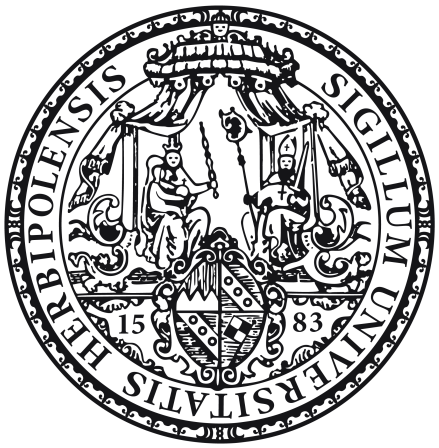

Targeting Temporally Stable Vulnerability Factors in the Prediction of Long-Term Courses of Depression: Diagnostic Considerations and Therapeutic Protocols Based on Transcranial Ultrasonic Neuromodulation of Endophenotypes

Untersuchung Zeitlich Stabiler Vulnerabilitätsfaktoren für die Vorhersage Langfristiger Depressionsverläufe: Diagnostische Erwägungen und Therapeutische Protokolle auf der Grundlage Transkranieller Ultraschall-Neuromodulation von Endophänotypen

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Julius-Maximilians-Universität Würzburg,
Section Neuroscience
submitted by

André Forster

from

Kassel

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Submitted on: . . . . . .
Office stamp

Members of the *Promotionskomitee*:

Chairperson: Prof. Dr. Matthias Gamer

Primary Supervisor: Prof. Dr. Johannes Hewig

Supervisor (Second): Prof. Dr. Erhard Wischmeyer

Supervisor (Third): Prof. Dr. John JB Allen

Date of Public Defence: . . . . . .

Date of Receipt of Certificates: . . . . . .

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Abstract

Depressive disorders represent one of the main sources for the loss of healthy years of life. One of the reasons for this circumstance is the recurrent course of these disorders, which can be interrupted by current therapeutic approaches, especially in the short-term, but seem to be maintained at least in part in the long-term. Subsequently, on one hand, this thesis deals with methodological measurement issues in the longitudinal prediction of depressive courses. On the other hand, it addresses two currently discussed neuroscience-based treatment approaches, which are investigated experimentally in a basic-psychological manner and reviewed in the light of their potential to translate results to the application in patient care. These two approaches each address potential mechanisms that may negatively impact long-term disease trajectories: First, stable endophenotypes for vulnerability factors that could regain control over the organism and reactivate maladaptive experiences, or behaviors with increasing temporal distance from therapeutic methods are focused on. In the studies presented, these were influenced by a recently rediscovered method of neuromodulation (transcranial low-intensity focused ultrasound) which is discussed in light of its unique capability to address even deepest, subcortical regions at a high spatial resolution. Lastly, as a second approach, an experimental design for the use of reconsolidation interference is presented, which could provide a first insight into the applicability of corresponding protocols in the field of depressive disorders and thus contribute to the modification, instead of inhibition, of already mentioned endophenotypes. In sum, methodological considerations for monitoring and predicting long-term courses of depression are deducted before two approaches are discussed that could potentially exert positive influences on the recurrent nature of depressive symptoms on their own, in combination with each other, or as augmentation for existing therapeutic procedures.

Zusammenfassung

Depressive Erkrankungen stellen eine der Hauptquellen für das Einbußen gesunder Lebensjahre dar. Einer der Gründe für diesen Umstand liegt im rezidivierenden Verlauf dieser Erkrankungen, der auch durch bisherige Therapieansätze vor allem kurzfristig unterbrochen werden kann, jedoch langfristig zumindest in Teilen erhalten zu bleiben scheint. Daran anschließend befasst sich die hier vorgelegte Thesis zum einen mit der Messproblematik longitudinaler Vorhersagen depressiver Verläufe und zum anderen mit zwei aktuell diskutierten neurowissenschaftlich begründeten Behandlungsansätzen, die experimentell-grundlagenpsychologisch aufgearbeitet und im Lichte eines translationalen Ansatz hin zur Anwendung in realen Patientensituationen erörtert werden. Die beiden genannten Ansätze adressieren dabei jeweils Mechanismen, die sich negativ auf langfristige Krankheitsverläufe auswirken können: Zunächst werden hier stabile Endophänotypen für Vulnerabilitätsfaktoren, die mit zunehmendem zeitlichem Abstand zu Therapiemethoden erneut Kontrolle über den Organismus gewinnen und maladaptives Erleben und Verhalten reaktivieren könnten, in den Fokus gestellt. Diese wurden in den hier vorgestellten Studien mit einer vor wenigen Jahren wiederentdeckten Methode der Neuromodulation (transkranieller, niedrigintensiver, fokussierter Ultraschall) beeinflusst und vor dem Hintergrund der einzigartigen Möglichkeit dieser Technik, auch tiefste, subkortikale Regionen bei hoher räumlicher Auflösungsfähigkeit adressieren zu können, diskutiert. Zuletzt wird ergänzend, als zweiter Ansatz, ein experimentelles Design zur Nutzung der Rekonsolidierungsbeeinflussung vorgestellt, das erste Informationen über die Anwendbarkeit entsprechender Protokolle im Bereich der depressiven Erkrankungen liefern und somit zur Veränderung, Anstelle von Inhibition bereits genannter Endophänotypen beitragen könnte. Zusammengenommen ergeben sich hieraus zunächst allgemeine methodische Überlegungen für das Überwachen und Vorhersagen langfristiger Verläufe der Depressionen, aber auch zwei Ansätze, die für sich genommen, in Kombination miteinander oder auch als Augmentation für bestehende Therapieverfahren, potentiell positive Einflüsse auf die rezidivierende Natur dieser Diagnosegruppe haben könnten.

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Part I - Theoretical Background

1 Introduction

To some, it is a burden that weighs heavier than the finality of death.

For most of us, it is hard to understand and even harder to accept this sentence that is a truth to thousands and thousands of patients, relatives, and strangers each and every year. It describes a state of mind that is especially present in those who share a certain diagnosis even though they may not share much else: Depression.

Depression describes a subjective state that is characterized by a conglomerate of affective, cognitive, and somatic symptoms which are accompanied by significant functional forfeiture. According to the *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-V) and the *International Statistical Classification of Diseases and Related Health Problems 10* (ICD-10), these symptoms enclose depressed mood, loss of interest, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, issues in maintaining concentration, feelings of insufficiency, worthlessness or guilt, and finally, suicidal ideation, as described above (World Health Organization, 1993, American Psychiatric Association, 2014). However, even though, in common parlance, depression is often referred to as a single diagnosis, it rather describes a whole class of diagnoses that differ in their severity and course, including exacerbated episodes that may include symptoms such as delusions (World Health Organization, 1993).

Nonetheless, across all cultures, even less severe forms have also been reported to cause significant suffering in affected patients (e.g., Lépine and Briley, 2011; Kirmayer et al., 2017; World Health Organization, 2017), their relatives (e.g., Fadden et al., 1987; McGuffin et al., 1988; Lépine and Briley, 2011; Skundberg-Kletthagen et al., 2014; Q. Liu et al., 2020), offspring, who appear to carry a genetic vulnerability (e.g., Demirkan et al., 2011; Flint and Kendler, 2014; Reznik and Allen, 2018) and society as a whole (e.g., Greenberg and Birnbaum, 2005).

These substantial strains are among other factors caused by the general clinical course of depression which appears to be highly recurrent and often chronic (see Section

2). In addition, depressive symptoms may exacerbate virtually every other somatic illness, including viral infections (e.g., Kiecolt-Glaser and Glaser, 2002; Glaser et al., 2003; Dowlati et al., 2010) but also chronic or progressive (somatic) disorders (e.g., T. A. Hughes et al., 2004; Byers et al., 2012; Fidika et al., 2014).

Against this background, therapy and possibly even more importantly, prevention of depressive episodes is a highly relevant and pressing task for international and interprofessional scientific but also practicing communities alike. Unfortunately, although today's society knows several effective methods to combat this disease, even these interventions, which have robustly been shown to decrease suffering, seem to lose their therapeutic influence over time (see Section 2.1). For instance, medication-based therapy trials show antidepressant effects only as long as the substance is taken (e.g., Glue et al., 2010; Reid and Barbui, 2010; DeRubeis et al., 2020). Unfortunately, psychotherapeutic interventions show similar patterns as these are also not able to prevent recurrences in the long-term (e.g., DeRubeis et al., 2020; also see Sections 2 and 2.1). As a result, approximately 50% of patients suffer from more than one episode (e.g., Keller and Shapiro, 1981; Keller et al., 1992; Solomon et al., 1997; T. I. Mueller et al., 1999). Consequentially, it seems that the therapies established thus far are mainly effective in relieving acute symptoms, but not in combating their causes lastingly. Therefore, the most effective treatment against the development of lifelong recurrence may remain to be primary prevention.

The work presented here addresses this issue of therapy effect longevity by discussing general considerations in the analysis and prediction of longitudinal data within this field of research. In this context, the given thesis addresses inter- and intraindividual vulnerability factors that may qualify to shape long-term clinical courses of depression by discussing stable influences, such as personality traits but also chronic conditions (cognitive decline in the elderly and cystic fibrosis) that may represent or induce additional temporally invariant factors contributing to the emergence of affective symptoms. The manuscript then moves on to introduce two novel treatment approaches, which are currently discussed within the clinical and translational neurosciences literature and may result in increased sustainability of effects due to their ability to interfere with the aforementioned stable vulnerability factors. This thesis thus attempts to add to two techniques

that may be suitable to produce more long-lasting preventive and curative effects:

The first approach focuses primarily on changing the neural bases underlying vulnerabilities for the development of depressive symptoms. To accomplish this, a recently rediscovered method of neuromodulation (transcranial low intensity focused ultrasound neuromodulation; litFUS) has been used to affect an endophenotype for depression-related vulnerability factors to the point of altered processing of emotional stimuli and hopelessness by inhibiting the right inferior frontal gyrus (riFG) of the lateral prefrontal cortex (lPFC).

The second method discussed is reconsolidation modification, which, in contrast to extinction learning, is intended to enable actual change in depression-related neuronal connections rather than masking them with inhibitory novel learning (as in extinction learning). In this regard, a protocol for a pilot study concerning reconsolidation modification in depression is presented. At the same time, this thesis analyzes the influence of neural network activity during memory and 'schema' updating, which may define regions of interest for the use of litFUS to influence this reconsolidation process directly.

To address all of these topics and to point out their interconnections in a coherent manner, in Part I of this thesis, several theoretical frameworks are established before their direct and indirect implications for one another are discussed in detail within Part IV. Part I thus begins by highlighting the need for long-lasting therapy effects by addressing epidemiological and socioeconomic descriptives and consequences of depressive disorders. To provide an additional overview, Figure 1 illustrates the main axioms, aims, results, and conclusion of this thesis.

1.1 Epidemiology of Depressive Disorders

Statistically, psychological/psychiatric diagnoses account for an ever-increasing proportion of disorders due to which healthy years of life are lost, whether to death or to periods marked by illness (World Health Organization, 2017), which possibly leads to far-reaching social, professional and personal consequences.

According to a report by the *German Psychotherapists Association* (DPtV; Rabe-Menssen et al., 2021), the lifetime prevalence of suffering from at least one psychi-

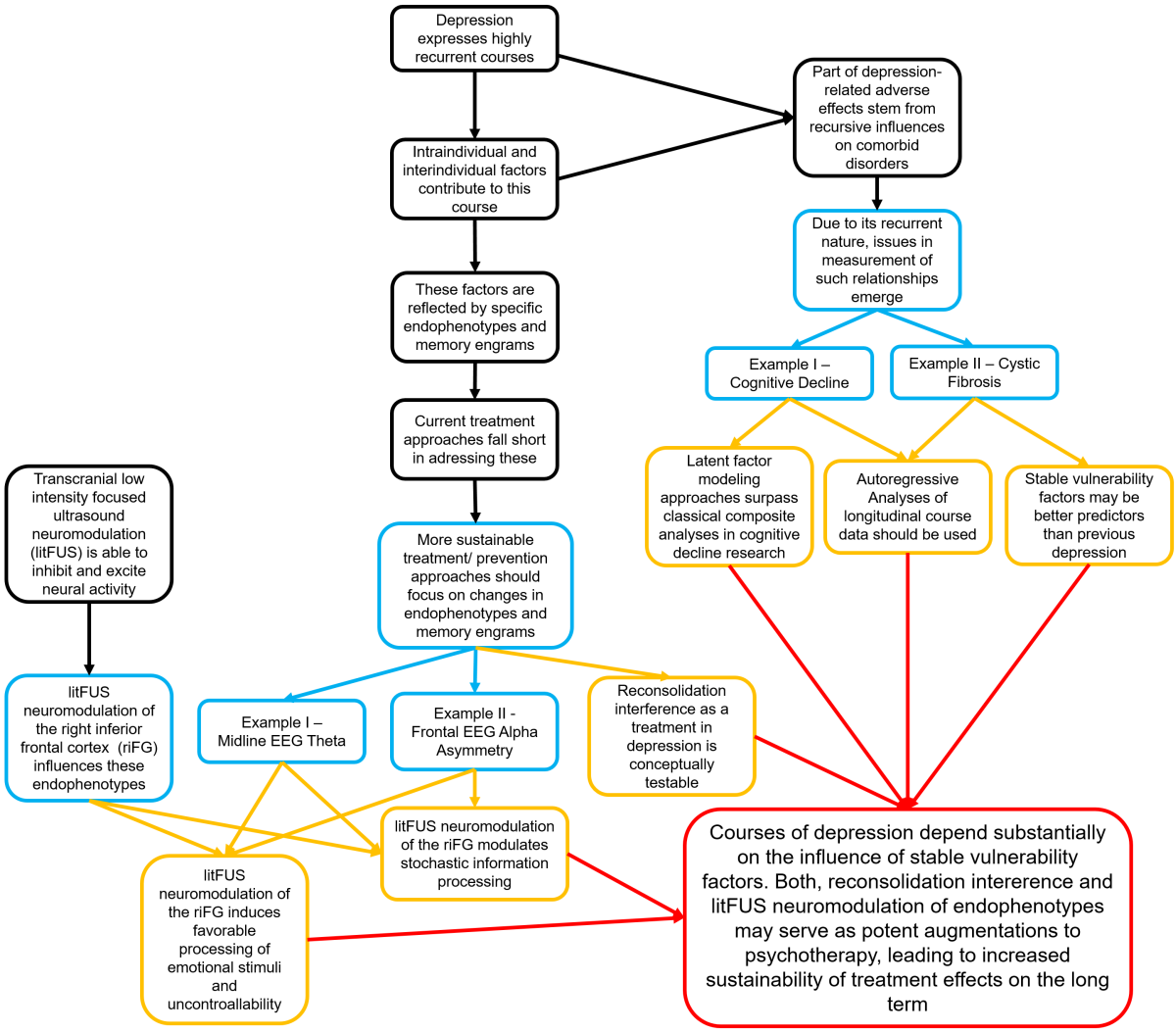

Figure 1: Visual outline of this thesis. Black boxes indicate axioms, while blue boxes indicate hypotheses that have in some regard been statistically addressed within the manuscript. Orange boxes indicate broadly described results, which culminate in the red box, stating the overall conclusion of this thesis.

atric disorder in Germany is 42.6%. The highest risk was given for unipolar depression (17.1%) and somatoform disorders (16.2%)[1]. In terms of 12-month prevalence, anxiety disorders were found to be the most common form of psychiatric diagnoses (15.4%), again followed by unipolar depression (8.2%).

According to the report, overall, depressive disorders represent the third-largest factor influencing the disease-adjusted life years in Germany among women; among men, it is the seventh largest. A total of 345,221 (for men) and 593,348 (for women) healthy life years were lost to depression within one year as early as 2010 (with an existing upward

[1]Due to huge differences in reports on the lifetime prevalence for anxiety disorders across studies, no conclusive number is given for these

trend; Plass et al., 2014). These years may, however, not only have been lost to the fact that often chronic courses and high recurrence rates lead to many years to be lived with the disease but also to the fact that depression itself is a disorder that can on its own lead to death (through suicide) and generally increase morbidity through its numerous influences on other (somatic) diseases (e.g., Dowlati et al., 2010). Taken together, data from all statutorily insured persons in Germany show an odds ratio of 1.4 for death within two years among those suffering from depressive disorders as compared to those who do not (F. Schneider et al., 2019).

In terms of suicides, in Germany, between 9,000 and 10,000 people take their own lives each year (about half as many as in the 1980s). This is more deaths than those from traffic accidents (3,177), drugs (1,272), homicide (405), or manslaughter (1,858) combined (Statista, 2020 as cited in Rabe-Menssen et al., 2021). Furthermore, it is worth noting that there are about 15 to 20 times as many suicide attempts as there are 'successful' suicides, which further highlights the still enormous prevalence of suicidal ideation. According to Wolfersdorf (2008a; 2008b), inadequately treated or untreated depression, as well as treatment-resistant depression, are among the greatest factors contributing to these numbers. Wittchen et al. (2010) further estimate the lifetime prevalence of suicide in patients with severe major depressive episodes to be as high as 14.4% and averaged across all severity levels to equal 4%.

Even though depressive disorders go along with substantial suffering, economic issues, and mortality, approximately 68% of individuals suffering from depression but not a second mental health diagnosis do not seek treatment. Overall, only 34.6% of depressed individuals were receiving treatment in 2011 (Mack et al., 2014). Even though these numbers may have increased to this date, it is highly unlikely that full coverage of all those in need has been reached.

In addition to this, it may be worth mentioning that these statistics refer to a phase of society-specific normality. This means that, on average, substantial stressors such as the experience of violence, economic insecurity, or physical illness persist at a relatively stable level for individual countries. However, in the wake of the ongoing global pandemic, there has been a dramatic rise in many of these stressors all around the world,

increasing psychiatric illnesses across most countries. In a U.S. sample of the general population, for example, a threefold increase in depressive symptoms was already observed by summer 2020. Here, especially the socioeconomic status was associated with higher symptom burden (Ettman et al., 2020). Among medical personnel, who suffer primarily from persistently overwhelming workloads and the dramatic scenes they are to witness as health care systems are on the brink of collapse, more than 64% of study-respondents reported significant depressive symptoms, according to one study (Elbay et al., 2020). Among Covid-19 survivors, more than 30% fulfill the requirements for a diagnosis of depression (Mazza et al., 2020). Similarly, large increases in the prevalence of depressive symptoms are also seen in Germany (Bäuerle et al., 2020), with those with preexisting affective disorders appearing to be particularly affected by symptom exacerbation (Bendau et al., 2021). Overall, the current pandemic imposes dramatic stress through many different ways of effect, severely impairing psychological well-being to an extent that will probably not be fully understood until years to come.

1.2 Socioeconomic Impact of Psychiatric Disorders

The impact of psychiatric disorders on the everyday experiences of those affected cannot be measured solely by epidemiological data. In addition to self-rate data on the subjectively perceived quality of life and other psychometric measures, the economic consequences of such disorders can also provide insights, as they offer indirect quantification of the functional impairment caused by the symptoms.

According to the DPtV report (2021), in Germany, in 2015, approximately €44.4 billion were spent on the statutory care of patients suffering from psychiatric and behavioral disorders (excluding nicotine dependence). This diagnosis group ranks second behind cardiovascular diseases (€46.4 billion). Converted to each individual citizen, the direct costs amount on average to about €540 per person per year. The largest share of direct costs was accounted for by inpatient treatments (€24.9 billion) while outpatient care accounts for €2.48 billion for statutory health insurers.

Indirect costs, such as those arising from lower productivity at the workplace cannot be recorded directly. In contrast, the statistics on working days lost due to illness

represent a calculable lower limit for indirect costs. In Germany, for the year 2017, the financial damage caused by psychological and behavioral disorders is estimated at €21.7 billion (0.7% of the gross domestic product). Again, positioning second, this time following diseases of the musculoskeletal system with the greatest losses. Concerning affective disorders alone, in 2017, approximately 32.33 million missed workdays were attributable to unipolar depression, while 18.77 million are connected to adjustment and stress disorders. Finally, 11.8 million missed workdays stemmed from recurrent depressive disorders.

According to the health ministry of Germany, converting the days of absence to the individual case, the most psychiatric disorder related absence occurs with regard to specific personality disorders, with an average of 86.1 days/year, followed by patients suffering from recurrent depressive disorders (84.0 days/year) and unipolar depressive episodes (62.9 days/year). Since 2006 (through 2018), mental health-related absenteeism has increased by 92% (*Bundesministerium für Gesundheit*, 2020, as cited in Rabe-Menssen et al., 2021)

2 Courses of Depression

According to the ICD-10 and DSM-V, depressive disorders are in general divisible into specific diagnoses based on their severity, recurrence, and chronicity. While other attempts to subtype depression outside of these course descriptions mostly fall short in terms of external validity (e.g., by showing differential treatment effects and clinical courses based on subtypes; Harald and Gordon, 2012), this classification approach has been shown to pose as a valid distinction between depressed individuals, concerning both, prognosis and type of treatment needed (see Section 2.1 and Figure 2). However, even though the impact of these course-related variables is widely agreed upon, there often is a lack of consensus about what defines depressive episodes, recurrences, relapses as well as chronic or residual courses in the literature. Table 1 gives an overview of terminology according to the systematic review by de Zwart et al. (2019), who attempted to summarize and synthesize definitions within the literature based on empirical observations. Building on their remarks, in the following, definitions presented in Table 1 are used within this thesis.

	Episode	Full Remission	Partial Remission	Asymptomatic	Recurrence	Relapse
Symptom course	For the first time, symptoms persist for at least two weeks	Asymptomatic phase of undefined duration		Symptom free period that is not interpreted as remission yet	An episode occurs after full remission	An episode occurs after partial remission
Symptom severity	Qualify for at least a mild depression	No significant symptoms present	Severity or number of symptoms decreased but perseveres on a significant level	No significant symptoms present	Qualify for at least a mild depression	Qualify for at least a mild depression
Recommendation by Zwart et al.	Symptoms should persevere for at least two weeks, better more	Duration threshholds are unnessesary		Less than 5 points on the HAMD-17	Symptoms should persevere for at least two weeks, better more	

Table 1: Definitions of clinical course-sections according to de Zwart et al., 2019. HAMD-17 = Hamilton rating scale for depression.

The overall recurring clinical course of depression and its modification by treatment approaches is often targeted within randomized controlled trials. Most studies investigate the impact of specific treatment approaches in comparison to treatment as usual (TAU) care. Here, a number of studies point towards evidence of cognitive and mindfulness-based therapy (Teasdale et al., 2000; Michalak et al., 2008; Godfrin and van Heeringen, 2010; Jarrett et al., 2013; Bockting et al., 2018; Farb et al., 2018; McCartney et al., 2021) to exceed the preventive potential for relapse and recurrence of other approaches even though the effects are still inconsistent across meta-analyses (Piet and Hougaard, 2011; Wojnarowski et al., 2019). In particular antidepressant medication has been reported to perform significantly worse than psychotherapy approaches (e.g., Cosci et al., 2020), especially after discontinuation of its intake (e.g., Melfi et al., 1998; Geddes et al., 2003; also see Bosman et al., 2018).

However, evidence on naturalistic courses of depression from non-treated samples remains scarce as these are neither easily accessible nor assessable for and in scientific investigations. In 2008, Eaton and colleagues report one of the few studies that provide data for a non-clinical sample[2] that included those who sought and those who did not seek treatment. In this sample, 92 participants suffered from their respective first episode within the time of observation. About 50% of these recovered without any recurrent episode within the following years of investigation, while the rest showed recurrent or

[2]A probability sample of more than five thousand adults in an urban area of East Baltimore over the course of 23 years in two waves of assessment

chronic courses. Of all those who suffered from their first episode within the study trial, 58.7% told investigators that they had talked about their symptoms with a medical professional (further treatment details were not assessed). These results are in general similar to those of many other investigations of mixed (including treated and untreated) samples, mostly agreeing on an approximate 50% chance to suffer from at least more than one episode (e.g., R. M. Post, 1992; Kupfer and Frank, 1996; Burcusa and Iacono, 2007; Curry et al., 2011). Also, spontaneous remission within months is a well-replicated finding:

In comparison to their own data, the authors (Eaton et al., 2008) further reference the highly impactful 15-year collaborative longitudinal study by the National Institute of Mental Health (NIMH; Keller and Shapiro, 1981; Keller et al., 1992; Solomon et al., 1997; T. I. Mueller et al., 1999). In this study, the authors investigated only those patients that sought treatment. They report recovery within the first year to take place in 67% of cases while 81% were recovered two years after onset. Five years after onset a total of 88% recovered and by 10 years 7% remained depressed. Interestingly, in this sample, the authors also found 50% of those who suffered from one episode to recover without any recurrence or relapse within the study's time frame, which equals the results from Eaton and his colleagues. According to Hardeveld et al. (2010), recurrence rates may even be higher in treated patients as compared to the general (untreated) population (but also see Wojnarowski et al., 2019, who in their systematic review, report a recurrence rate of 33% following cognitive behavioral therapy). Figure 2 illustrates these clinical-course statistics in a *Sankey*-plot.

These results indicate that courses of depression are in general highly recurrent and tend towards chronicity, regardless of treatment. However, this view is controversial due to one major argument: Since a minority of depressed individuals seek treatment (e.g., Mack et al., 2014), a selection bias may significantly impair the comparability of treated-patient-sample data and data from the general (untreated) population. Unfortunately, this effect is not trivial to estimate as wait-list controls, which would represent the best control group as it would be reasonable to assume that these individuals are not fundamentally different from those who receive treatment, will often be eventually treated themselves. This in turn, complicates long-term follow-up investigations to assess recurrence rates in

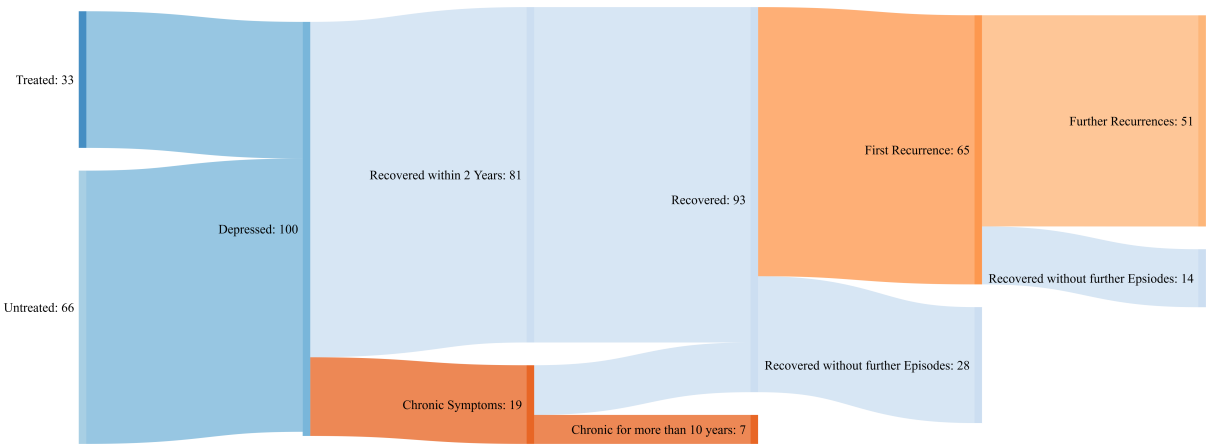

Figure 2: Sankeyplot of the course of depression for 100 hypothetical depressed individuals. Of 100 individuals, according to the numbers provided by Mack et al., 2014, approximately two-thirds remain untreated. Following the results of the collaborative longitudinal study by the National Institute of Mental Health, 81% will recover within two years. Of all those, who recovered, approximately 70% will suffer from at least one additional episode. For individuals who experienced three episodes, the estimated risk for further recurrences is 90%. This plot represents a schematic illustration of tendencies based on empirical data and statistical estimations of the referenced literature. It will, in part, provide an insufficient illustration of complex effects, such as the higher risk for recurrence in those who endured a chronic course in comparison to those who did not.

such samples.

Other evidence may stem from studies investigating treatment-seeking behavior and its predictors: Here a systematic review paper suggests, that symptom severity and the number of previously endured episodes may show a positive correlation to treatment-seeking behavior (Magaard et al., 2017). However, mixed results were reported, indicating some sort of sample-characteristic-based moderating variable. Lin and colleagues (1999) report this effect to at least partly rely on sociodemographic data, which may be plausible since women, who tend to suffer from more severe and recurrent courses (e.g., Parker and Brotchie, 2010; Albert, 2015; A. Cavanagh et al., 2017; Hyde and Mezulis, 2020), also seek help more often than men in many countries (see Magaard et al., 2017). Furthermore, Maargard et al. (2017) point towards the retrospective nature of most data in this field of research, which may allude to the idea that patients who were treated may evaluate their previous state differently than those who did not undergo therapy. In sum, it may not yet be fully understood, whether a selection bias plays an impactful role in the comparison of treated and untreated sample data.

Nevertheless, overall, the question arises whether existing therapies influence the long-term course of this disease. Irrespective of this, however, a general trend can be observed that also seems to occur in samples that are being treated: In approximately half of all those, who are depressed, recurrence of symptoms will occur.

In addition, further evidence indicates that recurrences are not only frequent but they also seem to become more and more probable as the number of episodes already experienced increases (American Psychiatric Association, 2000), thereby decreasing symptom-free periods between episodes. Already in 2000, Solomon et al. describe that the median time between the first and the second episode is estimated at 83 weeks, while the next interval between the second and the third episode is only 77 weeks. By the fourth episode, he finds only 68 weeks, and by the fifth, 57 weeks. This trend of shortening has been replicated in numerous studies (Kraepelin, 1921; Angst and Preisig, 1995; Angst et al., 1973; Kessing and Andersen, 1999; Ehnvall and Agren, 2002; Kessing et al., 2004).

This suggests that affected patients may undergo some kind of sensitization that makes them increasingly susceptible throughout their disease, which therefore reduces the number of healthy weeks between episodes. In line with this, several studies show that the duration of depression until remission is a vulnerability factor for poorer treatment outcomes later on (e.g., Patten, 2006; Hung et al., 2017).

However, even though it seems plausible to assume sensitization due to previous episodes, this view could be contrasted with the interpretation that this is not an acquired vulnerability, but that both the initial duration and severity of depressive episodes and the vulnerability to worse treatment response could be triggered by a common predisposition (for a discussion, see Section 3.2).

2.1 Impact of Current Therapies

A huge variety of interventions, starting at mere physical exercise (e.g., Kvam et al., 2016; Wegner et al., 2020) over a variety of psychotherapy approaches (e.g., Cuijpers et al., 2008; Cuijpers et al., 2011; Cuijpers et al., 2021) and different neurochemical agents (e.g., T. Z. Tang et al., 2009; Dale et al., 2015; also see treatment guidelines: e.g., F. Schneider et al., 2017; Gautam et al., 2017) to neuromodulation (e.g., Gaynes et al., 2014) have

been shown to be effective in context of depression.

Especially among psychotherapy and medication-based approaches, very different mechanisms are thought to induce therapy effects, increasing the overall portfolio to treat the heterogeneous patient pool of depressed individuals. Interestingly, however, the effect sizes seem to be comparable across these different approaches (e.g., Cuijpers et al., 2008; Cuijpers et al., 2010; Fournier et al., 2010; Cuijpers et al., 2011; Cuijpers et al., 2013; Barth et al., 2016; Cuijpers et al., 2021), which questions the respective validity of supposed modes of action.

One often-cited argument to answer this finding is that this effect results from the fact that patients choose the form of therapy that suits them best, which leads to equality of outcome even though different ways of effect are indeed evident. As meta-analyses show, small *self-selection effects* can be found, even though these do not seem to play a particularly great role: Neither in psychotherapy, nor medication (Wampold, 2015; Cuijpers et al., 2021). Instead, it seems that (on average) all currently established forms of therapy seem to work similarly well for most patients.

Along the same line of evidence, both antidepressant medication and psychotherapy have been questioned in their respectively supposed mode of action. As a result, antidepressant medication research has to contend with clear indications of placebo effects (e.g., Kirsch et al., 2002; Fournier et al., 2010; Jakobsen et al., 2020) while psychotherapy research also has to deal with similar effects, even though it may not be intuitive to assume such in this treatment approach. Nonetheless, many studies report findings that allude to placebo-like influences in psychotherapy. For instance, similar therapeutic effects are seen between trained therapists and lay counselors in milder courses of depression (e.g., Montgomery et al., 2010; Bryan and Arkowitz, 2015; Weobong et al., 2017). In addition, with a few exceptions (that is, training of emotion regulation skills and activity-boosting interventions), studies using dismantling approaches often fail to provide evidence for the necessity of certain therapeutic steps that are theoretically deemed crucial (e.g., Ahn and Wampold, 2001; Bell et al., 2013; Berking et al., 2013; Kellett et al., 2018; Garland, 2014).

At the same time, it seems that the field of depression treatment is primarily

characterized by the *common factors of therapy* (Laska et al., 2014; Wampold, 2015). These include all those variables that do not require a school-specific technique but are regarded as prerequisites across all psychotherapy approaches. These include, for example, the *therapeutic alliance*, which has the greatest predictive power for the clinical course during therapy (e.g., Wampold, 2015). Nonetheless, even though many studies point towards the idea of common factors to predict therapy outcomes to a bigger degree than specific interventions, there remains a huge lack of evidence as Pim Cuijpers points out in his 2019 study, where he criticizes the correlational nature of most analyses in the field (Cuijpers et al., 2019).

Overall, this line of evidence indicates that many forms of therapy can be considered effective in their own right, but that it seems plausible that the existing forms of therapy primarily lead to symptom-alleviation rather than cause-combating effects. Otherwise, there should be clear differences in effectiveness and prognoses between the different treatments. In this case, one or more treatment approaches should work closer to the actual vulnerability than others, thereby modifying it more directly and lastingly. Since this does not seem to be the case, it can be assumed that, as of today, there is no evidence that vulnerability to depressive disorders can already be treated effectively in the long-term (at least not in the majority of patients). In line with this, as discussed in Section 2, there is no clear difference in the course of the disease between treated and non-treated patients (according to the scarce data). The risk for relapses, chronic, and residual courses remains high.

Nevertheless, studies continue to provide predictors and indications of how existing approaches could be modified to increase their effectiveness. For example, several studies show that cognitive changes that can already be found in the early treatment responses of psychotherapy (*sudden gains*), may predict fewer relapses to occur. However, the effects are not large enough to substantially reduce the still high probability of further episodes emerging (Bockting et al., 2005; T. Z. Tang et al., 2007; Bockting et al., 2009; Bockting et al., 2018).

Fittingly, residual symptoms after cognitive therapy also predict relapses. This includes, in particular, persistent anxious cognition (Taylor et al., 2010), which is highly

plausible given the high comorbidity of anxiety disorders and depression (e.g., Wittchen et al., 2000; Lamers et al., 2011). In addition, research on mindfulness-based cognitive therapy (MBCT) approaches of the *third wave of cognitive-behavioral therapy* in particular repeatedly provide findings that show their advantage over other methods in the area of relapse prevention (Teasdale et al., 2000; S. H. Ma and Teasdale, 2004). The (very heterogenic) procedures of MBCT have usually in common that they seek to increase cognitive flexibility, which is, among other things, thought to reduce *symptom-stress*[3].

In summary, since cognitive therapy, MBCT, and behavioral activation (Dobson et al., 2008) have been reported to be superior to medication (Vittengl et al., 2007), it seems important to teach patients cognitive strategies that can be used in the long-term and go along with heightened activity levels.

This would also be in line with the idea of stable cognitive styles to predict recurrence in depression. According to the often-cited review by Burcusa et al. (2007), such styles may be correlated to stable personality traits or acquired as a 'scar' left behind by previous depressive episodes. In this view, previous depression may trigger the intraindividual development of a vulnerability for its of recurrence in the future.

3 Intraindividual Development of Vulnerability

The previous section discussed the general and therapy-influenced course of depressive disorders, which highlighted current insufficiency of treatments to modulate long-term outcomes via medicinal and psychological interventions even though especially cognition- and activity-focused interventions may show greater potential than others do. In sum, the presented empirical evidence suggests that established therapy approaches are indeed effective in alleviating acute symptoms but may fail to lastingly change a person's vulnerability for further episodes.

Hence, from this point on the main issue that this thesis focuses on, lies within the question of how to predict and change long-term courses of depression by addressing

[3] A definition shaped by the rationale-emotive therapy by Ellis; Ellis, 1989). It describes the phenomenon that symptom itself may become a trigger for other symptoms: For example, when the symptom-associated worries lead to symptom-exacerbation

its stable predictors (vulnerability or resilience factors). Here, two lines of arguments are explored in detail:

- First, due to their constant influence, temporally stable and therapy resistant traits, such as personality, or otherwise stable circumstances may lead to the onset of several episodes of depression throughout the lifetime.
- Second, in contrast to this view, previous depressive episodes may predict subsequent recurrence by stimulating the development of additional vulnerability factors within the individual. This could shape a progressively increasing risk for future episodes that may constitute independently from internal traits or external risk factors (for a discussion of these two notions in the existing literature, see e.g., Burcusa and Iacono, 2007).

While the first argument will be addressed in Section 4.2, the following paragraphs focus on the second idea concerning the intraindividual development of vulnerability. To do so, first the concept of learned helplessness is explored. It provides a model and experimental procedure that formalizes the emergence of affective symptoms as a chain of conditioning events. Then, in context of the kindling/sensitization hypothesis, neuronal processes are discussed that possibly underlie the emergence and recurrence of depression-related reactions within the learned helplessness framework. Taken together, the following sections provide a model to describe the mechanism behind the onset of initial episodes of depression before moving on to discuss the neural foundation that may allude to the long-term recurrent nature of these episodes as described above.

3.1 Learned Helplessness

In parallel with the rapidly growing body of neurophysiological research on neuroplasticity (see Section 3.2), unipolar depression was operationalized for the first time in such a way that valid animal models could be developed and, at the same time, experimental studies in humans became possible. At that time, Richard Solomon's group at the University of Pennsylvania was mainly responsible for this, which was later continued mainly by the work of Steven Maier and Martin Seligman, two of Solomon's students (2016). The

research group had initially succeeded by accident in demonstrating in dogs how instrumental learning can lead to depressive reactions. In this context, dogs were confronted with 64 mild but unavoidable electric shocks that were announced by a tone. The next day, according to the experimental protocol, the two-factor theory of fear (Mowrer, 1951; Mowrer, 1956; Levis et al., 1989) was tested. It predicts that at first, by classical conditioning, an association between tone and pain was learned in the dogs, which should subsequently, by operant conditioning, lead to the dogs seeking to avoid the pain (omission of pain by avoidance behavior corresponds to a negative reward and should thereby increase the probability of behavior). To test this, the dogs were placed in a shuttle box in which they could avoid the electric shock by jumping over a small hurdle since the shock was only applied to one of its sides.

Surprisingly for Seligman and his students, however, this resulted in the problem that seven out of eight dogs (87.5 %) simply endured the shock passively instead of fleeing. In experiment-naive dogs, only eight out of 21 (38.1%) exhibited this behavior (Leaf, 1964; Overmier and Leaf, 1965). The subsequent research of Seligman and Maier took up this effect and formulated the model of learned helplessness on the basis of numerous follow-up studies (Seligman and Maier, 1967; Weiss, 1968; Maier, 1970; Abramson et al., 1978; Alloy et al., 1984; Maier and Seligman, 2016). The model describes that after certain conditioning experiences and under certain circumstances a state is reached in which adaptive behavior is no longer shown due to too stable negative expectations. This state is described by the terms helplessness and hopelessness. It is widely regarded as a model for depression. Fifty years later, the authors themselves defined helplessness in a review of their own work and that of the now very large scientific community in this field as follows:

'The intuitive notion of helplessness entails, we reasoned, the belief that nothing one does matters. This decomposes into objective and subjective helplessness. More formally, an animal is objectively helpless with respect to an important outcome (O) such as shock offset if the probability of (O), given a response (R) is not different from the probability

> *of (O) given the absence of that response (notR). When this is true of all responses, objective helplessness exists. But being subjectively helpless is another matter. We theorized that helplessness was cognitive and that it was learned. The animal must detect the lack of contingency as defined above and so must have expected that in the future shock would be independent of its responses.'* (Maier and Seligman, 2016, p. 350)

This helplessness, which describes the core mechanism of the model, has been able to experimentally generate all DSM-IV criteria for depression, except for suicidal ideation, across multiple studies, highlighting its validity (Maier and Seligman, 2016). The many findings, and especially the formalization of helplessness just presented, have been of enormous value for translational research, as it defines a narrowly circumscribed and well-studied conditioning process that seems to do justice to the heterogeneity of depressive states.

Furthermore, as stated in the quote above, the model posits cognition in a critical and central spot, which is in line with the idea of cognitive therapy to be especially effective (in the long-term). According to Seligman and Maier (2016), in subjective states of helplessness (without being objectively helpless), a certain cognitive style connects the stressful situation to depressive symptoms. This style includes an internal, global, and stable attribution of the failure to control/avoid the aversive event. The combination of these would in turn lead to *transsituationality* of reactions. Translated to humans, this idea suggests that a student, who repeatedly failed his/her/their exams without being able to improve over time, may at some point adopt the belief that this is the result of insufficient intelligence. Since intelligence is widely regarded as a global (relevant for many situations and domains), stable and internal trait, the student may subsequently not only cease to put effort into his studies but also resign from demanding or frustrating tasks outside of his academic career (e.g., quitting to learn to play an instrument). This transsituational translation of reactions may then ultimately lead to depressive symptoms. However, this example is only plausible as long as the student cannot elude his/her feeling of insufficiency in either the academic or other contexts, which is especially the case when

this particular style of attribution is evident.

In addition, this framework provides a clear experimental procedure to test helplessness, which guides current and future research within the field: The *triadic* design. According to its underlying idea, at least three groups need to be formed, including 1) a group that received controllable aversive stimulation (mostly electroshocks), 2) a group that receives the same stimulation that group 1 got, without being able to avoid it, and 3) a group that does not receive any stimulation/shock. When these three groups are then compared on a second test-day where shocks are applied once more, group 1 and 3 should have learned to once again, avoid/control the shock, while group two has not. While the comparison of group 1 and 3 indicates the difference between naive reactions and trained responses to a specific stressor, the difference between group 3 and 2 shows that the helpless response on day two was indeed learned on day one rather than a generally shown behavior in context of shocks (Maier and Seligman, 2016).

The theory further provides for a detailed neural mechanism underlying the emergence of helplessness/hopelessness. In brief, three networks are proposed, including a neural foundation for the *detection* of control, a network for the *expectation* of control, and finally for the emergence and suppression of stress and anxiety responses. These modules were at first derived from the formal definition of helplessness, stated above. According to this, helplessness should only emerge, if a person or an animal was unable to perceive control over a certain outcome. If this experience would prevail, at a certain point in time, a stable expectation would be formed. Importantly, this expectation would then drive the organism's behavior to an extent that no further action would be shown to assess possibilities to regain control later on. As a result, in this state of actual helplessness and subsequent expected helplessness/hopelessness anxious stress responses are triggered as this kind of powerlessness is a genuinely averse state.

From a neural point of view, the expectation of controllability is mostly correlated to neurons of the prelimbic (PL) area of the ventromedial prefrontal cortex (vmPFC). Descending from this structure, excitatory projections stimulate inhibitory interneurons in the dorsal raphe nucleus (dRN). The dRN then addresses several target regions like the amygdala or the periaqueductal grey (PAG), which drive the anxious and stress-related

response. Thus, the control-expectation module, consisting of the vmPFC (including the PL) and its descending projections, would in accordance with the model be able to inhibit the anxiety eliciting module, consisting of the dRN, amygdala, PAG, and other stress-related structures. Finally, other neurons within the PL with its reciprocal connections to the dorsal medial striatum (DMS) are thought to reflect the control detection module, which will drive the emergence of an expectation (see Maier and Seligman, 2016 for a comprehensive review).

In sum, first, the PL will, in a joint action with the DMS, detect controllability. It then sets a distinct ensemble of neurons within the PL off to excite the dRN, which inhibits the stress/ anxiety response[4]. Following this, neuronal plasticity within the PL-dRN circuit sets in to establish a lasting memory (a sensitization process) that conveys the expectation of control. (see Section 3.2). For a comprehensive review and discussion of evidence alluding to these remarks, see Maier and Seligman, 2016. Figure 3 summarizes proposed networks and their interconnections, regarding these modules (also see Section 5.1.1 for electrophysiological correlates of these networks).

3.2 Kindling/Sensitization

Donald Olding Hebb is often recognized as the founding father of modern neuropsychology as he was able to provide seminal evidence for the biological (synaptic) processes behind conditioning events and learning in general (Hebb, 2005; P. R. Martin, 2021). At McGill University, Hebb had many students who would later become influential scientists themselves. Among them was Graham Goddard who first described a phenomenon that he referred to as *'kindling'*. In his publication Goddard (1967, p. 1020) describes the phenomenon as follows:

> *The experiments to be reported show that daily electrical stimulation of certain sub-cortical areas of the rat brain will eventually cause convulsions even though the*

[4]Please note, that from this point of view, helplessness is not learned. Rather, uncontrollability is the default mode that needs to be inhibited actively by establishing control (expectation). Thus, *not* being helpless would be the learned response (see Maier and Seligman, 2016)

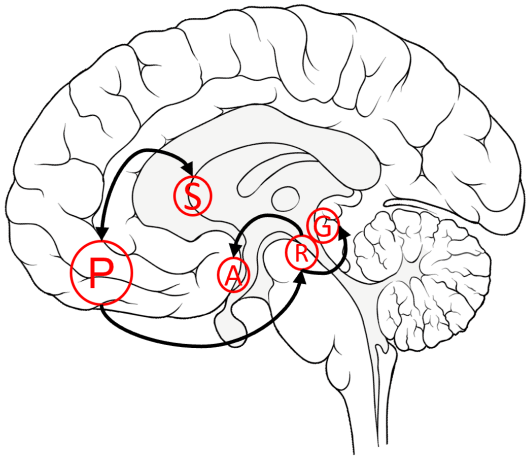

Figure 3: Schematic representation of the neural networks underlying helplessness/hopelessness. P= prelimbic area, S= dorsal medial striatum, A= amygdala, R= dorsal raphe nucleus, G= periaqueductal grey

> *intensity of stimulation is relatively low and initially has no such effect. (...) The primary observation is that not one animal [of the 77 rats included in the experiment] had a convulsion on the first day [of stimulation]. (...) The number of days of stimulation required before the first convulsion varied considerably, the range being between 4 and 136 days (...) [O]nce convulsions have been elicited in a given animal, subsequent convulsions occur reliably in response to stimulation.'*

In sum, his finding described the phenomenon that frequent stimulation (with a constant intensity) of neuronal ensembles can, in the long-term, result in reactions that were not originally caused by the stimulation; a process Goddard referred to as *kindling*. Furthermore, in later publications, he was able to significantly extend this finding by showing that neuronal tissue exhibits a similar 'kindling effect' when exposed to the chemical agent carbachol. Carbachol is a structural analog of acetylcholine, which is why it can open muscarinic-nicotinic receptor types (Goddard et al., 1969 but also see Blitzer et al., 1990; Hasselmo and Barkai, 1995; Shimoshige et al., 1997).

Goddard describes an effect that seems to be taking place in all test subjects reliably. However, it also shows clear differences concerning its onset across test subjects, which is also well in line with the findings discussed above, stating that dogs varied considerably in their respective helplessness reaction: Some dogs remained agile after the conditioning-phase, while others showed signs of helplessness even though they were naive to the procedure. As a result, only two years after the initial finding by Seligman's team, Goddard provided first evidence for underlying mechanisms that would not only lead to advances in the understanding of intraindividual developments leading to disease but also replicate interindividual differences in the susceptibility to express these developments rather fast or slow.

Building on these findings, Timothy Bliss, who also studied and earned his doctorate at McGill University and Terje Lømo, were able to demonstrate the basis for the effect described by Goddard, just a few years later: Long-Term Potentiation (LTP; Bliss and Collingridge, 1993; Lømo, 2003). LTP is to this day still considered the most important molecular biological basis for learning. It describes an N-methyl-D-aspartate (NMDA) receptor-mediated intra- and intercellular adaptation process following suitable stimulation, which can increase the ability of individual cells and large cell assemblies to 'learn' in the long-term. This enzymatic and later morphological change, exceeding the duration of the stimulation, is epigenetically ensured by altered transcription processes. LTP was later researched and described in great detail and placed in context of psychological results and models (see Section 10.1).

While LTP processes are mostly described on a molecular biological or cellular level, early on, neural network influences on this process were added to the picture. In this regard, an important role of the Ascending Reticular Activating System (ARAS) was described as it was shown to have a great influence on the important NMDA receptors through its dopaminergic, noradrenergic but also acetylcholinergic nuclei (e.g., Klancnik and Phillips, 1991; Frank et al., 1992; Bergado et al., 2007; Lim et al., 2010); a finding for which Goddard already provided the basis early on by demonstrating that the acetylcholine-like agent carbachol could induce the kindling he described. Over time, other substances also proved to induce strong LTP: For instance, a cocaine-mediated

strong LTP effect in the ventral tegmental area was reported, which already occurred after a single administration (e.g., R. Post and Kopanda, 1975; Stripling and Ellinwood Jr, 1977; Ungless et al., 2001); a finding that provides the basis for modern neurophysiological explanatory models in addiction diseases (P. R. Martin, 2021; Wegener, 2021).

In the early 1980s, these findings were also applied to affective disorders, when Robert Post and Susan Weiss used the rapidly increasing number of results within the field of *seizure kindling* to address issues of *cycling* within neuropsychiatric disorders (R. M. Post, 1982). Post and Weiss initially relied on the findings provided directly by Goddard and found that the phenomenon he produced can be divided into three phases, which are defined by different molecular and cellular processes but also by different effect-responsiveness to medication (R. M. Post and Weiss, 1996). In the first phase, they summarize the process of sensitization through LTP processes that increasingly ensure that even small stimulation can trigger seizures. This is characterized by recurrent sub-threshold stimulation. Second, this is followed by the phase of *completion*, in which seizures reliably follow stimulation, and finally by the phase of spontaneously occurring seizures, which occur entirely without stimulation. Robert Post combined these kindling phenomena with findings from behavioral sensitization which referred to increased motor responses following repeated cocaine administration, especially if given in the same environment (in contrast to the kindling-related dichotomy of seizure vs. no seizure).

Following this, Post and Weiss assumed that traumatic experiences, but also non-traumatic stressful life events would analogously to electrostimulation lead to the accumulation of long-term memory traces, which then induce gradual sensitization of the organism until finally, analogous to seizures, reliably, depressive responses are triggered. According to the authors, this process seems to be reinforced by the fact that seizures (depressive episodes) can themselves become an event that contributes to the sensitization (kindling) of the system. Accordingly, initial triggering events that can induce depressive episodes would only play a role at the beginning of a recurrent illness, while further episodes can also feed on the vulnerability that arises from episodes already suffered. In this context, initial trigger-events would be viewed as either so strong that it can directly trigger an episode or as (initially) sub-threshold stress that qualifies for a trigger-event

because sensitization had already taken place (through other consecutive sub-threshold stress) so that it finally becomes sufficient, nonetheless. This would ultimately lead to a transition towards the spontaneous phase, in which renewed episodes can occur without concrete triggers (e.g., R. M. Post and Weiss, 1996; R. M. Post, 1982; Kendler et al., 2000; R. M. Post, 2007a; R. M. Post, 2007b; R. M. Post, 2010; R. M. Post, 2016a; R. M. Post, 2016b).

This kindling/sensitization theory of affective disorders would predict that the correlation between external events and depressive responses should become smaller depending on the number of depressive episodes that have already been experienced. In fact, there are numerous findings suggesting this (e.g., Perris, 1984; Dolan et al., 1985; Ezquiaga et al., 1987; Cassano et al., 1989; Ghaziuddin et al., 1990; G. W. Brown et al., 1994; Bruce, 1998;P. B. Mitchell et al., 2003; You and Conner, 2009; Mazurka et al., 2016). Patients with a higher number of episodes retrospectively describe them as less *environmentally* influenced than persons with fewer previous episodes. Similar findings were later demonstrated prospectively, with data from 2395 female-female twin pairs suggesting that sensitization within individuals may reach a plateau at which no further kindling process by prior episodes occurs (Kendler et al., 2000). Regardless, the evidence for such a kindling sensitization process is numerous and well established due to the reduced influence of external stimuli on the onset of episodes, the faster succession of episodes when many have already been experienced, and the eventual spontaneous occurrence without prior triggers (see Section 2).

However, even though substantial evidence was collected throughout the decades, the validity of effects is not without question. Anderson et al. (2016) point out that especially evidence for decreased healthy phases between episodes may not follow a kindling/sensitization process but may be a statistical artifact that results from insufficient differentiation of within- and between-person variance. Following the early remarks by Elliot Slater (1938), the authors suggest that decreasing between-episode intervals may not be a result of within-person changes (kindling/sensitization) but a between-group effect that may stem from the fact that individuals who tend to experience more recurrences may also in general show less pronounced healthy episodes. This notion is plausible as individu-

als who may tend to experience 5-6 symptom-free years between episodes will undoubtedly suffer from fewer relapses within a (for example) 20 year period as compared to patients who experience relapses once every two years. Thus, even if the interval between episodes remained unchanged for a given person, statistically, one will surely still find a correlation of less inter-episode interval duration and number of relapses/recurrences. Furthermore, as the proportion of individuals with the 'decreased-time-to-relapse-trait' becomes more dominant within samples as a function of the number of episodes endured, statistically, one may even find a decreasing duration of healthy phases depending on the number of relapses/recurrences. However, this effect may not indicate within-person decreases of between-episode duration but the increasing influence of a certain sub-population on the data. Consequently, Anderson et al. (2016) used a mixed model approach, that is specifically suited to distinguish within- and between-person variance on multiple levels, to test whether evidence for a within-person kindling/sensitization effect may in fact reflect stable personality traits. Their results show that indeed, no within-person change was present, while between-person differences were eminent. In conclusion, the authors suggest that part of the evidence for the kindling/sensitization hypothesis is a statistical artifact that stems from the *Slaters fallacy* of interpretation of between-variance as within-variance (named after Elliot Slater, who first described it; Slater, 1938).

Nonetheless, the kindling sensitization theory may still hold, as the cyclic emergence of episodes due to interindividual differences is not new but one of the early and well-replicated findings that Post and Weiss built their model on. The kindling mechanism itself suggests stable vulnerability factors with a prominent role of genetics that shapes the likelihood of suffering from an episode of depression in the first place but also to experience recurrences and positive responses to medication. With this, they once again, built directly on early findings by Goddard who described substantial interindividual differences in the time it took to kindle seizures in rats. Following this, another way to bring together the idea of kindling/sensitization and the evidence highlighting inter- instead of intraindividual changes relies on the fact, that these stable vulnerabilities may be substantially but *not entirely* genetically determined. Conversely, such traits may be the result of complex gene-environment interactions themselves, as they are in general thought to rely

on endophenotypes rather than the sole genomic code. Only around 50% of the variance in the temperament of infants and children are attributable to the genome (e.g., Saudino, 2005), which implies that even in such early stages of development a considerable influence of experiences with the environment is present.

In other words, one may argue, that the within-person changes predicted by the kindling/sensitization hypothesis may indeed determine the course of recurrent affective disorders but do so in other ways than Post and Weiss suspected initially: From a developmental psychological point of view, the sensitization may take place way before the first depressive episode emerges, e.g., by kindling the hypothalamus-pituitary-adrenal (HPA) axis as early as prenatally, which in turn makes an early onset as well as a trait vulnerability to suffer from more episodes more likely. Kindling/sensitization would thus shape the long-term course of depression by producing the initial vulnerability that would robustly predict recurrence and symptom severity. Studies that have examined the stability of personality over the life span support this idea: In their meta-analysis, Roberts and DelVecchio showed in 2000 (2000) that the long-term retest correlation of personality tests increases gradually with age from about r=.35 in childhood to about r=.75 in midlife. These data thus clearly indicate that personality and thus stable vulnerability factors still change strongly in childhood and adolescence. Daniel Klein, Roman Kotov, and Sara Bufferd summarize this and other evidence on the topic evidence as follows (Klein et al., 2011, p. 274):

'For example, one can posit a dynamic precursor model in which early temperament defines the baseline level of risk but subsequent experiences modify personality liability to depression. This model explains variability in disorder onset as a function of the initial level of risk and steepness of the trait trajectory over time. Given the evidence on patterns of personality continuity and change (Roberts and DelVecchio 2000), it appears likely that trait vulnerability is more malleable early in life, but significant life events can alter its trajectory even in old age.'

It would hence seem plausible, that kindling/sensitization but also other forms of learning shape what would later transition into interindividual differences influencing the onset and the cyclic course of the disease. This would then be in line with the mixed-model results by Samantha Anderson et al. (2016) who would partially have captured variance attributed to this in their fixed effects (as they included a person-average inter-episode-interval predictor variable) and partially in their random intercept model.

Since no further fixed or random slope effect/variance was found, Anderson's data reject the idea of a sub-sample of participants that increase in recurrence speed over time. Thus, these data allude to the idea of kindling/sensitization mostly impacts the course of depression by forming initial interindividual vulnerabilities in prodromal stages of depression or even long before that.

This is also in line with findings from the learned helplessness model of depression since the scientific community behind it widely accepted the fact that a stable cognitive style (internal, stable, and generalized attribution of failure) is a necessary condition for the emergence of depressive-like behavior. Furthermore, once implemented, this cognitive style could be reinstated easily (Hannum et al., 1976), which would also fit the predictions by the kindling/sensitization idea.

Ultimately, from this perspective, two questions concerning stable interindividual differences arise: First, which stable traits do empirically pose as influential vulnerability factors for the onset and course of depression? Second, which interindividual differences make an individual prone to react faster/more vigorously to stressful events like subjectively unsolvable or overwhelming tasks (as in learned helplessness tasks) and the emerging kindling/sensitization which may arguably describe the biological learning process behind it (R. M. Post, 1985)?

4 Interindividual Differences in Vulnerability and Resilience

In the previous sections, intraindividual developments of depression-related reactions and possible neural and neuronal foundations for their stability were discussed. In the following this thesis goes on to explore stable interindividual traits and context factors that may provide answers to the questions raised in the discussion above.

In this regard, to be able to shape the course of disease throughout the lifetime, interindividual differences that had the potential to do so would need to be very temporally stable. As a result, especially those factors that are stable (by definition), such as personality traits, genetic markers, or endophenotypes may be the most promising predictors. However, a second way to approach this topic may lie in analyzing samples that tend to exhibit certain vulnerability factors less variably than it would be the case in others. In short, one can either directly select (by definition) stable factors or analyze samples in which otherwise 'fluctuating' factors appear more stable, which may provide additional insights into why certain variables bear more predictive power in one sample than in others: Because they may be more stable in certain (sub)populations.

Such stability of otherwise state-like predictors may be found mainly in samples for which no acute improvement or deterioration of inner states or contextual factors can be assumed. Thus, patient samples who show chronic, incurable, or hardly improvable symptoms could be targeted for this field of research as they may suffer from relatively constant types and intensities of stress. One indirect indication for the stability of comorbidity-related stressors and vulnerability factors to play a crucial role in the emergence of depressive episodes lies in the robust finding that depressive symptoms are substantially elevated in many chronic disorders (e.g., Evans et al., 2005):

4.1 Chronic Comorbid Disorders

Depression is one of the most common comorbid disorders in psychiatric but also somatic disorders (e.g., Maes et al., 2011). In her review, Brenda Penninx and her colleagues (2013) cite several meta-analyses showing that depression significantly and markedly correlates

to the likelihood of stroke, cardiovascular disease, obesity, Alzheimer's dementia, diabetes, and overall mortality. In doing so, she also summarizes several possible pathways that could at least partially explain these effects:

First, she describes the well-replicated finding that increased inflammation is a depressive-symptom inducing condition (e.g., A. H. Miller et al., 2009; Zunszain et al., 2013; A. H. Miller and Raison, 2016). As a result, in chronic somatic disorders, such as diabetes or cardiovascular diseases, the chronic dysregulation of hormonal immunological molecules such as *interleukins 6* and *10* or the *tumor necrosis factor* α may act as stable vulnerability factors for depression. Nevertheless, the direction of influence is not entirely clear since depression itself has also been shown to add to such dysregulation, thereby exacerbating somatic symptoms actively (Penninx et al., 2013).

Next, Penninx et al. (2013) go on to describe sensitization of the HPA axis to play a critical role in the stress response in depression (e.g., Kammerer et al., 2006; Pariante and Lightman, 2008; Belvederi Murri et al., 2014) but also high blood pressure and other chronic diseases. Thus, once again, since depression and chronic illness share a biological basis, the relationship between chronic somatic disorders and depression may not be unidirectional but include recursive, bidirectional, or third-variable-driven effects.

Furthermore, depressed patients report significantly less physical (exercising) activity (e.g., Alosco et al., 2012) and unhealthier eating behavior (e.g., Ciechanowski et al., 2000) than non-depressed do, which in turn can have a negative influence on the body as a whole. The same is generally true for treatment adherence, which appears to be significantly lower in depressed individuals than in non-depressed individuals (e.g., Ciechanowski et al., 2000; DiMatteo et al., 2000; Wing et al., 2002; C. M. Goldstein et al., 2017), and thus may impose negative consequences in any condition that requires a long-term treatment approach.

Especially this well-replicated impaired treatment adherence may also highlight why psychotherapy approaches may fall short in the long-term. For psychotherapy to work, changes in cognition and behavior seem to be most promising predictors for long-term effects. However, it is also plausible to assume that therapeutic effects attributable to this, will mostly last only as long as these changes do. Depending on the type of cogni-

tion/behavior, the risk of relapse or recurrence may thus depend on the patient's ability to maintain the cognitive style or specific behavior that conveyed the effect after the end of therapy (e.g., reminding oneself to go out and meet people or to plan positive activities regularly). Unfortunately, since depression (and possibly its vulnerability factors) seems to inherently impair this kind of *health-behavior*, long-term treatment effects may cease eventually and do so even more rapidly if a stable vulnerability factor contributes to residual or chronic sub-episode symptoms.

In summary, these lines of evidence thus highlight that the relationship between chronic somatic disorders and depression may consist of complex and cyclic processes, where depression increases somatic symptom-load via various ways of effect, while somatic disorders recursively exacerbate depression. In conclusion, if chronic somatic disorders were inducing (or representing) stable vulnerability factors shaping the recurrence of depression throughout the lifetime, this model would assume that in depression-off phases, the ongoing stress/vulnerability attributable to the chronic disorder would at some point be able to restart this vicious cycle.

Hence, to investigate the idea of *stable* somatic disorder-related predictors to shape long-term courses of depression, only those samples would qualify that may undergo exacerbation by depression but no substantial alleviation of symptoms due to its absence. In this case, even in depression-off phases, somatic symptoms persevere, posing as a stable vulnerability for affective symptoms since they may restart a recursive cycle that may spiral into a full depressive episode.

In the following, two clinical conditions that may fulfill this requirement are discussed, starting with cognitive decline as an indicator for mild cognitive impairment; a condition that may not undergo remission due to increases in affective disorders but exacerbates substantially due to decreases in well-being:

4.1.1 Depression and Cognitive Decline in the Elderly

One of the most studied correlates of depressive symptoms is a cognitive capability (e.g., Cherbuin et al., 2015). From a historical perspective, major depressive episodes, which sometimes have formerly been (among other disorders) described as *pseudodementia* (e.g.,

Shraberg, 1978) have always been tightly linked to cognitive ability and its decline. There are several explanatory models for this relationship, all of which appear to be empirically tenable (and in part generalizable to other somatic illnesses) pointing towards a complicated interplay of various influences (Steffens et al., 2006):

For instance, depression has been reported to result in (or at least correlate to) decreases in brain volume (Steffens et al., 2000; Koolschijn et al., 2009; van Tol et al., 2010; Ancelin et al., 2019), which, especially regarding hippocampal volume loss, is also a vulnerability factor for unfavorable courses in dementia and its precursor, *mild cognitive impairment* (MCI; He et al., 2009; Henneman et al., 2009; Tabatabaei-Jafari et al., 2015). In addition, other causal mechanisms may lead to depression-induced changes in cognition. For example, the influence of depression on cognitive decline is shown to be mediated in part by sleep quality (X. Liu et al., 2021), although the effect appears to explain only about one-tenth of the total association between depression and cognitive decline.

Furthermore, chronic stress, inflammation (Wuwongse et al., 2010; Daulatzai, 2014) or neurodegeneration (Kanner, 2004; Chi et al., 2014) may act as third variables, causing both depression and cognitive decline, since, again, decreased brain volume is correlated to depression and dementia[5]. On the other hand, depression may also be a result of progressive cognitive decline, as the frustration and hopelessness in light of a potentially unstoppable worsening of this course may result in severe affective dysregulation (Lyketsos and Lee, 2004); a phenomenon that may be present in several somatic illnesses (Evans et al., 2005). Also, stress, which is in any case inclined in depression, has been reported to aggravate MCI and dementia courses. Finally, depression and cognitive decline-related disorders, such as MCI, express common symptoms like concentration deficits and sleep disturbances, complicating the measurement of aforementioned relationships even more (Baquero and Martín, 2015). Figure 4 summarizes the possibilities of interplay between cognitive decline and depression in the context of correlational results.

These remarks allude to a general issue in the causal inference within statistical analyses. The overall idea behind analyzing cognitive decline was to use it in the

[5]Even though a large number of studies report correlational results linking depression and volume reductions, only a few investigated longitudinal changes as a function of depression scores, possibly increasing the risk for *cum hoc ergo propter hoc fallacies*. For longitudinal investigations see e.g., Dotson et al., 2009; Ahdidan et al., 2011; Yüksel et al., 2018)

prediction of depression. However, since depression may also predict cognitive decline, a significant prediction would not be sufficient to attribute effects. For instance, if the kindling/sensitization hypothesis was true (see section 3.2) one may argue that depression, which will act as its own vulnerability factor, increases cognitive decline (thereby leaving a 'scar'). If depression scores of the previous measurement occasion are not included in the model, this effect would be attributed to the cognitive decline variable, even though it may only act as a mediator. As a result, the prediction analysis would favor the *interindividual differences notion*, rather than the accurate *intraindividual development idea* of vulnerability. Thus, to assess the causal relationship between depression and cognitive decline, modeling their correlation via simple regression analyses may not be sufficient. Rather, a regression model, including both, the stable vulnerability factor and depression at previous measurement occasions or a mediation model should be analyzed.

In this particular case, the assessment of these interactions is further complicated by measurement issues in both, depression and cognitive decline. In addition to the aforementioned overlaps between both conditions, building on the idea of Paterniti and colleagues (2002) and the findings reported in Section 2, it seems that depression scores may not be indicative of general stress responsiveness or individual symptom-courses since depression is inherently a highly volatile (but recurrent) disorder. Thus, depression scores may indeed represent an accurate measure of the current status but may not reflect long-term susceptibility to persistent psychiatric impairment (even though more severe symptoms may predict increased recurrence to some degree; for a discussion and review see Burcusa and Iacono, 2007). However, especially in the assessment of chronic diseases that go along with macroscopic neurodegeneration, *persistent* stress and *persistent* depression may be needed to find robust results, since only shortly present symptoms should not be able to exert much influence on the integrity of brain structures or chronic inflammation processes.

4.1.1.1 Issues of Reliability in Longitudinal Prediction Studies

The previous section highlights several possible (recursive) influences between depression and MCI but also other somatic disorders. To address these relationships sufficiently, the most effective

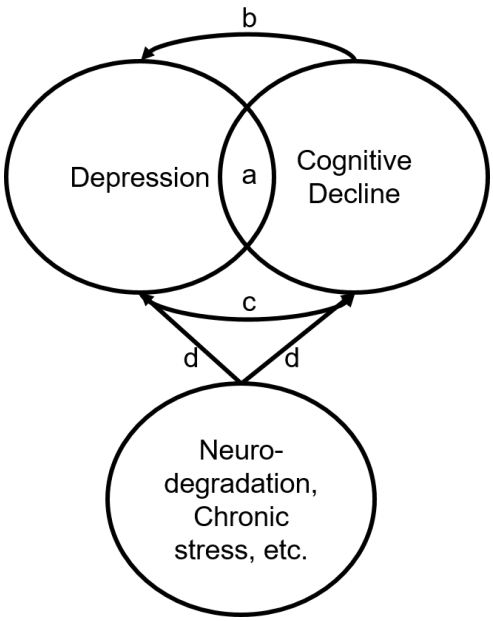

Figure 4: Illustration of possible effects driving the correlation of depression and cognitive decline. a) Depression and cognitive decline share a conceptual overlap, such as impaired concentration capability. b) Cognitive decline induces depressive symptoms e.g., via frustration or stress over performance deficits. c) Depression induces cognitive decline e.g., due to impaired sleep quality, which in turn leads to cognitive performance deficits. d) Third variables cause both, depression and cognitive decline. For instance, neurodegeneration, underlying Alzheimer's but also Parkinson's, and other forms of dementia may also lead to affective symptoms.

method may lie in longitudinal data analyses as these may support a causal interpretation of results. However, additional methodological issues stemming from the volatile nature of depressive courses and unreliable estimation of predicted variables may substantially bias conclusions to be drawn.

In the context of MCI, evidence points towards the influence of persistent depressive symptoms rather than acute depression scores to predict higher impairment (Paterniti et al., 2002), which also indicates chronic rather than acute/current stress-related responses to play a crucial role in cognitive capability. Against this background, the assessment of stable vulnerability factors for depression, such as personality traits, could provide better predictors than the current psychological status.

The latter in particular seems to show rather fluctuating courses with several relapses but also phases of remission and thus is not necessarily a measure for long-term vulnerabilities. Although stress-prone individuals are more likely to be assessed with a higher depression score when randomly drawn, other less volatile predictor variables

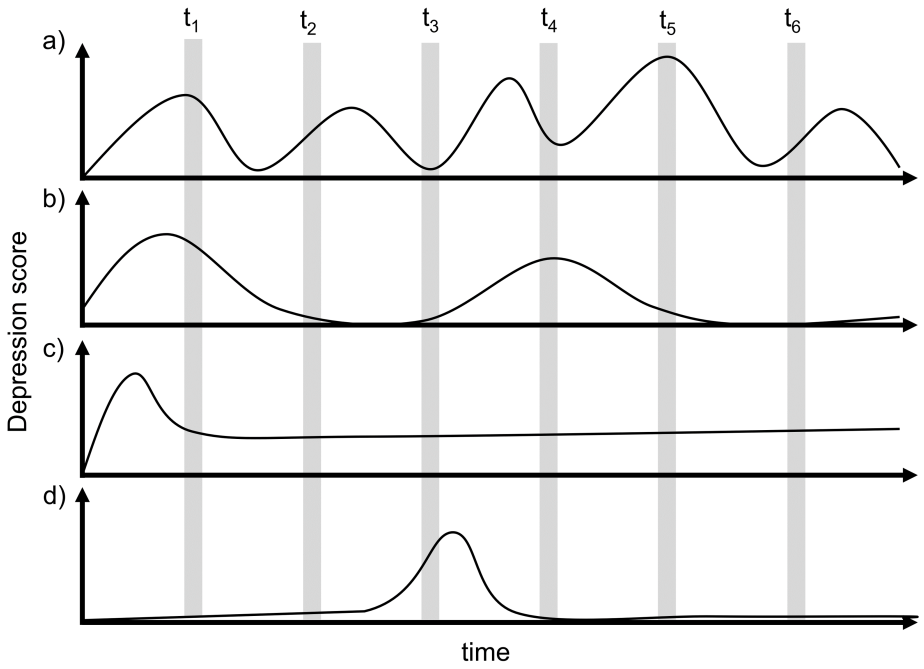

Figure 5: Issues in the measurement of depression as a predictor. Suppose the four diagrams a) to d) depict four individuals and their respective courses of depression scores over time. Further, assume that those individuals that show the highest score on average are more prone to suffer from unfavorable outcomes in the long-term. Each participant's score is assessed at the measurement occasions t1 to t5. Even though on average, individuals with more severe courses, either due to persistent symptoms as in c) or high recurrence as in a) measurements can assess individual risk to a satisfactory degree. In the case of only one measurement, however, depending on the time point, the assessment may still be accurate for the respective measurement occasion but may severely misinterpret individual risk, thus impairing correlation to and prediction of other variables. In sum, by assessing individuals only once, substantial error may be introduced as the highly recurrent nature of depression may decrease the interpretability of single assessments.

appear to be more reliable estimators. Figure 5 illustrates this issue in more detail.

An example of potentially more stable predictors would be the personality trait neuroticism, which shows relevant and robust predictive power for dementia (Wilson et al., 2011; Low et al., 2013; Terracciano et al., 2014; Luchetti et al., 2016). Further evidence is present for the influence of loneliness and social isolation (Lara et al., 2019).

Issues of Reliability in Cognitive Decline Estimation. Issues of reliability may not only be evident in the assessment of depression but also in the assessment of cognitive decline. For instance, longitudinal assessments of cognitive decline (which seems to be the best way to address relationships to other variables in this field according to the discussion above) are often done via analyses of composite variables. To do so, results of

neuropsychological tests are often averaged to form a new score that is on one hand more abstract to interpret but on the other hand thought to represent the overall cognitive ability more generally, thus more accurately (Haberstumpf, Forster, et al., 2021). If the authors of a given study agree upon the idea that cognitive decline is best operationalized as a conglomerate of different neuropsychological domains (e.g., visual-spatial processing-, memory-and attention capacity), such a composite approach may be valid. However, this formulation of the general-cognitive-capability variable implicitly assumes that all cognitive domains contribute equally to this (supposedly) higher-order construct. Furthermore, this contribution is also thought to remain stable across measurement occasions. These assumptions may not hold as three lines of arguments may illustrate in the following:

First, often not just one score per cognitive domain is used to quantify cognition but many are. For example, one may consider both, immediate-as well as delayed-recall performance to assess memory capacity. However, to compute memory capability from this, it remains elusive whether it is a valid choice to simply average over the performance scores of these tests. Especially since the measures may not be independent of one another, thus complicating the subject further by dependencies within test scores. As a result, the composite score representing memory performance by a given subject may be unreliable, if conceptually, it is not safe to assume that all included variables contribute to the overall constitution of the higher-order factor to the same extent. Also, sometimes investigators may want to measure one domain not only by using scores from several sub-scales within one standardized test but with several completely different tests, which may especially be useful if one test on its own may fall short in some regard (see the next argument for an example). As a result, often it may not be enough to assume a general cognitive capability factor represented by several specialized cognitive domains, but researchers often face the issue of a multilevel estimation with manifest test scores on level one, (latent) domain-specific abilities on level two, and the general cognitive skill on level three.

Second, to compare and average the variables used to form a composite, these are needed to be on the same scale. Usually, each test-score is normalized with regard to age- (and sometimes gender- or education-) matched samples. However, norm samples often face one of two issues: They usually either lack appropriate participant numbers

within one sample category (i.e. 20 participants in the norm sample for the category: age 70-72) or their categories become very large (e.g., age 70-80), which may lead to biased normalization in some but not all tested individuals, depending on their age (gender or education). Since each test within a test battery employs its own norm-sample to normalize scores, the participant's score-bias may vary not only between individuals but also between tests.

This issue may also be further complicated by sampling issues that may increase with the age of the norm-sample: As the norm sample is usually gathered in a between-type approach rather than re-measuring the same sample over their course of aging, if at least one of the samples is not representative (norm-sample or the participants' sample) more biases may emerge. In the context of cognitive decline in the elderly, this may for instance be the case due to increasing sampling biases in higher age as only the highly resilient, healthy, and socially functioning individuals may take part in studies. As a result, the norm-sample may at some point increase the risk for underestimation of cognitive ability relative to the respective (true) age average. Thus, by simply averaging across normalized test scores, the raw composite approach will be unable to account for differences in the reliability of its component variables (which may *inter alia* be introduced by said normalization biases).

Third, it may not be appropriate to assume the stability of reliability of measures or test-score representativeness for a given domain over time. For instance, when individuals become severely depressed, verbal fluency may become more dependent on concentration capacity and less indicative of actual verbal ability. In this hypothetical example, the onset of depression between measurement occasions may impair the comparability of verbal-ability-composite variables if this method of calculation (averaging across the same variables each time) is used. Many other forms of longitudinal comparability issues touching on the same issue have already been reported in other fields of research. An example of the health-related quality of life (HRQoL) research is that individuals who experience severe illness may tend to adjust their internal metrics so that they describe significantly more pain after the illness at a pain score of 8/10 than they would have at 8/10 before the illness. This refers to a conceptually similar issue to the example

regarding verbal fluency in cognitive decline prediction, as both relate to distinct types of longitudinal measurement invariance (e.g., Oort, 2004; Fokkema et al., 2013; Reissmann et al., 2016; P.-Y. Chen et al., 2017).

Measurement invariance in general refers to the idea that a given test can assess a certain construct equally across participants and measurement occasions. The probably most often cited use-case would be cross-cultural validation of standardized questionnaires that may show the non-invariance of certain parameters across groups of individuals. Several parameters can be (non)invariant across groups/measurement occasions. To assess such, a latent variable approach is needed (Oort, 2004). The following approach originates from the item response theory and combines it with factor analytic considerations. In his study Oort (2004) formulates

$$y_{it} = \upsilon_t + \Gamma\xi_{it} + \Lambda_t\eta_{it} + \epsilon_{it}, \tag{1}$$

where the test values y are composed additively of the intercept υ, a latent factor ξ which describes a general latent ability (trait) as well as its regression coefficient Γ. Further, an item-specific latent trait η and its regression coefficient Λ, plus an error ϵ. η represents all systematic influences on measured values that cannot be explained by the factor ξ, which is constant for all associated indicators. There should be no correlation between these two parameters. Both latent factors are called latent traits in the terminology of the item response theory. Figure 6 illustrates the relationship of these variables as a latent factor model.

Considering the affiliation of this model to the probabilistic test theory, Oort distinguishes into person parameters (ξ, η, ϵ) and item parameters $(\upsilon, \Gamma, \Lambda)$, which determine the solution probability of an item (the response category in ordinal models) by their relation to each other. Oort also makes statements about the covariance structure of two measurement occasions (2):

$$\text{Cov(y,y')} = \Gamma\Phi\Gamma\text{ '} + \Lambda\Psi\Lambda\text{ '} + \Theta, \tag{2}$$

with Φ as the covariance of ξ and ξ' and Ψ as the covariance of η and η' and Θ

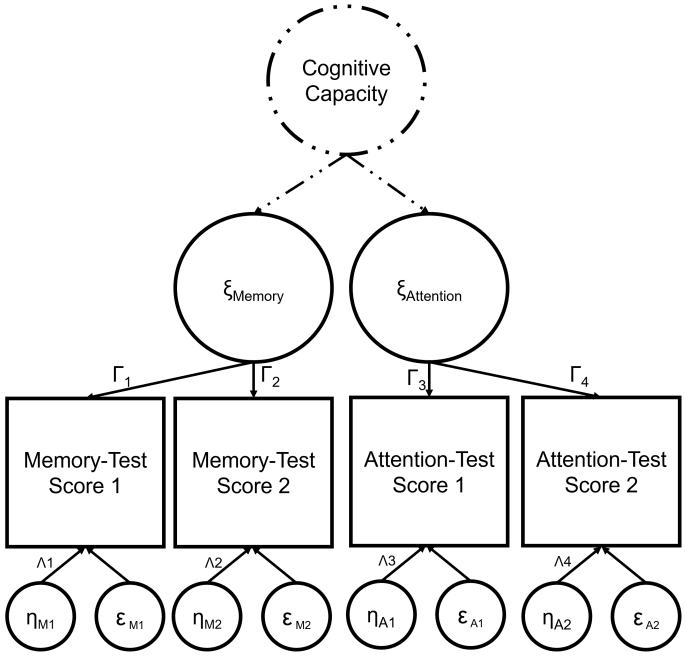

Figure 6: Measurement model of an exemplary assessment of cognitive capacity. A total of four manifest test scores, shown in the rectangular boxes, are used to estimate cognitive abilities in two domains. The two domains, memory and attention, are each represented by a latent ability coefficient that influences two test scores respectively. These manifest test scores are additionally predicted by a test-specific ability coefficient and an error term. The extent to which test-specific and unspecific latent factors influence a score is given by their respective regression coefficients (factor loadings). If desired, the model could be supplemented by a second-order latent factor, which in turn influences the two subordinate factors (indicated by the dotted lines). This illustration was adapted and modified from Oort, 2004.

as the covariance of ϵ with ϵ'. Similarly, changes in arithmetic mean are given by formula 3, where the influence of measurement error, which does not occur systematically, should have an average of zero. Furthermore, the author assumes that residuals are not correlated with latent traits. He describes the formula

$$\mu = \Gamma\alpha + \Lambda\beta, \tag{3}$$

where α represents the average value of ξ and β the average of η. The composite approach generally assumes measurement invariance (thus, parameter equality across measurement occasions) across all variables across the previous formulas except for α and β, as these represent true score courses. However, these assumptions may not be true and should thus be tested. To do so, structural equation modeling provides the necessary

framework by enabling researchers to systematically test for equality (variability) of coefficients between groups/measurement occasions. If coefficients remained invariant (equal) across time/group, measurement invariance can be assumed implying the suitability of (weighted) composite-based analyses. To assess this (non-)invariance, Oort states that both chi-square tests and the likelihood ratio (LR) are suitable for detection.

An overview of the parameter equivalences to be tested between measurement occasions can be found in Table 2. It describes the equivalence of Γ and Λ over time and in the context of the cognitive capability to reflect changes in connection between test scores and latent traits. This may, for instance, be the case, if some sort of re-test effect takes place in one of the tests (e.g., a participant may recall that in the last test-session, a unannounced delayed recall test took place). As a result, the test score may become more independent from one latent capability (ξ), while it may become more dependent on other latent traits (η), such as conscientiousness or neuroticism scores (this may affect whether a test-person bothered to contemplate the previous test session afterward, which may have led to an increased encoding of test-details). Furthermore, if such re-test effects took place similarly across the complete sample, changes in the manifest test performance (υ) may also take place. In contrast to this, also latent traits may change over time, reflecting a sample level true change in memory (with regard to the example made before; α) or sample level true changes in neuroticism/conscientiousness in this case (β). Finally, if the invariance of covariance matrices is not met, this may indicate different trajectories of latent ability scores for sub-samples within the population (complete sample; see Paper II for further discussion).

4.1.2 Depression in Cystic Fibrosis

In the previous sections, the idea to use samples that may exhibit particularly stable vulnerability factors due to a prevalent chronic condition was discussed. Following this, cognitive decline was described as a first example to show the required properties. Subsequently, general and MCI-specific measurement issues in the context of longitudinal prediction analyses were added.

In the current section, the second example for a chronic disease that may induce

Invariance Test	Interpretation
$\Gamma = \Gamma$ ’	Test scores become more or less indicative of a specific cognitive ability ξ
$\Lambda = \Lambda$ ’	Test scores become more or less indicative of a latent test-specific ability η
$\upsilon = \upsilon$ ’	Sample level change of manifest test performance
$\Phi = \Phi$ ’	Some participants show different latent ability (ξ) trajectories over time than others
$\Psi = \Psi$ ’	Some participants show different latent ability (η) trajectories over time than others
$\alpha = \alpha$ ’	True change of the latent factor ξ on a sample level
$\beta = \beta$ ’	True change of the unobserved, test-specific abilities (η) on a sample level, that are not explained by ξ

Table 2: Overview of invariance tests and their interpretation. Each coefficient is compared to its pendent at the second measurement occasion.

or act as a temporally stable vulnerability factor for depression is highlighted. In Part IV of this thesis, both samples concerning cognitive decline in the elderly and cystic fibrosis are investigated in terms of their predictive validity for long-term courses of affective symptoms.

Cystic fibrosis (CF) was chosen as a second example due to its long-term properties. It is a chronic and incurable genetic disease that affects patients for their whole life. It is characterized by a change in metabolism, which is manifested by increased viscosity of the secretion of exocrine glands and thus causes far-reaching functional impairments. These include, for example, reproductive limitations, susceptibility to musculoskeletal diseases such as osteoporosis, intestinal obstructions, and, above all, impaired lung function. In this regard, due to the increased tenacity of the bronchial mucus, a higher risk of severe infection, but also general and chronic shortness of breath and low exercise tolerance sets in. Even though no cure is available, following advances in treatment approaches, the life expectancy of those affected could be raised to about 40 years with an existing upwards trend (e.g., Jaffé and Bush, 2001; M. N. Hurley et al., 2014).

In such a disease, affective disorders, including anxiety and depression play a significant role. Similar to what has already been described in the area of cognitive decline,

it can also be assumed here that the somatic impairments following CF symptoms lead to depression and that, at the same time, persistent or acute depressive states influence the somatic symptoms.

Evidence points towards a worsening of lung function (Riekert et al., 2007; Fidika et al., 2014), decreased body mass index (Snell et al., 2014) as well as worse treatment adherence (Holder et al., 1975; B. A. Smith et al., 2010; Hilliard et al., 2015) due to depressive symptoms. Overall, an increased morbidity for depressed CF patients was reported recently (Schechter et al., 2021), indicating detrimental effects of depression onto somatic parameters.

On the other hand, there is a generally higher depressive burden among patients and their family caretakers (Havermans et al., 2008; Quittner et al., 2008; Cruz et al., 2009; Quittner et al., 2014; but also see Duff et al., 2014). Since this finding is not only true for patients themselves but also in their (usually) unaffected caretakers[6] this line of evidence alludes to an increase in depression due to CF symptoms and their consequences (e.g., not being able to go to the movies within the current pandemic, since infection with the Sars/Cov-II virus poses a substantial threat to individuals suffering from this precondition).

Nonetheless, once again, the relationship between depression and somatic symptoms may not be unidirectional. However, regardless of these details, affective disorders were deemed so influential and prevalent in this disease that an expert panel was formed in 2016 to recommend an annual screening for depression and anxiety symptoms in both, patients and caretakers (Quittner et al., 2016). Due to this guideline, in many facilities, now a basic (annual) screening for affective disorders is in place. Nonetheless, several other psychological variables may be of interest to the scientific community.

For instance, health-related quality of life (HRQoL) has been a widely used construct in the context of psychosomatics. Comparisons between the quality of life in patients, their caretakers and the general population showed decreases in physical-related HRQoL measures among individuals suffering from CF (de Jong et al., 1997; Goldbeck et al., 1999; Britto et al., 2002; Sawyer et al., 2004) as well as psychosocial HRQoL decreases

[6] In the study presented in Section 13, most caretakers were mothers of the patients. Since CF compromises the ability to reproduce, these relatives should usually not be affected by the disease themselves

that were also present in their caretakers (e.g., Burton-Smith et al., 2009; Chevreul et al., 2015; Fitzgerald et al., 2018). Along the same line, Sawicki et al. (2011) showed in a longitudinal study that the health status of patients influences the subjectively perceived quality of life. Nevertheless, health status alone could only explain a small portion of variance in HRQoL measures (Sawicki et al., 2011). This was also the result of other studies that found only small to moderate correlations between lung function and HRQoL (Bradley et al., 2001; Staab et al., 1998).

These results suggest that besides the disease-related forfeiture in somatic functioning, subsequent psychosocial issues (that are also present in caretakers), but also other third variables may pose as additional stressors (vulnerability). However, the direction of effect may once more not be entirely clear as existing literature on the relationship between HRQoL and depression is mostly correlational (e.g., Riekert et al., 2007; Havermans et al., 2008).

One additional interesting finding from this field of research is that an influential longitudinal study reports that HRQoL, after remission from depression, may not be as high as it is in those who never suffered from depression (Angermeyer et al., 2002). As a result, one may argue, that depression leaves some kind of persisting 'scar', which goes on to cause strains in well-being, even without current symptoms.

In sum, these lines of evidence highlight the bidirectional relationship of depression and somatic disorders, which is in line with the discussion of Section 4.1.1. Furthermore, HRQoL research in the context of CF has shown hints towards depression-induced 'scars' that may carry on influencing patients even after remission from depression, which would be well in line with the idea of intraindividual developing vulnerability factors that may themselves stem from previous episodes of depression; a notion well in line with aforementioned remarks of Section 2.

In the following, personality traits that may pose as other stable predictors alongside chronic physical conditions, are discussed in light of their long-term predictive power for the course of depression. In this regard, several models including the 'scar' model of interindividual differences in vulnerability are reviewed against the background of the current literature.

4.2 Personality Traits

By definition, stable traits that refer to a habitual way of spontaneous or reactive behavior, cognition, or emotion are deemed as personality. Interindividual differences that may affect the course of affective illness (the random intercept effects in Anderson's study, 2016) should thus reflect variance from the influence of various personality traits, as it is plausible that trait-like behavior such as withdrawal-tendencies, certain cognition, like internal attribution styles, or affect, such as dispositional anxiety, increase the risk of depression.

However, interpreting data on this topic may not be an easy task since in general seven different models describing the interplay of personality and psychopathology exist. Klein et al. (2011, p. 272) describe these as follows:

'These proposed relations include: (a) personality and depressive disorders have common causes; (b) personality and depressive disorders form a continuous spectrum; (c) personality is a precursor of depressive disorders; (d) personality predisposes to developing depressive disorders; (e) personality has pathoplastic effects on depression; (f) personality features are state-dependent concomitants of depressive episodes; and (g) personality features are consequences (or scars) of depressive episodes.'

The original kindling/sensitization idea (as well as previously stated evidence from CF patients) hypothesized something along the lines of (g): The habitual (trait) vulnerability forms as a result of illness, which may then influence the course of disease (e). However, in this interpretation, the kindling process itself is not meant to reflect a trait but to describe the process by which a trait vulnerability emerged from the consequences of diseases. This vulnerability is then thought to influence the cyclic nature of affective disorders. However, taking into account the insights from the mixed model-based analysis of courses of depression (S. F. Anderson et al., 2016), this idea may not be accurate. Rather their findings point towards models (d) and/or (e). Nonetheless, in the literature,

there is evidence for most, if not all of these perspectives (see Klein et al., 2011 for a review of studies).

Independently from the best fitting model, to prevent recurrences, relapses, and chronic courses, the main focus of this dissertation lies within the identification and modification of personality traits that qualify as vulnerabilities for depression. These may, according to the above-mentioned list and in the context of the aforementioned findings, most likely already exist in early stages and persevere treatment as well as symptom-off and on-phases. Furthermore, even though some studies suggest that *scarring* may also take place, current findings support the idea that traits resulting from depression are not fundamentally different from those, leading to the disorder in the first place; if this phenomenon exists at all[7].

4.2.1 Five Factor Model of Personality

One of the most replicated findings in terms of personality-related vulnerabilities is that high neuroticism (emotional instability, negative affectivity) predicts depression onset (R. M. Hirschfeld et al., 1983; R. M. A. Hirschfeld et al., 1989; Kendler et al., 1992; Rorsman et al., 1993; L. A. Clark et al., 1994; de Graaf et al., 2002; Ormel et al., 2004; Durbin et al., 2005; Kendler et al., 2006; Fanous et al., 2007; Naragon-Gainey et al., 2009; Kotov et al., 2010; ;Anttila et al., 2018).

Interestingly, high neuroticism but also low extraversion, which is another but more inconsistently found predictor within the five-factor Model (FFM) of personality, seem to remain stable even after depression, which fits the above argument (Shea et al., 1996; Ormel et al., 2004; Jylhä et al., 2009; A. L. Williams et al., 2020). Studies reporting otherwise show trend increases in vulnerability from these traits, which may, again, indicate that further kindling/sensitization or other learning processes take place throughout depression (Kendler et al., 2000; Fanous et al., 2007). Nonetheless, this effect is rather small and at the least, inconsistent.

Furthermore, some studies were able to find interactions of vulnerability factors within the FFM. Here, especially the combination of low conscientiousness, and high

[7]Results on this issue remain inconclusive, as findings often contradict each other. According to Klein et al. (2011), this may be a result of methodological inconsistencies

neuroticism, as well as low extraversion and high neuroticism describe the most prone personalities (e.g., K. A. Smith et al., 2017; Boudouda and Gana, 2020; Y. Li, He, et al., 2020).

Also in line with the findings by Anderson et al. (2016), the evidence further highlights the pathoplastic impact of high neuroticism on the course of depressive disorders, predicting worse outcomes including more recurrences, relapses, and increased chances for chronic progression. Again, similar but more inconsistent findings are reported for low extraversion (de Fruyt et al., 2006; Quilty, de Fruyt, et al., 2008; Morris et al., 2009; Eldesouky et al., 2018). A recent meta-analysis of the FFM further provides insights into the nature of possible pathoplastic effects within the FFM: The authors found evidence for worse outcomes of psychotherapy in patients scoring high in neuroticism and low in extraversion, possibly hinting to therapy resistance of symptoms concerning personality traits, which would ultimately lead to more chronic courses and higher recurrence rates (Bucher et al., 2019).

One idea on the inconsistent nature of results regarding extraversion is rooted in the heterogeneity of depressive symptoms. For instance, possibly extraversion may only pose as a significant predictor in individuals who suffer especially from subtypes of anhedonia, which usually encloses motivational as well as consummatory aspects (an idea that is closely linked to *wanting* vs. *linking*, see Treadway and Zald, 2011 for a more detailed discussion). Furthermore, since negative affectivity is mostly measured within the neuroticism scale, a more consistent correlation between this dimension and depression also seems plausible as depression will always go along with some sort of prolonged negative affect, whereas pronounced but heterogenous anhedonia-symptoms may not be present in every individual.

Bringing this evidence back to the aforementioned arguments on the influence of kindling/sensitization and in the early development of stable personality traits, one would expect to find early interventions in children with a certain temperament to be particularly powerful in changing later personality development. Thus, to further underpin this idea, studies targeting the longitudinal development of neuroticism/extraversion from early childhood to adolescence of adulthood could provide a missing link:

Evidence stems from animal research. Akaysha C. Tang and hear colleagues (A. C. Tang et al., 2012) report that rats showing substantial behavioral inhibition in novel contexts would increase their exploration behavior after being exposed to novel situations repeatedly for a short amount of time. They thus use a psychological intervention, not unlike the stress inoculation training for treatment and prevention of stress-related psychiatric disorders proposed by Meichenbaum (1977; 1988; 2017) to interfere with temperament-like traits. The authors conclude that the temperament, as well as the effect of the intervention, was significantly predicted by the sensitivity of the HPA axis in mother animals of the test rats.

Fitting these findings, even though direct evidence for the longitudinal variability of personality traits due to interventions is scarce, seven years before Tang's study, Rapee and colleagues (2005; 2010) started a study to test a preventive parent-focused program for children who displayed a behaviorally inhibited style. The authors were able to decrease the risk for and severity of anxiety disorders and reported significant changes in behavioral inhibition that seemed to increase over time. This possibly indicates early interventions targeting personality traits to grow into more pronounced and impactful influences on vulnerability factors and resources (Barlow et al., 2014). Since the temperament of behavioral inhibition seems closely related to neuroticism and has been proposed to precede it (Muris and Dietvorst, 2006; Muris et al., 2007; Muris et al., 2009; Barlow et al., 2014), these studies provide indirect evidence for the idea that stable personality traits are subject to early experiences (thus to sensitization processes). In the perspective of the results shown in Section 6 behavioral inhibition (even though behavioral inhibition in the context of temperament may slightly differ from the behavioral inhibition postulated by the authors of the BIS scale used in the factor analysis) is closely linked to neuroticism.

In addition to these data on early interventions, which would best be qualified to translationally inform preventive programs, the workgroup around Tony Z. Tang conducted a study on the mediation of effects from curative interventions by personality traits (T. Z. Tang et al., 2009). Here, the authors first administered a placebo for eight weeks and then changed to an antidepressive substance (also for eight weeks), which allowed for a within-person investigation of dependent variables (a depression score as well as FFM

traits). The results show that in the selective-serotonin-reuptake-inhibitor (SSRI) paroxetine, the non-placebo fraction of the antidepressant effect relies on increases in extraversion and decreases in neuroticism, as significant changes in these were only present in the SSRI but not in the placebo phase. However, it is worth noting, that most of the antidepressant effects set in within the eight-week placebo administration while only a small part of the complete effect was added after the change to the active substance. Nonetheless, given the results discussed in Section 2.1, these findings speak to the trustworthiness of Tang's data as they seem to replicate the emerging consensus on highly placebo-driven effects of antidepressant medication. Similar personality-change-dependent effects may be present in psychotherapy as well, since Huber, Zimmermann, and Klug report long-term courses after treatment to depend on pre-post therapy changes of personality. Furthermore, the authors report an interaction of within-treatment changes and pre-therapy personality, which is in line with above mentioned pathoplastic effects of neuroticism and extraversion as well as with the negative impact of these traits on the effectiveness of psychotherapy (Huber et al., 2017).

All in all, these studies highlight how personality in general but also neuroticism and extraversion in particular influence both, the onset and course of affective disorders. The current section also indicates that there is merit in early preventive programs as these may lead to the greatest effects over time.

Nonetheless, even though personality factors may be most volatile during childhood and adolescence, to some degree they may also continue to change throughout a lifetime. This may highlight the influence of life events that may either stimulate the emergence of coping and resiliency or vulnerability throughout (Mroczek, 2014). However, since it is impractical (if not impossible) for health care workers to prevent certain life events from taking place, the main focus of practitioners should lie in influencing the reaction to such events rather than influencing the events themselves.

Again, this reaction to stressful events is to a great part dictated by personality traits, such as neuroticism (e.g., Kendler et al., 2004). However, since the FFM mostly measures stable behavior and cognition, in response to such and other events, the correlation of neuroticism and negative outcomes of the experience of life events may mostly be

derived from the fact that an individual describes their usual reaction as neurotic, which is an importantly different notion than thinking of neuroticism as the cause of this negative response (W. A. Cunningham et al., 2005; Revelle, 2008) as the following statements highlight:

> *'As Pickering proposes, people are probably not be aware of their sensitivities to cues for positive and negative reinforcement, but rather are aware of the patterning of behaviors associated with those cues.'* (Revelle, 2008, p. 13)
>
> *'The Big-5 model is a descriptive rather than a process model (Pervin, 1994), (...)'* (W. A. Cunningham et al., 2005, p. 203)

Following this, to model such sensitivities, which may modulate the resulting behavior to become 'neurotic' other traits should be taken into account. Against this background, especially the reinforcement sensitivity theory (RST) is discussed as a promising model to predict interindividual differences in reactivity to certain stimuli, forming stable responses. Just as the theory's name suggests, the traits formulated within this theory describe inter-individual differences in the sensitivity to certain types of reinforcements, which may thus provide a way of thinking about the emergence of traits like neuroticism as a result of the interaction between an organism's responsivity and appropriate stimuli within the environment (life events).

4.2.2 Reinforcement Sensitivity

In 1970, 35-year-old Jeffrey A. Gray published his manuscript called 'The psychophysiological basis of introversion extraversion' in which he contradicted the most influential biological model of personality of that time: Hans Jürgen Eysenck's theory of arousal dependent traits (Eysenck, 1967; J. A. Gray, 1970; J. A. Gray, 1972). In this paper, Gray argued that building on the growing number of papers targeting reward and punishment-related neurophysiological bases, personality theories should focus on interindividual differences in

the sensitivity of these structures rather than on general cortical arousal. However, Gray did not discard Eysenck's theory but tried to explain the empirical findings supporting his idea with explanations derived from his own hypotheses: Eysenck thought of extraversion and introversion as two poles of one dimension that is defined or at least influenced by the amount of arousal that dominates during resting periods (a time without extensive external stimulation, like sitting at home and reading a book). Since extroverts were thought to experience less arousal in these situations as compared to introverts, he hypothesized that this circumstance leads extroverts to seek increased external stimulation, while introverts would withdraw from such as it may overwhelm these already highly aroused individuals, causing a *transmarginal inhibition* (a protective mechanism averting and ultimately reversing increasing arousal; Eysenck, 1973; Matthews and Gilliland, 1999). Gray on the other hand thought of this as a byproduct of interindividual differences in the sensitivity (thus activity) of punishment- and reward-related neural networks: If introverts were more sensitive to punishment, and building on the finding that punishment usually elicits more arousal than reward, it would be plausible, that introverts, on average, would show more arousal than extroverts (Knyazev et al., 2002; Corr, 2004).

In his model, Gray postulated three neural systems that conveyed interindividual differences in the sensitivity to certain stimuli and events: the fight-flight freezing system (FFFS), the behavioral activation system (BAS), and the behavioral inhibition system (BIS). While the FFFS was postulated to react to unconditioned aversive stimuli leading to negative affectivity in the sense of anger or panic, the BAS reflected sensitivity to conditioned appetitive stimuli, eliciting positive affectivity. The BIS was modeled to react to conditioned averse stimuli (including not only actual punishment but also loss of reward). Especially the differentiation between systems that specifically react to the conditioned and unconditioned variant of stimuli was seminal for the time and described why the conditioned response (e.g., anxiety around stimuli that imply a painful experience) is often dissimilar from the unconditioned response to a situation (e.g., screaming after a painful experience; for a review of the early work leading to this notion see Corr, 2004).

Gray's theory was later refined following empirical evidence for the crucial distinction between fear- and anxiety-related responses, which alluded to the fact that the

difference in behavior to conditioned and unconditioned stimuli may be a byproduct of different systems conveying either fear or an anxiety-related response (J. A. Gray and McNaughton, 2000; McNaughton and Corr, 2004; Corr and Corr, 2008). Neil McNaughton and Philip J. Corr (2008) argue that fear responses reflect reactions to a known threat that is immediate and perceivable (e.g., seeing a bear in the woods, charging at oneself). A situation that qualifies to elicit fear would most likely cause a fight, a flight, or a freezing reaction based on the perceived immediacy (or distance, as the authors call it).

Anxiety on the other hand is now defined as a reaction that facilitates a more detailed assessment of the situation directed toward a possible but not distinctively known threat (e.g., supposing that a bear might be in the woods will not lead to flight, fight, or freezing but rather to careful investigation of the surrounding area, possibly even motivating an individual to approach the woods to assess the threat).

As a result, the revised reinforcement sensitivity theory (rRST) comprised: 1) the FFFS, reacting with a fear-related response to conditioned and unconditioned cues for immediate threat; 2) the BAS, reacting with positive affect and approach motivation to conditioned and unconditioned cues for reward; and 3) the BIS, reacting with an anxiety-related behavioral inhibition to facilitate further assessment that reacts to conflicting tendencies within the individual (e.g., wanting to run away from the bear, while looking to find more information or a child lying in bed anxiously as it is not sure whether a monster is hidden under its bed: If it was sure about this situation, it would immediately call for help [FFFS response] or feel save [BAS response]). As such, the BIS is the only of the three systems that reacts not to external stimuli but to the internal conflict of goals which as a side aspect also elicits an anxious response (probably to facilitate additional resource activation, like increasing attention on potentially harmful stimuli).

The authors further substantiate these distinctions with data from medicinal studies which largely show that drugs that alleviate symptoms of panic disorders usually will not diminish symptoms in generalized anxiety disorder and the other way around. Interestingly the same is true for depressive symptoms, which hints at distinct neural correlates for fear, anxiety, and depression (for an overview of studies see McNaughton and Corr, 2004 and McNaughton and Corr, 2008).

However, investigating the influence of rRST systems on depression is not an easy task as depression represents a diagnosis that encloses very heterogenic individuals. Hence, one may argue that some depressed patients may be susceptible to episodes of this disease as they are somewhat hyposensitive to reward (low BAS). Others may suffer from depression as a result of prolonged stress, which may base on hypersensitive BIS functioning, just as anxiety-related disorders do (Hewig, 2018). In fact, depression and neurotic disorders are highly comorbid (see Section 2.1). This aspect also highlights, why statistically, some drugs may not alleviate depressive symptoms even though anxiety and depression share a common variance (and thus, probably the same roots in some sense): Probably, due to the large heterogeneity, these drugs should only improve symptoms in a certain sub-sample of the population, which makes it hard for studies to robustly find overlaps of drug efficacy.

5 Endophenotypes of Vulnerability and Resilience

With regard to the previous Sections (4.2.1 and 4.2.2), a total of four personality traits that pose as exceptional vulnerability factors for the emergence and detrimental course of depressive episodes have been identified. Even though more interindividual risk factors may significantly contribute to these characteristics (e.g., see Section 6), this thesis focuses especially on neuroticism and extraversion of the FFM and the behavioral inhibition and behavioral activation system of the rRST.

If one was to adopt a physicalistic view in response to the mind-body problem, stating that psychological functioning results solely from physical processes of the body (brain), there is a necessity for neural correlates of stable traits. However, since personality reflects a highly complex, heterogeneous, and transsituational tendency that may show spontaneously but also in response to a wide array of stimuli, finding distinct endophenotypes is not an easy task. Against this background, especially correlates of neuroticism and extraversion may not be identifiable as readily as those for rRST based measures, since the latter are more specifically modeled to respond to distinct stimuli and events, which makes experimental investigations more readily available.

Interestingly, many authors suggest that the FFM and rRST models share common neural correlates. For instance, according to DeYoung (2013; 2015), a key aspect of extraversion is the sensitivity to reward, which stimulates positive affect and approach behavior. Along the same line, Depue and Collins argued that the most prominent neurotransmitter within the extraversion network is dopamine, which is also in line with the neurochemical basis of the BAS, as suggested by Gray (J. A. Gray, 1982; Depue et al., 1994; Depue and Collins, 1999; Derryberry and Reed, 1999; Pickering and Gray, 1999 J. A. Gray and McNaughton, 2000; Wacker and Stemmler, 2006; Chavanon et al., 2013; Wacker et al., 2013; E. M. Mueller et al., 2014). Further evidence stimulating the idea of BAS-extraversion similarity comes from the substantial correlation of their respective questionnaire scores (Carver and White, 1994; Quilty et al., 2014; Smillie et al., 2006; Wacker et al., 2012), which is also discussed in the results of Section 6. According to Smits and Boeck (2006), especially the BAS-facet reflecting the desire and drive to pursue potentially rewarding events is correlated to extraversion (r=.69).

Analogically, the constructs of neuroticism, behavioral inhibition, and the FFFS have been associated not only historically but also statistically and regarding their neural substrates: According to Timothy Allen and Colin DeYoung (2017), neuroticism reflects a higher-order factor comprising the FFFS and BIS as its lower-order aspects. The authors come to this conclusion since the psychometrically robustly found facets *withdrawal* and *volatility* of neuroticism are conceptually connected to the BIS related slowing and inhibition of behavior as well as to the FFFS related tendency to rapidly engage in anger, fear, or negative emotional irritability in general. Corr and DeYoung even state that BIS scales are often used to assess neuroticism, again highlighting the close relationship of these constructs (Corr et al., 2013). This was replicated by the factor analysis reported below (see Section 6).

Moreover, not unlike dopamine in extraversion- and BAS- related networks, neurotransmitter-systems are shared between these constructs as well: Both, serotonin and noradrenaline influence BIS, FFFS and neuroticism measures alike (McNaughton and Gray, 2000; Tauscher et al., 2001; Du et al., 2002; Quilty, Meusel, et al., 2008; T. Z. Tang et al., 2009). In line with this, there also seems to be a substantial overlap of

neural networks reflecting neuroticism, BIS, and FFFS activity. For instance, a significant amount of research points towards increased sensitivity of the HPA axis and subsequent humoral and neural responses in all three constructs (G. E. Miller et al., 1999; Polk et al., 2005; Nater et al., 2010; Garcia-Banda et al., 2014) as well as towards blunted cortisol responses to specific stressors (Netter, 2004; Phillips et al., 2005; Oswald et al., 2006).

In sum, these studies point towards common endophenotypes of the stable vulnerabilities addressed within this thesis. Furthermore, before the background of overlap between both, psychometric measures and neural systems, in a broader sense, these findings highlight two central psychological aspects in the context of affective disorders: One, positive affect and associated states (extraversion, BAS), which may contribute to pathogenesis due to insufficient manifestation and two, negative affect and correlated states (neuroticism, BIS, FFFS) which increases susceptibility due to excessive activity. Importantly, these are not two poles of one dimension, which is why they may vary independently from one another, thereby possibly contributing to the manifestation of a variety of symptom-combinations within the diagnoses of depression (see Hewig, 2018; also Section 6).

However, since such tendencies (towards certain affect, motivation, and behavior) will always include a highly complex and wide array of chemical, neuronal and neural influences, the above-mentioned similarities between traits are without a doubt just a small excerpt of the complete picture. Nonetheless, against the background of the discussion in Section 3.2, intraindividual mechanisms may be suited to allude to the emergence of such interindividual vulnerability factors. Therefore, rather than addressing every single neural correlate of each personality trait on its own, it may be more conducive to postulate a universal framework of cognitive-emotional processing and discuss trait differences like neuroticism-related increases in responsiveness to certain stimuli as a specific manifestation of this superordinate model later on.

One such unifying framework that grounds on the idea of the research domain criteria (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml; last checked July 4, 2022) is the hierarchical reinforcement learning model of the anterior cingulate cortex (HRL-ACC; Holroyd and Umemoto, 2016); an influential model that is further discussed

in the following section.

5.1 Anterior Cingulate Cortex Function

In 2016 Clay B. Holroyd and Akina Umemoto refined Holroyd's previous model of the anterior cingulate cortex (ACC) mediated reinforcement processing (Holroyd and Yeung, 2012) in light of the research domain criteria (Holroyd and Umemoto, 2016) of the NIMH. The authors propose three modules working together in order to ensure motivated goal-directed behavior: The *task selector* (ACC), the *actor* (dorsolateral prefrontal cortex [DLPFC] and dorsal striatum [DS]) as well as the *critic* (orbitofrontal cortex [OFC], ventral striatum [VS] and dopamine-related networks in general). According to their model, the ACC first learns (or reverts to existing knowledge about) the value assigned to tasks and chooses an *option* (a task to commit to) in the process. It then imposes the minimally necessary control over the *acting* DLPFC and DS to maintain action towards the goal. This process is associated with increased frontal-midline theta activity in the EEG. The DLPFC and the DS will then proceed to learn the best way to achieve the goal chosen by the ACC.

This *actor* module is thought to be effort averse, which is highlighted by the fact that immediately rewarded behavior can still be carried out after ACC lesion, while effortful tasks with delayed or low reward rely on intact ACC functioning. As a result, frontal-midline theta may be interpreted as necessary modulation of the effort-averse actor to carry out tasks, that comprise a low-effort/immediate-reward ratio. Finally, the *critic* gets involved by evaluating the progress towards the formulated goal. It then informs the ACC about the result of this evaluation by computing a better- or worse-than-expected ratio that can be measured via a reward prediction error (the event-related potential component *reward positivity*) that is conveyed via the midbrain dopamine system and facilitates both, reinforcement learning in the actor to optimize goal-directed action and the anticipation of actual reward for goal achievement inside the critic (see Holroyd and Umemoto, 2016 for a review). Figure 7 summarizes these relationships in a schematic illustration. The authors summarize their model with a handy example:

'On this view, the ACC would be responsible for deciding to go for a long run, directing the actor to place one foot ahead of the other and the critic to monitor progress toward the finish line.' (Holroyd and Umemoto, 2016, p. 421)

Following the ideas of this model, interindividual differences in extraversion and the BAS would be positioned in the general activity and more importantly the sensitivity and volatility of the dopamine system in response to cues for immediate but also delayed reward, facilitating valuation within the critic. Differences in BIS functioning and neuroticism on the other hand may especially be correlated to ACC function as the ACC plays a major role in directing resources towards closer assessment of situations by modulating the actor and choosing tasks to commit to.

Since the HRL-ACC provides specific ideas on the testability of these hypotheses by postulating frontal-midline theta and reward positivity as correlates of the respective functions of the actor and the critic, these EEG measures seem especially valuable to test for and interfere with stable vulnerability factors. Since the reward positivity is itself mainly driven by theta synchronization in the cingulate cortex (J. F. Cavanagh et al., 2012)[8], the general analysis of EEG-midline (electrode positions Fz, Fcz, Cz, Pz) electrodes will be promising to assess both measures.

5.1.1 Midline Theta

Theta activity describes the process of large-scale neuronal activity synchronization at a level of approximately 4-8Hz (even though theta band limits may vary between individuals). The EEG based midline theta measure, reflecting ACC orchestrated oscillations of extracellular charge shifts has been shown to underlie prominent event-related-potentials (ERPs) that represent feedback driven components like the feedback related negativity but also the N2 (J. F. Cavanagh et al., 2012). All of which reflect the evaluation of action-outcome dyads. Accordingly midline theta has been correlated to conflict (e.g.,

[8]By many, the reward positivity is currently understood as functionally equivalent to the error-related negativity. For a discussion see Proudfit, 2015

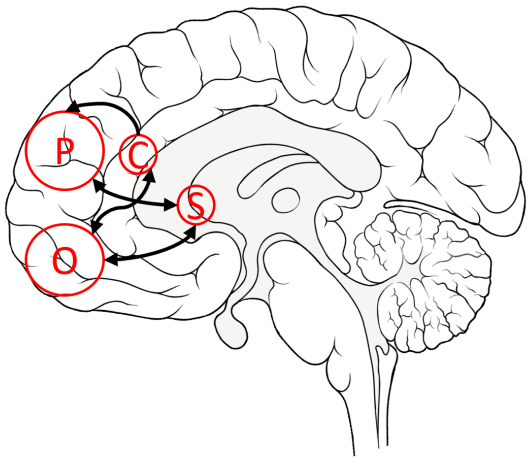

Figure 7: Schematic representation of the neural networks underlying HRL-ACC

Botvinick et al., 2001; Nigbur et al., 2012), error processing (J. F. Cavanagh et al., 2012), attention (Shackman et al., 2011), task selection (Hadland et al., 2003; Kennerley et al., 2006; Holroyd and Umemoto, 2016) as well as learning (Shenhav et al., 2013; Shackman et al., 2011), including memory retrieval (Hsieh and Ranganath, 2014), and updating (Enriquez-Geppert et al., 2014) but also effort (Wisniewski et al., 2015; Mussel et al., 2016), anxious states and traits (Osinsky et al., 2017), as well as motivation (Reznik, Nusslock, et al., 2017; Gheza et al., 2019).

This is well in line with Holroyd's and Umemoto's model and alludes to the idea that ACC-related EEG measures indicate anxiety, BIS, and neuroticism-related properties, which indicates it to be an endophenotype of these constructs. This should show especially in posterior electrodes, while frontal electrodes should relate to the less prolonged effort (Thomas-Yeo et al., 2011; Alexander and Brown, 2011; Shenhav et al., 2013).

The cingulate cortex is subdivided into several divisions with different structural but also functional properties including an anterior (Brodmann areas 24, a24', 25, as well as 32, a32') and a posterior (Brodmann area p24') section. The ACC is further divided into a subgenual (sgACC; Brodmann area 25 and portions of area 24 and 32), pregenual (pgACC; Brodmann areas 24, 32), and a dorsal part (dACC; Brodmann areas 32' and a24'; Vogt et al., 2005; Dixon et al., 2017). While the sgACC, a region that plays a

prominent role within the rumination and worrying related default mode network (e.g., Cooney et al., 2010; Jacobs et al., 2014) lies in such a position that scalp based measures may be very inaccurate in measuring its activity, pgACC activity was found to shape the error-preceding-positivity at electrode position Fz and surrounding sites. (Chang et al., 2015)

The dACC maintains extensive subcortical connections to the spinothalamic system conveying nociceptive signals. Furthermore, it is thought to activate the periaqueductal gray (PAG) to resolve conflicts between passive and active defensive behaviors, which also highlights its relevance in goal-directed and motivated behavioral responses as well as its positioning in the regards of rRST but also learned helplessness (see Section 3.1). Further evidence for the dACC's involvement in motivated responses comes from the fact that it also employs connections with DLPFC and parietal motor- and attention-related areas, which may indicate a mechanism by which the ACC directs the actor while also increasing cognitive resource expenditure in situations that still require action-outcome learning or control to maintain an effort towards a far-away goal (Holroyd and Umemoto, 2016; Dixon et al., 2017).

The pgACC plays a crucial role in the evaluation of interoceptive signals in context of current knowledge about the oneself and the environment (Amemori and Graybiel, 2012; Bartra et al., 2013; Clithero and Rangel, 2014). This idea grounds on several findings (Dixon et al., 2017): First, pgACC activity is correlated to subjective emotional feelings (e.g., Vogt et al., 1996; Vogt and Laureys, 2005). Second, its activity increases in response to internal rather than external attention focus (see Dixon et al., 2017 for a comprehensive review and discussion). Third, neuroanatomically, the pgACC expresses only minor connections to areas conveying sensory information from the outside of an organism, while it on the other hand shows significant connectivity to the default mode network (Paus, 2001; Raichle et al., 2001; Buckner et al., 2008; Thomas-Yeo et al., 2011; Andrews-Hanna et al., 2014; Dixon et al., 2014; Ellamil et al., 2016) that focuses on internal stimuli processing, conveying worrying or rumination (Alexopoulos et al., 2012; Forster et al., 2015; Mohlman et al., 2017; Barker et al., 2018; Morgenroth et al., 2020).

The dACC includes strong dopaminergic pathways that are thought to convey

wanting, a reward-driven motivational desire depending on a meso-corticolimbic network including the nucleus accumbens and the ventral striatum as well as the amygdala. This system mainly drives goal-directed behavior to obtain anticipated rewards but does not reflect the actual affective response to the reward itself (Haber and Knutson, 2010; Salamone and Correa, 2012). Conversely, the hedonic response to reward that is often referred to as *liking* in contrast to *wanting*, relies on other neural and neurochemical agents. However, the meso-corticolimbic system is also thought to engage in reinforcement learning in so far as that actions are evaluated in terms of their usefulness in reaching the current goal, which leads to trial and error-driven learning by investigation of action-outcome associability (Shima and Tanji, 1998; Camille et al., 2011; Hadland et al., 2003; B. Y. Hayden and Platt, 2010; Kennerley et al., 2006; Tricomi et al., 2009).

Crucially, dysfunction in this network has been associated with anhedonia, one of the key symptoms of depression. Pizzagalli (2014) hypothesizes that prolonged experience of uncontrollability of external stimuli or events induces dysfunction in the dopaminergic pathway of the meso-corticolimbic system. Similarly, DeRaedt and Hooley (de Raedt and Hooley, 2016) propose that previous experiences of insufficiency will project themselves into future behavior by diminishing the amount of cognitive resources expended before a novel demanding task even starts. As a result, these findings add to the remarks made above, which stated that extraversion may not be as a reliable predictor for depression as neuroticism is. Against the background presented here, one may argue that the prediction may become more robust if one would not analyze extraversion in general but its facets. Here especially the meso-corticolimbic correlated drive to pursue reward (the facet where extraversion and the BAS overlap most) may be a more promising predictor. This would link the inconsistently found correlation of extraversion to the loss in drive and energy rather than to (a reduction in) positive affect.

The results concerning action-outcome associability are furthermore conceptually similar if not equal to what the learned helplessness/hopelessness theory proposed and thereby brings together two important neuroscientific and theoretical frameworks. According to Holroyd's model (2015) the PL, which is strongly implicated as the *detector* and *expector* of control within the learned helplessness framework, chooses the overall

setting or *meta-option* (e.g., participating in an experiment or not) based on the average expected value of the general commitment, before the ACC subsequently adds information (on value and needed effort) on specific actions (e.g., participating in the experiment at eight in the morning or in the evening). He describes this relationship to be hierarchically organized as the PL makes the first (high-order) selection of options, which will then, mediated by the ACC, control the striatum (in the learned helplessness framework, the PL-striatum network was proposed to detect controllability). Even though Holroyd later focused more strongly on the ACC instead of the PL (as seen in the HRL-ACC), these considerations highlight the connection between results from learned helplessness studies and ACC-related measures. Thus, in context of the results presented in the previous paragraphs, one may argue that the ACC (hence, midline theta) is directly involved in the emergence of helplessness by providing information on the cost-effect ratio of current action-outcome dyads.

Additional evidence for similarities between the previously discussed frameworks comes from the result that in rodents, the PL shows extensive descending projections to the dorsal raphe nucleus, which in turn modulates the amygdala and PAG. These are correlated to the FFFS, and neuroticism as stated above. Within the learned helplessness literature, this connection between PL and dRN is widely accepted to be a sufficient trigger for the stress response within learned helplessness tasks (Maier and Seligman, 2016), highlighting the relevance of controllability as a mediating factor between stressors and FFFS, BIS, or neuroticism-driven reactions that seem closely related to depressive responses. In sum, the meso-corticolimbic system and especially the dACC are thought to detect action-outcome contingency thereby guiding goal-directed behavior under influence of the DLPFC and the striatum. Furthermore it is implicated to initialize fear and anxiety-related stress responses, if no sufficient action could be found to avoid an impactful negative event or approach a meaningful positive reward.

In line with this, theta activity at central electrode positions has been shown to correlate to the *reward positivity*. The *reward positivity* is thought to react to surprising events that inform about unexpectedly more positive or negative outcomes of actions. It seems to originate from dACC related Brodman areas (Heydari and Holroyd, 2016;

Proudfit, 2015). Nevertheless, it does not directly predict the actual value of the reward that is sought (Gheza et al., 2018), which is well in line with the above-mentioned dACC dependent *wanting* but not *liking* function. In addition, since the dACC is preferentially computing action-outcome dyads to facilitate goal-directed reinforcement learning, it is most implicated in actions that have not yet been learned (non-routine actions), while the dorsal striatum on the other hand plays a crucial role in conveying routine behavior (MacDonald et al., 2000; Botvinick et al., 2001; Kouneiher et al., 2009; Shackman et al., 2011).

Along the same line, several studies suggest that the dACC may be especially part of model-free reinforcement learning, which is reflected by said trial and error learning, while model-based learning, which is reflected by specific assumptions about the future that may be refined by disagreeing evidence, seems PFC-guided (Daw et al., 2005; Hampton et al., 2006; Dayan and Niv, 2008; Gläscher et al., 2010; Dixon and Christoff, 2012; McDannald et al., 2012; Dolan and Dayan, 2013; Smittenaar et al., 2013; S. W. Lee et al., 2014; Stalnaker et al., 2014).

Taken together, these findings are well in line with the HRL-ACC model as the dACC was hypothesized to guide the actor via increasing activity in those tasks that require (cognitive) effort to maintain an action for goal achievement. Also, the idea of the dACC to play a major role in task-selection is widely supported by evidence of different neuroscientific disciplines as this online evaluation of action values is also the basis for adaptive changes of actions (Turken et al., 1999; Picard and Strick, 1996; Dixon et al., 2014; Stuss et al., 2005). Furthermore, it has been shown to react to the difficulty and number of actions required to reach a goal (Shidara and Richmond, 2002; Croxson et al., 2009; Kennerley et al., 2009; Kurniawan et al., 2013).

As a result, it seems plausible to assume that as the dACC learns values of actions online, it is also a key region to select which action makes the most sense based on the current knowledge. Further refinement of the now model-based prediction of action-outcome dyads may then ultimately be refined in the prefrontal cortex, which reflects a motivation-driven driven actor towards the chosen goal. The PFC may then influence the ACC and other regions, which is well in line with studies describing the functional

connectivity between ACC and DLPFC areas (Wise, 2008; Passingham and Wise, 2012). Further evidence on the important role of this interference comes from literature on the effectivity of DLPFC focused neuromodulation, which implies that results vary as a function of PFC-ACC connectivity (M. D. Fox et al., 2012; M. D. Fox et al., 2013; Cash et al., 2019; Cash et al., 2021).

Another very consistent finding regarding both, rRST and FFM-related vulnerability factors is the prefrontal EEG-based activity (and activation). Here, measures related to negative affect, and withdrawal behavior and motivation have robustly been found to elicit greater right than left-hemispheric activity, while a greater left than right hemispheric activity was found in correlation to positive affect as well as approach behavior and motivation (see Section 5.2).

In line with these general remarks, neuroticism, FFFS and BIS have been associated with right hemispheric prefrontal dominance (Sutton and Davidson, 1997; Gale et al., 2001; Wacker et al., 2008; Shackman et al., 2009; Wacker, Chavanon, and Stemmler, 2010; Rodrigues et al., 2018), while extraversion and the BAS were connected to greater left hemispheric activity (Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997; Coan and Allen, 2003; Amodio et al., 2008; de Pascalis et al., 2013).

5.2 Frontal Alpha Asymmetry

Following these cingulate cortex-based findings discussed in the previous section, similarly robust evidence for endophenotypes of vulnerability to affective disorders can be found in cortical prefrontal activation (e.g., Henriques and Davidson, 1991; Langenecker et al., 2007; Lopez-Duran et al., 2012; J. J. B. Allen and Reznik, 2015; Forster et al., 2015; Vai et al., 2015; Adolph and Margraf, 2017; Reznik, Nusslock, et al., 2017). Frontal cortical activity patterns are related to ACC function in several regards: Prefrontal and ACC regions reciprocally inhibit and excite each other while exhibiting higher or lower functional connectivity depending on the current task (Schlösser et al., 2008; Floden et al., 2011; Tik et al., 2017). For example, since both areas are part of the default mode network, higher connectivity mediates mental functions such as rumination or worrying in task-off phases (Alexopoulos et al., 2012; Forster et al., 2015; Mohlman et al., 2017; Barker

et al., 2018; Morgenroth et al., 2020). In other situations, prefrontal and ACC areas may work together to enable updating of cognitive models in the face of new information (see Section 10.3). Further, the HRL-ACC views the ACC as a superordinate decision maker, instigating PFC-conveyed action (Holroyd and Umemoto, 2016).

In summary, frontal asymmetric activation of hemispheres is not independent of cingulate function. Nevertheless, over 40 years of research on the topic of frontal asymmetry (FA) as measured by EEG and other methods point towards a role for this endophenotype beyond the midline theta associated correlates:

In 1979 Richard Davidson and his colleagues published the first of many papers to come regarding an anterior cortical model of emotion (R. Davidson, 1979). By that time, Davidson already described the basic features anterior asymmetry, which is still strongly researched today, and which was originally shown as an asymmetry measurable in the EEG in the frequency range of the alpha waves (8-12 Hz). For this purpose, the calculation method described in Formula 4 is still used:

$$FA = Ln(\alpha\text{-power in right hemisphere}) - Ln(\alpha\text{-power in left hemisphere}), \quad (4)$$

where Ln indicates that the natural logarithm of the calculated alpha power (share of the frequencies between 8 and 12Hz in the total spectrum of the EEG signal at an electrode) is calculated. Classically, either the electrode pairs F8 and F7 or F4 and F3 are used for the calculation. Since alpha power (also called 'alpha activity' in the following) is inversely related to cortical activity, a higher right-sided alpha activity compared to left-hemispheric alpha power would predict a stronger left-sided than right-sided activity. According to the calculation of Formula 4, positive FA values result for this case. Higher FA values consequently imply greater left-sided than right-sided cortical activity.

Positive FA is understood by Davidson in his original model as a correlate for state and trait positive affect, whereas lower or even negative values would indicate a corresponding higher intensity of negative emotions and emotionality (R. Davidson,

1979). This influential modeling of affect on the PFC was revised about 20 years later by John JB Allen and his then doctoral student Eddy Harmon Jones, who showed that trait anger is associated with greater left- than right-hemispheric activity, which contradicts Davidson's model in that it would locate negative affect (and thus anger) on the right (Harmon-Jones and Allen, 1998). Against this background, it was no longer affect but rather the motivational direction associated with affect that was placed in the focus of anterior alpha asymmetry (e.g., Depue and Iacono, 1989; Harmon-Jones, 2003; Wacker et al., 2003; van Honk and Schutter, 2006; Rodrigues et al., 2018). The revised model now mapped approach motivation to greater left than right hemispheric activity and greater right than left hemispheric activity to withdrawal motivation. Against this background, the finding of positive FA scores in trait anger as an approach-related but negatively valent emotion was now in line with the theory. This also offered an explanation for possible conflicting findings, since the same emotion can be associated with different motivations and behavioral goals depending on the context (Hewig et al., 2004),

The model of frontal alpha asymmetry was theoretically extended in other ways, too, so it was possible to integrate the systems of BIS, BAS and FFFS formulated by Gray into the theory (e.g., Carver and White, 1994; Alloy et al., 2008; de Pascalis et al., 2013; also see Reznik and Allen, 2018 or Hewig, 2018 for reviews). Initially, the BAS was assumed to be associated with positive affect and higher left hemispheric activity, whereas the behavioral inhibitory BIS was primarily involved asymmetrically in the right hemisphere. Hewig and colleagues later revised this model in light of, among other things, findings from a reinforced go/no-go task, proposing a bilateral BAS system. This idea was derived from the fact that both active avoidance/inhibition and active approach require a behaviorally activating co-component, such as the ARAS, which is one of the bases of the BAS (Hewig et al., 2004; Hewig et al., 2005; Hewig et al., 2006; Rodrigues et al., 2018). Wacker and colleagues, on the other hand, proposed another model building on the revised RST, assuming a left-hemispheric BAS and FFFS, and at the same time a right-hemispheric BIS correlate[9]; (Wacker et al., 2003; Wacker et al., 2008; Wacker, Chavanon, et al., 2010). An overview of the models can be found in Rodrigues et al., 2018. Figure 8

[9]Please note that these terms still refer to relative rather than the absolute activity of hemispheres

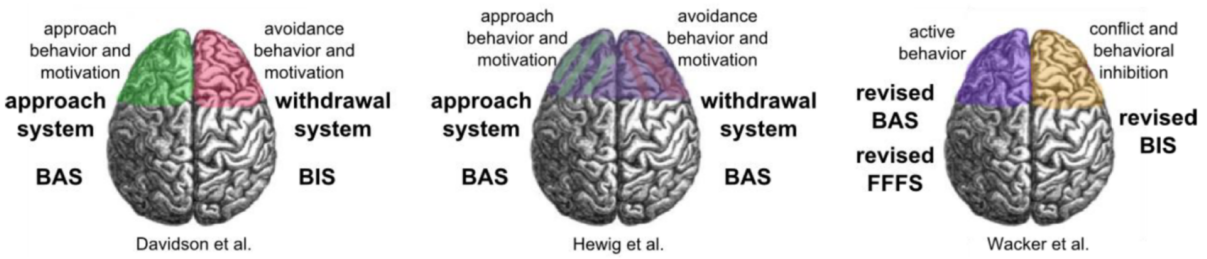

Figure 8: Illustration of currently discussed frontal asymmetry models regarding rRST traits. This illustration was originally published and made by Johannes Rodrigues (Rodrigues, 2017)© and reused under the license CC BY-NC-ND (see: https://opus.bibliothek.uni-wuerzburg.de/frontdoor/index/index/docId/14328; last checked July 4, 2022)

illustrates the mentioned models based on Figure 1 from Johannes Rodrigues' doctorate thesis (Rodrigues, 2017).

Concerning the genesis and course of affective disorders, frontal asymmetry is known to be a particularly stable predictor over time. Thus, as a trait[10], it does not change with regard to acute, treated, or remitted depression (Papousek and Schulter, 2002; J. J. B. Allen et al., 2004; Vuga et al., 2006; Vuga et al., 2008; van der Vinne et al., 2019). Along the same line, a number of studies suggest that once depressed but remitted patients carry increased right-sided asymmetry as compared to never-depressed controls (e.g., Henriques and Davidson, 1990; Stewart et al., 2010, for a review also see (B. L. Goldstein and Klein, 2014), which is well in line with epidemiological data, suggesting high recurrence risks, thus indicating FA to be a valid predictor for such clinical courses. However, it is worth noting that these results may not point towards 'scarring' by previous episodes since FA measures seem to be temporally stable even through depressive episodes (see the arguments above). These findings are rather interpreted as indication for a trait vulnerability that those, who suffered from a depressive episode carried to a higher extent as those, who did not. Furthermore, FA predicts higher depression scores and even episode onset at follow-ups (Nusslock et al., 2011; Stewart and Allen, 2018).

In addition, trait FA measures seem to be partially heritable, as shown by studies analyzing FA of mothers and their offspring, which fits with the general heritability of depressive disorders (e.g., Jones et al., 1997; Diego et al., 2004; Tomarken et al., 2004; Jones et al., 2009; Feng et al., 2012). However, the direct genetic influence may be

[10] According to Hagemann et al., 2002, FA consists of approximately 60% trait variance

substantially lower than the overall correlation of maternal and infant/child FA scores, as twin studies show (Y. Gao et al., 2009; Anokhin et al., 2006; Smit et al., 2007). These estimate the direct genetic influence to reside between 10-37%. Furthermore, direct genetic influence was decreased in F8/F7 as compared to F4/F3 asymmetry (Anokhin et al., 2006), highlighting differences between PFC compartments.

In sum, FA represents one of the most important endophenotypes of depression (and/or its vulnerability factors) that seems to be at least partly genetically mediated (B. L. Goldstein and Klein, 2014; J. J. B. Allen and Reznik, 2015) and it fulfills the requirements of vulnerability according to Anderson's results (2016): A stable vulnerability that is neither worsened by depression in the sense of a scar model, nor is it *treatable*, but it nonetheless shapes the course of affective disorders in the long-term while being present before the second episode emerges (see Section 2 to review the arguments in favor of these properties concerning the prediction of recurrence in depression).

6 Excursus: Jangle-Fallacies in Self-Rate Measures Described in Previous Sections

The constructs described above have been shown to partly rely on similar neural correlates (see Section 5). Furthermore, substantial correlation between FFM and RST measures as well as models to connect these in a latent-factor model were described. All of these show predictive validity concerning depressive symptoms. Additionally, building on the concepts of learned helplessness, several other control-perception related measures have been proposed in the literature. Again, many of these have been shown to predict depression significantly:

One prominent example is the *locus of control*, derived from social learning theory, which describes the general tendency to view environmental conditions susceptible to one's own behavior or to external influences (Rotter, 1966). A related construct is self-efficacy, which, unlike the locus of control, does not refer to the general susceptibility of environmental conditions to influences of individuals in general, but the possibility of influence given situations for a specific person. It could therefore be that people believe

in general that a situation could be influenced by personal action (locus of control), but do at the same time not believe that they have the corresponding opportunities to do so (self-efficacy). Even though, self-efficacy may be domain-specific (e.g., Hofstetter et al., 1990; Rodgers et al., 2009; Scherer, 2013), a generalized self-efficacy measure may indicate a similarly generalized vulnerability to depression (G. Chen et al., 2001). Both locus of control and self-efficacy correlate robustly with depression (e.g., Abramowitz, 1969; Benassi et al., 1988; Maddux and Meier, 1995; Bandura et al., 1999).

Two additional constructs are the personal sense of power and autonomy. Interestingly, these domains, which at first glance do not appear to be validly related to the aforementioned constructs, nevertheless overlap considerably in terms of content and concept. In principle, power is defined as the ability to influence others (or circumstances in general; C. Anderson et al., 2012). Whether this is done in an aggressive, subversive, manipulative, or other way depends on the individual case and the style of the person exercising it. Nonetheless, according to Anderson et al., but also Lammers and colleagues (Lammers et al., 2016), a personal desire for power is on average mostly directed towards the capability to become autonomous from the power of others. In general, however, power also implies the possibility of changing external conditions, just as self-efficacy and the locus of control would do. Autonomy, in turn, is as stated before closely linked to the construct of power, since autonomy can only exist if there is the possibility of living out one's desires and goals (self-efficacy) as well as the possibility of resisting the power and influence of others (which could be two facets of a construct; Deci and Ryan, 1987).

Overall, from this, the question arises as to the extent to which these concepts and constructs are a *jangle fallacy*[11] (e.g., van Petegem et al., 2013), possibly due to their simultaneous development or different definitions due to different contexts of application (e.g., social psychology vs. clinical psychology or intraindividual vs. interindividual focus in depression research).

To test this, 353 subjects were surveyed and their data were subjected to a principal component analysis with *oblimin* rotation. This rotation was chosen to avoid restricting the data artificially to become independent. Instead, the rotation should itself

[11] Jangle fallacies are defined as the false interpretation that two scales refer measure different phenomena/traits because they bear different names (e.g., T. L. Kelley, 1927;Marsh, 1994)

lead to such an orthogonal solution, if it corresponds to the empirical situation. The variables used were the sum scores of self-efficacy, personal sense of power, internal and external locus of control as well as neuroticism, extraversion, behavioral inhibition style, fight-flight-freezing style, behavioral activation style and autonomy. While neuroticism and extraversion reflect two facets of the five-factor model of personality, behavioral inhibition, fight-flight-freezing, and behavioral activation reflect the main traits described by the reinforcement sensitivity theory. These were further discussed in Section 4.2.1 and 4.2.2 respectively. The final choice to include these variables was made due to the idea that neuroticism, BIS, and FFFS are conceptually related to predictability and controllability of averse stimuli or situations, while extraversion and BAS should reflect a general belief to be able to handle uncertain but also specific situations, just as the personal sense of power and autonomy orientation would do. For neural evidence for this notion, see the discussion in Section 5.1.1. In brief, the results presented there indicate that the neural activity following the detection of uncontrollability substantially overlaps with BIS, FFFS and neuroticism related systems. Also BAS and extraversion were shown to be highly correlated as well.

The Kaiser-Meyer-Olkin criterium was .789, which indicates an overall fit of the data to the method of factor analysis. The Bartlet test for sphericity was $\chi^2(45)$=1154.766, p <.001.

Based on *Eigenvalues*, the results show a two-factor solution, with factor one explaining 37,748% and factor two explaining 15,443% of the variance. The rotated factor solution, as well as communalities, are shown in Table 3. Figure 9 illustrates the arrangement of manifest sum-scores in the rotated factor space.

Estimated factor scores for each participant were then extracted and surveyed for correlation depression. In the same sample of 353 persons, the first factor correlates to BDI-V scores by r=-.564, while the second factor correlates with r=-.469. Both factors correlate with one another at r=.312. All correlations are highly significant (p <.001).

As a result, factor two, which comprises FFFS, BIS, ELC, and neuroticism at one pole of the dimension and self-efficacy as well as autonomy on the opposite end, may best be described by intrinsically motivated prospective action on one end and stress-

	Rotated Loadings on Components		Extraction (Communality)
Factor	1	2	
Neuroticism	-0,748		0,706
Extraversion		0,807	0,713
ILC		0,534	0,416
ELC	-0,487		0,269
Autonomy	0,704		0,459
SelfEfficacy	0,479		0,354
BIS	-0,794		0,679
BAS		0,946	0,807
FFFS	-0,664		0,401
PSOP		0,579	0,517

Table 3: Rotated loadings and communalities of indicator variables. loadings under .4 are not shown. ILC= internal locus of control, ELC= external locus of control, BIS= behavioral inhibition system, BAS= behavioral approach system, FFFS=fight flight freezing system, PSOP= personal sense of power.

related reactive behavior to existing aversive stimuli and conditions on the other end.

This definition stems from the common idea of self-efficacy and autonomy to be able to pursue self-determined goals (especially in regard to autonomy), while the FFFS, BIS, neuroticism share their strong emotional response to subjectively aversive situations (even though these responses may not be directed towards the same goal, see Section 4.2.2). Further, ELC, also clustering on this end of factor one, indicates these affective and behavioral responses to be somewhat related to the idea of an externally controlled nature of situations.

Factor one, however, describes BAS and extraversion as main indicators, which may highlight its neural and conceptual overlap in regards of approach behavior but also positive affect. Furthermore, ILC and PSOP seem to relate to both factors similarly, while showing slightly greater proximity to factor one, which again highlights that these constructs combine features of approach-related behavior (being able to influence others, needs approach) and self-efficacy beliefs alike.

In sum, also concerning extracted communalities, it seems evident that all of these variables share substantial common variance. Nonetheless, these results also point

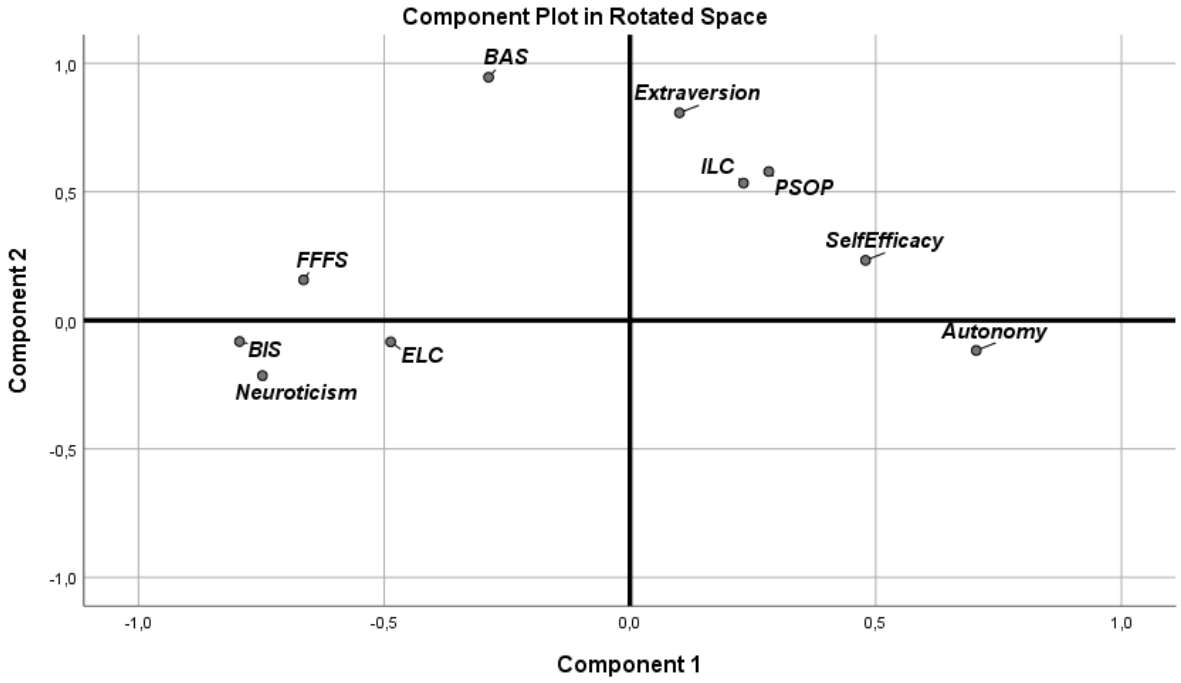

Figure 9: Illustration of variable-positionings in the two-dimensional rotated factor space.

towards substantial differences between constructs as less than 50% of variance could be explained in five out of ten variables. However, especially BIS, BAS, FFFS, extraversion, and neuroticism showed the highest communalities and the most unequivocal allocation to either factor, indicating similarities between BAS and extraversion as well as FFFS, BIS, and neuroticism, which is well in line with the discussions of the previous sections (see Section 4.2.1 and 4.2.2)[12].

7 Current Neurobiobehavioral Interventions

The previous chapters introduced the idea that especially long-term effectivity of therapeutic approaches may depend on two things: a) Stable personality traits that influence the onset and course of disease in the presence but also the absence of interventions and b) long-lasting forms of intraindividual learning that may increase the overall vulnerability of an organism and may not be directly modifiable by therapy.

These two issues are not independent from one another. Rather, building on the discussion above, long-lasting learning, which may come in the form of kindling/sen-

[12]Please note that the solution presented here largely depends on the included variables. If some of these variables were excluded due to theoretical or empirical implications, other solutions may be found

sitization within stress-related neural and somatic networks like the HPA axis but also other LTP-based processes such as stable and easy to reinstate cognitive attribution styles may ultimately lead to stable personality. This personality then reflects a transsituational and lasting trait response to a variety of stimuli, which has been sensitized and probably over-learned to become a habit before the third depressive episode emerged[13].

As a result, long-lasting therapeutic intervention or prevention programs would be most efficient if they were able to influence trait-like responses to the point of self-perpetuating change exceeding the phase of active therapy. In that sense, one could argue that current therapy approaches fall short the same way that diets often fall short: The individual will be able to maintain the active changes in lifestyle (e.g., engaging in subjectively unpleasant activities to induce habituation; engaging in a healthier but less tasty eating habit) while the motivation to do so can be maintained either due to external stimulation (e.g., by a therapist or a fitness trainer) or due to internal processes (e.g., being able to motivate oneself to maintain activities according to the therapists' suggestions even after the therapy has ended or being able to skip the dessert after being told to have gained weight). However, if the underlying tendency to behave (e.g., to engage in avoidance behavior or to eat calorie-heavy) has not been extinguished, there is a high possibility for recurrences, once the initial goal has been reached (e.g., 'I'm well now, I don't need to push myself to habituate to social contexts anymore' or 'I lost enough weight so I can eat some more chocolate cake'), frustration sets in (e.g., 'why do I have to torture myself for the rest of my life?'), or enough time has passed and beneficial activities gradually cease in favor of 'old' habits (trait responses) that added to the initial manifestation of the problem. Furthermore, as remarked in Section 4.1, the state of depression may be inherently prone to increase this existing tendency towards impaired protocol adherence even more. Thus, once adherence is low enough that depressive symptoms recur, these symptoms will further impair the ability to regain adherence in the sense of a vicious cycle. In short, interventions of all kinds may lose to stable vulnerability factors in the long run if the therapy effect grounds on behavior, cognition, and emotional response that

[13]This idea is based on the fact that Anderson et al. (2016) investigated inter-episode intervals and report no change of these throughout recurrences. However, the first interval is measured between episodes one and two, which means that the stable trait, leading to equally stable inter-morbid intervals does not need to be present before the first but before the third episode

need active maintenance while the vulnerability does not.

Unfortunately, all current treatment approaches seem to rely on such active maintenance to some degree (Griens, 2002), including cognitive behavioral therapy, psychodynamic approaches, mindfulness-based interventions as well as physical exercise-based or medicinal treatment. This notion builds on two arguments: 1) stable personality traits measured at the beginning or before the first episode predict the long-term course of the disease even if some sort of therapy was applied throughout (e.g., Struijs et al., 2018; also see Section 2). 2) Trait-incompatible behavior needs significantly more (sustained) effort (P. Gallagher et al., 2011).

Interestingly, even though this would suggest, that personality traits do not change during therapy, which would subsequently escalate effort costs to maintain therapy-related behavior and cognition, there is evidence for personality changes taking place during medication, skills training, cognitive behavioral therapy, and psychoanalytical therapy. Furthermore, this change of traits seems to predict the treatment outcome (see Roberts et al., 2017).

Hence, assuming a treatment-resistant personality trait that slowly regains control over the organism's trait reaction contradicts these lines of evidence as these studies would predict that the stable, effort-escalating trait has been altered throughout the treatment. However, one solution to these incompatible ideas may lie in the way that personality traits are usually measured: Questionnaire-based measures will always to some extent be influenced by states rather than traits (e.g., mood-related negativity biases may shape the answer to a trait-focused item). Regarding the FFM and depression, Karsten et al. (2012) report symptom-related increases in neuroticism and decreases in extraversion and conscientiousness, which may not be surprising as neuroticism includes facets describing negative emotional responses, extraversion comprises positive affectivity, and conscientiousness describes one's capability to complete tasks and organize oneself; all of which reflecting issues of patients suffering from depression. Nonetheless, in theory, such traits should not readily change with increasing symptom-scores but adapt slowly following prolonged depression-related suffering.

As a result, changes in personality through treatment may describe changes

in state-dependent proportions of the psychometric measure whereas the original trait remains largely unchanged leading to said escalating costs of effort. Furthermore, even though questionnaires may find treatment-related changes in trait responses, one always needs to take into account that such measurement modalities assess the narrative about oneself rather than the 'real' trait response-susceptibility. Hence, patients answering items on the topic of personality may to a certain extent especially be prone for state- instead of trait-changes, since patients could be somewhat 'trained' to focus on current changes to their own behavioral, cognitive and emotional repertoire. This may influence the narrative about the current positive change throughout the therapy but not the actual biological responsivity to stimuli and events. Hence, endophenotypes may prove more stable and unchanged while the narratively biased (e.g., by mechanisms of cognitive dissonance: 'My therapist tells me that I am doing better and I have invested so much work that I must have changed!') and state-dependent way to measure personality via pen and paper may diverge from findings showing overall stability of FA measures[14]. Thus, the idea of trait-driven recurrence/relapse vulnerability over time may still hold.

Further evidence for this comes from results of a meta-analysis by Roberts et al. (2017), who report effect sizes of personality change to decline in studies that investigate time-spans of one year or more after the end of therapy[15]. In addition, the authors report significantly less change in personality in depression as compared to anxiety, which is often treated via some sort of (extinction-based) exposure therapy. By doing so, this treatment may severely change the measurable reaction to certain stimuli but may not show a particular focus on overall personality traits. Also, personality changes are often reported within weeks of treatment, which again, indicates no lasting change in underlying endophenotypes.

Still, therapy-related changes in questionnaire-based personality traits have been shown to predict a beneficial long-term outcome (Huber et al., 2017), stimulating the hypothesis that changes in underlying neural correlates will be able to further

[14]This is a hypothetical example that does not seek to invalidate the questionnaire approach. However, since such measures are directed to measure subjective appraisal rather than 'objective' responses intentionally, the present example still illustrates a theoretical but surely oversimplified possibility

[15]Please note that the authors interpret their results differently even though effect sizes drop from d= .48, 95% CI [.36, .60] at the peak change after 6 months of treatment to d= .37, 95%CI [.26, .47] for follow-ups after 1 year

strengthen evident effects. Hence, the following sections discuss two approaches within the cognitive-behavioral-therapy framework to tackle endophenotypes and learning underlying treatment-resistant or recurrent affective disorders in detail.

7.1 Extinction Learning

Early behaviorists like Edward Lee Thorndike or John Broadus Watson tried to explain normal but also pathological psychological functioning by investigating conditioning processes that are usually connoted with the terms UCS (unconditioned stimuli), CS (conditioned stimuli), UCR (unconditioned reactions), and CR (conditioned reactions). In sum, the classical conditioning process describes the learning of a relationship between two stimuli (e.g., a doorbell and getting mail). However, one of the most prominent founding fathers, Pavlov, described not only acquisition but also extinction of learned associations (Watson and Rayner, 1920; Thorndike, 1927; Pavlov, 1927).

The procedure to extinguish such an acquired connection counters that of initial learning: While during acquisition two stimuli are presented in close proximity and reliably together, extinction of this memory was thought to require the presence of one stimulus without the other. By doing so, scientists thought that the initial association of the stimuli could be unlearned. However, early descriptions of spontaneous recovery of extinguished associations were one of the key findings by Pavlov, leading to early ideas about extinction related inhibition of learned associations that would not disappear by presenting one stimulus repeatedly without the other (Pavlov, 1927; Konorski, 1967). Later work added to this finding by providing evidence for two other mechanisms that would theoretically require the initially learned association to remain stable throughout an extinction training, namely reinstatement and accelerated re-acquisition (Rescorla, 1988; Rescorla, 2001; Bouton and Moody, 2004).

While spontaneous recovery describes the unprompted/untriggered/unprimed reemergence of once learned but then extinguished memory, reinstatement refers to the recovery of such memories following singular reactivation of the initially learned association. Accelerated re-learning points towards increased slopes of learning curves, if the addressed association has been learned before.

To give an illustrative example, one can imagine a piano player who has learned a piece that includes the sequence of notes F, D, C. Once the pianist wants to learn a new piece with the sequence, F, D, E, the pianist needs to relearn that D is not always followed by C, which reflects extinction learning from the perspective of the first sequence. However, even after several weeks of practicing without playing C after D out of old habit, the pianist may occasionally commit this error, which means that the 'old' association regained control over the organism spontaneously as no intended relearning of the FD-C sequence took place. Furthermore, if the pianist chose to practice the old piece while learning the new one, the singular event of again playing the FD-C sequence may increase the chance for the player to inappropriately again play it through the new piece. Here the old association of FD-C was reinstated, leading to increased risks for conflicts with the newly learned FD-E sequence. Finally, the pianist may experience that the FD-C sequence can more readily be relearned after years of only playing FD-E as compared to an FD-F sequence that has never been played (learned before).

This example illustrates that associative learning takes place in many settings, following the same rules. It also shows how these three mechanisms provide for adaptive and flexible behavior in complex situations as a good pianist should be able to perform many different but similar sequences seamlessly; a skill that can most efficiently be acquired if learning adds novel information to existing memories instead of overwriting them constantly (otherwise the pianist would not be able to remember a piece he/she learned years before in its original form since all pieces learned since then that share sequences with the first one would alter/erase the memory).

Neuroanatomical and -imaging studies investigating the neural basis of extinction learning report two main correlates including the infralimbic (IL) and PL cortex in rodents; the same structures that were suggested to play crucial roles in learned helplessness tasks, with the prelimbic area (vmPFC) posing as the main system to relay expectation for and detection of controllability (see Section 5.1).

Early works report direct projections descending from the vmPFC to the amygdala (K. M. Hurley et al., 1991; Mcdonald, 1991; McDonald, 1998), igniting the idea of vmPFC driven inhibition of fear responses. However, several lines of evidence alluded

to the fact that the vmPFC may not generally interfere with learning and extinction but specifically orchestrate the retrieval of already learned associations: Milad and Quirk (2002) discuss findings implicating prelimbic area driven fear responses from single-cell recordings. Similarly, two influential papers showed increased metabolic activity in the same area during extinction retrieval (Hefner et al., 2008, Knapska and Maren, 2009). Moreover, microstimulation of the Infralimbic cortex leads to increased extinction efficacy (Milad and Quirk, 2002).

On a molecular level extinction seems to be driven by a calcium-mediated intracellular cascade involving NMDA receptor activity, protein kinase A and others as well as cannabinoid receptors (Marsicano et al., 2002; Hugues et al., 2004); Burgos-Robles et al., 2007, Sotres-Bayon et al., 2007; H.-C. Lin et al., 2009) leading to novel protein synthesis. This may then lead to the increased burst-type firing of said neurons contradicting fear-conditioning induced intrinsic depression of cell activity. (Burgos-Robles et al., 2007, Santini et al., 2008). In sum, especially in the context of fear conditioning, LTP processes within the IL/vmPFC seem to guide the retrieval of extinction memories, which is further substantiated by the observation that the degree of IL neuron bursting correlates to extinction retrieval and that artificially induced increased excitability of these neurons has similar effects (Santini et al., 2008; Santini and Porter, 2010)

Conversely, the PL seems to play a major role in the initial fear acquisition as its inhibition reduces fear expression (K. A. Corcoran and Quirk, 2007; Laurent and Westbrook, 2009; Sierra-Mercado et al., 2011). Furthermore, PL activity was shown to correlate to freezing during fear conditioning and that these neurons sustained their firing on a single cell level in response to conditioned stimuli, predicting less extinction retrieval (Burgos-Robles et al., 2009). While the IL comprises descending projections to the amygdala, the PL also receives ascending signals from the amygdala. Further, it is reciprocally able to prolong amygdala responses, stimulating additional fear responses (Vidal-Gonzalez et al., 2006, see Milad and Quirk, 2012 for a detailed discussion of the previous paragraphs.

Interestingly, evidence from rodents also highlights differences in the capacity to profit from extinction learning across the lifespan. Milad et al. (2012,p. 139) summarize:

'Richardson and colleagues report that extinction in pre-weanling rats violates the rules of extinction: it is not context-dependent, does not require NMDA receptors, and does not require the prefrontal cortex (reviewed in Kim and Richardson 2010). Instead of potentiating inhibitory systems, early life extinction appears to erase fear memories from the amygdala (Kim and Richardson 2008, Gogolla et al 2009). During adolescence, extinction again becomes compromised (Esmoris-Arranz et al 2008), as twice the number of training trials are needed to learn extinction and activate the IL (Kim et al 2011a). Finally, aged rats show impaired extinction coupled with a shift of excitability from IL to PL (Kaczorowski et al 2011.)'

This is well in line with results from the discussion above, highlighting the role of kindling/sensitization or learning in general before the first (at least before the third) affective episode emerges, leading to stable vulnerability factors that then drive the course of recurrence, chronicity and therapy resistance.

Since the extinction-learning based literature indicates that symptom alleviating experiences and learning lead to novel inhibitory memory trace formation rather than a direct change of the vulnerability factor (e.g., associating dogs with strong pain is a cognitive vulnerability for the emergence of a dog phobia), these findings add neurobiological mechanisms for the stability of once achieved traits to the discussion. While early (prenatal, childhood) experiences may shape implicit associations that influence the formation of stable personality (e.g., 'angry faces predict pain', an association learned by many children that are victim to abuse), may, later on, add to the manifestation of neurotic behavior, cognition, and emotional responses. Later interference with this trait, probably including those made within therapy, will most likely not change the original memory trace but add 'control' mechanisms that can modulate trait responses to a certain degree.

However, while the extinction-based literature usually focuses on fear and anx-

iety disorder-related conditioning processes, their predictions may still hold for other (affective) disorders as well. For instance, spontaneous recovery, reinstatement, and accelerated re-learning are no fear/anxiety-specific traits of extinction learning and extinction learning-based therapies like exposition but are usually deemed common knowledge in substance use disorders (reinstatement is a common issue in drug use disorders, e.g., Anker and Carroll, 2010), post-traumatic stress disorder (PTSD; e.g., Le Dorze and Gisquet-Verrier, 2016) and also in depression (e.g., R. M. Post and Kegan, 2017).

Further evidence for this idea's applicability to depression comes from the fact that the neural correlates of fear acquisition and extinction seem to be equal to the neurobiological foundation of learned helplessness (see Sections 5.1 and 3.1) which reflects one of the most widely accepted models for the emergence of the heterogeneous disorder that is depression: In fear conditioning paradigms, the vmPFC conveys the retrieval of extinction memories, inhibiting fear and anxiety associated structures, which is almost the same function that the learned helplessness community attributed to the vmPFC. Here it is understood as an area that can form an expectation on the controllability over (aversive) stimuli, which is essentially just another way of phrasing *memory retrieval*. Along the same line, there is extensive evidence pointing towards the inhibitory control mechanism imposed by the IL/vmPFC on subcortical structures with a focus on the amygdala in fear conditioning and a focus on the dorsal raphe nucleus in learned helplessness research. However, the raphe nucleus is also thought to modulate amygdala activity.

Furthermore, in the context of learned helplessness, the PL-dACC-striatum connection was mostly described in terms of controllability detection, which it does according to Section 5.1 by evaluating action-outcome associations. Concerning fear learning, the dACC was described to modulate the associative learning underlying fear acquisition. As the dACC is part of the larger cingulate cortex that also assesses interoceptive signals, the dACC may very well function as a general integrator of contingent information leading to associative stimulus-stimulus or reinforcement-based stimulus-outcome learning.

Finally, one may argue that the idea of helplessness emergence may be formalized as a simple conditioning process: An organism learns that there is no contingency between actions and desired outcomes. As a result, fear conditioning-focused researchers

may expect dACC activity to increase to maintain a fear response. Finally, the vmPFC would in the long-term appear less active, when no extinction learning (being able to influence the probability of the desired outcome) took place. These predictions would be the same in the context of learned helplessness theory and be in line with the literature on midline theta, which describes greater theta activity to reflect conflict, anxiety, and increased cognitive resource allocation to situation assessment, possibly predicting subcortical stress-related network activity (see Section 5.1.1).

Also in line with this are the interindividual differences in susceptibility of subjects to learn stress related associations on the one hand and to extinguish these on the other hand, which seems to depend on the same variables as depression and helplessness emergence does: Serotonin and the brain-derived-neutrotophic-factor (BDNF; Vollmayr et al., 2001; Maier and Watkins, 2005; Heldt et al., 2007; Shalev et al., 2009; Peters et al., 2010; Soliman et al., 2010; Cowen and Browning, 2015; Su et al., 2016; Colucci-D'Amato et al., 2020; Duman et al., 2021)

Thus, all of these findings add to the idea that fear conditioning and extinction-based concepts/therapies may apply to depressive disorders as well; including the benefits of extensive knowledge about neurobiological mechanisms of emergence and treatment as well as disadvantages like the fact that inhibitory therapy-related memory traces may not erase vulnerability factors from the brain, which leaves room for spontaneous recovery, reinstatement or accelerated re-learning of these.

7.2 Transcranial Non-Invasive Neuromodulation

Before the background of the previous sections, highlighting the stability of personality-related endophenotypes and even single memory traces throughout affective disorders and during treatment, more direct approaches to directly influence these were called for. As a result, stimulation (or modulation) of neural correlates of vulnerability factors may induce therapeutic effects. For instance, based on the previous sections, one may argue that vmPFC-targeted neuromodulation may alleviate stress symptoms and increase therapy efficacy.

Unfortunately, even though extensive research on the use of different forms of

neuromodulation in affective disorders exists (e.g., Brunoni et al., 2016), target regions like the PL of the vmPFC are rarely[16] modulated/stimulated due to several reasons: i) systemic rather than focal forms of neuromodulation are not suited to directly address the vmPFC without side effects as it does not rely on a single, distinct neurotransmitter, which is an argument against 'classical' approaches like medication. ii) the compartments of the vmPFC that convey beneficial treatment effects in learned helplessness and fear conditioning/extinction contexts are positioned more deeply (PL) inside the brain than traditional transcranial neuromodulation techniques such as transcranial magnetic stimulation (TMS) could reach it (e.g., Zangen et al., 2005; Roth et al., 2007) . iii) Other transcranial methods like transcranial direct current stimulation (tDCS) or electroconvulsive shocks may be able to reach as deep as the vmPFC but are not suited to target this area focally (e.g., Datta et al., 2009; Sadleir et al., 2010). Rather tDCS will modulate several regions and structures within the line of the two electrodes applied and produce an exciting effect on one end while also an inhibiting effect on the other, complicating interpretation of results (e.g., Nitsche and Paulus, 2000). The same line of argument is true for the modulation of the dACC, another key region in both, the learned helplessness and extinction paradigms.

As a result, many researchers, who despite these complicating factors seek to target these regions with some sort of neuromodulation, rely on functional connectivity between the target regions and more readily available areas like superficial cortices such as the PFC (e.g., Raij et al., 2018 but also see Pennington and Fanselow, 2018). Along the same line, several studies report functional connectivity between cortical and subcortical/deep structures to predict the antidepressant response to TMS, which is most prominently focused on DLPFC regions as these are accessible to the method and implied in many affective, motivational, and cognitive functions: TMS of the left DLPFC has repeatedly and robustly been shown to rely in its effectivity on the left DLPFC-sgACC connectivity (M. D. Fox et al., 2012; M. D. Fox et al., 2013; Cash et al., 2019; Cash et al., 2021), implying that the antidepressant effect at least partly relies on indirect modulation of the default mode network (Liston et al., 2014), which on the other hand builds an en-

[16]For examples of tDCS studies targeting the vmPFC directly via tDCS see Gilam et al., 2018; Y. Li, Wang, et al., 2020

dophenotype for worrisome and rumination-prone personality (Servaas et al., 2014; Zhou et al., 2020; Feurer et al., 2021).

It is an ongoing debate whether to modulate the left or the right DLPFC. A meta-analysis from 2013 indicates that both approaches reach similar results, even though side effects seem to be less prominent in right-hemispheric modulation studies, thus advising to modulate the right rather than the left hemisphere (J. Chen et al., 2013). It is also worth mentioning, that, before the context of FA, right hemispheric neuromodulation should be inhibiting, while left-hemispheric should be exciting, as both approaches would lead to a net increase in FA scores (see Formula 4).

Part II - Approaches of the Present Thesis

8 Interim Summary

Affective disorders, such as depression, cause billions of euros of financial damage to the German and global economies every year. However, more important than this, the subjective suffering of those affected as well as substantial strains for their families and caretakers are evident and tend to increase both acutely (against the background of the current pandemic situation) and as a long-term trend. Furthermore, major depression has also been repeatedly and robustly described as a risk factor for worse outcomes in other diseases, including psychiatric and somatic illnesses, which alludes to possibly even more detrimental effects attributable to depressive disorders and their respective vulnerability factors.

Although we know of a wide range of effective treatments to attenuate or even cure an episode of depression, many interventions seem to work mainly in the short-term, sometimes failing to stop further episodes to occur. This is true for antidepressant medication as well as for all (well researched) forms of psychotherapy and neuromodulation. One reason for the long-term ineffectiveness could be that vulnerabilities can form even before, or presumably immediately after, the first episode of depression, which are difficult to change through intervention and may therefore regain control over the organism's

experience and behavior over time. These vulnerabilities can be described as stable and temporally persistent traits whose neural and neuronal correspondence is presumably to be found in a well-conditioned linkage of stimuli and reactions (e.g., being invited on a romantic date as a trigger for self-deprecation instead of excitement, because a stable negative self-concept in this regard was manifested in the individual before).

Accordingly, previous therapy methods seem to have the problem of establishing self-perpetuating effects, which in themselves create a long-lasting incentive to avoid 'old' (symptom triggering or sustaining) patterns that may be connected to the aforementioned trait-like tendencies. One reason for this could lie in the brain's property to retain 'old' depression-related memory traces, protecting them against 'competing' therapy effects. Thus, memory traces that are risk factors for affective disorders of all kinds (e.g., avoidance behavior) are preserved and thus susceptible to reinstatement, spontaneous recovery, and accelerated re-learning.

In addition, unlike psychotherapy, medication and neuromodulation methods are not able to work in a target-specific way: Medication acts primarily systemically and does usually not cause focal changes in specific neuronal ensembles or even receptor-types, but often rather addresses several different receptor-families that mediate different psychological functions (depending on the structure they are located in) causing side effects and impairing *targeted* interventions. Neuromodulation methods, on the other hand, have a comparatively higher spatial resolution capacity, but may not have the technical prerequisites to reach the identified target regions directly, which is why in Parkinson's disease, for example, complex neurosurgical procedures are necessary for the invasive implementation of electrodes. Similarly, in affective disorders, it is usually only possible to influence the limbic system or other target areas like the PL indirectly or, again, without spatial specificity.

In sum, it seems that psychotherapeutic and other interventions may improve their long-term effects if the original vulnerability can be addressed and changed. As a result, existing therapy approaches may profit from methods that can specifically reach and modulate/stimulate subcortical regions of interest. In this regard, even though neuromodulation effects are themselves only short-lasting, augmenting psychotherapy via direct

interference at the site of certain endophenotypes may prove effective in the long-term as well.

Especially three regions of interest conclude from the previous sections: The dACC (midline theta), the lPFC (FA), and the PL. If these regions could be addressed, subsequent therapy sessions may be more effective as patients would probably become more receptive to therapy-related influences (due to the modulation of motivation and affect [lPFC], increased capability to draw resilience from existing memories [PL] or more readily available effortful action control, less inhibited response styles, and increased control-perception [dACC]).

Nonetheless, even though greater therapy effects due to such augmentation may lead to increased sustainability of results, patients may still be prone to spontaneous recovery, reinstatement, and accelerated new learning. Thus, the best possible augmentation would need to add further mechanisms to this approach. As a result, in the following sections, a novel neuromodulation approach that would qualify to address all of these areas of interest, as well as a therapy protocol that may be able to *change* existing memory traces instead of inhibiting them, will be discussed.

9 Low Intensity Transcranial Focused Ultrasound Neuromodulation

Since currently employed non-invasive neuromodulation techniques either suffer from the inability to hit targeted areas with spatial precision or to reach deeper regions of interest, the search for a non-invasive, focally applicable, and deep-reaching reversible method that can complement and expand existing possibilities has been going on for decades. One method to fulfill these requirements is transcranial low intensity focused ultrasound (litFUS) neuromodulation, which theoretically and practically can achieve spatial resolution in the range of mm^3 even in subcortical brain structures and is both (f)MRI compatible and rapidly applicable (Tufail et al., 2010; Legon et al., 2018). As already implied in its name, the method uses sound instead of (electro)magnetic fields, making it indeed a completely new approach to the task of modulating neural activity (e.g., Bowary and

Acoustic Intensity Spatial Peak Time Average	Duty Cycle	Pulse Repitition Frequency	Mechanical Index	Frequency	Administration Duration
199mW/cmš	0.5%,	0.5Hz	1.53	0.5 MHz	120s

Table 4: Table of liFUS Parameters used in This Thesis.

Greenberg, 2018).

Sound is physically described as waves of particle displacement between 20Hz and 20kHz; the boundaries within humans can perceive tone from the sound. Under 20Hz, the sound would thus be termed *infrasound* while above 20kHz the range of *ultrasound* begins. Traveling in form of longitudinal waves, ultrasound is able to penetrate the human skull, delivering mechanical energy to the tissue (J. Mueller et al., 2014; Tyler, 2011; Tufail et al., 2011; Plaksin et al., 2016). Nonetheless, depending on the properties of these waves, other effects, such as heating may occur. Table 4 gives an overview of parameters describing the emitted sonic wave that was utilized to deliver neuromodulation within the studies of this thesis.

Historically, in 1929 Edmund Newton Harvey published a paper on the modulation of neuromuscular activity via ultrasonic waves, laying the foundation for a small number of studies, investigating the modulation of neural tissue more than 30 years later showing neuromodulation effects in different animals (Young and Henneman, 1961; Foster and Wiederhold, 1978), and finally humans (Gavrilov et al., 1976). However, these early studies focused mainly (but not exclusively, see F. J. Fry et al., 1958) on thermal effects following high-intensity ultrasound, which produces effects through destruction of tissue (ablation; W. J. Fry, 1956). Similar protocols are still in place today as ultrasound-induced thermal ablation of tumors is a growing neurosurgical subject due to its non-invasiveness and high spatial specificity (e.g., E. Martin et al., 2009).

Nonetheless, as such heat-related protocols are not suited to provide focal, reversible, and temporally specific effects, ultrasonic neuromodulation needs to make use of other ways to affect neural tissue apart from the heat. In the 1990s and early 2000s several studies reported interference with electric currents within *in vitro* brain tissue, showing for the first time, that neurons react to the physical distortion imposed by the sinusoidal traveling waves in a way that reflects common neuronal responses instead of heat-related

disruption of such (Mihran et al., 1990; Rinaldi et al., 1991; Bachtold et al., 1998; Tsui et al., 2005; Tyler et al., 2008; Colucci et al., 2009). Since then, numerous studies further developed this new method to the point of safe *in vivo* application in animals and finally to use it as a therapeutic tool in humans (Reznik et al., 2020; J. L. Sanguinetti et al., 2020 also see Fini and Tyler, 2017 for a review). Figure 10 illustrates this method's rising popularity.

After a pilot study by Stuart Hameroff et al. (2013), who used ultrasonic neuromodulation in the treatment of chronic pain patients, further applications quickly developed, which were initially mainly pilot studies in the field of subclinical depression published in the form of poster contributions (e.g., J. L. Sanguinetti et al., 2013; Reznik, Sanguinetti, et al., 2017; J. Sanguinetti and Allen, 2017). At the same time, a growing community developed to test the boundaries of the new method by addressing deeper target regions (e.g., Legon et al., 2018).

Following these results, the overall consensus was that ultrasound appears to be suitable for safe, reversible, and focal application in humans (e.g., J. K. Mueller et al., 2016; Pasquinelli et al., 2019; Legon et al., 2020a). However, to further diminish the risk for such adverse events, in the current thesis, a conservative set of parameters was chosen that would in general qualify to convey effects but do so with the minimal amount of intensity (risk). As a result, findings provided within this manuscript may be best interpreted as indications for the overall applicability and general potential of the method instead of a reliable estimate of effect sizes. Figure 11 shows the parameters presented in Table 4 in context of a current computational model to estimate litFUS effects. It shows that the parameters chosen are positioned at the lower limit to produce inhibitory (but also *any*) effects.

9.1 litFUS Mode of Action

The currently most widely accepted mechanism of action regarding litFUS is the model underlying Figure 11: After several in vitro studies on the influence of ultrasound on electrical currents in neurons, various membrane-stem mechanosensitive receptors that undergo conformational changes due to distortions of the double lipid membrane (in which

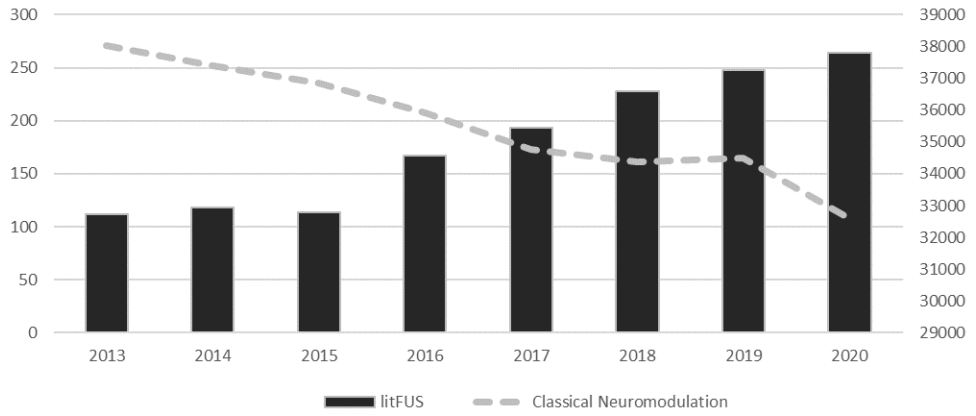

Figure 10: Illustration of publication numbers according to *pubmed* regarding litFUS and other neuromodulation methods. The left y-axis corresponds tolitFUS publications, while the right depicts classical neuromodulation publication numbers. Search query: '(transcranial ultrasound neurostimulation) OR (transcranial ultrasound neuromodulation)) OR (focused ultrasound neuromodulation) OR (low intensity focused ultrasound)' vs. '(((neuromodulation) OR (neurostimulation)) OR (tms) OR (tdcs)'

they are localized) were found. These changes then alter the in- and outflux of ions in neurons.

These receptor groups include *two-pore-domain-potassium-channels* (TREK; especially *TREK-1*, *TREK-2* and *TRAAK*; Kubanek et al., 2016), voltage-gated Na^+ and Ca^+ channels (Tyler et al., 2008) but also the *Piezo* channel family (*Piezo1* and *Piezo2*; Prieto et al., 2018; Qiu et al., 2019), and glia-stem *transient receptor potential ankyrin 1* channels (Oh et al., 2019; Kamimura et al., 2020). Interestingly, especially TREK receptors have also been reported to simultaneously act as a target for the antidepressants (e.g., J. A. Gordon and Hen, 2006; Mazella et al., 2010; Ramaker and Dulawa, 2017). Nonetheless, other mechanisms are also conceivable, as Tyler (2012) describes in his review:

Tyler mentions several other mechanosensitive cell compartments that could convert physical sound waves into a change in the firing propensity of neurons, such as the plasma-membrane, microtubules, neurofilaments, or cell adhesion molecules. Nevertheless, most findings seem to point to the influence of membrane-stem receptors that respond to ultrasound parameters depending on their biochemical composition (Plaksin et al., 2016). Accordingly, ultrasound waves of certain properties may only address certain receptor groups or also certain neurons (which, due to their specific properties, such as

their size, are more or less sensitive to distortions of the cell membrane) and thus lead to either inhibition or excitation, depending on the ion permeability.

One model that describes this mechanism but is so far purely theoretical/mathematical is the *neuronal intramembrane cavitation excitation* (NICE) model, which describes how net inhibition or excitation arises as a function of duty cycle and acoustic intensity (Plaksin et al., 2014; Plaksin et al., 2016). It assumes that in certain parameter constellations, mainly T-type calcium channels are activated, which lead to net inhibition in cell ensembles by increasing activity in low-threshold spiking interneurons. These T-type calcium channels are also instrumental in the production of alpha rhythms (8-12Hz) in the cortex-derived EEG, as they contribute significantly to the synchronization of larger cell areas in the 10Hz range (see Bazanova and Vernon, 2014). This is due to the property of these receptors to have such a refractory period that an inherent 10Hz firing rate is generated. Since EEG alpha activity is consensually associated primarily with cortical inactivity, one would expect an increase in alpha activity in response to inhibitory ultrasound. To my knowledge, this has not yet been demonstrated (see J. Mueller et al., 2014 for EEG based analyses of effect). The estimated effects by the NICE model are shown in Figure 11[17]

10 Reconsolidation Interference

In light of the shortcomings of extinction based treatment approaches in affective disorders, it remained elusive why people were to the best of their efforts not able to forget memories that shaped their vulnerabilities for depression, anxiety, and PTSD symptoms while on the other hand, it has been common sense that phenomena exist in which memories are seemingly lost forever and possibly even modified by external intervention. One example for this would be that witnesses before court sometimes replaced details of their original memory with suggestions by others (e.g., Bartlett and Remembering, 1932; Loftus, 1979). This effect was later shown to be modifiable by having witnesses recall the incident before adding misinformation externally to the narrative (Chan et al., 2009; Chan et al.,

[17]The original image can be reviewed in Figure 5 of the paper by Plaksin et al., 2016 (DOI: 10.1523/ENEURO.0136-15.2016). The paper was published under license 4.0 international (CC BY 4.0)

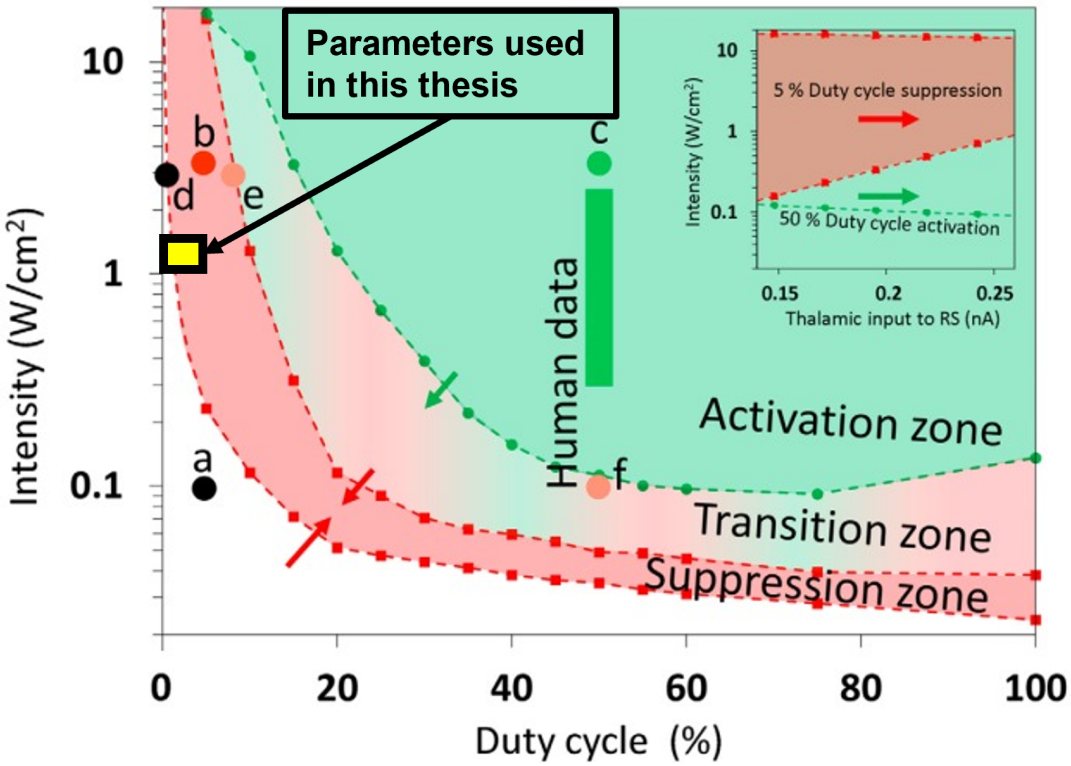

Figure 11: Illustration of Predicted litFUS Effects According to the NICE Model (Plaksin et al. 2016). Parameters used in this thesis are indicated on the left-hand side, in the yellow box. This location indicates the parameters to build the lower boundary of necessarily needed intensity and duty cycle to induce neuromodulation effects. These are predicted to be inhibitory. The yellow box and the corresponding text and arrow are modifications to the original image provided under license CC BY 4.0 by the original authors of the study Plaksin et al., 2016©.

2012; Chan et al., 2017). In line with the results presented above arguing that in earlier life phases extinction learning may change original memory traces, this suggestibility and the subsequent mixing of original and newly added memory contents seems inflated in children (e.g., Doris, 1991). Furthermore, forms of forgetting have been reported throughout the complete history of modern medicine following certain head injuries or neurological interventions like electro-convulsive shocks (ECS) or deep body cooling (see Riccio et al., 2006).

In sum, these lines of evidence point towards existing mechanisms driving actual modification of original memory traces within the brain instead of inhibitory new learning processes (as seen in classical extinction learning). However, not all of these findings may point towards similar processes: Over 120 years ago Müller and Pilzecker (1900) discovered that newly learned information is susceptible to interference from even more

novel information and to be forgotten due to brain-related injuries (Ribot, 1881). Building on this, extensive work in the field of memory formation, consolidation, and retrieval has been performed, leading to the idea that newly formed memories can still easily be distorted, while consolidated long-term memory becomes more and more immune to erasure or modification to the point of life-long stability. Thus, modifying an already consolidated memory trace is a much more difficult task than imposing retrograde amnesia for newly acquired information. Unfortunately, especially the modification of consolidated memory traces is the more clinically relevant task, since patients often wait for months or years before undergoing therapy.

To understand possible mechanisms to interfere with consolidated memory traces, in the following, Bliss and Lømo's work building on Goddard's observations (Bliss and Collingridge, 1993; Lømo, 2003) need to be followed up by more detailed and recent findings:

10.1 Molecular, Cellular and Systemic Foundations of Memory Consolidation

The basis for memory formation is LTP, which describes long-lasting changes in synaptic strength following appropriate (usually high frequency) stimulation of a presynaptic neuron (see Section 3.2). The intracellular cascade underlying early stages of LTP (eLTP) starts with glutamate binding to postsynaptic AMPA receptors, which leads to subsequent cell depolarization that then induces current-dependent NMDA receptor conformation changes leading to acute calcium influx and several calcium-dependent intracellular processes including several modifications of membrane stem (AMPA) receptors and cytoplasmatic kinases. As a result, the cell will enter a state of prolonged, adjusted excitability thereby temporarily strengthening synapses for minutes. Late LTP (lLTP) on the other hand relies on *de novo* protein synthesis, which requires enhanced gene transcription mostly dependent on the CREB transcription factor, discovered by the Nobel prize awardee Eric Kandel (e.g., Kandel, 2012). Resulting from this increase in gene transcription and subsequent synthesis of proteins (e.g., AMPA receptors), synapses can

be structurally enhanced for unlimited amounts of time, theoretically (see Axmacher and Rasch, 2017 for a comprehensive summary of studies).

These processes are usually synapse-specific, even though several phenomena point towards exceptions from this rule which resulted in the 'synaptic tagging and capture hypothesis' stating that eLTP induced changes in synapse activity can later be 'captured' by lLTP mechanisms even if the situation that led to said lLTP was not directed to the same synapse but another one in the same cell. In this case, lLTP related morphological synapse refinement may not only involve the synapse conveying the signal but also other synapses that have been 'tagged' afore by other stimulation that at least qualified for eLTP. Wang et al. (2010) translated these findings to 'behavioral tagging', which describes the effect of increased memory performance for weakly learned information if these are followed by stronger learning processes afterward. However, this effect is only present if the latter learning process qualifies for lLTP-related de novo protein synthesis and if it takes place in the same neurons as the weak learning beforehand did (Axmacher and Rasch, 2017).

Interestingly, this contradicts the above-mentioned findings indicating interference of two learning processes in close proximity, resulting in significant modification or erasure of the firstly learned memory. However, further evidence alludes to the idea that first-memory retrograde strengthening may take place if the first memory was weak (eLTP-driven) and the second one is strong (lLTP-driven), while retrograde interference takes place when both memories are equally strong (lLTP-driven; Moncada et al., 2015).

In addition to these molecular and cellular parts within the complex framework behind memory formation, consolidation, and retrieval, information storage also undergoes relocation within the brain. Notably, at first, memories are mostly depending on the hippocampus before this reliance transitions to (neo)cortical areas over time; a process called *systems consolidation* (Scoville and Milner, 1957; Squire et al., 2015; Zola-Morgan et al., 1994). However, memories are not moved from hippocampal regions to the widespread neocortex. Rather, recent evidence points towards a *multiple engram model* of information storage that leads to a detail-favored hippocampal and fuzzy-schematic represented cortical representation of newly learned information. The hippocampus will

then over time proceed to establish connections between the widespread neocortical 'array' (mostly during slow-wave sleep or resting phases), thereby strengthening these memory traces while losing its own more and more over time. Again, this process seems to take place according to the tagging and capture hypothesis as cortical engrams are initially AMPA and NMDA receptor dependently tagged and then rewritten progressively by hippocampus driven replay (reactivation of network activity, reflecting a piece of information) and synaptic scaling (modification of synaptic weights to reduce the signal to noise ratio; Lesburguères et al., 2011; Tononi and Cirelli, 2006; Diekelmann and Born, 2010; Lewis and Durrant, 2011; Peyrache et al., 2009; Mednick et al., 2011). This process is usually thought to successively take place for weeks or months before memory becomes mostly independent from the hippocampus. However, according to several studies, this time may be drastically reduced to 24-48 hours if the new information can be incorporated into existing schema (Tse et al., 2007; van Kesteren, Fernández, et al., 2010; van Kesteren, Rijpkema, et al., 2010; van Kesteren et al., 2012; Wagner et al., 2015; Bethus et al., 2010).

Several theories regarding the exact procession of this systems consolidation exist. However, one of the most important findings that lead to reformulation and extensive discussions of these theories and the emergence of new models was the fact, that cortically stored memories differed qualitatively from hippocampus-dependent ones (Nadel and Moscovitch, 1997; Fujii et al., 2000; Corkin, 2002; Rosenbaum et al., 2000; Rosenbaum et al., 2005). Compared to hippocampus-related memory retrieval, information stored in cortical areas seemed to lack perceptual, temporal as well as contextual details (Axmacher and Rasch, 2017). Overall, they are described as more 'semantic' than 'episodic'. A theory able to explain this finding is the *Multiple Trace Theory*. According to this idea, cortical memory traces mostly represent semantic 'schemas' that are integrated into existing 'schematic' networks of information. However, vivid, detail-rich context- and perception-related parts of a memory seem to remain relying on hippocampus functioning, which contradicts the standard model of systems consolidation. Finally, a view combining both theories (the *Trace Transformation Theory*; TTT) states that the cortical representation of the memory remains as a gist-like schematic knowledge, not depending on the hippocampus but that the cortex will consult the hippocampus to regain detailed and

perceptual information related to the retrieved information, regardless of its age (Moscovitch, 2007, Winocur and Moscovitch, 2011; for a comprehensive review see Axmacher and Rasch, 2017).

In line with this, older memories seem to become more cortical dependent, and generalized/fuzzy, even though detailed context information may still be present in the hippocampus. According to Winocur et al. (2009) putting a rat back into the conditioning chamber (reactivating the contextual information of a memory) led to labilization of this already systems-consolidated memory, making it susceptible to modification or erasure. It also brought back the hippocampus-dependency of the originally conditioned fear memory as lesions to the hippocampus following reactivation alleviated fear response (regardless of contexts the rat was tested in). Nonetheless, these lesions did not disrupt other memories that were not reactivated afore. As a result, one may argue that 1) the context of the conditioning procedure was not lost, 2) brief reactivation of a memory by information that is thought to be hippocampus-dependent makes the memory susceptible to disruption and 3) that non reactivated memories remain cortex-dependent which immunized them from hippocampus-directed interference. This would be well in line with the TTT as it predicts the hippocampus-based and cortex-based storage to coexist and cross-talk depending on the information needed in a given situation (also see Einarsson et al., 2015 for further evidence for this idea).

In sum, these results highlight that memories form and consolidate in a widespread array all around the brain but that these regions represent distinct qualities of the information. As a result, even though it may superficially look like memories are processed in different modules that become independent over time, to ensure full memory retrieval (including semantic and episodic information) both cortical and hippocampal regions refer back to each other. In conclusion, memories that underlie psychiatric disorders in the way of stress-related stimulus-stimulus or stimulus-outcome experiences, which may evolve into stable expectations and ultimately guide goal-directed behavior, cannot easily be changed. This is the case since a) well established cortical memories lose their specificity over time, generalizing to several contexts and stimuli (e.g., Xu and Südhof, 2013; Schlichting and Preston, 2015), a phenomenon widely discussed in several affective

disorders (e.g., Kuriyama et al., 2010; Dymond et al., 2015), b) information that fits the existing schema will be incorporated into these cortical memory traces more easily and lastingly and c) even though the cortical memory generalizes, hippocampus-dependent detailed context information may also still be available leading to increased risks for context-driven reinstatement (e.g., a person who was able to change their self-concept during therapy may experience a reinstatement of the pre-treatment self-concept that was significantly molded by their ex-partner by running into him/her on the street or driving by his/her home).

Interestingly, however, according to the aforementioned results, the latter property of memory storage may also help to establish novel therapy methods by using this susceptibility to reactivation by minor cues related to the original memory formation context in order to make an already cell- and systems-consolidated information labile, hence susceptible to lasting disruption. Promising results by Debiec and LeDeoux (2002) also indicate that this disruption of hippocampus-dependent labile memories after reinstatement with the protein synthesis inhibitor anisomycin does not only disrupt the cellular form of memory restabilization (reconsolidation) but also systems reconsolidation, which is also protein synthesis-dependent. This is also well in line with other findings concerning the hippocampus orchestrated replay of memories during slow-wave-sleep, which may use similar mechanisms to enhance memories by frequent reactivation, inducing further (re)consolidation (Diekelmann et al., 2011; see Atherton et al., 2015 for a review). Further evidence for the equivalence of these mechanisms comes from studies manipulating memories during sleep (see Axmacher and Rasch, 2017 for a review of studies). Nonetheless, memory may not always undergo (re)consolidation in case of reactivation/replay as this would lead to extremely labile memory storage in general. Unfortunately, exact boundary conditions are still not fully understood (see Section 10.2).

Another complicating factor influencing memory formation, consolidation, reconsolidation, and retrieval is stress; a reaction accompanying conditioning within affective disorders. Stress is usually conveyed by activation of the HPA axis leading to the release of glucocorticoids (GC). Since GCs are lipophilic, they can pass through the blood-brain barrier easily (McEwen et al., 1968). In the brain, GCs mainly bind to two receptor

types: the highly affinitive Mineralocorticoid (MR) which are found in limbic areas, and the lower affinitive glucocorticoid (GR) receptors (de Kloet et al., 1998; Joëls et al., 2006), which are present throughout the whole brain. Both receptor types are furthermore co-localized in the hippocampus and the prefrontal cortex (Joëls and Baram, 2009; Reul and de Kloet, 1985). Summarizing studies on the effect of GCs on different phases of memory formation Meir-Drexler and Wolf (Meir Drexler and Wolf, 2017a) argue that stress shortly before or shortly after encoding enhances memory while stress before retrieval decreases performance. Also, mixed results were present regarding reconsolidation.

10.2 Boundary Conditions of Reconsolidation

Reconsolidation describes the process of restabilization after transient lability of memories that have at least once before been consolidated. Thus, reconsolidation itself is not a therapeutic intervention but its presence indicates a (preceding) time window in which interventions may have especially potent and long-lasting effects as it may be able to directly incorporate new information into existing memory traces before the reconsolidation process 'seals' the memory once again. By doing so, issues of new learning instead of unlearning-based therapies (which arguably could refer to all existing conversation-based methods including exposition) like reinstatement or spontaneous recovery of symptoms as well as accelerated new learning may be diminished.

A large number of studies was able to show that in order to open this reconsolidation window (RW; the time of memory instability before reconsolidation restabilizes it) a brief memory reactivation needs to take place (e.g., Misanin et al., 1968; A. M. Schneider and Sherman, 1968; W. C. Gordon, 1977a; W. C. Gordon, 1977b; Nader et al., 2000; Litvin and Anokhin, 2000; Milekic and Alberini, 2002; M. P. Walker et al., 2003; Tronson et al., 2006). However, this reactivation needs to be of a certain strength since too brief or too intensive reactivation will not qualify to open the RW. Furthermore, among the reconsolidation based scientific community, it has been widely accepted that in addition to the reactivation, a prediction error (PE, a mismatch of expectation and outcome) needs to take place in order to render a memory unstable (e.g., Pedreira et al., 2004; Díaz-Mataix et al., 2013; Reichelt et al., 2013; Sevenster et al., 2013; Sevenster et al., 2014; Exton-

McGuinness et al., 2015; Sinclair and Barense, 2018; Cahill et al., 2019; Sinclair and Barense, 2019). Based on the nature of expectation-mismatch, synaptic modification may take place in a number of ways, including de novo protein synthesis (Nader et al., 2000; Milekic and Alberini, 2002; Suzuki et al., 2004), ubiquitin-proteasome guided degradation system (S.-H. Lee et al., 2008; Kaang et al., 2009) and autophagy (Ecker, 2015; Shehata et al., 2018; Santiago and Tort, 2020).

Unfortunately, to this day, it is still unclear how reactivation and mismatch induction need to be structured quantitatively and qualitatively. One reason for this is that the boundary conditions of these parameters are subject to intraindividual differences like age, strength, modality, and affectivity of a memory and to interindividual differences as well, as one could argue that personality differences will influence how much expectation-outcome mismatch is needed in order to ensure a certain neural signal strength.

Due to the lack of conclusive knowledge about the optimal way to address a memory in real-life situations to render it labile, many studies either report null findings or the need for several experimental groups that differed slightly in their respective reactivation and mismatch induction in order to find effects in one of these groups. Following this, discussions emerged tackling the idea and concept of reconsolidation, proposing other possible mechanisms like state-dependent learning processes (Millin et al., 2001; Gisquet-Verrier et al., 2015), new learning (Eisenhardt and Menzel, 2007), facilitated extinction (Myers and Davis, 2002), retrieval impairment (Lattal and Abel, 2004) or uninhibited memory extinction (Trent et al., 2015).

In their review of current literature on the topic of reconsolidation and its translation to clinical settings, Jonathan Lee, Karim Nader, and Daniela Schiller, three influential scientists within the field, conclude that three major outstanding questions need to be answered to enhance replicability and applicability of the reconsolidation based approach (J. L. C. Lee et al., 2017, p. 14 of the author manuscript):

'How can we assess whether memory has been destabilized? Behavioral triggers, especially those carrying prediction error, may return memory to a labile state, but to

reliably achieve destabilization, specific neural markers should be demarcated. (...) Is there an optimal process of reconsolidation updating? Given the individual variability in the critical boundary parameters, the most effective updating approach should probably be tailored to the individual.(...) 'How can clinicians exploit reconsolidation mechanisms? Novel treatment protocols could be structured to include behavioral triggers, Behavioral and/or pharmacological destabilization and updating, followed by long-term recovery assays.'

10.3 Neural Mechanisms of Cognitive Model Formation and Updating

The previous sections alluded to the neural and neuronal foundation of temporally stable interindividual differences and their intrainindividual development by highlighting the role of learning within the formation of long-lasting behavior, cognition, and affect. These findings thus add neurobilogical underpinnings to the issues discussed in Part I of this thesis: Conditioning events (e.g., such that take place within the learned helplessness paradigm) may in the long-term lead to systems-consolidated multiple memory traces that are widely spread throughout the whole brain and may therefore not be easily modified. Furthermore, information that fit the abstract schema of this memory may be especially easily incorporated into the network, while therapy-related information may not. According to the results concerning boundary conditions in reconsolidation and RW induction, this view is substantiated further since prediction errors could be shown to trigger new learning instead of 'unlearning' if the information was too novel. Hence, one may argue that therapy-related information may be especially prone to trigger inhibitory new learning rather than modification of existing traces as these are directed towards the implementation of new (self)concepts.

As a result, once learned helplessness/hopelessness may reemerge at some point after therapy, as the original memory trace may still linger in (at least in part) within the brain. By doing so, not the depressive episode itself but the vulnerability factor for it (e.g., working in an overstraining job) may lead to long-lasting sensitization towards

the onset and recurrence of affective symptoms. This would be in line with the idea of kindling/sensitization and the results by Anderson et al. (2016) as it is plausible to assume that a greater number of depressive episodes may somewhat strengthen the depression-related memory trace against competing traces, which would decrease therapy-efficacy, while the overall vulnerability within the individual still reflects an interindividual trait.

Thus, to increase the longevity of therapy effects against this background, again the best approach may reside in primary prevention in childhood (early) years or in targeting the modification of consolidated vulnerability factors within the individual. Especially relevant factors in this regard are represented by the cognition and behavior correlated to neuroticism, BIS, and FFFS as both, findings in the field of personality- and clinical psychology allude to (see Section 4.2 and 2.1)

Building on these remarks the need for learning and especially memory-updating process is highlighted. In this regard, one may argue that the PE, which is needed to induce the RW, builds upon stochastic information: The prediction error regarding the occurrence of a certain outcome will be small if the probability for a given outcome is not anticipated to be high. Hence, prediction errors depend on the estimated probability of an outcome. However, since this estimation is no natural constant but a subjective evaluation, it should rely on neural processes analyzing stochastic patterns of previously made experiences. In this context, due to its ability to evaluate action-outcome dyds, especially the ACC has been discussed above (see Section 5.1.1). Interestingly, however, many other neural substrates have been shown to be involved in stochastic information processing and subsequent model building as well:

Alexandre Filipowicz and his colleagues (2016) argue that in general, an asymmetrically higher right than left hemispheric sensitivity to stochastic information exists, which involves a highly complex interaction of a widespread network. In their review, in 2016, they argue that structures contributing to the emergence of '*world models*' include the right anterior insula as well as a right hemispheric neocortical network comprising the inferior parietal lobe and the inferior frontal gyrus (IFG) and finally anterior and posterior compartments of the ACC.

According to their review, parietal regions may mostly be involved in noticing

surprising events by shifting attention to such. Evidence for this notion comes from oddball studies and clinical studies in patients suffering from *change blindness*. Also in line with this view is extensive work on the event ERP component *P300*, a large positively poled event correlated to attention. However, this effect seems to take place independently from model-updating, indicating a general sensitivity to attention eliciting stimuli and events, which may contribute to subsequent learning. This, as stated above will mostly take place in ACC-related regions as these comprise neurons that are particularly suited to assess contingency of sensory and/or internal (such as somatic or emotional) inputs.

Filipowicz (2016) describes the ACC as the driver for hypothesis formation and updating. Finally, they highlight the role of the anterior insular cortex, which is highly connected to both, dACC and prefrontal neurons. It is most active in situations, that indicate current models to be false or ambiguous. Taken together, to update a model based on new information, following these remarks, an attention-relying and error-driven network consisting of the dACC, and the anterior insula is proposed that indicates the need for updating.

Interestingly, then, only in the moment of conscious model change, bilateral inferior frontal regions join this network (Stöttinger et al., 2015; Stöttinger et al., 2018), while the insula and ACC were most active when the need for updating was signaled (*before* the updating took place). Taken together, this implies that a (more right hemisphere heavy) parietal attention network scans for novel or surprising events, which will in combination with the ACC and insula-driven signaling for the need of expectation updating lead to inferior frontal gyrus (IFG) involvement which is connected to internal model modification.

In principle, this indicates either that at the time of modification of preexisting mental models an IFG orchestrated process is taking place in other areas or that the IFG itself is the site of updating. Either way, based on these results, the dACC, the IFG, and the anterior insula will be defined as regions of interest for studying and influencing model updating. Since these mental models are associated with specific expectations, they may represent the foundation of the prediction error. Overall, this suggests that the same processes discussed in this literature also occur for updating in the aftermath of successful

memory labilization. In line with this, first studies have already been published showing that the intervention in the IFG or other lPFC associated areas influence and indicate reconsolidation (Stramaccia et al., 2017; Borgomaneri et al., 2020; Javadi and Cheng, 2013).

Even though reconsolidation interference research provides promising results in several contexts, its history has always been connected to the failure to replicate (e.g., Hardwicke et al., 2016), issues to translate basic scientific results to clinical settings (e.g., Ecker, 2018), and vast discussion on its validity (for a review and discussion on alternative interpretations of the reconsolidation process see J. L. C. Lee et al., 2017).

All of these issues are connected to the problem of reliability of effects. Whether a memory will undergo labilization or not is theoretically predictable (Sevenster et al., 2014; Elsey and Kindt, 2017) but not easily controllable. This is further complicated as reconsolidation induction may need different boundary conditions depending on stable traits, as these may translate to differences in cortical but also affective responsiveness (Soeter and Kindt, 2013).

Furthermore, establishing usable therapeutic protocols under these circumstances is not an easy task since many influencing factors, such as memory age or stability cannot be controlled in naturalistic, therapeutic settings as opposed to laboratory studies. Unfortunately, this is also true for the reactivation that is needed to induce labilization. Nonetheless, several studies were able to show beneficial results and successful protocols in a variety of affective disorders except for depression.

10.4 Reconsolidation-Based Protocols in Other Disorders Than Depression

So far, over 50 studies using some sort of reconsolidation interruption based protocol in clinical trials of a variety of psychiatric disorders have been published, including mostly fear and anxiety related impairments (Schiller et al., 2010; Agren et al., 2012; Soeter and Kindt, 2012; Marks and Zoellner, 2014; Kindt et al., 2014; Steinfurth et al., 2014; Wood et al., 2015; Steenen et al., 2015; Maples-Keller et al., 2017; Meir Drexler and Wolf, 2017b;

Elsey et al., 2020), PTSD (Brunet et al., 2018; R. Gray et al., 2019; Roullet et al., 2021) as well as drug related disorders (Zhao et al., 2009; Zhao et al., 2011; Saladin et al., 2013; Das et al., 2015; Pachas et al., 2015; Jobes et al., 2015; Lonergan et al., 2016; Das et al., 2018; Das et al., 2019; J. E. Becker et al., 2020; Brunet et al., 2021).

In addition, one study targeted depression-related suicidality with what the authors claim is a reconsolidation-focused protocol (Högberg and Hällström, 2018). However, at close inspection, the study falls significantly short in employing sufficient methodological prerequisites to investigate this phenomenon. That is, the commonly used protocol encompasses at least 3 groups that follow from the two prerequisites of reactivation (plus prediction error) and some sort of intervention. Most studies stated above employ some sort of chemical agent that qualifies to interrupt the process of reconsolidation after memory labilization. Hence, one group usually includes both, the reactivation, PE, and intervention, another group receives the intervention without any preceding reactivation and the last group receives a reactivation without any subsequent medication. The same groups would also be feasible for non-invasive rather than medicinal interventions like extinction training or transcranial neuromodulation. By designing studies this way, one can infer differences between the treatment as usual approach (TAU), which would in this case resemble the extinction training without preceding reactivation and the reconsolidation approach. The third group then adds to this by providing evidence for the unique potency of reactivation and intervention as a combination in contrast to sole reactivation.

11 Neuromodulation of Personality and Reconsolidation

Now that the idea of reconsolidation modification has been introduced as a method to lastingly alter neural underpinnings of habitual behavior (e.g., withdrawal behavior), the following paragraphs move on to discuss another way to modify such:

Neurostimulation of the left DLPFC leads to decreases in neuroticism and depression (Spronk et al., 2008; Berlim et al., 2013). However, Berlim and colleagues (2013) report no significant mediation of antidepressant effects by changes in neuroticism, high-

lighting that the existing literature, which repeatedly reports a significant correlation between antidepressant responses to neurostimulation (Spronk et al., 2008; Berlim et al., 2013), psychotherapy (Roberts et al., 2017) and medication (T. Z. Tang et al., 2009 Quilty et al., 2010; Roberts et al., 2017) to be accompanied by neuroticism decreases, may in fact describe changes in personality traits due to depression alleviation rather than depression decreases due to trait changes. Another possibility would be that both neuroticism and depression symptoms share a common neurobiological basis.

On this note, again, neuroticism, BIS, and depression vulnerability have been correlated to interhemispheric PFC asymmetry. However, while FA scores are not responsive to antidepressant therapy, both, depression and neuroticism are. As a result, it is plausible to assume that both latent trait-vulnerability factors and depression share a common neural foundation in the stable frontal EEG alpha asymmetry but may not otherwise be related. Unfortunately, this view would be inconsistent with previous ideas and findings highlighting the influence and importance of neuroticism and other stable traits (e.g., Quilty, de Fruyt, et al., 2008).

In turn, a synthesis of these findings might be that the mediating influence of neuroticism on change in depressive symptoms varies by treatment approach. Thus, one could hypothesize that systemic antidepressants (the same is true for psychotherapy), which do not exert their mechanism at any particular site of effect, trigger a different mechanism than does locally applied neuromodulation. If this is the case, this might indicate that the augmentation of established procedures with neuromodulation methods could be particularly effective, since both effects should complement each other through their different mechanisms of action. Bormann et al. (2021, p. 206) summarize:

'It remains to be explored whether adaptive stimulation protocols may offer a solution for this symptom recrudescence or whether this aspect of relapse could be effectively addressed by coupling invasive neuromodulation with intensive psychotherapy in which patients learn new coping mechanisms during a therapeutic window where disabling symptoms are transiently improved.'

However, not only personality but also reconsolidation can be modified via transcranial neuromodulation techniques. Building on findings regarding the right (but not the left) lPFC as a critical hub for memory encoding, retrieval (Sandrini et al., 2003; Manenti et al., 2012) and reconsolidation itself (Diekelmann et al., 2011; Schwabe et al., 2014), several neuromodulation studies, using TMS, tDCS or ECS report positive effects of modulation following memory retrieval (Sandrini et al., 2013; Kroes et al., 2014; Sandrini et al., 2015; Sandrini et al., 2018; Crossman et al., 2019 Borgomaneri et al., 2020, also see Stehberg et al., 2009). The results from these studies can be summarized as follows:

Stimulation/modulation of the right lPFC interferes with the reconsolidation process after the target memory was reactivated (reminded of) beforehand. Depending on the procedure following from this, either new memories could be incorporated more effectively (Borgomaneri et al., 2020) or initial memories could be strengthened significantly (which is also deemed reconsolidation; Sandrini et al., 2013; Sandrini et al., 2018).

As a result, neuromodulation (possibly including litFUS neuromodulation in the future) is already an established way to interfere with existing memories. However, current protocols employing this kind of interference usually use this externally administered influence on neural activity by enhancing learning after labilization. Even though these findings are remarkable in their potential use within the reconsolidation interference procedure, to this date, (to my knowledge) no neuromodulation study has been carried out to induce the labialization itself, which may be the bigger issue (see Section 10.2).

12 Aims of This Dissertation

This thesis deals with the problem of sustainability of therapeutic methods for prevention and curative intervention in affective disorders, with a focus on depression.

Depression is a disease that is characterized by many recurrences as well as chronic courses. Unfortunately, it retains this characteristic even after successful therapeutic interventions such as antidepressant medication, neuromodulation, or psychotherapy.

One reason for this may lie in temporally stable vulnerability factors, such as personality traits that dictate the course of the disease in the long-term, possibly regaining control over an organism's experience and behavior with increasing temporal distance to therapeutic interventions. While some of the sections highlight the importance of vulnerabilities that already existed at the beginning of the clinical course, others argue that depressive episodes themselves may leave 'scars' behind, which will influence individuals to the point of an increased risk for further episodes to come. A synthesize of these contradictory findings was introduced above: The evidence presented afore implies that 'scarring' in the form of LTP- and systems-consolidation driven learning through negative life events, prolonged stress or depression itself, will most likely take place before the third episode of depression takes place. Hence, intraindividual developments may precede and induce stable vulnerabilities. Furthermore, the following list provides a brief overview over the additional main arguments of this thesis, before the main research questions are summarized:

- Depression is highly recurrent and reflects a growing challenge for individuals and society as a whole
- This volatile, yet recurrent course may be shaped by the influence of stable (therapy-resistant) vulnerability factors that qualify to reinstate depressive-symptoms
- Due to these properties, long-term prediction of depressive symptoms may profit from measures regarding stable vulnerability factors rather than acute symptom severity
- Stable traits such as personality but also chronic comorbid diseases fulfill the prerequisites to potentially pose as temporally stable vulnerability factors.
- The most impactful personality traits to predict depressive courses share common neural substrates, including frontal asymmetric cortical activity and ACC reactivity
- On a neuronal level, such traits may be represented by complex stimulus-(re)action pairs that have been implemented in the brain via various memory traces

- These memory traces may be responsible for the therapy-resistance of stable traits
- Therapy effect longevity may thus be increased via methods that allow direct changes of such widespread traces
- Reconsolidation interference and neuromodulation may qualify to do so

Against this background, five studies are described below that address different aspects of the influence and influenceability of stable traits and chronic disorders as vulnerability factors. These can be summarized in three research questions:

Which stable vulnerability factors predict long-term courses of depression in the context of chronic somatic disorders? As discussed above, complex and possibly circular relationships between comorbid symptoms and depression scores exist. In this thesis, two exemplary somatic illnesses are used as a context to investigate these relationships in longitudinal prediction studies. First, the course of depressive symptoms in CF patients is analyzed among both, (n=103) patients and their (n=46) caretakers (mostly their mothers). In this sample, further vulnerability factors, extracted from HRQoL measures were used to predict the course of depression, while taking into account previous depression severity in the same model. In conclusion over the course of four years, this study investigates the predictive power of depression for itself, while also evaluating the stability of predictive power by possibly stable risk-factors. According to the remarks made above, depression may not be able to predict itself in the long-term due to its sinusoidal course, whereas stable vulnerability factors should not lose their predictive power. Furthermore, to allude to the possibly recursive nature of the relationship between depressive symptoms and chronic comorbidities, path models were calculated that may qualify to investigate these dependencies within a longitudinal dataset.

Following this, cognitive decline in a (mostly) healthy sample of 330 elderly citizens of the city of Würzburg was used as a (potentially) stable predictor for the course of depression. These data were also utilized to investigate and discuss possible methodological shortcomings in the field of longitudinal prediction research of and by depression. Furthermore, the same path model that was fit in the CF patients, was refit in this sample in order to compare end replicate the findings.

In sum, the longitudinal data acquired from these samples qualified to investigate causal relationships between vulnerability factors and depression by formulating regression analyses (that include the previous depression score as independent variable) based on hypothesis-driven modeling approaches. The results may qualify to add significant evidence for either a more vulnerability-heavy interpretation of both the course of affective disorders themselves and for their possible correlates, such as cognitive or somatic detriments, or for a more affective-episode-focused perspective.

Is litFUS capable of directly influencing endophenotypes of vulnerability factors for depression? In addition to the aforementioned studies, this thesis seeks to investigate the neural underpinnings of person-inherent vulnerability and resilience factors. As described before, extensive work points towards dorsolateral and midfrontal as well as cingulate regions to relay fundamental cognitive, emotional, and motivational functioning possibly underlying a variety of symptoms present in affective disorders. Remarkably, one of these regions, the right lPFC (and the rIFG as one compartment of it), is implicated in different stages of all of the discussed models comprising these regions of interest. In the HRL-ACC, the prefrontal cortex poses as the main actor, carrying out goal-directed, motivated behavior. In regards to the frontal asymmetry research, especially the right DLPFC serves the function of withdrawal-related motivation and negative affectivity. Lastly, the DLPFC and especially the right hemispheric area plays a crucial role in learning and updating as it is part of the working memory and hippocampus-related memory reactivation system. It was further implicated in the preferentially right-hemispheric stochastic processing of information that will in cooperation with ACC signaling serve to monitor changes in probabilities and the related issue of expectation. As a result, the right IFG serves as the key region of interest for a total of four more studies that employed litFUS to carry out an inhibition of the region underlying the F8 electrode position of the 10-20-system (which is supposedly the rIFG).

Following this, in the first study to address this research question, litFUS induced inhibition of the right IFG was used to influence the subjective control perception of 41 participants in a two-day, double-blind, cross-over experiment with a control illusion task. This task was chosen against the background of learned helplessness/hopelessness,

which defines control perception as the fundamental building block of the emergence of depression-like behavior. The results may thus add basic-psychological evidence for mechanisms of effect to the possible antidepressant influence of litFUS neuromodulation at this site of interest. In addition, as the theoretical background behind control perception grounds on the difference of stochastic properties of outcomes given a certain action or non-action this study also adds to the understanding of IFG based stochastic processing of action-outcome dyads. This in turn may also modulate the likability for expectation mismatching, which may induce memory or schema updating, as the reconsolidation related literature suggests expectation-outcome mismatches to drive new learning (in regards to both, overwriting original neural traces and creating a new one).

The second study used the same neuromodulation approach before a learned helplessness task was administered to evaluate its use to facilitate resilience based on the modulation of an endophenotype of vulnerability factors for affective disorders. Even though the neuromodulation itself may lose its effect after a few hours, if litFUS was able to increase resilience, this proof of concept would pave the way for regular neuromodulation-based prophylaxis in high-risk individuals or litFUS augmented psychotherapy protocols respectively. It further enriches the results of the previously described study as somewhat seeks to replicate the control-perception findings in the context of a task with increased ecological validity. Furthermore, if the results were promising since litFUS is generally able to reach deeper structures as well, such protocols would be able to adapt to the direct modulation of other regions of interest like the dACC in the future.

The third study regarding this topic addressed the issue that especially the right hemisphere seems to react sensitively to emotional cues. Since human faces and their expressions are a fundamental cue within social interactions that may pose as ongoing stressors in individuals with stable vulnerabilities in this regard, being able to modulate the initial neural response to such cues would probably benefit prevention and curative intervention significantly. Again, even though litFUS effects may vanish soon after the active modulation phase, a variety of protocols integrating longer-lasting approaches with the method may prove beneficial, if it was clear, what kind of benefit was to be expected. Hence, this study investigated the 41 participants' (the same described in the previous

study) neural and behavioral reactions to emotional facial expressions. Once more, this study used the stochastic processing capabilities of the rIFG to explain part of the effects, leading to two possible mechanisms under investigation: influence of the frontal asymmetry as part of an intervention to alleviate the influence of stable endophenotypes and the influence of neural stochastic processing as a possible way to modulate stable stimulus processing traits. Furthermore, this study followed the same two-day, cross-over, double-blind experimental design as described in the previous paragraph.

Taken together, these studies would be able to provide first, direct evidence for litFUS induced changes in neural oscillation that guide task-specific behavior, cognition, emotion, and motivation. Furthermore, they would be able to provide insights into the variety of rIFG functioning that may modulate such domains via several mechanisms. Two of these (modulation of the frontal asymmetry and stochastic information processing) are in the focus of this thesis. The first mechanism may qualify to lastingly change vulnerability factors by providing additional power to overcome individual hurdles that may lead to vicious cycle manifestation (e.g., avoiding social interactions due to insecurities, which may decrease one's social skills or their retrievability even more). As a result, neuromodulation may help to manifest such changes that intervention-induced modification of personality may become self-perpetuating, a status that is implied to not usually take place (as inferred from recurrence rates).

How may the use of reconsolidation interference be investigated in depression and how can results become more robust? Following the results of the studies presented in previous paragraphs, the modulation of stochastic information processing via litFUS may be able to induce lasting treatment-related effects by adding to the probability for reconsolidation and its interruption. In this regard, some studies have already been able to show that neuromodulation of the right lPFC can interrupt reconsolidation once a memory was rendered labile, which would most likely also be possible via litFUS. However, a remaining issue within reconsolidation protocols is the induction of such lability in the first place. Hence, the experimental designs described before are not only built to investigate direct beneficial effects for the processing of depression-related stimuli and situations but also seek to close this knowledge gap by providing insights

into the capability and direction of modulating the expectation-related computational functioning within the neocortex, possibly leading to future applications to provide the necessary neural status that is needed to support labilization processes.

As a result, the final study presented in this thesis provides a protocol to investigate reconsolidation-based therapy in depression during a well-controlled experimental setting. To my knowledge, no study was published directly investigating depression in this regard. No data is available for this study due to pauses precipitated by the Sars/Cov-2 pandemic. However, the protocol shown below represents the methods and background of this approach. If this study produces promising results, against the background of the previous paragraph, litFUS may be used in future studies to increase the effect size of these or other protocols' findings.

Part III - Manuscripts and Additional Analyses - Analyses of Depression Score Courses

Based on the results of the section on courses of depression and the kindling sensitization hypothesis, the impression is that past depression in particular predicts future depression. However, the study by Anderson et al. (2012), implying a Slater's fallacy in corresponding analyses, suggests that this may also be a misconception and that both past course and current depression scores are more likely to be triggered by stable vulnerability factors. Therefore, the influence of vulnerability factors is used in conjunction with the prior depression measure in a mixed model approach to examine the extent to which incremental explanations are provided. Paper I looks at this in the context of cystic fibrosis, where patients are dealing with stressful experiences relatively consistently, so the interplay of resilience/vulnerability factors and current score may be better revealed. Also, depression should therefore not fluctuate too much in this sample, as stressors are present all the time and vulnerabilities should therefore have an ongoing influence. As an additional analysis, a path model is calculated to test the prediction of depression by vulnerability factors and depression in its full complexity.

Paper II attempts to replicate this model by analyzing a sample of individuals

where enduring stress is triggered by the decline of cognitive abilities. However, since possible masking effects in the specific test scores introduce unreliability into this variable, the paper first devotes itself to a relatively elaborate method of calculating reliable predictors, which are then used again in the additional analyses to test the pathway model.

13 Paper I - Depressive Symptoms in Cystic Fibrosis Patients

The following text represents an author manuscript that was accepted by the Journal of General Hospital Psychiatry (Elsevier) as a letter to the editor. As such, it does not comprise distinct sections. Further, it should be noted that the following text does not represent the published version as it may include some changes in phrasing, layout, grammar, or other details. The appendices are shown in Section 27.1. When citing this text, the following notation should be used: Hornig et al., 2021. Further, it is recommended to review the final published article here: https://doi.org/10.1016/j.genhosppsych.2021.12.010 (last checked on July 4, 2022):

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Title: Depressive symptoms in cystic fibrosis patients and their caretakers are best predicted by their respective sense of belonging

Authors: Isabella Hornig[a12] André Forster[a1] Annette Katscher-Peitz[b] Johannes Hewig[a] Markus Rose[b]

[a]Julius-Maximilians-Universität Würzburg, Marcusstraße 9-11, 97070 Würzburg, Germany

[b]Olgahospital, Klinikum Stuttgart, Kriegsbergstraße 62, Germany

[1]Authors contributed equally

[2]Corresponding author

Manuscript. Cystic fibrosis (CF) is a congenital metabolic disease that leads to a changed composition of glandular secretions due to a genetic defect. As a result, the secretion formed is very viscous resulting in functional disorders of several organs, especially the lungs. Both symptom severity and treatment efficacy are subject to influence of states of depression and anxiety, which are common in patients and caretakers alike (Quittner et al., 2008; Schechter et al., 2021).

In response to this, in 2015, the International Committee on Mental Health in Cystic Fibrosis adopted a Europe-wide guideline for the detection and treatment of mental comorbidity in patients with CF. The guideline foresees a mental health screening (MHS) that once a year collects anxiety symptoms with the Generalized-Anxiety-Disorder-7 (GAD-7) questionnaire and depression symptoms with the Patient Health Questionnaire (PHQ-9) (Quittner et al., 2016).

Since most studies in this field of research are correlative, the current investigation seeks to add longitudinal results of this MHS over the course of 1 year. Furthermore, the additional prognostic value of health related quality of life (HRQoL) measures are investigated by including a HRQoL questionnaire in addition to the PHQ-9 and GAD-7.

The PLC (the German title of this questionnaire translates to Quality of Life with Chronic Disease; Siegrist, J., Broer, M. & Junge, A., 1996) includes the subscales working capacity (WC), positive mood (PM), enjoyment and relaxation ability (EaR), contact ability (CA), sense of belonging (SoB) and negative mood (NM). The items are answered on a five-level Likert scale. In order to keep the positively and negatively connoted items in a ratio that diminishes risk of negative mood induction effects, the NM scale was not part of the present survey.

Scores on the PLC, GAD-7 and PHQ-9 from a total of 149 participants including 103 patients and 46 relatives were collected twice (one year apart). Descriptive metrics of this sample are provided in Table 5. All participants agreed to the publication of their data (ethics committee approval reference: GZEK 2019-10)

The course of depression and anxiety was then analyzed in both caretakers and underage CF patients using a mixed effects regression analysis. We hypothesized that depression and anxiety after one year can be predicted by the HRQoL metrics of the PLC

one year before.

In order to account for the hierarchical structure of the data (participants nested in families or groups (patients vs. caretakers)) a multilevel model (MLM) approach was used. Since it was not clear at the beginning, which nesting perspective of the data was more appropriate, a random intercept model was calculated for a shared intercept per family and another one with differing intercepts between patients and caretakers. Following the data-driven MLM approach, the best fitting model was subsequently used for further model comparisons that progressively added fixed effect variables to the equation. The order of variable inclusion was hypothesis driven. At first, PHQ-9 and GAD-7 were added since depression and anxiety should explain most variance in depression and anxiety one year later. Then, PLC-related measures were included so that they would only be recognized in further analyses if they added predictive value beyond prior of depression and anxiety. Finally, the fixed effect variable group was included. It separates patients from caretakers. No interaction term was allowed since no specific hypothesis was formulated beforehand. The models were fitted via restricted maximum likelihood (REML) estimation and the default optimizer function of the lme4 package (Bates et al., 2007) in R, which is a combination of Nelder-Mead and bobyqa. Metric variables were grand mean centered. Finally, the best fitting model was chosen to further examine fixed effect significance.

The best fitting models were those that included a shared random intercept for the family, indicating shared variance. The corresponding model comparison tables are shown in Supplements 30 and 31 . Subsequent fixed effects analyses of the best fitting model for anxiety scores showed that GAD-7 scores are best predicted by the same scores collected a year before ($t(89.547)=4.161$, $p(\text{holm}) < .001$, $\beta=0.552$). Other than that, no significant contribution of other variables such as depression was found ($t(81.581)<1$).

On the other hand, depression was best predicted by the sense of belonging ($t(83.843)=-2.932$, $p=.004$, $\beta=.035$). Interestingly, with SoB in the equation, depressive symptoms a year ago predicted current depression insignificantly after Bonferroni-Holm adjustment ($t(52.822)=2.178$, $p=.034$, $\beta=.215$). Furthermore, CF patients depicted descriptively higher PHQ-9 scores as compared to their caretakers, which did also not remain

	PHQ	GAD	WC	PM	EaR	SoB	CA
M(t1)	5.34	4.44	2.54	2.44	2.62	3.15	2.63
SD(t1)	4.25	4.05	0.83	0.86	0.86	0.66	0.91
M(t2)	4.92	4.06	2.55	2.55	2.73	2.88	2.79
SD(t2)	4.16	3.55	0.77	0.92	0.83	0.76	0.96

Table 5: Descriptive Statistics of the Final Sample

significant after alpha adjustment. These results indicate that beyond a shared variance within families CF patients may show increased depressive reactions in comparison to their mothers (mothers represent the majority of caretakers in this sample). Nonetheless, both parties may significantly profit by increasing the sense of belonging, which is well in line with evidence of psychotherapy research, which highlights the role of social interactions for the treatment of depression (M. S. Lee et al., 1996).

In summary, this study provides direct longitudinal evidence for the additional value of HRQoL measures in mental health screenings in the context of CF. Especially the sense of belonging depicted significant predictive value for future depressive symptoms.

14 Additional Analyses - Paper I

Based on the findings reported in the previous section, to develop the idea of SoB-driven depression scores further, a path diagram was modeled via *Jamovi's* (2021) modules *medmod* and *jamm*. In the model, three variables are used to predict depression (PHQ-9 scores) at t2. These variables are shown in Figure 12.

From the theoretical considerations in the first part of this dissertation, it appears that SoB, as a vulnerability factor, could be both, an outcome and a driver of depression. Based on this idea, a mediation model was set up in which SoB at t2 can be predicted by SoB at t1 and depression at t1. At the same time, all three variables influence depression at t2.

The results presented in Figure 12 and Table 6 indicate that SoB itself is not influenced by depression, but does influence depression by itself. At the same time, it is noticeable that SoB at t1 predicts SoB at t2 only to a relatively small extent, which

Type	Effect	Estimate	SE	Lower	Upper	β	z	p
Indirect	Depression at t1 → SoB at t2 → Depression at t2	0.038	0.030	-0.020	0.096	0.039	1.276	.202
	SoB at t1 → SoB at t2 → Depression at t2	-0.092	0.046	-0.183	-0.001	-0.077	-1.980	.048
Component	Depression at t1 → SoB at t2	-0.144	0.100	-0.341	0.052	-0.168	-1.442	.149
	SoB at t2 → Depression at t2	-0.261	0.095	-0.448	-0.074	-0.232	-2.742	.006
	SoB at t1 → SoB at t2	0.352	0.123	0.111	0.592	0.333	2.863	.004
Direct	Depression at t1 → Depression at t2	0.369	0.093	0.187	0.551	0.380	3.966	< .001
	SoB at t1 → Depression at t2	-0.276	0.118	-0.507	-0.046	-0.232	-2.348	.019
Total	Depression at t1 → Depression at t2	0.407	0.096	0.218	0.595	0.419	4.229	< .001
	SoB at t1 → Depression at t2	-0.368	0.118	-0.599	-0.137	-0.310	-3.122	.002

Table 6: Model parameters of the regressive mediation model including depression and sense of belonging. SoB= Sense of belonging, Upper/Lower = Limits of the 95% confidence interval. SE= standard error.

speaks for the variability of this influencing factor.

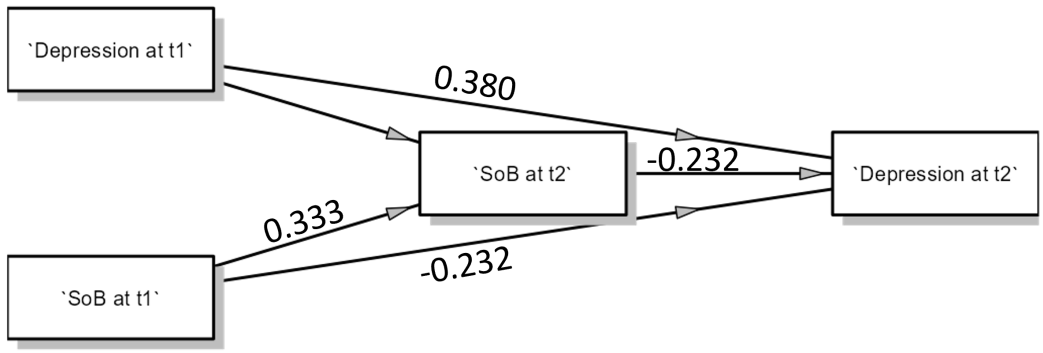

Figure 12: Path-Diagram with depression at t2 as the dependent variable. Values reflect estimated β coefficients for individual nodes. Only significant values are shown. While depression predicts itself one year later, it has no significant influence on the sense of belonging (SoB) of the next measurement occasion. Sense of belonging, on the other hand, predicts both, itself and depression at follow-up.

To test the stability and Influence of the prediction of PHQ-9 scores over further courses and to replicate the effects previously found, the sample presented in Paper 1 was assessed for three further years. The data accrued for this purpose has not yet been published and are presented here in the preliminary form:

To test whether SoB is indeed a more stable predictor than previous depressive symptoms in the long-term, several simple regressions were calculated. The PHQ-9 score at t5 was always the dependent variable. Subsequently, one simple regression was calculated for the prediction of this score from SoB and depression for each measure-

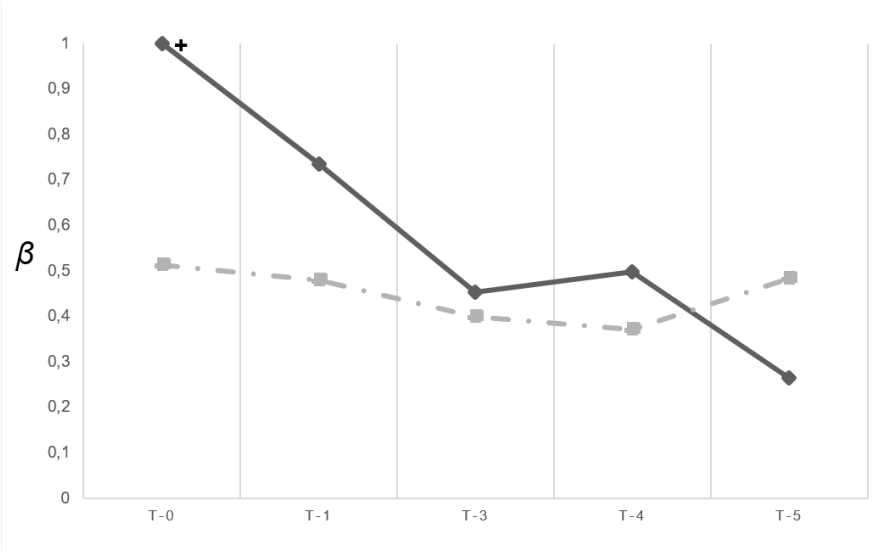

Figure 13: Estimated Beta-Coefficients in the Prediction of Depression Over Time. Data points represent absolute beta coefficients of regression analyses comprising only one predictor (SoB= dotted line or PHQ-9 scores= solid line). Each predictor was tested a total of five times; once for each measurement occasion. PHQ-9 scores at t5 were the dependent variable. T-0 thus reflects t5, while T-3 reflects T2 (5-3=2) As a result, estimates of T-5 represent the estimated beta coefficient for the regression equation $PHQ(t5) = intercept + \beta SoB(t1) + \epsilon$. The Figure shows a relatively stable influence of SoB, regardless of the time difference between the predicted PHQ score and SoB measures. PHQ-scores as predictors, however, seem to lose their predictive power over time. += the regression behind this estimate could not be computed as PHQ-9 scores at T5 (T-0) predict themselves perfectly, indicating a beta-coefficient of 1.

ment occasion (t1-t5). In Figure 13 measurement occasions are defined by the distance to t5. Accordingly, t-0 reflects the fifth measurement occasion and t-4 the first. Figure 13 highlights that the estimated β coefficient of the predictive power of depressiveness for itself decreases almost linearly from recent to distant measurement occasions, while the influence of SoB remains comparatively steady.

This result is particularly surprising because the Sars/Cov-II pandemic started during the assessment of the later measurement occasions, which should have a direct impact on the social isolation of the respondents. The group of CF patients should be even more affected than others, as they are at high risk for severe courses and should therefore show even more pronounced contact reductions as a precautionary measure. Nevertheless, the influence of SoB remains relatively stable, which may highlight that even while the expression of SoB may change, its predictive power for depression does not change.

15 Embedding in the Thesis Framework (Paper I)

The high influence of SoB on depressive symptoms one year later, as described in the first script, indicates that vulnerability factors have a long-lasting influence on affective symptoms. The influence seems to be comparable to that of the previous depressive symptoms, if both variables are included in the regression. It is also striking that depressive symptoms at t1 do not seem to have a significant influence on SoB at t2. In other words, according to these results, the greatest vulnerability factor for depression within the present analysis (SoB) does not seem to be worsened by current affective symptoms.

At the same time, SoB at t2 seems to be predicted only to a comparatively small extent by its own expression at t1, suggesting substantial variability of this factor. Interestingly, even in data that were collected throughout the pandemic, the influence of SoB did not change on a large scale, possibly indicating that the influence of SoB on depression. Taken together, this sense seems to be subject to variability even though the influence on depression scores remains stable over time.

Furthermore, the preliminary analyses of these (additional) data also show, that the idea of a stable influence of vulnerability factors in contrast to a diminishing predictive power of depressive symptoms for the prediction of future depressive states, is in line with the data collected in CF patients.

It can be deduced that a therapeutic intervention that only treats the current symptoms would probably not be able to prevent relapses unless the sense of belonging is also addressed. These data thus provide indications of the necessity of treating depressive causes, although, as can be seen from this example, these are also subject to external (e.g., social) influences.

In the following section, the same path diagram as in 12 is calculated again. This time with a focus on a completely different variable and sample, whereby again a model was chosen that, due to two (in this case 3 years) separated measurement occasions, also allows the analysis of whether changes in the variable are depression consequences or preconditions. First, however, another manuscript (already published) describes how the variables were calculated.

16 Paper II - Measurement Invariance in Longitudinal Neuropsychiatric Test Scores

The following text represents the accepted version of the author's manuscript for the publication: Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J. and Herrmann, M.J. (2021), Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. J Neuropsychol. https://doi.org/10.1111/jnp.12269.

While minor corrections in style, referencing of Tables and Figures or grammar and layout were made in comparison to the publication by Haberstumpf, Forster, et al., 2021, the following text largely reflects the original version. However, a thorough review of the published version is strongly recommended. The manuscript should be cited as stated above.

Title: Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research

Authors: Sophia Haberstumpf[a12], André Forster[b1], Jonas Leinweber[c], Stefanie Rauskolb[d], Johannes Hewig[b], Michael Sendtner[d], Martin Lauer[a], Thomas Polak[a], Jürgen Deckert[a], Martin J. Herrmann[a]

[a]Center for Mental Health, Department of Psychiatry, Psychosomatics andPsychotherapy, University Hospital Würzburg, Würzburg, Germany

[b]Institute of Psychology, Julius-Maximilians-University, Würzburg, Germany

[c]Alexianer Psychiatric Hospital Köln-Porz, Köln, Germany

[d]Institute of Clinical Neurobiology, University Hospital Würzburg, Würzburg

[1]Authors contributed equally

[2]Corresponding author

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16.1 Abstract

Objective. Alzheimers disease (AD) is a growing challenge worldwide, which is why the search for early-onset predictors must be focused as soon as possible. Longitudinal studies that investigate courses of neuropsychological and other variables screen for such predictors correlated to mild cognitive impairment (MCI). However, one often neglected issue in analyses of such studies is measurement invariance (MI), which is often assumed but not tested for. This study uses the absence of MI (non-MI) and latent factor scores instead of composite variables to assess properties of cognitive domains, compensation mechanisms, and their predictability to establish a method for a more comprehensive understanding of pathological cognitive decline.

Methods. An exploratory factor analysis (EFA) and a set of increasingly restricted confirmatory factor analyses (CFAs) were conducted to find latent factors, compared them with the composite approach, and to test for longitudinal (partial-)MI in a neuropsychiatric test battery, consisting of 14 test variables. A total of 330 elderly (mean age: 73.78ś1.52years at baseline) were analyzed two times (3years apart).

Results. EFA revealed a four-factor model representing declarative memory, attention, working memory, and visualspatial processing. Based on CFA, an accurate model was estimated across both measurement timepoints. Partial non-MI was found for parameters such as loadings, test- and latent factor intercepts as well as latent factor variances. The latent factor approach was preferable to the composite approach.

Conclusion. The overall assessment of non-MI latent factors may pose a possible target for this field of research. Hence, the non-MI of variances indicated variables that are especially suited for the prediction of pathological cognitive decline, while non-MI of intercepts indicated general aging-related decline. As a result, the sole assessment of MI may help distinguish pathological from normative aging processes and additionally may reveal compensatory neuropsychological mechanisms

16.2 Introduction

Mild cognitive impairment (MCI) and Alzheimers disease (AD). Due to the constantly aging society, neurodegenerative diseases such as dementia represent a growing challenge for health care systems worldwide (Abbott, 2011; Bickel, 2001; Prince et al., 2013). Affecting 60-70% of people suffering from dementia, one of the most usual forms is Alzheimers disease (AD; World Health Organization, 1993). An early indicator is mild cognitive impairment (MCI), which often progresses into AD Arnáiz and Almkvist, 2003). According to Petersen (Petersen, 2000), 10-15% of MCI patients convert into AD per year, and up to 15-20%of the general population express MCI symptomatology. Even though there is no cure available to date, early interventions can dampen the course of the disease (Mayeux, 2010; Winblad et al., 2006), which highlights the necessity of diagnostics in the early stages. Thus, finding variables with high predictive power for neuropsychiatric changes is a focus of MCI related research.

According to the consensus formulated in DSM-V and ICD-10 (American Psychiatric Association, 2000; World Health Organization, 1993), diagnostics of MCI and AD heavily rely on neuropsychiatric tests as their first symptoms are deficits in cognitive performance such as memory loss (Arnáiz and Almkvist, 2003; Jahn, 2013; Nestor et al., 2006; Riedel and Blokland, 2015). As a result, finding predictors for such neuropsychological symptoms may allude to targets for early interventions. The statistically and methodologically most efficient way to address this topic is analyzing longitudinal within-subject course data (Cooper et al., 2015; Hendrix et al., 2015; Makkar et al., 2020).

16.2.1 Shortcomings of the composite approach

A valid approach to increase robustness and significance of prediction analyses may be to create composite variables consisting of a sum- or average-score of potential predictors of interest. For example, multiple performance scores can be combined by forming a composite score. However, by simply adding the test scores, it is implicitly assumed that all scores are equally meaningful for the target construct (e.g., declarative memory). However, since the target construct is often a latent factor, it should be empirically verified that this assumption is indeed true. To do so, however, a latent

factor approach would be more adequate. This problem is further complicated by the fact that the extent to which a predictor is relevant to the latent construct can vary across groups and over time. As a result, both the classical composite approach and weighted composite approaches that impose fixed weights on scores within the composite (e.g., $1 \cdot immediatememoryperformance + 0.3 \cdot workingmemoryperformance = latentmemoryability$) may fall short if the actual relationship of the manifest test scores differs from the weights chosen by the researcher (in the classical approach, each variable is multiplied by a weight of 1). Factor analyses may provide the most reliable weights for calculating composites. This may be particularly the case in longitudinal studies, as weights may change over time, which may affect the comparability of measurement occasions within the follow-up data. This effect ("response shift") has been described in other areas of research (e.g., Oort, 2005). However, different weights are not the only parameters that can change over time, which further complicates analyses and suggest new ways to examine course data in detail. For instance, if a sample achieved a mean score of 10 on a composite variable described by researchers as an indicator of memory at both the first and second measurement occasions, one would conclude that the sample's memory performance had not changed. However, this null finding could be misleading, as this samples latent declarative memory performance may have decreased, even if this did not manifest in the composite variable due to compensatory mechanisms (e.g., coping strategies, test-memory effects). Thus, to estimate latent ability changes and to detect effect-concealing or inflating mechanisms, the intercorrelation matrix of different neuropsychiatric tests can be used. For example, an altered covariation between memory and attention scores at the second measurement occasion may indicate that the ability to modulate attention might make a decline in memory performance less noticeable. Also, memory abilities might have a lower covariance with other latent skills if its scores were affected by retest effects, while other neuropsychiatric domains were not. Hence, merit lies in the analysis of test score interplays rather than absolute values. The classical method to deal with such complex matrices between multiple test scores is the (confirmatory) factor analysis, which extracts latent abilities from manifest test scores and estimates changes in the intercorrelation of manifest and latent variables based on these data. In summary, this approach inves-

tigates the equivalence of parameters within a structural equation model (SEM) across groups/time and can find indicators of possible bias mechanisms that may distort the results of the composite approach. Measurement invariance (MI; no significant variation of a parameter across groups/time) of parameters would imply that the manifest sum score approach would be largely unbiased. The following section gives interpretations for (non-)invariance for a subset of central parameters within such analyses.

Longitudinal MI. In most studies investigating MI, SEM comparing increasingly restricted confirmatory factor models is the method of choice. Due to its ability to integrate latent and observed variables out of many test variables, this approach is expected to offer an appropriate statistical method to reveal latent factor structures and to prove construct validity by factorial invariance measurements of neuropsychiatric test batteries across time, sample subgroups and different cognitive levels (Berndt and Williams, 2013;Kline, 2005; Mungas et al., 2011; Park and Festini, 2017; Rahmadi et al., 2018; Rowe, 2010;Schumacker and Lomax, 2004).

Intercepts. One often recognized MI parameter is the estimated intercept of single items/tests and latent means. In the context of regression (which reflects the relationship of a latent factor to its manifest indicators), intercepts reflect the (grand) mean score of a given population. Non-MI, e.g., in-/decreases in intercepts, may thus reflect sample-level in-/decreases of latent traits (latent trait level) or manifest test-performance (indicator level). In turn, non-MI of intercepts can be interpreted similarly to in-/decreases in composite scores: It indicates changes of ability (on a latent factor level) or test-performance (on the indicator level). Thus, this kind of invariance violation would not be a problem in longitudinal MI research but reflects an anticipated effect.

Variances. Another indicator for performance change are variances, as these may (inter alia) increase if at least two groups of individuals develop in different directions. In contrast, whole-population changes in one direction would only result in intercept but not variance changes. Therefore, non-MI of variances (on latent and indicator levels) would not be a problem but could indicate subpopulations within the sample.

From this perspective, an increase in latent factor score variance may highlight that some participants depict no change in the target construct or even increases while

others suffered from decreases. On the other hand, decreasing variances over time may indicate retest effects that diminish inter-individual differences in performance capability or the diminishing influence of variance-inducing third variables such as trait anxiety (e.g., habituation effects) or simply normative aging processes that diminish smaller interindividual differences over time.

However, other mechanisms may lead to similar changes in variance. For instance, increases in variance may also be attributable to increasingly fluctuating cognitive capabilities following cognitive decline and ageing in general. Nonetheless, in the context of neuropsychological longitudinal MI research, non-invariance of variances may indicate that a certain domain is especially potent to distinguish healthy from abnormal courses or to at least indicate a certain cognitive domain to show some kind of ageing dependent variability.

Loadings. Another parameter that may show non-MI is the correlation of indicators and latent factors, which resembles weights within the composite approach. If loadings that previously were small enough to be neglected in increase to the extent that a new indicator should be added to the model or shifted from one latent factor to another, the factor structure may change in its entirety Cheung and Rensvold, 2002; Oort, 2005).

In the context of neuropsychiatric measures, the neuronal bases of performance in psychometric tests may change (e.g., verbal skills deficits may affect memory performance and lead to a reorganization of the factor structure). However, this effect may also be observed in normative age-related processes.

Nonetheless, regardless of the etiology of the loading shifts, invariance across measurement occasions would be a requirement of the classical composite approach, as it implicitly assumes that all included variables contribute equally to the neuropsychiatric domain. Usually, weighted composite calculations are more beneficial. As weights of all variables entering a composite should reflect the loading of indicators on the latent factors, non-MI over time would imply that weights should also vary over time. Thus, non-MI is a general issue in this context and may highlight the shortcomings of classical composite approaches.

Longitudinal MI research based on neuropsychiatric test-batteries. In contrast

to the vast number of longitudinal research papers implemented on the prediction and the course of MCI/AD, far fewer of these have focused on latent factor structures and factorial invariance underlying cognitive domains within neuropsychiatric test batteries to ensure generalizability Health, National Institute of Mental, 2011; Wicherts, 2016). Rather, some studies used the SEM approach to investigate between-group-MI (Avila et al., 2020; M. B. Mitchell et al., 2012; Mungas et al., 2011;Sayegh and Knight, 2014; Tuokko et al., 2009). Others investigated latent factors and tested for MI in neuropsychiatric test batteries without keeping the longitudinal aspect in mind (Y. Ma et al., 2021).

To our knowledge, only a few longitudinal measurement invariance studies, including the within-group latent factor approach based on neuropsychiatric test batteries, were published: For example, in a large multicenter sample of N=12020 cognitively healthy participants and participants with diagnosed MCI or dementia (age: 55 years; M=75.6 years), researchers derived a four-factor structure from a neuropsychiatric battery (12 test variables) including the factors memory, attention, executive function, and language (K. M. Hayden et al., 2011; K. M. Hayden et al., 2014). These factors remained invariant across the span of 1 year and predicted sample subgroups and cognitive impairment 3 years later. Moreover, Moreira et al. (Moreira et al., 2018) examined a two-factor model including memory performance and executive functioning in an elderly sample of 86 participants from a neuropsychiatric test battery. Defined factors remained invariant for two years. Similar studies concentrated on the two factors memory and executive functioning, extracted out of large test batteries over periods of up to eight years (Bertola et al., 2021; B. D. Williams et al., 2018).

Aims of the current study. As part of the prospective, observational, long-term follow-up Vogel Study of a large German sample (M=73.9 $\pm$ 1.55 years of age at first out of three visits; see also Polak et al., 2017), this current analysis aims to investigate longitudinal MI in a sample of (mostly) healthy elderly (at the first measurement occasion) over 3 years. However, in contrast to between-group MI-testing, we hypothesize and aim for the absence of MI especially concerning variances of latent and manifest variables, as these may indicate at least two groups of participants differing in their performance trajectory over time. Other mechanisms that may also result in increased variance may

hint towards the importance of affected variables as potential targets for future studies. An Increased variance may be result fromthe cognitive decline within the total sample (instead of within two distinct groups), which leads to more fluctuation in performance and thus longitudinal heteroscedasticity (Koscik et al., 2016). Nonetheless, non-MI would still provide for the insight that the affected variable is a valuable candidate for further investigation as it would have been indicated to be sensitive for cognitive decline or aging in general (see more on this in section 4). This non-MI may thus single out promising variables for further analyses as they possibly differentiate normal from pathological cognitive changes. Moreover, general decreases in intercept estimates (in both latent and manifest variables) are also anticipated, reflecting sample based average changes in cognitive abilities on a latent level and changes in average test performance in manifest test-scores. Additionally, MI of factor loadings is investigated to estimate possible shortcomings of the usual procedure to analyze sum-scores/composites.

16.3 Methods

16.3.1 Sample characterization

As described earlier in Polak et al. (Polak et al., 2017), the Vogel Study was carried out with the authorization of the local ethics committee (vote no. 23/11) and complied with the Helsinki Declaration (Association, 2013). Residents (with or without origin) of the city of Würzburg born between April 1936 and March 1941 (age: 70-77 years) were included in the study. All of them were informed about the project. They gave their written consent to participate in the Vogel Study, which started in the year 2011 and has now completed two out of 3 measurement time points (visit 1 [V1], visit 2 [V2], and visit [V3]). The project intends a total study duration of 10 years with 6 years of observation per participant.

Participants were excluded if they 1) suffered of a severe internal, psychiatric, or neurologic disease within the last 12 months (e.g., brain infarction) or 2) had a severe and uncorrected impairment of vision or hearing on the first day of data collection. Thus, a total of N=604 subjects attended in the baseline examination of the Vogel Study.

At V2 approximately 3 years after V1, n=97 participants no longer participated in the study (n=507). This was, for example, due to death, the fulfillment of study exclusion criteria, study termination, relocation, or the deregistration of the telephone connection. For the current data analysis, depicted below, participants who did not perform the neuropsychiatric test battery (n=125) or exhibited more than 5 missings within the neuropsychiatric test battery (n=44) because of rejection or high-stress experience at baseline or first follow-up examination were excluded. Even though this indicates dropouts to be dependent on personality or ability traits (e.g., cognitive abilities may have been worse in those who died within the next three years as existing disorders may have had impact at V1 already), we assume that the remaining missings within the final dataset were random.

We then calculated Mahalanobis-distances (cut off: p <.001; n=4; Tabachnick and Fidell, 1996) as well as z-scores (cut off: ś3.29; n=4; Tabachnick and Fidell, 1996) for each neuropsychiatric test to find and subsequently exclude uni- and multivariate outliers pairwise.

Therefore, the remaining sample of this papers final data set consisted of n=330 participants (age: 70-77 years with M=73.78, SD=1.52 years at baseline examination; age: 73-81 years with M=77.67, SD=1.60 years at first-follow up examination; n=138 females, n=192 males; see Figure 14). So far, as described above, we still are in preparation for the second follow-up examination and have no data available yet.

16.3.2 Neuropsychiatric test battery

Besides the examination of various demographic, anamnestic (e,g., lifestyle, medical history, etc.), affectivity, autonomy, blood, and lifestyle variables to characterize our sample, we conducted a neuropsychiatric test battery comprising of: a) the Verbal Learning And Memory Test (VLMT; Helmstaedter et al., 2001), b) the Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000), c) the Regensburger Verbal Fluency Test (RWT; Aschenbrenner et al., 2000), d) the Rey Complex Figure Test (CFT; Fimm and Zimmermann, 2001; Meyers and Meyers, 1996), and e) the battery of Tests for Attentional Performance (TAP; Fimm and Zimmermann, 2001). For a more detailed description of the general

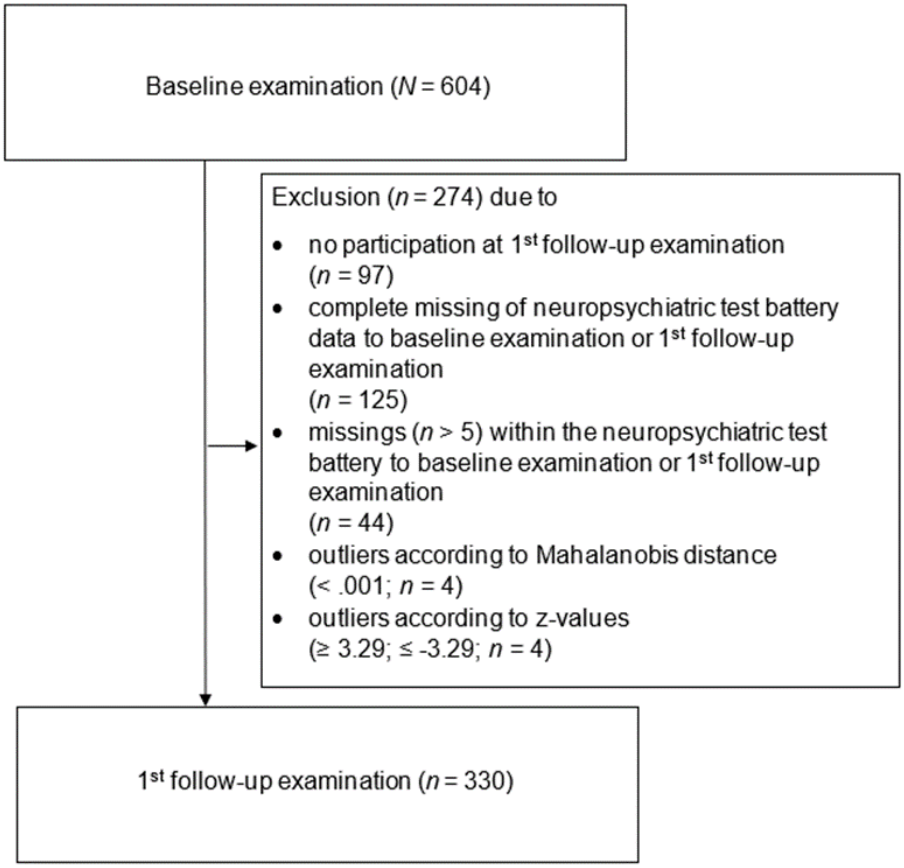

Figure 14: Course of exclusion for data analysis. CNS=Central Nervous System.

examination procedure within the Vogel Study, see our previous methods study (Polak et al., 2017).

The subsequent test scores were used in further latent factor analyses: VLMT immediate recall (sum score words), VLMT delayed recall (sum score reproduced words), VLMT recognition (sum score recognition word list), WMS-R digit span (sum score), WMS-R block span (sum score), RWT verbal fluency (sum score), RWT category fluency (sum score), CFT memory (sum score both reproduction times), CFT visuoconstruction (drawing score), TAP tonic alertness (median of reaction time [RT]), TAP phasic alertness (RT-parameter for phasic alertness), TAP divided attention (omission error), TAP GoNoGo (error number), TAP incompatibility (F-value of field of vision x hand interaction). Thus, the following latent factor analysis comprised of 14 test variables detached from 5 neuropsychiatric tests.

16.3.3 Statistical analyses

The data preparation, outlier detection, testing of prerequisite assumptions, and the EFA were conducted in IBM SPSS Statistics for Windows (version 25, SPSS inc., USA). Further CFA analyses were completed in R (lavaan package version 0.6-5; (Rosseel, 2012; Team, 2016). Predictive mixed models were also fitted via R (lme4 and lmerTest packages; Bates et al., 2014;Kuznetsova et al., 2017; Kuznetsova et al., 2015).

Acceptable cut-offs for fit indices, e.g., the root mean square error of approximation (RMSEA) and comparative fit index (CFI), were set to $<.05$ and $>.95$, respectively. The alpha level to test for significance in 2-tests was set to $<.05$.

Regarding the SEM, standardizing manifest variables may lead to biased estimates in longitudinal data (Kline, 2005; Schumacker and Lomax, 2004). Also, some tests did not provide samples that qualified for T-value calculation in all ages of participants who were included in this study. To get an unbiased estimation of course effects, raw test-scores were used for further latent factor analyses (13 raw scores and 1 F-value for TAP incompatibility[18]).

Moreover, as unstandardized test scores exhibited substantial differences in their respective scales, those tests depicting variances greater than 10 times the magnitude of the smallest variance found in the dataset, were rescaled. This procedure is thought to diminish chances for Heywood cases and other estimation issues (Kline, 2005; Schumacker and Lomax, 2004). Finally, reaction-time-based variables were transformed via natural logarithm (TAP tonic and phasic alertness). However, no other transformation was carried out, which led to non-normality of several test scores. Even though this may, in theory, impair reliable estimation, several simulation studies reported only a small non-normality impact on standard errors (Lei and Lomax, 2005) or model fit (S. Gao et al., 2008). Furthermore, since the effect of non-normality may vary across different estimation methods, robust maximum likelihood estimation was used. This function leads to reliable model estimations considering misspecification, non-normality of data, and/or small sample sizes (C. Gao et al., 2020; Lai, 2018; Yilmaz, 2019).

[18]This test calculates an F-test to evaluate slowing in reaction time due to incompatible compared to compatible trials in a flanker task (the higher the percentage rank, the lower the incompatibility effect)

16.3.4 Exploratory factor analysis (EFA)

To find a fitting latent factor structure, an EFA was carried out, including data of both measurement occasions. A parallel analysis was carried out to define the number of factors that were subsequently extracted after Varimax rotation. The Kaiser-Meyer-Olkin (KMO) criterium and Bartletts test of sphericity were assessed to ensure suitable prerequisites for the analysis. Only those tests depicting rotated loadings of .4 or higher on only one factor were included in the final model.

16.3.5 Invariance testing

The concluding factor structure, indicated by the EFA, was tested in a multigroup CFA using full information maximum likelihood estimation in the handling of missings, the lavaan-default nlminb optimization method, and robust maximum likelihood estimation (MLR) for the calculation of standard errors. Groups were defined by test sessions, which were 3 years apart, enabling a longitudinal interpretation of cross-group effects. Each participant remaining in the dataset was present on both occasions.

As stated before, MI is usually tested via increasingly restrictive CFAs. In this context, restriction refers to the fact that a given parameter is not allowed to vary across groups (measurement occasions): Suppose the fit between a predefined model and the actual data decreases by imposing such a restriction. In that case, this restriction seems to have violated the actual data structure in the sense that the data would be better represented by allowing varying parameters across groups, indicating non-MI.

Hence, each of the following models adds certain parameters to the previous models' restrictions. Comparing model fit across these, significant decreases in fit indices would indicate non-invariance (the restricted parameter varies over time). To test this, χ^2 statistics were calculated. These statistics indicate differences between one model and the model before (model 2 vs. 1, model 3 vs. 2, model 4 vs. 3). Following theoretical remarks, a total of four models was fit (Cheung and Rensvold, 2002; Dowling et al., 2010; van de Schoot et al., 2012), including the following:

Configural model. In this model, only the factor structure (assignment of tests to latent factors) implied by the EFA was restricted for all variables. Otherwise, this

model is built to freely estimate as many parameters as possible. However, to ensure the model to be identifiable, some restrictions need to be made. In this study, two separate approaches are discussed to give examples on possible modeling decisions concerning two different use cases.

First, to investigate measurement invariance with a focus on manifest-latent-factor-interaction, the loading of one indicator variable per factor was restricted to 1. Also, the means/intercepts of the latent factors were restricted to 0 to give the latent factors a metric. Since means of the latent factors are not allowed to differ from 0, changes within latent abilities will be propagated to manifest test score intercept differences over time, enabling the investigation of test properties (i.e., how well they are suited to investigate latent ability changes). This approach was used at first.

In addition, one may consider the extraction of latent ability scores for further investigation (e.g., to use it as dependent variables within regression analyses or ANOVAs). Thus, for this goal, it is more beneficial to allow free latent score estimation at the second measurement occasion. To do so, in an exemplary use case, the configural model was later refitted with a restriction of latent variable means to 0 and latent variable variances to 1 for the first measurement occasion only. Furthermore, loadings of one manifest indicator variable per factor were restricted to be equal across both measurement occasions, which enabled the model to estimate latent factor means and variance freely at the second measurement. Thus, in this model, significance of changes over time can be easily assessed by investigation of latent variable estimates at V2 (intercepts are significant if they differ significantly from 0, variances are significant if they differ significantly from 1).

Regardless of these modeling choices, overall (absolute) fit of this kind of model indicates that the model structure (association of tests to a certain latent factor) is invariant over time. If this was violated, latent abilities would not be indicated by the same tests across time, which would imply severe issues with the composite approach and question the validity of course data in general.

Metric model. In the next model, investigating (construct-level) metric invariance, all loadings across groups/time were restricted to equal one another. The means of the factors themselves were still fixed to 0, while the loading of one indicator per factor

was fixed to 1. In this model, invariance implies that manifest test scores equally indicate the given latent constructs over time. Violation of this loading invariance would imply that the weights of variables used for composite approaches must be adjusted over time.

Scalar model. The third, scalar model, added a cross-group restriction of manifest indicator intercepts. By doing so, the measurement model is identifiable without latent mean fixation. Thus, latent means were estimated freely instead of fixed to 0. In this model, non-MI across groups indicate changes in the difficulty of tests (changes in performance by participants). Furthermore, latent factor intercepts may be analyzed to find longitudinal decreases/increases in latent abilities. Violation of intercept invariance would not pose a problem but may indicate anticipated effects of ability/performance decline.

Variance model. Finally, additionally to these restrictions, variances of latent factors were held constant across groups/time. Non-invariance in this model may reflect the presence of at least two groups of participants whose latent abilities evolve into different directions over time or the presence of other mechanisms that affect the overall variability of measured ability within the whole sample. Thus, violation of the invariance assumption would be in line with anticipated effects as this may highlight variables/parameters that could possibly be best suited for detection of early MCI related whole-sample or sub-sample-based changes (e.g., healthy vs. abnormal cognitive courses).

16.3.6 Composite approach

To assess the benefit of latent-factor-score analyzation with the more common composite approach, unweighted composite variables were calculated for comparison. To do so, the test score of each subject was standardized for each individual test by placing the score obtained in the context of an age- as well as gender- and education-matched norm sample (all test scores except the VLMT and CFT). In total, four composites were calculated before the context of the factor structure defined by the EFA by simply averaging test scores assigned to a common factor (see Figure 16). The models investigated the same n = 330 participants.

To then compare the benefit of the latent factor approach over the unweighted

	Eigenvalue	Explained Variance	Cumulative Explained Variance
Factor 1	2.463	17.591	17.591
Factor 2	2.007	14.339	31.930
Factor 3	1.827	13.052	44.982
Factor 4	1.705	12.176	57.158
Factor 5	1.091	7.792	64.950

Table 7: Estimations of factor properties.

composites, as an example, a mixed effect regression model was fit once with the latent factor estimate for declarative memory as dependent variable and once with the respective composite as such. As a result, the two models can be compared directly by comparing the estimated effects of predictors (which are the same across both models) for these two dependent variables.

16.4 Results

16.4.1 Exploratory factor analysis

Both, the KMO criterium (.688) and Bartletts test of sphericity ($\chi^2(91)$=1974.583, df=91, p<.001) implicated suitable prerequisites to conduct the analysis. Subsequently, a total of 5 factors was extracted following the suggestions of both Eigenvalue and parallel analysis. Estimations of factor properties, and a scree plot, are shown in Table 7 and figure 15. Rotated loadings .4 are displayed in Table 8.

Cognitive domains were assigned to describe the factors as denominated in Table 9. However, only four factors of those implicated by the EFA were analyzed further as the fifth factor comprised only one indicator complicating estimation (Kline, 2005; Schumacker and Lomax, 2004).

16.4.2 Measurement invariance testing

Four increasingly restricted models were fit and compared to analyze measurement invariance (see Table 10). Both the RMSEA and CFI indicated acceptable model data assuming that the assignment of manifest test scores to latent factors stays equal across time. Hence, the conceptual representation shown in Figure 16 represents the suitable

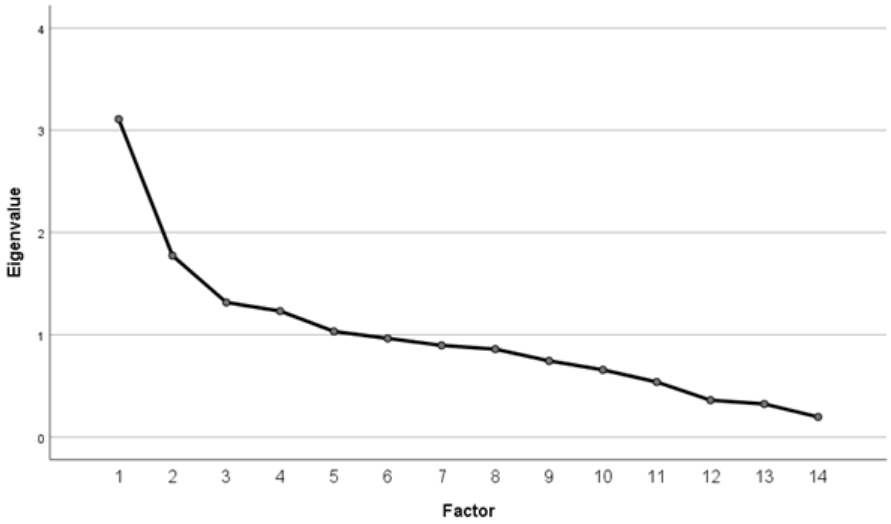

Figure 15: Scree plot showing the five-factor solution of the Exploratory Factor Analysis (EFA).

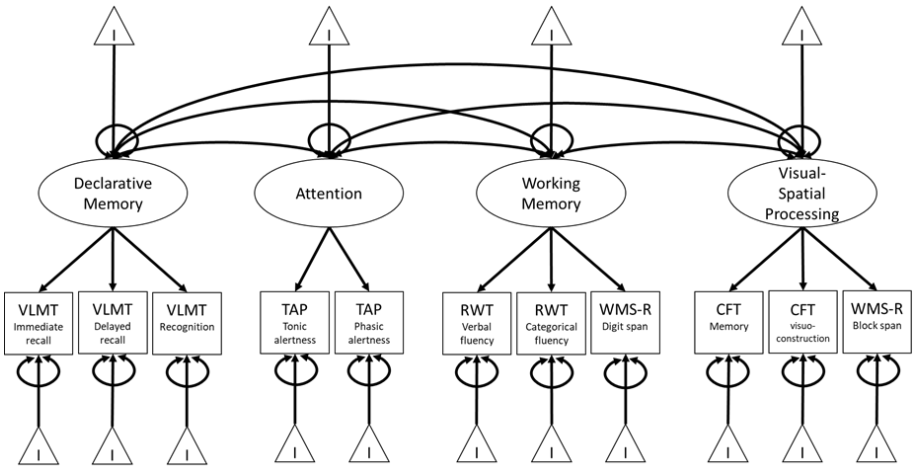

Figure 16: A conceptual model for the CFAs depicting estimated parameters. Oval variables depict latent factors, while rectangles reflect manifest test scores. Triangles represent intercepts.

structure for both measurement occasions. However, Table 10 further summarizes that factor loadings, test intercepts, latent means, and latent variances depict substantial non-MI over time.

However, as non-MI is not per se a property of the whole model but rather of certain parameters, further analyzes were carried out to clarify which (test-)parameters significantly changed over time and which did not. To assess this, the configural model yields the best insight as all the more restrictive models showed decreasing fit to the data. Furthermore, as the configural model allows for the greatest number of freely estimated parameters, non-invariance in the data that would influence the fit indices of more restric-

Scale	Factor loadings after Varimax Rotation				
	1	2	3	4	5
VLMT immediate recall	.898	-	-	-	-
VLMT delayed recall	.888	-	-	-	-
VLMT recognition	.861	-	-	-	-
TAP tonic alertness	-	.997	-	-	-
TAP phasic alertness	-	.997	-	-	-
WMS-R digit span	-	-	.536	-	-
RWT verbal fluency	-	-	.833	-	-
RWT category fluency	-	-	.867	-	-
WMS-R block span	-	-	-	.565	-
CFT memory	-	-	-	.724	-
CFT visuoconstruction	-	-	-	.744	-
TAP compatible	-	-	-	-	.888
TAP divided attention	-	-	-	-	-
TAP GoNoGo	-	-	-	-	-

Table 8: Factor rotation of the five-factor solution of the Exploratory Factor Analysis (EFA).EFA Coefficients .40 are exhibited. VLMT=Verbal Learning an Memory Test (Helmstaedter et al., 2001); TAP=battery of Tests for Attentional Performance (Fimm and Zimmermann, 2001); WMS-R=Wechsler Memory Scale-Revised (Härting et al., 2000); RWT=Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); CFT=Rey Complex Figure Test (Meyers and Meyers, 1996.

tive models negatively should be reflected in significantly changing estimates over time. Table 11 summarizes the results by providing estimates across both measurement occasions. Furthermore, to provide information on the tendency of statistical significance of descriptive differences, the standard error of a variables mean was multiplied by 1.96. By doing so, a 95% confidence interval (CI) was obtained. If the CI of either value (measurement occasion 1 or 2) included the estimated mean of the other measurement occasion, no significant difference was assumed. Please note that this comparison included two tests for each variable, which was not corrected for. Shading in Table 11 thus indicates trends (exploratory findings) but not confirmatory hypothesis testing as no specific assumption on non-MI of specific parameters was formulated beforehand.

Nonetheless, results indicate partial non-MI for loadings in VLMT recognition and immediate recall (declarative memory) and WMS-R block span (visual-spatial pro-

Latent Factors	Cognitive Domain	Included neuropsychiatric test scores
Factor 1	declarative memory	VLMT immediate recall, VLMT delayed recall, VLMT recognition
Factor 2	attention	TAP tonic alertness, TAP phasic alertness
Factor 3	working memory	RWT verbal fluency, RWT category fluency, WMS-R digit span
Factor 4	visual-spatial processing	CFT memory, CFT visuoconstruction, WMS-R block span

Table 9: Designation of the four latent factors. VLMT=Verbal Learning an Memory Test (Helmstaedter et al., 2001); TAP=battery of Tests for Attentional Performance (Fimm and Zimmermann, 2001); RWT=Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); WMS-R=Wechsler Memory Scale-Revised Härting et al., 2000); CFT=Rey Complex Figure Test (Meyers and Meyers, 1996.

CFA model	RMSEA	CFI	AIC	BIC	2	df	p
Fixed structure	.049	.969	22068	22418	135.22	76	
+ Fixed loadings	.051	.963	22073	22392	154.33	83	.007**
+ Fixed intercepts	.080	.902	22182	22469	277.16	90	<.001
+ Fixed variances	.097	.849	22281	22550	384.20	94	<.001

Table 10: Confirmatory Factor Analyses (CFAs) for the sample of n=330 participants. Reported fit-parameters base on a robust maximum likelihood estimation. RMSEA=Root Mean Square Error of Approximation; CFI=Comparative Fit Index; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion.

cessing). Furthermore, VLMT immediate recall, VLMT recognition, and CFT visuoconstruction intercepts seem to decrease while CFT memory, tonic alertness, and WMS-R scores increase. Finally, VLMT delayed recall, RWT category fluency, and WMS-R digit span scores also seem to decrease in their variance over time, while two of three working memory relates scores RWT verbal fluency and CFT visuoconstruction increase in variance.

Furthermore, additionally to the (manifest) indicator-level analyses of Table 11, latent factor estimates are summarized in Table 12. While indicator level estimations of Table 11 were made following the restriction of one indicator variable loading per factor to 1 and latent means to 0, results in Table 12 were produced by restricting the loading of one indicator per factor to the same value across groups while setting the latent means to 0 and the latent factor variance to 1 for the first measurement occasion, allowing for free estimation of these parameters at the second occasion. By doing this, free estimation of latent factor parameters could be ensured, which would be necessary for subsequent longitudinal prediction analyses using these latent factor scores as dependent variables.

Variables and Factors	Unstandardized loadings		Intercepts		Variances	
	V1	V2	V1	V2	V1	V2
VLMT Delayed Recall (F1)	1	1	6.004 (0.119)	5.437 (0.183)	2.461 (.383)	0.575 (.193)
VLMT Recognition (F1)	0.731 (.032)	.410 (.018)	5.391 (0.104)	4.858 (0.130)	1.692 (.192)	1.913 (.247)
VLMT Immediate Recall (F1)	0.810 (.031)	.620 (.027)	9.704 (0.098)	8.990 (0.171)	.829 (.119)	1.262 (.212)
TAP Phasic Alertness (F2)	1	1	23.128 (0.067)	23.172 (0.109)	.012 (.003)	3.423 (1.402)
TAP Tonic Alertness (F2)	1.754 (0.718)	2.840 (1.198)	26.653 (0.114)	26.974 (0.123)	.036 (.005)	0.979 (1.836)
RWT Verbal Fluency (F3)	1	1	2.701 (0.068)	2.672 (0.062)	.286 (.111)	.534 (.081)
RWT Category Fluency (F3)	1.090 (.146)	1.125 (.117)	3.534 (0.061)	3.533 (0.061)	.724 (.122)	.296 (.089)
WMS-R Digit Span (F3)	.799 (.145)	.829 (.138)	8.291 (0.117)	9.558 (0.107)	4.004 (.276)	3.263 (.277)
CFT Visuoconstruction (F4)	1	1	34.836 (0.107)	34.102 (0.160)	2.668 (.375)	4.216 (.793)
CFT Memory (F4)	1.389 (.357)	1.368 (.289)	7.259 (0.144)	7.811 (0.165)	4.62 (.617)	2.825 (1.157)
WMS-R Block Span (F4)	.490 (.112)	.217 (.050)	7.394 (0.078)	6.982 (0.079)	1.743 (.146)	1.894 (.157)

Table 11: Model parameters for a configural model. V1=Visit 1, V2=Visit 2. Unstandardized estimates and Standard Errors (SEs; in parentheses) are reported. Light grey cell shadings reveal significant increases of estimates over time, dark grey cell shadings reveal significant decreases, which indicates non-MI.

To demonstrate this idea, this model was used for parameter extraction, as it imposes the least restrictions while allowing free latent factor estimation.

Before the findings reported above, models fixating more parameters fit the data significantly worse. Hence, again, this model provides the most unbiased estimates. Table 12 highlights that the covariance between declarative memory and visual-spatial processing increases over time. Furthermore, intercepts decrease in declarative memory as well as in working memory. Finally, variances increased in both declarative memory and visual-spatial processing.

Comparison between the latent factor approach and the composite approach Figure 17 illustrates the course of latent factor means and composites across V1-V2. Descriptively, both, the composite and latent factor approach indicate decreasing performance/ability scores for declarative memory over time. However, the latent factor approach indicates greater significance and effect size. Regarding attention, again, both approaches indicate a similar trend, this time towards increases in scores. Since attention scores are indexed by reaction time, depicted increases indicate decreases in reaction speed (thus, worse performance/capability) with a seemingly greater effect estimate in the composite approach. In working memory, the composite approach suggests increases

		Covariances		Intercepts		Variances	
		V1	V2	V1	V2	V1	V2
Declarative Memory	Attention	-0.004 (0.054)	0.089 (0.136)	0	-0.568 (0.218)	1	9.737 (1.196)
	Working Memory	0.355 (0.052)	0.718 (0.181)				
	Visual-Spatial Processing	0.364 (0.070)	1.716 (0.369)				
Attention	Working Memory	-0.244 (0.089)	-0.187 (0.093)	0	0.044 (0.128)	1	0.499 (.271)
	Visual-Spatial Processing	-0.179 (0.104)	-0.169 (0.096)				
Visual-Spatial Processing	Working Memory	0.343 (0.094)	0.478 (0.151)	0	-0.734 (0.193)	1	3.283 (.982)
Working Memory	-	-	-	0	-0.029 (0.092)	1	0.733 (.107)

Table 12: Latent factor model parameters for a configural model. V1=Visit 1, V2=Visit 2. Unstandardized estimates and Standard Errors (SEs; in parentheses) of latent factor estimates are reported. Light grey cell shadings reveal significant increases of estimates over time, dark grey cell shadings reveal significant decreases, which indicates non-MI. These results indicate increases in the co-dependency of declarative memory and visual-spatial processing over time. Furthermore, it seems that the latent ability of declarative memory as well as visual-spatial processing decreased on average over time. Finally, the variance of declarative memory, working memory and visual-spatial processing increased as well.. Attention is estimated by variables expressing reaction times. Thus, higher values indicate worse performance

in performance over time, while the latent factor approach shows no particular change. Finally, concerning visual-spatial processing, a significantly greater decrease in scores is shown in the latent factor as compared to the composite approach over time (indicating a decrease in processing capability).

16.4.3 Example procedures for the prediction of latent ability scores

The current paper focuses on the general applicability of the SEM approach for describing the course of cognitive abilities and their decline. While the central part of this paper is based on the description of measurement invariance as a potential source of information for such questions, the estimated latent ability scores of the analysis can also be used directly to test specific predictor variables for their predictive ability. Two ways of doing this will be briefly described: First, the predictor variables themselves can be included in the model. The SEM approach allows both latent and manifest scores to be predicted by both fixed (e.g., genetic vulnerabilities) and variable predictors (e.g., depression scores varying over each measurement occasion). Thus, for datasets with at least three measurement occasions (for linear trends; more may be needed for non-linear trajectories (e.g., Byrne and Crombie, 2003; Felt et al., 2017;Grimm and Ram, 2009), a latent growth curve model could be defined, in which second order latent factors are assumed that define a slope

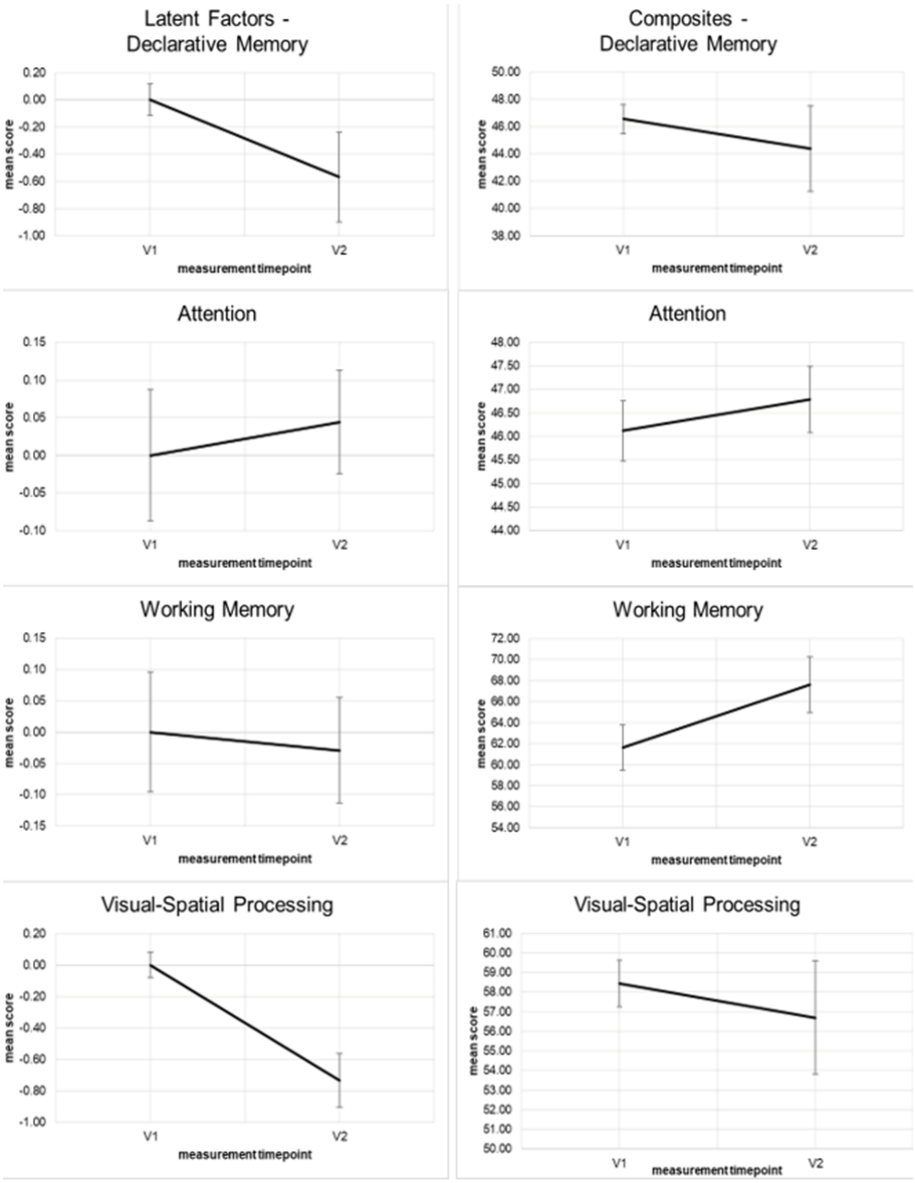

Figure 17: Latent factor approach (left column) compared with the composite approach (right column). V1=Visit 1, V2=Visit 2. Lines indicate mean (M), error indicators represent 95%-Confidence Interval (CI).

across the measurement occasions as well as an intercept, influencing the first order latent ability factors. At the same time, if one assumes that not all latent abilities (e.g., memory vs. visual-spatial processing) show the same slopes over time, a second-order latent slope and intercept could also be defined for each latent ability factor individually. These factors (slope and intercept) can, in turn, be predicted by predictor variables, making it possible to predict the temporal variation of latent factor scores with parameters such as genetic vulnerability factors. At the same time, the manifest variables measured per time point can also be predicted by influences that also change over time (e.g., BDNF levels,

depression scores). This modeling approach establishes a link between measured values that would otherwise be mistakenly treated as between rather than within effects (e.g., the manifest test scores of a person in a test at two measurement times). However, such estimation would require significantly more study participants (Willett and Sayer, 1994), with the advantages of directly estimating the influence of predictors at the manifest and latent levels while simultaneously allowing for measurement invariance estimation.

As a second possibility, the latent factor scores could be read from the model and included as a dependent variable in a regression analysis or ANOVA. To illustrate this approach (which is also possible with the current dataset), a mixed model approach was chosen in which various predictor variables collected in the study were used as independent variables. In contrast, the extracted latent factor scores were used as dependent variables.

The dependent latent factors were included with a random intercept for each subject and time as a fixed effect predictor (levels one and two, model 1). Due to their relevance in the literature (for an overview, see Xu et al., 2015) and supposedly low multicollinearity (or redundancy), the covariates age and gender (model 2), the Brain-Derived Neurotrophic Factor (BDNF; model 3), depressiveness (measured by the Beck Depression Inventory-II [BDI-II],Beck et al., 1996; model 4), and vitamin B12 (quantified by blood plasma; model 5) were included as potential predictors (see Appendix for more details). Overall, one set of models was tested for each latent factor. The model with the highest fit index was subsequently chosen as the best model for the interpretation of fixed effects. Results revealed plausible predictive effects, mostly involving gender, age, and their respective interaction with time for all latent factors except for attention. For instance, concerning declarative memory, the best model revealed a significant main effect for age (β=-0.11, $t(299)$=-2.340, p=.019), time (β=-0.13, $t(299)$=-2.898, p=.004) and gender (β=0.44, $t(299)$=4.765, p<.001), indicating declining scores with higher age and over time as well as in men as compared to women.

In order to draw a comparison between the classical composite approach and the latent factor approach presented here, the same model was again fitted with an unweighted composite approach. Thus, the same predictors and their respective interactions were used with the composite declarative memory as dependent variable (see section 2.3.3. for

details). This mixed model, revealed only one effect for gender (β= 0.22, $t(299)$=2.483, p=.014), which was also less significant as compared to the latent factor approach. As a result, concerning the declarative memory domain, the same predictor model within the latent factor approach was able to find more significant and greater effects for the given list of predictors as compared to the composite approach.

16.5 Discussion

The current longitudinal analysis was performed to identify hints towards cognitive decline in a sample cohort totaling 330 individuals. As part of this, longitudinal MI of a test battery of 14 neuropsychiatric test variables was investigated across three years, which led to the identification of four stable latent factors of cognitive abilities: declarative memory, attention, working memory, and visual-spatial processing. Furthermore, predictive analyses using scores of these domains as a dependent variable indicated that latent ability scores increased significance of regression analyses in comparison to composite scores.

Longitudinal Measurement Invariance. To this day, there are only few studies available that analyzed longitudinal MI in neuropsychiatric test batteries and defined latent factor scores as dependent variables in the prediction of pathological cognitive decline. The SEM approach allows for concurrent testing of group/time-related differences in latent and manifest variables. Table 10 indicates that loadings of indicator variables significantly vary over time, leading to small but significant changes in model fit. Table 11 further clarifies this non-MI stems from VLMT, RWT, and WMS-R-related measures. In the context of the classical composite approach, this highlights a possible reason for null-findings: In the current study, the WMS-R block span test score becomes less indicative of the latent visual-spatial processing performance. Thus, if a researcher imposes the same weighting on this test score at both measurement occasions, the resulting trend over time may be biased.

To put the study results in a simple context, the following section compares approaches by using loadings of the configural model as weights while using actual mean standardized test scores (standardized to M=50, SD=10) of the 330 participants as variables. For unweighted composites, researchers may usually use the formula shown in

equation (5):

$$(1 \cdot 73.95 + 1 \cdot 59.76 + 1 \cdot 41.74) - (1 \cdot 70.20 + 1 \cdot 66.0 + 1 \cdot 35.07) = 4.18 \quad (5)$$

Here, (5) indicates the implicitly imposed weight of 1 for each variable and other numbers reflecting the average test score. By subtracting the scores of the second measurement occasion from the first, the result reflects the mean change of the visual-spatial processing composite over time. A positive score indicates decreases over time. However, Table 11 suggests that performances in the three tests are not equally relevant to the latent ability of visual-spatial processing. Thus, equation (6) modifies the previous approach by imposing different weights for each variable (according to Table 11):

$$(1 \cdot 73.95 + 1.389 \cdot 59.76 + 0.490 \cdot 41.74) - (1 \cdot 70.20 + 1.389 \cdot 66.0 + 0.490 \cdot 35.07) = -1.65 \quad (6)$$

The result indicates an overestimation of the unweighted composite approach in comparison to the weighted one. The latter implies an overall increase in skill. However, equation (6) would be appropriate only if measurement invariance for factor loadings were given. Since Table 9 indicates otherwise, the formula is once again adapted by varying weights over time. The resulting equation is given in equation (7):

$$(1 \cdot 73.95 + 1.389 \cdot 59.76 + 0.490 \cdot 41.74) - (1 \cdot 70.20 + 1.368 \cdot 66.0 + 0.217 \cdot 35.07) = 9.31 \quad (7)$$

Since equation (7) results from the model that fits the data best, we assume that its result is the most unbiased. Equation (5) would only be unbiased if all test scores were equally relevant/indicative/correlated to/of the target-construct (visual-spatial processing), while equation (6) would only hold if metric invariance was given. This example illustrates the value of SEM-driven course analyses and possible shortcomings of the most often used approach as equation (7) produced an effect more than double in size as the

unweighted composite approach did.

The maximal misestimation due to non-MI is given by the sum of absolute factor loading differences between measurement occasions (N. Schmitt et al., 2011). For instance, in this study, the sum of for the factor visual-spatial processing equals 0.137 $((0.410 - 0.487)| + |(0.620 - 0.540)|)$.

Furthermore, apart from changes in loadings over time, test intercepts also partially varied. For instance, WMS-DS test intercepts significantly increased while WMS-block-span performance decreased (see Table 11). This result highlights that even though these two subscales were taken from one test-(battery), the performance trajectories were opposed to one another. Interestingly, this fits well with the factorial structure. While both visual-spatial processing and declarative memory seem to pose as promising cognitive domains to assess early changes in abilities (indicated by Table 12.), working memory was mostly characterized by invariance over time, which may be why mostly VLMT measures, along with WMS-block span showed decreasing intercepts in Table 11.

Course of latent factor scores. On a latent factor level, variances of declarative and working memory as well as visual-spatial processing increased over time, indicating the existence of at least one mechanism that may drive increases in sample-based variance statistics of latent ability scores. One explanation may lie in the existence of at least two groups that develop into different directions. At the same time, another possibility is given by the increasing inner-individual variance in ability retrieval in those who suffer from cognitive decline (memory capacitance may vary more greatly from day to day in those who show signs of an MCI than it does in healthy young adults). Either way, this indicates declarative memory, working memory, and visual-spatial processing to pose as early indicators for age-related changes in cognition.

Moreover, in the context of neuropsychiatric test scores, differences in covariances, including factor loadings and latent factor covariance, may reflect compensatory mechanisms between initially independent neuronal systems and functions. On that note, the connection between visual-spatial processing and declarative memory increased over time, possibly indicating at least one subsystem to rely on the other increasingly. Other interpretations may assume a third variable to produce these changes in covariance matrices.

For instance, an uncontrolled third variable may affect both factors, thereby increasing their correlation over time. One such factor may be early signs of cognitive decline, which would be plausible given that only test intercepts of these two factors expressed non-MI. However, these interpretations are not yet reliable, basing them solely on the data of this one study. Further research and discussion are needed. Nonetheless, since covariance between those two factors that show the greatest changes in variance and intercepts increased, it would be plausible to assume that the connection between these constructs increases as a function of age and/or pathology-related cognitive decline.

Prediction of pathological cognitive decline. Finally, the current study provided a short example on the topic of latent score prediction based on covariates, psychometric parameters, and biomarkers.

Since the exemplary effects in latent factor score related analyses were generally more significant than in the composite models, these data highlight the possible benefit from investing in the more complex but possibly more reliable and valid SEM approach. This is especially relevant since the composite models produced effects that may not be plausible, such as increased working memory capability in older individuals.

16.6 Conclusions

Methodologically, it may be appropriate to calculate (weighted) composite variables instead of latent factors. However, it is important to note that composite variables do not adapt to the data over time. This indicates active neglect of compensation mechanisms, retest effects, habituation to test settings, the influence of increasingly severe disease, and many more factors of influence, as these may cause significant changes in the interdepend ability of neuropsychiatric functioning. For instance, loss of function in certain brain areas may affect the intercorrelation of neuropsychiatric domains by making them dependent on other compensating areas/functions. Moreover, psychological variables like trait anxiety may impair performance in the first measurement occasion to other extents as it does in the second due to habituation effects.

SEM, on the other hand, estimates such influences indirectly by addressing changes in the correlation matrix among manifest test scores obtained. As a result,

changes in manifest scores, latent performances and their correlation can be addressed all at once. In fact, in this study, we found hints to either compensation mechanism or neurological change over time, as the covariance between visual-spatial processing and declarative memory increased. Since the variance of both latent factors also increased, while their intercepts decreased, these results may hint at least two sub-samples within the analyzed participants that showed different trajectories in their cognitive abilities across measurement occasions or a general decline in capabilities on these domains that results in increased inner-individual variability of skills (or a mix of both). However, this interpretation is speculative and needs clarification by identifying predictors for these latent score changes. The above-mentioned interpretation would become very plausible if the covariance pattern between both factors would decline to their baseline level after controlling for such predictors. Hence, again the SEM approach provides additional ways to gain more detailed insights into the data as the composite approach does. Moreover, in the example for one of the latent factors provided above, we were able to show that the composite approach underestimated the effect of change over time by more than 50%, which again highlights possible shortcomings of the classical composite approach and may reveal mechanisms by which classical longitudinal analyses may have trouble finding reliable and significant change.

Ultimately, the exemplary prediction analysis depicted in this study provided further evidence of the superiority of the SEM approach over the composite approach, supporting the idea that this approach produces more reliable results. To conclude our findings, this study was able to find four latent factors that are in line with previous research. Furthermore, by testing these factors for longitudinal measurement invariance, this study provides insights into calculating the extent of bias that may lead to inflation or false null-findings in the classical composite approach. In addition, even though measurement invariance was not present for most parameters, this study also discussed how this may be beneficial to understanding both normative and pathological aging. In sum, the SEM approach adds highly relevant information to the interpretation of longitudinal neuropsychiatric data.

16.6.1 Limitations

First, the generalizability of the factor structure may be impaired as the results are specific to the neuropsychiatric test battery used. Also, although supported by the residents registration office, participant recruitment was not fully representative for the general population (Polak et al., 2017). In the case of the Vogel Study, participants had a relatively higher education level in comparison with the general German population (Statistisches Bundesamt, 2018). Additionally, one problem of this latent factor model was the factor attention as it comprised only two manifest indicators, which may have significantly biased results for this domain (Kline, 2005). This may be one reason why no significant effect was present regarding this factor. Nonetheless, we do not anticipate significant misestimation of other factors and their indicators due to this issue.

Also, we want to note that the use of factor scores may propagate estimation errors within the SEM to the analysis of predictor variables which is an inherent risk to this approach and may lead to false results.

Due to relatively small sample size concerning the complex methodology, the precision of model estimation may have suffered. However, larger sample sizes may lead to smaller error terms and increased significance even for small non-invariance, which may also pose an issue as this may lead to overly sensitive analyses. As a result, we argue to estimate the difference of effects due to variability of parameters (by using the formulas (1), (2) and (3)) to estimate the relevance of effects than to solely rely on significance. By doing so, greater sample sizes will lead to better estimation without introducing overinterpretation of significance.

Finally, the dataset included missings. Due to dropouts resulting from the longitudinal study setting and incomplete datasets, the sample size decreased from N = 604 participants at V1 to n = 330 at V2. Reasons for data exclusion may have correlated to cognitive ability and thus imply a selection bias for the remaining 330 participants, which indicates that the current study may have excluded such participants who had particularly bad courses. As a result, generalizability of results presented in this methods-focused paper may be considerably impaired. Within the remaining data set, only 0.0048% were missing implying no substantial influence on the estimation procedure within the SEM

analysis.

Finally, as only n = 330 participants remained in the model, this study relied on the lower bound of necessary data to address such models as discussed in the current manuscript, even though more complex models like (second-order) latent growth curve models would be superior as they would be able to model the within-subject nature of the data more properly. Nonetheless, to our understanding, this sample size was sufficient for whole-model comparisons within the current approach.

17 Additional Analyses - Paper II

The method of calculating cognitive skills described in Paper II could, as already discussed in the manuscript, contribute to a more reliable estimation than would be possible with classical composite approaches. For this reason, the latent skill estimates calculated within Paper II are now used for further analyses investigating the influence of and on depressive symptoms.

First, a total of four path analyses were calculated for this purpose. These correspond in their structure to what is illustrated in Figure 12. Again, depression at t2 is defined as an endogenous variable, while its counterpart at t1 and another predictor (measured at both measurement occasions) are included as exogenous variables. In total, four of these models were run, each differing only in which cognitive domain was included as the additional predictor. The results can be seen in Supplements 40 to 43. In summary, however, it can already be stated at this point that there were no significant predictive effects for cognitive skills (at t1 or t2) on depression scores at t2 in any of the four models. At the same time, depressiveness at t1 did not predict the expression of cognitive skills at t2 in any of the models.

These results suggest that, at least for (mostly) healthy aging subjects, no significant deterioration of cognitive skills by higher depression scores is to be expected over 3 years. At the same time, none of the latent constructs specified in Paper II appear to worsen (or improve) depression in such a sample.

17.1 Embedding in the Thesis Framework (Paper II)

The influence of depression on cognitive skills has been described in numerous studies. However, meta-analyses show a different picture: although there may be significant effects, they seem to be rather small (e.g., J. Q. Li et al., 2016; Song et al., 2018; Prado et al., 2019). The statistical method presented in Paper II was utilized to increase the reliability of the estimation of such skills. It ultimately produced such estimates that the replicated the small effect sizes found in meta-analyses. This can be seen in the Appendix 27.2: While the mixed model regression analyses produced meta-analysis compatible and plausible effects, the composite approach, on the other hand, produced results that differed significantly in some cases, which could explain the great heterogeneity of findings beyond the meta-analytic papers.

The validity of the estimated latent factors is further substantiated by the results of Haberstumpf et al. (2021),who used equivalent estimates from the complete sample at t1 to predict drop-out at t2.

In the additional analyses for Paper II, it was then shown that depression and cognitive skills appear to be largely independent of each other. This may be because the period studied here was too small to find any real influence of one on the other, or that the sample was too healthy. Thus, it could follow that in people with greater functional limitations in everyday life, there could also be greater correlations with depressiveness. Nonetheless, it seems that affective symptoms in the general population are not significantly influential in the course of cognitive skills (see Supplements 40 to 43) and that cognitive skills themselves are not a significant or relevant predictor for depression three years later.

Independently from this, these analyses further indicate a significantly greater β-coefficient from depression at t1 on depression at t2 in the sample from Paper II (~.74) than in the sample from Paper I at the same time interval (T-4 ~.53). This could indicate higher stability of depression scores at older compared to younger ages.

Overall, the findings described here, also taking into account the results from Paper I, indicate that depressive symptoms have an impact on the course of comorbid illnesses, especially if they are long-lasting or at least highly recurrent. This is indicated

by the fact that depression does not seem to have any influence on the course or point-prevalence of cognitive decline. On the other hand, the findings from Papers I and II also provide evidence that depressive symptoms themselves may vary in their stability depending on age or unreported confounding influences related to age. As the additional analyses to Paper I show, there may be other predictor variables that are more stable. While Paper I shows that a sense of belonging seems to be a good predictor, Paper II shows that 'objectified' performance does not seem to be a good predictor. This could also be due to various reasons, which will be discussed further in the concluding discussion of this thesis.

Part III - Manuscripts and Additional Analyses - Neuromodulation of the Right Inferior Frontal Gyrus

According to the previous sections, to a substantial extent, depression is predicted by vulnerability factors which may be stable (e.g., neuroticism) but also variable (e.g., SoB). Thus, against the background of Anderson's study (S. F. Anderson et al., 2016) it may be concluded that psychotherapy aiming for long-term effects must also bring about a long-term change in these factors, although so far therapeutic approaches seem to have little access to this[19].

To address this issue, in the following manuscripts, a new (neuromodulation) approach to directly modulate such vulnerability factors is presented. In light of the impact shown by SoB, the following manuscripts may thus add insight on a psychotherapy-augmenting neuromodulation method that may be suited to either stimulate social approach behavior or induce beneficial cognition, motivation or affective processing in the wake of social feedback or stimulus processing in general.

Nonetheless, other influential vulnerability factors than SoB have been discussed. For instance, helplessness, in accordance to section 3.1 is a major contributor to the intraindividual emergence of depression. In addition, the inherent neural mecha-

[19]Otherwise there would be differences in the effect of treatment which would have to be explained by the very different assumed mechanisms of action. see Section 2.1

nisms preventing the *overwriting* of established neural connections were highlighted as a potential contributor to the recurrence of vulnerability and disease. Finally, high neuroticism, high BIS, low BAS, and high extraversion were summarized as the biggest influences in regards to stable personality traits.

As a result, since a neuromodulation approach was used, the following sections focus on social cues and their processing, the basis of helplessness and its processing, and the processing of stochastic information (which may be the foundation of memory labilization). Furthermore, the modulation was focused on cortical sites that are implied in all of the aforementioned personality traits.

18 Paper III - The Right Lateral Prefrontal Cortex Impacts Control Perception

The following text has been published as a preprint. Minor changes in style, figure, and table referencing or grammar were made in comparison to the preprint version. It is strongly recommended to review the preprint version and cite the text as follows: Forster, A., Hewig, J., Allen, J. J., Rodrigues, J., Ziebell, P., & Sanguinetti, J. (2021, November 14). The Right Lateral Prefrontal Cortex Impacts Control Perception as a Function of Probabilistic Stimulus Processing. https://doi.org/10.31234/osf.io/g97ky.

Title: The Right Lateral Prefrontal Cortex Impacts Control Perception as a Function of Probabilistic Stimulus Processing

Authors: Forster, A.[a1], Rodrigues, J.[a], Ziebell, P.[a], Sanguinetti, J.[b], Allen, J. J.[b], Hewig, J.[a]

[a]Institute of Psychology, Julius-Maximilians-University, Würzburg, Germany

[b]University of Arizona, Tucson, USA

[1]Corresponding author

18.1 Abstract

Being able to control inner and environmental states is a basic need of living creatures. Control perception (CP) itself may be neurally computed as the subjective ratio of outcome probabilities given the presence and the absence of behavior. If behavior increases the perceived probability of a given outcome, action-outcome contingency is met, and CP may emerge. Nonetheless, in regard of this model, not much is known on how the brain processes CP from these information. This study uses low-intensity transcranial focused ultrasound neuromodulation in a randomized-controlled double-blind cross-over design to investigate the impact of the right inferior frontal gyrus on this process. Fourty healthy participants visited the laboratory twice (once in a sham, once in a neuromodulation condition) and rated their control perception regarding a classical control illusion task. EEG alpha and theta power density were analyzed in a hierarchical single trial based mixed modeling approach. Results indicate that the right lateral PFC modulates action-outcome learning by providing stochastic information about the situation with increased alpha responses during low control situations (in which the ratio of probabilities is zero). Furthermore, this alpha response was found to modulate mid-frontal theta by altering its relationship with self-reported effort and worrying. These data provide evidence for right lateral PFC mediated probabilistic stimulus processing during the emergence of CP.

18.2 Introduction

Having a sense of control over both, inner and environmental states is a basic need of living creatures, including humans. In order to achieve such, as there usually is no complete data about a given situation present, an organism needs to form subjective rather than objective conclusions on whether alterations of states are contingent responses to its own action (Presson and Benassi, 1996; Alloy and Abramson, 1982; Ajzen, 2002; Niv, 2009). As a result, individual differences in control-beliefs may stem from interactions of self-perceived agentic behavior and the evaluation of contingency of its consequences (Matute, 1996; Blanco et al., 2011; van Elk et al., 2015). As these individual differences in control expectation are implicated in a variety of psychiatric disorders such as depression (Golin et al., 1977; Alloy and Abramson, 1982) and may also pose as a trait to predetermine future episodes of such (Alloy and Clements, 1992), being able to induce a greater sense of control, is a key aspect of both, preventive and curative interventions (Wallston et al., 1987; J. D. Brown and Siegel, 1988; Ledrich and Gana, 2013; Alsawy et al., 2014; M. W. Gallagher et al., 2014; Hogendoorn et al., 2014). One method to alter control perception in individuals who are otherwise resistant to interventions is non-invasive neuromodulation (Borckardt et al., 2011; Chambon et al., 2015; Vanneste and de Ridder, 2012). In the current study, low-intensity transcranial focused ultrasound neuromodulation (litFUS) was applied to increase the sense of control over an unpredictable rewarding stimulus by inhibiting the right inferior gyrus (riFG) of the lateral prefrontal cortex (lPFC). litFUS is a novel method to precisely inhibit or excite neural ensembles even in subcortical structures. Its effect is investigated in self-report measures as well as in EEG oscillations of the individual alpha and theta frequency bands.

18.2.1 Neural bases of control perception.

In context of the learned helplessness theory, control perception was subject to extensive research in regards of its protective properties against stress and disease. In the theories' beginnings, in order to stimulate further research on the topic of learned helplessness/hopelessness, Maier and Seligman (Maier and Seligman, 1976,Maier and Seligman, 2016) provided an influential definition for the emergence of subjective control perception:

The authors hypothesize control perception to ground on the estimated ratio between two perceived probabilities: First, the probability of a specified outcome following some kind of action by the subject. Second, the probability for this outcome in the absence of such action. As a result, if the subject's behavior changes the probability of an outcome in comparison to its probability in the absence of behavior, action-outcome contingency is perceived. In turn, this experience of contingency paves the way to the overall sense of control over the outcome.

In summary, this model implies control perception to be a function of conditional probabilistic learning that then guides behavior-outcome contingency detection on which control perception builds.

The neural basis of contingency perception has been extensively researched throughout the past decades and produced several models including several regions of interest. On that note, one integrative model postulated by Holroyd and Umemoto (Holroyd and Umemoto, 2016) depicts several modules to interact on a hierarchical basis during goal-directed behavior and its online evaluation. Here, the anterior cingulate cortex (ACC) decides which task or objective to pursue as a function of its overall estimated value weighted against the necessary effort. It thus increases in activity to regulate effortful behavior to the point when the effort is not worth the reward anymore. The ACC's role in effortful and goal directed behavior modulation has also been shown to partly rely on its capability to learn from action-outcome contingency. For instance, ACC lesions in monkeys critically impaired their ability sustain rewarded behavior, which the authors attribute to failure to utilize information of the recent reinforcement history to compute the potential value of behavioral decisions (Kennerley et al., 2006). Interestingly, this was true for both, error and reward driven learning processes. In line with this, Cavanagh and Shackman (J. F. Cavanagh and Shackman, 2015a) state in their meta-analytic review that ACC activity reflects both, prediction errors (with implications in anxiety and conflict processing) and adaptive behavior by signaling the *need* for control, enhancing the attention to relevant stimuli and initiating cognitive control mechanisms in general.

In addition to the ACC, according to Holroyd's and Umemoto's model, the lPFC and the dorsal striatum pose as the main actor of the brain, connecting internal

signal processing with behavioral outputs. Furthermore, this network is thought to be effort-averse, avoiding low reward/high effort tasks and behavior. Correspondingly, the lPFC has already been described several times as an area of interest in the context of control perception (Fletcher et al., 2001; O'Dhaniel et al., 2011). Lorenz et al. (Lorenz et al., 2015) show that activity of the right inferior frontal gyrus (riFG) of the lPFC in combination with the ventral striatum (VS) may correlate with the illusion of control. However, there is some debate on the nature of this relationship, as right lPFC activity has been reported to inhibit reward-related networks (including the VS (Aron et al., 2004), thereby possibly signaling diminished reward related processing. On that note, several studies have reported increases in right lPFC phasic activation to devaluate immediate rewards (Fecteau et al., 2007; Camus et al., 2009; Cho et al., 2010; Staudinger et al., 2011), which is in line with its effort-averse role in the model of Holroyd and Umemoto. Similar to these results, extensive research on frontal EEG alpha asymmetry implies a role of the right lPFC in withdrawal motivation, withholding and negative affectivity (e.g., Hewig et al., 2005; Wacker, Chavanon, et al., 2010; Reznik and Allen, 2018; Hewig, 2018; Rodrigues et al., 2018).

Correspondingly to this role in motivation and emotion, the lPFC had soon been associated with reinforcement sensitivity and reinforcement learning (see Rodrigues et al., 2018 for a review of current models). In context of such learning, the lPFC needs to be informed about reinforcement patterns/probabilities. Without such, behavioral and motivational tendencies (as defined by frontal asymmetry research but also Holroyd's and Umemoto's model) would not be able to adapt to a given situation. Here, especially the right hemispheric lPFC may serve a unique function as evidence suggests it to be sensitive to probabilistic learning and "model building" (M. B. Miller and Valsangkar-Smyth, 2005; Roser et al., 2011; Danckert et al., 2012; Stöttinger et al., 2014; Janacsek et al., 2015; Filipowicz et al., 2016), including probabilistic processing of associative relationships (Fletcher et al., 2001). Even though some evidence also suggests the left lPFC to serve similar functions (Wolford et al., 2000; Hecht et al., 2010), findings in favor of right hemispheric dependence in stochastic information processing prevails. Thus, in summary, especially the right lPFC may either provide or at least process information about the

above-mentioned estimation of probability ratios that ultimately build the basis for overall control perception as suggested by Maier and Seligman.

Taken together, given a situation of uncertainty, the ACC would be predicted to respond by increased activity reflecting the need for control, facilitating effort despite unclear probabilities of reward. Hence, it may pose as a neural basis of behavioral adaptation (Botvinick et al., 2001; J. F. Cavanagh et al., 2009; J. F. Cavanagh and Frank, 2014; J. F. Cavanagh and Shackman, 2015a). However, at some point, its activity may cease due to devaluation of the anticipated outcome in context of the escalating effort to maintain behavioral activity. According to the model of Holroyd and Umemoto, this effect may be mediated by the effort averse lPFC, which may do so, based on the processing of stochastic information.

18.2.2 Neuromodulation of the personal sense of control.

One method to intervene directly in above-mentioned neural systems is non-invasive neuromodulation. However, to our knowledge only one study has directly investigated changes in the perception of control in response to such treatment. Borckardt et al. (Borckardt et al., 2011) increased the activity of the left lPFC via transcranial magnetic stimulation (TMS) in a task that required participants to exercise control via fast button presses over the onset of heat induced pain. Even though, unbeknownst to the participants, reaction time of their response did not influence the pain inducing mechanism, TMS receiving participants reported significantly less perception of control than the sham-group did. The authors concluded that the lPFC plays a role in control perception mediated analgesic placebo effects. Interestingly, this result in combination with the findings of Lorenz et al. (Lorenz et al., 2015) indicates an asymmetrical contribution of lPFC activity to the perception of control, as left sided activity decreases, while right sided activity increases the illusion of control.

However, in order to choose a site of modulation based on these findings, a three-dimensional region of interest must be defined. As stated above, the lPFC is part of a cortico-striatal network, posing as the actor in goal directed behavior. Since lPFC areas that encompass strong projections to according subcortical areas are mostly located

in lower-order cortical laminas, neuromodulation may be especially effective if such (more deeply located) areas are targeted. Currently established techniques of modulation such as electro-magnetism-based applications are able to reach high spatial specificity in superficial cortical areas, but are mostly inefficient to use in deeper structures (Zangen et al., 2005; Roth et al., 2007). Transcranial direct current stimulation (another widely utilized method) on the other hand is capable of reaching deeper structures but loses its spatial resolution on the way (Datta et al., 2009; Sadleir et al., 2010).

Taken together, several target regions for neuromodulation of control perception emerge, including the OFC, ACC, subcortical nuclei and the lPFC. However, in general, targeting any these regions faces substantial issues before the background of spatial resolution and depth of modulation. Even though, the method utilized in the current study would in general be capable of reaching these, low-intensity transcranial focused ultrasound (litFUS) was used to inhibit the right lPFC due to safety regulations at the time. litFUS is a novel method to excite and inhibit neural tissue via ultrasound with a high spatial resolution and the capability to reach structures as deep as the brain stem (Legon et al., 2018; Tufail et al., 2010). Several studies throughout the recent years have shown its potency in modulating neural tissue in humans (J. L. Sanguinetti et al., 2020; Reznik et al., 2020; Hameroff et al., 2013) and animals (Kim et al., 2015; Yoo et al., 2011), giving rise to several theories of functioning mechanisms (e.g., Tyler, 2012; Plaksin et al., 2016; Alloy et al., 1981).

litFUS was used in order to hit not only superficial but also deeper laminas, which will supposedly comprise a larger amount of inhibitory projections involved in cognitive control. Additionally, this inhibitory control was often described in context of EEG alpha oscillations (8-13 Hz) that are thought to be differentially modulated by inhibitory litFUS administration. This hypothesis builds on findings that alpha oscillations (partly) rely on T-type Ca^{2+} channels that pose as one mechanism of thalamus driven synchronization (see Bazanova and Vernon, 2014 for a short review). These channels inherently fire at a rate of approximately 10Hz, inducing alpha synchronization via thalamic relays (Bollimunta et al., 2011; Bright et al., 2007; S. W. Hughes and Crunelli, 2005; S. Hughes et al., 2011). Following the NICE-model of channel specific effects of ultrasonic neuromod-

ulation (Plaksin et al., 2016), neurons expressing this type of channel play a crucial role in delivering inhibitory effects by the (generally exciting) ultrasound waves since excited inhibitory interneurons of this type may decrease net network-level activity.

18.3 The present study.

In the present study, litFUS is used to investigate the impact of the right lPFC on the constitution of control perception. As stated above, this relationship is thought to ground on the processing of probabilities. Thus, a hierarchical design of analysis was chosen in order to relate single-trial based reactions to probabilistic contexts and higher order self-rate measures. Furthermore, since control perception depends on the actual experience with a given stimulus, study designs investigating the influence of within-subject effects should either fixate the experience in each individual trial across all participants or restrict the stimulus' behavior to a stochastic function with a known distribution (the latter was used in this study). As a result, on a single trial level, sequence effects of the experience with the stimulus can be analyzed while on a higher level within-subject effects can be analyzed independently. In this study, a task presenting a stimulus randomly (which was unknown by the participants) was used to investigate the emergence of control illusion (which is in this context equivalent to control perception). The right lPFC's reaction to the emergence/absence of the stimulus was then measured and put in context of the previous experience with the task. This was done by calculating the rate of stimulus presence up to the given trial (e.g., in trial 10, if the stimulus was present 3 times, the rate equals 0.3). Thus, immediate reactions to the stimulus (possibly reflecting a process of valuation) and a reaction to an implicitly estimated probability can be analyzed for interactions and the relation to control perception as well as mid-frontal theta (MFT).

MFT is thought to reflect ACC activity. It is investigated as it is (a) thought to interact with the right lPFC's information on probabilities and (b) reflects an important area involved in contingency processing itself. Furthermore, it is thought to reflect effortful control and conflict considering goal directed behavior.

To do so, an EEG was applied in a task asking participants to gain as much control as possible over an (unbeknownst to them) uncontrollably emerging, rewarding

stimulus. Additionally, each participant completed this task twice, once in a sham, once in a neuromodulation condition making this a randomized controlled double-blind cross-over study design. Dependent measures were EEG based midfrontal theta frequency band density power (to inspect ACC activity) and alpha frequency band density power at right lPFC regions as well as psychometric self-rate measures.

18.3.1 Hypotheses

18.3.2 The role of the riFG in control perception.

Since the right lPFC has been reported to model "the world" in a stochastic fashion, we hypothesize the neuromodulation to interfere with its processing of reinforcer presentation rates. Thus, alpha power density at the F8 electrode position (10-20-system) hovering the right inferior gyrus of the lPFC was used as dependent variable. Increases in this measure are thought to reflect decreased cortical activity. It should vary as a function of stochastic processing and correlate to control perception.

Hence, in order to investigate these relationships, two variables were calculated and included into a hierarchical mixed model. First, since no fixed sequence of reinforcer presence was provided, on a single trial level inter- and intraindividual differences in presentation sequences emerge (between participants and between sessions within participants). Therefore a variable depicting the number of trials since the last presence of the reinforcer was included into the model.

Furthermore, this effect should also alter immediate responses to the presence of a reinforcer in context of its previous sequence of presentation. Hence, in subsequent analyses, an estimator for the response to the sequence presence of a reinforcer as well as an estimator of the overall presentation rate of the stimulus are reported. We anticipate a three-way interaction of overall reinforcement rate, litFUS and the presence/absence of the reinforcer in a given trial. Furthermore, litFUS may increase control perception directly, by interfering with the processing of probabilities. Since the least amount of contingency/control perception should result from reinforcer-rates of 50%, not only linear, but quadratic functions are included.

18.3.3 Midfrontal Theta mirrors conflict and effortful control.

As mid-frontal theta is thought to reflect ACC activity, which is correlated to both, effort and conflict, we hypothesize this measure to either correlate to worrying (as a marker for cognitive control mechanisms) or effort (both self-rated). Furthermore, we hypothesize mid-frontal theta to rely on right lPFC processing, as it provides valuable information about needed effort to attain a goal though its probabilistic processing. Thus, we also hypothesize mid-frontal theta to be directly modulated by right lPFC alpha density power.

18.4 Methods

18.4.1 Sample.

A total of 41 healthy volunteers was investigated after collecting written consent. Due to one participant taking part only in one session, only 40 data sets are analyzed. Participants were recruited via an online platform of the University of Wuerzburg, Germany and postings on bulletin boards within the university. Of the 40 remaining participants, 28 were female. Mean age was 24.1 (SD: 8.159). Participants were required to be at least 18 years old, not pregnant, right handed and without previously diagnosed neurological or psychiatric diseases. All participants gave their consent to publication of their data. The neuromodulation procedure was approved by the local ethics committee of the institute of psychology (reference: GZEK 2017-18) Further descriptive variables are presented in Table 13.

18.4.2 Material.

The task was programmed in PsychoPy version 2.7 (Peirce, 2009) and presented on a 24-inch screen (1920x1200 pixel). The rewarding stimulus was taken from emojipedia.org (Thumbs up sign, Apple IOS version 13.3). The thumbs up emoji was chosen in order to minimize confounding effects like interactions with the participant's gender (e.g., in response to faces) or other traits (like materialism in context of monetary reward or loss).

18.4.3 Procedure

Overall Setting. This experiment was part of larger study that comprised three independent tasks. Each participant visited the laboratory setting twice. The arrangement of tasks did not change between sessions, with this one to be last of all three. It began approximately 20 minutes after the start of the experimental battery and approximately 40 minutes after litFUS administration. Before participants visited the EEG-laboratory an online-survey was completed, including a number of questionnaires that are relevant to the other two studies of the experimental set but are not reported here. The rewarding stimulus was solely used in this task but not in preceding.

This study was conducted in a randomized-controlled double-blind cross-over design. Each volunteer received either sham or litFUS modulation at session one and the remaining at session two. The order of modulation was randomized across participants. Furthermore, neither experimenters, nor participants knew whether sham of litFUS was applied in a given session.

Task. The task was largely designed following the task and instruction of Alloy, Abramson and Viscusi (Alloy et al., 1981, p.1134). In the original study, the authors presented the judgement of control problem, which was previously developed by the same group (Alloy and Abramson, Alloy and Abramson, 1979). Over the course of 40 trials, participants were asked to behave in the way of either pressing a button or not doing so. In 50% of trials, a green light would appear, in the remaining 50% it would not. Afterwards participants were asked how much control they were able to exert on the green light. The authors were able to replicate findings on greater control illusions in healthy as compared to depressed individuals, highlighting that depressed subjects showed a more accurate estimation of contingency.

The exact instruction is given at page 1134, in the paper of Alloy, Abramson and Viscusi (Alloy et al., 1981). This text was translated and used in the current study as well. In short, participants were asked to gain as much control as possible over the emergence of a positive reinforcer. In a time window of 3 seconds, they were asked to try and make the stimulus appear by pressing the space button as much as they wanted. They were also informed, that the stimulus may sometimes appear, even though no button-press

was made and sometimes may stay away even though press(es) preceded. Contrary to the original study, participants were allowed to press as often as they wanted within one trial. A total of 40 trials was completed in each session. Also, just like in the original study, unbeknownst to the participants, the stimulus was presented at completely random leading to a Bernoulli-distributed succession of events. As a result, on a single trial level, the experience of participants with the reinforcer (e.g., by the number of trials including the reinforcer in context of the overall number of trials) can be analyzed independently from immediate responses to its current presence of absence. However, the expected value of trials depicting the reinforcer was 20. If shown, the stimulus remained present for 1 second.

After each session, participants rated the effort put into the task (how much effort did you put into the task?), the perceived control over the emergence of the stimulus(how much control did you gain over the emergence of the stimulus?), their assumption on how well they performed in comparison to others (how well did you do in comparison to others?) and their worrying about their performance (how much did you worry about your performance?) on a 1-100 visual analog scale (VAS). The ends of the VAS were described by not at all and very much/good Each was measured via one custom question.

18.4.4 litFUS Neuromodulation.

Neuromodulation was applied at F8 electrode position of the 10-20 EEG system. Its administration lasted for 120 seconds with a duty cycle of 0.05%, a frequency of 500 kHz and a pulse repetition frequency of 40 Hz leading to an acoustic power of 199mW/cmš and a mechanical index of 1.53. The ultrasound was emitted by a transducer, which connected to a gel pad that was directly placed on the F8 position of the scalp. Neuromodulation was operated by a manufactured device (Thync, Los Gatos, USA) and carried out by two experimenters at a time (one fixating the transducer and the gel pad to the participants head and one starting the procedure on the device). While the two minutes of modulation/sham were running, participants were asked not to move or talk in order to prevent distortions of the transducer relative to the targeted location. According to current computational models, litFUS neuromodulation with these parameters inhibits

neural excitability (Plaksin et al., 2016) Since ultrasonic waves are too high in frequency to be heard by humans, litFUS can easily be shamed. In this study, experimenters either pointed the transducer at the desired region of interest or in the opposite direction, away from the test-persons head. However, litFUS was emitted either way, keeping the preparation process for experimenters constant across litFUS-and sham-modulation. Nonetheless, depending on condition and session (t1 vs. t2) experimenters were required to point the transducer into said directions without knowing which end of the transducer was actually the active one.

The same device was used before by J. L. Sanguinetti et al., 2020, who differing parameters to the same region of interest as it was in this study (for more details on the device and the method in general, please see J. L. Sanguinetti et al., 2020).

18.4.5 EEG recording and preprocessing.

EEG recordings were collected via a 64-electrode montage and a brain vision recording system (Brain Products, Gilching, Germany). However, due to unforeseen technical issues, 13 participants were tested with an 32 electrode cap but an otherwise equal recording system. Bazanova and Vernon (Bazanova and Vernon, 2014) report the cap montage to not influence alpha-related measures. Additionally, in all analyses depicted below, only those electrodes were included, that were present in both sets. Electrodes were brought under 5 k. Online reference was Cz, ground was Afz.

The preprocessing was conducted via the Matlab (The MathWorks, Massachusetts, USA) extension EEGLAB (Delorme and Makeig, 2004) including plugins MARA (Winkler et al., 2011), Adjust (Mognon et al., 2011), SASICA (Chaumon et al., 2015), the CSD-toolbox (Kayser and Tenke, 2006a; Kayser and Tenke, 2006b) and the restingIAF toolbox (A. W. Corcoran et al., 2018). The procedure mostly followed Rodrigues et al. (Rodrigues et al., 2021) preprocessing pipeline: Electrodes were at first re-referenced to average. Afterwards, channels were automatically rejected and interpolated based on their averaged z-score on the three dimensions kurtosis, probability and spectrum. A z-score (calculated for the mean of one channel in comparison to all others) of more/less than ś3.29 (following suggestions by Tabachnik and Fiedell Tabachnick et al., 2007 on outlier

detection) qualified a channel for rejection. Epochs were extracted (-300 ms. to 1000 ms.) and a 1Hz high-pass filter was applied. Then, an ICA was conducted, and trials were automatically rejected by the same procedure as the channels had been. Following this, ICA weights and indices of rejected trials were saved. The preprocessing started once again and applied the saved parameters to the new set that was now missing the 1Hz filter in its pipeline. Afterwards, MARA was used to reject components based on Adjust and SASICA evaluations of the data. Finally, the data was CSD-transformed.

Following this, Morlet wavelets (fixed cycles of 3.5s, log-spaced) were used to extract the power of frequency bands, that were identified individually for each participant by analyzing an eyes closed resting condition that preceded the experimental test battery at each session via the restingIAF toolbox. Individual alpha frequency peaks (IAF) and band width were determined by averaging calculated IAFs across a minimum of 17 channels (15 in 32 electrode setup) and a frequency range of 1-40 Hz. Bounds of the IAF search window were set to 7-13Hz and a Savitzky-Golay filter of 11 bins was administered. The theta frequency band was set from the lower alpha bound to -2 Hz of it. All EEG measures were normalized via natural logarithms.

18.4.6 Statistical analyses.

All analyses were conducted via the R (R Core Team ,2013) based package lme4 (Bates et al., 2015). A total of 2707 observations were included into the final models reported in section 3.1. and 3.2. respectively.

18.4.7 Measures.

In order to differentiate immediate riFG reactions to the presence of the reinforcer and the influence of overall reinforcer presentation rates, two measures were included in the analyses: First, the presence and absence of the reinforcer in a given trial reflects immediate reactions to an (un)expected emergence of a positive reinforcement cue. Second, a moving average was calculated and included. It was calculated by the number of reinforcements so far, divided by the number of trials so far. This equals the rate of presence so far (for a given trial), reflecting the current context of experience with the reinforcer.

Furthermore, as level two variables, subjective control perception, effort, worrying and internal attribution of ones own performance were included as parameters. The latter was operationalized by the custom questions asking how well a participant thinks to have done in comparison to others. Higher scores are interpreted as an indicator of external attribution (e.g., the task was rigged, this is uncontrollable for everyone, and thus I did well in comparison to others). As a result, this variable needs to be included into the models as a control variable to negate confounding.

18.4.8 General multilevel approach.

The models reported below (section 3.1 and following) describe random intercept models (for each participant) as high intra-class correlations indicated their superiority over classical regression analyses. Furthermore, a random slope was included for *trial*, since EEG responses may show general tendencies that differ between participants throughout the task (e.g., by getting tired). Moreover, as most of these data are nested (e.g., trial specific reinforcement vs. overall control perception), hierarchical analyses are most efficient and unbiased towards Simpsons-paradoxes. However, following Barr et al. (2013) no random slope for parameters like *litFUS* was included as these may distort results when applied. Furthermore, all analyses are single-trial based models. Metric predictors were grand mean centered, the two nominally scaled variables, *litFUS* and *presence of the reinforcer*, were simple coded to the references *sham* and *presence*.

The final models are summarized in Table 14 and 16, which also report and compare fit indices. Finally, the best fitting model was picked for parameter interpretation of fixed effects. Fixed effects were tested against a Bonferroni-Holm adjusted alpha.

Role of the riFG in control perception and reward processing. A set of models with an increasing number of parameters was calculated, including alpha density at F8 as dependent variable. Table 14 and 15 give the complete set of model parameters.

Mid-frontal theta mirrors conflict and effortful control. One set of mixed models was conducted including litFUS, worrying and effort as variables. The complete set of variables in the final model is shown in Table 16 and 17.

	IAF	Control Perception	Effort	Worrying	Internal Attribution of Performance
Sham	10.2 (0.785)	23.0 (22.3)	61.5 (28.9)	22.0 (19.9)	35.7 (22.7)
litFUS	9.98 (0.673)	22.5 (21.2)	62.5 (27.4)	20.1 (21.6)	36.1 (23.1)

Table 13: Summary of self-ratings and IAF (individual alpha-peak frequency) for this studies sample including means and standard deviation

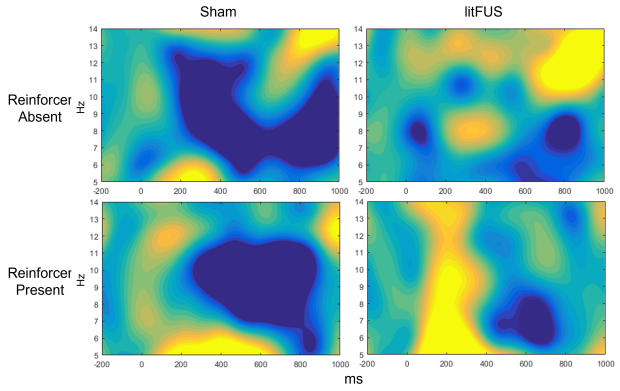

Figure 18: Time-frequency plot of electrode position F8.

18.5 Results

18.5.1 Role of the riFG in control perception and reward processing.

Time frequency plots depicted in Figure 18 show increased alpha synchronization at around 10Hz in response to the presence of the reinforcer during litFUS sessions. Furthermore, this effect is most prominent between 0 and 500 ms. Thus, further analyses averaged across this time window and the individual alpha bands.

In order to clarify the role of the riFG in aforementioned processes, a set of mixed effect regression models were calculated. Table 13 summarizes their model parameters. According to this, the best model is described by the inclusion of litFUS, presence of the reinforcing stimulus and the reinforcement rate. Furthermore, for each quadratic term, its linear pendant was also included. Subsequently, fixed effect parameters were calculated and tested for significance using the *Satterwaite* method. The results are reported in Table 14. All p values were Bonferroni-Holm corrected.

Finally, to get a first impression of the lPFC's contribution to the perception of control (a level 2 variable), self-rates control perception was used as dependent variable for a subsequent regression model. This model comprised the mean alpha response of

	AIC	BIC	χ^2	df	$p(\chi^2)$
RI	6371.8	6389.5			
RS	6345.7	6375.2	30.033	2	<.001*
Lvl1	6314.6	6373.7	41.086	5	<.001*
Lvl2	6288.2	6382.7	38.397	6	<.001*

Table 14: Model comparisons of random intercept (RI) models with alpha density at F8 as dependent variable. AIC= Alkaike information criterium, BIC= Bayesian information criterium, df= degrees of freedom. RI= random intercept model, RS= random intercept + slope model, Lvl1= RS + reinforcement rate and presence/absence, Lvl2= Lvl1 + litFUS

	Estimate	SE	df	*t*	*p*	*holm*	β
(Intercept)	10.235	0.132	47.722	77.599	<.001*		
litFUS:Rate	-1.615	0.387	2349.792	-4.169	<.001*	<.001*	0.140
$Rate^2$*litFUS:Presence	5.876	1.867	2557.789	3.147	.002*	.017*	0.032
$Rate^2$*litFUS	-3.552	1.423	2458.381	-2.496	.013*	.114	-0.055
litFUS	0.078	0.049	2654.455	1.601	.110	.876	0.093
Presence	0.059	0.049	2655.226	1.201	.230	1	0.018
Presence*Rate	0.400	0.371	2658.527	1.079	.281	1	-0.083
$Rate^2$*Presence	-1.332	1.291	2613.460	-1.032	.302	1	0.008
$Rate^2$	-1.002	0.986	2521.029	-1.016	.310	1	0.034
litFUS:Presence	0.030	0.067	2656.106	.452	.651	1	0.010
Rate	0.116	0.264	2576.379	0.437	.662	1	-0.146
litFUS*Rate	-0.159	0.530	2657.989	-0.300	.764	1	-0.081

Table 15: Model parameters of the best model of Table 23. SE= standard error, df= degrees of freedom, Satt.=Satterhaite, holm=bonferroni-holm adjusted p-values

each session averaged across (a) worse-than-chance trials (with a rate of <.4) and (b) better-than-chance trials (with a rate of >.6). This type of analysis was chosen in order to avoid type-I error inflation by the prediction of level 2 variables with level 1 predictors such as *trial*. The mean alpha response at worse-than chance trials was significantly able to predict control perception ($t(26.020)$=-2.865, p=.008, β= -.54), while no such effect was present for alpha at better-than chance trials ($t(26.977)$<1). This result indicates greater inactivity during worse-than-chance trials to predict lower control perception.

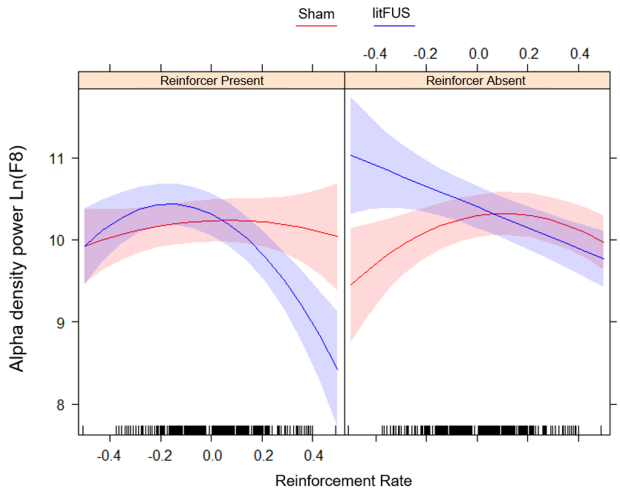

Figure 19: Relationship of alpha activity and reinforcer presence rates according to the model in Table 15. In the absence of the reinforcer, a quadratic course is revealed indicating highest alpha activity at rates of .5 to .6. This effect is diminished in the presence of the reinforcer and significantly distorted by litFUS. Please note that the x-axis is mean centered with zero equaling a rate of .5

	AIC	BIC	χ^2	df	$p(\chi^2)$
RI	6705.9	6723.6			
RS	6700.9	6730.4	9.0209	2	.011*
Lvl1	6624.2	6665.5	80.7143	2	<.001*
Lvl2	6510.5	6575.4	121.6525	4	<.001*

Table 16: Model comparisons of random intercept (RI) models with theta density at Fz as dependent variable. AIC= Alkaike information criterium, BIC= Bayesian information criterium, df= degrees of freedom,RI= random intercept model, RS= random intercept + slope model, Lvl1= RS + Alpha(F8), Lvl2= Lvl1 + litFUS

18.5.2 Mid-frontal Theta mirrors conflict and effortful control.

Again, a set of mixed models was compared in order to find the best fitting equation to describe the data. Afterwards, fixed effects were interpreted and analyzed. The model comparison is summarized in Table 16

Mid-frontal theta activity was significantly negatively correlated to worrying. As seen in Table 16 and Figure 20, this relationship was further nullified by litFUS compared to sham. Moreover, litFUS increased the relationship of effort and theta power density. Finally, alpha activity at F8 significantly predicted theta at Fz revealing a positive relationship, which indicates a correlation of midfrontal theta to less cortical activity at right lateral sites.

	Estimate	SE	df	*t*	*p*	*holm*	β
(Intercept)	9.853	0.234	573.024	42.140	<.001*		
Alpha(F8)	0.204	0.020	2660.166	10.094	<.001*	<.001*	0.197
litFUS*Effort	0.008	0.001	2681.119	5.861	<.001*	<.001*	0.177
litFUS*Worrying	0.009	0.002	2667.400	5.317	<.001*	<.001*	0.162
Worrying	-0.010	0.002	2121.420	-4.989	<.001*	<.001*	-0.167
Effort	0.003	0.002	1382.219	1.981	.048*	.096	0.077
litFUS	0.001	0.031	2663.084	0.046	.964	.964	0.001

Table 17: Model parameters of the best model of Table 3. SE= standard error, df= degrees of freedom, Satt.=Satterhaite, holm=bonferroni-holm adjusted p-values

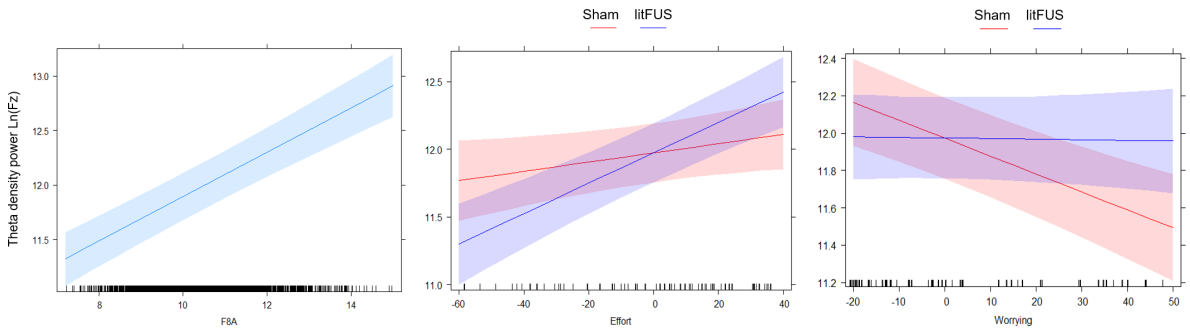

Figure 20: Effects of the model depicted in Table 5. While a strong relationship between alpha at F8 and theta at Fz exists, the correlation of effort and worrying is depending on litFUS. .Please note that the x-axis are mean centered with zero equaling a rate of 5

18.5.3 Additional, exploratory analyses

Additionally to F8, the final model chosen in section 3.1. was again investigated with its contralateral pendant, F7 in order to check for hemispheric specificity of effects. Results show a somewhat different pattern, as none of the effects shown in Table 15 was significant. Finally, a random intercept model including litFUS and its interaction with IAF was carried out, revealing a highly significant interaction (t(2691.210)= 6.332, p(holm)< .001, β = 0.173) that is illustrated in Figure 21 and shows that during sham sessions a higher individual alpha peak frequency is associated with less alpha power density. litFUS reverses this relationship with the point of intersection at approximately 10Hz, which is in line with current theories regarding litFUS and the IAF.

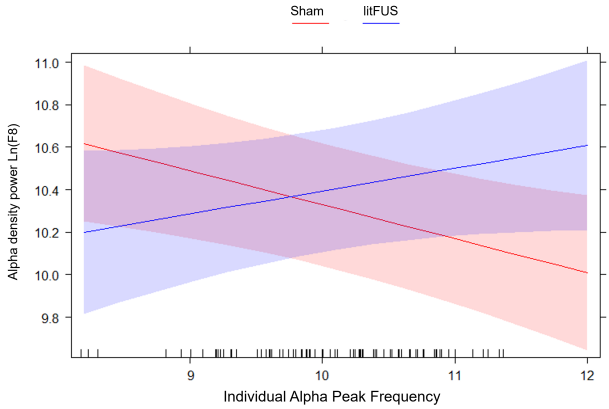

Figure 21: Interaction of litFUS and IAF in context of alpha activity at F8. While higher IAF predicts lower alpha levels across all trials during sham sessions, following litFUS this relationship is reversed. The estimated point of intersection is depicted at approximately 10Hz

18.6 Discussion

In this study a multilevel modeling approach was used to dissociate the influence of current reinforcer presence, overall estimated probability of its presentation and the emerging perception of control on the activity of the riFG. By using this type of hierarchical analysis and allowing cross-level interactions to predict single-trial variance, a model of context-dependent processing of current stimuli was introduced. Furthermore, differences in individual starting conditions and reaction to the task were model via a random intercept-random slope model.

In addition, since reactivity of the riFG was manipulated by transcranial ultrasound neuromodulation within subjects, a more direct attribution of results is possible.

This task was used to investigate differences in control believes during a control illusion task. Table 23 indicates that on average a significant illusion of control was induced. However, control believes are still weakly pronounced. Nonetheless, Table 23 also indicates that this control believe is on average interpreted as one's own failure and (crucially) not as a property of the task. This notion is also supported by the fairly high self-reported effort. As a result, it can be argued that the overall objective of the task was met, even though no direct changes due to litFUS were present.

18.6.1 Role of the riFG in control perception and reward processing

The results depicted in section 3.1. (Figure 19) show that in the sham condition, the riFG reacted with increased alpha synchronization to rates near complete randomness (.5), which is in line with previous work by Fletcher et al. (Fletcher et al., 2001), who observed lPFC activity to be highest in learning phases and in response to surprising stimuli. This is thought to reflect cognitive control exertion with the purpose of learning associations to gain predictability. Following this idea, the quadratic relationship described in section 3.1. may thus reflect learning attempts that selectively take place in situations that signal some sort of noteworthy deviation from complete randomness, which is reflected by rates of .5. Additionally, it is worth noting that the reinforcer rate reported in this study included all previous trials (maxing at 40-1=39 trials). The resulting moving average is not easily calculated during task execution; hence participants may not have been able to explicitly perceive or calculate said rates. Therefore, the idea of a riFG driven *implicit* learning process, taking into account the previous learning history in order to modulate the overall perception of control seems highly probable.

Interestingly, this quadratic effect is significantly diminished in the presence of the reinforcer, indicating the right lPFC to not only serve as a processing tool for probabilistic learning but also to react directly to the current stimulus. More precisely, signaling of probabilistic information is implied to cease during the presence of reinforcers as compared to their absence. Additionally, this seems to be true without taking the person's action into account, as this variable was neither included in the model nor indicative for the outcome at all (since this is a task with completely randomized presentation of reinforcers). As a result, this indicates a general reaction to positive stimuli instead of contingent outcomes.

Furthermore, as discussed in 3.1. litFUS conveyed inhibition of the riFG moves the probabilistic processing's effect peak to lower reinforcement rates by forming a linear rather than quadratic relationship during the absence of the reinforcer. Before the results of Flechtcher et al. (Fletcher et al., 2001) , this implies decreased associative learning in reaction to worse-than-chance rates. Along the same line, in the presence of the reinforcer, litFUS increases associative learning from better-than-chance rates.

These results fit the idea of current models of frontal asymmetry as the right lPFC has been described to facilitate learning from punishment. Since litFUS was used to inhibit this region, attenuation of this learning susceptibility would be the result. A greater left than right hemispheric lateralization of lPFC activity, which would be a result of unilateral right sided inhibition, is on the other hand often described to increase learning from reward, that is better than expected/chance.

Also, this study was able to show that especially the alpha response to worse-than-chance trials predicted overall control perception. In line with the findings of Lorenz et al. (Lorenz et al., 2015, see section 1.1.), greater riFG activity predicted increased control illusion. However, concerning the specificity of worse-than-chance trials, this effect may stem from the design of this task especially since no real control could be attained. As a result, being able to interpret the over-chance absence of the reinforcer as a significant event that holds information doubles the content to possibly learn from. Greater control perception may follow. Thus, even though the current data provide first hints towards a special contribution of worse-than-expected learning in the right lPFC, further research is needed to support this idea in other experimental tasks.

Finally, this study points out that the riFG has a (possibly) unique ability to model stochastic data as none of the F8 related effects could be replicated at F7.

18.6.2 Mid-frontal Theta mirrors conflict and effortful control.

The second objective of this study was to investigate the use of litFUS to ACC mediated cognitive reactions to the perception of low controllability.

Table 4 shows that in the sham condition theta activity at the mid-frontal electrode Fz is negatively correlated to worrying. Before the background of section 1.2, this relationship is not in line with previous research discussing the idea of ACC activity reflecting the need for control. If this was the case, worrying would positively correlate to mean ACC activity as the need for control but also anxiety should rise with its theta power. However, in the context of the remarks by Holroyd and Umemoto (Holroyd and Umemoto, 2016), prolonged activity of the ACC would also signal valuation of long-term goal that is gaining control over the reinforcer. On that note, decreases in ACC signaling

may reflect impaired action-outcome contingency perception, frustrating subjects on the way. However, as absolute worrying self-rates are still rather low, anxiety-related findings concerning ACC signaling may not come into play significantly. Nonetheless, worrying may increase in situations of low controllability, given internal attribution of the lack/illusion of control. Thus, worrying would be highest in low activity states. On the other hand, self-reported effort does not correlate with ACC activity during sham measurement occasions. Before the aforementioned perspective, this may indicate that ACC driven theta activity decreases are not a result of goal abandonment but rather contingency perception. This idea is also further supported by exploratory analyses allowing interactions of control perception and internal attribution with worrying.

Furthermore, litFUS was found to alter these relationships significantly. First, litFUS was able to decouple ACC driven theta from worrying. Fittingly, a recently published study shows that litFUS mediated inhibition of the riFG decreases worrying and anxiety. According to Sanguinetti et al. (J. L. Sanguinetti et al., 2020) riFG inhibition via litFUS was able to decrease the functional connectivity of networks related to worrying and mood. This notion is also supported by the current finding of this study.

Second, litFUS introduced a significant correlation of self-reported effort and theta density power at Fz. As mentioned afore, the right lPFC hast strong inhibitory projections to subcortical structures, including the VS. The VS on the other hand carries out part of the reward estimation and uses dopaminergic projections to inform the ACC about the current rewarding status, as well as better and worse than expected values. Subsequently, the ACC then chooses tasks, behavior and goals on this basis and exerts the minimum amount of control over other cortical areas that is needed in order to come closer to a goal (see section 1.2.). The ACC does this via frontal theta synchronization. As a result, disinhibition of the VS by litFUS modulation of the riFG may lead to amplified reward valuation and thus increase the relationship of ACC emitted theta with goal approach (effort) while diminishing its correlation to conflict related cognition (e.g., not being able to find an appropriate behavior) including worrying.

Finally, alpha density power at F8 significantly predicted theta density power at Fz. This may follow two hypothetical remarks. First, aforementioned disinhibition

of subcortical areas may connect right lPFC inhibition to ACC disinhibition. Second, also as stated above, alpha activity at F8 may be interpreted as activity, which would relate right sided activation of the lPFC to increases in conflict processing. This would be in line with the literature. Again, this idea follows the finding, that alpha and theta at F8 are positively correlated, possibly indicating litFUS indcued oscillations that serve other functions than they would do naturally. However, even though EEG based data alone may not be able to solve answer this question conclusively, all described effects still remain significant thereby indicating a riFG-ACC interaction in the emergence of control perception and the consequences of lacking it.

18.6.3 litFUS

litFUS showed the anticipated effects on alpha synchronization predicted by computational models. Thus, this study provides empirical evidence for the applicability of the NICE-model. Furthermore, since this model builds on the same receptor type that may play a crucial role in genetic determination of individual alpha peak frequencies, litFUS effects may vary in size due to trait (before modulation) IAFs. The exploratory analyses depicted in 3.3. show first evidence for this idea being worth further investigation.

18.7 Summary

In summary, these data provide overall evidence for involvement of the riFG in the processing of control perception by contributing information based on probabilistic estimation. Since control perception is thought to build upon action-outcome contingency, the attribution of outcomes to a certain behavior is crucial. However, if this attribution is complicated by factors of uncertainty (e.g., in situations of only intermittently occurring action-outcome contingency), estimation of conditional probabilities provides an important context. In the current study, the riFG's inactivity is greatest in response to patterns that depict randomness, which is interpreted as an indicator for decreased associative learning. Thus, we conclude the riFG of the lPFC to integrate probabilistic context information with responses to current stimuli, thereby modulating the experience of contingency. Finally, this was found to predict control illusion and ACC related MFT.

These effects were unique to the right hemisphere and were not present at the left inferior frontal gyrus.

Furthermore, inhibition of the riFG via lilitFUS provided evidence that the modulation of the riFG itself may be subject to other contextual cues and interference as the modulation towards its inhibition significantly altered both, the reaction to the probabilistic context and the current stimulus. In addition, by influencing ACC activity, MFT was decoupled from worrying and increased in its correlation to self-reported effort. As a result, even though this study is not able to provide direct evidence for this idea, one might argue that modulation of the riFG by other neural networks or regions may cause similar effects. Again, this highlight the role of the riFG in the processing of control related mechanisms.

18.7.1 Outlook

Given the current data, further research is needed replicating the results and enriching them by multi-level analyses based findings. On that note, especially level 1 control-perception measures of some kind would greatly benefit the discussion and significantly improve statistical power. Furthermore, additional (e.g.) fMRI data on the subject of probabilistic learning in the right lPFC will be needed in order to clarify the role of alpha activity in this study.

19 Embedding in the Thesis Framework (Paper III)

According to these data, inhibition of the excitability of neurons within the riFG was able to alter the alpha response of such to probabilistic information that was extracted supposedly implicitly by the participants. This altered EEG response was then able to predict subjective control-perception ratings, which are thought to reflect an illusion of control against the background of the study's experimental design.

Thus, according to Section 3.1 the most important factor contributing to helplessness and hopelessness, an influential etiological model for the emergence of depression was successfully modulated via litFUS. The effect and its size are especially interesting

before the background of Section 9, as the chosen parameters represent the lower limit of what litFUS can achieve, due to the cautious application of this still very new method. As a result, findings presented here should be interpreted as an indication for regions-and effects of interest, rather than definitive estimation of litFUS' general potency.

From this study, in particular, one may thus argue that litFUS is indeed able to alter control perception, thereby possibly being capable to influence the course and onset of helplessness/hopelessness.

A further takeaway from these results is, that neuromodulation of the riFG propagates its effects to midline theta activity, which is well in line with results discussed in Section 5.2, stating that PFC and ACC connectivity is both anatomically and functionally relevant and implicated in mediating neuromodulation effects as well. However, interestingly, in contrast to papers discussed in Section 5.1.1, this manuscript's findings point towards alpha at the right lPFC but not midline theta to correlate to the illusion of control. Conversely, since it was argued that the ACC investigates contingency of action-outcome dyads, one may assume ACC activity (measured via midline theta) to represent the main source of control perception.

In this regard, a more detailed review of studies underlying this idea may yield additional insights: ACC-stem neurons were shown to signal contingency, thereby building the foundation for control perception, as defined in Section 3.1. For a given trial within the presented experiment, this may lead to varying results in EEG activity, depending on what a participant expected and what event followed this expectation. Four possible combinations emerge: i) expecting a reinforcer but receiving none; ii) expecting no reinforcer but receiving it; iii) expecting a reinforcer and receiving it; iv) expecting no reinforcer and receiving none.

Following from this, in trials that feature reinforcer presence, on average, in half of all trials ACC neurons would signal no expectation-outcome-match while in the other half of trials, they would. Thus, due to the experimental design chosen here, a midline theta effect may most likely have been diminished by averaging across these trials.

Interestingly, since the lPFC-alpha effect did not fall for the same methodological issue, this indicates that the riFG may not directly react to trial-wise contingency

detection but the overall estimation of expectation-met vs. expectation-not-met trials. Hence, neuromodulation of the riFG may not lead to altered contingency perception but modulate the way that conscious perception is built upon this information. This notion would also be in line with the HRL-ACC model as it formalizes the (DL)PFC as the main actor, carrying out and building on the basic information of the ACC.

In sum, this paper shows that an influential cognitive process, describing the emergence of a vulnerability factor for depression, was successfully modulated via neuromodulation of the riFG by litFUS. It also highlights the joint action of ACC and lPFC regions in the processing of complex cognitive processes.

20 Paper IV - litFUS Modulates the Emergence of Learned Helplessness

The following text has not yet been published.

Title: Transcranial Focused Ultrasound Modulates the Emergence of Learned Helplessness via Midline Theta Modification

Authors: Forster, A.[a1], Rodrigues, J.[a], Ziebell, P.[a], Sanguinetti, J.[b], Allen, J. J.[b], Hewig, J.[a]

[a]Institute of Psychology, Julius-Maximilians-University, Würzburg, Germany

[b]University of Arizona, Tucson, USA

[1]Corresponding author

20.1 Abstract

This study addressed cingulate cortex (CC) functioning as a physiological vulnerability for affective disorders. By directly manipulating the right DLPFC via low intensity transcranial focused ultrasound (litFUS), we were able to change activity in CC associated electrophysiological measures during a learned helplessness task.

litFUS was applied in a randomized controlled double blind experimental design with 54 participants who were instructed to play 8 games of chess against a computer that was unbeatable to them, while an EEG was recorded.

The results show a strong influence of litFUS on midline theta activity (Fz and Pz) and several other psychological levels including self-report data on emotion, cognition and arousal as well as behavioral measures.

Consequentially, the development of learned helplessness/hopelessness could be positively influenced in its course by litFUS. In line with previous results, especially the posterior midline electrode Pz seems to be an interesting target for further research in this field as theta activity at this electrode is correlated to control perception and motivated behavior. To our knowledge, this is the first study to use neuromodulation to monitor and manipulate the development of helplessness in the laboratory.

20.2 Introduction

Depression is a stress-related pathopsychological condition that is currently one of the most burdensome diseases worldwide (e.g., Lépine and Briley, 2011; Vos et al., 2017; Mokdad et al., 2018; R. M. Cunningham et al., 2018) and responsible for tremendous economic (Sobocki et al., 2006) and social issues, such as social isolation and distress in relatives (Weissman et al., 1988; Goodman et al., 2011) or caretakers (van Wijngaarden et al., 2004). As a result, extensive research has been conducted to advance both, existing psychotherapeutic approaches like antidepressant medication and psychotherapy but also to establish novel treatments like neurofeedback trainings (J. E. Walker and Lawson, 2013), reconsolidation of affective memories (R. M. Post and Kegan, 2017) or neuromodulation (Allan et al., 2011; J. Chen et al., 2013; Meron et al., 2015; Brunoni et al., 2016). This study adds to these approaches by utilizing a novel method of reversible transcranial neuromodulation (focused ultrasound) to inhibit the right DLPFC before a learned helplessness task was administered. By doing so, this study seeks to provide novel insights into the process during the initial manifestations of depressive episodes and the contribution of trait-like endophenotypes to its course.

20.2.1 Initial and Recurrent Manifestations of Depression

Though many treatments have proven effective in decreasing stress and depressive responses on the short term, recurrence rates remain high with depressive episodes becoming more and more probable after each episode endured (T. I. Mueller et al., 1999; Richards, 2011; Buckman et al., 2018). As a result, prevention rather than curative treatment seems to be the best intervention to depression and affective disorders in general. Unfortunately, long-term follow up studies indicate that effects of preventive programs may also mostly be present on the short term and perform only marginally better than controls on the long run, with no substantial differences between program/therapy approaches (e.g., Hetrick et al., 2016; Yap et al., 2016; Conradi et al., 2017).

One idea to tackle these diminishing effects of preventive and therapeutic approaches over time focuses on the influence of stable trait variables, which pose as general vulnerabilities for affective disorders and may not be lastingly modifiable by therapy. On

this note, in their meta-analyses, Roberts et al., 2017 report significant changes in Big-5 dimensions following a variety of therapeutic approaches. The biggest effects were found for increases in *emotional stability* that persisted over the course of over a year. However, effect sizes are declining over time and no sufficient data on the differentiation between state and trait effects in these data are currently available. Closer examination of the course of personality change as a function of therapy duration also reveals a similar picture to that of research on early rapid therapy effects (e.g., compare Roberts et al., 2017 and Stiles et al., 2003): Both, personality and early symptom changes occur in early sessions and asymptotically decline to zero in later stages. Although no causal relationship can be inferred from this, it suggests that therapy effects may in some sort be related to the change in personality variables. Further support for this idea follows from results by T. Z. Tang et al., 2009 who showed that antidepressant effects of selective serotonin re-uptake inhibitors are also based on changes in emotional stability and extraversion, while placebo effects are not. Taken together, there is evidence for the influence of trait variables. In addition, with a decrease in treatment-induced effects on these personality dimensions over time, recurrences would at some point become a plausible course (Buckman et al., 2018). As a result, one may argue that lasting changes in trait-like constructs may decrease recurrence.

In this context, this study focused on the electrophysiological marker *midline theta*, which previously has been shown to correlate to stable personality traits including dispositional anxiety Osinsky et al., 2017, motivation (Mussel et al., 2016) and conflict processing (Pinner and Cavanagh, 2017). As these traits are in turn correlated to depression (eg. Hewig, 2018, Kanske and Kotz, 2012), the endophenotype(s) underlying midline theta activity may contribute to the manifestation of depression, initially and recurrent, in a trait-like fashion.

Thus, in order to understand the effect of this marker, it was indirectly modulated via low intensity transcranial focused ultrasound (litFUS) just before a learned helplessness task was administered. Self-reported data as well as EEG based measures provide evidence for the role of cortical processes in the emergence of helplessness/hopelessness as a model of depression. Further, this marker was correlated to personality traits

and the perception of control, which is a crucial factor in the constitution of resilience to psychopathology.

20.2.2 Helplessness and Hopelessness as a Model of Depression

Learned Helplessness was first described by Seligman and Maier, 1967 who discovered that dogs that were deprived from any chance to intervene with a punishment would cease to try to resolve or flee pain administration even after they would be able to do so. The scientific community later concluded that it was internal, global and stable attribution of the inability to oppose the likelihood or severity of aversive events that would facilitate the transfer of passivity from one context to another (Abramson et al., 1978; Maier and Seligman, 2016).

Thus, if one would experience him-/herself powerless to evade punishment in one situation and attribute this to a general lack of power/intelligence/attractiveness (...) this person would show less motivation to approach a given problem in other contexts as well. By utilizing this paradigm all symptoms of depression have been replicated in laboratory settings except for suicidal ideation (Maier and Seligman, 2016). In fact, the experience of a loss of control and its anticipation has been implicated in many contexts of depression and seems to constitute a general issue for most depressed individuals (Twenge et al., 2004; Bandura et al., 1999; Muris, 2002), who are apart from that usually regarded as a very heterogenic group (Goldberg, 2011). As a result, the learned helplessness theory provides a model that is eligible for the investigation of mechanisms during (first) depressive symptom emergence.

20.2.3 Neural Bases of Control Perception

50 years of research on the topic of learned helplessness provided extensive evidence for experimentally induced depressive symptoms to rely on the dorsal raphe nucleus. It was reported to be both, necessary and sufficient for conflict related anxiety/passivity responses. Moreover, retrograde tracing studies in rodents found it to be modulated by ventromedial projections stemming from the prelimbic region. According to current reviews, these neurons are thought to be able to detect control over environmental states

via action-outcome contingency computation which may be formalized as the ratio of conditional probabilities (the perceiveived probability of electro-shocks given that a certain behavior was shown compared the probability of shocks in the absence of such behavior). As a result, prelimbic detection of controlability inhibits depressive like symptoms via direct cortical-brain stem links (for overview of studies see Maier and Seligman, 2016).

In humans, sensitivity to action-reaction contingency has often been found in anterior cingulate cortex (ACC) neurons. A number of results indicate functional and architectal equivalence of prelimbic regions in rodents and the rostral part of the cingulate cortex in humans (for a summary of evidence see (Holroyd and McClure, 2015).

The ACC was often described as a neural substrate of effortful control and conflict related anxious arousal (J. F. Cavanagh and Shackman, 2015b), which both are linked with learned helplessness related changes of behavior (depressive symptoms) (Bench et al., 1992; Devinsky et al., 1995). A number of lesion studies provide evidence for dramatically impaired rule learning and behavioral adaption correlated to decreased functionality of the ACC (eg. Amiez et al., 2005, for overview see J. F. Cavanagh and Shackman, 2015b or Holroyd and Umemoto, 2016). Furthermore, another impactful investigation was able to show neurons of the ACC to be able to specifically code action reaction outcome contingency (Kennerley et al., 2006). As a result, a considerable amount of evidence points to the ACC to manifest adaptive behavior by evaluating not only the rewarding capacity of long and short term goals but also previously shown instrumental behavior (Walton et al., 2003;Holroyd and Umemoto, 2016; Monosov et al., 2020) Thus, dynamic changes in behavioral, affective and physiological responses may partly rely on ACC function, which is in line with the often rodent based literature on learned helplessness that suggests a control detection system in prelimbic regions.

This contingency-based estimation of behavior-outcome dyads and their value to short-and long-term goals may further lead to an (asymmetric) recruitment of the DLPFC. According to the hierarchical reinforcement learning theory of anterior cingulate cortex function (HRL-ACC theory, Holroyd and Umemoto, 2016), in the process of goal directed behavior and its monitoring, the ACC, signals long-term goals and exerts control over the per se effort-averse DLPFC in order to facilitate both, behavioral adaptation and

long-term goal pursue despite immediate obstacles.

20.2.4 Prefrontal Modulation of Cingulate Networks

The DLPFC itself has been subject to extensive research on its functional role in behavioral tendencies and affect. Current reviews as well as original studies discuss strong evidence for greater right as compared to left DLPFC activity and activation in tasks eliciting negative affectivity, withdrawal behavior and motivation (eg. see Reznik and Allen, 2018, Rodrigues et al., 2018; Rodrigues et al., 2021). Matching results are reported in lesion studies (eg. Starkstein et al., 1991, Narushima et al., 2003), experimental designs using some sort of reversible neuromodulation (N. J. Kelley et al., 2017, Reznik et al., 2020, J. L. Sanguinetti et al., 2020) and correlative studies tackling interindividual differences specifically (see Rodrigues et al., 2021). Many of these results show converging evidence for greater trait-like right sided frontal asymmetry in participants who score higher on depression and anxiety scales. Furthermore, this endophenotype seems to be stable across phases of depression, remission and recurrences, thereby once again highlighting its role as a possible trait marker for the overall suspectability of an individual to suffer from such states, rather than a state-dependent correlate of current symptomatology (Reznik and Allen, 2018).

The DLPFC has also been described in conflict processing during goal directed behavior. Here, it has long been theorized that a DLPFC-ACC cooperation is crucial (Tik et al., 2017 ;Mansouri et al., 2009). Following the HRL-ACC theory, this association may be the result of ACC driven DLPFC activation. However, several studies, directly modulating the DLPFC report evidence of subsequent ACC activity changes following this procedure (Paus, 2001; X. Li et al., 2004; Sibon et al., 2007; Cho and Strafella, 2009), also including changes in functional connectivity between the ACC and a meso-corticolimbic network (Tik et al., 2017).

In summary, evidence suggests that (right) DLPFC focused neuromodulation is able to alter ACC activity, Such activity can then be measured via midline electrodes on the scalp; a measure that is commonly analyzed in terms of theta power within the EEG scalp measures (eg. J. F. Cavanagh et al., 2012).

20.2.5 Previous Results

To date, we are aware of only one study that examined EEG markers of frontal DLPFC asymmetry and ACC in the context of learned helplessness (Reznik, Nusslock, et al., 2017). As far as frontal asymmetry is concerned, contrary to their hypothesis, the authors found no difference between a control group that had to master a solvable task and an experimental group that failed an unsolvable task. Instead, a significant difference was found between the ratio of theta activity at the posterior central electrode Pz and the frontocentral electrode Fz. Post hoc investigations showed a particular relevance for theta activity at Pz, as it seemed to be related to controllability (manipulated by group membership).

While the ACC has often been described in context of stimulus-outcome contingency, the posterior cingulate cortex (PCC) which may supposedly play a key role in theta synchronisation at posterior central electrode positions, has been implicated in other functions. One example is its correlation to the default mode network (DMN) and its corresponding role in the processing of self-relevant information processing or the modulation and direction of attention (see Leech and Sharp, 2014 for a brief summary). As the DMN is thought to decline in its activity due to external-focused attention and processing (eg. Buckner et al., 2008), decreases in PCC activity as seen in the control but not the experimental group of Reznik's study (Reznik, Nusslock, et al., 2017) may hint at frustration related disengagement from the unsolvable task. This in turn may correlate to control perception. Further support for the relevance of the PCC is provided by an fMRI study showing a specific correlation of hopelessness in depressed individuals and PCC activity, thereby also highlighting possible functional specificity within the DMN (Grimm and Ram, 2009)

Following on from this, the study presented here also investigates a learned helplessness task and tests theta activity on midline electrodes. However, contrary to previous work, the present study seeks to investigate the preventive potency of direct neuromodulation of the right DLPFC via the novel method of transcranial ultrasound neuromodulation. In general, a DLPFC conveyed effect on conflict and motivation processing is anticipated to diminish or delay learned helplessness onset during the task as

indexed by midline theta and self-report data.

20.2.6 Transcranial Ultrasound Neuromodulation

A new method for both neuromodulation and -stimulation is provided by transcranial focused ultrasound (litFUS). It is not only able to reach even subcortical structures but also to maintain its spatial precision while doing so (Legon et al., 2018). Tyler (Tyler, 2012) describes various molecular biological structures and movements that are part of internal plasiticity processes of cells, which could be modulated by mechanical influence by transcranial ultrasound. Following on from this, one of the most recognized models is provided by Plaksin and his colleagues who describe ultrasound to alter the capacitive properties of the double-lipid membrane by the formation of small bubbles (cavitation) between the outer and inner lipid layers, which ultimately influences the threshold for triggering action potentials (Plaksin et al., 2014). These changes may be related to the modulation of membrane-stem receptors that change in conformation according to the deformation of the membrane (Plaksin et al., 2016).

A first investigation of the method in humans was led by Hameroff et al. (2013), who administered litFUS to the right DLPFC of chronic pain patients. Compared to a sham control group, patients reported slight improvements in pain, with an even greater effect on the subjects' mood. Since then, two additional peer-reviewed studies provide further evidence for its effectiveness in modulating the right DLPFC in humans neuromodulation (Reznik et al., 2020; J. L. Sanguinetti et al., 2020)

Building on this, in this study, low intensity litFUS was utilized to inhibit the right DLPFC in order to indirectly modulate ACC activity. The ACC itself was reported to reflect trait-like dispositions (see section 1.) and control perception in learned helplessness task (see section 1.5.).

20.2.7 The current study

This study seeks to investigate the potency of litFUS in interfering with the emergence of helplessness in context of a realistic manipulation of frustration as a model of depression. In order to facilitate internal, stable and global attribution of repeated failure in the test-

subjects who may have had experience with cover stories in psychological experiments already, the task was presented on a freely accessible website, "*chess.com*".

On this website, participants played chess against one of the most powerful chess engines worldwide. Without their knowledge however, a java script was automatically infused, if this website was opened on the laboratory computer that would change the depiction of levels so that participants witnessed how the experimenter changed the opponents strength to level 2 of 10 while in fact level 10 of 10 was chosen. The setting of chess was chosen for several reasons: first, performance in a game of chess is often thought to be correlated to general intelligence (a stable, global and internal attribution), even though there is substantial evidence against this depiction in the scientific community (Bilali et al., 2007). Second, amateur players would not be able to estimate the actual difficulty/level of a game. Third, as the assessment of chess situations is complex and ambiguous in its nature, which strongly improves external validity of conclusions to be drawn. Fourth, participants can be provided with a feedback on the quality of their moves (as a result of the computers updated estimate to win), thereby making sure that participants experience the feedback of failure, even though they tried their hardest. Fifth, as the estimated chance to win is recorded, drops in participants effort to win, can be seen as a function of behavior, since helplessness should go along with giving up on the idea that effort changes the way of the game, making blunders more probable (for further discussions on chess-based psychological research, see Vaci and Bilali, 2017).

Before a total of 8 games were played, participants received litFUS-, sham- or no modulation at all, depending on the testing condition. EEG, ECG and EDA were recorded throughout the complete experiment. However, only EEG related analyses tackling the midline theta as neural substrate of both conflict/anxiety and effort as well as rating scores and behavioral data are presented.

20.2.8 Hypotheses

In context of learned helplessness/hopelessness, based on the above-mentioned findings, theta activity at the electrode Pz is especially of interest. According to Reznik, Nusslock, et al., 2017, this activity seems to separate control and experimental groups, presumably

due to theta activity at Pz being correlated to control perception, which differs between the groups. The authors also describe the electrode Fz as a possible target. Theta at this electrode correlates especially with anxious arousal and the need for control. Also, as it is measuring ACC activity, it may also play a crucial role on itself during the constitution of helplessness. We therefore assume that if litFUS influences the effect of the learned helplessness task, it does so via a change in theta activity at Pz and Fz. Furthermore, we anticipate a between-within interaction of *condition*, *game* and *time(second) within each game* as the emerging helplessness should differentiate the groups best in later games and later stages within each game. This idea builds on the hypothesis that litFUS may prolong the onset of helplessness. Finally, as this is a task to induce depression-like states, we also hypothesize the effect at electrodes to rely on pre-task depression scores of participants as the ACC and PCC have been reported to correlate to depressive symptoms.

Our hypotheses therefore conclude as follows: First: theta power density at electrodes Fz and Pz are significantly reduced by the modulation with greater effects in late games and late stages within each game. This effect should interact with depression scores.

Second: This theta activity predicts the behavior during the task. Higher values in theta activity should be associated with faster resignation, which in turn predicts worse moves. In addition, similar to the first hypothesis, move quality may be predicted by a condition x game x game stage interaction. Here, no interaction with depression is anticipated since no indication for such an effect was found in the literature

Third, the influence of neuromodulation on self-reported control perception is mediated by the change in theta activity at Pz. This mediation model was build on previous results by Reznik et al. (2017).

20.3 Methods

20.3.1 Ethical considerations

Due to the novelty of litFUS, just a few studies have reported findings in human test subjects. However, before, it has been reported to be secure in students, chronic pain

patients and mildly depressed. Moreover, as litFUS is especially potent in dealing focal modulation, side effects by unwillingly triggered modulation of non-target networks should be less likely. Participants were informed about the method to the fullest of our current knowledge (including open questions like long-term effects) in order to ensure informed consent. Nonetheless, no side effects, after-effects or contraindications other than epilepsy, have been reported to this date.

20.3.2 Participants

54 participants (11 male, mean age = 26) were recruited via a website of the University of Würzburg and rewarded with 24,50 or course credits. Descriptive statistics of the final sample can be found in Table 18. Inclusion criteria were age of 18 years or older as well as mental and neurological health, both current and in medical history.

Furthermore, in order to avoid that very chess-experienced people participated in the study (they may have noticed from the computer's moves that manipulations were being made), it was initially not expressed what the task in this experiment was. For this reason, no chess knowledge was required before the start of the experiment. After the experiment 3 participants reported to have visited the website chess.com before the experiment.

20.3.3 Sample Size Calculation

Given the complex hierarchical "single-trial" based analysis of this study, to our knowledge no robust method of sample size calculation was available. Thus, a conservative estimation via G*Power was conducted for a more common method of a repeated measures ANOVA (8 repeated measures and 4 groups). We expected a significant within-between interaction on an $\alpha = .05$ niveau. Since no effect size was available from previous study results, a medium effect size of partial $\eta^2 = .09$ was further assumed. G*Power estimated a power of 95.32% with a total sample size of 52 participants.

		Afraid	Confused	Sad	Angry	Energetic	Chess Skills
M (SE)	litFUS	8.33 (2.71)	15.9 (5.31)	7.93 (2.88)	3.6 (1.23)	48.7 (6.04)	8.27 (3.34)
	Sham	7.29 (2.88)	18.9 (5.42)	4.43 (0.716)	4.14 (1.17)	45.6 (6.78)	5.5 (1.42)
	Control	13 (4.5)	6.5 (1.12)	7.5 (2.37)	5 (2.07)	52.7 (4.11)	8.46 (2.18)
	Exp.	6.18 (2.1)	8.27 (3.75)	3.36 (0.691)	8 (3.63)	47.9 (7.95)	8.82 (2.28)
Median	litFUS	4	5	4.5	3	41	2
	Sham	4	9.5	4	3.5	42.5	5
	Control	9	7	3	2	47	5
	Exp.	4.5	5	3.5	3.5	51	5
		Tired	Happy	Tense	Will to win	SPI	
M (SE)	litFUS	50.7 (6.85)	36.3 (5.13)	26.1 (5.86)	57.1 (7.72)	64.3 (2.57)	
	Sham	46.5 (7.24)	45 (5.8)	27.9 (7.19)	57 (7.49)	59 (3.52)	
	Control	42.2 (7.74)	33.3 (7.01)	24.1 (5.5)	62 (6.08)	63.1 (2.68)	
	Exp.	43 (8.47)	40.8 (6.03)	10.7 (2.57)	44.7 (5.88)	63.4 (2.02)	
Median	litFUS	60.5	29	40	50	53.8	
	Sham	46	39	22.5	66	52.5	
	Control	36	33	26	58	51	
	Exp.	39	37.5	11	48	51.5	
		BDI-V	Industriousness	Withdrawal	Volatility	Enthusiasm	
M (SE)	litFUS	25.8 (3.64)	33.3 (1.54)	27.9 (1.83)	27.3 (0.939)	35.9 (1.64)	
	Sham	22.1 (3.66)	33.2 (1.77)	27.4 (1.61)	25.9 (1.57)	35.4 (1.54)	
	Control	25.1 (3.25)	31.6 (2.24)	28.5 (1.95)	30.2 (1.94)	34.1 (2.01)	
	Exp.	26.9 (4.23)	34.2 (2.38)	27.5 (2.01)	26 (1.79)	31.8 (2.15)	
Median	litFUS	24.5	33	28	28	36	
	Sham	22.5	32.5	28.5	27.5	34.5	
	Control	20.5	32.5	30.5	29	38	
	Exp.	29	35	26	25	35	

Table 18: Descriptive statistics of ratings before the first game of chess. M = mean, SE= standard error, SPI = self-perceived-intelligence, Exp. = experimental group

20.3.4 Procedure

Participants completed an online-survey including several questionnaires before joining the experiment in the laboratory setting.

After that, participants visited the lab where they were disclosed that the task consisted of them playing chess against a computer at the website chess.com. Following this, litFUS was delivered to electrode position F8, targeting the inferior prefrontal gyrus. While electroencephalographic, electrocardiographic and electro dermal electrodes were prepared, test subjects had the opportunity to review the general chess rules. After preparation was completed, participants were asked for any further questions with the remark that during the experiment, no more questions could be asked.

The experimental procedure started with 8 minutes of resting EEG that followed

the script used in J. J. B. Allen et al., 2004 including auditory instructions to open and close the eyes in one minute intervals. A second resting EEG recording was conducted at the end of the procedure (results addressing the resting EEG are not presented in this study)

Next, the first game of chess started. Participants were shown how the experimenter chose level 2 of 10 and set a timer of 8 minutes, which denoted the maximum time, participants had to win against the computer. However, unbeknown to the participants, a JavaScript was infused to change the appearance of the website to the extent that level 2 would actually activate level 10 of 10. After being check mate, having set the computer check mate or expiry of the time limit, the experimenter stopped the game and presented the items shown in section 2.4. Afterwards, the next game started until a total of 8 games was reached. Following a second resting EEG and some additional questions that have no direct relation to this manuscript can be seen in supplemental material 27.4. Finally all participants were debriefed.

20.3.5 State and Trait Questionnaires

The pre-task online survey was presented on the website *soscisurvey.de* and included a subset of scales of the Big Five Aspect Scale (industriousness, withdrawal, volatility and enthusiasm; Mussel and Paelecke, 2018), the BDI-V (a questionnaire building on the BDI-II. It is especially suited for subclinical differentiation;M. Schmitt and Maes, 1999;M. Schmitt et al., 2006) and a measure for self-perceived intelligence (Rammstedt and Rammsayer, 2002). The latter asked participants to rate their subjective perception of intelligence on 11 dimensions (such as verbal intelligence, mathematical intelligence, etc.). For this studies purpose, a g-score was estimated by calculating the mean of these dimensions. Since the original scale ranged from 0 -100, scores can be interpreted as percentiles with a score of 50 depicting the 50th percentile of an IQ normal distribution (reflecting a self-perceived intelligence of 100).

Before the first game began, participants were presented with visual analog mood scales (VAMS) whose items were taken from Arruda et al., 1999. These comprise a total of 8 mood-related adjectives to which the participants were asked how much a given

item would apply to them right now. The list of items can be drawn from Table 18. In addition, before the first game, they were also asked how much they wanted to win the next game. Finally, participants were asked how good their chess playing skills were on a scale from 1-101 (see Table 18)

After each game played, the VAMS were presented once again. They were accompanied by four questions asking for the participant's will to win the next game, as well as an item on "how much do you worry about your performance in the game", "how much effort did you put into the game" and "how much control did you feel to have over the game?". Since the latter items referred to the past game, they were only depicted 8 times (after each time), while the item on the will to win was presented before each game. The VAMS were presented before the first and after each game, totaling 9 measurement occasions (after each of the 8 games and once before). As a result, between the first resting EEG and the first game, the VAMS and the item on the will to win were presented. Then, after each game, the VAMS and all four above mentioned items were shown. following the last game, the item on "will to win" was missing.

In summary, the currently presented set of data comprises state and trait measures on constructs that may correlate to the dependent variables (theta activity), which may thereby help interpret these measures, game-related state-measures and EEG based dynamics during the task.

20.3.6 litFUS Administration and experimental groups

The low intensity transcranial focused ultrasound application was delivered via a manufactured device by Thync (Los Gatos, USA). The same device was used before by J. L. Sanguinetti et al., 2020, who differing parameters to the same region of interest as it was in this study (for more details on the device and the method in general, please see J. L. Sanguinetti et al., 2020).

In order to ensure standardized modulation at approximately the area of interest (rifG), participants heads were measured and equipped with an EEG cap. Afterwards, F8 electrode position was marked on the participant's head, the cap was removed partially, so the sonication would not be distorted by the electrode and modulation would start.

Additionally, in order to facilitate ultrasound delivery, a one inch thick gel pug was placed between transducer head and skull. The modulation itself took two minutes, with a duty cycle of 0.5%, and pulse repetition frequency of 40Hz. A mechanical index 1.53 and an acoustic intensity spatial peak time average of 199mW/cm^2 resulted from these parameters. Immediately following, the EEG, ECG and EDA were prepared, taking approximately 30 min. With no further delay, the resting EEG was started.

litFUS compared to sham application followed the exact same procedure with the only difference being the pointed direction of the transducer head during application. Thus, in the litFUS condition, ultrasound would be directed to the head while in sham condition, it would still be emitted but directed away from the participant. However, neither participants nor experimenters knew which side of the transducer head was active. Furthermore, as ultrasound cannot be heard by humans, neither participants, nor experimenters could be unblinded by the power of the modulation.

In total, four groups emerged: one control group, that would play against a computer at level 2 and should gain control over the game to at least some extend. This group would not be in contact with the ultrasound device at all. One experimental group that would play against level 10 and never be in contact with the ultrasound device. One sham group, that would play against level 10 but receive a sham modulation, with the active side of the transducer head facing away from the brain. One litFUS group, that would play against level 10 and receive the litFUS modulation.

20.3.7 EEG Measurement and Preprocessing.

EEG measures were recorded via a 32-electrode montage and a brain vision recording system (Brain Products, Gilching, Germany). Electrodes were brought under 10 k. Online reference was Cz, ground was Afz.

Preprocessing was carried out with Matlab's (The MathWorks, Massachusetts, USA) extension EEGLAB (Delorme and Makeig, 2004) including plugins MARA (Winkler et al., 2014), Adjust (Mognon et al., 2011), SASICA (Chaumon et al., 2015), the CSD-toolbox (Kayser and Tenke, 2006a;Kayser and Tenke, 2006b) as well as the restingIAF toolbox (A. W. Corcoran et al., 2018). The procedure mostly followed Rodrigues et al.,

2020 preprocessing pipeline (in submission): At first, electrodes were re-referenced to average. Then, channels were automatically rejected and interpolated based on their averaged z-score on the three dimensions kurtosis, probability and spectrum. A z-score (calculated for the mean of one channel in comparison to all others) of more/less than ś3.29 (following suggestions by Tabachnick and Fidell, 2013 on outlier detection) qualified a channel for rejection. The data was then epoched into 1s long non-overlapping snippets. A 1Hz high-pass filter was applied. Afterwards, an ICA was conducted, and trials were automatically rejected by the same procedure as the channels had been. Following this, ICA weights and indices of rejected trials were saved. The preprocessing started once again and applied the saved parameters to the new set that was now missing the 1Hz filter in its pipeline. Finally, Adjust was used to reject components based on MARA and SASICA evaluations of the data, before the data was CSD-transformed.

Following this, Morlet wavelets (fixed cycles of 3.5s, log-spaced) were used to extract the power of frequency bands, that were identified individually for each participant by analyzing an eyes closed resting condition that preceded the experimental task via the restingIAF toolbox. Individual alpha frequency peaks (IAF) and band width were determined by averaging calculated IAFs across a minimum of 15 channels and a frequency range of 1-40 Hz. Bounds of the IAF search window were set to 7-13Hz and a Savitzky-Golay filter of 11 bins was administered. The theta frequency band was set from the lower alpha bound to -2 Hz of it. All EEG measures were normalized via natural logarithms.

20.3.8 Statistical analyses

Statistical analysis was performed via a mixed effect multilevel modeling approach to match the nested structure of the data (seconds or moves in games, nested in subjects, divided into groups). For this reason, several multilevel mixed models were formulated.In each one, the level one variable (move or second) was included as a random slope and the subject was modeled as a random intercept. All mixed models were fitted via restricted maximum likelihood estimation and R's (R Core Team, 2017) lme4 package's (Bates et al., 2007) default method of optimization (*bobyqa*). In total, three hypotheses with several subhypotheses were investigated:

First, theta power at the electrodes Fz and Pz was investigated. For this purpose, a separate model was set up for each electrode, which included the corresponding theta power density at either Fz or Pz as a dependent variable. Following above mentioned theoretical considerations, the variables *depression* (measured with the BDI-V, metric, level 3), *game* (ordinal with eight steps ranging from one to eight, level 2), *second* (metric index for the second within a game, level 1), and *condition* (nominal with the levels *litFUS*, *sham*, *control*, and *experimental*, level 3) were included. All interactions up to a four-way interaction were allowed. Also, while *condition* was simple coded to the reference of *litFUS*, *game* was analyzed in a linear fashion. All metric variables were grand mean centered. Furthermore, *BDI* and *second* were rescaled by division by 10 and 100 respectively. In order to to ensure reliable results all linear interaction terms containing *condition* are presented, even though a four-way interaction is anticipated. The presented effects are then used to perform a Bonferroni-Holm adjustment of effects, which lays the foundation for further interpretation.

Second, to test whether litFUS has had effects not only on EEG based measures but also on behavior, the computer-generated ratings for the subjects' chess moves were included as dependent variables in another hierarchical mixed model. The data were first adjusted for moves in which the website no longer calculated a rating (if it was clear that the engine would win, instead of a numerical rating only the fact that a checkmate was imminent in X moves was displayed). In this model, the level 1 variable included as both fixed effect and random slope was the index of the *current move*. As level 2 variables, *game* was included. In addition, *condition* was again included as a level 3 variable. All possible interactions between *game*, *condition*, and *move* were allowed.

Then, another model with *current move* as random effect variable the estimated rating for this move as dependent variable was computed. This time, only theta power densitiy at Pz and Fz were included. These measures were this time averaged across each game respectively, making them a level two variable. This separate model was chosen to prevent adverse effects from potentially correlated effects of theta activity and condition. Furthermore, since no direct allocation of a certain move and a certain second of EEG recording was possible, theta activity was averaged to prevent distortions in the estimation

process.

Third, based on the previous findings, a mediation model was build. To this end, the mediation of theta (at Pz) was analyzed for the effect of *condition* on self-reported *control perception*. In this analysis, theta activity was again averaged per game. The mediation was conducted via the *mediate* package for R (Tingley et al., 2014). Its functions are able to compute mediation models of data fit with lme4 and does so by computing paired comparisons of groups. For this reason, since we would not expect differences in the size of mediation across all groups other than the litFUS condition, a new group was formed, including the *sham*, *control* and *experimental* conditions. This group was then analyzed against the litFUS group, as it would be plausible if the neuromodulation induced a change in mediation effects. This method resembles a deviation factor coding. However, due to unforeseen results, unplanned post hoc comparisons of each of the original groups with the litFUS group as reference were computed. This procedure resembles a simple contrast coding with the litFUS condition as reference group.

The general alpha level for all analyses was set to .05 for Bonferroni-Holm adjusted p-values. Adjustments were made separately for each analysis. Exploratory and supplemental analyses were not corrected.

20.4 Results

20.4.1 Manipulation check

First, it was examined whether the task was able to produce a helpless/hopeless status to begin with, thereby separating the experimental and control group from one another (neither of which ever interacted with the ultrasound device during the experiment). Table 19 illustrates the self-ratings following each game. Comparing the *Control* and *Experimental* group, in line with the idea of hopeless states, the experimental group showed increased anxiety, sadness and tiredness, while participants of this group also felt less energetic, happy, effortful, in control of the situation and motivated to win. Furthermore, contrary to our expectation, worrying was highest in the control group. In addition, the descriptive also show that even though substantial differences between

	Afraid	**Confused**	**Sad**	**Angry**	**Energetic**	**Tired**
litFUS	4.33 (0.429)	25.8 (2.42)	7.3 (0.764)	8.37 (0.823)	39.7 (2.32)	35.6 (2.36)
Sham	5.4 (0.427)	27.8 (2.46)	9.48 (0.872)	11.8 (1.28)	32.8 (2.39)	35.6 (2.23)
Control	4.86 (0.481)	19.7 (2.52)	8.61 (0.891)	13.2 (1.42)	47.2 (2.25)	25.9 (2.43)
Experimental	8.4 (1.57)	19 (2.21)	15.4 (2.11)	14.3 (2.19)	38.6 (2.27)	39.5 (3.31)
	Happy	**Tense**	**Will to win**	**Effort**	**Control Perception**	**Worrying**
litFUS	32.7 (2.11)	25.8 (1.64)	53.8 (3.13)	61.8 (2.7)	22.3 (2.26)	21.5 (2.16)
Sham	28.8 (2.03)	24.2 (2)	59.1 (2.78)	57.3 (2.27)	16.3 (1.42)	36.7 (2.57)
Control	38.1 (2.43)	32.5 (2.22)	68.4 (2.4)	64.3 (2.25)	30.2 (2.42)	43.6 (2.51)
Experimental	30.6 (2.3)	29 (2.83)	49.8 (2.08)	60.4 (1.95)	23.1 (1.94)	29.6 (2.67)

Table 19: Descriptive statistics of self-ratings averaged per group across all games. Depicted are means and standard errors of the mean in parentheses. The scale ranges from 1 to 101

groups emerged, negative emotionality still ranges in the lower third of possible scores, indicating a low risk of dramatic damage to the mental health of the participants.

20.4.2 litFUS' Influence on Theta Power Density

The results of the two mixed models show significant differences for the comparisons of litFUS and all other conditions on different grades of interactions. In terms of significance, it seems to be crucial that the factor *game* occurs in an interaction term. Since the four-way interactions (condition x game x second x BDI-V) was specifically predicted, this type of effect will especially be discussed in the following. The corresponding effects are presented in Table 20 and 21, while all other effects of interest are summarized in Appendix 44 and 45. All effects including litFUS as a factor qualified for inclusion. Furthermore, Bonferroni-Holm correction was conducted based on the respective effect lists of Appendix 44 and 45.

Regarding the theta power density at electrode position Fz Figure 22 shows that interindividual differences in depressivity seem to have less influence in the experimental group as well as in the litFUS group than in the control and the sham group (comparison of the red and blue lines of each graph). This seems to be the case for the early as well as for the later playing phase with the exception of the first two games in the litFUS group. While the level in the litFUS group remains principally low, it seems to be elevated in the experimental group. The largest differences for depressivity are found in the control group, where the BDI-V predicts increased theta activity over several games, regardless

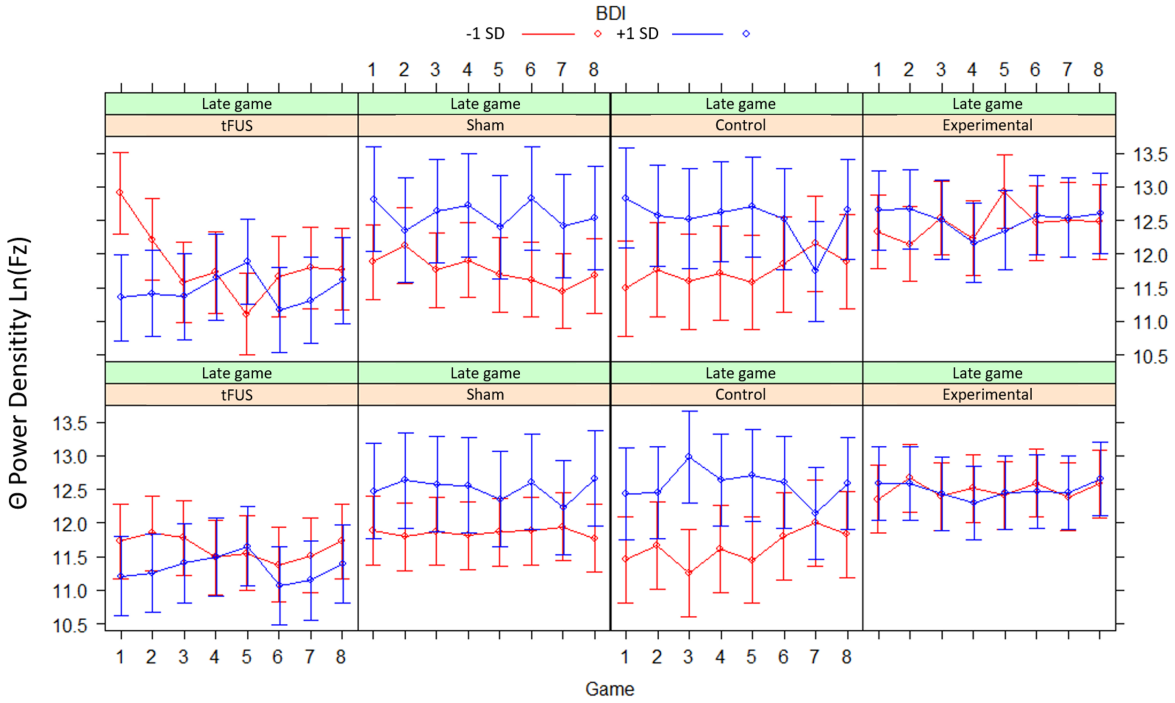

Figure 22: Four-way interaction of BDI-V, litFUS, Game and Second (within a game) predicting theta at Fz. Blue lines indicate estimates for participants with BDI-V scores 1 SD above the sample mean, while red lines indicate those with scores 1 SD below this mean. Likewise, early and late game facets distinguish (grand)mean - 1 SD and (grand)mean +1 SD estimates. Error indicators represent 95% confidence intervals

of playing time. Similar effects are depicted for the sham group. In addition, in the later stages of playtime, depressivity seems to gain more influence contributing to increased theta activity (comparing the overlap of the red and blue error indicators in one plot within a column to the other plot within the same column). The model results are summarized in Table 20

Figure 23 shows theta power density at electrode position Pz. Again, the picture is similar, with less influence of the BDI-V in the litFUS and experimental group than in the sham and control group. In addition, just like at electrode position Fz, a low BDI-V predicts about the same level in all groups except the experimental group. Table 21 summarizes the effects.

20.4.3 litFUS' Influence on Behavior

Next, the quality of individual moves on a single trial level was analyzed. First, the model results revealed a highly significant influence of theta power density at the electrode Pz

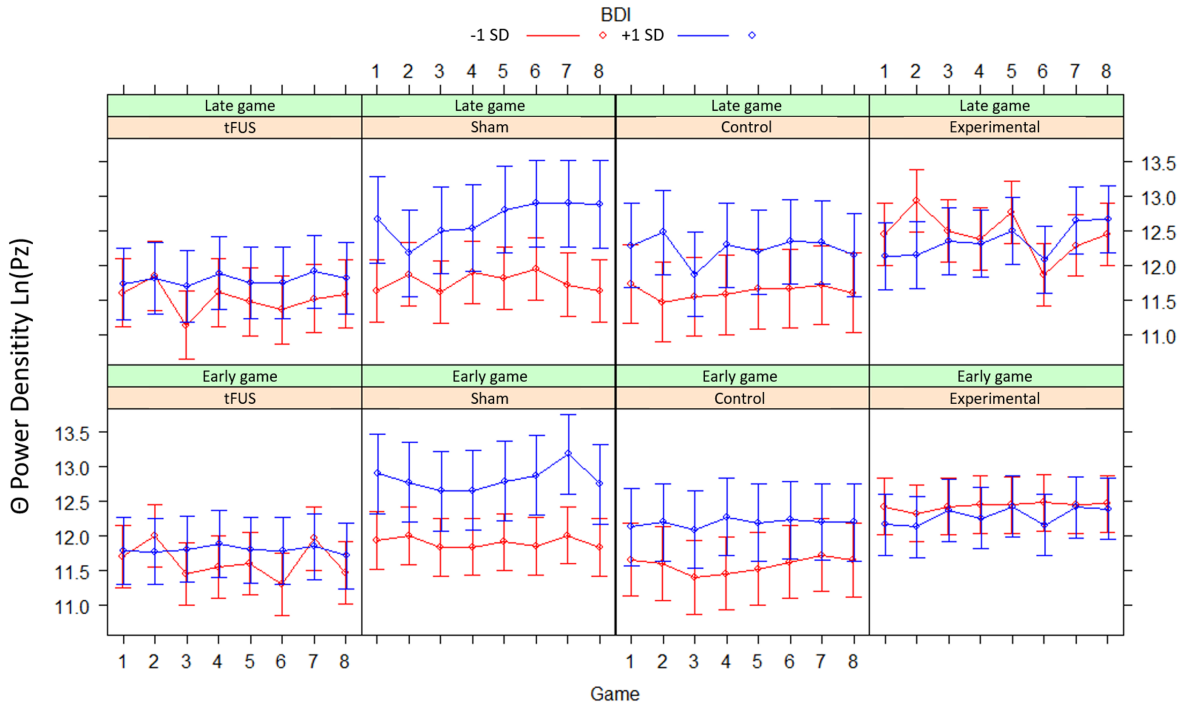

Figure 23: Four-way interaction of BDI-V, litFUS, Game and Second (within a game) predicting Theta at Pz. Blue lines indicate estimates for participants with BDI-V scores 1 SD above the sample mean, while red lines indicate those with scores 1 SD below this mean. Likewise, early and late game facets distinguish (grand)mean - 1 SD and (grand)mean +1 SD estimates. Error indicators represent 95% confidence intervals. Comparing the sham and control group, both columns indicate significant differences between higher and lower BDI-V scoring individuals. No such effect is shown for the experimental group, which reflects heightened theta activity regardless of depression scores and the litFUS group, which shows lowered theta activity independently from BDI-V measures.

(t(545.632)=-6.951, holm= <.001, β = -0.092) but not at Fz. The direction of this effect suggests that higher chess playing performance is correlated to decreases in theta power at the Pz electrode position.

Furthermore, the second model showed the predicted three-way interaction, this time between condition, game and move (Table 22). However, following the Bonferroni-Holm adjustment, only a marginally significant effect was found for the interaction contrast of sham and litFUS. The comparison of litFUS and Control, as well as litFUS and Experimental remained significant in this interaction term. Figure 24 illustrates the anticipated three-way interaction. It depicts a clear difference between litFUS and the control group, but also a smaller one for the comparison with the experimental group. In general, the control group performed significantly better than the rest.

Also, in the late game, litFUS (but also sham to some extend) show a somewhat

Effect	Estimate	SE	Df	t	p	holm		β
Sham-litFUS*Sec*Game*BDI	-0.026	0.008	102809.279	-3.103	.002	.023	*	-0.041
Control-litFUS*Sec*Game*BDI	-0.084	0.007	122682.491	-11.619	<.001	<.001	***	-0.134
Experimental-litFUS*Sec*Game*BDI	-0.051	0.009	114086.636	-5.457	<.001	<.001	***	-0.080

Table 20: Model parameters for the mixed model predicting theta power density at Fz. Estimate =unstandardized regression coefficient, SE= standard error of the mean, Df= Satterthwaite degrees of freedom, holm = holm adjusted p, β = standardized regression coefficient, Sec = seconds played in a given game

Effect	Estimate	SE	Df	t	p	holm		β
Sham-litFUS*Sec*Game*BDI	0.027	0.007	91450.727	3.694	<.001	.003	**	0.051
Control-litFUS*Sec*Game*BDI	-0.008	0.006	122047.378	-1.236	.216	1		-0.015
Experimental-litFUS*Sec*Game*BDI	0.052	0.008	108009.694	6.398	<.001	<.001	***	0.100

Table 21: Model parameters for the mixed model predicting theta power density at Pz. Estimate =unstandardized regression coefficient, SE= standard error of the mean, Df= Satterthwaite degrees of freedom, holm = holm adjusted p, β = standardized regression coefficient, Sec = seconds played in a given game

increasing trend in moves, while the experimental group, seems to decrease in their quality of moves of over time.

20.4.4 Theta Mediated litFUS Effects on Self-Ratings

The mediation model defined changes in theta activity at electrode position Pz as a mediating parameter for the effect of condition on control perception. The initial model tested a deviation coded contrast, assigning all groups except litFUS to one condition. This novel group was then labeled as a control condition to the remaining unchanged litFUS group. Only a marginally significant mediation effect was found if averaged across these groups (95% CI: -0.2435 - 1.88, p=.184). However, single group analysis revealed a great difference in the mediating effect of theta between the litFUS (95% CI: -0.7339 - 1.85, p= .484) and the "others" (95% CI: -0.013 - 2.13, p= .054) group . As a result, further unplanned paired comparisons were computed, resembling a simple effects coding with litFUS as reference category. Three comparisons between litFUS and each group respectively emerged. They reveal a significant mediation effect in the control group (95% CI:0.302 - 6.14, p=.028), the sham group (95% CI:0.01 - 2.23, p=.046) and a marginally significant effect in the experimental group (95% CI:-0.099 - 12.53, p=.058). In summary, this suggests that litFUS was able to "decouple" theta activity at the Pz electrode position

Effect	Estimate	SE	Df	t	p	holm	β
Sham-litFUS	-1.243	1.415	53.890	-0.878	.384	1	-0.115
Control-litFUS	5.098	1.443	53.074	3.534	.001	.009	0.507
Experimental-litFUS	-1.259	1.577	53.345	-0.799	.428	1	-0.119
Sham-litFUS*Sec	-0.894	0.850	53.445	-1.051	.298	1	-0.129
Control-litFUS*Sec	2.715	0.865	52.225	3.138	.003	0.025	0.393
Experimental-litFUS*Sec	-0.823	0.948	53.043	-0.868	.389	1	-0.119
Sham-litFUS*Game	-0.163	0.441	13364.252	-0.370	.711	1	0.019
Control-litFUS*Game	-0.801	0.369	13323.626	-2.171	.030	.210	-0.042
Experimental-litFUS*Game	-0.938	0.497	13327.560	-1.890	.059	.353	-0.061
Sham-litFUS*Sec*Game	-1.023	0.381	13208.304	-2.682	.007	.059	-0.148
Control-litFUS*Sec*Game	-1.416	0.298	13334.321	-4.748	<.001	<.001	-0.205
Experimental-litFUS*Sec*Game	-1.353	0.426	13327.283	-3.174	.002	.015	-0.196

Table 22: Model parameters for the mixed model predicting Behavior. Estimate =unstandardized regression coefficient, SE= standard error of the mean, Df= Satterthwaite degrees of freedom, holm = holm adjusted p, β = standardized regression coefficient.

from self-reported control perception. On the other hand, in individuals, who did not experience litFUS neuromodulation, greater subjective feelings of control may be correlated to lower theta activity in posterior midline electrode position(s).

20.4.5 Additional analyses

To provide further information that may be of interest for the interpretation of current results and for future research on the field, Figure 25 illustrates a correlation matrix depicting the central electrodes in order from anterior to posterior with variables we assessed without formulating distinct hypotheses beforehand.

The correlation was highest for variables reflecting traits as compared to after-game self-reports. In Addition, electrodes that are located in more posterior regions correlate to self-ratings related to control perception (positive affect, surge of energy and motivation) to a greater degree than anterior electrodes do. These however correlate to a grater degree with traits like self esteem, industriousness and self-perceived IQ.

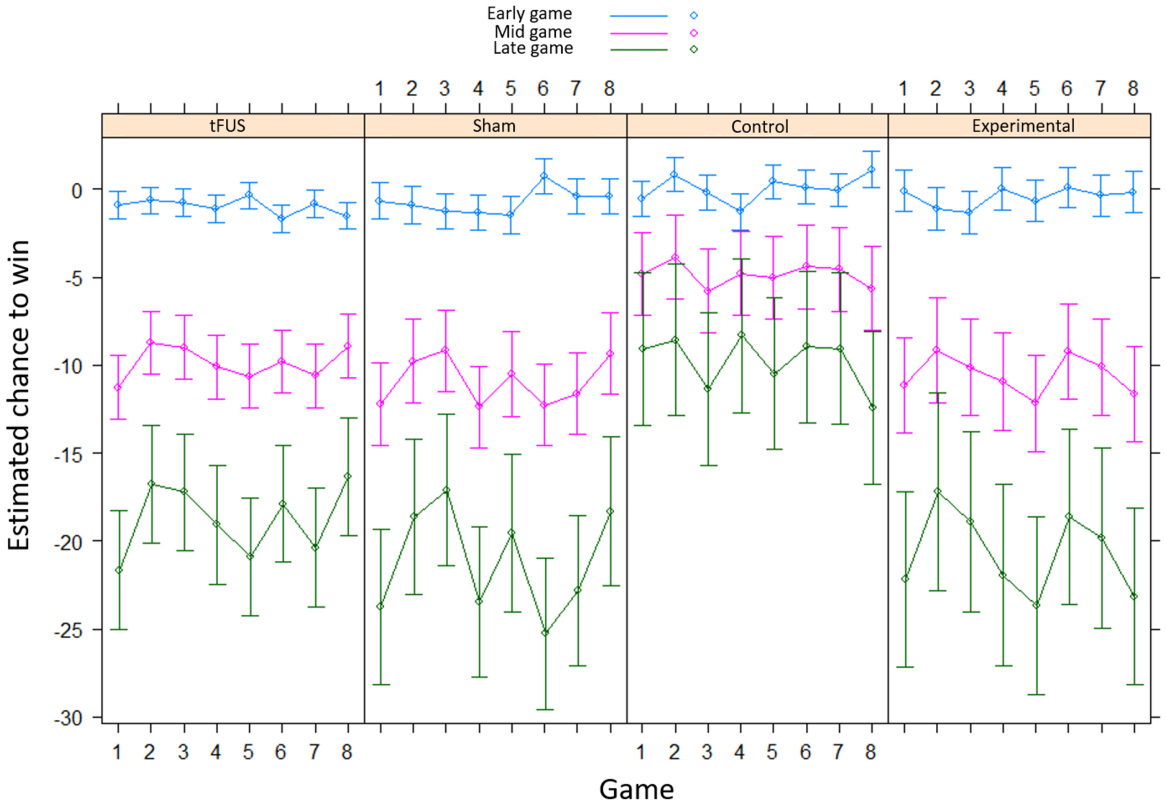

Figure 24: Three-way interaction between Game, Move and Condition with the computer-estimated chance to win as dependent variable. Higher values indicate better chances of winning. The early game (blue line) represents an estimate at the (grand)mean - 1 SD move, while the pink line represents the (grand)mean move. The green line indicates the (grand)mean + 1 SD move. Error indicators represent 95% confidence intervals

20.5 Discussion

In this study, litFUS conveyed inhibition was used to inhibit the neural excitability of the right inferior gyrus of the DLPFC. Following the ideas of frontal asymmetry research and the reinforcement sensitivity theory, such modulation may diminish depression related processing including cognition, emotion and behavior alike. Thus, in order to investigate the effect of litFUS in context of this background, EEG responses previously related to conflict, uncontrollability and anxiety were measured during a learned helplessness task.

20.5.1 Induction of Helplessness/Hopelessness

The results presented in the previous section first show that the task used in the current study is well suited for generating hopelessness. Descriptively, it produced increased negative affect while decreasing motivation, control perception and vigor (the feeling of

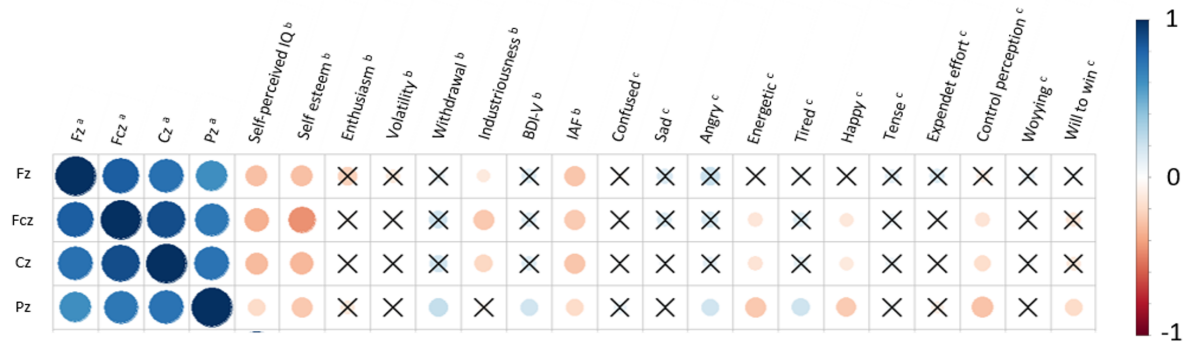

Figure 25: Correlation overview including: a = theta power density at central electrode positions measured during each game, b= trait-like variables that were measured only once before the experiment began and c= self-reported data that were generated after each game. Crossed cells indicate non-significance on an uncorrected $\alpha = .05$ basis. Higher transparency and smaller radius of circles indicate smaller correlation coefficients. Blue circles indicate positive, red circles indicate negative correlations. The autocorrelation of theta activity provide a reference for a correlation of 1.

being energetic and tired). Also effortfulness was diminished. We thus conclude, that this task was not only able to produce stress (as many other tasks would do) but to induce a state that fulfills the requirements of helplessness/hopelessness on many levels, while also being safe for the participants. Interestingly the control group produced the highest ratings in worrying, which may be interpreted as a correlate of the increased effort and will to win. On this note, participants who feel some kind of control over the game may worry more than others, since the alternating experience of hope and failure may increase the feeling of narrow misses. This, in turn may alter processing of game situations (Ulrich and Hewig, 2014). In comparison, the other groups may just have entered a state of acceptance, that the following games/moves will not be any different than the last, which would be well in line with the idea of hopelessness. A further support for this comes from the large differences in move quality between the control and all other groups. Since participants got a feedback on their estimated chance to win after every move made, the data in Figure 24 reflect the feedback given to the participants, showing more positive feedback for this group as compared to the others, thereby possibly inducing the feeling of near misses. At last, the group differences do not seem to result from pre-experimental group-level differences in traits or ratings, since these are mostly equally distributed across the conditions.

20.5.2 litFUS Modulates Midline Theta During Formation of Helplessness/Hopelessness

The first analyses following the manipulation check investigated the influence of neuromodulation on theta activity at the electrode positions Fz and Pz, which were already discussed as potential targets in previous research. For both electrodes, a highly significant interaction of experimental conditions, game and stages within a game was found, also depending on the depressiveness of subjects. Both the litFUS group and the experimental group showed a pattern in which depression did not seem to play a role, unlike in the sham and control groups. This finding fits well with the idea that interindividual differences do not show up in extreme situations (during a pandemic, people all behave cautiously, regardless of their trait anxiety). This interpretation is supported by the fact that although depressiveness seems to have little influence in the experimental group, the general level of theta activity is significantly higher than in the other conditions, which may also indicate a ceiling effect in this particular group. The litFUS group, on the other hand, has a lower level of theta activity regardless of their depressiveness, which could hint to the idea of stronger effects on the more depressed than on the less depressed, which therefore ultimately amounts to the same level for all. These two analyses therefore show on the one hand that litFUS is suitable for lowering midfrontal theta even in acute stress situations that may qualify to induce depression-like states, on the other hand it also shows that the method may be suitable for people who are already noticeably depressed before they encounter a stressor.

The additional analyses provided some insights into the meaning of theta activity at the given electrode positions. It highlights a negative correlation to trait-like constructs related to self esteem in mid-frontal electrode positions, while posterior midline electrode positions show increased sensitivity to state-influences connected to the perception of control, including happiness or the feeling of being energetic and willed to win in a dire situation. In summary this also highlights the potency of litFUS in the modulation of electrophysiological correlates of trait-like but also state-like measures.

20.5.3 litFUS Sustains Functional Goal Directed Behavior

In the next step, evidence was also provided to suggest that litFUS could elicit an improved behavioral response even in hopeless situations. This is indicated by the (after holm-correction only marginally significant) effect in Table 22. Even though effects may be minimal, these results still provide promising evidence for greater effects in measures that are more reliable. Nonetheless, this study was purposefully designed to increase external validity, which increased the variability of the data. Given the fact that effects are still present, these results highlight the potency of litFUS.

20.5.4 Mediation Effects Following litFUS Induced DLPFC Inhibition

Finally, a mediator model was tested. Even though the initial hypothesis of theta activity generally mediating self-reported control perception was not supported, unplanned post hoc tests revealed this effect to take place in all conditions but in the active litFUS-group . For all other groups but this one, a full mediation was found, while the effect vanished in the litFUS condition.

Even though these results are preliminary and uncorrected due to their exploratory nature, it indicates that theta activity may in fact not reduce control perception. Conversely, litFUS may have been able to decouple theta at Pz from the perception of control. This idea was deduced from the circumstance that if theta was an ubiquitous mediator, the mediation effect should not vary significantly between conditions. However, since especially the litFUS condition showed no sign of significant mediation, even though the other groups did, this leads to the idea, that the correlation of control perception and theta is different for individuals in this condition. As a result, diminished theta activity may not be the cause but the result of neuromodulation-induced changes in either psychological variables (control perception decreases theta) or it is the result of neuromodulation-induced decoupling of these variables (neither control perception nor theta cause one another).

This notion would be well in line with the idea of PCC involvement in the DMN. Taking this into account, litFUS induced changes in DMN activity (shifting attention away from the task, funneling resources into processing of internal stimuli rather than external),

may be correlated to decreased control perception and increased PCC activity (which we would measure as increases in theta activity). Inverting this model, this would imply decreased theta activity at Pz to go along with greater task-focus, which may in turn be positively correlated to control perception (equalling our results). Further supporting evidence for this comes from the correlation table in Figure 4, which shows that decreases in theta activity at Pz are also correlated to decreases in anger and tiredness, while being connected to increases in motivation, which fits the existing clinical literature on DMN functioning (e.g., Sheline et al., 2009.

In this context, results of section 3.4. may reflect a correlation between control perception and theta activity due to the influence of a third variable, which is the DMN. This may either produce or react to control perception and correlate to PCC acitvity which we measured indirectly via theta activity at Pz. The fact that no such mediation (correlation) was found in the litFUS condition may thus hint to some sort of functional decoupling of the DMN by litFUS. This notion would also be in line with the area of modulation (the right DLPFC is part of the DMN) and previous results by J. L. Sanguinetti et al., 2020, who used the same device and site of modulation, to alter said DMN functional connectivity. They report decreased functional connectivity between the PCC, the parahippocampal gyrus and temporal cortex, a network within the DMN which is connected to negative affectivity (Renner et al., 2017).

Another supporting evidence for this would be a correlation of Pz to the self-reported measure on worrying. Surprisingly no correlation to worrying was found. However, worrying was still most reduced in the experimental and litFUS condition, both of which depicted no/a marginally significant mediation effect. One possibility to this effect may lie in the complexity of the DMN, which may itself be functionally dissociable in emotion/motivation-based compartments and those that are more cognition-focused. The PCC in this regard may selectively react to the emotion/motivation aspect of the DMN, which is also highlighted by evidence of hopelessness in depressed being selectively correlated to PCC activity (;Grimm and Ram, 2009; ;Sheline et al., 2009; Jang et al., 2011; Renner et al., 2017). On the other hand, prefrontal areas may be connected to cognition-based functioning such as worrying or rumination (Hofmann et al., 2005; Ferdek et al.,

2016;Blackhart and Kline, 2005;Andersen et al., 2009;Ray et al., 2005).

However, this notion needs further evidence as the unplanned post hoc mediation findings may be able to inform future hypothesis formulation but not conclusive statements due to the possibility of floor effects in self-reports, the small sample size (which is especially striking in this analysis since all variables were averaged to the *game* level) and its exploratory (uncorrected) nature.

Nonetheless, it can be summarized that litFUS induced beneficial effects on many levels. The effects are indicated to rely on the modulation of complex neural networks connected to the right DLPFC. The effects did not show a noticeable decrease over time (max. 8 times 8 minutes) and seemed to have larger effects on more depressed individuals.

20.6 Conclusions

The study presented here addressed the manipulation of an electrophysiological marker for traits that may play into the development of affective disorders. By indirectly manipulating cingulate cortex function, via low intensity litFUS conveyed inhibition of the right DLPFC, we were able to show that differences in trait-like neural responses to hopeless situations present risk factors for depressive responses at all psychological levels including (self-reported) emotion, cognition and arousal, as well as behavior. As a consequence, by decreasing this neural response, the development of learned helplessness could be positively influenced in its course. Apart from the ACC related electrode Fz, especially the posterior midline electrodes seem to be interesting targets for further research in this field as theta activity at Pz was correlated to the effects of experimental manipulations (manipulation of actual control over the task and manipulation via litFUS or sham) on self-perceived controlability . To our knowledge, this is the first study to use neuromodulation to descriptively monitor and manipulate the development of helplessness in the laboratory. All in all, these results thus add to the overall understanding of the constitution of control perception and the emergence of depressive states.

20.6.1 Limitations

Due to the small sample, further research is needed to replicate the findings. Although a complex task was explicitly chosen to generate higher external validity, other methods with simpler behavioral responses should be investigated in the future.

In addition, the litFUS parameters used in this study were chosen to be maximally conservative but still effective. Other (higher) intensity of sonication could further increase the efficacy.

Finally, the conclusions reached in this study cannot be readily applied to patients. This is due to the facts that this study investigated a healthy sample and that there is no comparative data on depressed individuals available, neither with litFUS nor the task described here.

20.6.2 Acknowledgements

We would like to thank Rouven Aust, Simeon Schäfer, Anica Pilz, Larissa Haak and Sophia Zuleger for their conscientious and reliable support in data collection.

21 Embedding in the Thesis Framework (Paper IV)

Having already addressed the basis for the emergence of learned helplessness/hopelessness in the manuscript described above, this paper demonstrated that there are positive influences of riFG neuromodulation on the manifestation of helplessness-associated responses. These positive influences were shown (again in small effect sizes) in all areas of psychology: emotion, cognition, motivation, and arousal.

Whereas in the previous manuscript the lPFC alpha effects were in the foreground, now midline theta seems to be particularly important. This probably results from the fact that in this study midline theta does not show any event-related activity with regard to contingency, but rather reflects the previously discussed non-stimulus or response-locked, tonic anxiety, stress, and effort(lessness) response (see Section 5.1.1).

Nevertheless, these results show again that ACC function could be influenced by the modulation of riFG. Overall, before the results of this manuscript, it appears

that litFUS neuromodulation represents a powerful augmentation for preventive programs regarding depressive disorders.

22 Paper V - The Right lPFC Processes Emotional Features as a Function of Their Likelihood of Occurrence

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Title: The Right Lateral Frontal Cortex Processes Features of Emotional Faces as a Function of Their Likelihood of Occurrence

Authors: Forster, A.[a1], Rodrigues, J.[a], Ziebell, P.[a], Sanguinetti, J.[b], Allen, J. J.[b], Hewig, J.[a]

[a]Institute of Psychology, Julius-Maximilians-University, Würzburg, Germany

[b]University of Arizona, Tucson, USA

[1]Corresponding author

22.1 Abstract

The lateral frontal Cortex serves an important integrative function for converging information from a number of neural networks. It thus provides context and direction to both stimulus processing and accompanying responses. Especially in emotion related processing, the right hemisphere has often been described to serve a special role including a special sensitivity to stochastic learning and model building. In this study, the right inferior frontal gyrus (riFG) of 41 healthy participants was targeted via ultrasound neuromodulation to shed light on the involvement of this area in the representation of probabilistic context information and the processing of currently presented emotional faces. Analyses reveal that the riFG does not directly contribute to processing of currently depicted emotional stimuli but provides for information about the estimated likelihood of occurrence of stimulus features.

22.2 Introduction

The processing of emotional stimuli has been subject to extensive research in the translational neurosciences. One cortical area strongly involved in the general evaluation of (un)emotional stimuli and the individual's response to these is the lateral prefrontal cortex (lPFC, Dixon et al., 2017). The lPFC is often recognized for its integrative capability, constructing a consistent model of the world from a variety of information and stimulating consistent and goal directed responses (Filipowicz et al., 2016; Holroyd and Umemoto, 2016). It has (among other results) been reported to transmit information regarding mood (Reznik and Allen, 2018), motivation (N. J. Kelley et al., 2017; Gable et al., 2018), memory (Balconi and Ferrari, 2012; Barbey et al., 2013) and inhibitory control (Hewig et al., 2005; Wacker, Chavanon, et al., 2010). Even though a large number of studies have been conducted to clarify its role in these and other fields of research, the lPFC's functional dissociation into specialized subregions and networks as well as its hemispheric specificity is still up to substantial debate (e.g., Dixon et al., 2017; Harmon-Jones and Gable, 2018; Lacey et al., 2020; Lacey et al., 2020). Furthermore, a unifying framework associating these subregions and their respective networks with complementary steps in the processing of emotion and emotional stimuli is still lacking. This may in part be owed to the complex patterns of network interactions that can lead to contradictory or null-results as well as to differences in methodology used in the current literature (Rodrigues et al., 2021).

One increasingly utilized way to partly disentangle such patterns is the neuromodulation of narrowly circumscribed areas. Therefore, the present study seeks to provide insights into the unique contribution of the right inferior gyrus of the lPFC (riFG) to the reaction to and processing of emotional stimuli by modulating its excitability via low intensity transcranial ultrasound neuromodulation (litFUS). The main focus of this investigation is the right hemispheres supposedly unique capability to model stochastic information and experience, which may reflect processing of contextual information about currently presented emotional stimuli.

22.2.1 Specialization of the Right lPFC

Research on frontal asymmetry (FA) suggests a relative rather than an absolute interpretation of hemispheric activity. It mostly but not solely builds on an EEG index that is calculated by subtracting the natural logarithm of the alpha power in left hemispheric electrodes (usually F3 or F7) from right hemispheric ones (F4 or F8). Positive values of the resulting measure indicate greater left than right lPFC activity, while negative scores imply greater right than left cortical excitation. Furthermore, even though the theory behind FA has notably evolved throughout the past decades (Harmon-Jones and Allen, 1998; Wacker, Chavanon, et al., 2010; R. J. Davidson, 2004; Hewig et al., 2005) an overall consensus on its correlation to motivational states has been established (N. J. Kelley et al., 2017; Rodrigues et al., 2018). As approach and withdrawal motivation go along with certain emotions, a substantial body of literature further describes its implications in mood and emotion processing (Reznik and Allen, 2018;). Moreover, FA has been researched in a number of contexts including a variety of disorders like depression (J. J. B. Allen and Reznik, 2015), ADHD (Keune et al., 2015) or anxiety (Smit et al., 2007) hinting to its role as a possibly trait-like vulnerability to disorders that comprise some sort of dysregulation of motivational tendencies (Thibodeau et al., 2006; Stewart et al., 2010; Nusslock et al., 2015; Jesulola et al., 2015; Hewig, 2018) but also see: van der Vinne et al., 2017).

Other studies focused on one hemisphere at a time instead of their relative activity. On that note, for the right lPFC two hypotheses emerged, one stating a general preference of the right hemisphere for emotion processing (Borod et al., 1988; Dimberg and Petterson, 2000; Hagemann et al., 2005; S. D. Smith and Bulman-Fleming, 2005; Wallez and Vauclair, 2011; Yang et al., 2018), while the other suggests a specific involvement in negative or generally withdrawal-related emotions (Wheeler et al., 1993; Wyczesany et al., 2009; Baijal and Srinivasan, 2011; Ran et al., 2016)

In addition, Yang et al. (Yang et al., 2018) point out that both hypotheses may coexist in the way that a special sensitivity for negative emotional processing is build on top of the general processing capability of emotions inside of the right lPFC. In conclusion, even though the discussion on the correct mapping of emotional processing to either side of the lPFC is still ongoing, a consensus emerges that the right lPFC plays a crucial role

at least in the processing of negative emotion and negatively valenced stimuli.

Moreover, the (bilateral) lPFC shows another specialization, which is attention modulation (e.g., Posner and Cohen, 1984; Johnson et al., 2007; Christakou et al., 2013). In general, lPFC dependent attention processes show mood and context congruent selectivity, which is highlighted by reports on differences in attention modulation in patients suffering from depression, PTSD, addiction and other diseases (e.g., Elliott et al., 2002; Fani et al., 2012; Zhang et al., 2018). A few studies using neuromodulation techniques show a specialized right hemispheric involvement in the detachment from emotional faces in general with a greater effect for angry faces. More precisely, these results describe greater right lPFC activity to impair attentional shifting away from emotional stimuli. (Leyman et al., 2009; de Raedt et al., 2010; Sanchez-Lopez et al., 2018).

Finally, a number of studies described the specificity of the right lPFC for probabilistic learning (Fletcher et al., 2001) as well as stochastic model building and updating (Filipowicz et al., 2016) including evidence for impairments in stochastic model building and updating in brain damaged and split brain patients (Wolford et al., 2000; M. B. Miller and Valsangkar-Smyth, 2005; Roser et al., 2011; Danckert et al., 2012). In addition, Stöttinger et al., 2014 report no such impairment in patients with left sided brain damage.

In summary, the lPFC has been described to play an important role in the processing of emotions, motivation and attention with a hemispheric specification for non-verbal stochastic representations of the recent history of events for right lateralized networks including right prefrontal areas. Taken together, these insights highlight the bilateral lPFC's and specifically the right lPFC's importance in psychopathological states as the prolonged or excessive display of fear, dysphoria, withdrawal and many other symptoms may be a result of a highly entangled combination of these features. For instance, an impaired representation of the probability for positive reinforcement due to an excessive activity in the right lPFC, may lead to decreased approach motivation, increased anxiety or sorrowfulness. As a result, a mood congruency effect facilitating attention focusing on and learning from negative events may follow. However, to this date, no process model detailing such sequences of processing steps has been described.

For this reason, this direction of action could also occur in reverse: A mood effect may contribute to the display of congruent behavior (withdrawal, worrying, etc.), which could ultimately lead to an altered representation of matching emotional stimuli. In summary, all of these consequences may by themselves be the starting point for such sequential or concurrent stages of processing, leading to the symptoms described above.

22.2.2 Emotional Faces and Depression

One set of stimuli combining many features that are supposedly linked to right lPFC processing are faces depicting emotional states (Sanchez-Lopez et al., 2018; Sanchez et al., 2016;). Yang et al., 2018). Not only does it provide ground for emotional, non-verbal learning, which plays a crucial role in the pathogenesis of depression, a highly social disorder, but it may also disentangle emotional processing from those of other features, like sex (which may arguably also include emotional associations, see section 4).

Depression describes a very heterogeneous state that goes along with increased processing of negative stimuli and impaired social functioning (World Health Organization, 2004). As a result, over the last decades, several studies have focused on depressed individuals to investigate neural substrates of diverging processing of both emotional and social cues (e.g., R. J. Davidson et al., 1985; Y. Li et al., 2015; Koller-Schlaud, Ströhle, et al., 2020; Koller-Schlaud, Querbach, et al., 2020). As the frontal asymmetry of lPFC activity and activation has previously been described to play a role in trait-vulnerability for depressive episodes, motivational states and affect (Reznik and Allen, 2018), results stemming from the literature on the lPFC conveying emotional face processing and general neural substrates of emotion and motivation may converge at this area. One example is the study by Kerestes et al. (Kerestes et al., 2012), who described the time elapsed after the last depressive episodes to be associated with decreased left-sided lPFC activity in response to anxious compared to neutral looking faces. This fits the idea of FA research, which shows that depression is associated with a less left-compared to right sided lPFC activity (Hewig, 2018). Although this difference may be due to several reasons, for example less left frontal activity or more right frontal activation, these correlative findings in studies comprising individuals showing trait vulnerability to the over-representation of

negative affective cues when viewing emotional faces are in line with experimental evidence. For instance, Sanchez-Lopez et al., 2018 report decreased gaze disengagement from negative cues in emotional faces following tDCS conveyed excitation of the right dorsolateral prefrontal cortex.

Another study addressing the relationship of negative affect in emotional faces and neural responses is provided by Ran et al., 2016. The authors conducted two experiments that manipulated both, predictability of the emergence of fearful or happy faces as well as the participant's attention to these. Their results indicate a right-hemispheric attention-modulated neural response to fearful faces and a left-hemispheric sensitivity to happy faces.

Accordingly, the current study also used a set of emotional faces as stimuli. They were presented in a protocol described by Lissnyder et al. (de Lissnyder et al., 2012), who examined sequence effects of emotion expression in comparison to sex in context of cognitive shifting capabilities. In summary, in blocks of 11 faces, a random sequence of stimuli was presented. These depicted either a male or female, angry or neutral looking face. The task consisted of participants trying to internally count either the number of angry/neutral looking faces or male vs. female faces as fast as they could (the focus of counting altered for each experimental block). Thus, in a given block, explicit processing of one feature (i.e. sex), but not the other (i.e. emotion) was primed.

22.2.3 Low Intensity Transcranial Ultrasound Neuromodulation

litFUS is a novel method to alter neural excitability. Unlike other methods such as TMS or tDCS, litFUS uses mechanical waves (sound) to oscillate neural tissue and thereby influence its reactivity. Even though to this point no conclusive mechanism of effect has been established, several ideas about mediating biophysical properties of neurons have been formulated. For instance, mechanosensitive receptors like the two-pore-domain-potassium channels of the TREK family were shown to react to the ultrasound induced conformatory changes in cell membranes (Kubanek et al., 2016). Furthermore, several other cellular structures have been hypothesized to convey the effect due to their mechanosensitivity (Tyler, 2012).

The model used to estimate the litFUS effect in this study is described by the NICE-model, which predicts inhibitory effects to result from the excitation of inhibitory interneurons that express a large number of T-type calcium channels, thus leading to a net inhibition from a network level point of view(Plaksin et al., 2016). Interestingly, these channels have also been described to influence the general EEG alpha response and account for individual differences in the individual alpha peak frequency (IAF) as T-type channels fire at a rate of approximately 10Hz (see Bazanova and Vernon, 2014). Therefore, by exciting these channels, increases in the alpha-band (which is inversely correlated to cortical activity) power may emerge following inhibitory litFUS modulation. Throughout the past years a few but steadily increasing number of studies used this method to safely modulate neural tissue in humans (in vivo, Hameroff et al., 2013; Legon et al., 2014; Legon et al., 2018; Legon et al., 2018; J. L. Sanguinetti et al., 2020; Reznik et al., 2020; Legon et al., 2020b).

22.2.4 The current study

Building on the aforementioned remarks, this study examines the unique properties of the right lPFC regarding probabilistic processing of non-verbal information and its modulating role in emotion processing. Accordingly, the present study used emotional faces to elicit stimulus-driven EEG oscillations on a single trial level, which allowed for the investigation of the influence of stimulus probability on the reaction to a given trial.

Thus, we hypothesized EEG alpha oscillations, which are part of the frequency range that is targeted by our settings of litFUS, to be modulated by the likelihood of stimuli. Furthermore, since many studies reported the right lPFC to be especially involved in emotion processing, this effect should also be present in the probabilistic processing of emotional features. Nonetheless, as many studies investigating the stochastic learning capability of the right hemisphere also reported positive results for stimuli and tasks without emotional features, we also assume this effect to be present regarding the sex of depicted faces. In conclusion, the alpha response at F8 should depend on an interaction of the estimated likelihood of occurrence regarding a specific emotion and a certain sex. Furthermore, the alpha response to this interaction should also be altered depending

on the focus of attention (on either sex or emotion). Hence a three-way interaction is anticipated between the likelihood of occurrence of sex, emotion and attention focus. Moreover, this interaction (targeting the current history of experiences) may additionally impact the processing of the currently depicted emotional faces, leading to a four-way interaction. At last, this already complex term may be modulated as a whole or in part by the ultrasound neuromodulation, which would further strengthen the idea of the direct involvement of the right lPFC (more specifically the right inferior frontal gyrus [riFG]) in these processes.

As a result our hypotheses (concerning the alpha power density at F8 electrode position as dependent variable) are modeled including a four- way interaction of litFUS, likelihood of an emotion and sex of a depicted face and focus of attention, as well as another four-way interaction comprising litFUS, the currently depicted emotion, focus of attention and the estimated likelihood of an emotion. This split into two separate interaction terms was chosen as the currently depicted emotion specifically is not thought to rely on the estimated likelihood of a given sex to be depicted. Thus in order to reduce the already complex pattern of interactions, a five-way interaction was avoided leading to the present solution.

In addition, since inactivity of the riFG is in general interpreted to signal decreased emotion processing (depending on the the theory, either for emotions in general or specific to withdrawal-related ones) we also hypothesize the right lPFC's alpha response to be inversely correlated to reaction time (RT). Furthermore, even though no directed idea is formulated for the influence of litFUS, an interaction of the neuromodulation and alpha is anticipated for RTs. In addition, litFUS is thought to modulate RT differences between sequences of faces. On that note, decreases in RT in trials comprising shifts from angry to neutral faces in comparison to other sequences were found to correlate to trait worrying, which may build on impaired capabilities to detach from the negative/threatening face of the previous trial (de Lissnyder et al., 2012). As a result, since litFUS is thought to decrease the processing of (negative) emotions, we anticipate an interaction of litFUS and sequence of depicted emotions. At last, this effect may vary depending on the focus of attention.

22.3 Methods

22.3.1 Sample.

Participants were recruited from a stock of test-persons registered to a website specifically set for the purpose of enrollment in psychological studies hosted by the University of Würzburg, Germany. Forty-one right-handed, healthy participants, who were at least 18 years of age took part in this study (29 female) including 36 undergraduate or graduate students (23 students of psychology). Participants received either course credit or 15 as a compensation for taking part in this study. Average age was 24.46 (SD= 8.58). Mean BDI-V [20] scores were 22.8, mean IAF was 10.0 The procedure of neuromodulation was assessed by the psychological institutes ethical committee and deemed ethically unproblematic (reference: GZEK 2017-18). Informed consent (also including publication of their respective data) was given by all participants before taking part in the experiment.

22.3.2 Material.

For the Internal Shift Task (IST) 24 image files from the KDEF collection were used (KDEF; Lundqvist et al., 1998). The image files contained 19 aggressive looking faces (9 male and 10 female), and 20 image files with neutral expressions of faces (9 male and 11 female).

22.3.3 Procedure.

Participants completed an online survey before visiting the laboratory in order to give them the opportunity to finish questionnaires in a natural setting, thereby preventing possible biases that arise from interactions of the lab-setting with personality variables (e.g., inducing worrying in test-persons who might become unsettled by the general lab-setting). With the exception of the BDI-V (M. Schmitt et al., 2003), none of the questionnaires were used for this study. However, the present experiment was part of a battery of three independent tasks that did not change in their sequence of presentation between partici-

[20]The BDI-V is a questionnaire building on the BDI-II. It is especially suited for subclinical differentiation. Individuals with scores over 35 are considered to show a clinically relevant depression with a sensitivity of 90%;M. Schmitt et al., 2003;M. Schmitt et al., 2006

pants or between sessions. The current task was always presented as the second of three. No stimulus material of the task was reused in other tests. No other task comprised faces or angry looking nor anger eliciting stimuli.

After completing the survey, participants attended two experimental sessions (exactly seven days apart) consisting of the same task and procedure. However, on one measurement occasion, participants received litFUS modulation while sham was applied in the remaining one. The experiment thus represents a double blind cross over design with two groups that differ in their respective session of modulation (t1 or t2). Unfortunately no exact measure of the time passed between administration of litFUS to the start of the task can be provided. However, approximately 30 to 45 minutes are estimated based on the time it took to prepare the passive EEG electrode setup (which introduces the most variability to the estimate) and to complete the preceding task (less than 10 minutes). Following litFUS or sham-modulation, EEG electrodes were administered. Participants were seated in a distance of approximately 60 cm from a 24-inch screen. Subsequently, testing of participants began.

Internal shift task. The internal shift task (IST, de Lissnyder et al., 2012) was one of three independent tasks in a larger assessment of effects of litFUS-modulation. During the task, participants are instructed to (internally) either count the number of angry and neutral faces or to count the number of female and male faces presented (de Lissnyder et al., 2012).

Displayed faced (326 x 326 pixels) were randomly chosen (with replacement) from a subset of 19 neutral and 20 angry faces selected from the *Karolinska Database of Emotional Faces* (Lundqvist et al., 1998). This subset equaled the selection of the 20 most valid pictures per emotion as depicted by Goeleven et al., n.d. with one exception (AF16 in neutral condition). Whether sex or emotion is in the focus of internal counting during one block alternated and was indicated before the next one started. Moreover, in order to rule out effects from contextual cues, hair, clothing and background were cropped out of the pictures.

A total of 24 blocks, each consisting of 11 trials was completed in one session with half of the participants starting with sex and half starting with emotion in focus. To

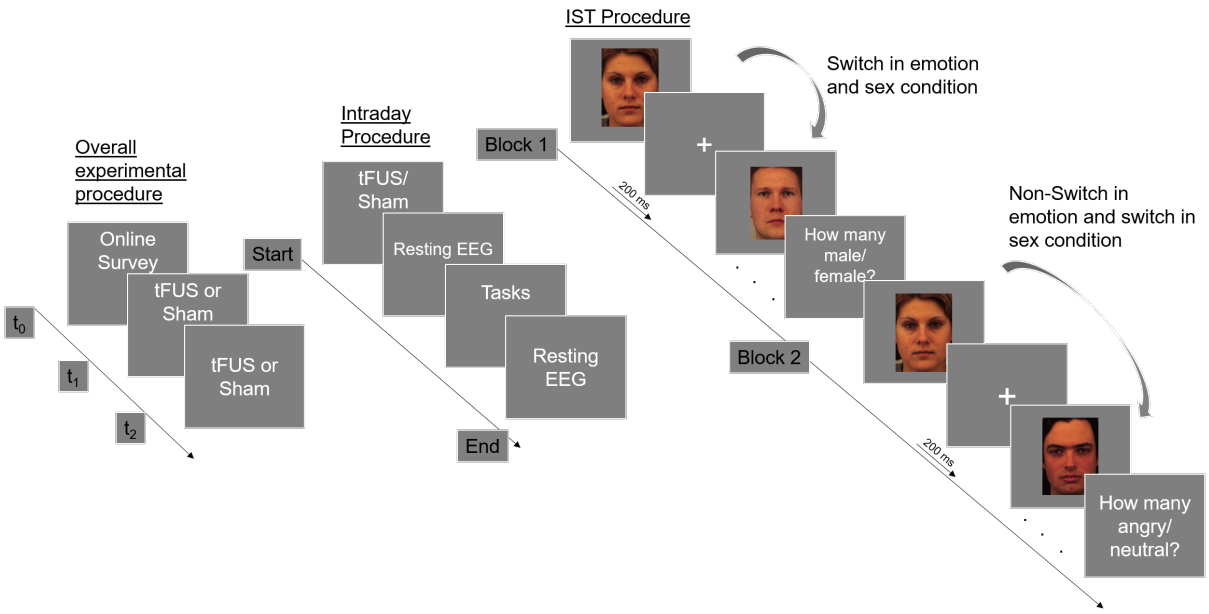

Figure 26: Conceptual representation of the overall-, intra-day- and task procedure. This experiment was the second of a total of three tasks within a test-battery. The same test-battery was presented two times, once under the influence of litFUS, once following sham. THe stimuli of this study were not used in other parts of the test-battery. Each session started and ended with a resting EEG of 8 minutes, which is beyond the scope of this paper. The present task comprised 24 blocks, each consisting 11 presented faces with an alternating focus on either sex or depicted emotion of shown faces. In this figure, two trials are presented within 2 blocks that differ in their focus on sex or emotion. The dots depicted before the question for the number of internally counted features indicate that he sequence of image depiction and fixation cross presentation continued 11 times.

correct for sequence effects, participants were randomized to either group and began in different order of blocks on session two.

In each trial, after they are finished updating the two numbers they were supposed to keep in mind, participants pressed space to continue to the next picture so they can update their numbers in mind again. After pressing space, a fixation cross was presented for 200ms before the next face appeared. Following each block, participants were asked how many angry vs. neutral faces or male vs. female faces they had counted. Subsequently, test subjects were told what was to be counted during the next block. The procedure is illustrated by Figure 26

22.3.4 Transcranial Ultrasound Neuromodoulation.

Neuromodulation was applied at F8 electrode position of the 10-20 EEG system. This location was chosen not only because of the underlying riPFC an area with strong implica-

tions in the cognitive control network (Cole and Schneider, 2007) and frontal asymmetry but also due to the underlying temporal window of the skull. This structure is (compared to other skull locations) relatively thin making it less likely to distort or absorb energy.

Neuromodulation was applied for 120 seconds with a duty cycle of 0.5%, a frequency of 500 kHz and a pulse repetition frequency of 40 Hz leading to an acoustic intensity spatial peak time average of 199mW/cmš and a mechanical index of 1.53. The ultrasound was emitted by a single element transducer (with a two-part lens focused at 30 mm) that was connected to a manufactured gel pad (product number SS-6060 by Silicone Solutions, Cuyahoga Falls, Ohio, USA), which was in turn directly placed on the F8 electrode position of the scalp. Neuromodulation was operated by a manufactured device (Thync, Los Gatos, USA) and carried out by two experimenters at a time (one fixating the transducer and the gel pad to the participants head and one starting the procedure on the device). While the two minutes of modulation/sham were running, participants were asked not to move or talk in order to prevent distortions of the transducer relative to the targeted location. The same device has been used before by Sanguinetti et al. (J. L. Sanguinetti et al., 2020). Further detail on its utilization and profile of emission may be reviewed there.

Since ultrasonic waves are too high in frequency to be heard by humans, litFUS can easily be shamed. In this study, experimenters either pointed the transducer at the desired region of interest or in the opposite direction, away from the participant's head. However, litFUS was emitted either way, keeping the preparation process for experimenters constant across litFUS- and sham-modulation. Nonetheless, the experimenters were not aware of which direction would direct energy from the transducer, thus allowing for a double-blinded protocol.

22.3.5 EEG administration and preprocessing.

EEG recordings were collected via a 64 electrode brain cap system and recorded via the brain vision recorder (Brain Products, Gilching, Germany). However, due to technical issues, 13 participants were tested with an 32 electrode cap but an otherwise equal recording system. Nonetheless, according to Bazanova and Vernon (Bazanova and Vernon, 2014)

,the cap montage does not influence alpha-related measures. Also, all following analyses rely solely on those electrodes that were included in both sets. Electrodes were brought under 5 k. Online reference was Cz, ground was Afz. An online 80Hz low-pass filter was applied. The sampling rate was 250Hz.

The preprocessing pipeline was executed via the Matlab (The MathWorks, Massachusetts, USA) extension EEGLAB (Delorme and Makeig, 2004) including plug-ins *MARA* (Winkler et al., 2011), *Adjust* (Mognon et al., 2011), *SASICA* (Chaumon et al., 2015), the *CSD-toolbox* (Kayser and Tenke, 2006a, Kayser and Tenke, 2006a) and the *restingIAF toolbox* (A. W. Corcoran et al., 2018). The procedure followed the *EPOS* preprocessing pipeline of Rodrigues et al. (Rodrigues et al., 2021): As a first step, electrodes were re-referenced to average. Following this, channels were automatically rejected and interpolated depending on their averaged z-score on the three dimensions kurtosis, probability and spectrum. A z-score (calculated for the mean of one channel in comparison to all others) of more/less than ś3.29 (following suggestions by Tabachnick and Fidell, 2013 on outlier detection) qualified a channel for rejection. Epochs were extracted (-300 ms to 1200 ms) and a 1Hz high-pass filter was applied. Then, an ICA was conducted, and trials were automatically rejected by the same procedure as the channels had been. Following this, ICA weights and indices of rejected trials were saved. The preprocessing started once again and applied the saved parameters to the new set that was now missing the 1Hz filter in its pipeline. Afterwards, SASICA was used to reject components based on MARA and Adjust evaluations of the data. At last, the data was CSD-transformed.

Following this, Morlet wavelets (fixed cycles of 3.5s, log-spaced) were used to extract the power of frequency bands, that were identified individually for each participant by analyzing an eyes closed resting condition that preceded the experimental test battery at each session via the restingIAF toolbox (A. W. Corcoran et al., 2018). IAFs and band width were determined by averaging calculated IAFs across a minimum of 17 channels (15 in 32 electrode setup) and a frequency range of 1-40 Hz. Bounds of the IAF search window were set to 7-13Hz and a *Savitzky-Golay* filter of 11 bins was administered. The IAF was then used to split the alpha band into two parts: *upper alpha* (IAF to upper band border) and *lower alpha* (low band border to IAF). Afterwards, the both measures were added

up and the respective contribution of each band to this sum was calculated. At last, the general alpha response was expressed as a weighted composite of both bands multiplied with their respective contribution-parameter. All EEG measures were normalized via natural logarithms. All further analyses regarding EEG measures build upon the average between 100 and 300 ms after stimulus onset.

22.3.6 Measures.

For the following analyses a number of measures are included that may not be obvious in their interpretations. Thus, this section provides an overview of the authors perspective on the reflected effects.

Stimulus presentation rates. This task presented a total of 264 faces in random order. Each face exhibited a combination of specific features which were summarized to the categories of emotional expression (angry vs. neutral) and sex (male vs. female). As a result, for each given trial a rate of the presence of a certain feature was calculated by the number of features present thus far divided by the number of trials thus far. The concluding moving average produces a number between 0 and 1 that in this study reflects the overall rate of male and angry faces. The these rates were calculated independently for the feature sex and emotion. Also, calculation of these measures did not consider whether a given trial urged particpants to process a feature explicitly or implicitly. We interpret these rates as the objective representation of the presentation of stimuli, which may provide data for subjective interferences about the likelihood of feature presentation in current or future trials.

Block. The experiment asks participants to either focus on the expressed emotion or the sex of presented faces. This focus of processing changes after 11 trials. As explicit processing of one feature and inhibition of processing of the other feature is part of the task, we conclude the block to represent a shift in selective attention. Explicit vs. implicit processing, block and shift of attention are thus used interchangeably throughout the text.

Emotion. The variable emotion describes the valence of the currently expressed emotion by the presented face in a given trial. It thus marks the immediate response to

the currently depicted stimulus, neglecting sequence effects.

Trial. in the following analyses, Trial refers to the cumulative trial, given by the overall index of a given trial within one session. It rises continuously without interference of block or other variables and reaches a maximum of 264 (24x11).

Sequence. Sequence describes the sequence of depicted emotions from the current trial and the one before. As a result, four sequences emerge (angry → neutral, neutral → angry, neutral → neutral, angry → angry). Following the theoretical remarks of De Lissnyder, Koster and De Raedt, (de Lissnyder et al., 2012), especially the relation of angry → neutral to the other sequences should be correlated to worrying, depression and anxiety as participants scoring high on these constructs may have trouble shifting their attention away from the threatening stimulus, which may conclude in slowed reaction speed.

22.3.7 Statistical analyses.

In order to answer the questions raised by the hypotheses, two sets of mixed effects models with an increasing number of parameters were calculated. All models comprise a random intercept for each test-person, a random slope for *trial* and grand mean centered metric predictor variables. The nominally scaled variables *Emotion*, *litFUS* and *Block* were dummy coded to the reference levels of *neutral*, *sham* and *focus on emotion/explicit processing of emotion*, respectively. Thus, main effects as well as interactions of third variables not including one of these variables, can be interpreted in the fashion that the given effect is present in the given reference category. For instance, a significant main effect for emotion reflects a difference between neutral and angry faces in the sham condition. However, in order to test for the same effect in litFUS trials, the interaction term comprising both, emotion and litFUS needs to be consulted. The sequence of faces was simple-coded, introducing the grand mean of all levels as intercept (as opposed to dummy coding, which sets the mean of the reference level as intercept). Hence, other effects may be interpreted in light of no particular sequence of faces. Variables coding feature presentation rates, such as the rate of male or angry faces (Tables24 and 28) represent of the last trial before the current one (trial -1). Hence, the variance of the

current trial, which is reflected by the variable *emotion* would not be included by the rate-measures. As a result, feature rates give more of a context to the given trial, while *emotion* catches the immediate response to the current event selectively.

Following the data-driven approach of mixed effects modeling, only the best fitting model was analyzed for fixed effects estimates. All models started with a random intercept (for each participant) and a random slope (*trial within session*).

Resulting from the theoretical foundation introduced above, a complex pattern of interactions may be present including a four-way interaction of the rate of angry faces, rate of male faces, block and litFUS. However, also lower order interactions of this term may emerge as well as main effects. Including all of these into the model may lead to substantial multicollinearity. Nonetheless, as this issues will generally decrease the likelihood of effect detection rather than inflating its probability, this way is estimated to be more conservative for a first investigation on this topic. All (non-exploratory) effects were *Bonferroni-Holm* adjusted with the exception of the estimate for the model's intercept, since no hypotheses were calculated for these. Furthermore, additional exploratory analyses were conducted to further clarify confirmatory results. Only those trials, that were within 3.29 SD from the grand mean of reaction times were included in the following analyses in order to exclude those that comprised some sort of distraction (leading to excessively high reaction times) or improper stimulus processing (by pressing before cognitive processes could take place).

All analyses were conducted via *R*'s (R Core Team, 2017) *lme4* (Bates et al., 2014) package and plotted with the *effects*(J. Fox et al., 2016) package.

22.4 Results

Before reporting the results of above stated hypotheses, topographical plots for all conditions of this experiment are shown in Figure 27. This figure illustrates that the topographical map of alpha responses was in general more dependent on the likelihood of occurrence of features than on the depicted face within the current trial: Regarding the alpha response to the currently depicted emotion, no prominent difference between plots is present within the sham and litFUS conditions. While litFUS seemed to decrease alpha

at frontopolar and right lPFC regions, no other effect of *emotion* or *implicit/explicit* is evident (Figure 2a). Figure 2b further illustrates decreasing alpha responses at the right lPFC in trials that followed a history of lower angry men rates as compared to those with higher rates during sham sessions (comparing the upper to the lower sham topoplots). However, this effect is reversed within litFUS sessions as the right lPFC increases its activity with higher rates of previously depicted angry men (comparing upper to lower topoplots within the litFUS condition). Figure 2c also shows, that the effect was similarly present when comparing block-wise rates of previously shown angry men. Nonetheless, the effect was most prominent when looking at the overall probability within the complete session rather than feature likelihoods within one block.

In line with these plots, Figure 28 illustrates the time frequency plots for each experimental condition at electrode position F8. These indicate a possible effect at at frequencies in the alpha and theta band with decreasing alpha responses in litFUS as compared to sham (comparing the top time-frequency plots within Figure 29 and Figure 27a).

22.4.1 Hypothesis testing

Table 23 summarizes the first subset of random intercept models. It shows that no increase in model fit was accomplished by introducing the depicted emotion of the stimulus into the model. The same is true for the difference between implicit vs. explicit processing of features. However, in general the significance of model 3 and 5 imply significant contribution of probabilistic learning and litFUS to the synchronization of alpha at the riFG.

Table 24 shows the full fixed effects estimates of model A5. The parameters are organized in ascending order of uncorrected p values. After *Bonferroni-Holm* correction, significant effects were in general found for the influence of feature rates, litFUS and block but not the current emotion depicted in a given trial. All main effects are estimated with respect to the reference categories of current emotion (neutral), block (attention on emotion) and litFUS (sham).

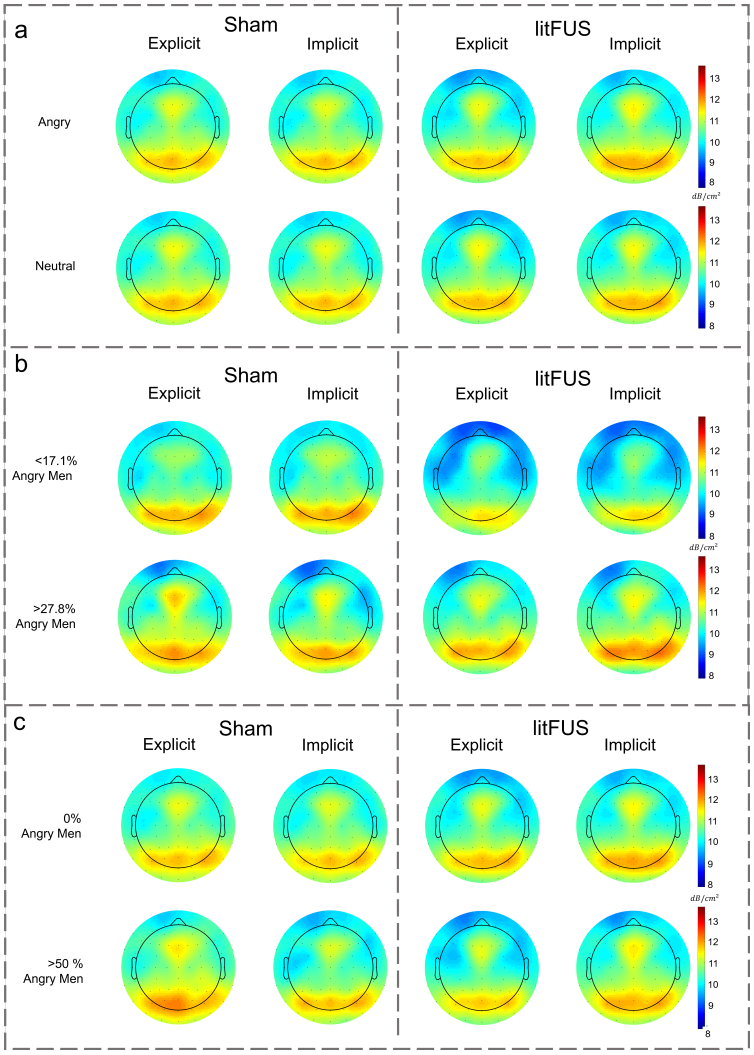

Figure 27: Topographical plots of the alpha response to experimental conditions. Colors represent db/cmš averaged from 100 to 300 ms after stimulus onset. a) Alpha activity following explicit or implicit presentation of angry or neutral faces. Only small fluctuations of activity is present within the sham and litfus conditions. However, less alpha activity seems present in both frontopolar and right lPFC regions when comparing the overall litfus and sham activity. Overall, the topographic response in the EEG seems to be hardly dependent on the currently presented emotion. b) Alpha activity in trials in which no more than 17.1% of the previous trials (representing the lowest 10% of rates found in the complete data set) or at least 27.8% percent (representing the highest 10% of rates found in the complete data set) of all images shown thus far depicted angry men. Plots (comparing high vs. low. rates among explicit and implicit blocks) indicate decreases in alpha activity at right prefrontal areas if more angry men have been shown before. This is true for both implicit and explicit feature processing but seems more pronounced in implicit emotion processing trials. c) Alpha activity in trials within one block where no angry men have been shown (representing the lowest 10% of rates) or at least 50% percent (representing the highest 10% of rates found) of images shown thus far within a given block depicted angry men. The pattern depicted in *b* is also present in context of within-block likelihoods but seems less pronounced than in *b*, where the overall likelihood within one session instead of block was plotted. This indicates differences in right lPFC alpha activity in response to session-spanning likelihood of features assessments.

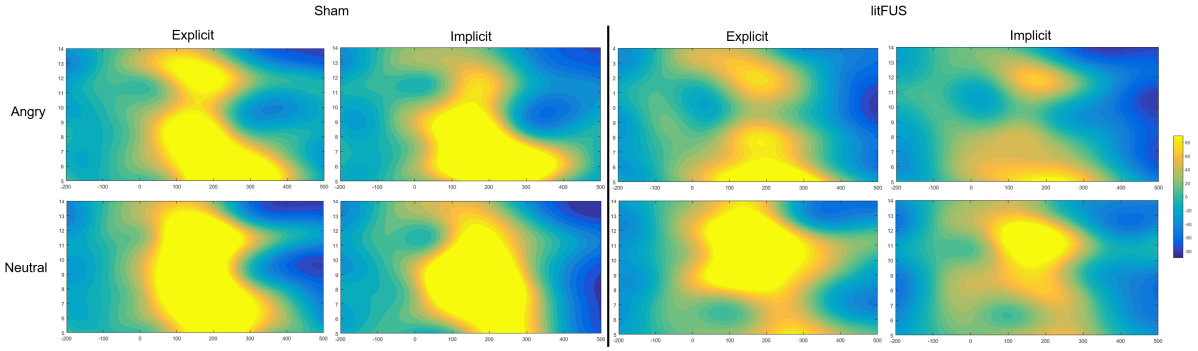

Figure 28: Time-frequency plots of experimental conditions at electrode position F8. Time-frequency plot averaged across implicit and explicit trials as well as across depicted emotions. The images show decreased alpha and theta responses to angry faces during litFUS sessions as compared to sham measurement occasions. Also, an alternated response in lower frequencies following neutral face depiction seems evident.

	Df	AIC	BIC	χ^2	Df (χ^2)	$p(\chi^2)$
A1	4	28513	28550			
A2	5	28515	28559	0.3968	1	.529
A3	9	28475	28548	48.172	4	<.001***
A4	15	28482	28599	4.827	6	.566
A5	27	28238	28442	267.853	12	<.001***

Table 23: Summary of model comparisons with alpha power density at F8 electrode position as dependent variable. A1= random intercept + random slope (*trial*), A2= A1 + *emotion*, A3= A2 + rate(angry)* rate(male) + emotion* rate(angry), A4= rate(angry)* rate(male)* block+ emotion* rate(angry)* block, A5= rate(angry)* rate(male)* Block*litFUS+ emotion* rate(angry)* block*litFUS; DF=degrees of freedom, AIC = Akaike information criterion, BIC = Bayesian information criterion. DF(χ^2)= degrees of freedom for the χ^2 test. *= p<.05. *** = p<.001

Just like the main effects, the interactions indicate the EEG alpha response at the riFG to change as a function of stochastic processing of stimulus features and attention focus but not processing of current emotional stimuli. Furthermore, litFUS introduces differences for all variables but the current emotion, again highlighting the riFGs role in stochastic processing.

In summary, Table 24 indicates higher rates of male and angry faces to decrease the alpha response. However, before the properties of the mixed model estimation procedure, these effects result in context of the reference categories of nominal predictors that are not included into the effect's (interaction-)term. Thus, higher rates of male and angry faces were found to decrease alpha reaction in sham sessions during trials with explicit

	Estimate	SE	Df(Satt.)	t(Satt.)	p(Satt.)	*holm*	β
(Intercept)	16.160	0.863	5795.307	18.729	<.001		
Rate(male)	-12.436	1.740	8200.946	-7.148	<.001	<.001	-0.100
Rate(male):Block	12.548	1.772	8615.182	7.080	<.001	<.001	0.100
Block	-6.032	0.872	8765.966	-6.915	<.001	<.001	0.060
Rate(Angry)	-11.730	1.733	8429.161	-6.770	<.001	<.001	-0.040
litFUS:Rate(male)	17.531	2.652	9766.579	6.611	<.001	<.001	0.220
Rate(Angry):Rate(male):Block	-23.484	3.553	8335.600	-6.610	<.001	<.001	-0.100
Rate(Angry):Rate(male)	23.010	3.494	8038.097	6.585	<.001	<.001	0.100
litFUS:Rate(male):Block	-17.276	2.693	9944.537	-6.415	<.001	<.001	-0.190
litFUS	-8.357	1.306	9595.001	-6.399	<.001	<.001	0.180
Rate(Angry):Block	11.450	1.792	8663.708	6.391	<.001	<.001	0.007
litFUS:Block	8.443	1.333	9841.110	6.334	<.001	<.001	-0.060
Rate(Angry):litFUS:Rate(male):Block	30.286	5.767	9815.728	5.251	<.001	<.001	0.130
Rate(Angry):litFUS:Block	-15.013	2.876	9729.021	-5.220	<.001	<.001	-0.020
Rate(Angry):litFUS:Rate(male)	-29.499	5.709	9719.230	-5.167	<.001	<.001	-0.120
Rate(Angry):litFUS	14.542	2.826	9581.805	5.146	<.001	<.001	0.020
litFUS:Block:Emotion	0.444	0.465	10870.160	0.955	0.340	1	0.100
Rate(Angry):litFUS:Block:Emotion	-0.687	0.999	10869.744	-0.687	0.492	1	-0.040
Block:Emotion	-0.201	0.327	10868.876	-0.614	0.539	1	-0.070
Rate(Angry):Emotion	-0.250	0.557	10870.987	-0.450	0.653	1	-0.010
Emotion	0.114	0.260	10870.395	0.437	0.662	1	-0.001
Rate(Angry):litFUS:Emotion	0.312	0.831	10873.017	0.376	0.707	1	0.020
litFUS:Emotion	-0.145	0.386	10872.477	-0.375	0.708	1	-0.001
Rate(Angry):Block:Emotion	0.248	0.701	10868.809	0.354	0.724	1	0.010

Table 24: Fixed effect estimates of model A5. Effects are presented in ascending order of their initial level of significance. A total of 10946 observations nested within 37 individuals was included in this analysis. Estimates reflect unstandardized effects, β indicates standardized effects, SE=standard error, Df(Satt)= Satterwaite degrees of freedom, p (Satt.)= Satterwaite based p statistic. *holm* = holm-adjusted p-value, *** indicates significance with p *<.001*,

focus on the depicted emotion.

In addition, litFUS produced greater differences between explicit and implicit processing of features. This effect was greater in trials targeting emotion processing. Finally, a complex four way interaction was found, indicating litFUS to alter the influence of a complex interplay of stimulus features (sex vs. emotion) for trials of explicit emotion processing. This interaction is illustrated in Figure 29.

Next, in order to clarify the role of alpha power in the processing of emotional faces, RTs were analyzed via a second set of random intercept models. The model comparison is summarized in Table 26.

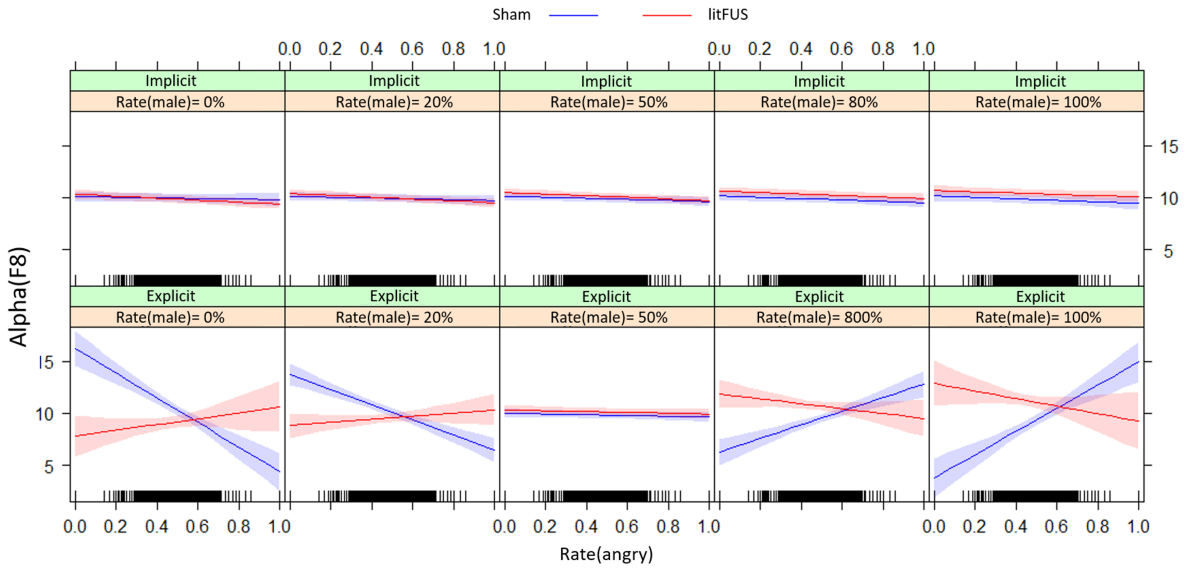

Figure 29: Estimated effects of the four-way interaction described in Table 24. In trials with focus on emotion processing (explicit), the alpha response to the stimulus in a given trial depends on the likelihood of previously presented male and angry faces while it does not in trials with a focus on sex (implicit [emotion processing]). The interaction of sex and emotion depiction rates inverses from low angry men rates to high angry men rates. This effect is upturned in litFUS compared to sham sessions.

Since the best fit was given by model B5, it was further analyzed for fixed effects. Table 26 shows a significant difference between the angry → neutral sequence in comparison to neutral→ neutral and neutral → angry. Furthermore, Alpha showed a highly significant contribution to improved performance. However, as alpha activity is negatively correlated to cortical activity, this implies inactivity of the right lPFC to decrease the reaction time, increasing processing speed.

22.4.2 Additional analyses

Since frontal alpha (FA) asymmetry measures have been shown to react to emotional stimuli, FA measures calculated from alpha at F7 and F8 electrode position were analyzed. Frontal alpha asymmetry was significantly predicted by depressivity and the individual alpha peak frequency as well as litFUS. The results of the calculation are shown in Table 27. They are illustrated in Figure 30. It shows a general increase of frontal alpha asymmetry from lower to higher IAF. Furthermore, during sham sessions, higher BDI-V measures correlate with lower frontal alpha asymmetry in those who have IAFs below 10Hz. This effect is reveresed by litFUS. Nonetheless, in individuals, who show higher IAF in lit-

	Df	AIC	BIC	χ^2	*Df* (χ^2)	*p*(χ^2)
B1	5	14454	14490			
B2	8	14272	14330	187.868	3	<.001***
B3	12	14270	14358	9.580	4	.048*
B4	20	14257	14403	29.244	8	<.001***
B5	22	14199	14360	61.685	2	<.001***

Table 25: Summary of model comparisons with reaction time as dependent variable. DF=degrees of freedom, AIC = Akaike information criterion, BIC = Bayesian information criterion. DF(χ^2)= degrees of freedom for the χ^2 test. *= (p)<.05. ** = (p)<.01. *** = *p*<.001. B1 =random intercept (for each participant) + random slope (*trial*). B2= B1+ *change of emotion from previous to current trial*). B3= B2+ Block. B4=B3 + litFUS. B5=B4 + Alpha(F8)

FUS sessions, higher BDI-V scores once again correlate to less positive FA measures even though the overall level of FA constantly rises from low to high asymmetry scores.

Furthermore, the same analysis from model A5 was performed again with theta at the F8 electrode position as dependent variable, since the time-frequency plots indicated that significant differences may also be found at these frequencies. The picture is very similar to the results in alpha. it is noticeable that the effect sizes are smaller. The effects are summarized in Table 28.

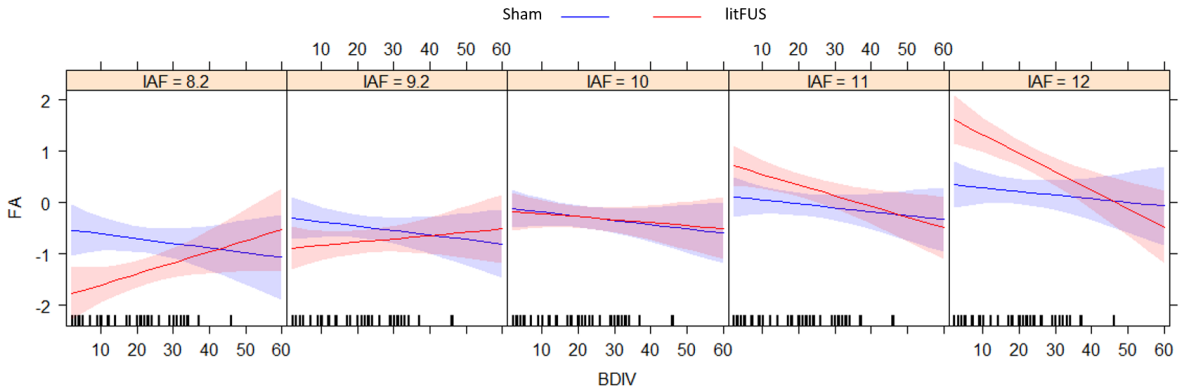

Figure 30: Frontal alpha asymmetry as predicted by litFUS, IAF and BDI-V scores. Frontal alpha asymmetry was calculated by subtracting ln(Alpha at F7) from ln(Alpha at F8). In sham sessions, higher depression scores were associated with less positive frontal asymmetry measures. In addition, higher individual alpha peak frequencies (IAF) predicted this effect to be diminished. litFUS reverses the connection between BDI-V and frontal asymmetry while increasing the estimated lower bound of effect lineally with the IAF.

	Estimate	SE	df(Satt.)	t	*p*	*holm*	*β*
(Intercept)	-0.023465	0.040596	39.142991	-0.578	0.56656		
Alpha(F8)	-0.043	0.006	10709.550	-7.294	<.001	<.001	-0.110
N→N A→N	-0.113	0.024	10860.136	-4.685	<.001	<.001	-0.210
N→A A→N	-0.105	0.027	10860.006	-3.896	<.001	.001	-0.200
litFUS	0.036	0.013	10897.968	2.854	.004	.060	0.070
Block	-0.037	0.013	10876.731	-2.757	.006	.076	-0.070
Block:litFUS	0.033	0.018	10882.173	1.835	.067	.799	0.060
N→A A→N :Block:litFUS	-0.078	0.052	10860.404	-1.493	.136	1	-0.150
litFUS:Alpha(F8)	0.011	0.007	10895.188	1.419	.156	1	0.030
A→A A→N :Block	-0.041	0.036	10855.413	-1.125	.260	1	-0.080
N→A A→N :litFUS	0.033	0.036	10860.077	0.911	.362	1	0.060
A→A A→N	0.021	0.025	10855.408	0.838	.402	1	0.040
N→N A→N:Block	-0.028	0.036	10859.545	-0.800	.424	1	-0.050
N→N A→N:Block1:litFUS	-0.023	0.048	10860.272	-0.466	.641	1	-0.040
A→A A→N :Block:litFUS	-0.021	0.049	10855.492	-0.427	.669	1	-0.040
N→A A→N :Block	0.010	0.039	10859.084	0.257	.797	1	0.020
→N A→N:litFUS	-0.005	0.033	10858.838	-0.157	.875	1	-0.010
A→A A→N :litFUS	-0.004	0.034	10855.628	-0.113	.910	1	-0.007

Table 26: Fixed effect estimates of B5 with RT as dependent variable. Effects are presented in ascending order of their initial level of significance. A total of 10946 trials nested within 37 test persons was used for this analysis. Estimates reflect unstandardized effects, β indicates standardized effects, SE=standard error, Df (Satt)= Satterwaite degrees of freedom, p (Satt.)= Satterwaite based p statistic. ** indicates significance with p <.01, *** with p <.001

22.5 Discussion

The results depicted in section 3.1 show that the alpha response at F8 electrode position (indicating cortical inhibition of the riFG) is significantly modulated by the recent history of feature occurrence, regardless of it being a direct emotional stimulus or not (rate of angry faces vs. rate of depicted men). Nonetheless, the direction of this effect seems to depend on several parameters including overall susceptibility of a neural response (manipulated by litFUS), an interaction of extracted features (task-relevant or irrelevant; sex vs. emotion) and focus of attention (manipulated by implicit vs. explicit processing blocks of trials for a given feature).

Accordingly, a predicted four-way interaction was found. Here not only the four-way but also all lower order interactions proved significant. On the other hand, no

	Estimate	SE	Df	t	p
(Intercept)	-2.410	0.919	1742.107	-2.622	0.009
litFUS	-6.963	0.505	10936.457	-13.792	<.001
IAF:litFUS	0.691	0.049	10936.169	14.136	<.001
BDIV:IAF:litFUS	-0.016	0.002	10923.581	-7.204	<.001
BDIV:litFUS	0.159	0.023	10923.218	7.058	<.001
IAF	0.231	0.087	3355.062	2.664	0.008
BDIV	-0.014	0.039	2342.107	-0.351	0.726
BDIV:IAF	0.001	0.004	4206.840	0.149	0.882

Table 27: Fixed effects estimates with frontal alpha asymmetry as dependent variable. Effects are presented in ascending order of their level of significance. Estimates reflect unstandardized effects, SE=standard error, Df (Satt)= Satterwaite degrees of freedom, p (Satt.)= Satterwaite based p statistic. ** indicates significance with p <.01, *** with p <.001

significant interaction was found for the set of interaction terms that included the currently depicted emotion. In addition all main effects with the exception of the currently depicted emotion also showed a highly significant influence. We therefore conclude that especially stochastic feature processing may take place in or be modulated by riFG neuronal ensembles, while processing of the currently depicted emotional value of a stimulus by itself has no impact on its EEG alpha response. Thus, the riFG may contribute to emotion processing in the way that it provides an estimate of the recent history of relevant and irrelevant information, thereby introducing a proper model of the "world" for further evaluation of situations. This notion is suggested by the strict division of effects containing the current emotion and those that don't in terms of significance in Table 26. As this also includes litFUS related effects, this data provides strong evidence that a manipulation of the riFG does not interact with this variable. Conversely, litFUS exhibited significant interactions with all other parameters, indicating their effect to depend on the neural context, that is excitability. Thus, modulation of the riFG addressability by other neural structures or networks that lead to either excitation or inhibition of the riFG may regulate the learning ability of this area.

Furthermore, given that the neuromodulation from litFUS in this study was hypothesized to decrease the general excitability of the neural tissue underlying F8 electrode position, the main effect showing greater alpha responses in sham compared to litFUS

	Estimate	SE	Df(Satt.)	*t*(Satt.)	*p*(Satt.)	*holm*	*β*
(Intercept)	15.975	0.942	5959.535	16.962	<.001		
Rate(male):Block	11.882	1.940	8152.066	6.124	<.001	<.001	0.090
Rate(male)	-11.631	1.904	7687.199	-6.109	<.001	<.001	-0.100
Block	-5.686	0.955	8319.962	-5.955	<.001	<.001	0.050
Rate(Angry)	-10.809	1.896	7937.959	-5.700	<.001	<.001	-0.030
Rate(Angry):Rate(male):Block	-21.983	3.888	7840.178	-5.653	<.001	<.001	-0.090
Rate(Angry):Rate(male)	21.289	3.824	7509.047	5.568	<.001	<.001	0.080
litFUS	-7.872	1.430	9286.778	-5.504	<.001	<.001	0.180
litFUS:Block	8.009	1.460	9580.280	5.486	<.001	<.001	-0.060
litFUS:Rate(male)	15.887	2.904	9489.703	5.470	<.001	<.001	0.200
Rate(Angry):Block	10.669	1.961	8205.003	5.440	<.001	<.001	0.004
litFUS:Rate(male):Block	-15.668	2.950	9702.318	-5.312	<.001	<.001	-0.170
Rate(Angry):litFUS:Block	-14.308	3.150	9451.373	-4.542	<.001	<.001	-0.060
Rate(Angry):litFUS	13.627	3.094	9272.175	4.404	<.001	<.001	0.050
Rate(Angry):litFUS:Rate(male):Block	27.254	6.317	9552.578	4.315	<.001	<.001	0.110
Rate(Angry):litFUS:Rate(male)	-26.197	6.253	9435.563	-4.190	<.001	<.001	-0.100
litFUS:Block:Emotion	0.200	0.510	10871.984	0.393	.695	1	0.090
Block:Emotion	-0.130	0.359	10870.811	-0.362	.717	1	-0.060
Rate(Angry):litFUS:Emotion	-0.278	0.911	10875.202	-0.306	.760	1	-0.010
litFUS:Emotion	0.125	0.423	10874.633	0.295	.768	1	-0.003
Rate(Angry):litFUS:Block:Emotion	-0.176	1.096	10871.559	-0.160	.873	1	-0.009
Rate(Angry):Block:Emotion	0.085	0.769	10870.758	0.111	.912	1	0.004
Emotion	-0.008	0.285	10872.487	-0.028	.978	1	-0.004
Rate(Angry):Emotion	0.006	0.610	10873.120	0.010	.992	1	0.000

Table 28: Fixed effect estimates following model A5 with Theta at F8 as dependent variable. Effects are presented in ascending order of their initial level of significance. A total of 11164 trials nested within 37 individuals was included in this analysis. Estimates reflect unstandardized effects, *β* indicates standardized effects, SE=standard error, Df(Satt)= Satterwaite degrees of freedom, p (Satt.)= Satterwaite based p statistic. *(*holm) = holm-adjusted *(*p)-value, *** indicates significance with *(*p) <.001

trials is somewhat surprising. However, consulting the estimates of Table 26 reveals a number of interaction terms, showing opposite directions. This indicates that the effect of neural activity suppression leading to an conversely directed main effect may mostly rely on opposed neuronal recruitment between conditions that adds up to a residual (main) net excitation effect (also see Figure 26).Furthermore, as stated above, main effects are estimated before the context of explicit emotion-focus and average feature rates. Hence, this effect may be interpreted more like a simple effect. As a result, a random intercept model including only litFUS as a fixed factor and trial as random slope, thus estimating the effect regardless of all other predictor values, reveals a hypothesis congruent effect

that points in the opposite direction as it does in Table 26 (Estimate (SE): 0.221(0.018), $t(10912.95839)=12.53$, $p<.001^{***}$). In brief, litFUS was thus found to increase the alpha response generally. Nonetheless, process specific alterations of this effect may also emerge.

Moreover, Figure 27 further shows this effect of overall excitability (the litFUS effect) to also affect the processing of non-emotional features in a condition that demanded participants to focus on emotion, while no such effect is seen in trials that govern attention focus to sex (illustrated by the changes in sham slopes across the top row of graphs). Thus, in summary, both features (sex and emotion) seem to interact with each other and with litFUS mostly in situations that include a subject's attention to emotional features. This finding is well in line with above mentioned theories on the specialized role of the right lPFC in emotion processing. However, taken together with the reported null-finding regarding effects that comprise the currently depicted emotion, this result leads to the conclusion that the riFG has a specialized role in providing contextual information for other processes of emotion processing, which may take place in other subdivisions of the (right) lPFC. In other words, the riFG seems to provide a stochastic model of task- or goal-relevant and irrelevant features specifically if an emotional cue is in focus of attention but leaves the processing of said cue to other areas and networks. As a result, the lPFC as a whole may be especially suited to integrate current experiences with those of the recent history. However, whether this integration also takes place in the right hemisphere or how this function is exactly operationalized is beyond the scope of the current analyses and needs further investigation.

Furthermore, litFUS transmitted inhibition resulted in inverted directions of the sex-emotion interaction effect during explicit emotion processing trials. Such interaction effects may stem from sex-specific interactions that may have occurred on a number of levels: First Adams Jr et al., 2012 report female faces showing no affection to be perceived somewhat less negative (e.g., more cooperative and honest, less angry) than men, making the same expression. Second, an interaction of the gender of participants and sex of the depicted social cues may be present in so far as that either the opposite or same gender/sex might introduce significant emotions in participants. A few studies reported female participants to be generally more sensitive to male emotional expressions

as compared to females' (Erwin et al., 1992; Wingenbach et al., 2018). Furthermore, others reported a general advantage of women compared to men in facial emotion recognition (Thayer and Johnsen, 2000, Montagne et al., 2005). In addition, an increased autonomous response was found in men reacting to angry male faces as compared to women, reacting to the same stimuli (Mazurski et al., 1996), which may be part a greater defensive response in men to male threatening stimuli (Kret and de Gelder, 2012).As a result, the non-emotional feature *sex* may vary in its effect depending on the sample composition. However, as the inversion of effects by litFUS is a within-subject effect, even though the participant's gender may contribute to sham-related effects significantly, the litFUS induced alteration would still reflect a general process of neural excitement/inhibition rather than a sub-population based artifact. Nonetheless, the direction of effects and the related litFUS-induced digression from these may thus change in other samples. Since only a few male subjects took part in this study, no analysis concerning interactions of the volunteers gender and the task was conducted as results would be insufficiently powered. Becker et al. (D. V. Becker et al., 2007) further state a general difference in the perception of angry male vs. angry female faces. Thus, from this point of view, intra-session reversing of effects (changes in intercept and slope of the sham/litFUS regression from left to right in Figure 27) may be interpreted in the way that angry men in general elicit other responses as do angry women, resulting in opposed effects for trials that follow lessno angry men and those that follow many/just angry men. Hence, taking these studies into account, it is unknown whether (in this task) sex is an unemotional feature. However, as mentioned before, litFUS interestingly reverses this possibly confounded effect.

Following this, to make concluding remarks regarding this and other effects it may also be beneficial to give an impression of what increases or decreases in alpha activity actually reflect within the given task. Thus, its connection to RT was calculated. On that note, the underlying presumption for all further interpretations is that a decrease in RT (increase in speed) reflects advantages in processing capabilities:

In this set of data, increases in alpha at F8 contributed to decreases in RT. Furthermore, in comparison to the shift from angry to neutral faces a general increase of RT was present for all combinations of sequences other than angry $\rightarrow$ angry. Thus, even

though the sequence neutral → angry also contains a shift between depicted emotions, detaching from the angry face still took significantly longer independently from implicit vs. explicit processing or litFUS. Moreover, even though in a currently given trial the sequence neutral → neutral comprises the same depicted emotion as does angry → neutral, participants still reacted slower. Hence, the slowing process did not result from differences in reaction to the currently shown valence. However, as no significant difference was present to angry → angry, these data indicate an overall decrease in reaction speed following trials including angry faces. This effect was not interacting with litFUS or focus of attention. Thus, we conclude this effect not to result from litFUS induced changes in attention but from processes that are not measured directly, such as processing depth.

Further evidence from additional analyses finally show similar results for theta activity as compared to above mentioned alpha activity. In general, theta related findings are pointing into the same direction as did alpha-focused results. However, effect sizes were greater for effects in alpha response.

Lastly, frontal alpha asymmetry, an indicator of affect and motivational tendencies was analyzed as an inhibitory neuromodulation at F8 electrode position should impact the relative activity of right compared to left hemispheric activity. The subsequent analysis showed a strong interaction between depression scores, IAF and litFUS. While frontal asymmetry seems to decrease with increasing depression averaged over all trials, litFUS can reverse this effect. The "normal" direction of this effect (in sham sessions) is consistent with the existing literature (e.g., Reznik and Allen, 2018). Also, the left-to-right increase in frontal asymmetry with increased IAF seems consistent with current theories on the correlation of IAF with cognitive resources and thus possibly resilience (e.g., Klimesch, 1997; C. R. Clark et al., 2004; Angelakis et al., 2007; Grandy et al., 2013; Ramsay et al., 2021. these results suggest that the effects of litfus may produce different effects depending on depressivity and IAF. It should be emphasized that litfus may have negative effects on frontal asymmetry, especially for individuals with particularly low IAF who are not showing sings of depression. On the other hand, these findings also show that in the current (healthy sample) relatively more depressed individuals may also benefit particularly strongly from neuromodulation, depending on their IAF.

However, by integrating this finding into aforementioned results, the role of inactivity of the riFG for reaction speed should be reconsidered. In fact, this exploratory finding may help interpreting contradicting results concerning the role of the right lPFC in RT based experiments like the go/no-go task.

22.5.1 Summary

The experimental neuromodulation of the riFG was carried out via litFUS. It produced an overall decrease in alpha power within the task and further revealed a complex pattern of covariates to interact with its effect. For instance, litFUS effects were substantially altered by estimated likelihoods of feature emergence (emotional and non-emotional). In general, analyses of these interactions strongly suggest that the riFG of the right lPFC shows a special sensitivity to stochastic learning, that is a representation of the estimated likelihood of certain features of stimuli throughout the task. However, the impact of this probabilistic learning was most prominent in trials that demanded participants to focus on emotional cues. Interestingly, the alpha response of the riFG did not rely on the currently presented stimulus , nor did it rely on its interaction with stochastic estimations, indicating the integration of present stimulus features into the recent history of experiences to take place somewhere else.

Furthermore, even though, in this study, neuromodulation was carried out via litFUS, we do emphasize the idea that similar conditions may be subject to the interference of other neural networks signaling contextual factors such as mood-effects. Thus, congruence effects of mood and learning or attention may either partly rely on the subsequent alteration in stochastic learning capabilities of the right lPFC or this capability is by itself a result of these congruence effects. Nonetheless, this study provided evidence for the role of the right lPFC in the correlated processing of the recent history of stimulus presentation. In addition, other features, which are not part of the current focus of attention were found to significantly interact with probabilistic representations of emotional faces. Also, this effect was almost completely reversed depending on the excitability of neuronal tissue, which was minpulated via litFUS.

In addition, this data set provides evidence for differential slowing of RTs fol-

lowing aversive/threatening stimuli.

22.5.2 Limitations

This study used emotional faces as stimulus material. As the reported interactions indicate, this study was possibly unable to test the differential sensitivity of the right lPFC for emotional as compared to unemotional features, since these may be confounded. Furthermore, even though on a single trial level more than 10,000 data points were used for calculations including only within-subjects effects (with the exception of the random intercept), larger studies replicating the effects with more (diverse) participants are needed.

22.6 Conclusions

This study provides evidence for a specialized role of the riFG in stochastic learning and the representation of recent experiences. Furthermore, the present data indicate this property is expressed depending on the neural excitability that was successfully altered via litFUS neuromodulation. Finally, these effects had stronger implications ind situations with an explicit focus on emotional features. In brief, the riFG may contribute to a emotional processing by providing probabilistic information for further processing of emotional stimuli in nearby compartments of the right DLFPC or other networks.

22.6.1 Acknowledgements

We thank Myriam Metzulat and Adrian Dernbach for the conscientious and reliable data acquisition.

23 Embedding in the Thesis Framework (Paper V)

In addition to influencing the emergence of learned helplessness as a unifying mechanism for the intraindividual development of depression, in this manuscript an aspect that is not normally reflected in learned helplessness paradigms was addressed: The processing of social stimuli. While learned helplessness research mainly investigates data in the context of (insufficient) performance in intellectual tasks, it seems plausible that apart

from cognitive insufficiency especially in highly recurrent depressive disorders there might be an additional, specific vulnerability to social interaction patterns, as this domain has constant relevance for people regardless of most contextual factors. Social interactions are therefore well suited to provide a background for the emergence of helplessness, although psychological experiments on the topic are usually not able to map this area methodically. For this reason, and against the background of the findings reported in Paper I, this study focused on the processing of emotional expressions, which may pose the foundation of complex social interactive patterns.

The results show that at the F8 electrode position in the analyzed frequency bands no direct processing of the emotion shown takes place. instead, the riFG seems to be particularly sensitive to the probability distribution of these emotional expressions occurring over the entire experiment. At this position, in particular, contextual information seems to be processed in terms of probability of occurrence (possibly expectation of occurrence), which in turn could influence the processing in the current event.

This is particularly interesting in light of Paper III, which found a similar effect. Overall, this result thus replicates the finding that the riFG may contribute to general stimulus and cognition processing mainly by coding stochastic information. This is also interesting from the point of view of reconsolidation research and is consistent with the aforementioned studies, which attribute a special role to the riFG in updating schemata and cognitive models.

Assuming that reconsolidation can only take place after sufficient labilization, which in turn is based on a prediction error, influencing the riFG seems to be a good way to influence this error. This idea is based on the fact that the prediction error should come about with the help of the stochastic information just described. Well in line with this, the studies described in Section 10.3 already showed a riFG effect during the reconsolidation process.

Taken together, the results of this study thus suggest that litFUS neuromodulation of the right lPFC could result in altered processing of social-emotional stimuli, that the riFG provides a special role in the provision of stochastic contextual information, and lastly, in its additional analyses, that the effect of the modulation may vary depending on

depressive symptoms and IAF, but in sum may be positive. This effect was also described in the additional analyses of the previous studies.

Part III - Manuscripts and Additional Analyses - Reconsolidation Interference in Depression

24 Reconsolidation Interference in Learned Helplessness

Post and Kegan state in their review 'Prevention of recurrent affective episodes using extinction training in the reconsolidation window: A testable psychotherapeutic strategy' (R. M. Post and Kegan, 2017, p. 327):

'Extinction training in the reconsolidation window (which opens about 5 min to 1 h after active memory recall) can revise, reverse, or eliminate the long-term memories associated with PTSD and other anxiety disorders and with drug abuse craving. We hypothesize that similar cognitive-behavioral work in the reconsolidation window could inhibit stress-induced and spontaneous affective episodes'

To be able to test this claim, a paradigm that would allow close proximity to existing methods in the field of fear and anxiety research would be the most promising. Fear research may be particularly suitable for research in this area since it has shown positive results in analyses capitalizing on trial- by- trial measurement and tracking of conditioning and subsequent responses: In a classical conditioning paradigm, repeated pairing of the CS with a UCS could establish an associative memory trace in subjects that are reinforced with each subsequent pairing of the two stimuli, so that behavioral but also physiological responses to the CS can gradually increase. This could show a progression on an individual-trial level, which can be interpreted similarly to the first

studies on rodents.

The advantage of this trial-based observation is that the intercept, the initial response at the first coupling, as well as the slope of learning can be measured and modeled easily. Both should be things that can provide indications of reconsolidation vs. extinction: Whereas after extinction a very high level of response would be expected after a single recoupling of UCS and CS (reinstatement, measured by intercept differences), a steeper slope should indicate accelerated re-learning, with both phenomena indicating extinction rather than reconsolidation-interference.

Correspondingly, for the study of reconsolidation interference in depressive disorders, it is necessary to find a paradigm that allows a similar description of the course of the disease/response. Here, the paradigm of learned helplessness described above may be promising. Indeed, this paradigm is suitable in that it operationalizes depression equivalently to anxiety and fear disorders through a sequence of conditioning processes. As already described in section 3.1, in the context of helplessness, the repeated perception of expectancy-outcome incongruence leads to the establishment of certain cognition (internal, global, and stable attribution of this incongruence), which in turn induces a reduction of effort that may ultimately generalize transsituationally and lead to depressive symptoms.

A paradigm that is already used to induce learned helplessness and is also suitable for single-trial analyses is the unsolvable anagram task. Here, unsolvable anagrams, which are falsely declared to be solvable for the test subjects are presented. As a result, through continuous failure, helplessness/hopelessness should eventually set in. Today, such unsolvable tasks are mostly used for stress induction but are also discussed in the literature on learned helplessness (e.g., Frankel and Snyder, 1978; Snyder et al., 1981). In sum, it may lead to the experience of stress, that may be *associated* with helplessness but may not take on its full dimensions: According to the definition by Abramson et al. (1978), learned helplessness is characterized by the internal, global attribution of the cause of uncontrollability. This ends in passive endurance of the averse situation. Accordingly, at a certain point, subjects would begin to accept this circumstance of uncontrollable failure and would make no further attempts to change it. A prediction that may well be confirmed in performance decrements (presumably caused by subjects' reduced com-

mitment) after exposure to unsolvable tasks (Snyder et al., 1981). Previous findings on unsolvable anagram tasks, however, also show the rise of anger, an emotion with a motivational approach component (Harmon-Jones and Allen, 1998; Lench and Levine, 2008), which is contrary to what has just been said (Habel et al., 2001).

Despite this limitation, it can be assumed that unsolvable anagrams in principle lead to a helplessness-like state. However, to be able to test whether this is a maladaptive state or an adaptive one (in the case of unsolvability, it could be argued that passive endurance is a useful coping strategy), solvable tasks should also be integrated into the paradigm, in which premature effortlessness becomes apparent. Accordingly, the paradigm should not contain unsolvable tasks *per se* but may profit from solvable anagrams that are presented so briefly that a correct solution is very unlikely but not impossible. This method also has the advantage that subjects can subsequently be presented with the solutions to the anagrams, which could increase internal attribution of failure, as it becomes clear that performance within the task is not due to its general unsolvability. In addition, this setup could be extended by sometimes presenting anagrams, which can be worked on without a time limit. If the participant is already hopeless here, they will either need considerably longer to work on them, since they will not make any considerable effort at first, but wait passively for the trial to end, or they should simply give up (if made possible by the task) and end the trial actively (without a solution). By doing so, a similar progression could be measured as in fear conditioning, with a clear conceptual difference to conditioning in the context of anxiety and fear disorders. Figure 31 illustrates the courses based on hypothetical data and illustrates which courses in a three-day design would indicate which type of effect.

Furthermore, the paradigm presented here needs to be extended to include psychophysiological measurements on days one and three, as previous research indicates that semantic memory about the associative link between UCS and CS is not directly erased. Along this line, Soeter and Kindt (2015) report that spider phobics state after successful reconsolidation that they were still afraid/fearful of spiders, but failed to show a corresponding physiological response. The knowledge about one's fear was therefore not changed. This semantic, still intact knowledge only adapted to the now changed reaction

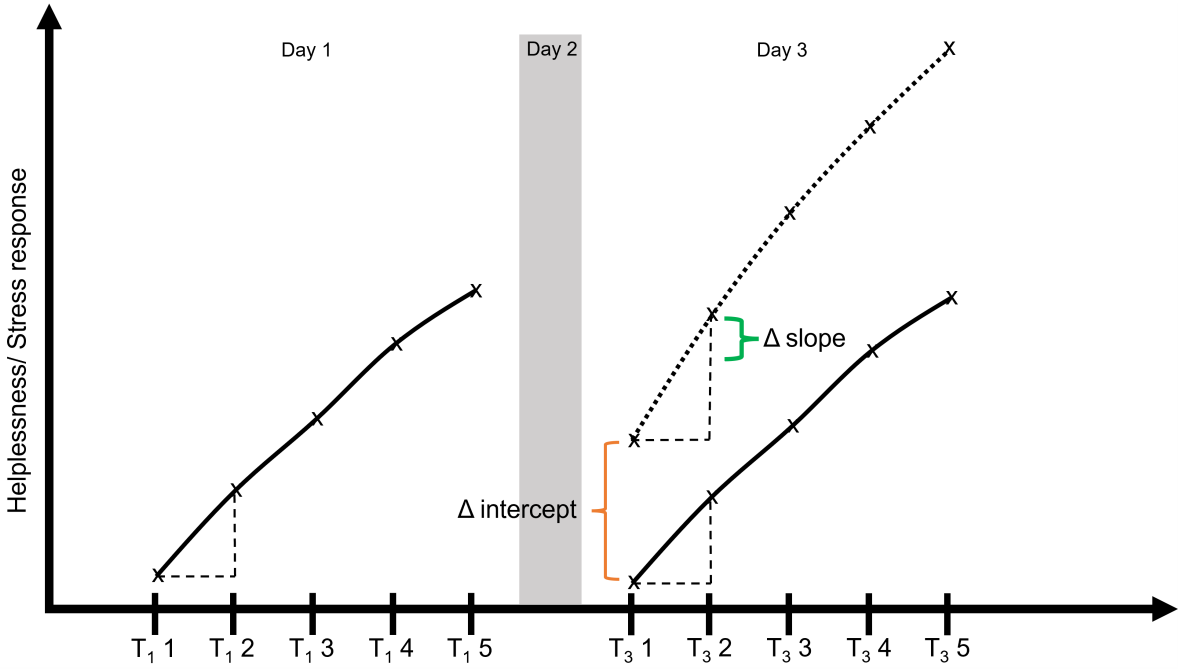

Figure 31: Conceptual Illustration of Reconsolidation Effects. On day one, all participants should express an increase in hopelessness/stress responses. On day two, experimental and control groups are formed by applying either extinction, reconsolidation, or control protocols. On day three, the solid line indicates the same course of effect as participants experienced on day one, indicating erasure of the memory trace formed before as participants react to the task similarly as they had the first time. Thus, a successful reconsolidation interruption should have taken place. The dotted line indicates a reaction that corresponds to extinction learning on day two, as participants start with an average response that is significantly higher at the first measurement (indicated by $\delta intercept$) and show accelerated new learning (indicated by increased slope steepness as compared to day one; $\delta slope$).

to spiders and cues associated with them over a longer period. This suggests that the reconsolidation-interference effect on day three should probably not be detectable by self-ratings but by behavioral and especially psychophysiological measures.

Classical stress-associated values such as heart rate, heart rate variability, skin conductance level (SCL; a measure of effort, e.g., I. B. Goldstein and Shapiro, 1988; Moya–Albiol et al., 2001) or EEG responses in the area of the right lPFC (see section 5.2) or midline (see Section midlinetheta) are suitable measures. Additionally, especially the EEG-based measures in the lPFC seem to be an indicator for successful reconsolidation-interference, especially on day two, while motivational measures such as midline theta (which has already been shown to be an indicator for learned helplessness; Reznik, Nusslock, et al., 2017) or frontal asymmetry could be promising measures for stress and effort.

Although, especially FA as an indicator for helplessness could not be empirically shown in Reznik's study so far (2017).

24.1 Methodological Considerations

Based on these preliminary considerations, several prerequisites that need to be considered and reconciled to directly demonstrate the potential of reconsolidation interference for depressive disorders in the laboratory for the first time should be considered:

- A three-day design is needed to allow for overnight consolidation of memory traces
- The classical reconsolidation study design calls for at least three groups: a reconsolidation group (including a reminder + extinction protocol), an extinction group (including only the extinction protocol), and a control group (including only the reminder)
- The *triadic design* of learned helplessness research calls for three groups either: a helplessness group that experiences an unsolvable issue, a control group that experiences an equal, but a solvable issue, and a control group that does not experience the issue at all before all three groups are given a solvable task.
- Psychophysiological data is needed to monitor the progression of helplessness

Since the *triadic design* aims for the investigation of the overall potency of a task to induce helplessness and since unsolvable anagrams have repeatedly been shown to be able to do so, the final task described here, may not need both control groups formulated by this approach.

The three groups defined by the reconsolidation approach, however, should be addressed in the experimental design. Also, as the experimental task of (un)solvable anagrams are completed while sitting still, psychophysiological measures can easily be applied. Further, behavioral measures may also be assessed in accordance with the ideas discussed above.

Hence, a three-day, three-group design emerges, that still lacks an operationalization of day two (formation of the groups). Concerning this, the first question is, whether

the procedure should take place in a different environment than the helplessness induction did. Two main lines of arguments may be applicable here: First, memory reactivation may be context-dependent if the context itself acts as a cue for the UCS (helplessness in this case; e.g., Besnard et al., 2012; Vaverková et al., 2020). However, a core idea of helplessness/hopelessness is that the attributional style, triggered by the helplessness task leads to transsituationality. Thus it should not matter, in which environment the reconsolidation procedure is applied. Furthermore, it should not even matter, if the reconsolidation procedure used the same task to apply an extinction protocol (e.g., presenting anagrams that are presented for so long that they become solvable). The linking factor between different contexts, environments, and tasks as described by learned helplessness is the person itself, that acts as a constant in different situations: Conversely to fear and anxiety conditioning, it is not an environmental cue that is stress-eliciting but an internal one (the feeling of insufficiency). Thus, by applying this kind of task, reconsolidation should also be probable, if a setting-change was made with regard to day one.

Second, if this was not the case, translation of this and other protocols to a clinical setting may not be feasible as it is most likely not possible to recreate the original helplessness-eliciting conditioning experience within the therapy session and even less possible (nor desirable) to do so in the original conditioning setting. As a result, from a theoretical perspective, a setting-change in between test days may be feasible, while from a translational perspective, it may be necessary.

Consequentially, day two may take place in a different laboratory than day one. However, other degrees of freedom on this experimental day may still need further discussion. In general, following previous remarks, on day two, three modules need to be taken care of:

- The reminder (reinstate the helplessness experienced on day one)
- The interfering extinction protocol (a task that gives participants back their confidence/sense of power/hope to be able to cope with demanding tasks)
- The expectation error that drives the labilization of the reinstated memory trace

The reminder in the context of learned helplessness may in itself be the presentation of a demanding task, including tasks that may just *seem* demanding. Here, thus two groups emerge One that will fail to handle a demanding task once again and one that will just *think* that they will fail once again but never experience it. In the latter, an expectation error is already taken care of, while in the former, participants would need to experience a change in their performance while completing the task. In both groups, then an extinction-based protocol (being able to complete the demanding task successfully) would be administered.

Unfortunately, this leads to the problem of designing a control group, that will not accidentally also undergo reconsolidation just because they expect whatever task comes up, to be overwhelmingly hard, which would then lead to an expectation error as they undergo the extinction protocol. One way to address this would lie in an experimenter on day two explicitly stating that the previous task usually does not predict the performance in the current one. However, this may lead to a variety of effects, influencing the outcome that may not be specifiable explicitly at this stage.

On another note, it may also be feasible to ignore this issue in the sense that, if indeed every positive experience would trigger reconsolidation of helplessness-based vulnerability, clinical depression would not be as prone to recur as it does. Thus, it may be reasonable to assume, that a certain, more direct form of reactivation needs to be undertaken. This would also be in line with early findings by Grawe (1998), who stated that *reactualisation* within therapy is one of the main drivers of positive therapy outcomes, thus indicating a direct recall of stress-inducing memories to increase the effectiveness of interventions. Therefore, on average, applying an extinction protocol without preceding explicit reinstatement trials, may still hold up as a control group. Still, differences in participants may emerge, as some may already react to the announcement of an experimental task by reinstating their previous experience on day one without further reinstating cues. To address this issue, a task was chosen, that may, in the case of Null-findings based on group-average-measures provide for an additional way to analyze the data:

On day two participants ought to solve simple arithmetic equations, such as $2 + 3/3$. This task is not directly connected to the verbal-skill-based task of the previous

day but is linked to it nonetheless, as again, participants have a limited amount of time to solve these equations. As a result, one may argue that the extinction-control group may experience their success in this task as not directly connected to their failure on the previous day, as participants may undergo discrimination learning by experiencing high mathematical abilities in one task and low verbal abilities in the other, instead of thinking of the previous failure in regard of a global disability (which would reflect the classical helplessness attribution style). Thus, this group may experience extinction but not reconsolidation as this represents new learning rather than interference with the memory trace formed on day one.

Nonetheless, in the reconsolidation group that at first, experiences (again) to be unable to solve the equations in time, a clear connection to the previous day should be perceived as both tasks highlight their insufficient processing speed. Later on, when the task becomes easier (unnoticeably to the participants), this group should then experience an expectation error before the extinction protocol takes effect.

To manage these subtle changes and provide comparability across groups while also being able to operationalize the reinstatement of day one in a metric rather than nominal (group-based) fashion, the task was programmed to include three modules. First, a training block, showing nine equations is presented. In this block, in the background, the program calculates the average time needed to solve the equation. In the next block, then, depending on the group, either 10% of this average are subtracted or added to form the time limit that each participant has to solve the following equations, individually. Thus, in the reconsolidation group, participants will on average experience slightly too narrow time windows to be able to solve the task, while the extinction group experiences a *I made it just in time*-effect. Further, in the reconsolidation group, in the next block of trials, the maximum time limit shifts towards the same protocol that is programmed in the task for the extinction group. As a result, subtle but significant changes in the rate of positive experience can be made, while also providing the experience of the task being highly demanding.

Following this, it also becomes apparent, that not all participants within their groups will be able to solve the same amount of equations. This circumstance, however,

may provide a metric measure to assess the individual helplessness present at the beginning of the task (e.g., the first block), which should be linked to the reinstatement of the memory trace of the previous day. Thus, if a participant of the extinction group was unable to solve 4 out of 7 equations in the first block, while the average of this group solves 6 out of 7, the number of successful responses may directly indicate effortlessness relative to others, as each participant deals with individually calculated time limits.

Following this, on day three, the same procedure that was followed on day one should be applied once more, leading to the effects shown in Figure 31

Finally, it may be worth addressing possible confounding by experimenter-related effects. To minimize these, the three-day structure of this experiment can be exploited in that way that each day is handled by different experimenters, so that apart from the investigators who randomize participants into the three groups, applying the corresponding intervention, neither experimenters on day one nor on day three know, of the participants group-membership. Thus, a double-blind study design emerges, minimizing the risk of confounding.

24.2 Final Experimental Procedure

The procedure at T1 and T3 is identical with the exception that on day one, participants practice for the upcoming anagram tasks by three (solvable) test items. Following this, five blocks of ten anagram trails each are presented. While all anagrams are *per se* solvable, most of them are not presented long enough before the trial ends for the participants to solve them. Each trial starts with a fixation cross, after which the anagram appears. Then, after the time is up or the participant ends the trial actively, the program asks for the solution to the preceding anagram. Here, no time limit is given. After confirming the entered solution, participants receive verbal feedback with the words "Correct" or "Incorrect" (see Figure 32).

In total 50 anagrams are presented each day. 40 of these are presented in a randomized fashion with a jittered time limit between three and seven seconds. Ten anagrams were presented without time constraints, assessing the effort participants are still showing throughout the task as this makes it possible to measure how long the

subjects want to deal with the cognitive problem. Additionally, this also served to control for the mind wandering of subjects, which may set in as a coping mechanism. Between anagram blocks, screening questions can be collected (e.g., targeting self-ratings on stress or effort). Finally, to show subjects that all anagrams were solvable, thereby preventing external attribution, the solutions of the anagrams are presented at the end of each block. Throughout this procedure, participants are recorded via EEG, ECG, and electrodermal activity measures.

On day two, subjects are presented with simple math problems that include two arithmetic operations per trial. Again, a time limit was set. However, this time the limit is calculated dynamically by the program as stated above. This approach was adapted and reprogrammed after the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005). After entering the solution, subjects again receive feedback with the words "correct" or 'incorrect'. Furthermore, In parallel, they receive graphical performance feedback as a bar at the bottom of the screen indicates the current performance (see Figure 32). By introducing this, slightly better-than-performance feedback can be given in the extinction phase to facilitate positive experiences with the task, even though, failure may sometimes occur. The subjects are presented with nine tasks each with 54 trails nested within six blocks.

Part IV - Discussion of Findings, Conclusions and Outlook

Summary and Discussion of Findings

24.3 Prediction of Clinical Courses of and by Depression Scores

Based on the data presented above, depressive symptoms seem to become increasingly difficult to predict by previous depression scores in the long-term (see Figure 13). This finding is well in line with the idea of issues predicting the long-term clinical course of depression by current symptoms that were hypothesized to ground on the volatile

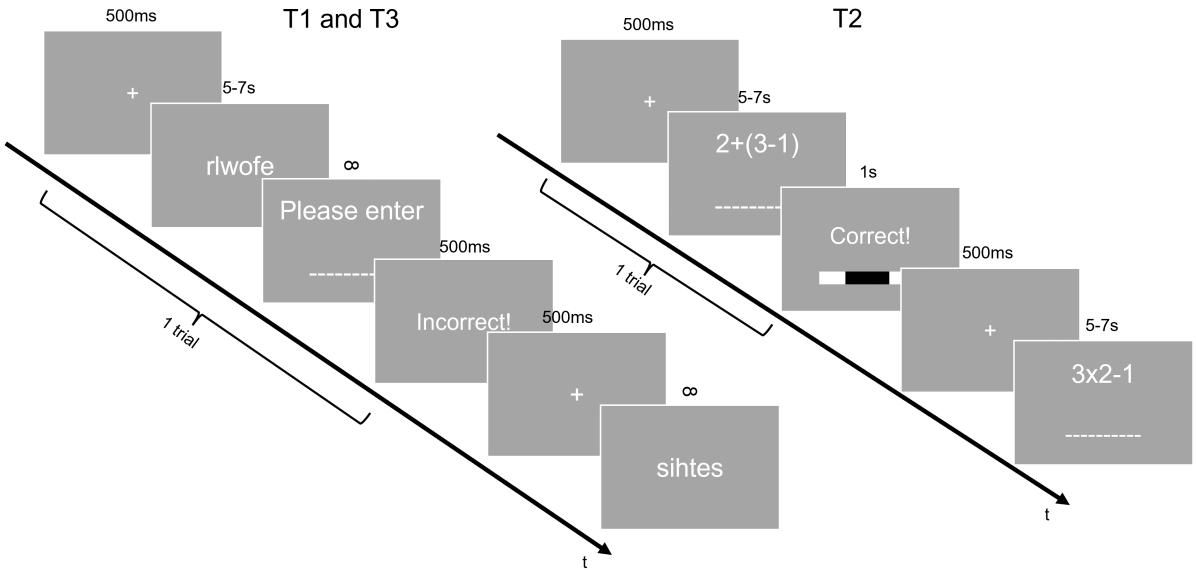

Figure 32: Schematic illustration of the study procedure. This figure illustrates the procedure on two exemplary trials within each measurement occasion. After 10 trials, participants are presented with the solutions to preceding anagrams. They may further take a break after answering screening questions, that are not discussed in detail within the current manuscript. On day two, a graphical illustration of the current performance is provided: The black band becomes wider or more narrow depending on the overall ratio of correct vs. incorrect trials.

nature of depressive episodes. In contrast, CF sample-based analyses also highlight that vulnerability factors for depression show predictive value (relatively) irrespective of the time passed. Hence, the idea of vulnerability factors mainly driving the long-term course of depression seems supported by these data.

Notably, in CF patients the predictive power of previous depressions scores decreases with greater temporal distance and seems significantly lower after 3 years than it does in the second sample (enclosing 330 elderly). This thus indicates differences in the stability of depressive symptoms, depending on sample characteristics. Here, several mechanisms may explain this phenomenon:

First, one may argue, that symptoms (of all kinds and most diseases) will be less volatile in the elderly due to less fluctuation in situational third variables (e.g., pensioners may not find themselves in changing workplace environments or relationships as often as the young CF sample does). Along the same line, one may argue that depression eliciting changes may tend to persist increasingly in old age (e.g., death of a close friend or relative). Also, vulnerability factors, such as personality traits may not be as flexible

as they are in adolescents or young adults (Roberts and DelVecchio, 2000).

In addition, the different somatic disorders may also contribute to significantly different sample characteristics. Finally, these differences may also indicate that the kindling/sensitization hypothesis is right in assuming that depression 'scars' patients to the extent of increased susceptibility for further episodes and more chronic courses. In this regard, supporters of the kindling/sensitization hypothesis would probably interpret the increased predictive power of previous depression scores in the elderly as an indication for increased dependence of future depressiveness on current symptoms which would be in line with this theories prediction.

The current data is not able to discard or approve this notion. It would be possible to include *age* as a covariate in the analyses of both samples, building on the idea of this variable to be the confounding variable indicating greater kindling/sensitization processes in one sample than to the other, but the variance in age would probably not be sufficient to draw concluding remarks. As a result, the data discussed so far hold evidence for the influence of stable vulnerability factors to dictate long-term courses, while depression-induced scaring may not be highly likely in the context of the studies discussed in Part I but can not be ruled out in the current set of data. Hence, for all we know, both effects may coexist.

However, both samples highlight that depression itself does not seem to contribute to the SoB and neither to cognitive capacity nor its course. As a result, this suggests that depression and comorbid courses can be predicted by vulnerability factors for depression, but that depression itself does not exacerbate vulnerabilities in general. Thus if depression indeed sensitizes an organism, it may do so by other means than modulating objectified cognitive capacity in the elderly or the SoB in young adults and adolescents.

In this regard, it is worth noting that these vulnerability factors do not represent a random sample of all risk factors known but are themselves specifically inclined in 'scaring'. For instance, as stated before, HRQoL measures in CF do not return to normal after remission from depression, with SoB being one of the HRQoL-related constructs (the construct with the greatest effect within the current analyses). Hence, if indeed kindling

took place, one could assume, that depression scores should have been found to influence SoB one year later.

Furthermore, if indeed, depression had sensitized the elderly sample, concurrent depression scores should also have predictive power for cognitive capability estimates one year later as the existing literature assumes affective disorders to induce detrimental courses in MCI and AD. Nonetheless, since the sample is mostly healthy, this effect may not show up. However, if depression, which seems more stable in this sample than as in the CF sample, has had an influence on the organism for many years, it is unlikely that cognitive functioning is indeed uncorrelated to the BDI-II measure (see Section 4.1.1 for a review of the many ways, that depression may correlate to cognitive performance).

Hence, if depression left 'scars' within the sample, this scar would not have had any significant impact on this kind of functioning, somewhat ruling out detrimental effects on social interactions as well, as these have been implicated in the prediction of cognitive decline. Thus, if depression left 'scars', these would, according to the present data, not be correlated to cognitive decline or capability in general since otherwise it would act as a mediating variable between BDI-II scores and performance estimates, which would subsequently be attributed back to the depression score since no such covariate was included into the models.

As a result, once again, it seems highly unlikely, that in this sample, kindling by previous depression episodes took place as these would most likely result in some sort of correlation between depressiveness and cognition. In sum, it may thus seem more conducive to assume the alternative interpretation of decreased volatility of vulnerability factors for depression in the elderly to produce the differences in the predictive power of depression scores between the samples.

Finally, it may be worth noting that in the CF sample, the PHQ-9 was used, while the BDI-II was employed in the other. Therefore, it may also be plausible to attribute the difference in effect sizes to differences in measures.

24.4 Utility and Properties of litFUS Neuromodulation

Neuromodulation via litFUS was performed with the same parameters across all studies in the thesis presented here (see Table 4). In addition, the same region of interest was always addressed in each of the studies. Since no MRI or other imaging method was used to check whether the focused region was modulated, it seems more appropriate to speak more generally of the lPFC instead of the riFG. Nevertheless, it should be stated that the results seem to fit well with previously discussed characteristics of the riFG in particular. For the individually adjusted alignment of the transducer across the test subjects, the EEG electrode position F8 was used. Overall, this seems to allow at least a comparability across the studies reported here.

The parameters used represent the lower end of what is needed to trigger effects according to the currently most widely accepted (NICE) model, which is why the following effects are not necessarily assessed in terms of their effect size. Instead, effects are considered in terms of content and discussed as a basis for stronger effects in future studies.

First, it should be noted that we expected an inhibitory effect according to the NICE model. This is, for example, also reflected in the increasing power in the alpha frequency range reported in Paper V, since the alpha activity is correlated with cortical inactivity. However, it also appears that this effect does not exist in general, but only seems to occur on average. In contrast, it looks like different effects can occur depending on the current task/demand; both, an increase and a decrease in alpha power.

This is not surprising at first, since the brain (usually) employs different network activity/connectivity depending on the task type. Thus, the cortical activity following neuromodulation should depend on task demands too. On the other hand, it could be argued that influencing inhibitory interneurons in general and independent of task-demands should result in a *general* relative increase in alpha power: If the litFUS effect is indeed mediated by a change in the responsiveness of certain receptor types, this effect should add to any dynamic change in the connectivity between the lPFC and other areas and should accordingly also be evident across all experimental conditions. That is, alpha should be more present after litfus than after sham in within-person comparisons. This idea follows

from litFUS-altered reactivity of interneurons that should ensure that inputs in the range of other frequency bands should always be met with increased alpha-frequency signaling from those neurons that significantly contribute to large-scale synchronization.

The fact, that this was not the case in Papers III and V. Both suggest that the effects exerted by litFUS, especially over a longer period, resulted in a change or neural dynamics that enclosed more extensive areas than would be expected from a focal administration: Mediation of task demands (operationalized by altered network activity or involvement of the lPFC) by the affected inhibitory interneurons should always lead to an increased alpha activity unless the brain can selectively bypass these neuronal assemblies for specific tasks. The same applies if one defines the relationship not as a mediator but as a moderator relationship. Following from this, there are two main possibilities to explain the present data:

First, there could be task-specific bypasses for the neuronal ensembles that were affected by litFUS. Second, there could be a decoupling, hence a change in the involvement of these neurons induced by cyclic feedback chains. Thus, a dynamically re-emerging alteration in functional connectivity could result, correcting for the litFUS induced neuronal ensembles that act as a non-network conforming unit.

A direct indication for the latter is given in the relationship between theta power at Fz and effort or worrying, which seem to vary depending on the neuromodulation condition (see Paper III). In this relationship between a non-directly modulated electrode position and self-rate data, litFUS seems to result in an altered functional role of areas or networks that are not the originally modulated location. Accordingly, these results provide evidence that effects in the studies presented, as well as those reported in other litFUS studies, may as well result from changes that differ from the site of modulation. Nevertheless, effects at individual electrode positions can still be considered as causal for specific effects (but other electrode positions than the site of modulation may be of interest). Taken together, while interpreting these effects, it should be noted that the signal at the electrode in question does not result from modulation of the lPFC alone, but rather from an overall change in brain dynamics.

Another circumstance suggesting that network-based dynamic adaptation pro-

cesses are involved relies on the idea that this process should depend on a change in the responsiveness of T-type calcium channel expressing interneurons, if it was indeed litFUS dependent and following the NICE model. Regarding this, findings from Study III and V that show the litFUS effect to depend on the IAF, which is an indirect indication for this and seems consistent with this hypothesized biological mediation of litFUS effects: The IAF itself seems to be dependent on interindividual differences in the expression and influence of these interneurons and channels (Bazanova and Vernon, 2014). Accordingly, these findings provide the first evidence for the validity of the idea of the NICE model.

In addition, Studies IV and V show different effects of litFUS neuromodulation for individuals with more or less depressive symptoms. The effects suggest benefits for those individuals who are more depressed, underscoring the potential utility of litFUS for translation into a clinical context. This is also confirmed by the results from the learned helplessness task, which show positive effects on cognitive, emotional, motivational, and physiological parameters. Since the study is explicitly committed to high external validity, a translation into the context of clinical samples does seem to be a reachable goal.

24.5 Contributions of the lPFC to the Processing of Emotional Stimuli and Situations

In Paper V, the lPFC was shown to be sensitive to the processing of emotion-expressing faces. However, it was noticeable that the emotion shown in the current trial did not directly trigger an EEG response at F8, but instead, stochastic contextual information did. Thus, the lPFC at the F8 electrode position was mainly reactive due to the probability of occurrence of certain emotions or even certain combinations of features (e.g., angry men) over the entire experiment. Therefore, the riFG (the region we sought to address) presumably contributes contextual information to the overall processing of emotional stimuli.

Interestingly, we found a statistically and topographically striking sensitivity not for the constellation of features within a single block, but across all blocks. This could be explained, among other things, by the fact that the blocks all comprised a length of eleven trials, which is why the internal counting within a block was also possible by

counting only one feature, instead of counting both possible feature expressions. Thus, it could be that the contextual information was processed differently on a block-by-block basis. Nevertheless, it remains to be stated that the across-all-blocks-counting of features was not relevant for the experiment and that there were nevertheless highly significant correlations. This in turn might suggest that even within blocks, although a specific counting method might work differently than across all blocks, a general sensitivity of the lPFC to this type of information would have been expected.

Overall, this suggests that stochastic contextual information is captured and processed independently of specific task settings. In turn, however, this seems not to be fully generalizable in that the effect seems to disappear when the focus is shifted away from emotional features. Thus, possibly, in the context of emotional processing, the lPFC processes the features associated with the emotions against the background of their likelihood of occurrence. However, this does not seem to be the case for situations in which no emotional relevance is seen.

Interestingly, this idea conflicts with the results from Paper III, which indicate that the lPFC was also sensitive to the probability of occurrence of an emotionally possibly irrelevant stimulus. Hence, the main question resulting from this is whether the thumbs-up emoji, which served as a reinforcer, is inherently emotionally charged or not. It could be argued that both the emoji and the emotional faces within trials in which gender was to be counted have in common a task-relevant count of occurrence-probabilities of certain features beyond the targeted processing of emotional stimuli. However, it may be countered that the appearance of the reinforcer in Paper III in itself triggers emotion since in its absence the inherently averse state of feeling 'out of control' could arise.

Whether the lPFC is also sensitive to stochastic contextual information that does not itself trigger an emotional state is therefore not clear from the data currently presented, since it is not immediately clear from them which feature or which stimulus-evoked which emotional consequence in the subjects. Nevertheless, at least the results of the studies on lPFC-based schema change discussed in Section 10.3 indicate that it seems to fulfill this function not only for emotional stimuli. This, in turn, suggests that the effect of the stimuli discussed in Paper V (Figure 29) is an active suppression process on

the part of the subjects that was shown in response to the specific task demand to focus on one feature, thus zoning out another. This idea, in turn, would be interesting for the question of intervention possibilities in the field of emotion regulation, which could be oriented towards this effect. The most obvious intervention based on these findings would be, for example, neurofeedback training with the target electrode F8, directed towards the suppression of emotional feature/stimulus processing.

Overall, inhibition of this electrode position has been shown to have positive effects in many areas of cognition, emotion, and motivation. First, in Paper III, neuromodulation of the right lPFC was shown to have a positive effect on the illusion of control, while in Paper IV, a transfer of this result to a setting with higher external validity was achieved.

Consistent with the previously mentioned ideas of a dynamic and systemic reorganization of functional connectivity of the brain after litFUS neuromodulation, it is also evident that more far-reaching effects, via the direct influence of F8 electrode placement and the underlying area, began. This pilot study (Paper IV) points to the potential of the method, which can be exploited even more through other parameters of neuromodulation, and provides first indications of its possible use for augmenting psychotherapeutic interventions by generally putting the organism in a more receptive, positive and also more resilient state (e.g., before performing *problem actualizing* interventions). The same may be true for prevention programs. Paper IV was explicitly designed as a pilot study for a neuromodulation-based prevention program, either set between two episodes of depressive illness or before the onset of the first one.[21].

24.6 Testability of Reconsolidation-Based Protocols in the Context of Depressive Disorders

The study presented in Section 24 offers a possible solution to the problem regarding a lack of evidence of transferability of reconsolidation-based interventions to the (phenomenologically and etiologically) heterogeneous depressive disorders. However, as the

[21]However, primary prevention via neuromodulation leads to substantial problems of applicability (e.g., from the point of view of medical ethics or the mere problem of application in larger samples)

study has not yet been peer-reviewed, it remains to be seen, as in other studies discussed here, whether it is a viable methodological basis for this area of research. The study was already started in 2019, but had to be interrupted due to the current pandemic and is now to be continued as soon as the infection- and hospitalization rates permit it.

Overall, the study builds on the theoretical considerations from Part I and II. It combines the idea of learned helplessness, as the unifying theory behind the numerous symptoms of depression, with the previously noted findings of midline theta but also the lPFC. The latter in particular stands out because it has been named several times as a region of interest concerning updating and reconsolidation. To be able to predict more precisely how the right lPFC behaves during reconsolidation (measured via EEG-based frequency analyses), a focus was placed on the processing of stochastic information in the previous studies. Since reconsolidation should be based on a prediction error, an effect at the electrode position F8 should be at least indirectly related to it.

The data presented here now show that the lPFC itself may contribute important information to this prediction error by signaling contextual information about the probability of occurrence of certain stimuli and features. This in turn seems to influence expectancy formation, as shown in Paper III, where it was shown that alpha activity at the lPFC contributes to the illusion of control, which can be indirectly defined as control belief but also expectancy.

Accordingly, the hypothesis arises that the lPFC is part of schema-actualizing networks because it provides crucial clues as to which prediction an organism implicitly makes (based on previous experience with the occurrence probability of stimuli or features), which in turn could shape the prediction error.

Hence, in the best-case scenario, the study presented here not only provides evidence of a reconsolidation-interference-based intervention in the field of depression but also evaluates a paradigm that can be extended in subsequent studies to include the use of neuromodulation methods, such as litFUS. In this context, for the first time, it might not be a matter of modulating learning after successful labilization, but of facilitating labilization itself, which still seems to be a major and so far poorly addressed problem (more on this in Section 10.2).

25 Concluding Remarks

In conclusion, the method of litFUS neuromodulation used here is suitable for use in (sub)clinical samples as well as for the basic psychological investigation of causal connections within neural networks and their contribution to psychological events. Its potential even seems to increase with higher depressive symptom load (but also see Section 25.1). Hence, the use of this new method can be recommended against the background of the results presented here, whereby it should also be pointed out that up to the time of the preparation of this thesis no side effect and no sequelae or damages have been reported, neither within the presented studies, other investigations within the working group, nor in internationally published manuscripts, provided that low-intensity parameters for neuromodulation (i.e. in contrast to ablation) were chosen.

Furthermore, this thesis shows the potential of the lPFC and supposedly specifically of the riFG. The latter seems to contribute to the classification of currently processed stimuli mainly by contributing stochastic background information. In addition, it seems to be part of neural networks that functionally restructure after inhibition of the right hemispheric lPFC in such a way that positive effects in the emotional, motivational, cognitive, and electrophysiological domains become evident.

Along the same line, the pilot prevention study of depressive symptoms by litFUS described in Paper IV is also to be regarded as particularly relevant before the context of two clinical samples that indicate stable interindividual differences, in particular, can contribute as drivers of long-term negative disease courses. This applies both to the course of depression itself and the course of other comorbid illnesses. According to these data, depression itself seems to contribute less to 'scarring', but rather seems to be influenced by preexisting scars/vulnerabilities themselves. Neuromodulation of endophenotypes for vulnerability factors for depression, as was done here, could accordingly ensure or contribute to more long-term therapeutic success[22].

However, neuromodulation itself can hardly bring about sufficiently large and also not temporally lasting effects, as, for example, psychotherapeutic interventions or

[22]Even though no personality factors were not addressed directly in the clinical samples, the overall idea of vulnerability factors to have long-lasting control over the organism was supported by the present data

prevention programs could. Accordingly, it is proposed above all to use litFUS but also other modulation methods as an augmentation to established therapies, so that positive synergy effects can arise.

As a further approach for augmenting or extending the existing therapy repertoire, a reconsolidation-based intervention approach was also proposed, which to my knowledge has not yet been demonstrated. This thesis aims to present a concept that allows for a basic psychological investigation of the feasibility of translation into everyday therapy and a well-controlled yet externally valid paradigm for investigating the effects.

Overall, this thesis thus contributes a small building block to the further development of existing therapeutic and preventive procedures for the treatment of depressive disorders by reporting first laboratory findings and methods that could provide initial findings for viable future research and application.

25.1 Limitations

At the time of writing this thesis, most of the studies presented here are still under review or have not been submitted yet. It, therefore, remains unclear to what extent statements made have to be revised with respect to discussions with independent colleagues (reviewers).

It should also be noted that the results concerning litFUS should always be interpreted against the background of the parameters used. Applications of this method at other electrode positions or with other parameters may yield significantly different results. Since participants were modulated at very low intensities as a precautionary measure, it is reasonable to assume that effect sizes could be amplified when this still restrained use of the methodology ceases. Nonetheless, greater effect sizes may not necessarily follow from increased modulation intensity.

It should also be noted that Papers III and V describe the same sample, so the findings are not completely independent of each other. Both experiments were following one another within one experimental session. A third task that was not described here preceded the two, as part of a superordinate study. In addition, the 41 subjects described, not all of whom could be included in each analysis, are insufficient to make statements

about personality effects, which is why this has been avoided here as far as possible. Accordingly, results relating to, for example, IAF or depression differences between subjects in these studies are also limited in their generalizability. However, even though personality measures and other between-person differences were not analyzed directly, their key neural correlates were experimentally modulated (mostly in within-person experimental settings), which strongly connects the present results and their causal claims to the idea of influences by interindividual differences.

Concerning the clinical samples, it should also be noted that results against the background of these two specific disorders do not necessarily express general effects.

25.2 Outlook

The presented data include strong evidence towards the safety and utility of litFUS. Judging from the preceding remarks, it may be suitable to augment existing therapy approaches by using it to inhibit the right lPFC. However, in the context of depression, its potential may only be fully capitalized in other regions of interest, such as the dACC, the amygdala, or even the dRN. Building on its property to reach even deep structures, other interventions may also be possible for a variety of disorders, such as neurodegenerative diseases that currently need a brain implant to reach target structures. Furthermore, its use in the investigation of basic neuroscientific research may spark seminal research, as for the first time, non-invasively, subcortical structures may be modulated directly. In addition, as it may be used across all species (except for very small animals, such as *Drosophila*), translation of results is easily possible. For instance, to estimate the potential use of litFUS in the prevention of depression, litFUS could be used with increased intensity in rodent-based learned helplessness protocols to investigate the optimal parameters and their respective safety in an animal model. The adapted modulation protocol could then be translated back to human laboratory studies and finally to clinical application.

Furthermore, as it has been established, that the riFG provides valuable stochastic context information for the processing of (emotional) stimuli, direct modulation of this region of interest may be used in a variety of ways. For instance, as stated before, interference with this structure may be able to lead to more robust findings in the field of

reconsolidation interference, as it modulates a neural basis of expectation formation. Furthermore, the circumstance that the riFG reacts to this type of information specifically, also informs the investigation of the right DLPFC responses to be handled with care. For instance, even though FA measures are investigated at several electrode position pairs, the current data indicates, that electrode position F8 and F7 may measure substantially different functionality than F4 and F3 do. As a result, in FA research but also other fields, such as in face-processing studies, single-trial analyses that 'correct' for such kind of information may increase the size of certain effects while decreasing others. One example of this would be the finding that the right lPFC did not react to the currently depicted face while the probability of face presentation was included in the model. Hence, this thesis provides evidence for the influence of effects, that may lead to misestimation or at least misattribution within a standard analysis of variance approach.

Finally, in conclusion, and regarding findings from the clinical samples, this thesis highlights the idea of vulnerability factors for depression to shape the long-term clinical course of depressive symptoms with relatively increasing power for long-term predictions. As a result, future studies may find merit in the inclusion of variables associated with this, instead of using depression scores themselves for their analyses. Further, treatment, may it be preventive or curative, may profit the most from targeting such factors.

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Part VI - Appendix

27 Supplemental/Additional Analyses and Figures

27.1 Supplemental Analyses of Paper I

	AIC	BIC	χ^2	$Df(\chi^2)$	p
RI(Pat.)	512.676	516.578			
RI(Fam.)	509.03	516.63			
+PHQ-9	490.48	500.61	20.548	1	**<.001**
+GAD	476.31	488.98	16.171	1	**<.001**
+PLC	480.49	505.81	5.826	5	.324
+Group	482.09	509.94	0.402	1	.526

Table 29: Comparison of random intercept (RI) models with GAD (t2) as dependent variable. Df= degreees of freedom. AIC= Akaike Information Criterion. BIC= Bayesian Information Criterion. Bold numbers indicate significance.

	AIC	BIC	χ^2	$Df(\chi^2)$	p
RI(Pat.)	536.812	544.41			
RI(Fam.)	534.68	542.28			
+PHQ-9	496.38	506.51	40.307	1	**<.001**
+GAD	497.55	510.22	0.823	1	.364
+PLC	494.52	519.84	13.037	5	**.023**
+Group	491.19	519.05	5.329	1	.021

Table 30: Comparison of random intercept (RI) models with PHQ-9 (t2) as dependent variable. Df= degreees of freedom. AIC= Akaike Information Criterion. BIC= Bayesian Information Criterion. Bold numbers indicate significance.

	Unstandardized Estimate	SE	Df (Satt.)	t value	*p (Satt)*	*p (Holm)*	*β*
GAD	0.036	0.142	82,170	0.250	.803	1	0.034
SoB	-1,900	0.648	83,843	-2,932	.004	.035	-0.301
WC	-1,412	0.885	83,968	-1,596	.114	.571	-0.277
CA	-0.179	0.604	70,357	-0.296	.768	1	-0.039
PM	0.252	0.668	74,021	0.377	.708	1	0.052
EaR	0.643	0.861	58,171	0.747	.458	1	0.133
PHQ	0.280	0.128	52,822	2,178	.034	.215	0.284
Group	-1,459	0.657	50,133	-2,223	.031	.215	-0.344

Table 31: Fixed effect estimates of the best model to predict depression.

27.2 Supplemental Analyses of Paper II

Model	**AIC**	**BIC**	**2**	**df**	***p (>2)***
DM1	2629.5	2647.1			
DM2	2600.4	2635.5	37.1459	4	1.681E-07***
DM3	2600.9	2644.9	3.4385	2	.1792
DM4	2600.5	2653.2	4.4083	2	.1103
DM5	2604.4	2665.9	0.1603	2	.923

Table 32: Mixed-model comparisons of declarative memory. DM=declarative memory; AIC=Akaike information criterion; BIC=Bayesian information criterion.

Model	AIC	BIC	2	df	*p (>2)*
AT1	1318.9	1336.5			
AT2	1322.9	1358.1	3.9687	4	.41026
AT3	1319.1	1363	7.8371	2	.01987*
AT4	1320.7	1373.4	2.3888	2	.30289
AT5	1322.5	1384	2.2136	2	.33062

Table 33: Mixed-model comparisons of working memory. AT=attention; AIC=Akaike information criterion; BIC=Bayesian information criterion.

Model	AIC	BIC	2	df	*p (>2)*
VSP 1	1859.3	1876.8			
VSP 2	1851.2	1886.4	16.0394	4	.002967**
VSP 3	1850.8	1894.7	4.4825	2	.106325
VSP 4	1848.6	1901.3	6.1641	2	.045866*
VSP 5	1850.8	1912.3	1.762	2	.414375

Table 34: Mixed-model comparisons of visual spatial processing. VSP=visual spatial processing; AIC=Akaike information criterion; BIC=Bayesian information criterion.

Model	**AIC**	**BIC**	**2**	**df**	***p (>2)***
WM1	1222.1	1239.7			
WM 2	1218.2	1253.4	11.9321	4	.01786*
WM 3	1220.3	1264.3	1.862	2	.39415
WM 4	1220.1	1272.8	4.2453	2	.11972
WM 5	1222.8	1284.3	1.3083	2	.51989

Table 35: Mixed-model comparisons of working memory. WM=working memory; AIC=Akaike information criterion; BIC=Bayesian information criterion.

	Estimate	SE	Df	*t*	*p*	*β*
(Inpercept)	-0.165/ 46.011	0.104/ 0.982	296/ 296	-1.582/ 46.856	0.115/ 0	0.03/ 0.02
Gender	0.999/ 4.896	0.21/ 1.972	296/ 296	4.765/ 2.483	0/ 0.014	0.44/ 0.22
Time	-0.3/ -1.249	0.103/ 1.194	296/ 296	-2.898/ -1.046	0.004/ 0.296	-0.13/ -0.06
Age	-0.16/ -0.091	0.068/ 0.642	296/ 296	-2.34/ -0.142	0.02/ 0.887	-0.11/ -0.006
Gender:Time	0.518/ -1.109	0.208/ 2.397	296/ 296	2.49/ -0.463	0.013/ 0.644	0.23/ -0.05
Time:Age	-0.071/ 0.689	0.068/ 0.78	296/ 296	-1.054/ 0.883	0.293/ 0.378	-0.05/ 0.05

Table 36: Best Mixed-models for the fixed effects of Declarative Memory for the latent factors and composite approach. DM=declarative memory; SE=standard error. Values before the slash refer to the latent factor approach and values after the slash to the composite approach.

	Estimate	SE	Df	*t*	*p*	*β*
(Intercept)	-0.012/ 64.297	0.046/ 1.148	296/ 296	-0.266/ 56.019	0.791/ 0	0.02/ 0.009
Gender	0.233/ 2.518	0.093/ 2.305	296/ 296	2.51/ 1.092	0.013/ 0.276	0.28/ 0.11
Time	-0.021/ 4.517	0.023/ 0.99	296/ 296	-0.905/ 4.562	0.366/ 0	-0.02/ 0.2
Age	-0.046/ -0.377	0.03/ 0.75	296/ 296	-1.507/ -0.503	0.133/ 0.616	-0.08/ -0.02
Gender:Time	-0.074/ -1.208	0.046/ 1.989	296/ 296	-1.597/ -0.608	0.111/ 0.544	-0.09/ -0.05
Time:Age	0.002/ 0.361	0.015/ 0.647	296/ 296	0.13/ 0.558	0.896/ 0.577	0.004/ 0.02

Table 37: Best mixed-models for the fixed effects of Working Memory for the latent factors and composite approach. WM=working memory; SE=standard error. Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

	Estimate	SE	Df	*t*	*p*	*β*
(Intercept)	-0.383/ 57.283	0.062/ 0.931	294/ 294	-6.195/ 61.531	0/ 0	-0.02/ -0.02
Gender	-0.272/ -5.151	0.127/ 1.905	294/ 294	-2.15/ -2.704	0.032/ 0.007	-0.21/ -0.24
Time	-0.527/ -1.325	0.049/ 1.116	294/ 294	-10.662/ -1.188	0/ 0.236	-0.41/ -0.06
Age	0.002/ 1.356	0.04/ 0.609	294/ 294	0.052/ 2.227	0.958/ 0.027	0.003/ 0.1
BDNF	0.002/ 0.028	0.002/ 0.027	294/ 294	1.192/ 1.06	0.234/ 0.29	0.06/ 0.05
BDI-II	-0.022/ -0.155	0.011/ 0.162	294/ 294	-2.003/ -0.955	0.046/ 0.34	-0.1/ -0.04
Gender:Time	-0.302/ -3.384	0.101/ 2.283	294/ 294	-2.987/ -1.482	0.003/ 0.139	-0.24/ -0.16
Time:Age	0.041/ 1.715	0.032/ 0.73	294/ 294	1.283/ 2.35	0.2/ 0.019	0.05/ 0.12
Time:BDNF	0.002/ 0.012	0.001/ 0.032	294/ 294	1.469/ 0.369	0.143/ 0.712	0.06/ 0.02
Time:BDI-II	-0.012/ -0.048	0.009/ 0.194	294/ 294	-1.443/ -0.249	0.15/ 0.803	-0.06/ -0.01

Table 38: Best mixed-models for the fixed effects of Visual-Spatial Processing for the latent factors and composite approach. VSP=visual-spatial processing; SE=standard error; BDNF=Brain-Derived Neurotrophic Factor; BDI-II=Beck Depression Inventory-II (Beck et al., 1996). Values before the slash refer to the latent factor approach, values after the slash to the composite approach.

	Estimate	SE	Df	t	p	β
(Intercept)	0.052/ 46.373	0.032/ 0.314	295/ 295	1.621/ 147.806	0.106/ 0	0.01/ 0.009
Gender	0.128/ 0.72	0.065/ 0.637	295/ 295	1.966/ 1.131	0.05/ 0.259	0.18/ 0.11
Time	0.034/ 0.46	0.039/ 0.27	295/ 295	0.852/ 1.707	0.395/ 0.089	0.05/ 0.07
Age	0.008/ 0.266	0.021/ 0.205	295/ 295	0.36/ 1.296	0.719/ 0.196	0.02/ 0.06
BDNF	-0.002/ -0.003	0.001/ 0.009	295/ 295	-2.278/ -0.288	0.023/ 0.774	-0.1/ -0.01
Gender:Time	0.017/ 0.517	0.08/ 0.548	295/ 295	0.214/ 0.944	0.831/ 0.346	0.02/ 0.08
Time:Age	0.026/ 0.252	0.026/ 0.176	295/ 295	1.026/ 1.43	0.306/ 0.154	0.06/ 0.06
Time:BDNF	0.002/ -0.001	0.001/ 0.008	295/ 295	1.612/ -0.091	0.108/ 0.927	0.09/ -0.004

Table 39: Best mixed-models for the fixed effects of Attention for the latent factors and composite approach. AT=attention; SE=standard error; BDNF=Brain-Derived Neurotrophic Factor). Values before the slash refer to the latent factor approach and values after the slash to the composite approach.

27.3 Additional Analyses for Paper II

				95% C.I.				
Type	Effect	Estimate	SE	Lower	Upper		z	p
Indirect	DM(t1)→DM(t2)→BDI(t2)	-0.090	0.057	-0.202	0.023	-0.044	-1.566	0.117
	BDI(t1)→DM(t2)→BDI(t2)	0.003	0.004	-0.004	0.010	0.003	0.828	0.408
Component	DM(t1)→DM(t2)	1.038	0.076	0.890	1.187	0.601	13.684	<.001
	DM(t2)→BDI(t2)	-0.086	0.055	-0.194	0.021	-0.073	-1.577	0.115
	BDI(t1)→DM(t2)	-0.035	0.036	-0.106	0.036	-0.043	-0.973	0.331
Direct	DM(t1)→BDI(t2)	0.084	0.095	-0.102	0.269	0.041	0.887	0.375
	BDI(t1)→BDI(t2)	0.708	0.036	0.638	0.779	0.733	19.722	<.001
Total	DM(t1)→BDI(t2)	-0.006	0.076	-0.155	0.143	-0.003	-0.077	0.939
	BDI(t1)→BDI(t2)	0.711	0.036	0.640	0.782	0.736	19.731	0.001

Table 40: Path analysis including declarative memory (DM) and depression

				95% C.I.				
Type	Effect	Estimate	SE	Lower	Upper		z	*p*
Indirect	AT(t1)→AT(t2)→BDI(t2)	0.001	0.003	-0.006	0.007	0.001	0.206	0.837
	BDI(t1)→AT(t2)→BDI(t2)	5.777	3.691	-1.457	13.011	0.034	1.565	0.118
Component	AT(t1)→AT(t2)	0.000	0.001	-0.001	0.001	0.010	0.207	0.836
	AT(t2)→BDI(t2)	5.730	3.618	-1.361	12.821	0.068	1.584	0.113
	BDI(t1)→AT(t2)	1.008	0.098	0.816	1.201	0.495	10.255	<.001
Direct	AT(t1)→BDI(t2)	0.713	0.036	0.642	0.784	0.738	19.714	<.001
	BDI(t1)→BDI(t2)	-8.685	7.420	-23.228	5.858	-0.050	-1.170	0.242
Total	AT(t1)→BDI(t2)	0.713	0.036	0.642	0.785	0.739	19.629	<.001
	BDI(t1)→BDI(t2)	-2.908	6.496	-15.640	9.824	-0.017	-0.448	0.654

Table 41: Path analysis including attention (AT) and depression

				95% C.I.				
Type	Effect	Estimate	SE	Lower	Upper		z	*p*
Indirect	WM(t1)→WM(t2)→BDI(t2)	-0.003	0.004	-0.010	0.004	-0.003	-0.818	0.413
	BDI(t1)→WM(t2)→BDI(t2)	0.210	0.219	-0.220	0.640	0.031	0.956	0.339
Component	WM(t1)→WM(t2)	-0.018	0.012	-0.041	0.005	-0.065	-1.574	0.116
	WM(t2)→BDI(t2)	0.163	0.170	-0.170	0.496	0.048	0.958	0.338
	BDI(t1)→WM(t2)	1.289	0.081	1.129	1.448	0.655	15.829	<.001
Direct	WM(t1)→BDI(t2)	0.716	0.036	0.645	0.787	0.741	19.748	<.001
	BDI(t1)→BDI(t2)	-0.091	0.333	-0.744	0.563	-0.013	-0.272	0.786
Total	WM(t1)→BDI(t2)	0.713	0.036	0.642	0.784	0.738	19.682	<.001
	BDI(t1)→BDI(t2)	0.119	0.252	-0.375	0.613	0.018	0.473	0.636

Table 42: Path analysis including working memory (WM) and depression

				95% C.I.				
Type	Effect	Estimate	SE	Lower	Upper		z	p
Indirect	VSP(t1)→VSP(t2)→BDI(t2)	-0.001	0.003	-0.006	0.004	-0.001	-0.358	0.720
	BDI(t1)→VSP(t2)→BDI(t2)	0.113	0.303	-0.480	0.706	0.017	0.373	0.709
Component	VSP(t1)→VSP(t2)	-0.006	0.005	-0.016	0.003	-0.044	-1.276	0.202
	VSP(t2)→BDI(t2)	0.153	0.409	-0.649	0.954	0.022	0.373	0.709
	BDI(t1)→VSP(t2)	0.740	0.033	0.675	0.805	0.772	22.216	<.001
Direct	VSP(t1)→BDI(t2)	0.711	0.036	0.640	0.782	0.736	19.663	<.001
	BDI(t1)→BDI(t2)	-0.191	0.391	-0.957	0.576	-0.029	-0.488	0.625
Total	VSP(t1)→BDI(t2)	0.710	0.036	0.639	0.781	0.735	19.651	<.001
	BDI(t1)→BDI(t2)	-0.078	0.248	-0.564	0.408	-0.012	-0.315	0.753

Table 43: Path analysis including visual-spatial processing (VSP) and depression

27.4 Supplemental Material of Paper IV

Effect	Estimate	SE	Df	t	p	holm		β
Sham-litFUS	0.511	0.323	44.191	1.581	0.121	0.662		0.511
Control-litFUS	0.550	0.318	44.088	1.727	0.091	0.662		0.544
Experimental-litFUS	1.004	0.333	44.123	3.013	0.004	0.047		0.965
Sham-litFUS*Sec	-0.049	0.028	42.865	-1.760	0.085	0.662		-0.058
Control-litFUS*Sec	-0.038	0.028	42.258	-1.363	0.180	0.662		-0.045
Experimental-litFUS*Sec	-0.047	0.029	43.725	-1.619	0.113	0.662		-0.056
Sham-litFUS*Game	0.095	0.018	109087.965	5.247	0.000	<.001	***	0.081
Control-litFUS*Game	0.333	0.016	116195.956	21.246	0.000	<.001	***	0.287
Experimental-litFUS*Game	0.289	0.019	98809.965	15.313	0.000	<.001	***	0.228
Sham-litFUS*BDI	0.414	0.233	44.119	1.775	0.083	0.662		0.495
Control-litFUS*BDI	0.491	0.256	44.205	1.915	0.062	0.558		0.608
Experimental-litFUS*BDI	0.237	0.251	44.380	0.943	0.351	0.702		0.282
Sham-litFUS*Sec*Game	0.006	0.012	110554.451	0.484	0.629	0.702		0.006
Control-litFUS*Sec*Game	0.025	0.011	118788.629	2.291	0.022	0.220		0.027
Experimental-litFUS*Sec*Game	0.084	0.013	108919.164	6.416	0.000	<.001	***	0.098
Sham-litFUS*Game*BDI	-0.151	0.012	105361.491	-12.928	0.000	<.001	***	-0.170
Control-litFUS*Game*BDI	-0.450	0.010	122481.383	-44.898	0.000	<.001	***	-0.502
Experimental-litFUS*Game*BDI	-0.121	0.014	104345.929	-8.948	0.000	<.001	***	-0.117
Sham-litFUS*Sec*Game*BDI	-0.026	0.008	102809.279	-3.103	0.002	0.023	*	-0.041
Control-litFUS*Sec*Game*BDI	-0.084	0.007	122682.491	-11.619	0.000	<.001	***	-0.134
Experimental-litFUS*Sec*Game*BDI	-0.051	0.009	114086.636	-5.457	0.000	<.001	***	-0.080

Table 44: Model parameters for the mixed model predicting theta power density at Fz. Estimate =unstandardized regression coefficient, SE= standard error of the mean, Df= Satterthwaite degrees of freedom, holm = holm adjusted p, β = standardized regression coefficient, Sec = seconds played in a given game

Effect	Estimate	SE	Df	t	p	holm		β
Sham-litFUS	0.542	0.250	43.229	2.165	.036	.396		0.630
Control-litFUS	0.238	0.247	43.133	0.964	.340	1		0.258
Experimental-litFUS	0.823	0.258	43.176	3.187	.003	.037	*	0.911
Sham-litFUS*Sec	-0.022	0.021	43.921	-1.070	.290	1		-0.033
Control-litFUS*Sec	0.028	0.021	43.076	1.364	.180	1		0.040
Experimental-litFUS*Sec	0.017	0.022	45.079	0.781	.439	1		0.025
Sham-litFUS*Game	0.217	0.016	99655.122	13.720	.000	<.001	***	0.228
Control-litFUS*Game	0.091	0.014	110425.671	6.604	.000	<.001	***	0.123
Experimental-litFUS*Game	0.043	0.017	86023.044	2.613	.009	.108		0.053
Sham-litFUS*BDI	0.255	0.181	43.162	1.409	.166	1		0.385
Control-litFUS*BDI	0.185	0.199	43.229	0.933	.356	1		0.281
Experimental-litFUS*BDI	-0.119	0.195	43.405	-0.611	.544	1		-0.187
Sham-litFUS*Sec*Game	0.032	0.011	102029.273	2.893	.004	.050		0.047
Control-litFUS*Sec*Game	-0.042	0.009	114879.157	-4.403	.000	<.001	***	-0.061
Experimental-litFUS*Sec*Game	-0.012	0.011	99809.286	-1.010	.313	1		-0.014
Sham-litFUS*Game*BDI	0.069	0.010	94814.895	6.748	.000	<.001	***	0.083
Control-litFUS*Game*BDI	-0.080	0.009	121661.406	-9.024	.000	<.001	***	-0.112
Experimental-litFUS*Game*BDI	-0.023	0.012	94157.096	-1.970	.049	.488		-0.073
Sham-litFUS*Sec*Game*BDI	0.027	0.007	91450.727	3.694	.000	.003	**	0.051
Control-litFUS*Sec*Game*BDI	-0.008	0.006	122047.378	-1.236	.216	1		-0.015
Experimental-litFUS*Sec*Game*BDI	0.052	0.008	108009.694	6.398	.000	<.001	***	0.100

Table 45: Model parameters for the mixed model predicting theta power density at Pz. Estimate =unstandardized regression coefficient, SE= standard error of the mean, Df= Satterthwaite degrees of freedom, holm = holm adjusted p, β = standardized regression coefficient, Sec = seconds played in a given game

28 Additional Information

28.1 Publications

Shared First Authorships:

Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J. and Herrmann, M.J. (2022), Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. J Neuropsychol. https://doi.org/10.1111/jnp.12269

Hornig, I., Forster, A., Katscher-Peitz, A., Hewig, J., & Rose, M. (2021). Depressive symptoms in cystic fibrosis patients and their caretakers are best predicted by their respective sense of belonging. General Hospital Psychiatry .https://doi.org/10.1016/j.genhosppsych.2021.12.010

Preprints:

Forster, A., Hewig, J., Allen, J. J., Rodrigues, J., Ziebell, P., & Sanguinetti, J. (2021, November 14). The Right Lateral Prefrontal Cortex Impacts Control Perception as a Function of Probabilistic Stimulus Processing. https://doi.org/10.31234/osf.io/g97ky

Forster, A., Hewig, J., Allen, J. J., Rodrigues, J., Ziebell, P., & Sanguinetti, J. (2021). The Right Lateral Frontal Cortex Processes Features of Emotional Faces as a Function of Their Likelihood of Occurrence. https://doi.org/10.31234/osf.io/gr42f

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WÜRZBURG

Graduate School
Life Sciences

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions and of legal second publication rights

Publication (complete reference): Forster, A., Hewig, J., Allen, J. J., Rodrigues, J., Ziebell, P., & Sanguinetti, J. (2021, November 14). The Right Lateral Prefrontal Cortex Impacts Control Perception as a Function of Probabilistic Stimulus Processing. https://doi.org/10.31234/osf.io/g97ky PREPRINT

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	AF	JH			
Data Collection	AF				
Data Analysis and Interpretation	AF	JR			
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	AF				
Manuscript Revision	JR,JH,JS,PZ,JA				

Explanations (if applicable): All Figures and Tables were created by AF. This paper was completed and sent to all co-authors at November, 11th , 2020.

Publication (complete reference): Forster, A., Hewig, J., Allen, J. J., Rodrigues, J., Ziebell, P., & Sanguinetti, J. (2021). The Right Lateral Frontal Cortex Processes Features of Emotional Faces as a Function of Their Likelihood of Occurrence. https://doi.org/10.31234/osf.io/gr42f SUBMITTED TO "CORTEX" (UNDER REVIEW)

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	AF	JH			
Data Collection	AF				
Data Analysis and Interpretation	AF	JR			
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	AF				
Manuscript Revision	JR,JH,JS,PZ,JA				

Explanations (if applicable): All Figures and Tables were created by AF. This paper was completed and sent to all co-authors at December, 2nd, 2020.

Publication (complete reference): Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J. and Herrmann, M.J. (2021), Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. J Neuropsychol. https://doi.org/10.1111/jnp.12269 PUBLISHED IN "JOURNAL OF NEUROPSYCHOLOGY" (SHARED FIRST AUTHORSHIP)

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	ML, TP, JD, MJH	-			
Data Collection	JL, ML, TP	SR, MS			
Data Analysis and Interpretation	SH, AF	JL, MJH, SR, JH, MS, ML, TP, JD			
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	SH, AF	-			

Explanations (if applicable): This publication is also part of another doctorate thesis (S. Haberstumpf). We share the first-authorship. All Tables were created with equal contribution by SH and AF.

Publication (complete reference): Haberstumpf, S., Forster, A., Leinweber, J., Rauskolb, S., Hewig, J., Sendtner, M., Lauer, M., Polak, T., Deckert, J., Herrmann, M.J. (n.d.). Measurement invariance testing of longitudinal neuropsychiatric test scores distinguishes pathological from normative cognitive decline and highlights its potential in early detection research. Under review. PUBLISHED IN "JOURNAL OF NEUROPSYCHOLOGY" (SHARED FIRST AUTHORSHIP)

Figure	**Author Initials,** Responsibility decreasing from left to right				
1	SH, AF	-	-	-	-
2	SH, AF	-	-	-	-
3	SH, AF	-	-	-	-
4	SH, AF	-	-	-	-
5	SH, AF	MJH	-	-	-

Publication (complete reference): Transcranial Focused Ultrasound Modulates the Emergence of Learned Helplessness via Midline Theta Modification WAITING FOR CO-AUTHOR APPROVAL					
Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	AF	JH			
Data Collection	AF				
Data Analysis and Interpretation	AF	JR, JH			
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	AF				
Manuscript Revision	JR, JH,JS,PZ,JA				

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Publication (complete reference): Hornig, I., Forster, A., Katscher-Peitz, A., Hewig, J., Rose, M., Depressive Symptoms in Cystic Fibrosis Patients and Their Caretakers are Best Predicted by Their Respective Sense of Belonging. General Hospital Psychiatry. https://doi.org/10.1016/j.genhosppsych.2021.12.010 PUBLISHED IN “GENERAL HOSPITAL PSYCHIATRY” (SHARED FIRST AUTHORSHIP)					
Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	IH	AKP	MR		
Data Collection	IH	AKP	MR		
Data Analysis and Interpretation	AF	IH			
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	 IH IH AF AF AF	 AF AF IH IH IH			
Manuscript Revision	AKP,MR,JH				

Explanations (if applicable): All Figures and Tables were created by AF and IH with equal contribution.

The doctoral researcher confirms that she/he has obtained permission from both the publishers and the co-authors for legal second publication.

The doctoral researcher and the primary supervisor confirm the correctness of the above mentioned assessment.

André H. Forster		Würzburg	
Doctoral Researcher's Name	Date	Place	Signature

Johannes Hewig		Würzburg	
Primary Supervisor's Name	Date	Place	Signature

28.3 Poster Presentations

Annual Meeting of the Society for Psychophysiology

- Forster, A., Ziebell, P., Rodrigues, J., Allen, J.J.B.,& Hewig, J. (2018). Effects of Transcranial Ultrasound (TUS) in a Virtual T- Maze Task: Global Affect Global Vigor What Does TUS Change?! Psychophysiology, 55, S94.

- Forster, A., Ziebell, P., Rodrigues, J., Allen, J.J.B.,& Hewig, J. (2019). TRANSCRANIAL ULTRASOUND INFLUENCES BEHAVIOR AND ELECTROENCEPHALOGRAPHY IN A GO/NO-GO TASK. Psychophysiology 56, S44.

- Ziebell, P., Rodrigues, J., Forster, A., Gram, A., Aumüller, N., Sanguinetti, J., Allen, J.J.B.,& Hewig, J. (2021) LOW-INTENSITY TRANSCRANIAL FOCUSED ULTRASOUND TARGETING THE RIGHT PREFRONTAL CORTEX LEADS TO ELECTROENCEPHALOGRAPHIC MIDFRONTAL THETA DECREASES WHICH SIGNIFICANTLY PREDICT APPROACH BEHAVIOR IN A VIRTUAL T-MAZE TASK. Psychophysiology (co-authorship)

Psychologie und Gehirn conference by the Deutsche Gesellschaft für Psychologie

- Forster, A., Ziebell, P., Rodrigues, J., Allen, J.J.B.,& Hewig, J. (2019). The Influence Of Transcranial Ultrasonic Neuromodulation On Emotional Stimulus Processing In The Internal Shift Task. Psychologie und Gehirn. *ID: 359*

- Forster, A., Ziebell, P., Rodrigues, J., Allen, J.J.B.,& Hewig, J. (2018). Transcranial Ultrasound (TUS): Exploring the Effects of TUS on Global Affect and Global Vigor in the Context of a Virtual T-Maze Task. Psychologie und Gehirn. *ID: 353* (shared first authorship)

- Ziebell, P., Rodrigues, J., Forster, A., Gram, A., Aumüller, N., Sanguinetti, J., Allen, J.J.B.,& Hewig, J. (2021) LOW-INTENSITY TRANSCRANIAL FOCUSED ULTRASOUND TARGETING THE RIGHT PREFRONTAL CORTEX LEADS

TO ELECTROENCEPHALOGRAPHIC MIDFRONTAL THETA DECREASES WHICH SIGNIFICANTLY PREDICT APPROACH BEHAVIOR IN A VIRTUAL T-MAZE TASK. *ID: 215* (co-authorship)

Deutsche Mukuviszidosetagung

- I. Hornig, A. Forster, A. Katscher-Peitz, J. Hewig, M. Rose (2019). Der ergänzende Einsatz des 'Profils der Lebensqualität chronisch Kranker' im Mental Health Screening am CF-Zentrum Stuttgart (co-authorship)

28.4 Talks

Conference: Annual Meeting of the Society for Psychophysiology (2018)

Symposium: Diversity Symposium (Flash Talk)

Title: Effects of Transcranial Ultrasound (TUS) in a Virtual T- Maze Task: Global Affect Global Vigor What Does TUS Change?!

Auhtors: Forster, A., Ziebell, P., Rodrigues, J., Allen, J.J.B.,& Hewig, J.

Conference: Wissenschaftskonferenz des Zentrums für Psychische Gesundheit (2019)

Title: Transcranial Ultrasonic Neuromodulation As A Potential Treatment Of Depression - A First Look Into Experimental Data From Randomized Controlled Cross-Over Studies

Authors: Forster, A., Rodrigues, J., Ziebell, P., Allen, J. J. & Hewig, J.

Conference: Psychologie und Gehirn conference by the Deutsche Gesellschaft für Psychologie (2021)

Symposium: Modulation emotionaler Effekte mittels nicht invasiver Hirnstimulation

Title: Transkranielle Fokussierte Ultraschall Neuromodulation Beeinflusst die Entstehung von Erlernter Hilflosigkeit durch Inhibition der Theta Aktivität an Zentralen Elektrodenpositionen

Authors: Forster, A., Rodrigues, J., Ziebell, P., Sanguinetti, J., Allen, J. J. & Hewig, J.

28.5 Funding & Awards

- Award for Best Teaching at the Institute of Psychology: 'Goldener FIPS' (category: seminars; awarded by the Fachschaftsinitiative) in WS and SS 17/18
- Fellowship by the DAAD to attend the annual meeting of the SPR (2018, ~€2000)
- Diversity-Travel Award by the SPR (2018) to attend the SPR annual meeting (2018, ~1300$),
- Funding by the Faculty of Human Sciences Overhead resources (2019, ~€7000)
- GSLS Travel Fellowship to attend the SPR annual meeting (2019, €1000)
- ProjektDEAL by the University of Würzburg (financed the open access charges for Paper II)

29 Affidavit & Eidesstattliche Erklärung

I hereby confirm that my thesis entitled *Manipulating the Right Inferior Frontal Gyrus via Transcranial Low-Intensity Focused Ultrasound. Towards a Translational Neurosciences Approach to Establish Sustainable Therapeutic Protocols for Prevention and Treatment of Affective Disorders* is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Place, Date Signature

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation*Manipulating the Right Inferior Frontal Gyrus via Transcranial Low-Intensity Focused Ultrasound. Towards a Translational Neurosciences Approach to Establish Sustainable Therapeutic Protocols for Prevention and Treatment of Affective Disorders* eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Ort, Datum Unterschrift

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30 Curriculum Vitae

Signature, Place, Date