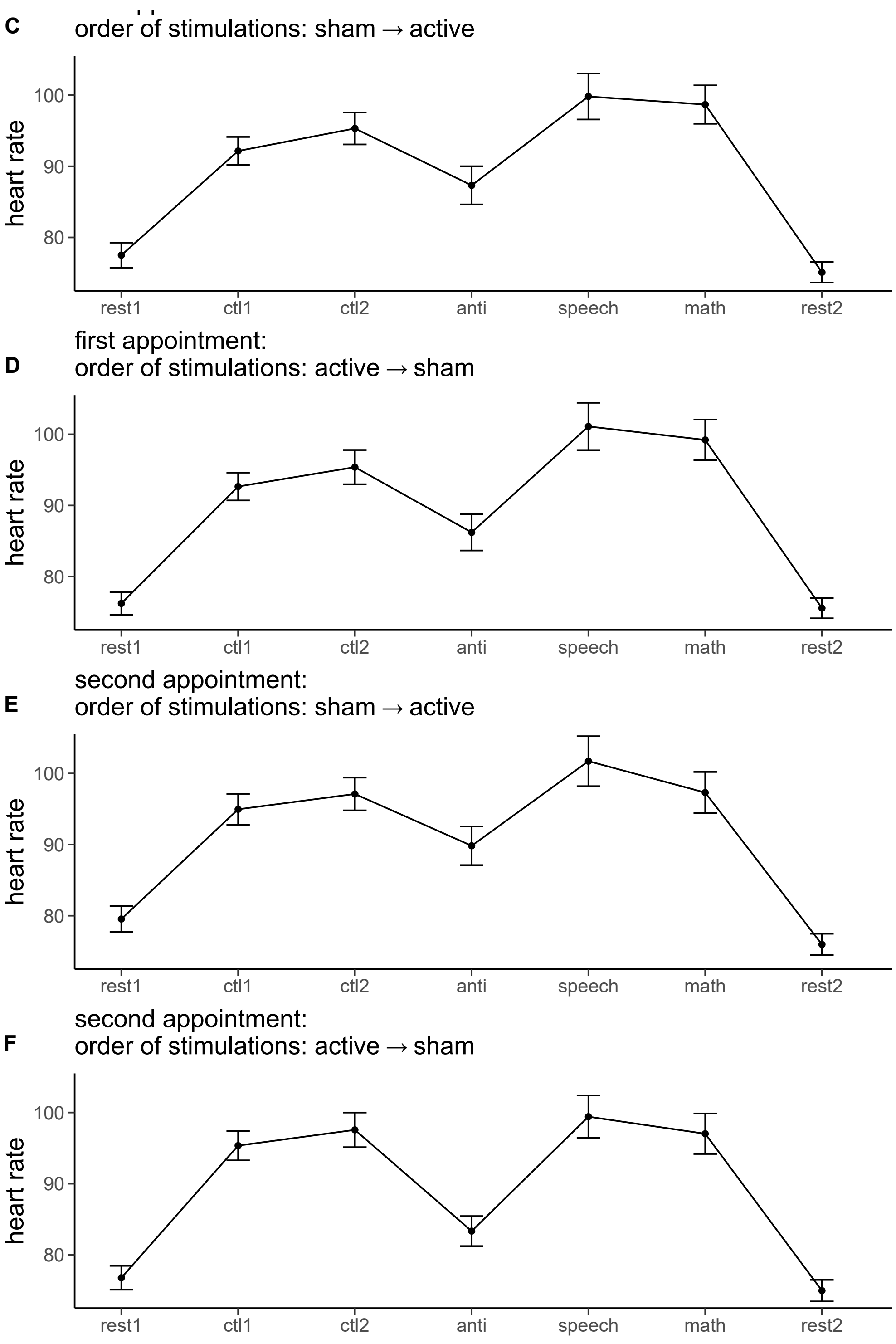


Figure S13

Line plot of the contrasts of heart rates in beats per minute (BPM) dependent on order of conditions (A = sham stimulation at the first appointment, active stimulation at the second appointment; B = active stimulation at the first appointment, sham stimulation at the second appointment) and line plot of raw data of heart rates in beats per minute (BPM) dependent on order of conditions and appointment (C = first appointment sham stimulation; D = first appointment active stimulation; E = second appointment active stimulation; F = second appointment sham stimulation). rest = resting-state measurement, ctl1 = control task 1, ctl2 = control task 2, speech = job interview of the TSST, math = arithmetic task of the TSST, TSST = Trier Social Stress Test, sTBS = sham theta burst stimulation, cTBS = continuous theta burst stimulation, iTBS = intermittent theta burst stimulation, 15 min = 15 min after the TSST. Error bars indicate 1 standard error of the mean.

S14 Details on blinding

According to a binomial test, participants were unable to identify sham from active stimulation during the first appointment (see table S14.1). Additionally, there were no significant differences in stimulation intensity between the cTBS (M = 43.89, SD = 6.93), iTBS (M = 40.80, SD = 5.20) and sTBS condition (M = 42.18, SD = 6.06), $F(2, 175)$ = 2.872, p = .059, η_p^2 = .03.

	percent	95 % CI	p-value
correct identification of sTBS as sham (first appointment)	46.67 %	[31.66; 62.13]	0.766
correct identification of iTBS as active (first appointment)	36.36 %	[17.20; 59.34]	0.286
correct identification of cTBS as active (first appointment)	50.00 %	[28.22; 71.78]	0.999
correct identification of sTBS as sham (second appointment)	65.91 %	[50.08; 79.51]	<.05
correct identification of iTBS as active (second appointment)	86.36 %	[65.09; 97.09]	<.001
correct identification of cTBS as active (second appointment)	78.26 %	[56.30; 92.54]	<.05
correct identification of sTBS as sham (overall)	56.18 %	[45.25; 66.68]	0.289
correct identification of iTBS as active (overall)	61.36 %	[45.50; 75.64]	0.174
correct identification of cTBS as active (overall)	64.44 %	[48.78; 78.13]	0.073

Table S14.1
Summary of exact binomial tests assessing the blinding of participants (H_0*: p = .5). sTBS = sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation.*

We further tested whether participants believed the stimulation had an impact on their performance (better or worse) using a logistic regression model (see table S14.2). Results indicated no significant effect of condition, $\chi^2(2)$ = 1.715, p = .424. As a second step, we fitted a linear mixed model dependent on the condition for ratings of "How confident are you in answering the question?" referring to the question about the impact of the stimulation on their performance: We fitted a model with the response to the respective item as DV, stimulation condition as a predictor and separate intercepts per subject. Again, we did not observe a significant main effect of the condition, $\chi^2(2)$ = 1.532, p = .465.

When fitting the logistic regression model and linear mixed model dependent on the RRS group, we also observed no significant effect of the group, $\chi^2(1)$ = 0.101, p = .751 and $\chi^2(1)$ = 0.00, p = .996, respectively. In the case of the low RRS group most participants believed that the stimulation had no impact on their performance (41.3% no change, 35.0% better, 23.8% worse), while in the high RRS group, most participants believed that the stimulation made them better (38.8% no change, 47.1% better, 14.1% worse).

			condition			total
			sTBS	cTBS	iTBS	
impact on performance	no change	count	38	15	13	66
		% within impact on performance	57.6%	22.7%	19.7%	100%
		% within condition	44.7%	36.6%	33.3%	40.0%
		% of all data points	23.0%	9.1%	7.9%	40.0%
	better	count	33	17	18	68
		% within impact on performance	48.5%	25.0%	26.5%	100%
		% within condition	38.8%	41.5%	46.2%	41.2%
		% of all data points	20.0%	10.3%	10.9%	41.2%
	worse	count	14	9	8	31
		% within impact on performance	45.2%	29.0%	25.8%	100%
		% within condition	16.5%	22.0%	20.5%	18.8%
		% of all data points	8.5%	5.5%	4.8%	18,8%

Table S14.2
Absolute and relative frequencies of participants rating the impact of the stimulation on their performance dependent on stimulation condition. sTBS = sham Theta Burst Stimulation, cTBS = continuous Theta Burst Stimulation, iTBS = intermittent Theta Burst Stimulation. Please note that 13 data points were missing as the item was not answered or was answered ambiguously.

S15 Illustration of Reliable Change Indices

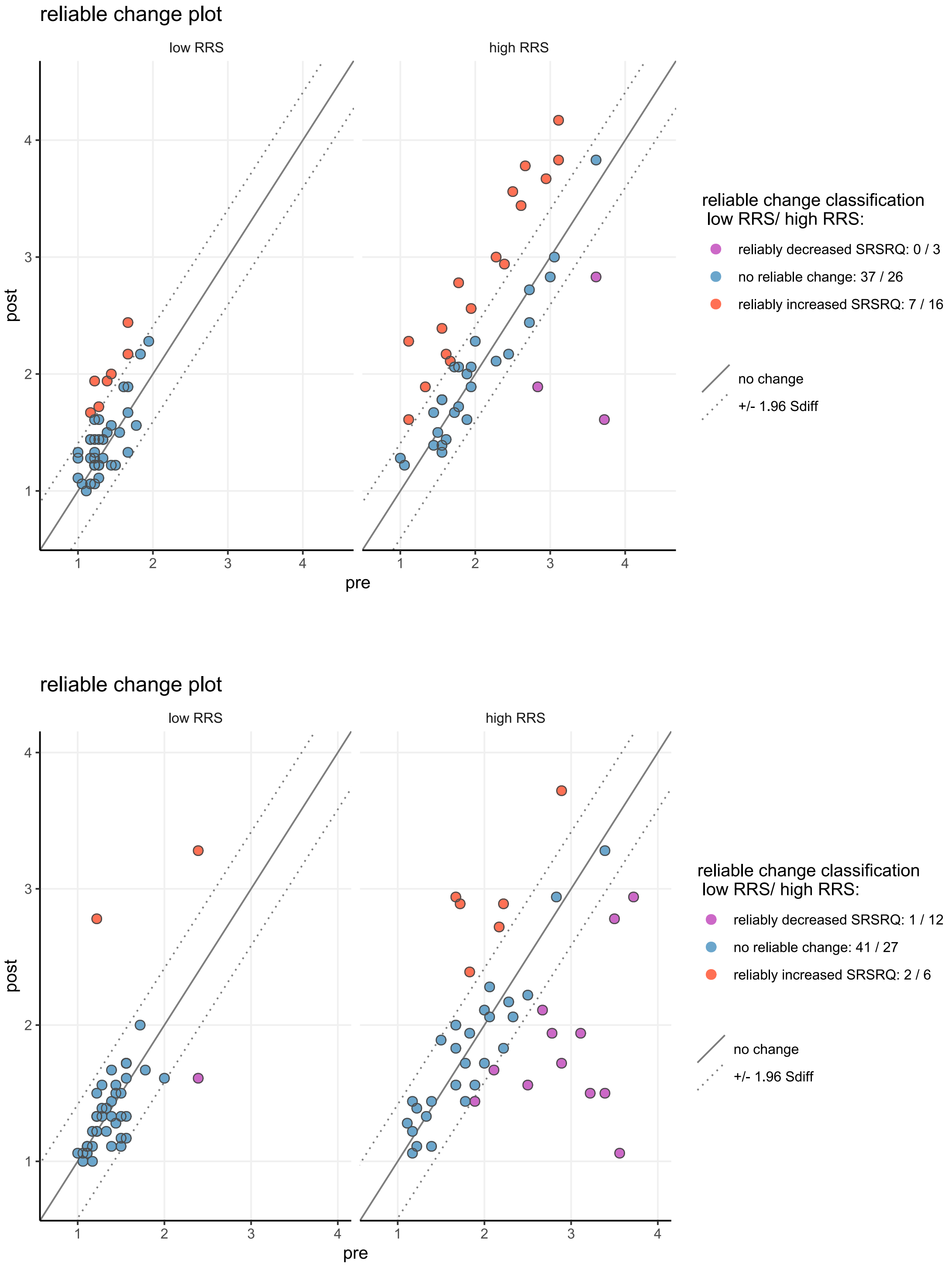


Figure S15
Reliable change indices plotted for changes in state rumination (SRSRQ scores) from before the stress induction (rest1) to after the stress induction (rest2) for the first appointment (A) and second appointment (B) dependent on RRS group.

S16 Brainmaps

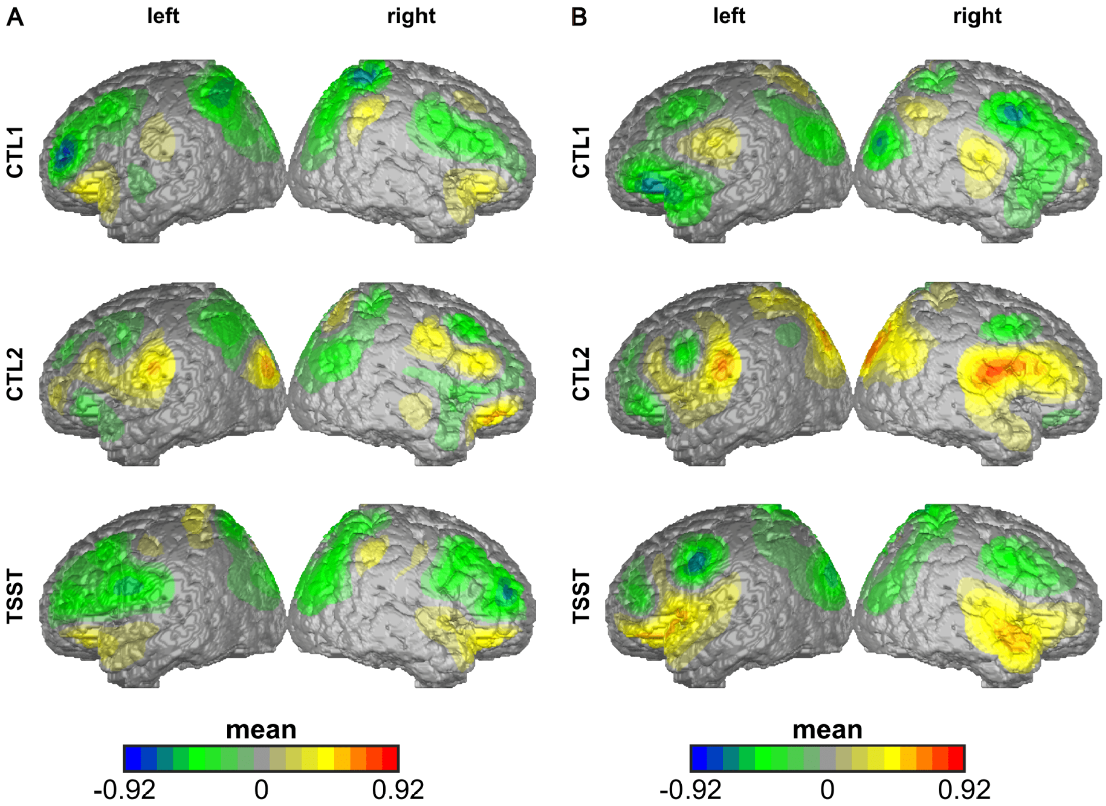


Figure S16.1
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of low ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions active → sham; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

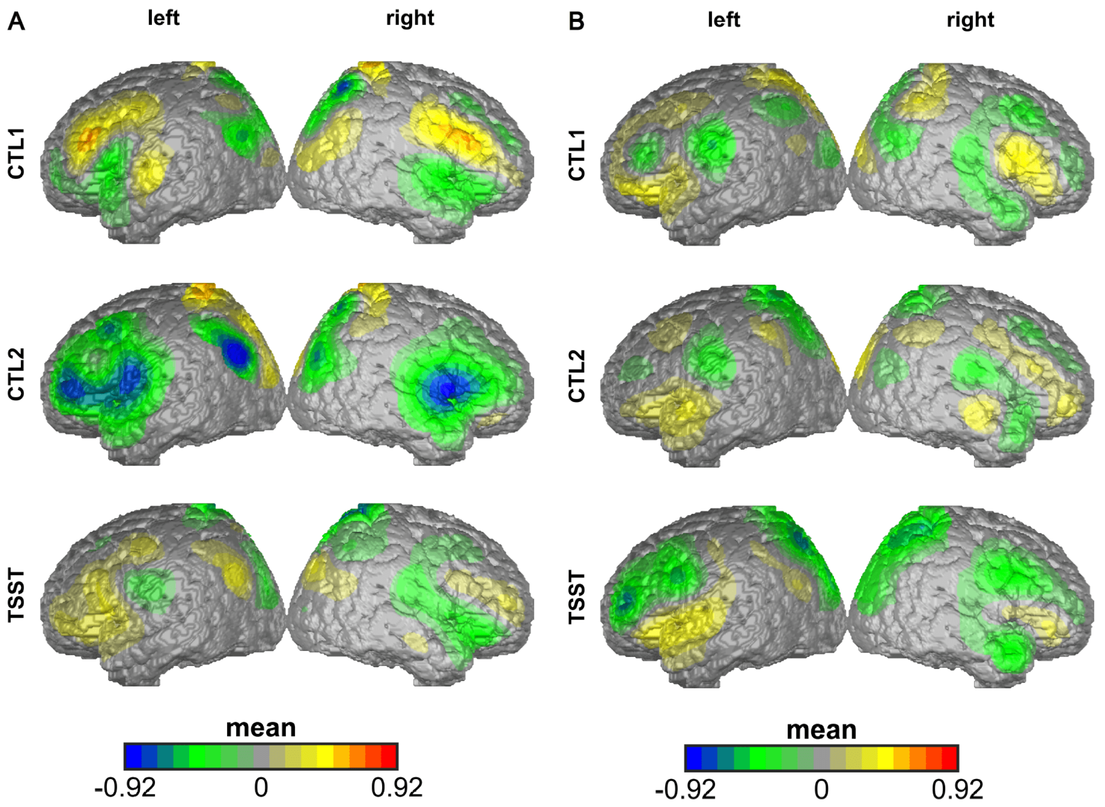


Figure S16.2
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of low ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions sham → active; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

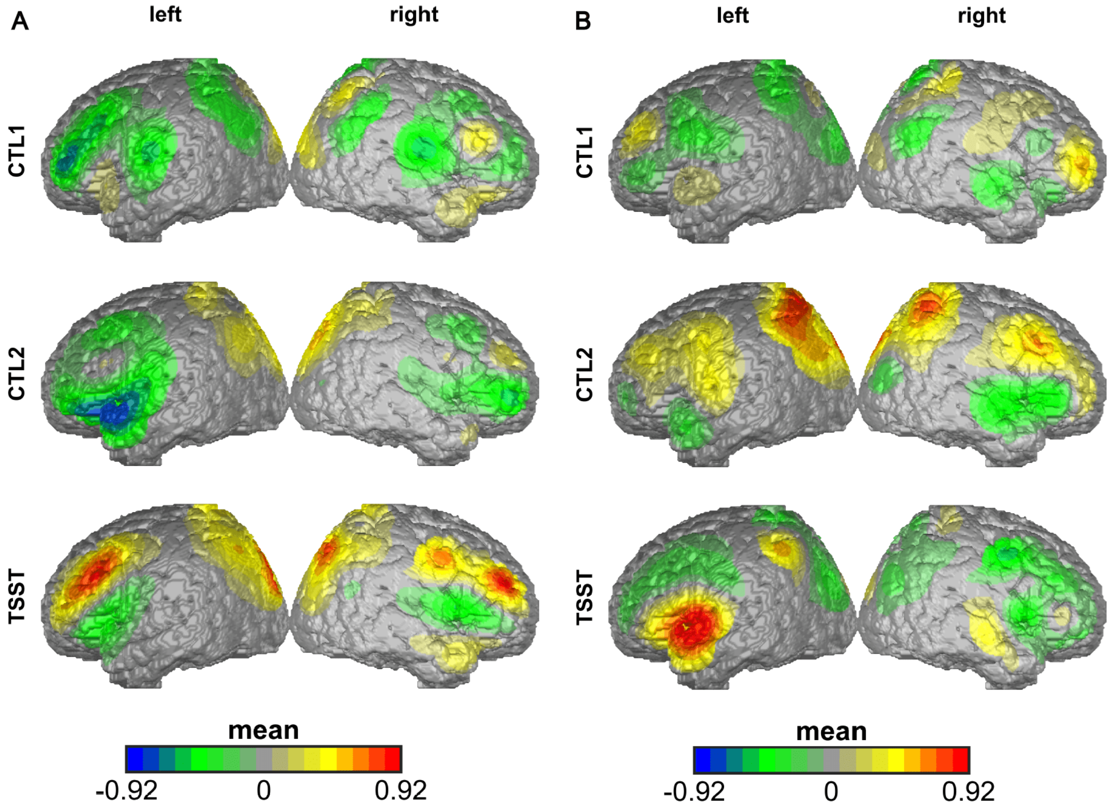


Figure S16.3
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of high ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions active → sham; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

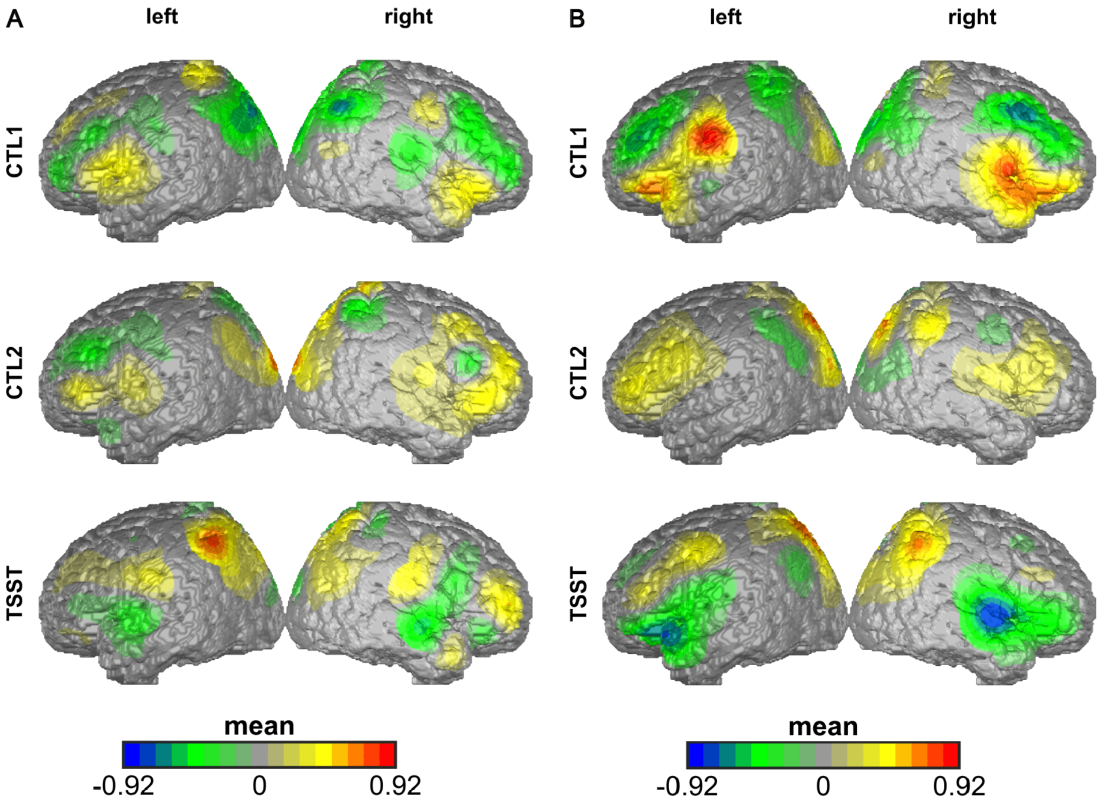
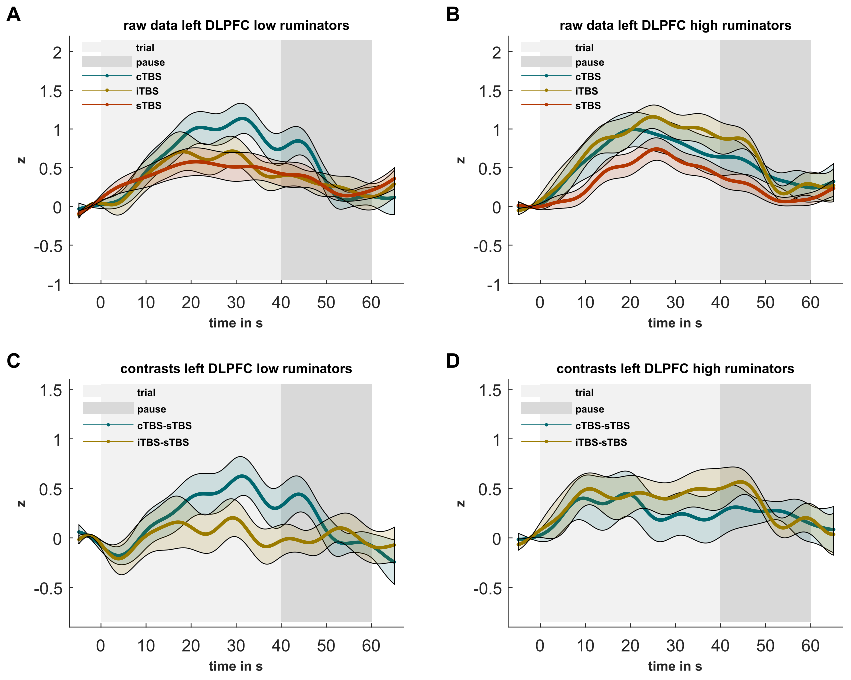


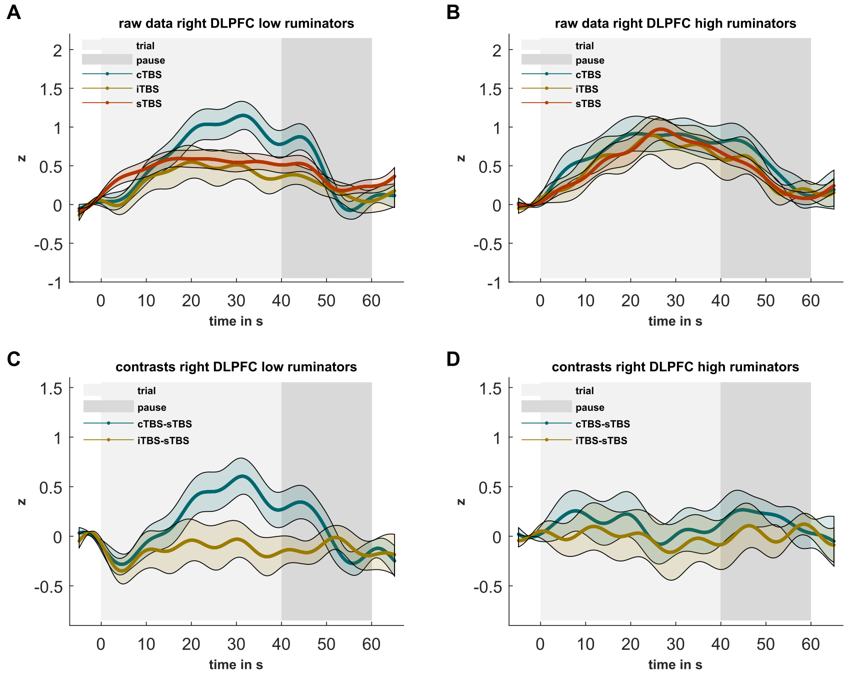
Figure S16.4
Standardized mean cortical oxygenation contrasts (active minus sham stimulation) of high ruminators having received A: cTBS or B: iTBS with the order of stimulation conditions sham → active; CTL1 = control task 1 (reading numbers), CTL2 = control task 2 (performing calculations without social stress); TSST = performing calculations under social stress. Warm colors indicate higher cortical oxygenation following the active stimulation compared to sham stimulation, cool colors indicate higher cortical oxygenation following sham stimulation compared to active stimulation.

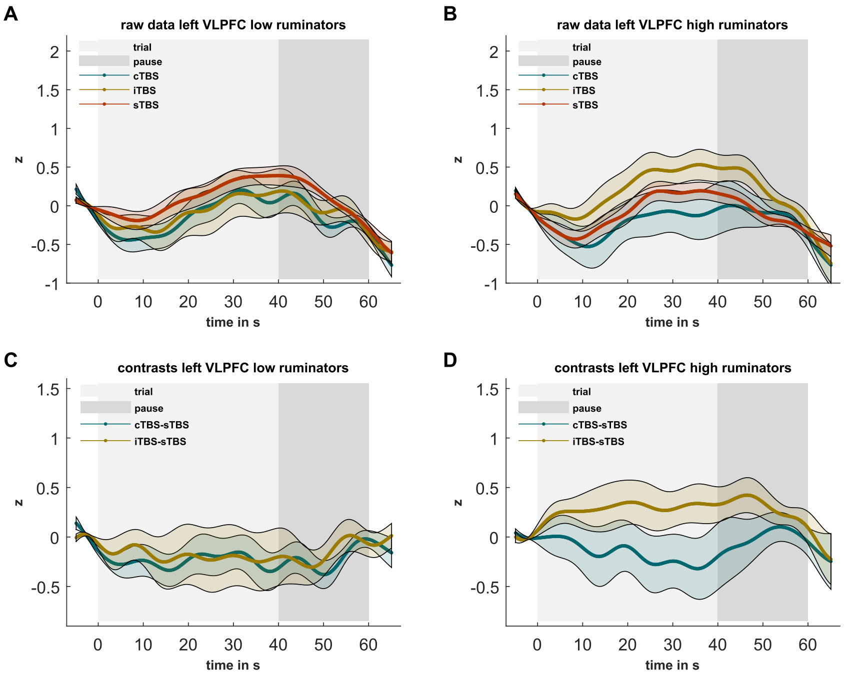
S17 Time series of the hemodynamic responses during the arithmetic task of the TSST

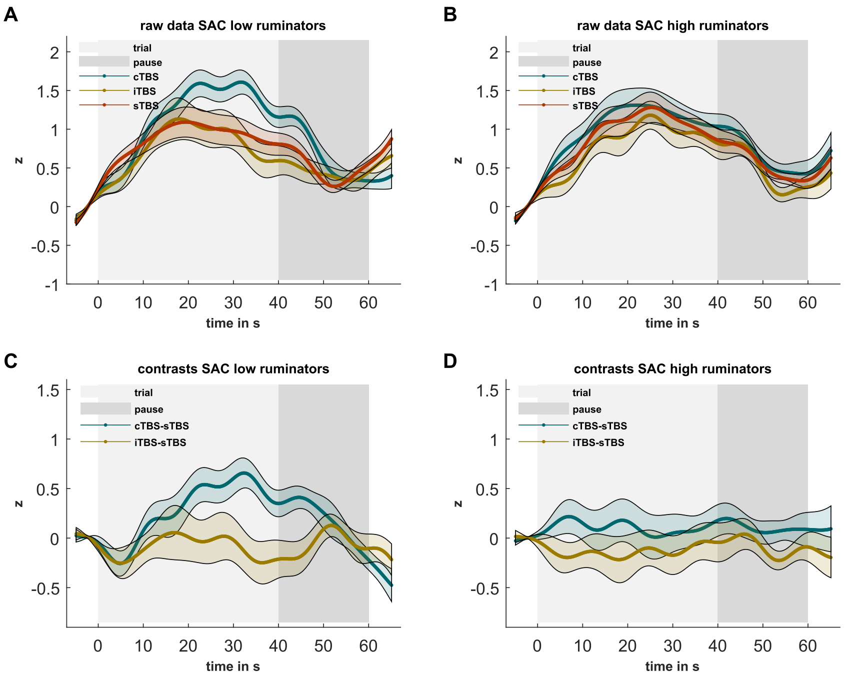
Illustration of the z-standardized hemodynamic responses during the arithmetic task of the TSST in the Regions of Interest in low and high ruminators depending on the TBS-condition. A and B illustrate the raw data, while C and D illustrate the contrasts (cTBS minus sTBS and iTBS minus sTBS). The light shading marks the 40 s trial and the dark shading the 20 s pause to allow the hemodynamic response to recover. Shadings around the hemodynamic curves reflect standard errors of the mean. The baseline includes the 5 s before each trial; 0 s on the x-axis marks the beginning of the trial.

Time series of the first appointment:

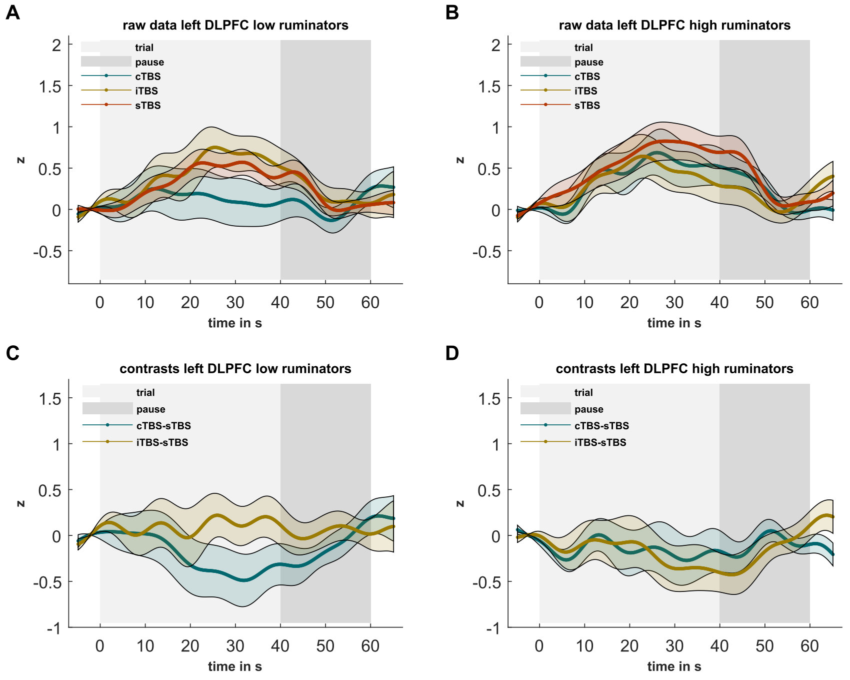


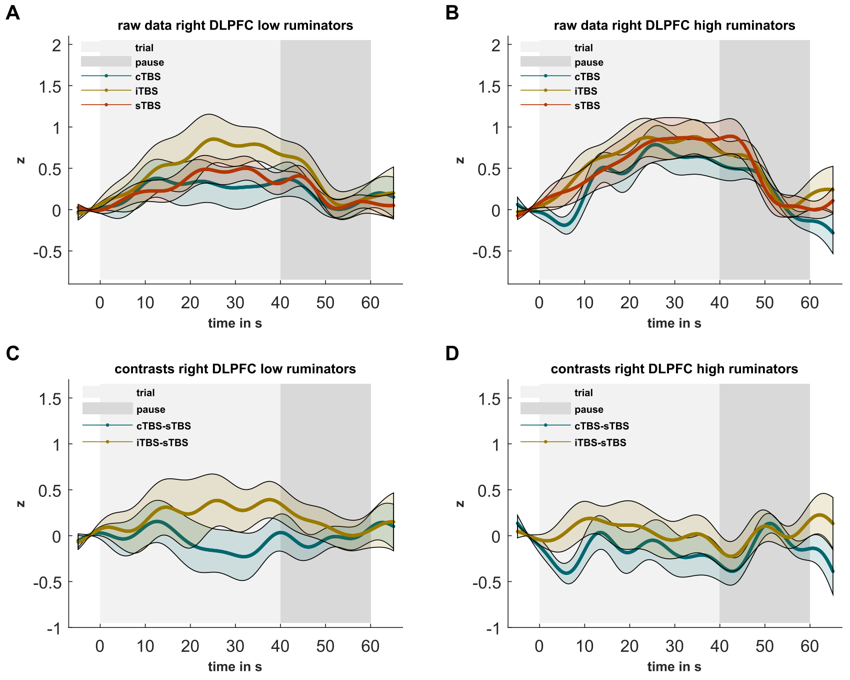


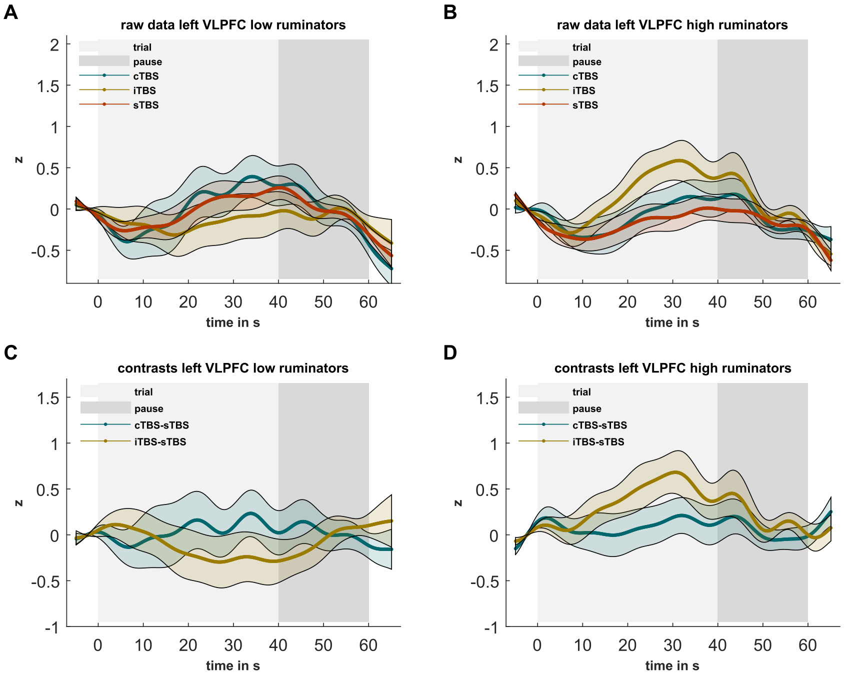

A
raw data left VLPFC low ruminators
B
raw data left VLPFC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
-1
0
10
20
30
40
50
60
time in s
C
contrasts left VLPFC low ruminators
D
contrasts left VLPFC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
z
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
time in s

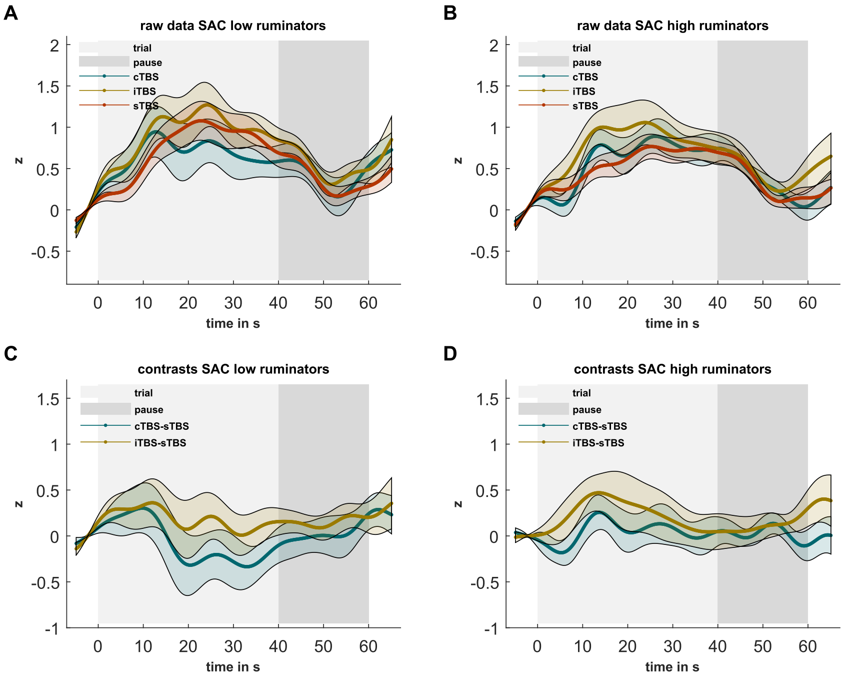

A
raw data SAC low ruminators
B
raw data SAC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
-1
0
10
20
30
40
50
60
time in s
C
contrasts SAC low ruminators
D
contrasts SAC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
z
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
time in s

Time series of the second appointment:






A
raw data left VLPFC low ruminators
B
raw data left VLPFC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
time in s
C
contrasts left VLPFC low ruminators
D
contrasts left VLPFC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
z
1.5
1
0.5
0
-0.5
-1
time in s


A
raw data SAC low ruminators
B
raw data SAC high ruminators
trial
pause
cTBS
iTBS
sTBS
z
2
1.5
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0.5
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10
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40
50
60
time in s
C
contrasts SAC low ruminators
D
contrasts SAC high ruminators
trial
pause
cTBS-sTBS
iTBS-sTBS
z
1.5
1
0.5
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-0.5
-1
time in s

Chapter 7

General discussion

In the following discussion, I will first explicitly address the research questions of the four conducted studies before providing a comprehensive summary and discuss their implications. Here, I will focus only on aspects that have not already been addressed in the individual studies. Subsequently, I will present the conclusions, followed by a discussion of the studys' limitations and potential directions for future research.

7.1 Addressing the research questions

1. To what extent are the neural correlates under stress in patients with depression (DP), compared to healthy controls (HC) (e.g., the frequently replicated prefrontal hypoactivation), associated with depressive symptomatology or rumination? In other words, in how far can brain activation be predicted by depressive symptomatology or trait rumination, which is highly correlated with it, or by stress-reactive state rumination?

Previous research has consistently demonstrated hypoactivation of the left Dorsolateral Prefrontal Cortex (DLPFC) in patients with depression (DP) during tasks that require emotional or stress regulation and cognitive control (for a recent review, see Pizzagalli & Roberts, 2022). Our findings from study 1 (Int-Veen et al., 2023), which included 75 DP and 65 HC, replicated these results. Specifically, while HC exhibited significant increases in cortical oxygenation in the superior left DLPFC, anterior right DLPFC, and an adjacent channel in the right Inferior Frontal Gyrus (IFG), DP showed no significant changes (i.e. a prefrontal hypoactivation).

A very similar activation pattern emerged when stress-reactive rumination was included as a predictor. However, stress-reactive rumination also significantly predicted activation in the left IFG and across a greater number of fNIRS channels. Notably, a subgroup of HC characterized by low baseline state rumination and no increase in rumination following stress induction showed significant prefrontal activation. In contrast, the remaining three clusters, comprising HC and DP, which exhibited either higher baseline state rumination or an increase in rumination due to stress, did not significantly differ from each other in neural activation and did not show respective increases during the TSST.

These findings suggest that state rumination may be more informative regarding prefrontal hypoactivation in the left DLPFC, among other regions, than diagnostic status alone. Unfortunately, due to the high inter-correlations of state and trait rumination, we were unable to differentiate their effects with respect to controlling for the corresponding other variable. Intuitively, trait and state measures share a substantial proportion of variance while also exhibiting unique variance. Analyses that control for one factor while examining the other may therefore be considered somewhat artificial and may not accurately reflect real-world conditions. Overall, however, it appears promising to predict situation-specific physiological measures (e.g. current brain activity) using situation-specific self-report measures (e.g. momentary rumination), as opposed to less sensitive measures such as depressive symptomatology averaged over the past two weeks.

2. How do differences in performance under stress influence the neural correlates observed during stress? In other words, how robust are the aforementioned associations when controlling for performance in the Trier Social Stress Test (TSST)?

Once neural activation patterns were adjusted for differences in performance, diagnostic group was no longer a significant predictor. The only remaining time-dependent group differences were observed in the state rumination cluster characterized by low baseline state rumination and no increases due to stress induction in the right IFG, which exhibited a significant increase in cortical oxygenation compared to all other groups.

This finding suggests that the previously reported results are strongly linked to actual task performance. However, the causal direction of this relationship remains unclear: Reduced brain activity in the other groups may contribute to impaired performance, or alternatively, factors such as motivation may lead to poorer performance, thereby limiting the recruitment of prefrontal regions.

The above finding is consistent with recent studies suggesting that poorer performance on neuropsychological tests observed in DP may be overestimated due to the influence of motivational factors (Moritz et al., 2017, 2023). Accordingly, the observed reductions in prefrontal activation might also be amplified. These findings highlight the importance of accounting for performance differences in analyses and underscore the need to explore potential factors influencing the observed associations in future studies.

3. Does a single session of intermittent Theta Burst Stimulation (iTBS), continuous Theta Burst Stimulation (cTBS), and sham Theta Burst Stimulation (sTBS) affect the psychological and physiological stress response in healthy individuals? More specifically, do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS?

In our study (De Smet et al., 2024), we observed an effect of a single session of TBS on salivary cortisol, heart rate, and positive affect, but not on subjective stress, state rumination, or heart rate variability (HRV). Specifically, we found a beneficial effect of cTBS in terms of reduced stress-induced cortisol responses, a buffering effect of cTBS on stress-related decreases in positive affect, and enhanced heart rate recovery in the case of both, cTBS and iTBS. The results are internally consistent, but cTBS did not have the hypothesized stress-amplifying effect via its presumed inhibitory impact on the DLPFC. A meta-analysis by Kirkovski et al. (2023) supports the idea that the putative inhibitory and excitatory effects of TBS protocols, which were originally demonstrated using the motor cortex, are in prefrontal areas much more variable than initially assumed. Specifically, they found that both inhibitory cTBS and excitatory iTBS can produce variable neurobiological effects, including both excitatory and inhibitory responses. This is on the one hand attributed to differences in targeting accuracy, but on the other hand also the the complex neural organization of the frontal cortex, and task demands. Additional influencing factors, such as genetics and age, have been identified (Corp et al., 2020; Ridding & Ziemann, 2010), though many remain unknown. The mostly absent iTBS effects on a physiological and behavioral level are well in line with the few studies that have been previously conducted. Namely, the two studies that applied iTBS to the left DLPFC prior to the TSST found no impact of the stimulation on mood, state rumination, or cortisol (De Witte et al., 2020; Pulopulos et al., 2019). Additionally, a study that applied cTBS prior to a rumination induction also observed an effect on cortisol, but the authors found, contrary to our findings, a buffering effect also on HRV (Era et al., 2021). A recent meta-analysis on the effects of NIBS (rTMS and tDCS) on emotional stress reactivity comes to the conclusion that a single session might be insufficient to produce reliable, clinically significant effects (Smits et al., 2020). Regarding HRV and heart rate, however, meta-analytical evidence suggests that rTMS has a significant impact (Lee, Lee, Hwang, & Kang, 2023). These findings question in how far a single session of TBS is sufficient to produce reliable effects at least on a behavioral level.

4. Do high trait ruminators benefit more from TBS? Namely, are the effects of the TBS more pronounced in individuals with higher trait rumination?

We identified a trait-rumination-dependent effect of TBS exclusively on salivary cortisol (De Smet et al., 2024). Specifically, high ruminators compared to low ruminators exhibited lower stress-induced cortisol responses from baseline to post-TSST following cTBS. This finding contradicts our initial hypothesis of more pronounced increases in salivary cortisol following cTBS. Nevertheless, our results partially align with those of De Witte et al. (2020), who also found trait-rumination-dependent TBS effects on cortisol recovery. Their study reported that higher levels of brooding were associated with a decrease in cortisol secretion following iTBS, but not in the sham condition. Please note, however, that in our study, we did not find a corresponding effect of iTBS.

Furthermore, while we did not observe a trait-rumination-dependent effect of TBS on stress-reactive state rumination, De Witte et al. (2020) found that the impact of stimulation on momentary rumination changes due to the TSST marginally depended on the level of brooding (i.e., trait rumination). What is important to note is that De Witte et al. (2020) only investigated the effects of iTBS and included a relatively small number of high ruminators in their sample. In our study (De Smet et al., 2024), on the contrary, a stratified sample of total of 127 low, medium and high ruminators was recruited, ensuring an equal proportion, respectively.

5. Are we able to replicate the findings of different TBS protocols on the stress response from study 2? Namely, do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS using a within-subjects design?

We are unable to draw any conclusions regarding salivary cortisol, as sample analysis could not be conducted due to a lack of approved funding. Furthermore, we did not replicate the findings of study 2 concerning an impact of the stimulation on positive affect and heart rates. However, in contrast to the findings of study 2, we found a significant effect of iTBS on subjective stress and negative affect, with increases in both negative affect and perceived stress during and following the TSST. This effect not only contradicts the originally proposed excitatory nature of iTBS — and, consequently, its anticipated beneficial effects on stress and affect — but also previous studies that reported no impact of rTMS and specifically iTBS on emotional stress reactivity (De Witte et al., 2020; Pulopulos et al., 2019; Smits et al., 2020).

6. Are the aforementioned effects of the TBS more pronounced in individuals with higher trait rumination?

The observed effects of stimulation on subjective stress and negative affect were indeed only observed in high ruminators. Together with the findings from study 2, this strongly suggests a highly complex interaction between rumination, stress, and the effects of TBS, thereby supporting the initial evidence on this topic reported by De Witte et al. (2020). Nevertheless, the underlying mechanisms appear to be multifactorial and effects seem to be rather small.

7. Does inhibitory stimulation of the left DLPFC using cTBS exacerbate prefrontal dysfunction in high trait ruminators under stress, compared to sTBS? Conversely, does excitatory stimulation with iTBS "normalize" prefrontal functioning? Are these effects also found in low ruminators who already exhibit higher prefrontal activation under stress?

Interestingly, we did not observe prefrontal hypoactivation in high ruminators during the TSST. This contrasts consistently replicated findings in Major Depressive Disorder (MDD) (for a review, see Pizzagalli & Roberts, 2022) as well as studies that have demonstrated prefrontal hypoactivation in patients with depression (DP) and high ruminators using the same experimental setup but without TBS (Rosenbaum et al., 2021, 2024; Rosenbaum, Thomas, et al., 2018). One possible explanation for the absence of prefrontal hypoactivation, even in the sTBS condition, is the influence of performance-related expectancy effects. Blinding was effective, meaning participants could not reliably distinguish between active and sham stimulation. Moreover, subjective ratings of the stimulation's impact on performance were evenly distributed across conditions, with approximately 30 % of participants believing that the stimulation enhanced their performance under stress. Combined with the findings from study 1, which suggest that prefrontal hypoactivation is closely linked to stress-induced performance declines, it is plausible that participants who believed TBS improved their performance — even regardless of the actual neurobiological effects of the TBS — demonstrated enhanced cognitive output during the TSST. As a result, the typical prefrontal hypoactivation may have been diminished or entirely absent.

Another point to mention here are the substantial changes in RRS scores we observed within weeks between recruitment and the first appointment at the laboratory, which question in how far high trait ruminators of the sample actually exhibited higher levels of trait rumination (for an extensive discussion of this issue see Int-Veen et al., 2024). Another explanation for the absence of prefrontal hypoactivation could be the findings of Burke et al. (2022). In their meta-analysis, the authors found that sham stimulation also leads to a significant increase in activation of the prefrontal cortex. This means that when the left DLPFC is stimulated, the effects of active and sham stimulation overlap. Future studies should reconsider the implementation of the sham condition in order to better differentiate expectation effects and consider, for example, “no stimulation” conditions.

Only when we did not correct for multiple comparisons and only when participants received active stimulation first did we observe highly complex interactions between trait rumination and TBS in the left VLPFC. Specifically, we found the expected inhibitory effect of cTBS in low ruminators, while high ruminators showed an excitatory response to cTBS in the left VLPFC compared to sTBS. Descriptively, a similar but reversed pattern emerged for iTBS versus sTBS, with low ruminators displaying greater activation following iTBS compared to sham, whereas high ruminators exhibited increased activation following sTBS compared to iTBS. Following these findings and in line with a recent meta-analysis (Kirkovski et al., 2023), we assume that the excitatory effect of iTBS and inhibitory effect of cTBS might be an oversimplification and especially within-subjects, repeated measures designs might not be optimal in terms of complex interactions regarding the order of stimulations and resulting expectation effects interacting with habituation.

8. Following stimulation applied to the right Ventrolateral Prefrontal Cortex (VLPFC), do we find beneficial effects of putatively excitatory iTBS compared to sTBS and adverse effects of putatively inhibitory cTBS compared to sTBS using a within-subjects design?

Partly in line with the findings of study 3, in study 4 we observed significantly higher stress after the TSST following iTBS compared to sTBS. We replicated the findings of study 2 and 3 regarding no impact of the stimulation on state rumination. Contrasting the findings of the two previous studies, however, we observed no impact of the stimulation on positive and negative affect, performance during the TSST or heart rates.

9. Again, are the aforementioned effects of the TBS more pronounced in individuals with higher trait rumination?

Due to the nearly generally absent effects of stimulation, we found no evidence that the effects of TBS were dependent on trait rumination. The significantly higher stress levels in the iTBS condition following stress induction were observed not only in high ruminators but also in low ruminators.

10. In how far does inhibitory stimulation of the left DLPFC using cTBS exacerbate prefrontal dysfunction in high trait ruminators under stress, compared to sTBS? Conversely, does excitatory stimulation with iTBS "normalize" prefrontal functioning? Are these effects also observed in individuals with low rumination, who already show higher prefrontal activation under stress?

Replicating the findings of study 3, we did not observe prefrontal hypoactivation in high ruminators during the TSST. Again, expected impact on performance was not significantly different dependent on the stimulation condition, however now even 40 % of participants believed the stimulation made them perform better during the TSST.

Again, similar to study 3, a substantial number of participants had to be excluded from the study due to changes in RRS scores between recruitment and the first appointment at the laboratory.

Nevertheless, we observed significantly higher cortical oxygenation under stress in high ruminators when considering cortical oxygenation in the right VLPFC following iTBS, which was in line with the expected excitatory effect of iTBS.

7.2 Summary and conclusions

The studies conducted were closely interconnected in terms of their design, applied methods, and analysis, fostering comparability of their respective results. However, the findings — particularly regarding the effects of TBS on psychological and physiological stress responses — were highly heterogeneous between the studies and remarkably complex. While the first study demonstrated a strong association between state rumination and widespread prefrontal hypoactivation in the left DLPFC, among others, modulating these neural alterations and thus investigating their causal role in the stress-rumination link appears to be far from trivial.

On the one hand, we observed hypothesis-consistent changes in cortical oxygenation following iTBS applied to the right VLPFC in high ruminators (study 4). On the other hand, we found not TBS-induced changes in cortical oxygenation in the respective ROI when we applied stimulation to the left DLPFC (i.e. differences previous to the stimulation) as well as a facilitatory effect of iTBS in low ruminators and cTBS in high ruminators and conversely, an inhibitory effect of cTBS in low ruminators and iTBS in high ruminators in the left VLPFC during the TSST (study 3). These heterogeneous findings are most probably a result of the finding that TBS effects at the neural level seem to be influenced by factors beyond stimulation parameters alone (see e.g., Corp et al., 2020; Kirkovski et al., 2023; Ridding & Ziemann, 2010; Schutter et al., 2023). Recent findings suggest that the excitatory or inhibitory nature, the magnitude and potentially also duration of TBS effects likely depends on multiple factors, including stimulation parameters (McCalley et al., 2021), baseline neural activity, cognitive processes (Nicolo et al., 2015), and affective states preceding or occurring during stimulation (Schutter et al., 2023), among others. In particular, stimulation of the prefrontal cortex has repeatedly yielded highly heterogeneous findings in task-related neural activity compared to the initial findings stimulating the motor cortex (for a meta-analysis see Kirkovski et al., 2023). One potentially important form of cognitive influence, that we investigated in an exploratory way in study 3 and 4, might be expectancy effects. These could act on the underlying processes (even independent of) actual neural effects of the TBS. It would be fascinating to investigate the extent to which expected effects at the subjective level may exert a stronger influence or potentially counteract neural effects. Additionally, examining the correlation between subjective perceptions of performance changes and objectively measured performance improvements — or potential compensatory effects between the two — could provide valuable insights in future studies. In sum, not only the effects of TBS on a neural level are far from understood, also the factors influencing the effects of TBS remain to be investigated.

In the notion of objectively measured performance, I would like to return to the introduction of this dissertation and the systematic review by van Oort et al. (2017), which investigated functional connectivity and neural activity in response to acute stress. The authors found no significant changes or even increases in regions of the CEN, where the DLPFC is a key component, following stress exposure. They suggest that this may be due to the higher cognitive demands under stress and propose an inverted u-shaped relationship between stress and CEN activation, potentially covering overall associations (for an illustration see figure 7.1) (see also Moses et al., 2023). This traces back to a proposed inverted-u-shaped relationship between cognitive performance and stress (Yerkes, Dodson, & others, 1908) and is supported by studies correlating working-memory related CEN activation with different behavioral and physiological measures of stress and task performance (Qin, Hermans, Van Marle, Luo, & Fernández, 2009; Weerda, Muehlhan, Wolf, & Thiel, 2010).

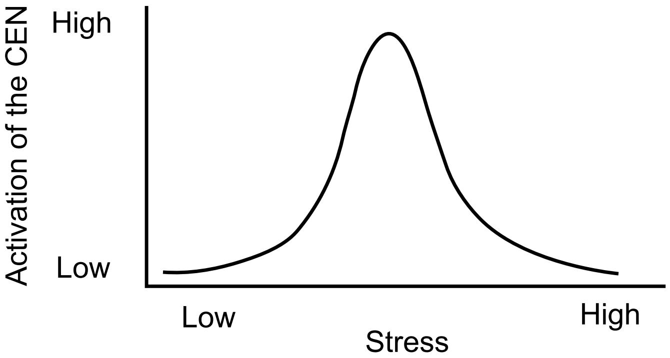

Figure 7.1
Schematic illustration of the relationship between the activation of the CEN and stress.

In all of our studies, we implemented the TSST, a potent psychophysiological stressor, as evidenced by observed significant increases in stress levels, negative affect, heart rate, and cortisol, even with repeated exposure (Allen et al., 2014; Kudielka et al., 2007). However, the TSST may not be optimal for investigating TBS effects, as the generally heightened recruitment of prefrontal regions in response to the TSST might cover up TBS-induced changes: If the TSST induces maximal recruitment of the CEN (or the specifically stimulated area), excitatory iTBS may have little additional effect in subjects with normal prefrontal functioning. Conversely, if stress is at its peak but the stimulated area is minimally engaged, cTBS may have no further impact. Crucially, this is likely an oversimplification that still assumes a binary facilitatory or inhibitory effect of a protocol (Hussain & Freedberg, 2025). However, it is important to acknowledge that substantial variability in subjective and neural responses to the TSST is expected across subjects (e.g. with prefrontal hypoactivation in high ruminators), especially when considering compensatory mechanisms, where factors such as motivation and expectancy may play a role. Additionally, since the TSST was administered after TBS, it is not possible to draw conclusions about baseline CEN activation during the stimulation. Combined with ongoing discussions regarding the duration of TBS effects, it remains unclear to what extent activation during or after TBS influences both neural and behavioral outcomes. In light of these considerations, future studies would benefit from continuously monitoring neural activity during TBS. This would allow to individually quantify baseline activation and to investigate, in real time, the neural effects of TBS.

Future studies could further benefit from employing stressors of varying intensity (i.e., inducing varying cognitive load) to investigate this hypothesis. Preliminary support comes from research using *n*-back tasks of different difficulty levels, which also engage cognitive control and the DLPFC. Ngetich et al. (2022; 2021) demonstrated in two independent studies that both iTBS and cTBS had no additional effect on the right DLPFC when task difficulty (comparing a 2-back to a 4-back task) — and consequently right DLPFC activity — increased. Building on these initial findings by Ngetich et al. (2022; 2021) and meta-analytical evidence suggesting variable effects of TBS dependent on the cognitive demands (see e.g. Kirkovski et al., 2023; Schutter et al., 2023), future research could systematically manipulate cognitive demand and task performance (see study 1) in paradigms that engage the CEN to investigate the potential effects of TBS as a function of these factors.

Intuitively, drawing conclusions about the effects of TBS on both physiological and psychological levels is challenging when the neural changes remain unclear. Notably, in most measures, we observed no significant effects of TBS, and the current studies do not support the notion that a single session of TBS is sufficient to induce robust neural changes that translate into behavioral or cognitive alterations in stress-reactive rumination. Repeated stimulation may be necessary, as long-term effects like neural plasticity, long-term potentiation, and long-term depression typically require multiple sessions, making it unlikely that a single session of TBS would produce significant effects (see e.g. Smits et al., 2020). Please note, however, that in the studies of this dissertation, only task-related neural activation was investigated. In another analysis of the data of study 2 and 3 (Int-Veen, Täglich, et al., n.d.), we focused on changes in resting-state functional connectivity and observed more coherent effects especially following iTBS.

In short, results indicated that iTBS elicited excitatory effects on prefrontal and fronto-parietal connectivity, whereas cTBS effects were more variable and trait rumination emerged as a modulator of TBS effects. Unfortunately, as previously mentioned, there is a relatively small body of research examining the effects of TBS at the neural level, with even fewer studies exploring neural changes in terms of functional connectivity, which intuitively links brain regions as components of dynamic brain networks. Potentially, the complex changes induced by TBS could be better captured in terms of changes in synchronicity, respectively. Nonetheless, also in this area of research, the factors influencing magnitude and direction of NIBS effects are still investigated.

7.3 Limitations

In addition to the limitations discussed within each individual study, several overarching limitations of the conducted research should be highlighted here.

One limitation concerns the selected study sample. While the first study included data from both HC and DP regarding their brain activity, the three subsequent studies solely focused on healthy participants. Recruiting a clinical analogue sample has the advantage of a relatively homogeneous sample, which is not confounded by additional factors, such as psycho-pharmacotherapy or psychotherapeutic treatment, that may also influence neural mechanisms. Another crucial factor in selecting the study population is ethical considerations. Specifically, recruiting a clinical sample appears problematic given that the general mechanism linking TBS, stress, and rumination has yet to be established. Nevertheless, it is plausible that the differences in neural activity, specifically prefrontal hypoactivation, would have been more pronounced in the sample of DP compared to high ruminators. Smaller effects of the TBS might therefore have been more detectable in a sample of DP versus HC. In line with the transdiagnostic nature of ruminative thinking, it would be especially interesting to investigate samples with other mental disorders, as well.

Another point to consider is that no neural correlates were assessed in study 2, and in studies 3 and 4, only during the stress induction and not simultaneously with the stimulation. Unfortunately, simultaneous fNIRS data collection was not feasible due to limitations of the device used. Even though unlikely, the process of placing and removing the cap may have led to slight variations in the positioning of the probeset. This, coupled with the absence of neuronavigation during TBS, raises the question of whether part of the variance in the results could be attributed to discrepancies in the alignment and positioning of the coil. A recently developed method for accurately localizing the DLPFC without the need for fMRI is Neuro-Cardiac-Guided TMS (Iseger, Padberg, Kenemans, Gevirtz, & Arns, 2017; Iseger, Padberg, Kenemans, van Dijk, & Arns, 2021).

More specifically, by taking advantage of the consistently observed effect of prefrontal stimulation inducing significant heart rate slowing, Neuro-Cardiac-Guided TMS utilizes the electrocardiogram (ECG) to precisely localize the DLPFC. Indeed, while we observed no effect of iTBS applied to the left DLPFC on heart rates in study 3, we did observe an enhanced heart rate recovery in study 2, which could explain differences in results between the studies.

7.4 Future perspectives

I would like to conclude with two additional thoughts on future directions that have not been addressed in the previous discussion.

First, the neurobiological effects of Non-Invasive Brain Stimulation (NIBS), particularly the factors that determine whether stimulation exerts excitatory or inhibitory effects, need to be better understood. This requires a more comprehensive investigation of stimulation effects beyond the motor cortex, as well as their interactions with associated brain networks and the impact of various other factors like genetics and age (Corp et al., 2020; Ridding & Ziemann, 2010). A major challenge in this context is the precise quantification of these neural effects. Recent technological advancements provide promising tools to address this issue — for instance, the simultaneous application of TMS and the measurement of neural activity using fNIRS has recently become possible. One potential solution to many of the methodological challenges associated with TBS would be the use of more potent stimulation methods, such as ECT or the implantation of deep brain stimulation electrodes. This would ensure that the targeted brain region is effectively stimulated, and the resulting neural changes would likely be more pronounced.

Second, regarding long-term clinical application, personalized medicine appears to be particularly promising. Tailoring stimulation protocols which specifically target neural alterations associated with personal symptoms may enhance treatment efficacy and optimize therapeutic outcomes once the neural effects of neuromodulation are better understood. For this, specific subgroups benefiting, for instance from TBS, have to be identified. Coming back to the presented efficacy of different treatments for depressive disorders, TBS with targeting the neural mechanisms is most probably superior if combined with other treatments. Not only are the underlying neural mechanisms complex, with stimulation of one brain region also affecting interconnected networks, but the interaction across different levels (e.g., cognitive, affective, physiological, and neural) is equally complicated, forming a dynamic interplay.

Nevertheless, the potential to utilize neuromodulation as an additional layer of treatment for mental disorders holds promise for enhancing therapeutic options in the future.

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