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„From Neural Impairments to Innovative Interventions: Investigating Major Depressive Disorder Using fMRI“

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Chapter 1.

General Introduction

Emotion and cognition determine how we view ourselves, our past, present and future, and our environment. Impairments in these fundamental human functions can severely affect the way we live our daily lives. Mental disorders can be limited in their manifestations to specific situations, or they can change the way we experience each day. One of the most common and debilitating mental disorders is Major Depressive Disorder (MDD), which can have devastating consequences for those who suffer from it. MDD is primarily associated with depressed mood and anhedonia, i.e. a loss of pleasure or interest in activities, and is often accompanied by symptoms such as hopelessness, feelings of worthlessness or guilt, loss of energy, changes in appetite or sleep, and suicidality (American Psychiatric Association, 2013; World Health Organization, 2004). Globally, suicide is the fourth leading cause of death among individuals aged 15–29 years (World Health Organization, 2021), and approximately half of all suicides can be attributed to MDD or other mood disorders (Hoertel et al., 2015). However, MDD not only imposes enormous costs on patients and the people close to them, but also has dramatic societal and economic consequences. With incidence and prevalence rates increasing since 1990, depressive disorders have affected more than 250 million people worldwide in recent years (James et al., 2018) and have become the second leading contributor to the global burden of disease, as measured by disability-adjusted life years, in both developed and developing countries (Global Burden of Disease Study 2013 Collaborators, 2015).

Despite decades of research into the neurobiology of depression and the development of various treatments, many questions remain unanswered and many patient needs unmet. In many areas of depression research, studies have focused on specific avenues of research while passing over what lies beyond. For instance, reward processing in MDD has been studied primarily with monetary incentives, music, or positive images, but few studies have focused on social reward. Non-invasive brain stimulation studies have overwhelmingly targeted the frontal cortex because it is more accessible than deeper cortical areas such as the hippocampus. Novel pharmaceutical interventions such as ketamine have shown promise in the treatment of MDD, but there is little evidence as to which patients it will benefit. Neuroimaging biomarkers have shown potential for predicting treatment outcome, but few studies have integrated data from different imaging modalities. Within the framework of this thesis, I focused on four research questions from different

areas of depression research: 1) how MDD affects the neural processing of social touch as an indicator of social reward (Chapter 2); 2) whether and how individualized parieto-hippocampal non-invasive brain stimulation can modulate hippocampal activation and connectivity and improve clinical response rates and memory function in patients with MDD (Chapter 3); 3) whether and how ketamine alleviates depressive symptoms in a patient with bilateral amygdala lesions (Chapter 4); and 4) whether combining task-based and resting-state functional neuroimaging data improves accuracy of predicting treatment response in patients with MDD (Chapter 5). To address these questions, four studies using functional magnetic resonance imaging (fMRI) were conducted in patients with MDD. In Chapter 2, a social touch paradigm was used to examine the neural processing of social reward in individuals with MDD before and after antidepressant treatment. In Chapter 3, we conducted a randomized controlled clinical trial to examine the effects of repetitive transcranial magnetic stimulation (rTMS) on clinical improvement, memory function, and neural activation and connectivity by using individualized cortical stimulation targets functionally connected to the hippocampus. In Chapter 4, we examined the clinical and neural effects, as measured by resting-state fMRI, of intravenous ketamine, an NMDA receptor antagonist, in a patient with treatment-resistant depression and bilateral amygdala lesions. In Chapter 5, we focused on the prediction of treatment outcome in patients with MDD using multimodal functional imaging approaches. Although each study examines different aspects of MDD and employs different methodologies, they all use fMRI to examine patients with MDD over the course of antidepressant treatment, with the overall goal of gaining new insights into the pathophysiology of MDD and improving existing treatments.

Understanding Major Depressive Disorder

MDD and other mood disorders are universal human experiences and have been documented since ancient times. Over time, the conceptualization of depression has gained complexity from simple humoral disease models to hemodynamic theories to Emil Kraepelin's concept of manic-depressive psychosis to Sigmund Freud's psychodynamic theories and eventually to Aaron T. Beck's cognitive model of depression, to name only a few milestones (Davison, 2006).

The last few decades of depression research have been characterized by groundbreaking technological and methodological advances. In addition to developments in the field of behavioral genetics (Flint & Kendler, 2014; Howard et al., 2019; Wray et al., 2018), these advances have been most evident in social, cognitive, and affective neuroscience, where the advent of modern neuroimaging methods has ushered in a new era of research. Instead of the radioactive tracers commonly used in positron emission tomography (PET), fMRI measures neural activation at rest or during task-related activities using the blood oxygen level-dependent (BOLD) contrast. In a process called the hemodynamic response, neuronal activation results in the release of oxygen

from the blood, causing a change in the ratio of oxygenated to deoxygenated hemoglobin, which can be measured based on its different magnetic properties. Due to its lack of radiation exposure, low invasiveness, and relatively wide availability, the development of fMRI in the 1990s has enabled medical facilities and research laboratories around the world to participate in the functional mapping of the brain.

Neuroimaging studies in MDD have identified numerous functional and structural alterations in a variety of brain regions and distributed neural networks, supporting the rejection of the outdated notion that a single brain region, gene, or neurotransmitter system is responsible for the pathophysiology of MDD (Nestler et al., 2002). More recent models describe MDD as a complex and multifactorial disorder involving pathophysiological alterations at multiple levels of organization, including the molecular, cellular, neural circuit, systemic, and social levels. While neuroimaging findings have contributed to the understanding of several hypotheses regarding the etiology and pathophysiology of MDD, including neuroendocrine, inflammatory, neuroplastic, and genetic disease models, it is primarily at the level of neural networks that fMRI studies have contributed to our understanding of the neurobiology of MDD.

At this level, several networks have been implicated in MDD. A notable neural model of depression proposed by Mayberg (1997), derived from brain regions shown to be altered in MDD patients, emphasizes the dysregulation of a distributed network of limbic-cortical pathways. The author argues that several cortical and dorsal limbic areas, including the dorsolateral prefrontal cortex (DLPFC) and parietal cortices, as well as the dorsal anterior and posterior cingulate, may become hypoactive in MDD. The DLPFC is primarily associated with cognitive and executive functions such as planning, attention, organization, response inhibition, working memory, and emotion regulation. Lesion studies have implicated the DLPFC in the development of MDD (Koenigs & Grafman, 2009; Padmanabhan et al., 2019) and neuroimaging evidence suggests a left-right DLPFC imbalance in patients with MDD (Grimm et al., 2008). It is also the most common target for antidepressant rTMS (Hebel et al., 2021). According to Mayberg's model, hypoactivation of these regions in turn leads to reduced regulation of hyperactive ventral paralimbic regions, including the subgenual cingulate (sgACC), an area critical for the modulation of negative mood states (Mayberg et al., 2005), among other brain regions such as the anterior insula, hypothalamus, and caudate nucleus. This hyperactivity of the sgACC is one of the most consistent findings in neuroimaging studies of MDD and has been shown to decrease with treatment response (Drevets et al., 2008). In particular, deep brain stimulation of the sgACC has been found to be effective in the treatment of MDD (Mayberg et al., 2005).

Beyond disease-derived models, there are several intrinsic large-scale brain networks that are altered in patients with MDD. Consistent findings suggest that the default mode network (DMN) is hyperconnected in MDD (Dutta et al., 2014; Kaiser et al., 2015) and has been linked to

rumination (Hamilton et al., 2015). The DMN includes the medial prefrontal cortex, posterior cingulate, precuneus, and angular gyrus, and is generally associated with self-referential thinking, remembering, imagining the future, and making social inferences (Buckner & DiNicola, 2019; Raichle et al., 2001). The frontal-parietal network (FPN), consisting primarily of the DLPFC and the posterior parietal cortex (PPC), is involved in cognitive control and executive function across a range of tasks (Cole et al., 2013). A meta-analysis found reduced within-network connectivity in MDD, which may reflect dysfunctional emotion regulation and goal-directed attention deficits (Kaiser et al., 2015). The affective salience network (SN) plays an important role in guiding motivated behavior by determining the biological significance of external stimuli. While the SN is primarily composed of two cortical core nodes, the anterior insula and the dorsal anterior cingulate (Seeley et al., 2007), it is also connected to other nodes such as the amygdala, caudate nucleus, and parts of the brainstem (Menon, 2011). A large meta-analysis found significant gray matter loss in the anterior insula and dorsal anterior cingulate in MDD and several other psychiatric disorders (Goodkind et al., 2015). Functional imaging studies have found hyperactivity in these same network nodes, which may reflect increased salience of negative information (Hamilton et al., 2012). The effects of ketamine on these large-scale networks, as measured by resting-state fMRI in a patient with MDD, are discussed in Chapter 4 of this thesis.

The SN is functionally coupled and structurally overlapping with the reward system, which is centered upon the ventral (nucleus accumbens) and dorsal striatum (caudate nucleus, putamen), but also includes the orbitofrontal cortex, anterior and posterior cingulate, insula, midbrain, and thalamus (Satterthwaite et al., 2015). Dysfunctional reward processing is a consistent finding in both neuroimaging and behavioral studies of MDD (Keren et al., 2018; Ng et al., 2019; Russo & Nestler, 2013). At the neural level, the reward system is hyporesponsive in patients with MDD, and has been linked to anhedonia, one of the two cardinal symptoms of MDD (Pizzagalli, 2014). Reduced engagement and connectivity of the ventral striatum and other reward-related areas results in decreased recruitment of saliency-processing regions of the SN (Pizzagalli, 2014; Satterthwaite et al., 2015). Research shows that the reward system is also impaired at the behavioral level in patients with MDD, particularly those with anhedonia (Keedwell et al., 2005; Russo & Nestler, 2013; Treadway & Zald, 2013). Reduced reward experience is often associated with blunted behavioral activation (Pizzagalli et al., 2008), creating dysfunctional feedback loops in which patients who derive less reward from positive stimuli, such as social interactions, exhibit reduced drive to seek out these situations, thus depriving themselves of the opportunity to have positive experiences (see Lewinsohn, 1974). While there is a substantial body of research on the processing of monetary incentives, music, or positive pictures as indicators of reward (Höflich et al., 2019), surprisingly few studies focus on the processing of social rewards in MDD (Hsu et al., 2015; Laurent & Ablow, 2012; Olino et al., 2015). A core component of social relationships in

humans and animals that is considered intrinsically rewarding is social touch (Ellingsen et al., 2016; Rolls et al., 2003). Therefore, in Chapter 2, I present a study examining how MDD affects the neural processing of social touch as an indicator of social reward.

In addition to these large-scale networks, several other brain regions and structures have been extensively studied because of their presumed importance in the pathophysiology of MDD. The amygdala has been a focus of mood disorder research for many decades (Price & Drevets, 2010), and its central role in the pathogenesis of MDD has been repeatedly highlighted (Russo & Nestler, 2013; Sibille et al., 2009). The amygdala has generally been found to be hyperactive and hyperconnected in patients with MDD (Hamilton et al., 2012; Janiri et al., 2020; McTeague et al., 2020). There is however also some evidence suggesting that the amygdala is instead hyporeactive, an apparent contradiction that may be due to discrepancies in contrast selection (Schulze et al., 2019). A recent large-scale study questioned the clinical relevance of altered amygdala reactivity (Tamm et al., 2022) and suggested that the amygdala may play a role in the etiology of MDD only in a subgroup of patients whose characteristics remain to be determined (Grogans et al., 2022). To further explore this question, in Chapter 4 we present the case of a patient who developed MDD in the absence of a functioning amygdala. The amygdala is structurally and functionally connected to several brain regions, including the prefrontal cortex, thalamus, caudate nucleus, and brainstem (LeDoux, 2003). In particular, it forms a complex network with the hippocampus, which has been implicated in the formation of emotional memory and mood fluctuations (Kirkby et al., 2018; Richardson et al., 2004) and is an extensively studied region in MDD research. It is critically involved in memory formation (Battaglia et al., 2011) and has been linked to cognitive symptoms in MDD (Ge et al., 2019; Hickie et al., 2005). While the role of the hippocampus in the pathogenesis of MDD has not been conclusively elucidated, reduced hippocampal volume is one of the most consistent findings in MDD research (Kempton et al., 2011) and is associated with longer duration of illness and decreased responsiveness to treatment (Caetano et al., 2004; Fu et al., 2013). In addition, functional connectivity of the hippocampus to the amygdala (Cullen et al., 2014) and the DMN (Kaiser et al., 2015) is reduced in patients with MDD. The hippocampus is also related to treatment effects. For instance, the effects of selective serotonin reuptake inhibitors (SSRIs) are thought to depend on hippocampal neurogenesis and neuroplasticity (Bessa et al., 2009; Santarelli et al., 2003), and response to electroconvulsive therapy (ECT) is associated with an increase in hippocampal volume (Oltedal et al., 2018). Given its important role in MDD, in Chapter 3 of this thesis we propose a novel approach to target the hippocampus in patients with MDD using non-invasive brain stimulation.

Treating Major Depressive Disorder

It is estimated that approximately 47% of untreated patients with MDD do not remit within 12 months (Whiteford et al., 2013). Given the severe impairment and costs associated with a prolonged depressive episode, effective treatment options are essential for individuals and society. According to current guidelines, the treatment of MDD rests on two main pillars: antidepressant medication and psychotherapy (Bundesärztekammer (BÄK) et al., 2022; Guideline Development Panel for the Treatment of Depressive Disorders, 2019). The discovery of the first antidepressants in the 1950s revolutionized the treatment of MDD. The success of these early monoamine oxidase inhibitors and tricyclics led to the development of other classes of antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), which are now widely used and have generally good response and remission rates (Cipriani et al., 2018). The other major pillar of treatment, psychotherapy, includes several different approaches to the treatment of MDD, such as cognitive behavioral, psychodynamic, or interpersonal therapy. Decades of clinical experience and empirical studies have shown that psychotherapy is effective in the treatment of MDD (Cuijpers et al., 2020). Current guidelines recommend starting treatment with either an antidepressant or psychotherapy and then switching to the other treatment or combining both after a partial or no response (Bundesärztekammer (BÄK) et al., 2022; Guideline Development Panel for the Treatment of Depressive Disorders, 2019). However, some subgroups of patients do not benefit sufficiently from conventional treatment. For example, severe side effects such as sexual dysfunction, weight gain, sleep disturbances, emotional blunting, and suicidal ideation are common to many antidepressants (Ferguson, 2001; Read & Williams, 2018). These side effects can outweigh the benefits of treatment and reduce adherence (Sansone & Sansone, 2012). In addition, many patients with treatment-resistant depression fail to achieve remission even after multiple treatment trials. One influential study found that one in three patients failed to remit after four consecutive treatment trials (Rush et al., 2006). To treat MDD more effectively and in more patients than is possible with traditional approaches, treatment alternatives are needed.

As one of the most promising treatment approaches, brain stimulation techniques have become increasingly diverse and common in recent decades. While ECT has been used to treat MDD since the mid-20th century and remains the most effective conventional antidepressant treatment (The UK ECT Review Group, 2003), rTMS is a more recently developed non-invasive brain stimulation technique that was approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in 2008 and has been adopted by current guidelines (Bundesärztekammer (BÄK) et al., 2022). While its clinical efficacy has been repeatedly demonstrated (Brunoni et al., 2017; Mutz et al., 2019), there is still potential for optimization of treatment practices with respect to stimulation protocols (Blumberger et al., 2018), number and frequency of sessions (Fitzgerald et al.,

2018; McDonald et al., 2011), targeting procedures (Fitzgerald et al., 2009), and selection of stimulation targets (Downar, 2019; Hanlon et al., 2018). Until recently, the latter aspect has been limited by the range of the TMS coil. Novel approaches use fMRI to indirectly target subsurface areas of the brain that were previously inaccessible to stimulation (Wang et al., 2014). A clinical study investigating the effects of individualized parieto-hippocampal rTMS in patients with MDD is presented in Chapter 3 using a similar approach.

At the pharmacological end of treatment options, ketamine was approved by the FDA for the use in MDD in 2019. Its rapid-acting but transient antidepressant effects make it very suitable for the acute treatment of suicidal depression (Grunebaum et al., 2018), but its mechanism of action remains unclear (Nemeroff, 2018). In Chapter 4, we present the clinical and neural effects of ketamine administration in a woman who developed MDD in the absence of a functioning amygdala.

While there are several effective treatment options for patients with MDD, the approach for choosing the right treatment for each patient ultimately amounts to trial and error. The weeks and months spent trying and adjusting medications are an additional burden for many patients. Recent research into predictive biomarkers of clinical response to different treatments is addressing this issue. Many neuroimaging studies focus on task-based or resting-state fMRI data (Phillips et al., 2015). A study that integrates these two approaches to improve prediction accuracy is presented in Chapter 5.

The four studies conducted as part of this thesis are presented in the following chapters. This is followed by the general discussion and conclusion of the thesis in Chapter 6, and the appendix containing the general abstract and my curriculum vitae.

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Chapter 2.

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Altered reward network responses to social touch in major depression

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ABSTRACT

Background: Social touch is an integral part of social relationships and has been associated with reward. Major depressive disorder (MDD) is characterized by severe impairments in reward processing, but the neural effects of social touch in MDD are still elusive. In this study, we aimed to determine whether the neural processing of social touch is altered in MDD and to assess the impact of antidepressant therapy.

Methods: Before and after antidepressant treatment, 53 MDD patients and 41 healthy controls underwent functional magnetic resonance imaging (fMRI) while receiving social touch. We compared neural responses to social touch in the reward network, behavioral ratings of touch comfort and general aversion to interpersonal touch in patients to controls. Additionally, we examined the effect of treatment response on those measures.

Results: Clinical symptoms decreased after treatment and 43.4% of patients were classified as responders. Patients reported higher aversion to interpersonal touch and lower comfort ratings during the fMRI paradigm than controls. Patients showed reduced responses to social touch in the nucleus accumbens, caudate nucleus and putamen than controls, both before and after treatment. Contrary to our hypotheses, these effects were independent of touch velocity. Non-responders exhibited blunted response in the caudate nucleus and the insula compared to responders, again irrespective of time.

Conclusions: These findings suggest altered striatal processing of social touch in MDD. Persistent dysfunctional processing of social touch despite clinical improvements may constitute a latent risk factor for social withdrawal and isolation.

Introduction

Major depressive disorder (MDD) is one of the most common mental disorders and a leading cause of years lived with disability (James et al., 2018). A core symptom of MDD, according to both DSM-V and ICD-10 criteria, is anhedonia, an array of deficits impacting various hedonic functions such as desire, motivation and pleasure (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016). Patients suffering from anhedonia show overall poorer treatment response (Spijker, Bijl, Graaf, & Nolen, 2001; Vrieze et al., 2014), possibly because preliminary evidence suggests that established pharmacotherapies, particularly selective serotonin reuptake inhibitors (SSRIs), are not well suited to treat motivational and reward-related dysfunctions in depression (Dunlop & Nemeroff, 2007; McCabe, Mishor, Cowen, & Harmer, 2010). On a neurobiological level, anhedonia has been associated with the reward network (for an overview, see Höflich, Michenthaler, Kasper, & Lanzenberger, 2019). Meta-analytical evidence from neuroimaging studies shows that patients with MDD exhibit reduced responses to monetary incentives and happy faces in various reward network nodes, such as the nucleus accumbens, caudate, putamen, insula and orbitofrontal cortex (Keren et al., 2018; Ng, Alloy, & Smith, 2019; Zhang, Chang, Guo, Zhang, & Wang, 2013). Moreover, higher reward sensitivity is associated with better outcome after psychotherapeutic interventions (Papalini et al., 2019).

Social interactions are considered natural rewards (Insel, 2003) and activate the reward network in healthy participants (Alkire, Levitas, Warnell, & Redcay, 2018; Izuma, Saito, & Sadato, 2008; Kawamichi et al., 2016; Redcay et al., 2010). Even though MDD patients often suffer from impairments in social functioning (for an overview, see Kupferberg, Bicks, & Hasler, 2016), few studies have probed the processing of social reward in MDD (Hsu et al., 2015; Olino, Silk, Osterritter, & Forbes, 2015). For instance, social touch can be inherently rewarding and is an integral part of nonverbal social communication and bonding (Hertenstein, Verkamp, Kerestes, & Holmes, 2006; Morrison, Löken, & Olausson, 2010), but it is still elusive whether MDD also modulates the processing of rewarding interpersonal, tactile stimulation.

Social distancing measures in the era of COVID-19 have vividly demonstrated the importance of interpersonal touch and the consequences of its absence. Social touch deprivation during the pandemic has been linked to increased anxiety and loneliness and resulted in a craving for interpersonal touch (von Mohr, Kirsch, & Fotopoulou, 2021). The processing of touch is mediated by different pathways in the nervous system. Myelinated Aβ-fibers enable rapid central processing and convey discriminative information, allowing for prompt responses to a stimulus. These fibers are preferentially activated by fast tactile stimulation, whereas unmyelinated C-tactile (CT) afferents respond to slow, caressing stimulation that corresponds to rewarding and affective properties of touch with increased firing frequency (McGlone, Wessberg, & Olausson, 2014). Functional magnetic resonance imaging (fMRI) studies indicate a possible association between interpersonal touch and the reward circuit. Being touched by another person, but not self-produced touch, increases neural activation in the caudate nucleus (Boehme, Hauser, Gerling, Heilig, & Olausson, 2019). Intranasal oxytocin, a neuropeptide crucially involved in social bonding, increases nucleus accumbens activity when participants believe they are being touched by their romantic partner (Kreuder et al., 2017). Similarly, increased pleasantness ratings and striatal activity have been observed when heterosexual male participants believe social touch is being delivered by a female as opposed to a male experimenter (Scheele et al., 2014; Zimmermann et al., 2019). Striatal response to affective touch seems to increase with age (May, Stewart, Paulus, & Tapert, 2014).

Besides the assumed involvement of the reward network, other pathological features of MDD

might also affect the processing of social touch. Cognitive biases, such as the negativity bias, are common in MDD and are associated with blunted responses to positive stimuli in striatal regions, the amygdala and the thalamus (Diener et al., 2012; Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). While interoceptive dysfunctions traditionally have not been regarded as a core symptom of depression, increasing evidence points toward substantial impairments in the perception of bodily signals (Harshaw, 2015; Paulus & Stein, 2010) and related neural representations in the insular cortex (Avery et al., 2014) in MDD patients. Recently, the perception of affective touch has been discussed as an interoceptive signal (Crucianelli & Ehrsson, 2023) and might therefore be sensitive to pathologically altered interoception in MDD.

The rationale of the present study was to probe whether MDD is associated with altered processing of social touch. We therefore examined patients with MDD before and after a multi-week course of antidepressant treatment and compared them to healthy controls who were examined over the same period. We employed a social touch fMRI paradigm, during which participants rated the comfort of slow and fast touch. Additionally, we assessed depressive symptom severity over the course of the study in MDD patients. We expected MDD patients to perceive social touch as less comfortable and to display decreased neural responses to social touch compared to healthy controls, particularly in regions associated with blunted neural response to reward in MDD patients: the nucleus accumbens, caudate nucleus, putamen and insula (Hsu et al., 2015; Keren et al., 2018; Zhang et al., 2013). We further hypothesized that these MDD-related alterations would decrease after treatment. Since anhedonia is associated with worse treatment outcome, we expected that non-responders to antidepressant therapy would report lower comfort ratings and exhibit lower neural responses to social touch compared to responders. We assumed that these effects would be particularly pronounced in response to slow as opposed to fast touch.

Materials and Methods

Participants and study design

Between June 2016 and April 2018, 53 patients with MDD (27 female, age 41.58 ± 13.09 years) and 41 healthy controls (22 female, age 40.61 ± 13.22 years) participated in this study (Table 1). To participate in this registered study (https://clinicaltrials.gov/show/NCT04081519), all patients had to meet DSM-IV criteria for unipolar MDD as diagnosed by an experienced psychiatrist and verified by the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), and were in-patients at the Department of Psychiatry, University Hospital Bonn, Germany. Exclusion criteria for all participants were suicidal ideation, psychotic symptoms, bipolar depression, substance abuse, eating disorders, post-traumatic stress disorder, personality disorders, neurological disorders and MRI contraindications. For healthy controls, additional exclusion criteria were any lifetime axis I or II psychiatric disorders and any past or current psychopharmacological medication. To assess a possible history of abuse and neglect, we administered the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). General attitude toward touch was assessed using a Social Touch Questionnaire (STQ; Wilhelm, Kochar, Roth, & Gross, 2001) and trait anxiety was measured using the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Patients underwent MRI scanning within 1–3 days after admission to the clinic and, again, 24 days later; accordingly, controls were examined twice at the same interval. For the duration of the study, patients received treatment according to current guidelines for MDD (DGPPN, BÄK, KBV, & AWMF, 2015; cf. supplementary information). To quantify clinical improvement, trained raters assessed depressive symptom severity on a weekly basis using the 17-item

Hamilton Depression Rating Scale (HDRS-17, Hamilton, 1960). As a measure of self-assessed depression severity, the Beck Depression Inventory (BDI-II; Beck, Steer, Ball, & Ranieri, 1996) was administered before and after the treatment course and every four weeks over a 12-week follow-up period.

Social touch paradigm

For the fMRI scans, we employed an adapted version of an established paradigm (Maier et al., 2019; McGlone et al., 2012), in which tactile stimulation was manually applied to participants at different speed levels. Stimulation was administered by an experimenter who performed vertical strokes with cotton gloved hands over 20-cm zones on the participants' shins that were marked prior to the fMRI scan. During the 4-s touch, the complete zone was covered either with a single stroke at a speed of 5 cm/s (slow, affective touch) or with four repeated strokes at a speed of 20 cm/s (fast, discriminative touch). Slow is experienced as more pleasant than fast touch (Löken, Wessberg, Morrison, McGlone, & Olausson, 2009) and specifically elicits responses by CT afferents, which are associated with rewarding properties of touch (McGlone, Wessberg, & Olausson, 2014). The experimenter was trained to keep stimulation pressure constant at both speed levels and received audio cues via headphones during the experiment to ensure constant stimulation velocity. No stimulation occurred during the no touch control condition. Each condition was repeated 20 times in randomized order. Each trial was initiated with the presentation of a white fixation cross (3 s). Fast and slow touch trials were then announced by the color of the fixation cross changing to blue (1 s). After each trial, the participant rated the comfort of the tactile stimulation on a 100-point visual analogue scale that ranged from not at all comfortable (0) to very comfortable (100) and was presented for a maximum of 5 s. To minimize context effects, participants were not informed about the identity of the person administering the stimulation and the opening of the scanner was covered with a blanket during the experiment.

MRI data acquisition

Functional and structural MRI data were acquired on a 1.5 T Siemens Avanto MRI system (Siemens, Erlangen, Germany) equipped with a 12-channel standard head coil at the Life & Brain Centre, Bonn, Germany. T2*-weighted gradient-echo planar images (EPI) images with blood-oxygen-level-dependent (BOLD) contrast were acquired during the social touch task (voxel size = 3×3×3 mm; TR = 3000 ms; TE = 50 ms; flip angle = 90°; FoV = 192 mm, matrix size = 64×64; 35 axial slices; ascending slice order with interslice gap of 0.3 mm). The first five volumes of each functional time series were discarded to allow for T1 equilibration. Additionally, a field map (voxel size = 3×3×3 mm; TR = 460 ms; TEfast = 4.76 ms; TEslow = 9.52 ms; flip angle = 60°; matrix size = 64×64; 35 axial slices; interslice gap of 0.3 mm) was acquired to correct for inhomogeneities of the magnetic field during preprocessing. Subsequently, a high-resolution structural image was acquired using a T1-weighted 3D MRI sequence (voxel size = 1×1×1 mm; TR = 1660 ms; TE = 3.09 ms; flip angle = 15°; FoV = 256 mm; matrix size = 256×256, 160 sagittal slices).

Data analysis

Data analyses focused on the comparison of patients with healthy controls, and on differences between those patients who responded (responders) and those who did not respond to antidepressant treatment (non-responders). The criterion for clinical response was defined as a $\geq$ 50% reduction in HDRS-17 scores.

The fMRI data were preprocessed and analyzed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB R2010b (The MathWorks, Natick, MA). The functional data were realigned, initially to the first image in the time series, then to the

mean of all images, and unwarped using the field map data. They were then coregistered to the anatomical volume acquired pre-treatment and normalized based on probabilistic tissue segmentation into 2-mm stereotaxic Montreal Neurological Institute (MNI) space. Subsequently, the images were smoothed using a 4-mm full width at half maximum (FWHM) Gaussian kernel. Two patients and one control had to be excluded from further fMRI analysis due to excessive head movement (> 3 mm or °) during data acquisition. This resulted in a sample size of 51 patients and 40 controls. A two-level random effects approach based on the general linear model as implemented in SPM12 was used for statistical analysis. After preprocessing, conditions based on combinations of stimulus (fast touch, slow touch) and time (pre-treatment, post-treatment) were entered into a GLM for each participant together with a constant term and six realignment parameters per session to account for subject motion. On the first level, we subtracted the respective no touch control regressor from the experimental regressors for each participant and condition. On the second level, we conducted two separate analyses of variance (ANOVA) to compare patients with controls, and responders with non-responders. For each analysis, we entered the first level contrasts in separate flexible factorial models to compute the within-subject main effects of speed (fast touch, slow touch) and time (pre-treatment, post-treatment), the between-subjects main effects of group (patients, controls) or response (responders, non-responders), and their respective interactions. For each analysis, we used multiple models to partition variance in SPM as recommended when using group-level repeated measurement designs (McFarquhar, 2019).

To validate the effect of the social touch paradigm, we performed a whole-brain analysis of the control group with an initial height threshold of $p < .001$. Peak-level p-values were then family-wise error (FWE) corrected for multiple comparisons and $p < .05$ was considered significant. The main analysis focused on a set of bilateral a priori defined regions of interest consisting of the nucleus accumbens, caudate nucleus, putamen and anterior and posterior insula. These regions were defined based on the automated anatomical labelling atlas 3 (Rolls, Huang, Lin, Feng, & Joliot, 2020). The peak-level threshold for significance was set to $p < .05$, FWE-corrected for multiple comparisons based on the size of each region of interest.

Behavioral data were analyzed using SPSS Statistics Version 27 (IBM Corp., Armonk, NY, USA) and all tests were two-tailed. To test for clinical improvement, a repeated measures ANOVA was performed for HDRS-17 ratings. In line with the fMRI analyses, we conducted separate mixed-design ANOVAs of social touch comfort ratings with touch speed (slow, fast) and time (pre-treatment, post-treatment) as within-subject factors and either group (patients, controls) or response (responders, non-responders) as a between-subjects factor to compare patients with controls or responders with non-responders, respectively. The threshold for significance was set to $p < .05$, and p-values were Bonferroni-adjusted if appropriate (Pcorr). Greenhouse-Geisser correction was applied in cases of lack of sphericity. A moderation analysis was conducted to examine the effect of potential confounders (age, sex, CTQ scores) on our analyses (cf. supplementary information). Partial eta-squared and Cohen's d were calculated as measures of effect size.

Results

Behavioral results

Analysis of HDRS-17 scores (shown in Fig. 1) showed a significant reduction over time ($F_{(2.59, 134.89)} = 36.82$, $p < .001$, $\eta_p^2 = 0.42$) in patients, 23 (43.4%) of whom met the criterion for a clinical response.

Analysis of social touch comfort ratings revealed main effects of speed ($F_{(1, 92)} = 99.46$, $p < .001$, $\eta_p^2 = 0.52$) and group ($F_{(1, 92)} = 7.12$, $p = .009$, η_p^2

= 0.07, shown in Fig. 1). As expected, comfort ratings were higher after slow, affective touch than after fast, discriminative touch. Patients overall rated social touch as less comfortable than control participants, particularly after fast ($t_{(92)}$ = 3.06, p_{corr} = .012, d = 0.64) but not slow touch ($t_{(92)}$ = 0.79, p_{corr} > .999, d = 0.16).

The analysis comparing responders and non-responders also revealed a significant main effect of speed ($F_{(1, 51)}$ = 70.86, p < .001, η_p^2 = 0.58) with higher comfort ratings for slow touch, but no other significant main effects or interactions.

Patients reported a higher aversion to social touch as measured by STQ scores than controls ($t_{(89.88)}$ = 4.89, p < .001, d = 0.97), while no difference was found between responders and non-responders ($t_{(51)}$ = 0.08, p = .936, d = 0.02).

fMRI results

In the control group, social touch relative to the no touch control condition revealed widespread activations in touch-processing networks at the whole-brain level including the insula, somatosensory cortex and supramarginal gyrus (Gazzola et al., 2012) (cf. supplementary information, Table S1).

In the region of interest analysis, patients showed diminished neural response to interpersonal touch irrespective of touch velocity and time (pre vs. post treatment) in the bilateral nucleus accumbens (peak MNI coordinates (x, y, z): −6, 16, −4; $F_{(1, 89)}$ = 15.59, p_{FWE} = .010, η_p^2 = 0.14; MNI: 4, 14, −2; $F_{(1, 89)}$ = 11.68, p_{FWE} = .041, η_p^2 = 0.11; shown in Fig. 2A) and in the bilateral caudate nucleus (MNI: −14, 20, 12; $F_{(1, 89)}$ = 21.88, p_{FWE} = .005, η_p^2 = 0.19; MNI: 10, 10, 14; $F_{(1, 89)}$ = 21.64, p_{FWE} = .006, η_p^2 = 0.20; shown in Fig. 2B) compared to controls. Furthermore, we found a significant interaction between speed, time and group in the left putamen (MNI: −28, 0, 2; $F_{(1, 89)}$ = 19.23, p_{FWE} = .016, η_p^2 = 0.18). Post-hoc tests revealed decreased responses to fast touch in patients compared to controls at baseline ($t_{(89)}$ = 3.06, p_{corr} = .036, d = 0.65) but not after treatment ($t_{(89)}$ = 0.38, p_{corr} > .999, d = 0.08).

Secondly, we examined the effect of treatment response. The main effect of treatment response indicated reduced activity during social touch in the right caudate nucleus (MNI: 22, 20, 12; $F_{(1, 49)}$ = 17.86, p_{FWE} = .039, η_p^2 = 0.26, shown in Fig. 3A) in non-responders compared to responders. A significant interaction between speed and group in the left anterior insula (MNI: -26, 26, 2; $F_{(1, 49)}$

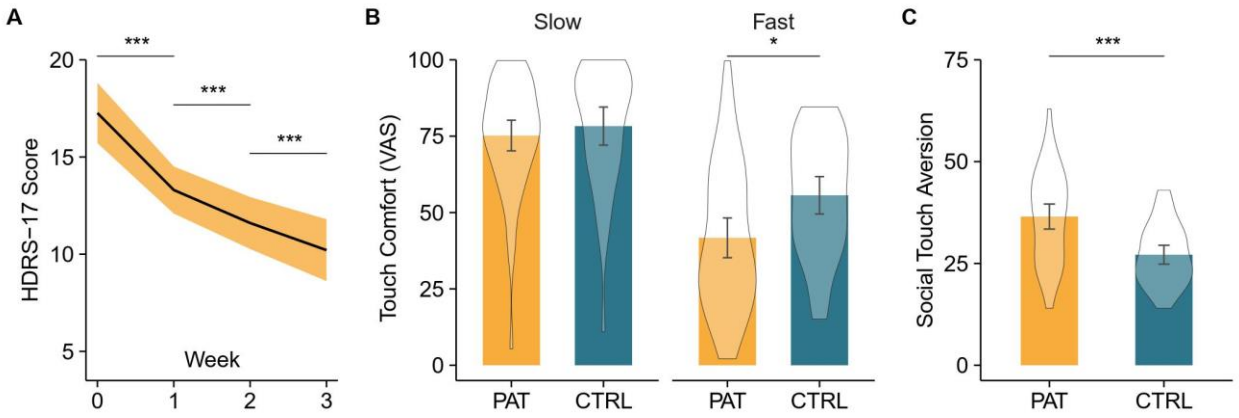

Fig. 1. Depression symptom severity as measured by Hamilton Depression Rating Scale (HDRS-17) scores decreased over the treatment course (**A**). Patients rated fast but not slow touch as significantly less comfortable than controls (**B**). At baseline patients reported a higher aversion to social touch than controls (**C**). Indicated p-values are Bonferroni corrected. Violin plots are kernel density plots comparable to histograms with infinitely small bin sizes. The ribbon and error bars indicate 95%-confidence intervals. Abbreviations: CTRL, controls; PAT, patients; VAS, visual analogue scale. *p < .05, ***p < .001.

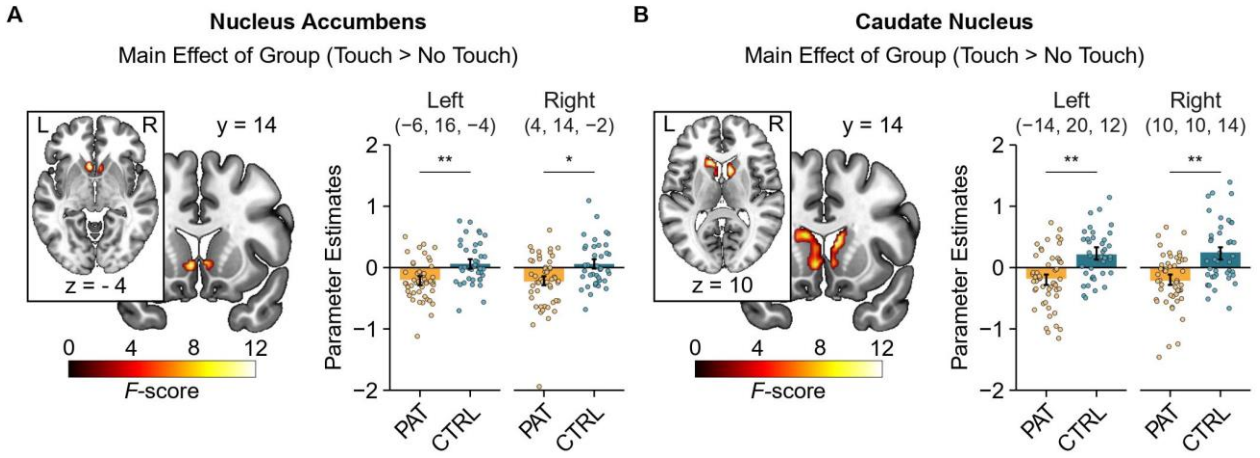

Fig. 2. Patients exhibited decreased neural responses to social touch in the bilateral nucleus accumbens (**A**) and caudate nucleus (**B**) across time (i.e. before and after treatment) compared with healthy controls. Significant clusters are displayed at a peak-level threshold of $p < .05$ uncorrected. Parameter estimates are displayed for peak voxels. Error bars indicate 95%-confidence intervals. Abbreviations: CTRL, controls; PAT, patients. *$p < .05$, **$p < .01$.

= 20.01, $p_{FWE} = .022$, $\eta_p^2 = 0.30$, shown in Fig. 3B) showed that non-responders exhibited reduced activation during slow touch compared to responders ($t_{(49)} = 3.75$, $p_{corr} = .002$, $d = 1.06$), but not during fast touch ($t_{(49)} = 0.01$, $p_{corr} > .999$, $d < 0.01$). For the interaction of speed, time and group, we found two significant clusters in the right putamen (MNI: 32, -2, -8; $F_{(1, 49)} = 19.33$, $p_{FWE} = .032$, $\eta_p^2 = 0.28$; MNI: 30, -6, 10; $F_{(1, 49)} = 18.20$, $p_{FWE} = .046$, $\eta_p^2 = 0.27$). Post-hoc tests revealed no significant effects after Bonferroni correction (all $p_{corr} > 0.05$). See supplementary information for main effects of time and speed.

The observed behavioral and neural effects of group were not significantly moderated by age or sex. We only found a significant suppressor effect of CTQ scores for the group effect on nucleus accumbens responses to social touch (cf. Supplement).

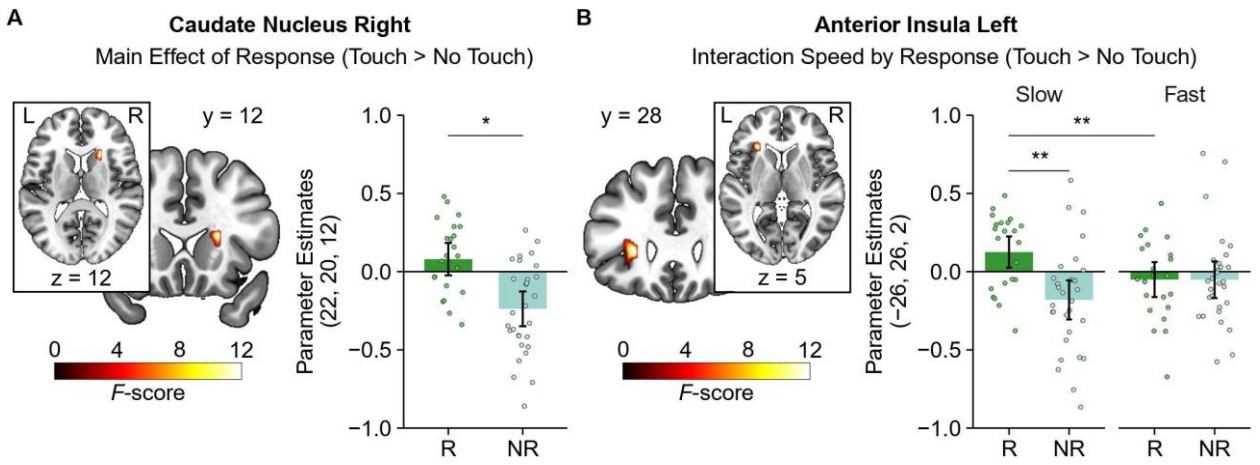

Fig. 3. Treatment responders exhibited heightened neural responses to social touch in the right caudate nucleus across time compared with non-responders (**A**). Responses to slow touch in the left anterior insula were increased in responders across time compared with non-responders (**B**). Significant clusters are displayed at a peak-level threshold of $p < .05$ uncorrected. Parameter estimates are displayed for peak voxels. Indicated p-values are Bonferroni corrected. Error bars indicate 95%-confidence intervals. Abbreviations: NR, non-responders; R, responders. *$p < .05$, **$p < .01$.

Discussion

To our knowledge, this is the first study to examine the processing of social touch in depression. Confirming our first hypothesis, MDD patients reported a higher aversion to interpersonal touch, experienced it as less comfortable and exhibited reduced neural activation in the reward network compared to healthy controls. Specifically, we found decreased responses to social touch in the nucleus accumbens, caudate nucleus and putamen. Contrary to our expectations, the differences in the nucleus accumbens and caudate nucleus persisted even after treatment. In line with our second hypothesis, non-responders to antidepressant treatment displayed reduced activation in the caudate nucleus, anterior insula and putamen.

Unexpectedly, patients reported decreased comfort ratings compared to controls only after fast touch. This is in line with a study that found differences in comfort ratings between participants with varying levels of childhood maltreatment during fast but not slow touch (Maier et al., 2019). These findings could be related to the use of the attribute 'comfortable'. Sailer, Hausmann, and Croy (2020) have shown that ratings of the attributes 'pleasant' and 'not burdensome' vary with touch velocity, but a similar modulation was not evident for other emotional attributes such as 'exciting'. In addition, possible group differences in comfort ratings after slow touch might be concealed by a ceiling effect due to high ratings in both groups. Neural effects in the nucleus accumbens and caudate nucleus were independent of touch velocity, indicating that MDD-related alterations in reward-associated brain structures are not restricted to social touch with C tactile-optimized velocity. However, in line with our hypothesis, non-responders exhibited reduced reactivity in the insula specifically during slow touch compared to responders.

These findings contribute to the notion that the processing of social reward in general (Hsu et al., 2015; Laurent & Ablow, 2012; Olino et al., 2015) and of interpersonal touch in particular is altered in MDD patients. Similar to patients with autism spectrum disorder who derive less pleasure from and engage in touch less frequently than healthy controls (Croy, Geide, Paulus, Weidner, & Olausson, 2016), the reported aversion to social touch in everyday life and altered reward-associated responses to social touch might relate to the emergence and reinforcement of social isolation in depression. MDD patients typically withdraw from their social circles, thus leading to smaller social network size (Elmer & Stadtfeld, 2020; Visentini, Cassidy, Bird, & Priebe, 2018) and increased loneliness (Achterbergh et al., 2020; Meltzer et al., 2013), which is associated with more severe symptoms and a worse prognosis (Holvast et al., 2015; Wang, Mann, Lloyd-Evans, Ma, & Johnson, 2018). This disruption of social functioning can have devastating consequences, as both social isolation and loss of social support have been linked to suicidal outcomes (Calati et al., 2019; Kim & Kihl, 2021). However, we cannot conclusively infer from reduced striatal activation that social touch is less rewarding in MDD (Poldrack, 2006). For instance, striatal activation may also reflect cognitive biases or the salience of social touch. Future studies are warranted to decipher the specific mechanisms that result in decreased comfort ratings of social touch.

Interpersonal touch is a crucial component of romantic relationships (Jakubiak & Feeney, 2017). Altered processing of social touch might blunt the drive to seek physical closeness or even result in an avoidance of interpersonal touch, which could negatively affect sexuality and the overall satisfaction in romantic relationships (Bell, Daly, & Gonzalez, 1987; Gulledge, Gulledge, & Stahmannn, 2003; Muise, Giang, & Impett, 2014). Eventually, this might lead to separation, which is again a predictor for worse illness trajectories (Law & Sbarra, 2009; Woods et al., 2021) and increased risk for suicidal behaviors (Calati et al., 2019).

Notably, the observed alterations of activity in the nucleus accumbens and caudate nucleus did not change over the treatment course. This could suggest a stable, phenotypical trait characterizing MDD patients that persists even after clinical improvement. This is in line with observations in remitted MDD patients who exhibit lasting impairments both in behavioral (Pechtel, Dutra, Goetz, & Pizzagalli, 2013; Weinberg & Shankman, 2017) and neural markers of reward processing (Dichter, Kozink, McClernon, & Smoski, 2012; Geugies et al., 2019; McCabe, Cowen, & Harmer, 2009), consistent with the persistence of anhedonia even after recovery from depression (Conradi, Ormel, & Jonge, 2011; Schrader, 1997). Another explanation for the persistence of these alterations might be the relatively short time between the two fMRI sessions. While depressive symptoms went down by 40.4% across participants, a longer observation period perhaps would have allowed for further clinical improvement and behavioral adaptations. Likewise, more pronounced alterations for slow touch were only evident in non-responders to treatment.

Considering the effect of response, we found reduced caudate nucleus and insula activation during social touch in non-responders both before and after treatment, indicating that those who show greater alterations in striatal and insular reward processing might be less responsive to established antidepressant treatment, both in terms of clinical recovery and normalization of altered processing of social rewards. In the light of the devastating consequences that can arise from social isolation, this emphasizes the need for targeted interventions that focus on reward processing deficits. For instance, behavioral activation therapy (Hopko, Lejuez, Ruggiero, & Eifert, 2003) has been shown to be effective in the treatment of depression (Luoto et al., 2018) and seems to affect striatal responses (Dichter et al., 2009). Furthermore, body-based interventions in the form of massage therapy (Arnold, Müller-Oerlinghausen, Hemrich, & Bönsch, 2020) and body psychotherapy (Röhricht, Papadopoulos, & Priebe, 2013) are promising approaches to specifically target disturbed body awareness and desynchronization in depression (Fuchs, 2001; Fuchs & Schlimme, 2009).

Our findings should be interpreted in light of some limitations. While reward network activation during touch is in line with studies in healthy controls using various kinds of social touch conditions (Boehme et al., 2019; Nummenmaa et al., 2016; Scheele et al., 2014; Zimmermann et al., 2019), other studies did not find activation of reward-related brain regions during social touch suggesting that the rewarding effects of social touch paradigms are not unambiguous (e.g., Lamm, Silani, & Singer, 2015). Because it is hard to dispute that an embrace from a loved one or the caresses of a romantic partner can be perceived as rewarding, this raises the question of the ecological validity of social touch paradigms, particularly in fMRI studies. While it is challenging to implement paradigms that model social rewards more accurately, previous studies examined social touch in close friends or romantic couples to increase ecological validity (Flores, Alarcón, Eckstrand, Lindenmuth, & Forbes, 2022; Kreuder et al., 2017; Nummenmaa et al., 2016). High experimental standardization can be retained using cover stories (Kreuder et al., 2017). Because our current findings were acquired in a highly standardized MRI setting, which might be anxiety-inducing especially for MDD patients, they should be validated by future studies using more naturalistic social touch paradigms. Future studies should also address a number of questions to aid contextualization of our findings: firstly, future research should ask participants to specifically rate reward in addition to comfort after receiving social touch, to gain a more multifaceted picture of participants' subjective experience; secondly, control conditions should be employed to explore whether the observed alterations in MDD are specific to social touch or extend to the processing of non-social tactile stimulation; and thirdly, future studies should also examine the

impact of MDD on the processing of social touch in other brain regions associated with social touch and mental disorders, such as the superior temporal gyrus (Davidovic, Jönsson, Olausson, & Björnsdotter, 2016; Strauss et al., 2019). Finally, antidepressant treatment in this study was naturalistic and heterogeneous, and its particular influence on our findings therefore remains uncertain. However, the treatment was in line with current guidelines for the therapy of depression reflecting clinical realities.

In conclusion, our findings elucidate the role of social touch processing in depression and indicate that touch-related changes may persist even after significant improvements of other symptoms. Collectively, our results demonstrate alterations of the experienced comfort of and neural response to social touch in patients with MDD. Moreover, these effects may constitute a risk factor for non-response and may persist even after recovery, leading to ongoing disruptions in social functioning. Future studies should corroborate these findings and might inform new treatment avenues targeting social reward and disturbances of body awareness.

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Conflicts of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Table 1. Demographic and clinical data for patients and controls

	Patients (n = 53)	Controls (n = 41)	*p*-value
Sex (male/female)	26/27	19/22	0.837
Age (in years)	41.58 (13.09)	40.61 (13.22)	0.722
Education (in years)	15.89 (5.42)	17.16 (3.76)	0.203
Handedness (left/right)	4/49	3/38	1.000
Duration current depressive episode (in years)	4.66 (5.52)		
Number of depressive episodes	3.15 (2.83) (n = 47)[1]		
HDRS-17			
Baseline	17.26 (5.63)	0.23 (0.58)	< 0.001
After treatment	10.21 (5.78)		
Improvement (in percent)	40.40 (28.67)		< 0.001
BDI-II			
Baseline	33.34 (8.75)	2.76 (3.27)	< 0.001
After treatment	19.28 (10.80)		
Improvement (in percent)	41.70 (28.25)		< 0.001
4 weeks after treatment[2]	22.28 (11.59) (n = 50)[1]		< 0.001
8 weeks after treatment[2]	23.73 (10.80) (n = 49)[1]		< 0.001
12 weeks after treatment[2]	24.37 (9.97) (n = 46)[1]		< 0.001
CTQ	45.08 (16.26)	29.68 (4.6)	< 0.001

Values are given as frequencies or as means (SD). The *p*-values report the significance levels reached for independent *t*-tests or Fisher's exact tests comparing groups or for paired *t*-tests comparing improvement within patients. [1] Sample size in parentheses indicates number of complete responses. [2] BDI-II Follow-up measurements are compared to baseline scores. The significance threshold was set at $p < .05$.

Supplementary Material

Supplementary Methods

Participants

Patients between 18 and 60 years of age who fulfilled criteria for unipolar major depressive disorder for at least four weeks were eligible for inclusion. Physiological exclusion criteria were metal in the brain or the skull, a cardiac pacemaker or intracardiac lines, medication infusion devices, heart or brain surgery, pregnancy, or any condition resulting in increased intracranial pressure, traumatic brain injury, a history of epilepsy, cerebral aneurysms, dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, stroke or transient ischemic attack (within the last two years). Psychiatric exclusion criteria included substance-induced depression, a history of substance abuse, psychotic episodes, bipolar disorder, anorexia, posttraumatic stress disorder (current or within the last 12 months), personality disorders, claustrophobia, or previous antidepressant treatment with repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (within the last 3 months), vagus nerve stimulation or deep brain stimulation. All patients received concomitant multimodal treatment according to current MDD guidelines. The majority of patients (N = 47) received pharmacotherapy for the duration of the study: selective serotonin reuptake inhibitors (N = 18), selective serotonin-norepinephrine reuptake inhibitor (N = 15), atypical antidepressants (N = 32), atypical antipsychotics (N = 10), anticonvulsants (N = 11), tricyclic antidepressants (N = 5), levothyroxine (N = 4), antihistamines (N = 2), benzodiazepine (N = 1), lithium (N = 1), monoamine oxidase inhibitor (N = 1), norepinephrine reuptake inhibitor (N = 1). In addition, all patients underwent repetitive transcranial magnetic stimulation (rTMS), group psychotherapy and cognitive training (Strobach & Huestegge, 2017). The data analyzed in this study were acquired as part of a larger clinical trial comparing different rTMS protocols (for further information see (Mielacher et al., 2020)). Patient groups were collapsed for the purpose of the present study. While the present paper uses an adapted version of the social touch paradigm as used by Maier et al. (Maier et al., 2019), independent samples were recruited for both studies.

See Table S1 for a characterization of responders and non-responders.

fMRI paradigm

Stimulus presentation and response collection was implemented using Presentation 14 software (Neurobehavioral Systems, Albany, CA), liquid crystal display video goggles (Nordic NeuroLab, Bergen, Norway) and an MRI-compatible response box. After the MRI scan participants were

asked to rate their positive and negative affect on the Positive Affect Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988).

Statistical analysis

Quantitative data were compared by repeated measures and mixed-design analyses of variance (ANOVA) and dependent and independent *t*-tests. Pearson's product-moment correlation was used for correlation analysis. Partial eta-squared was calculated as measures of effect size. For qualitative variables, Fisher's exact tests were used. All reported *p*-values are two-tailed and values of $p < 0.05$ were considered significant.

fMRI analysis

After the second level ROI analysis, parameter estimates were extracted from peak activation voxels for correlational and moderation analyses as well as display purposes (cf. Figure 2 and Figure 3). We used an in-house MATLAB script to extract parameter estimates from the appropriate first level within-subject contrast maps.

To evaluate the effects of the touch paradigm, we performed a whole-brain analysis in controls using the first level contrasts [Touch > No Touch] and [No Touch > Touch] and one-sample *t*-tests on the second level. A threshold for significance of $p < .05$ was used, family-wise error corrected (FWE) for multiple comparisons. The results of this analysis can be found in Table S2.

To answer the question whether controls exhibit striatal activation during social touch we conducted a region of interest analysis in the bilateral caudate nucleus and nucleus accumbens using the first level contrasts [Touch > No Touch] and one-sample *t*-tests on the second level. The peak-level threshold for significance was set to $p < .05$, FWE-corrected for multiple comparisons based on the size of each region of interest.

fMRI baseline analysis

To corroborate our main findings, we conducted post-hoc analysis of baseline fMRI data. First level contrasts averaged over both speed levels at baseline were analyzed using independent t-tests comparing patients to controls ([patients > controls], [controls > patients]) and responders to non-responders ([responders > non-responders], [non-responders > responders]) using SPM. In accord with our main analysis, we focused on the same set of regions of interest. The peak-level threshold for significance was again set to $p < .05$, FWE-corrected for multiple comparisons based on the size of each region of interest.

ICC test-retest reliability of fMRI scans

To assess the test-retest reliability of the fMRI scans, we masked first-level activation maps during touch for pre and post scans with postcentral gyrus, nucleus accumbens and caudate nucleus ROIs and calculated mean parameter estimates for each healthy control, time point and ROI. Then, we computed two-way mixed average score intraclass correlation coefficients using a consistency definition (ICC(3,2)) for the three ROIs (Caceres et al., 2009; Portney & Watkins, 2009).

Correlational analysis

For patients, controls, responders and non-responders, Pearson's product-moment correlation was used to test associations between fMRI peak-voxel parameter estimates from the region of interest analysis and comfort ratings, social touch aversion, HDRS-17 baseline scores and HDRS-17 item number 7 as a measure of baseline anhedonia. This item assesses “loss of interest in activities”, “decrease in actual time spent on activities” and “experiencing pleasure” (Hamilton, 1960).

Moderation analysis

We conducted a moderation analysis, using the PROCESS macro for SPSS, version 3.1 (Hayes, 2013) to test for the potential confounding influence of age, sex, CTQ and STAI scores as well as anxiety during the MRI scan as measured by the respective item of the PANAS on the effect of group (patients, controls) and clinical response (responders, non-responders) on behavioral ratings, touch aversion and parameter estimates extracted from the fMRI analysis. All potential moderators were assessed individually in separate models. Moderation was assumed when the interaction between the predictor (group or response) and the moderator was significant. Additionally, the Johnson-Neyman technique was applied to determine the conditional threshold of significance for any moderation effects.

Supplementary Results

Clinical results

When analyzing Hamilton Depression Rating Scale (HDRS) scores separately for responders and non-responders, both groups showed clinical improvement (responders: $F_{(2.11,\ 46.37)} = 48.54$, $p < .001$, $\eta_p^2 = .69$; non-responders: $F_{(2.13,\ 61.90)} = 8.63$, $p < .001$, $\eta_p^2 = .23$). Planned contrasts revealed continuous weekly improvement for responders (all p's < .001), while non-responders only improved after the first week of treatment ($p = .018$) but not over the following weeks (all p's > .200).

fMRI results

In addition to the effects reported in the main text, we found a main effect of time (pre vs. post treatment) in the right anterior insula while comparing patients and controls. Activation to social touch decreased over the three weeks of treatment (peak Montreal Neurological Institute coordinates (x, y, z): 36, 26, −4; $F_{(1, 89)}$ = 17.80, p_{FWE} = .024, η_p^2 = 0.17). We also found main effects of speed in the left nucleus accumbens (MNI: -6, 6, −4; $F_{(1, 89)}$ = 12.97, p_{FWE} = .030, η_p^2 = 0.13) and the left posterior insula (MNI: -34, 2, 12; $F_{(1, 89)}$ = 25.94, p_{FWE} = .001, η_p^2 = 0.22), both with heightened responses to slow touch compared with fast touch. Additionally, a significant main effect of speed in two clusters in the right posterior insula (MNI: 36, -14, 22; $F_{(1, 89)}$ = 20.25, p_{FWE} = .009, η_p^2 = 0.19; MNI: 34, -20, 20; $F_{(1, 89)}$ = 17.63, p_{FWE} = .025, η_p^2 = 0.17) showed an inverted pattern, with increased responses to fast touch compared with slow touch.

For the model comparing responders and non-responders, we found main effects of speed in the left caudate nucleus (MNI: -18, 20, 12; $F_{(1, 49)}$ = 19.14, p_{FWE} = .029, η_p^2 = 0.29) and the left (MNI: -36, 0, 12; $F_{(1, 49)}$ = 21.78, p_{FWE} = .012, η_p^2 = 0.32) and right posterior insula (MNI: 36, -16, 22; $F_{(1, 49)}$ = 27.13, p_{FWE} = .002, η_p^2 = 0.37). While the cluster in the left posterior insula exhibited increased response to slow touch compared with fast touch, the reverse pattern was evident in the clusters in the right posterior insula and the caudate nucleus.

In accord with our main findings, the baseline analysis of the contrast [controls > patients] revealed a significant effect in the bilateral caudate nucleus (MNI: -12, 20, 10; $t_{(89)}$ = 3.81, p_{FWE} = .041, d = 0.80; MNI: 8, 16, 6; $t_{(89)}$ = 4.20, p_{FWE} = .013, d = 0.88). Additionally, we found two significant clusters in the right posterior insula (MNI: 38, -2, 16; $t_{(89)}$ = 3.90, p_{FWE} = .030, d = 0.82; MNI: 42, -8, 4; $t_{(89)}$ = 3.79, p_{FWE} = .042, d = 0.79). However, no significant effect was found for the nucleus accumbens or any of the other regions of interest. Baseline analysis did not reveal any significant effects for the contrast [patients > controls], nor for the comparison of responders and non-responders to antidepressant treatment ([responders > non-responders], [non-responders > responders]).

Controls exhibited increased neural responses to social touch compared to the no touch control condition in two significant clusters in the left (MNI: -18, 18, 8; $t_{(39)}$ = 5.23, p_{FWE} = .002, d_z = 0.83; MNI: -20, 0, 20; $t_{(39)}$ = 5.11, p_{FWE} = .002, d_z = 0.81) and one in the right caudate nucleus (MNI: 16, 10, 10; $t_{(39)}$ = 4.69, p_{FWE} = .007, d_z = 0.74) but not in the nucleus accumbens (Figure S1).

ICC test-retest reliability

ICC analysis suggest fair to good test-retest reliability between the fMRI scans in the postcentral gyrus (ICC(3,2) = .56, $F_{(39,39)}$ = 2.29, p = .006), nucleus accumbens (ICC(3,2) = .60, $F_{(39,39)}$ = 2.52, p = .002) and caudate nucleus (ICC(3,2) = .59, $F_{(39,39)}$ = 2.43, p = .003) (Cicchetti, 1994).

Correlational analysis

No correlations survived Bonferroni correction.

Moderation effects

We found that none of our predictors significantly moderated the effect of group or treatment response on any of our behavioral ratings or touch aversion (all *p*'s > .05). For the moderation analysis of the fMRI results, we found that childhood trauma questionnaire (CTQ) scores had a moderating influence on the effect of group on parameter estimates in the right nucleus accumbens ($t_{(89)}$ = 2.17, p = .033). The Johnson-Neyman technique revealed that the relationship between group and parameter estimates in the right nucleus accumbens was significant when CTQ scores were less than 30.33. This suggests that the occurrence of clinical depression does not impact the response of the nucleus accumbens to social touch in who have suffered from more severe childhood maltreatment. No significant moderation effects were observed for parameter estimates in any other region.

Supplementary tables and figures

Table S1. Demographic and clinical data for responders and non-responders to treatment

	Responders (n = 23)	Non-Responders (n = 30)	*p*-value
Sex (male/female)	12/11	15/15	1.000
Age (in years)	43.57 (13.73)	40.07 (12.60)	0.340
Education (in years)	15.39 (3.87)	16.27 (6.39)	0.565
Handedness (left/right)	2/21	2/28	1.000
Duration current depressive episode (in years)	4.51 (4.94)	4.77 (7.60)	0.889
Number of depressive episodes	2.36 (2.17) (n = 21)[a]	3.79 (3.16) (n = 26)[a]	0.084
HDRS-17			
Baseline	16.48 (5.33)	17.87 (5.86)	0.378
After treatment	5.61 (2.39)	13.73 (5.09)	< 0.001
Improvement (in percent)	65.36 (12.14)	21.26 (22.11)	< 0.001
BDI-II			
Baseline	32.04 (9.52)	34.33 (8.14)	0.350
After treatment	13.35 (7.31)	23.83 (10.91)	< 0.001
Improvement (in percent)	57.96 (18.82)	29.23 (28.14)	< 0.001
4 weeks after treatment	19.13 (12.08)	24.96 (10.64) (n = 27)[a]	0.076
8 weeks after treatment	20.73 (10.43) (n = 22)[a]	26.19 (10.65) (n = 27)[a]	0.078
12 weeks after treatment	23.77 (8.42) (n = 22)[a]	24.92 (11.36) (n = 24)[a]	0.702
CTQ baseline	42.57 (13.74)	47.00 (17.95)	0.330

Values are given as frequencies or as means (SD). The *p*-values report the significance levels reached for independent *t*-tests or Fisher's exact tests comparing groups or for paired *t*-tests comparing improvement within patients. [a] Sample size in parentheses indicates number of complete responses. The significance threshold was set at $p < .05$.

Table S2. Whole-brain activation in healthy controls (Touch vs. No Touch)

Region	Right/left	Cluster size (voxels)	*t*-score	MNI Coordinates			*p*-value
				x	y	z	
Touch > No Touch							
Insula	L	14977	15.30	-40	-4	8	< 0.001
Postcentral Gyrus	L		14.18	-64	-22	22	< 0.001
Supramarginal Gyrus	L		13.72	-56	-22	18	< 0.001
Supramarginal Gyrus	R	9303	13.56	52	-28	24	< 0.001
Supramarginal Gyrus	R		12.70	60	-24	22	< 0.001
Postcentral Gyrus	R		12.61	18	-42	74	< 0.001
Middle Temporal Gyrus	R	842	11.75	54	-60	4	< 0.001
Cerebellum VI	R	1669	10.53	24	-52	-22	< 0.001
Cerebellum VI	R		8.78	18	-72	-18	< 0.001
Cerebellum VI	R		8.53	24	-64	-20	< 0.001
Middle Temporal Gyrus	L	609	9.15	-50	-66	6	< 0.001
Cerebellum VI	L	167	9.09	-24	-62	-22	< 0.001
Cerebellum VI	L		8.84	-16	-70	-20	< 0.001
Thalamus	L	309	7.34	-12	-16	4	0.001
Middle Frontal Gyrus	R	466	7.02	44	48	8	0.002
No Touch > Touch							
Inferior Parietal Gyrus	L	906	7.52	-36	-76	42	< 0.001
Angular Gyrus	L		7.33	-36	-66	38	0.001
Precuneus	R	1131	6.69	8	-48	40	0.005
Middle Cingulate Cortex	L		6.26	-2	-42	44	0.018
Middle Temporal Gyrus	L	629	6.39	-52	-38	-2	0.012
Middle Temporal Gyrus	L		6.33	-62	-42	-4	0.014
Inferior Occipital Gyrus	L	157	5.91	-22	-92	-6	0.045

An initial cluster-forming height threshold of $P < 0.001$ was used. Only clusters with FWE-corrected Ps < 0.05 on peak level are listed. Abbreviations: MNI, Montreal Neurological Institute.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

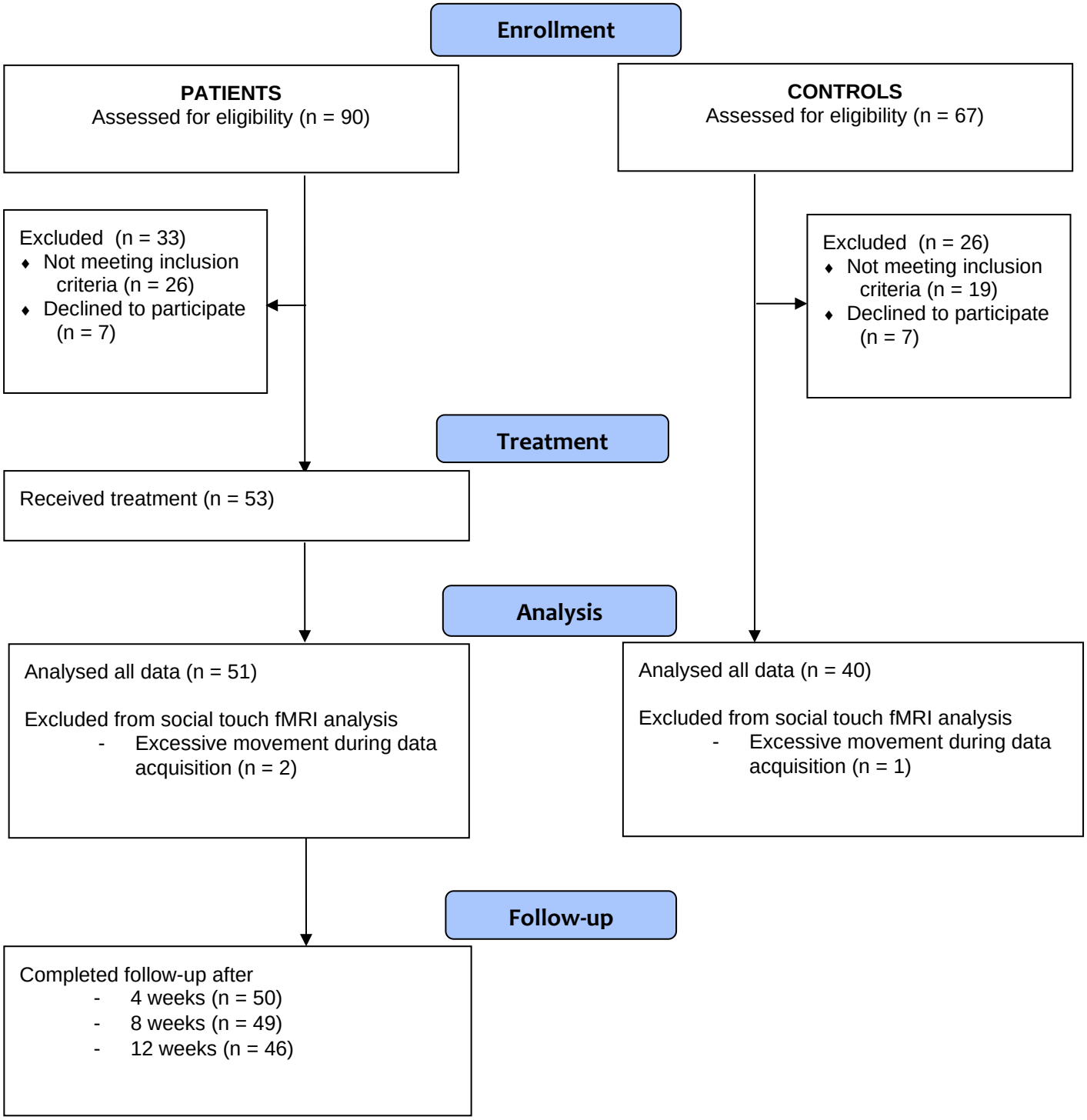

Fig. S1. CONSORT diagram.

References Chapter 2

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Chapter 3.

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Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder

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ABSTRACT

Background: While intermittent theta-burst stimulation (iTBS) has been shown to improve symptoms of major depressive disorder (MDD), research has been largely limited to targeting the dorsolateral prefrontal cortex (DLPFC). New approaches utilize patients' individual resting state fMRI data in order to identify superficial cortical stimulation targets functionally connected to deeper brain regions, thus enabling the modulation of previously inaccessible targets for antidepressant therapy.

Objective: To improve iTBS treatment of MDD by inducing plasticity in the hippocampus through stimulation of an individually mapped, functionally interconnected site in the parietal cortex.

Methods: Fifty-three MDD patients were randomized to three treatment groups and underwent 15 sessions of iTBS to the left DLPFC. This was augmented by adding a second daily session of (i) stimulation over individualized parietal targets functionally connected to the hippocampus, (ii) left DLPFC stimulation, or (iii) sham stimulation. To evaluate the improvement of treatment, we assessed depression severity, neuropsychological performance, functional connectivity and neural activation during an associative memory paradigm pre- vs. post-treatment.

Results: Augmentation of left DLPFC stimulation by parieto-hippocampal stimulation increased functional connectivity between hippocampus and DLPFC as well as encoding-related hippocampal activation; the latter was associated with better performance during a spatial planning task dependent on prefrontal and hippocampal contributions. Depressive symptoms improved in all groups after treatment, with best clinical outcomes following twice-daily left DLPFC stimulation.

Conclusion: Functional connectivity-guided stimulation of the hippocampus may serve as an adjunct to iTBS in order to target the cognitive symptoms of MDD.

Introduction

Intermittent theta burst stimulation (iTBS) [1] is a well-established repetitive transcranial magnetic stimulation (rTMS) protocol effective for the treatment of major depressive disorder (MDD) [2,3]. Many iTBS studies have focused on antidepressant effects of left dorsolateral prefrontal cortex (DLPFC) stimulation [3–5], whereas the curative potential of targets outside the DLPFC has received less attention [6]. Target selection has, traditionally, been constrained to regions near the surface of the brain due to the limited TMS pulses range (2-3 cm from the scalp [7]). Recent approaches utilize—in line with the emerging field of personalized psychiatry—patients' individual fMRI data to identify superficial cortical stimulation targets functionally connected to brain structures that are too deep to be targeted directly, thus enabling a top-down-propagation of stimulation effects [8–10].

This functional network-guided approach allows for the modulation of new potential targets for antidepressant treatment, such as the hippocampus, which is considered a crucial node of the neuroanatomic circuitry underlying MDD [11] and therefore a promising target for modulation. Hippocampal volume reduction is a consistently reported abnormality in MDD [12] and is associated with longer illness duration [13] as well as reduced treatment responsiveness [14]. Conversely, electroconvulsive therapy (ECT) increases hippocampal volume, although it remains disputed whether or not this effect is causally related to clinical improvement [15,16]. Hippocampal functional connectivity to the limbic system [17,18] and to the default mode network [19] are aberrant in MDD patients; functional connectivity has been found to predict response to antidepressant treatment, including pharmacotherapy [20] and ECT [21]. Lastly, animal studies have further emphasized the importance of hippocampal neurogenesis [22] and synaptic plasticity [23] for the mechanism of action of serotonergic antidepressants. Functionally, the hippocampus has indisputably been linked to cognitive function and, specifically, memory [24] which is commonly impaired in MDD [25]. Unsurprisingly, hippocampal volume reduction in MDD patients is associated with decreased memory performance [26], but both improve after antidepressant treatment [27].

Previous studies in healthy individuals have utilized fMRI data to determine individualized parietal rTMS targets functionally connected to the hippocampus in order to modulate hippocampal functional connectivity [10,28], memory-associated hippocampal network activity [29,30] and performance in various memory domains [10,28–32]. However, no study to date has investigated the therapeutic potential of this functional connectivity-based approach in MDD patients. Here, we tested for potentially synergistic effects of stimulation of individualized targets in the lateral parietal cortex (iLPC) functionally connected to the hippocampus as an add-on to iTBS of the left DLPFC with regard to depressive symptom severity, cognition and hippocampal plasticity. The latter was addressed by measuring hippocampal responses and connectivity during an associative memory task. Parieto-hippocampal stimulation was compared to sham stimulation as an add-on to active DLPFC stimulation and twice-daily DLPFC stimulation. We hypothesized that the former would improve cognitive performance and modulate both hippocampal functional connectivity and memory-related functional hippocampus activity and increase the therapeutic effect of iTBS on depressive symptoms. A second daily DLPFC stimulation session served as a second control condition, which we hypothesized would enhance improvement of depressive symptoms compared to the sham condition without influencing cognitive performance or hippocampus activity and connectivity.

Methods and Materials

Subjects

After giving written informed consent, 53 patients (28 female, age 42.02 ± 12.94 years) with

unipolar MDD participated in this study between June 2016 and April 2018. Diagnosis was verified using the Mini-International Neuropsychiatric Interview (MINI; [33]) according to DSM-IV criteria. All participants were in-patients at the Department of Psychiatry, University of Bonn, Germany, and received concomitant multimodal treatment including pharmacotherapy (see Supplementary Material, Table S1), group psychotherapy and daily cognitive training [34]. Demographic and clinical data for all study patients can be found in Table 1. The study was approved by the institutional review board of the Medical Faculty of the University of Bonn and was conducted in accordance with the Declaration of Helsinki.

Study design

We conducted a randomized, double-blind, sham-controlled, registered clinical study (https://clinicaltrials.gov/show/NCT04081519) in which patients received three weeks of iTBS treatment and underwent clinical and neuropsychological assessment as well as MRI scanning prior and subsequent to the treatment course (cf. Figure 1). Upon study inclusion patients were randomly assigned to either the DLPFC-iLPC (n = 18; 8 female), DLPFC-DLPFC (n = 17; 11 female) or DLPFC-SHAM group (n = 18; 9 female). Patients and raters were blinded regarding group assignment.

Patients underwent 15 days of stimulation with one session in the morning (S1) and one in the afternoon (S2) each day (median intersession interval = 2.7 hours, range = 1.5 to 6.5 hours). While all patients received active stimulation of the left DLPFC at S1, stimulation modalities differed between groups at S2. The DLPFC-iLPC group received active stimulation over individualized targets in both the left and right LPC. The sequence of bilateral iLPC stimulation targets was counter-balanced across subjects and kept constant over the treatment course. The DLPFC-DLPFC group received a second active stimulation session of the left DLPFC (identical to S1).

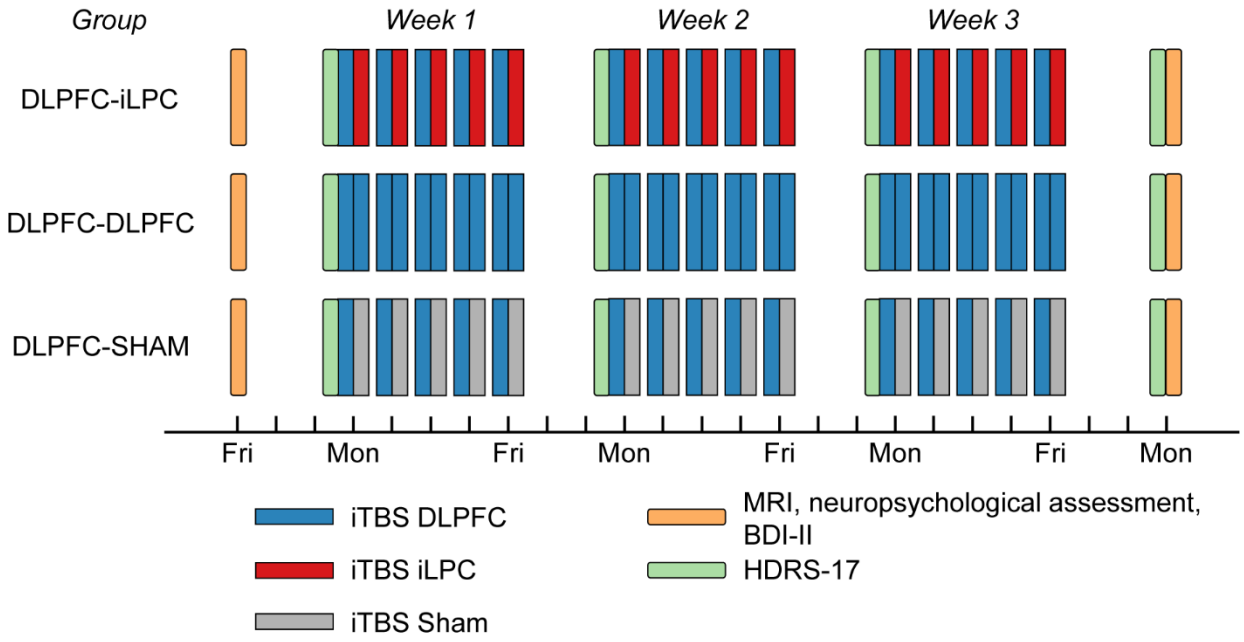

Figure 1. Study design. Patients received two daily stimulation sessions, one over the left dorsolateral prefrontal cortex (DLPFC), the other depending on group affiliation. Follow-up Beck Depression Inventory (BDI-II) scores were acquired 4, 8 and 12 weeks after the treatment phase (not depicted). HRDS-17, Hamilton Depression Rating Scale; iLPC, individualized lateral parietal cortex target.

Patients in the DLPFC-SHAM group were randomized to receive sham stimulation of either the left DLPFC (n = 9) or over iLPC targets (n = 9) at S2. Sham data were collapsed across both sites, as there was no influence of site as revealed in subgroup comparisons.

Stimulation protocol

rTMS was applied using a Magstim Rapid2 Plus1 magnetic stimulator (Magstim Company Limited, Wales, UK) with a figure-of-eight coil (air film double 70 mm coil). Sham treatment was implemented using a magnetically shielded placebo coil that provides sensory stimulation and discharge noise without stimulating cortical tissue. Each session consisted of two 3.2 min runs of iTBS [1,35]. During each run, 20 stimulation trains were applied with an 8-second intertrain interval, each train consisting of 10 consecutive 50 Hz pulse triplets applied at a 5 Hz frequency. Hence, a total number of 600 pulses were applied per run. There was a 5-minute pause between both runs. Patients who received active or sham stimulation over iLPC at S2 obtained two iTBS runs each over both the left and right iLPC target, thus receiving a total of 2400 pulses at S2 as compared to 1200 pulses administered to patients who were stimulated exclusively over DLPFC. Stimulation intensity was set at 80% of the individual resting motor threshold, which was assessed for each patient before the first stimulation session. A frameless stereotactic neuronavigational system (Localite TMS Navigator, Localite GmbH, St. Augustin, Germany) was used to ensure precise coil positioning. After each stimulation session patients completed a short questionnaire concerning potential side effects.

Statistical analysis

To investigate group differences, analyses of covariance (ANCOVA) with group as between-subject factor, pre-treatment values as covariate and post-treatment values as dependent variable was performed for all measures [36]. Change across groups was assessed using repeated-measures analysis of variance (rmANOVA) with time (pre-treatment, post-treatment) as within-subject factor. Fisher's exact test (χ^2) was used to compare categorical data. The threshold for significance was set to $p < .05$, and p-values were Bonferroni-adjusted if appropriate. fMRI whole-brain analyses were adjusted for multiple comparisons using family-wise error (FWE). Further information regarding group comparisons at baseline and additional analyses of change across groups is provided in the Supplementary Material. Statistical analysis was performed in IBM SPSS Statistic 24 (IBM, New York, NY, USA).

Clinical and neuropsychological assessment

To quantify clinical improvement, trained raters assessed depressive symptom severity using the 17-item Hamilton Depression Rating Scale (HDRS-17) [37] prior to the first stimulation session of each week and again three days after the final stimulation session. As a measure of self-assessed depression severity, the Beck Depression Inventory (BDI-II) [38] was administered before the first and after the final stimulation session and 4, 8 and 12 weeks after the treatment course.

Neuropsychological assessment was conducted to examine visual memory, spatial planning, visual sustained attention and working memory [25]. For that purpose, patients performed the Delayed Matching to Sample (DMS, percentage of correct answers), One Touch Stockings of Cambridge (OTS, mean choices to correct answer), Rapid Visual Information Processing (RVP, target sensitivity) and Spatial Working Memory (SWM, number of errors) computerized tests as implemented in the CANTABeclipse 6 battery (Cambridge Cognition Limited, Cambridge, UK).

Resting-state fMRI data analysis

Imaging data were acquired using a 1.5 T Siemens Avanto MRI system (Siemens, Erlangen, Germany) three days before and after the

treatment course. Resting-state data were preprocessed (see Supplementary Material) and analyzed employing the CONN toolbox for SPM [39]. For each subject and session, BOLD signal time courses were extracted and averaged from the following a priori defined stimulation-related regions of interest (ROIs): left and right hippocampus (3-mm spheres at MNI coordinates [-24 -20 -16] and [+22 -18 -18] based on encoding-related functional activation data from a pre-study; more information is given in the Supplementary Material), left DLPFC (5-mm sphere at [-38 +44 +26], stimulation target); and left and right iLPC stimulation targets (5-mm spheres at individualized coordinates). For the seed-to-seed analysis, BOLD signal time courses from all ROIs were correlated with one another and the resulting correlation coefficients were extracted for subsequent statistical analysis.

Additionally, we performed an exploratory whole-brain seed-to-voxel analysis. Time courses from each seed region were correlated with every voxel in the brain resulting in subject-specific correlational maps containing Fisher's *z* scores. These maps were then entered into a general linear model (GLM) with group as between-subject factor and time as within-subject factor. An *F*-test was used to detect clusters displaying differences between groups regarding change in functional connectivity (post-treatment > pre-treatment). Significance for seed-to-voxel analysis was set at a voxel height threshold of $p_{uncorrected} < .05$ and a cluster threshold of $p_{FWE} < .05$.

Stimulation target selection

The DLPFC target was defined as MNI coordinate [-38 +44 +26] previously identified as an optimal target for antidepressant rTMS treatment [40]. Bilateral iLPC targets were determined based on individual resting-state fMRI data. For each hemisphere, seed-to-voxel connectivity was calculated between the hippocampus ROIs and each voxel within a mask of the ipsilateral LPC. Subsequently, the voxel with the greatest positive correlation coefficient was selected as stimulation target. For additional information, see Supplementary Material.

Task-based fMRI experimental paradigm

An adapted version of an established associative memory paradigm that reliably elicits functional activation in the hippocampus [41,42] was employed to examine the effects of parieto-hippocampal stimulation. Patients underwent two encoding runs and one retrieval run. Before the fMRI session, patients were asked to familiarize themselves with two pairs of faces and written professions. During scanning, these two familiar pairs and 16 novel pairs were displayed for 4.6 s each. While novel stimuli were presented only once per run, familiar pairs were displayed repeatedly. Patients were tasked with memorizing these pairs and, to reinforce associative learning, had to indicate whether they thought the face fit the profession. During retrieval, previously presented novel faces were displayed again with the instruction to recall the associated profession and indicate their category (i.e. academic or artistic). For further information, see Supplementary Material.

Task-based fMRI data analysis

Data were preprocessed (see Supplementary Material) and analyzed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm)) running in MATLAB R2010b (The MathWorks, Natick, MA).

For the encoding task, conditions based on combinations of stimulus (novel, familiar, control), run (run 1, run 2) and time (pre-treatment, post-treatment) were entered into a GLM for each subject together with a constant term and six realignment parameters per run and session to account for subject motion. We then employed a data-driven leave-one-subject-out approach (LOSO) [43] to define subject-independent ROIs in the left and right hippocampus based on the main task effect, i.e. the contrast [novel >

familiar] across both runs and sessions. Parameter estimate images from all but one patient were entered into a flexible factorial model and whole-brain analysis was conducted with a height threshold of $p_{FWE} < .05$. Subsequently, we selected the supra-threshold cluster nearest to our hippocampal target voxels ([-24 -20 -16], [+22 -18 -18]) separately for each hemisphere. For the one patient who was left out, parameter estimates were extracted for all conditions using these subject-independent ROIs and averaged across voxels. To investigate group effects, the contrast [novel > familiar] was averaged across both runs for each session.

Analysis of the retrieval task was performed correspondingly using conditions based on combinations of stimulus (novel, control) and time (pre-treatment, post-treatment). The same LOSO approach was used to extract, average and subsequently contrast ([novel > control]) parameter estimates from subject-independent ROIs across voxels. Parameter estimate contrasts were used as a measure of functional activation and further analyzed in SPSS.

Results

Clinical and neuropsychological results

HDRS-17 scores (pre-treatment 17.21 ± 5.59, post-treatment 10.19 ± 5.79, $F_{(1,52)} = 91.06$, $p < .001$, $\eta_p^2 = .64$) and BDI-II scores (pre-treatment 33.45 ± 8.83, post-treatment 18.87 ± 11.11, $F_{(1,52)} = 87.05$, $p < .001$, $\eta_p^2 = .63$) improved across groups after treatment. A significant group effect ($F_{(2,49)} = 3.60$, $p = .035$, $\eta_p^2 = .13$) revealed better post-treatment HDRS-17 scores in the DLPFC-DLPFC group (adjusted mean = 7.62, SE = 1.15) compared to the DLPFC-iLPC (adjusted mean = 11.33, SE = 1.10, $t_{(33)} = 2.30$, $p = .026$, $d = 0.80$)) and DLPFC-SHAM groups (adjusted mean = 11.47, SE = 1.09, $t_{(33)} = 2.41$, $p = .020$, $d = 0.84$); Figure 2A) when controlling for pre-treatment scores. No group differences were found for BDI-II at the end of the treatment course ($F_{(2,49)} = 0.46$, $p = .632$; Figure 2B) or at

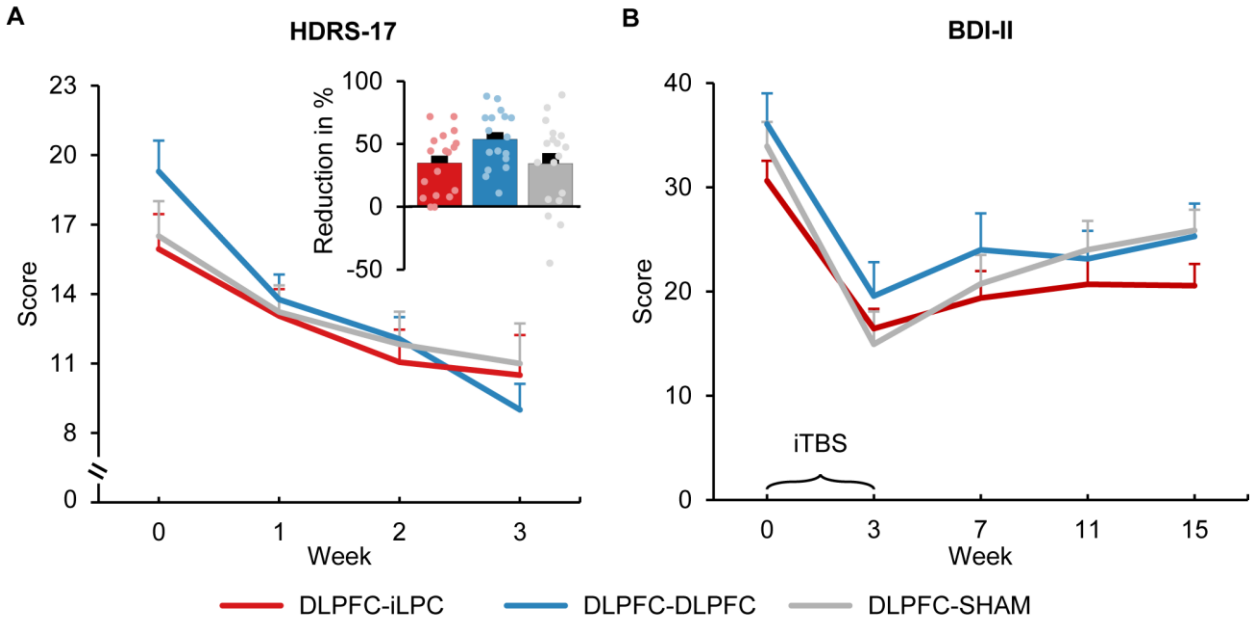

Figure 2. Change in depression symptom severity over time. **(A)** Patients in the DLPFC-DLPFC group showed better outcomes in the Hamilton Depression Rating Scale (HDRS-17) than patients in the other groups when controlling for baseline scores. **(B)** No group differences were found for Beck Depression Inventory (BDI-II) scores at the end of treatment or at any of the follow-up measurements (data is displayed only for patients that completed follow-up; DLPFC-iLPC: n = 17, DLPFC-DLPFC: n = 14, DLPFC-SHAM: n = 15). Error bars depict standard error of the mean.

any of the follow-up measurements (all p's > .701), which was completed by 46 patients (DLPFC-iLPC: n = 17, DLPFC-DLPFC: n = 14, DLPFC-SHAM: n = 15). There were no group differences in the occurrence of stimulation-related side effects (see Supplementary Material, Table S2).

Across groups patients improved in the DMS ($F_{(1,52)}$ = 9.24, p = .004, η_p^2 = .15), RVP ($F_{(1,52)}$ = 19.97, p < .001, η_p^2 = .28) and SWM ($F_{(1,52)}$ = 4.21, p = .045, η_p^2 = .08) tests but not in the OTS test ($F_{(1,52)}$ = 1.84, p = .181). No group differences were found (DMS: $F_{(2,49)}$ = 0.42, p = .660; OTS: $F_{(2,49)}$ = 1.74, p = .186; RVP: $F_{(2,49)}$ = 0.83, p = .443; SWM: $F_{(2,49)}$ = 1.33, p = .275).

Resting-state functional connectivity

We employed exploratory whole-brain functional connectivity analysis to investigate group-specific changes after treatment. Intriguingly, for the right hippocampus seed we found a significant cluster in the left DLPFC (peak at [-34 +38 +26]; cluster size 745 voxels, p_{FWE} = .041, Figure 3A). Post-hoc tests revealed a stronger increase in connectivity in the DLPFC-iLPC group than in the DLPFC-DLPFC ($t_{(33)}$ = 4.57, p < .001, d = 1.59) and DLPFC-SHAM group ($t_{(34)}$ = 7.46, p < .001, d = 2.56; Figure 3B). This cluster was topographically located close to the DLPFC stimulation target (7.21 mm Euclidean distance between correlation cluster peak and stimulation target coordinate). Whole-brain analysis of other seeds did not reveal significant results.

Seed-to-seed analyses revealed no significant group effects between ROIs in the left and right hippocampus, left and right iLPC and left DLPFC (all p's > .372). Analysis across groups, however, revealed a significant decrease of functional connectivity between iLPC and ipsilateral hippocampus both in the left ($F_{(1,52)}$ = 68.12, p < .001, η_p^2 = .57) and right hemisphere ($F_{(1,52)}$ = 142.22, p < .001, η_p^2 = .73). Since hippocampal seeds and iLPC stimulation target voxels were maximally correlated at baseline by design, this finding may result from stimulation-independent regression to the mean.

fMRI associative memory paradigm

Due to technical problems during MRI acquisition, one subject (DLPFC-iLPC group) was eliminated from task-based fMRI analyses. As predicted, in the encoding task, we found a significant group effect on activation in the left hippocampus ($F_{(2,48)}$ = 11.80, p = .002, η_p^2 = .23; Figure

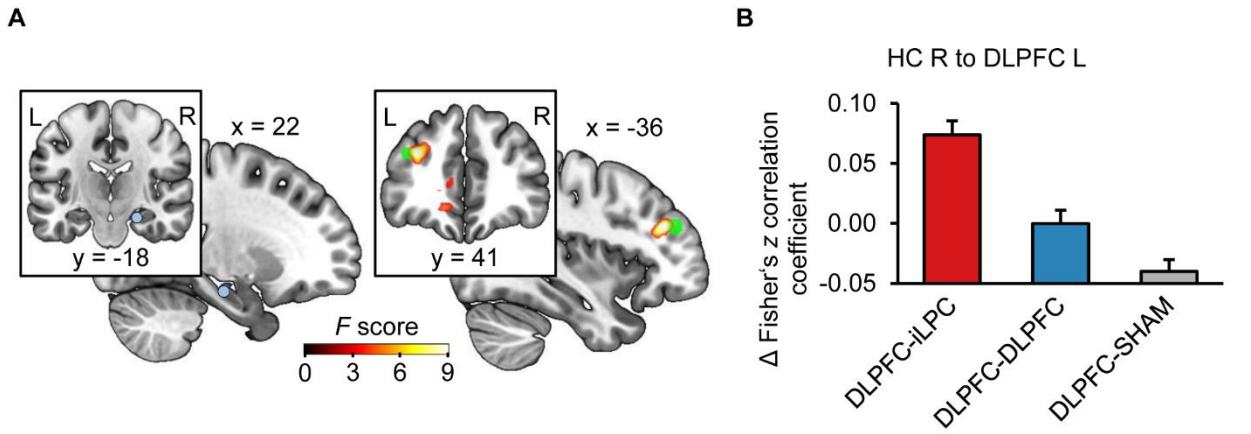

Figure 3. Whole-brain resting-state functional connectivity of right hippocampus (HC). **(A)** Exploratory seed-to-voxel analysis revealed a significant group effect on change of functional connectivity between the right hippocampus seed (3-mm sphere; blue) and a prefrontal cluster topographically close to the dorsolateral prefrontal cortex (DLPFC) stimulation target (5-mm sphere; green). **(B)** Visual representation of change in functional connectivity. Error bars depict standard error of the mean.

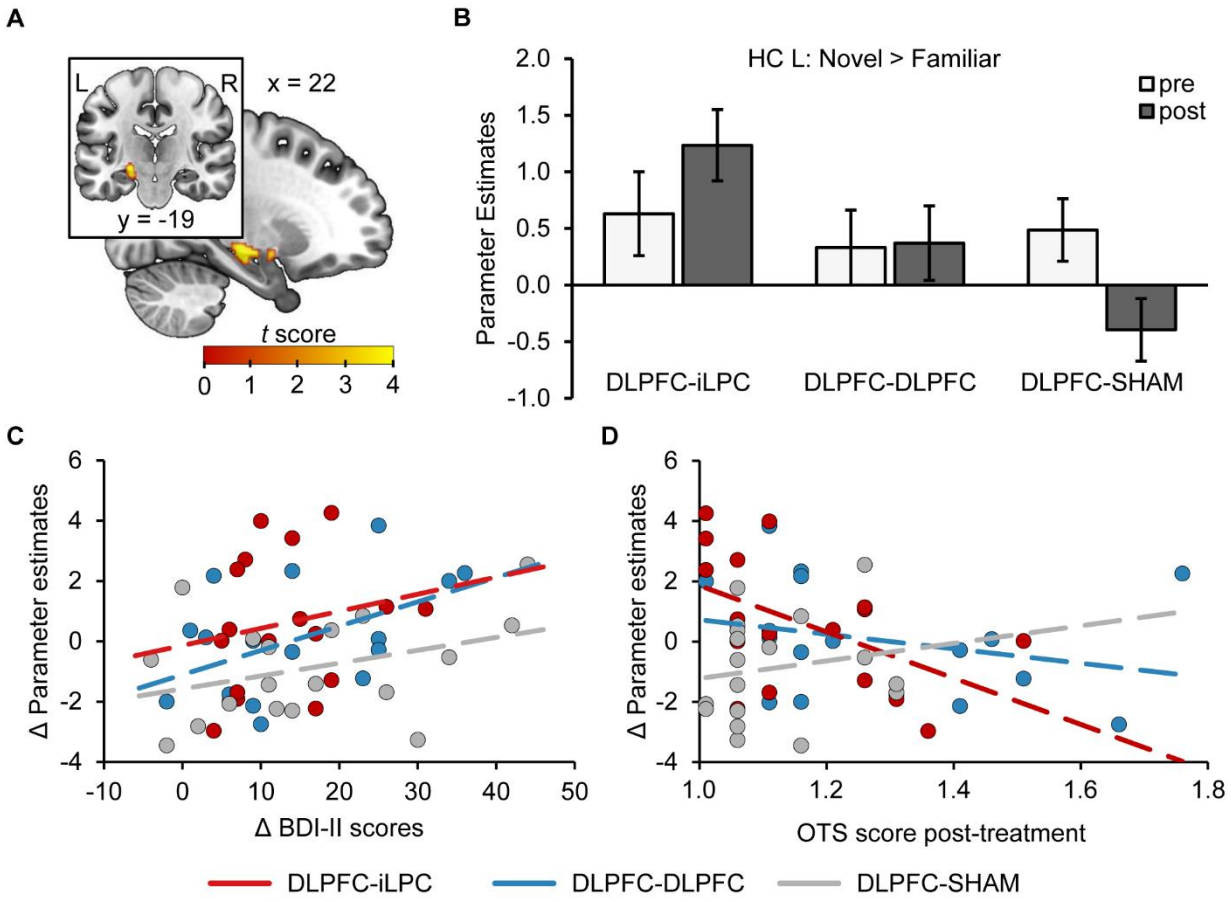

Figure 4. fMRI results from the encoding task. **(A)** A leave-one-subject-out approach was used to define subject-independent regions of interest (ROIs) in the hippocampus (HC) (displayed is an exemplary ROI). **(B)** After treatment, patients in the DLPFC-iLPC group showed a greater increase in hippocampal response during encoding compared to patients in the other groups. **(C)** This increase in activation significantly correlated with improvement in Beck Depression Inventory (BDI-II) scores across groups. **(D)** In contrast, activation increase correlated with better (= lower) post-treatment One Touch Stockings of Cambridge task (OTS) scores in the DLPFC-iLPC group, but not in the other groups. Error bars depict standard error of the mean.

4A; right hippocampus: $F_{(2,48)}$ = 1.63, p = .207) after treatment. Planned contrasts revealed higher activation in the DLPFC-iLPC group (1.23 ± 1.30) than in the other groups (DLPFC-DLPFC: 0.37 ± 1.36, p = .049; DLPFC-SHAM: -0.39 ± 1.17, p < .001; Figure 4B). No group differences were present in the retrieval task (p's > .107) and groups did not differ regarding their memory performance, assessed as the number of correct answers during the retrieval task ($F_{(2,48)}$ = 0.25, p = .777).

To test brain-behavior relationships, we conducted post-hoc correlational analysis. Increased activation in the left hippocampus during encoding positively correlated with absolute improvement in BDI-II scores after the treatment course across all groups ($r_{(52)}$ = 0.29, p = .041; Figure 4C). Also, we found a significant correlation between post-treatment OTS scores and the increase in activation in the left hippocampus during encoding in the DLPFC-iLPC group ($r_{(17)}$ = -0.50, p = .040), but not in the other groups (DLPFC-DLPFC: $r_{(17)}$ = -0.27, p = .295; DLPFC-SHAM: $r_{(18)}$ = 0.17, p = .494; Figure 4D).

Discussion

The rationale of the present study was to optimize iTBS of MDD using a precision medicine approach by augmenting daily stimulation over

the left DLPFC with an additional daily session of stimulation over individualized parietal targets. These targets were determined based on their functional connectivity to the hippocampus, a crucial node of the neuroanatomic circuitry underlying depression. This connectivity-based approach utilizes patients' individual fMRI data to identify superficial cortical stimulation targets that are connected to deeper regions of the brain, thus enabling the modulation of otherwise inaccessible targets. Our findings indicate that parieto-hippocampal stimulation combined with standard DLPFC stimulation led to increased functional connectivity between hippocampus and DLPFC, increased hippocampus response during encoding and a stronger correlation between encoding-related hippocampus response and performance in a spatial planning task. Although there was no additional benefit of parieto-hippocampal stimulation regarding depressive symptom severity compared to sham stimulation, our findings suggest that the administered stimulation protocol is effective in modulating hippocampal-prefrontal pathways and performance in tasks associated with these areas.

Firstly, exploratory functional connectivity analyses revealed that stimulation of both the individualized parietal target and the DLPFC augmented functional connectivity between the right hippocampus and DLPFC. These connectivity-enhancing effects produced by co-activation of hippocampus and DLPFC are reminiscent of studies on paired associative stimulation (PAS) over multiple cortical targets and cortico-cortical connectivity [44–47]. However, the effects of PAS are thought to reflect spike-timing dependent plasticity, which depends on either simultaneous administration of bifocal stimulation or interstimulus intervals in the range of milliseconds [44,48]. Effects on connectivity are usually measured within minutes after a single stimulation session. In contrast, we administered 15 days of stimulation, employed an intersession interval of 2-3 hours, and acquired fMRI data three days after the final stimulation session. In addition, we aimed for indirect modulation of the hippocampus, which, to our knowledge, has not been reported previously in the context of PAS. While PAS and our approach share the same premise of increased connectivity after bifocal stimulation, they differ in terms of the underlying mechanism of action. Our findings presumably rely on a more long-term and less timing-specific kind of plasticity and suggest that connectivity can be modulated by bifocal stimulation protocols even when stimulation is applied indirectly. However, since all patients received DLPFC stimulation, we cannot be certain that it is required for the observed effect. Possibly the same effect could be achieved with parieto-hippocampal stimulation alone. But, intriguingly, the connectivity cluster was located topographically right next to the DLPFC stimulation target, supporting the interpretation that this finding is indeed related to bifocal stimulation. While this effect was not accompanied by improvement of clinical symptoms, this approach might be used in future studies to achieve a targeted increase in connectivity in patients with conditions which are associated with prefrontal-hippocampal dysconnectivity, such as schizophrenia [49], memory disorders [50] and other disorders [51]. Sham-controlled studies are necessary to confirm and further explore this preliminary finding.

Secondly, parietal-hippocampal stimulation enhanced encoding-related activity near the left hippocampal stimulation site. This supports our hypothesis that our approach was successful on the neurophysiological level and is consistent with prior reports showing increased task-based hippocampus activation after parieto-hippocampal stimulation in healthy individuals [29,30].

Thirdly, correlational analysis revealed that only in patients who received parieto-hippocampal iTBS the observed increase in hippocampal response during encoding was associated with better performance in the OTS task, which is based on the extensively studied Tower of

London paradigm [52,53] and reflects spatial planning. This task is usually associated with prefrontal activity [54], but there is evidence for hippocampal engagement as a function of task difficulty [55], which might reflect additional demand for spatial memory capacities. A previous study has shown that spatial cognition mediates the negative impact of MDD on psychosocial functioning [56] indicating that patients with cognitive deficits might benefit from our stimulation approach. Across groups, increases in hippocampal activation were correlated with clinical improvement as measured by BDI-II scores, implicating an involvement of the hippocampus in antidepressant response.

We found that symptom severity decreased in all three groups, with better outcomes after twice-daily active DLPFC stimulation compared to additional parieto-hippocampal or sham iTBS. This finding contributes to the ongoing discussion regarding the optimal number and frequency of sessions [57–59] by demonstrating the superiority of twice-daily DLPFC stimulation in a sham-controlled design.

Unlike previous studies that employed comparable approaches [10,28,29,31,32], we found no improvement in memory performance or other neuropsychological parameters after parieto-hippocampal stimulation. These previous studies were conducted in healthy individuals as opposed to MDD patients who commonly suffer from cognitive impairment and might therefore be less responsive to subtle stimulation effects. Differences can also be found regarding stimulation protocols: whereas most of the aforementioned studies used 20 Hz high-frequency (HF) rTMS [10,28,29], two recently published studies found effects on associative memory after a single session of continuous [32] but not intermittent TBS [31], indicating that our chosen stimulation protocol might not have been ideal for this purpose.

While employing an innovative stimulation approach, the present study is limited by a small sample size and the number of analyses. Heterogeneity regarding concomitant pharmacotherapy and the tolerance of certain comorbidities such as anxiety disorders might have introduced variance that could have concealed further stimulation-dependent effects.

In conclusion, our findings suggest that stimulation of individualized parieto-hippocampal connectivity modulates hippocampal plasticity in MDD patients. An increase in hippocampus activation after parieto-hippocampal stimulation was associated with better performance in a spatial planning task that relies on both prefrontal and hippocampal contributions and, thus, may have therapeutic potential for depressed patients with cognitive deficits. Our findings are compatible with an increase in hippocampal-prefrontal connectivity through bifocal stimulation of DLPFC and a site functionally connected to the hippocampus. Future studies should evaluate whether this approach might be used to achieve a targeted increase in connectivity in patients or healthy controls.

Acknowledgements

The authors thank Paul Jung for outstanding programming assistance as well as Laura Schmitt and Lea Köster for their help with data acquisition.

Table 1. Demographic data

	DLPFC-iLPC (n = 18)	DLPFC-DLPFC (n = 17)	DLPFC-SHAM (n = 18)	*p*
Sex (M/F)	10/8	6/11	9/9	.481
Age (years)	40.28 (12.65)	43.59 (11.45)	42.28 (12.99)	.754
Education (years)	16.69 (7.59)	14.06 (3.06)	16.58 (4.43)	.278
Duration of current depressive episode (years)	4.01 (5.39)	3.09 (3.29)	6.46 (9.22)	.289
Number of depressive episodes [a]	3.57 (3.40)	3.28 (2.52)	2.72 (2.60)	.701

Values are given as mean (SD). The *p*-values report the significance levels reached for analysis of variance or Fisher's exact tests comparing groups. The significance threshold was set at $p < .05$. [a] Data missing for six patients (DLPFC-DLPFC: n = 16, DLPFC-iLPC: n = 15, DLPFC-SHAM: n = 16).

Supplementary Material

Supplementary Methods

Subjects

Patients between 18 and 60 years of age who fulfilled criteria for unipolar major depressive disorder for at least four weeks and who did not respond to a minimum of one or did not tolerate a minimum of two antidepressants in the current episode were eligible for inclusion. Physiological exclusion criteria were metal in the brain or the skull, a cardiac pacemaker or intracardiac lines, medication infusion devices, heart or brain surgery, pregnancy or any condition resulting in increased intracranial pressure, traumatic brain injury, a history of epilepsy, cerebral aneurysms, dementia, morbus Parkinson, Chorea Huntington, multiple sclerosis, stroke or transient ischemic attack (within the last 2 years). Psychiatric exclusion criteria included substance induced depression, a history of substance abuse, psychotic episodes, bipolar disorder, anorexia, posttraumatic stress disorder (current or within the last 12 months), claustrophobia or previous antidepressive treatment with rTMS, electroconvulsive therapy (within the last 3 months), vagus nerve stimulation or deep brain stimulation. Information about patients' psychiatric medication during the study can be found in Table S1. For a depiction of the trial profile see Figure S1.

Randomization procedure

For the allocation of patients to stimulation groups, a randomization table was generated before the start of recruitment. Patients were, then, allocated to one of the three groups based on the order of study inclusion. Patients and TMS operators were, by necessity, aware of the stimulation target at S2 and TMS operators were, also, aware of treatment modality (active or sham stimulation). Staff performing weekly clinical ratings were blinded to treatment condition. Patients were instructed not to discuss their stimulation target nor their suspected treatment modality (active or sham) with neither staff nor other study participants.

rTMS motor threshold assessment

To assess individual resting motor threshold, single TMS pulses were applied over the hand-motor hotspot in the left primary motor cortex (M1) with an interstimulus interval of at least 5 s. Corresponding motor-evoked potentials (MEPs) were recorded using surface electrodes on the abductor pollicis brevis of the right hand. Peak-to-peak amplitudes of at least 50 μV were registered as responses. The individual motor threshold (mean 58.13% ± 7.90% of maximum stimulator output) was determined based on a maximum-likelihood estimation procedure [60].

Task-based fMRI experimental paradigm

This paradigm consisted of an encoding and subsequent retrieval task. During the encoding task patients were tasked with memorizing pairs of stimuli. Each pair consisted of a face from the Karolinska Directed Emotional Faces database [61] displaying a neutral expression and a written profession (i.e., 'pianist'). Before the MRI session, patients were asked to consecutively memorize two stimulus pairs for 60 s each in order to gain familiarity. During scanning, patients were then presented with either these familiar stimuli, novel stimuli or control stimuli, the latter consisting of scrambled faces and a sequence of 'x' letters instead of a profession (Figure S2A). While novel and control stimuli were presented only once per run, familiar pairs were presented eight times each. These stimulus pairs were displayed for 3 s before two response options ('does fit', 'does not fit' for familiar and novel stimuli; 'longer', 'shorter' for control stimuli) were displayed additionally for another 1.6 s. While these options were present, patients were to indicate via button press whether the face fit the profession in their subjective opinion (familiar, novel stimuli) or whether the sequence of letters was longer than the width of the scrambled face (control stimuli). This served to engage patients and reinforce associative learning. For each condition, 16 stimuli pairs were presented in blocks of four. Stimuli pairs and blocks were interleaved with an inter-stimulus interval (ISI) jittered between 0.5 and 1.5 s and an inter-block interval (IBI) jittered between 4 and 5.5 s. During these intervals, the subjects viewed a white fixation cross on a black background. Participants underwent two encoding runs of about 6-min duration each. The same sets of stimuli were used for both runs; different sets (A and B), however, were used for the pre- and post-treatment scanning sessions.

During the 5-min retrieval task, previously presented novel and control faces were displayed without caption (Figure S2B). Instead of the written profession or the letter sequence, only faces and two response options were displayed for 4.6 s. For novel stimuli, patients had to indicate either whether the depicted person practiced an artistic or academic profession (set A), or whether they worked indoors or outdoors (set B). For control stimuli, patients had to indicate whether the left or the right ear of the scrambled face was larger. Stimuli were again presented in a block design with the same inter-stimulus and inter-block intervals as in the encoding task. Stimulus presentation and response collection was implemented using Presentation 14 software (Neurobehavioral Systems, Albany, CA), liquid crystal display video goggles (Nordic NeuroLab, Bergen, Norway) and an MRI-compatible response box.

MRI data acquisition

Functional and structural MRI data were acquired on a 1.5 T Siemens Avanto MRI system (Siemens, Erlangen, Germany) equipped with a 12-channel standard head coil at the Life & Brain Centre, Bonn, three days before the first rTMS session (pre-treatment) and again three days after

the last rTMS session (post-treatment). T2*-weighted gradient-echo planar images (EPI) images with blood-oxygen-level-dependent (BOLD) contrast were acquired during the associative memory task (voxel size = 2.5×2.5×5.0 mm; TR = 2690 ms; TE = 50 ms; flip angle = 30°; FoV = 200 mm, matrix size = 80×80; 29 coronal slices; ascending slice order with interslice gap of 0.5 mm) and at rest (200 volumes, 10 min; voxel size = 3×3×3 mm; TR = 3070 ms; TE = 45 ms; flip angle = 90°; FoV = 192 mm; matrix size = 64×64; 38 traversal slices; interleaved slice order with interslice gap of 1 mm), during which patients were asked to keep their eyes open and focused on a white fixation cross on a black background. Additionally, a field map (voxel size = 2.5×2.5×5 mm; TR = 460 ms; TE_{fast} = 4.76 ms; TE_{slow} = 9.52 ms; flip angle = 60°; matrix size = 64×64; 29 coronal slices; interslice gap of 0.5 mm) was acquired in order to correct for inhomogeneities of the magnetic field during preprocessing. Subsequently, a high-resolution structural image was acquired using a T1-weighted 3D MRI sequence (voxel size = 1×1×1 mm; TR = 1660 ms; TE = 3.09 ms; flip angle = 15°; FoV = 256 mm; matrix size = 256×256, 160 sagittal slices). The first five volumes of each functional time series were discarded to allow for T1 equilibration. We also applied two further experimental paradigms that are outside the scope of the present article and will be reported elsewhere.

Task-based fMRI data preprocessing

The fMRI data were preprocessed and analyzed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB R2010b (The MathWorks, Natick, MA). The functional data were realigned, initially to the first image in the time series, then to the mean of all images, and unwarped using the field map data. They were then coregistered to the anatomical volume acquired pre-treatment and normalized based on probabilistic tissue segmentation into 2-mm stereotaxic Montreal Neurological Institute (MNI) space. Subsequently, the images were smoothed using a 4 mm full width at half maximum (FWHM) Gaussian kernel.

Resting-state fMRI data preprocessing

We employed the CONN preprocessing pipeline which included realignment and unwarping, slice-time correction, segmentation and normalization into 2-mm MNI space. Functional data were then smoothed using an 8-mm FWHM Gaussian kernel. To limit the impact of head motion, cardiac and respiratory confounders, a linear regression model was created for each patient and the following regressors were added: 1) volumes that exceeded a threshold of 0.5 mm subject motion or three standard deviations from the global signal were automatically flagged by the artifact detection tool implemented in CONN; 2) realignment parameters; and 3) nuisance components derived from BOLD signal time courses extracted from white matter (WM, 16

dimensions) and cerebrospinal fluid (CSF, 16 dimensions) masks using the anatomical component-based noise correction method (aCompCor, [62]). Subsequently, the residual data were band-pass filtered at a frequency between 0.01 and 0.1 Hz.

Pre-study: localization of hippocampal targets

We recruited 60 healthy controls (30 female, age 44.18 ± 14.64 years) who underwent a single MRI session prior to the main study to determine 1) target voxels in the HC that showed encoding-related activation, and 2) clusters in the bilateral LPC which are significantly correlated with these HC target voxels. These LPC clusters were then used in the main study as ROIs for the determination of individualized stimulation targets based on their functional connectivity to the HC voxels. Exclusion criteria for the controls were current or previous psychiatric or neurological disorders, pregnancy and contraindications for MRI scanning. As in the main study, these subjects underwent structural and functional MRI both at rest and during performance of the associative memory paradigm. MRI sequences and the experimental paradigm were equivalent to procedures used in the main study. For the encoding task, preprocessing and subject-level analyses were the same as depicted in the main study. On the group-level, a t-test for the contrast [novel > familiar] was computed for the first run. Resulting maps were masked with a HC ROI derived from SPM Anatomy toolbox [63], and two peak voxels in the right ([+22 -18 -18] , $t_{(59)}$ = 4.14, $p_{uncorrected}$ < .001) and left HC ([-24 -20 -16], $t_{(59)}$ = 2.64, $p_{uncorrected}$ = .011) were selected as target voxels (Figure S3A). Resting-state functional connectivity data were preprocessed similarly as described above with the exception of denoising, where only five confound dimensions were extracted for white matter and cerebrospinal fluid and a band-pass filter of 0.008 to 0.09 Hz was used. Seed-to-voxel analysis was performed across all controls with seeds consisting of 3-mm spheres centered on the hippocampal target voxels, with a voxel height threshold of $p_{uncorrected}$ < .001 and a cluster threshold of p_{FDR} < .05 on the second level. Two clusters in the left ([-40 -70 +40], $t_{(59)}$ = 3.23, p_{FDR} = .001, 2936 voxels) and right LPC ([+48 -58 +28], $t_{(59)}$ = 3.23, p_{FDR} = .001, 2626 voxels) were selected for use as ROIs in rTMS target selection (Figure S3B).

rTMS target selection

Due to the neuronavigation system operating in subject space, we applied an inverse normalization procedure to an image containing the MNI coordinates of the DLPFC stimulation target ([-38 +44 +26]) using subject-specific deformation fields produced during normalization. Accordingly, since functional connectivity analysis to identify individualized LPC targets (iLPC) was performed in MNI space, these voxel coordinates were once again inverse normalized to subject space. The LPC ROI was based on data from the pre-study (see corresponding subsection). iLPC targets were calculated for all patients, though only those in the DLPFC+iLPC group received

rTMS over those targets. For a list of iLPC targets and corresponding Fisher's *z* correlation coefficients for all patients see Table S3.

Supplementary Results

Group comparison at baseline

One-way ANOVA was used to identify baseline differences between groups. There were no group differences regarding HDRS-17 ($F_{(2,50)}$ = 1.84, p = .169) or BDI-II scores ($F_{(2,50)}$ = 0.89, p = .417) at baseline. Also, there were no differences between groups regarding the DMS ($F_{(2,50)}$ = 2.14, p = .128), RVP ($F_{(2,50)}$ = 0.40, p = .671) or SWM ($F_{(2,50)}$ = 1.96, p = .151) neuropsychological tests. There were, however, significant differences in the OTS test ($F_{(2,50)}$ = 5.59, p = .006, η_p^2 = 0.18), with higher scores in the DLPFC-DLPFC group (1.39 ± 0.41) indicating worse performance than in the other groups (DLPFC-iLPC: 1.17 ± 0.16, DLPFC-SHAM: 1.12 ± 0.09). For the associative memory task, we found no group differences in activation in either HC during encoding (left: $F_{(2,49)}$ = 0.21, p = .815; right: $F_{(2,49)}$ = 1.50, p = .233) or retrieval (left: $F_{(2,49)}$ = 0.28, p = .761; right: $F_{(2,49)}$ = 0.87, p = .428). There were no differences in behavioral performance during the retrieval fMRI task ($F_{(2,49)}$ = 1.80, p = .177).

Across group analyses

Repeated measures analysis of variance (rmANOVA) with time (pre-treatment, post-treatment) as within-subject factor was used to assess change across groups. Patients that completed all follow-up BDI-II measurements showed long-term clinical improvement between baseline and 3-month follow-up (pre-treatment 33.65 ± 9.37, follow-up 24.28 ± 9.90, $F_{(1,45)}$ = 34.85, p < .001, η_p^2 = .44). Patients did, however, worsen between the end of treatment and 3-month follow-up (post-treatment 17.37 ± 11.03, follow-up 24.28 ± 9.90, $F_{(1,45)}$ = 11.74, p = .001, η_p^2 = .21).

For the associative memory task, no main effect of time on activation was found in either HC for the encoding (left: $F_{(1,51)}$ = 0.12, p = .736; right: $F_{(1,51)}$ = 0.72, p = .399) or retrieval fMRI task (left: $F_{(1,51)}$ = 1.16, p = .287; right: $F_{(1,51)}$ = 0.48, p = .491). Also, there was no significant improvement over time in retrieval task performance ($F_{(1,51)}$ = 1.20, p = .279).

Group blinding

Patients' assumptions regarding whether they had received active or sham iTBS at S2 were correct above chance ($\chi^2_{(1)}$ = 7.46, p = .009, φ = 0.38). However, only patients who received active or sham stimulation of the DLPFC ($\chi^2_{(1)}$ = 5.00, p = .041, φ = 0.20) but not those who received iLPC stimulation were able to guess correctly ($\chi^2_{(1)}$ = 2.67, p = .194). Repetition of all between-

group analyses with patients' assumed mode of stimulation (active or sham) included as an additional covariate provided results that did not differ from the original analyses reported in this article. However, this bears only moderate impact on our neuroimaging findings, as these were focused on parietal-hippocampal stimulation.

Supplementary Figures and Tables

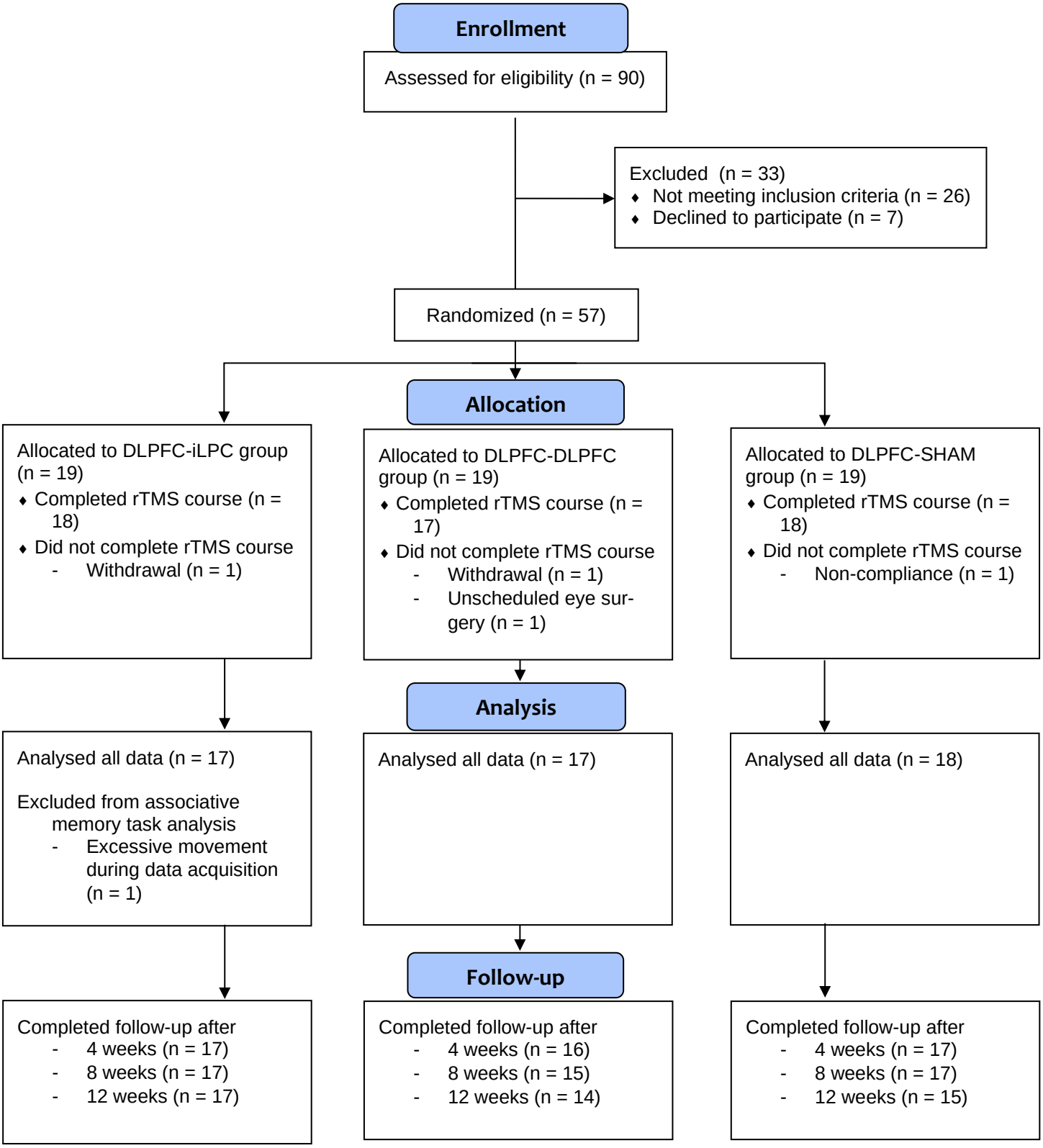

Figure S1. CONSORT diagram.

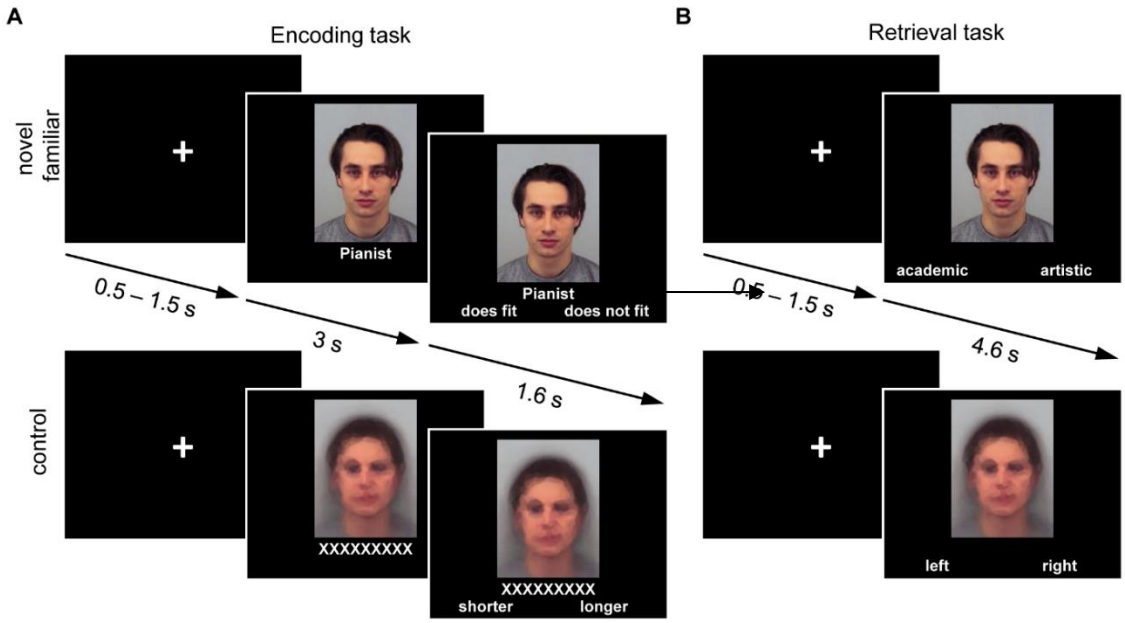

Figure S2. Experimental design of the associative memory task. **(A)** In the encoding task, four blocks of four stimuli were presented for the novel, familiar and control conditions. Subjects were tasked with memorizing the stimuli pairs and indicated whether they felt face and profession were a fit (novel, familiar stimuli) or whether the sequence of letters was longer than the width of the scrambled face (control stimuli) via button press. **(B)** In the retrieval task, four blocks of stimuli were presented for the novel and control conditions. Subjects had to assign stimuli to one of two categories based on the profession associated with the face (novel stimuli) or they had to indicate whether the left or right ear of the displayed scrambled face was larger (control stimuli).

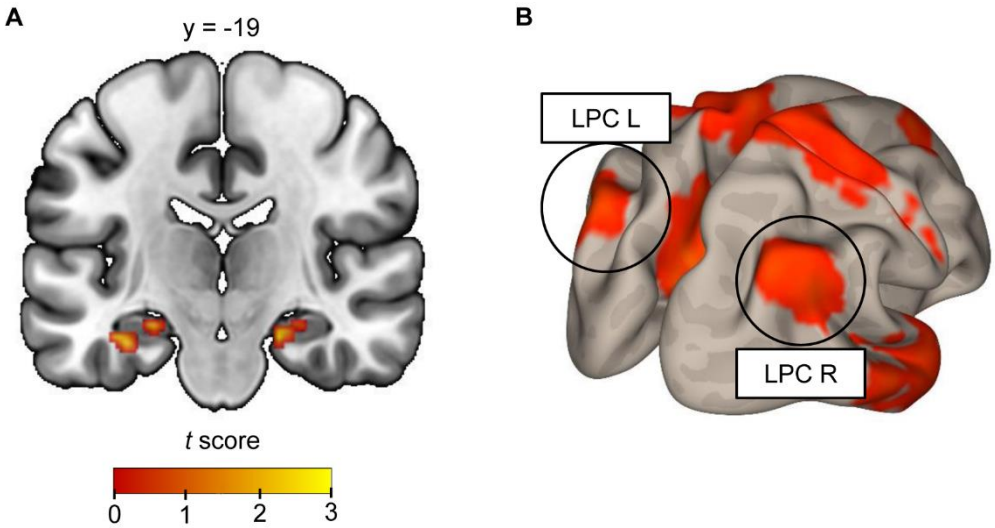

Figure S3. Results from the pre-study to determine HC targets and LPC mask. **(A)** Group-level neural activation in the left and right HC during the encoding task ([novel > familiar)] based on which HC targets were selected. **(B)** Functional connectivity analysis of bilateral HC seed revealed significant correlational clusters in the left and right LPC. These clusters were exported as masks for the selection of LPC targets in the main study. Abbreviations: HC, hippocampus; LPC, lateral parietal cortex.

Table S1. Psychotropic medication before and after the treatment course.

Group	Patient	Agent	mg/day before treatment	mg/day after treatment
DLPFC-iLPC	1	Agomelatin	25	25
		Venlaflaxin	300	300
	2	Tranylcypromin	10	0
	3	Mirtazapin	15	30
	4	Agomelatin	0	50
		Citalopram	40	40
		Quetiapin	75	25
	5	Sertralin	100	150
	6	Lamotrigin	15	15
		Quetiapin	75	125
	7	Agomelatin	50	50
		Escitalopram	10	10
	8	Agomelatin	25	50
		Amisulprid	100	100
		Duloxetin	120	120
	9	no psychotropic drugs		
	10	no psychotropic drugs		
	11	Agomelatin	25	50
		Escitalopram	0	0
		Mirtazapin	0	7.5
	12	Escitalopram	0	10
		Mirtazapin	15	15
	13	Bupropion	150	150
		Fluoxetin	0	10
		Mirtazapin	15	15
	14	Bupropion	150	300
	15	Citalopram	10	10
		Quetiapin	50	50
	16	Agomelatin	50	50
		Lamotrigin	175	125
		Quetiapin	150	150
		Valproinsäure	0	150
	17	Escitalopram	10	10
	18	no psychotropic drugs		
DLPFC-DLPFC	19	Fluoxetin	40	40
		Promethazin	75	75
	20	Agomelatin	50	50
		Quetiapin	200	20
	21	no psychotropic drugs		
	22	Mirtazapin	30	7.5
	23	Amitriptylin	12.5	37.5
		Bupropion	150	300

	24	Mirtazapin	30	30
	25	no psychotropic drugs		
	26	Agomelatin	0	50
		Sertralin	150	150
	27	Agomelatin	0	50
		Venlafaxin	300	300
	28	Amitryptilin	100	0
		Quetiapin	100	100
		Venlafaxin	150	150
	29	Agomelatin	25	50
		Hydroxyzin	50	50
		Paroxetin	20	0
	30	Escitalopram	0	10
		Sertralin	100	0
	31	Fluoxetin	10	20
		Venlafaxin	75	0
	32	Bupropion	0	150
		Venlafaxin	187.5	37.5
	33	Mirtazapin	45	45
		Pregabalin	275	275
	34	Bupropion	150	150
		Lamotrigin	25	25
		Sertralin	100	100
	35	no psychotropic drugs		
DLPFC-SHAM	36	Agomelatin	25	50
	37	Atomoxetin	40	40
	38	no psychotropic drugs		
	39	Agomelatin	50	50
		Mirtazapin	7.5	7.5
		Sertralin	100	100
	40	Escitalopram	0	15
		Pregabalin	300	300
		Risperidon	2	1
		Venlaflaxin	75	0
	41	Pregabalin	25	150
		Venlaflaxin	225	225
	42	Duloxetin	90	120
		Mirtazapin	7.5	15
	43	Agomelatin	50	50
		Sertralin	100	0
	44	Agomelatin	25	0
		Mirtazapin	0	30
	45	Carbamazepin	400	400
		Venlaflaxin	225	225
	46	Sertralin	150	150
	47	Duloxetin	60	0

48	Doxepin	25	25
	Lorazepam	3	3
	Mirtazapin	15	22.5
49	Lithium	675	900
	Milnacipran	0	25
	Quetiapin	100	100
	Venlaflaxin	150	0
50	Imipramin	30	30
	Lamotrigin	0	25
51	Bupropion	300	300
	Imipramin	75	75
	Valproinsäure	300	300
52	Bupropion	150	150
	Venlafaxin	75	75
53	Lamotrigin	25	25
	Venlafaxin	150	150

Table S2. Occurrence of side effects

	Number of participants reporting each side effect (%)			
	DLPFC-iLPC (n = 18)	DLPFC-DLPFC (n = 17)	DLPFC-SHAM (n = 18)	*p*
Headaches	6 (33%)	7 (41%)	8 (44%)	.830
Nausea	1 (6%)	3 (18%)	5 (28%)	.205
Dizziness	2 (11%)	7 (41%)	4 (22%)	.122
Muscle twitching	12 (66%)	9 (53%)	13 (72%)	.517
Pain	8 (44%)	6 (35%)	8 (44%)	.830

The *p*-values report the significance levels reached for Fisher's exact tests comparing groups. The significance threshold was set at $p < .05$.

Table S3. Individualized rTMS targets in the lateral parietal cortex (iLPC).

Group	Left iLPC MNI coordinates				Right iLPC MNI coordinates			
	X	Y	Z	Fisher's *z*	X	Y	Z	Fisher's *z*
DLPFC-iLPC	-64	-54	+14	0.24	+48	-58	+26	0.66
	-60	-56	+16	0.34	+42	-56	+26	0.20
	-60	-56	+20	0.38	+36	-70	+48	0.33
	-58	-66	+26	0.24	+38	-66	+42	0.24
	-54	-64	+26	0.43	+50	-76	+40	0.31
	-50	-62	+36	0.49	+50	-56	+40	0.32
	-50	-60	+14	0.28	+56	-66	+22	0.24
	-48	-66	+26	0.23	+58	-64	+38	0.23
	-46	-74	+44	0.33	+46	-50	+20	0.46
	-44	-68	+24	0.62	+40	-54	+28	0.31
	-44	-54	+36	0.40	+50	-58	+26	0.38
	-42	-50	+24	0.27	+38	-80	+40	0.23
	-40	-84	+34	0.30	+48	-76	+40	0.36
	-38	-58	+38	0.30	+44	-68	+46	0.34
	-36	-56	+26	0.25	+38	-64	+32	0.36
	-32	-86	+44	0.24	+36	-72	+32	0.16
	-32	-78	+54	0.40	+42	-72	+34	0.33
	-24	-76	+42	0.13	+44	-52	+30	0.27
DLPFC-DLPFC	-56	-72	+24	0.37	+50	-68	+44	0.32
	-52	-70	+44	0.32	+58	-62	+20	0.45
	-48	-68	+30	0.45	+48	-54	+30	0.33
	-48	-52	+30	0.30	+42	-58	+32	0.51
	-44	-56	+30	0.19	+38	-50	+26	0.13
	-40	-72	+24	0.27	+56	-60	+26	0.41
	-40	-62	+36	0.45	+50	-70	+24	0.20
	-40	-56	+34	0.35	+32	-70	+48	0.41
	-38	-84	+36	0.21	+62	-62	+34	0.34
	-38	-64	+28	0.41	+54	-54	+24	0.28
	-38	-56	+20	0.23	+40	-60	+28	0.28
	-34	-88	+40	0.21	+36	-80	+48	0.32

Table S3. Individualized rTMS targets in the lateral parietal cortex (iLPC).

Group	Left iLPC MNI coordinates				Right iLPC MNI coordinates			
	X	Y	Z	Fisher's *z*	X	Y	Z	Fisher's *z*
	-34	-66	+40	0.43	+46	-54	+24	0.28
	-32	-82	+38	0.44	+40	-74	+50	0.43
	-32	-72	+44	0.49	+40	-58	+28	0.29
	-30	-82	+38	0.35	+46	-60	+32	0.42
	-26	-76	+44	0.32	+60	-60	+36	0.32
DLPFC-SHAM	-54	-68	+22	0.43	+38	-68	+50	0.27
	-50	-74	+42	0.29	+50	-74	+42	0.39
	-48	-66	+22	0.28	+44	-58	+34	0.20
	-46	-62	+16	0.27	+38	-58	+38	0.34
	-46	-62	+18	0.27	+60	-66	+16	0.23
	-44	-60	+38	0.31	+50	-66	+46	0.25
	-42	-74	+52	0.45	+38	-78	+48	0.37
	-42	-64	+46	0.41	+58	-52	+24	0.30
	-40	-72	+48	0.57	+44	-62	+38	0.49
	-40	-66	+34	0.52	+42	-52	+30	0.37
	-36	-80	+44	0.36	+58	-64	+38	0.32
	-36	-76	+50	0.30	+54	-60	+40	0.45
	-34	-80	+46	0.39	+64	-58	+34	0.26
	-32	-68	+32	0.28	+42	-74	+34	0.49
	-32	-58	+30	0.24	+56	-56	+16	0.22
	-30	-76	+46	0.48	+54	-50	+24	0.26
	-30	-68	+44	0.21	+44	-60	+30	0.34
	-28	-80	+38	0.31	+34	-62	+30	0.30

References Chapter 3

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Chapter 4.

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Treatment-Resistant Depression and Ketamine Response in a Patient with Bilateral Amygdala Damage

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Case presentation

"A.M." is a 44-year-old woman who developed treatment-resistant major depressive disorder despite a history of stable and focal bilateral amygdala lesions caused by lipoid proteinosis of Urbach and Wiethe (OMIM #247100), an extremely rare autosomal-recessive disorder resulting from mutations in the extracellular matrix protein 1 gene (*ECM1*) located on chromosome 1q21 (1). We have repeatedly studied this patient and her monozygotic twin sister, who shares the same Urbach-Wiethe phenotype and amygdala pathology. Brain scans taken longitudinally over the past two decades have confirmed complete destruction of the basolateral amygdala bilaterally (Figure 1A; see also Figure S1 in the online supplement), and a large body of research involving the twins has helped identify brain functions and behaviors that do (2) or do not require amygdala integrity (3). In these studies, A.M. underwent extensive diagnostic screening, which confirmed preserved neuropsychological functioning, including memory, attention, and cognitive flexibility, in the absence of any psychiatric abnormalities, including no history of major depression (4, 5). Perhaps related to the extraordinarily strong, supportive bond with her mother, A.M. (but not her identical twin sister) displayed preserved recognition of fearful faces (6), but emotionally charged pictures never aroused her in a manner similar to the way they did control subjects (7). This was paralleled by a flat affect and the absence of anxiety in life situations experienced as stressful by her family (8).

The onset of major depression for A.M. started 4 years ago, and it was preceded by a series of major life events, all within a 1-year period, and all related to the loss of close attachment figures who were of central importance to her in providing support, care, and connectedness: her mother died from complications from a routine diagnostic medical procedure; she divorced her husband, who left her for another woman; and her teenage son decided to leave home and live with his father. Disabled by grief, broken-heartedness, and exhaustion, she stopped working and moved into her father's house. She attempted suicide and underwent five inpatient treatments in psychiatric hospitals. Notably, she did not benefit from any of the multimodal treatment attempts, including cognitive-behavioral therapy, multiple classes of antidepressants, and bilateral electroconvulsive therapy (see Table S1 in the online supplement).

On admission to our department last year, A.M. exhibited pronounced symptoms of anhedonia, loss of energy, and pervasive pessimistic thought biases expressing despair, resignation, and a passive wish to die (e.g., "I am hopeless; nothing has ever helped make me feel better; my life won't ever change for the better"). She displayed sleep disturbances, concentration deficits, and feelings of worthlessness and inferiority. Her cognitive distortions also affected her body image, evident in complaints about her appearance (e.g., "I am so ugly; I am not attractive to anybody; I will never find another partner who wants to share his life with me"). She refused to wear glasses despite moderate myopia. Her loss of appetite resulted in a diagnosis of cachexia (wasting syndrome) on admission (body mass index, 17.75). Furthermore, she suffered from a dry mouth, salty taste, and painful oropharyngeal ulcerations typical of Urbach-Wiethe disease.

Compared with a premorbid assessment 7 years earlier (6), her social network had declined both in size (the number of people in her social network was 17 in 2012, and 10 in 2018) and complexity (four embedded networks in 2012, and one in 2018; see the online supplement). In addition, she exhibited high levels of loneliness (a UCLA Loneliness Scale score of 47; see the online supplement). Clinical interviews confirmed that she had no other psychiatric disorder than major depressive disorder. Ten years ago, in an exploratory positron emission tomography study using the radioligand [^{18}F]altanserin (5), we detected a significantly decreased expression of

serotonin ($5\text{-}HT_{2A}$) receptors throughout A.M.'s brain, which may be linked to her amygdala pathology in ways neither investigated nor understood.

In light of the treatment-refractory and suicidal nature of A.M.'s major depression, the rationale of our therapeutic strategy was rooted in the assumption that her condition may be nonresponsive to serotonin-based therapies and may instead benefit from intravenous ketamine, which has shown transient efficacy for treatment-resistant symptoms in suicidal depression (9). Given associations that have been identified between major depression and dysfunction in large-scale brain networks (see the main text, below), we also decided to probe the effects of ketamine on the default mode network (DMN), salience network (SAN), and frontoparietal network (FPN) in the patient by collecting a series of resting-state functional MRI (rsfMRI) scans before and after her transient recovery from depression.

Four days after the patient was admitted to our hospital, intravenous ketamine (0.5 mg/kg) was administered over 40 minutes. The patient underwent rsfMRI scanning at baseline on admission as well as 200 minutes, 1 day, and 7 days after ketamine infusion. The rsfMRI data were compared with 12 sex- and age-matched inpatients with major depression who underwent scanning only once, at baseline; a voxel-based morphometry analysis showed normal amygdala gray matter volume in these patients (see the online supplement). Depressive symptoms were measured with the Beck Depression Inventory–II (BDI), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Hamilton Depression Rating Scale (see the online supplement). Suicidal ideation was assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS). Dissociative symptoms were evaluated with the Clinician-Administered Dissociative States Scale (CADSS).

On admission, the patient suffered from severe depression (scores of 43 on the MADRS, 54 on the BDI, and 21 on the C-SSRS). Antidepressant response was evident 50 minutes after ketamine infusion (a 73% reduction in MADRS score; the patient also had a 65% reduction in BDI score 170 minutes after infusion; see Figure 1A), with depressive symptoms returning to baseline after 3 days. In stark contrast to her previous behavior, she started showing interest in the lives of other patients and caretakers and proactively initiated conversations (e.g., "What are your plans for the holidays?"). The intensity of her suicidal ideation also substantially dropped (a score of 13 on the C-SSRS 200 minutes after infusion). Together, these observations suggest that ketamine transiently disrupted her negative self-referential bias and suicidal depression. Ketamine also induced dissociative symptoms that peaked 50 minutes after the infusion (a score of 24 on the CADSS; e.g., "I cannot feel my body, it's like being weightless") and vanished after 130 minutes (a score of 2 on the CADSS).

Results from rsfMRI analysis showed significant differences between the patient's measurements and those of the depression control group in the DMN, FPN, and SAN. Specifically, at baseline the patient exhibited significantly increased functional connectivity between the medial prefrontal cortex as seed of the DMN and the superior frontal gyrus (peak Montreal Neurological Institute coordinates: 12, −6, 76; t=4.02 [df=11 throughout], false discovery rate-corrected p [p_{FDR}]<0.01), and the anterior cingulate cortex as seed of the SAN and the precuneus (−4, −56, 34; t=4.02, p_{FDR}<0.01). Both differences were no longer detectable 200 minutes and 1 day after ketamine infusion, but the altered SAN-precuneus connectivity was again evident after 7 days (−2, −60, 32; t=5.12, p_{FDR}=0.06). During the acute period after ketamine infusion, across DMN seed regions, we found significantly increased coupling between the DMN and the frontal pole (left lateral parietal cortex as seed: −12, 66, 4;

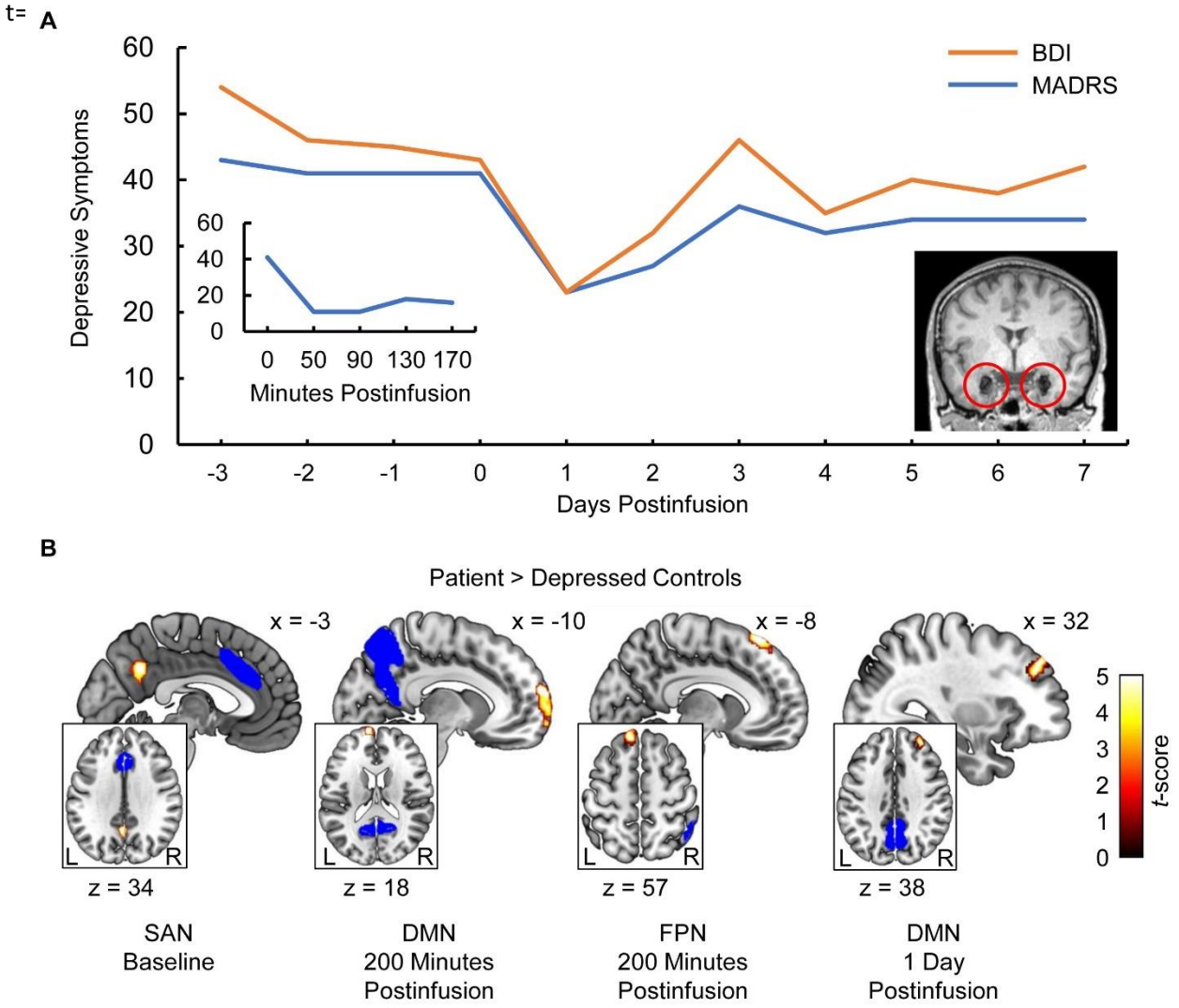

Figure 1. Depressive symptoms before and after ketamine administration in a patient with bilateral amygdala damage and severe treatment-resistant depression, and functional MRI comparison with depressed control subjects. Depressive symptoms were assessed for 10 consecutive days after the first subanesthetic i.v. dose (0.5 mg/kg) of ketamine in a patient with severe treatment-resistant depression despite bilateral basolateral amygdala damage (**A**). Both self-reported and clinician-evaluated depressive symptoms were reduced after ketamine administration. The two inlays display changes in the clinician-rated depressive symptoms in the 170 minutes after the ketamine infusion on the left and a high-resolution sagittal anatomical T1-weighted magnetic resonance image of the patient's brain with circles indexing the focal bilateral amygdala calcification damage on the right. Functional magnetic resonance imaging was used to measure the default mode network (DMN), frontoparietal network (FPN) and salience network (SAN) at baseline (i.e. three days before the infusion) and 200 minutes, one day, and seven days post infusion (**B**). Compared to 12 depressed controls (mean age ± SD: 43±13.2 years), at baseline the patient showed a significantly increased functional connectivity between the anterior cingulate cortex as seed of the SAN and the precuneus (-4, -56, 34; $t_{(11)}$ = 4.02, P_{FDR} < 0.01). Two hundred minutes after the ketamine infusion, the patient exhibited significantly increased functional coupling between the frontal pole and the posterior cingulate cortex as seed of the DMN (-10, 64, 18; $t_{(11)}$ = 10.22, P_{FDR} < 0.01) and the posterior parietal cortex as seed of the FPN (-12, 38, 58; $t_{(11)}$ = 8.10, P_{FDR} < 0.01) compared to the depressed controls. Significantly increased functional connectivity between the frontal pole and the posterior parietal cortex as seed of the DMN was also evident one day after the infusion (32, 44, 38; $t_{(11)}$ = 6.78, P_{FDR} < 0.01). The blue areas illustrate the seed regions. Abbreviations: BDI, Beck Depression Inventory-II; DMN, default mode network; MADRS, Montgomery-Åsberg Depression Rating Scale.

seed: −8, 70, 2; t=6.92, p_{FDR}<0.01; posterior cingulate cortex as seed: −10, 64, 18; t=10.22, p_{FDR}<0.01) (Figure 1B) in the patient 200 minutes after infusion and less pronounced after 1 day (medial prefrontal cortex seed: 30, 40, 34; t=5.65, p_{FDR}=0.08; posterior cingulate cortex seed: 32, 44, 38; t=6.78, p_{FDR}<0.01) compared with the depression control group. Likewise, we observed significantly increased functional connectivity between the right posterior parietal cortex as seed of the FPN and the frontal pole 200 minutes after infusion (−12, 38, 58; t=8.10, p_{FDR}<0.01).

Discussion

To our knowledge, this is the first reported case demonstrating that both treatment-resistant major depression and its response to ketamine can occur in the absence of the basolateral amygdala. Influential reports regarding the neurobiological origin of depression have highlighted a central role for the amygdala in the pathogenesis of depression (10–12). While there are heterogeneous findings of amygdala activity in major depression, possibly as a result of differences in contrast selection (13, 14), recent meta-analytic evidence indicates that major depression is associated with blunted amygdala responses to negative stimuli (13). Likewise, a meta-analysis found reduced amygdala volume in unmedicated patients (15), but there are also reports of amygdala enlargement in acutely depressed patients (16). Notably, pretreatment amygdala hyporeactivity has been identified as a general predictor of treatment response (17), and neurofeedback-based increases in amygdala hemodynamic activity can mitigate depressive symptoms (18). Furthermore, major depression has also been associated with dysfunctions in large-scale brain networks (19, 20). One of the most consistent findings is hyperconnectivity of the default mode network (DMN), which encompasses the posterior and anterior cortical midline structures and shows increased activation during self-referential processing in the resting state (21). It has been suggested that the DMN assigns valence to internally represented stimuli, and the DMN has been linked to self-focused rumination in major depression (22). By contrast, patients with major depression have been found to exhibit hypoconnectivity within the frontoparietal network (FPN) and salience network (SAN). The FPN plays a pivotal role in cognitive control of emotional responses (23) and the SAN, comprising the dorsal anterior cingulate cortex, fronto-insular cortex, and amygdala, is crucially involved in determining the biological significance of external stimuli (24). Interestingly, multiple depressive episodes may lead to a temporal decoupling of the amygdala from SAN regions (25).

Although we are not aware of any past reports of treatment-resistant major depression following bilateral amygdala damage, there have been reports of depressive symptoms in amygdala-lesioned patients, such as in the original case study of patient S.M. (32), where it was noted that “she has occasionally reported depressive symptomatology, related to difficult situational exigencies.” A more recent report (33) confirmed this observation and noted that one of the most difficult situations for patient S.M. is her social isolation, leading to feelings of loneliness and abandonment. Similarly, A.M. only developed major depression after a series of adverse life events, all happening in quick succession, and all involving the loss of close family members and feelings of loneliness and abandonment. If A.M.’s twin sister were to experience a similar fate, it remains possible that she would also be at risk for developing major depression. Clearly, a bilateral amygdala lesion is not sufficient for the development of major depression, but it may render individuals more vulnerable to the effects of social isolation, which appears to be a common consequence of having amygdala damage in free-ranging rhesus monkeys (34).

A.M.’s depression featured pronounced and uncontrollable negative cognitive biases and ruminations, and it is possible that an intact

amygdala normally helps to inhibit such dysfunctional thought processes, although this is still speculative and needs to be explored further. It has been hypothesized that the amygdala updates the valuation of "self" representations in the orbital frontal cortex (OFC) (35), and we recently showed (36) that an intact amygdala is required to protect us from illusory body experiences and distortions in self-perception. Interestingly, lesions of the basolateral amygdala hinder the formation of stimulus-outcome representations in the OFC of rats (37) and amygdala lesions in macaques significantly reduced, but did not abolish, the encoding of reward value in the OFC (38). Amygdala lesions in humans have also been found to result in reduced OFC activation associated with reward expectation (39). In the present study, at baseline, A.M. exhibited increased connectivity between the SAN and the precuneus, a functional core of the DMN. It has been found that structural integrity of the SAN is necessary for the efficient regulation of activity in the DMN (40). Thus, amygdala damage may affect the homeostatic interplay between large-scale networks (20), possibly facilitating hyperconnectivity within the DMN and leading to the self-centered, ruminative responding characteristic of major depression.

The recent discovery of rapid antidepressant effects of ketamine has stimulated a reconceptualization of how treatment-resistant major depression and suicidality could be targeted, but the mechanisms of action of ketamine remain obscure (26). Ketamine infusions in patients with treatment-resistant major depression have been found to induce an increase in glucose metabolism in the prefrontal cortex that correlates with the opposite effect in the amygdala (27). These changes could be causally involved in the antidepressant effect or a by-product of the symptom reduction. Interestingly, in mouse models of depression, infusion of ketamine into the amygdala was found to have no effects (28), while a subanesthetic intraperitoneal dose of ketamine normalized depressive-like behavior and was accompanied by reduced glutamate functional connectivity strength (29). In patients with major depression, ketamine was found to normalize insular connectivity with the DMN (30) and to increase global connectivity in the prefrontal cortex (31).

In the case of A.M., ketamine was able to initiate a rapid antidepressant effect that was associated with a reduction in connectivity between the DMN and SAN, and an enhancement of connectivity between the DMN and FPN (Figure 1). However, these findings should be interpreted cautiously given the limitations of an open-label case study and A.M.'s unique depression phenotype and brain lesion. While A.M. has complete destruction of the basolateral amygdala, we cannot rule out the possibility that functional residual tissue in the central amygdala and the amygdalo-hippocampal transition zone or damage to fibers passing through the calcified regions contributed to the observed results. Furthermore, it is conceivable that ketamine's effect on functional connectivity was altered by A.M.'s amygdala pathology, making the fMRI findings highly specific to A.M.'s brain.

The case of A.M. illustrates that treatment-resistant major depression can develop despite focal bilateral amygdala damage, highlighting the fact that the amygdala is not necessary for the subjective experience or behavioral presentation of clinical depression. Current conceptions of major depression emphasize heterogeneity in clinical phenotypes (41) and underlying biotypes (42–44), such that amygdala-based biomarkers may prove insightful for some but not all subtypes of the illness. Moreover, consistent with A.M.'s amygdala lesion, her major depression phenotype was characterized by marked anhedonia and cognitive biases but only modest symptoms of anxiety (45). Given the broad spectrum of major depression phenotypes, it is conceivable that the antidepressant effect of ketamine in subgroups of patients with major depression with strong anxiety features or comorbidities may act via amygdala-

dependent mechanisms, but our observations show that ketamine can rapidly exert its antidepressant effects with or without the amygdala.

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Supplemental Information

Supplemental Methods

Participants

The study was approved by the local ethics committee of the Medical Faculty of the University of Bonn, Germany. All participants gave written informed consent and the study was conducted in accordance with the latest revision of the Helsinki Declaration. The 12 control patients with major depressive disorder (MDD) received inpatient treatment at the University Hospital Bonn and were treated according to current guidelines. The treatment included psychotherapy and antidepressant medication. All MDD patients were scanned within three days after admission (mean age ± SD = 42.75 ± 13.23 years; mean MADRS score ± SD = 28.00 ± 6.61). Furthermore, to examine possible structural changes in the MDD patients, structural images of 16 healthy women (mean age ± SD = 39.88 ± 11.79 years; mean BDI score ± SD = 1.31 ± 1.53) were used that were collected on the same MRI system.

Screening questionnaires

Loneliness was assessed with the UCLA Loneliness Scale (46) and the Social Network Index (SNI) questionnaire was used to examine the patient's social network (47). Depressive symptoms were measured with the Beck Depression Inventory-II (BDI)(48) and the Montgomery-Åsberg Depression Rating Scale (MADRS)(49). Suicidal ideation was assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS)(50). Dissociative symptoms were evaluated with the Clinician-Administered Dissociative States Scale (CADSS)(51). Psychological disorders were assessed with a Structured Clinical Interview for DSM-IV (52) conducted by an experienced psychiatrist who was familiar with the patient's medical history.

Acquisition of the MRI data

T he MRI data were collected using a 1.5-tesla Siemens Avanto MRI system (Siemens AG, Erlangen, Germany) equipped with a 12-channel head-coil. T2*-weighted echoplanar (EPI) images with blood-oxygen-level dependent contrast were obtained [repetition time (TR) = 3070 ms, echo time (TE) = 45 ms, interleaved slicing, matrix size: 64 x 64, voxel size: 3 x 3 x 3 mm, FoV = 192 mm, flip angle 90°, 38 axial slices]. The duration of each resting state session was 6 minutes. In addition, high-resolution anatomical images were acquired on the same scanner using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 3.09 ms, matrix size: 256x256, voxel size: 1 x 1 x 1 mm, FoV = 256 mm, flip angle 15°, 160 sagittal slices).

Anatomical images of the amygdala patient were also acquired on a 3.0-tesla Siemens TRIO MRI system (Siemens AG, Erlangen, Germany), using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 2.54 ms, matrix size: 320x320, voxel size: 0.8 x 0.8 x 0.8 mm, flip angle 9°, 208 sagittal slices).

fMRI data analysis

Analysis of resting state functional magnetic resonance imaging (rsfMRI) data was performed using the CONN toolbox, version 18a (https://web.conn-toolbox.org/; (53)), and statistical parametric mapping, version 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12), implemented in MATLAB R2018a (MathWorks, Natick, Massachusetts). The first five volumes were discarded to allow MRI T1 equilibration. Preprocessing of the remaining volumes was done using CONN's standard pipeline including realignment, coregistration with a high-resolution anatomic scan, slice-time correction, structural segmentation, normalization to Montreal Neurological Institute standard brain template, and spatial smoothing (Gaussian kernel of 6 mm3 full-width at half maximum). After the preprocessing steps, data were denoised using the anatomical component-based noise correction (aCompCor) (54) method. White matter and cerebrospinal fluid time series along with the effect rest (rest condition convolved with hemodynamic response function) were regressed out. A band-pass filter (0.008–0.09 Hz) and detrending (removal of linear trends within each functional session) were applied to the time series to reduce low-frequency drift and noise effects. We used the masks provided within CONN as seeds for the default mode network (DMN) (medial prefrontal cortex MNI coordinates x, y, z: 1, 55, -3; posterior cingulate cortex MNI coordinates x, y, z: 1, -61, 38; left lateral parietal cortex MNI coordinates x, y, z: -39, -77, 33; and right lateral parietal cortex MNI coordinates x, y, z: 47, -67, 29), frontoparietal network (FPN) (left prefrontal cortex MNI coordinates x, y, z: -43, 33, 28; right prefrontal cortex MNI coordinates x, y, z: 41, 38, 30; left posterior parietal cortex MNI coordinates x, y, z: -46, -58, 49; right posterior parietal cortex MNI coordinates x, y, z: 52, -52, 45) and salience network (SAN) (anterior cingulate cortex MNI coordinates x, y, z: 0, 22, 35; left anterior insula MNI coordinates x, y, z: -44, 13, 1; right anterior insula MNI coordinates x, y, z: 47, 14, 0; left rostral prefrontal cortex MNI coordinates x, y, z: -32, 45, 27; right rostral prefrontal cortex MNI coordinates x, y, z:32, 46, 27; left supramarginal gyrus MNI coordinates x, y, z: -60, -39, 31; right supramarginal gyrus MNI coordinates x, y, z: 62, -35, 32). Correlation coefficients were converted to normalized z-scores using Fisher's transformation to allow subsequent general linear model analyses. Seed-to-voxel analysis was performed at an individual-subject level in CONN by computing BOLD signal temporal correlations between the previously mentioned seeds and all other voxels in the brain. First, we computed a separate analysis of variance (ANOVA) for each seed region in which we tested any difference between the patient's four resting state measurements and the MDD

controls. To evaluate differences between repeated measurements of patient AM, the MDD controls were modeled as 0 to obtain the necessary variance for a second-level analysis. In case of significant differences, we used independent *t*-tests to separately compare each resting state measurement of the patient with the MDD controls. All analyses applied a height threshold of $P < 0.001$ (uncorrected) at the whole-brain level. *P*-values were corrected for multiple comparisons (false discovery rate (FDR)) and $P_{FDR} < 0.05$ was considered significant. The structural images and contrast images of the resting state data were uploaded to a public repository (https://neurovault.org/collections/RDWCTHVB/).

Voxel-Based Morphometry

The CAT12 toolbox (Computational Anatomy Toolbox 12, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) implemented in SPM12 was used with default settings for the preprocessing of the structural images. All T1-weighted images were corrected for bias-field inhomogeneities, tissue classified and spatially normalized to MNI-space at a voxel size of 1.5 × 1.5 × 1.5 mm^3 using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm (55). Homogeneity of gray matter images was checked using the covariance structure of each image with all other images, as implemented in the check data quality function. In addition to visual inspections, all scans passed the automated data quality check protocol. Subsequently, the modulated gray matter volume (referred to as GMV) images were smoothed with an isotropic Gaussian kernel of 6 mm full width half maximum (FWHM). The GMV data were analyzed using an absolute threshold masking of 0.1. The amygdala was anatomically defined according to the Wake Forest University Pick Atlas (Version 3.0) and GMV values were extracted from the amygdala using the get_totals script (http://www.nemotos.net/?p=292)

Supplemental Results

Resting state data - Default mode network

We first tested whether there were any significant differences between the patient's measurements and the MDD controls. We detected significantly altered connectivity between the posterior cingulate cortex as seed and the left frontal pole (-10, 64, 18; $k = 20$, $F_{(4,11)} = 27.47$, $P_{FDR} = 0.05$; -24, 44, 40; $k = 18$, $F_{(4,11)} = 21.83$, $P_{FDR} = 0.05$). Separate comparisons of the patient's measurements and the MDD controls revealed significantly enhanced positive connectivity between the posterior cingulate cortex and the frontal pole 200 minutes after the first infusion (-10, 64, 18; $k = 70$, $t_{(11)} = 10.22$, $P_{FDR} < 0.01$) and one day after the infusion (32, 44, 38; $k = 53$, $t_{(11)} = 6.77$, $P_{FDR} < 0.01$). We also found a significant change in the correlation between the posterior cingulate cortex and the signal in the left cerebellum (negative correlation in the patient and positive

correlations in the MDD controls) 200 minutes after the infusion (-40, -60, -42; k = 41, $t_{(11)}$ = 6.27, P_{FDR} = 0.05).

Furthermore, we found significantly altered DMN connectivity between the right lateral parietal cortex as seed and the left frontal pole (-14, 66, 4; k = 22, $F_{(4,11)}$ = 24.74, P_{FDR} = 0.02) and the left cerebellum (-36, -64, -44; k = 22, $F_{(4,11)}$ = 52.59, P_{FDR} = 0.02). Separate comparisons of the patient's measurements and the MDD controls revealed significantly enhanced positive connectivity between the right lateral parietal cortex and the frontal pole 200 minutes after the first infusion (-12, 66, 4; k = 80, $t_{(11)}$ = 8.95, P_{FDR} < 0.01).

Significant differences were also evident in the functional coupling between the medial prefrontal cortex as seed and the superior frontal gyrus (12, -6, 76; k = 26, $F_{(4,11)}$ = 27.56, P_{FDR} = 0.02), the precuneus (4, -68, 18; k = 21, $F_{(4,11)}$ = 27.81, P_{FDR} = 0.02) and the left cerebellum (-38, -72, -40; k = 23, $F_{(4,11)}$ = 19.92, P_{FDR} = 0.02). Separate comparisons of the patient's measurements and the MDD controls revealed significantly enhanced positive connectivity between the medial prefrontal cortex as seed and the superior frontal gyrus (12, -6, 76; k = 78, $t_{(11)}$ = 9.83, P_{FDR} < 0.01) at baseline and the frontal pole (-8, 70, 2; k = 58, $t_{(11)}$ = 6.92, P_{FDR} < 0.01), the precuneus (2, -54, 44; k = 109, $t_{(11)}$ = 6.91, P_{FDR} < 0.01), the lateral occipital cortex (40, -74, 48; k = 46, $t_{(11)}$ = 8.56, P_{FDR} < 0.01), and the occipital pole (28, -92, 20; k = 50, $t_{(11)}$ = 5.85, P_{FDR} < 0.01) in the patient 200 minutes after the first infusion. There was also a trend-to-significant effect on the connectivity with the frontal pole one day after the first infusion (30, 40, 34; k = 34, $t_{(11)}$ = 5.65, P_{FDR} = 0.079). In addition, we observed negative correlations between the medial prefrontal cortex and the left cerebellum (-40, -68, -44; k = 41, $t_{(11)}$ = 7.57, P_{FDR} = 0.02), the middle temporal gyrus (60, -52, -4; k = 48, $t_{(11)}$ = 7.32, P_{FDR} = 0.02), the precuneus (4, -56, 14; k = 46, $t_{(11)}$ = 6.02, P_{FDR} = 0.02), and the right superior parietal lobule (36, -40, 54; k = 35, $t_{(11)}$ = 6.21, P_{FDR} = 0.03) in the patient 200 minutes after the first infusion compared to positive correlations in the MDD controls. The negative correlation between the medial prefrontal cortex and precuneus was also evident in the patient seven days after the infusion (4, -68, 18; k = 65, $t_{(11)}$ = 7.03, P_{FDR} < 0.01).

Resting state data - Frontoparietal network

We first tested whether there were any significant differences between the patient's measurements and the MDD controls. We detected significantly altered connectivity between the right posterior parietal cortex as seed and the left superior frontal gyrus and frontal pole (-8, 32, 58; k = 31, $F_{(4,11)}$ = 16.47, P_{FDR} < 0.01), the middle temporal gyrus (70, -40, -2; k = 19, $F_{(4,11)}$ = 29.18, P_{FDR} = 0.05) and the right cerebellum (38, -70, -50; k = 18, $F_{(4,11)}$ = 44.56, P_{FDR} = 0.05). There were no significant differences for other seeds of the frontoparietal network. Separate comparisons of the patient's measurements and the MDD controls revealed significantly enhanced positive connectivity between the right posterior parietal cortex and the superior frontal gyrus and frontal

pole (-12, 36, 60; k = 81, $t_{(11)}$ = 6.67, P_{FDR} < 0.01) and the right lateral occipital cortex (42, -90, 4; k = 52, $t_{(11)}$ = 6.28, P_{FDR} = 0.01) 200 minutes after the first infusion. Furthermore, there was a significantly enhanced positive correlation between the right posterior parietal cortex as seed and the left occipital pole (-34, -96, -2; k = 46, $t_{(11)}$ = 5.82, P_{FDR} = 0.05) one day after the infusion and with the right middle temporal gyrus (70, -40, -2; k = 48, $t_{(11)}$ = 5.82, P_{FDR} = 0.03) seven days after the infusion.

Resting state data - Salience network

We first tested whether there were any significant differences between the patient's measurements and the MDD controls. We detected significantly altered connectivity between the anterior cingulate cortex as seed and the frontal pole (-42, 42, 14; k = 20, $F_{(4,11)}$ = 29.26, P_{FDR} = 0.03) and the precuneus (-4, -56, 34; k = 26, $F_{(4,11)}$ = 16.35, P_{FDR} = 0.02). There were no significant differences for other seeds of the salience network. Separate comparisons of the patient's measurements and the MDD controls revealed significantly enhanced positive connectivity between the anterior cingulate cortex and the precuneus (-4, -56, 34; k = 60, $t_{(11)}$ = 6.63, P_{FDR} < 0.01) at baseline. There were no significant differences 200 minutes and one day after the first infusion, but the significantly altered connectivity with the precuneus was again evident after seven days (-2, -60, 32; k = 39, $t_{(11)}$ = 5.12, P_{FDR} = 0.06).

Second ketamine infusion

A second ketamine infusion with a reduced dose (0.25 mg/kg) was administered seven days after the first ketamine infusion to examine if a similar antidepressant effect could be achieved, while reducing the dissociative symptoms after the infusion. The ketamine-induced dissociative symptoms were diminished compared to the first infusion (50 minutes after the first infusion CADSS = 24; 50 minutes after the second infusion CADSS = 17) and vanished after 130 minutes (first infusion CADSS = 2; second infusion CADSS = 0). However, the antidepressant effect was also less pronounced (59% reduction of the MADRS score 50 minutes after infusion; cf. Supplementary Figure 1) relative to the first infusion with a ketamine dose of 0.5 mg/kg. Depressive symptoms returned to baseline after two days. This observation is in accordance with a recent dose-ranging trial of intravenous ketamine that found clear evidence for clinically meaningful efficacy only for the standard dose (0.5 mg/kg) and high dose (1 mg/kg) of intravenous ketamine (56). Ms. M. was discharged at her own request two weeks after the second ketamine infusion.

Venous blood samples were collected 50 minutes after the first and second ketamine infusions to measure serum concentrations of ketamine and norketamine (the active metabolite of ketamine). As expected, the second infusion yielded lower concentrations (ketamine = 40 µg/l,

norketamine = 30 µg/l) compared to the first infusion with the higher dose (ketamine = 149 µg/l, norketamine = 35 µg/l).

Additional ratings

The Hamilton Rating Scale for Depression (HAMD) (57) was administered six times: before, one day after and seven days after the first and second ketamine infusion. There was a clear reduction of HAMD scores after the first ketamine infusion (0.5 mg/kg) (before infusion = 31, one day after infusion = 16, seven days after infusion = 23), but only a small effect was evident one day after the second ketamine infusion with a lower dose of 0.25 mg/kg (before infusion = 25; one day after infusion = 23; seven days after infusion = 25). Two items of the HAMD assess psychological and somatic anxiety symptoms. Consistent with the clinical phenotype of Urbach Wiethe disease, the patient showed only low levels of anxiety (sum score anxiety items = 3; possible maximum 8) at baseline and these symptoms decreased after the first ketamine infusion (one day after infusion sum score anxiety items = 0; seven days after infusion sum score anxiety items = 1).

VBM results

The total GMV ($t_{(26)}$ = 0.91, P = 0.37) and the GMV of the left ($t_{(26)}$ = 1.25, P = 0.22) and right amygdala ($t_{(26)}$ = 0.60, P = 0.55) were not significantly different between MDD patients and healthy controls. Thus, it seems unlikely that MDD-associated structural changes in the amygdala volume of the MDD controls have contributed to the observed difference in functional connectivity.

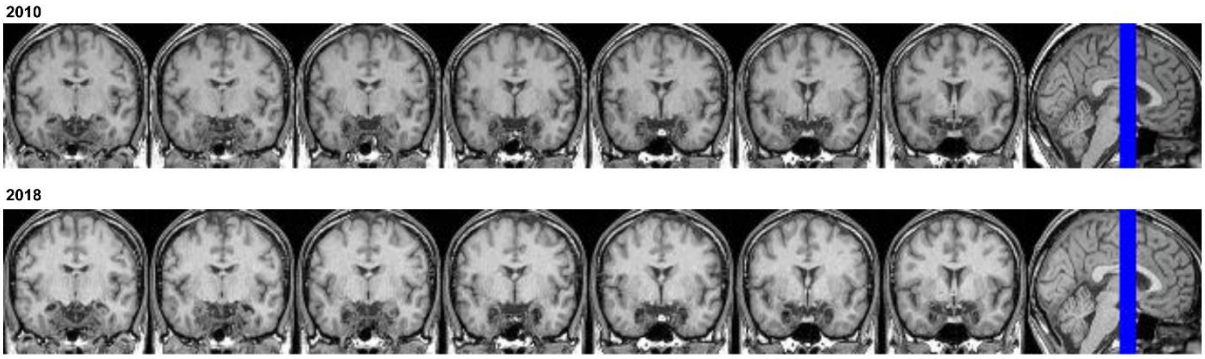
Supplemental tables and figures

Table S1. Failed antidepressant treatments in the amygdala patient

Treatment	Dose
Atypical antipsychotics with antidepressant action	
Quetiapine	100 mg/day
Olanzapine	5 mg/day
Cognitive-behavioral therapy (CBT)	1 session/week
Electroconvulsive therapy (ECT)	
Unilateral ECT	12 sessions
Bilateral ECT	15 sessions
Monoamine oxidase inhibitors (MAOIs)	
Tranylcypromine	20 mg/day
Norepinephrine and dopamine disinhibitors (NDDIs)	
Bupropione	150 mg/day
Other antidepressants	
Agomelatine	25-50 mg/day
Mirtazapine	30-60 mg/day
Tianeptine	37.5 mg/day
Selective serotonin reuptake inhibitors (SSRIs) and serotonin modulators	
Citaloprame	10-40 mg/day
Sertraline	100 mg/day
Vortioxetine	10-15 mg/day
Selective serotonin and norepinephrine reuptake inhibitors (SSNRI)	
Duloxetine	30-120 mg/day
Venlafaxine	150 mg/day
Tricyclics (TCAs) and heterocyclics	
Trimipramine	150 mg/day

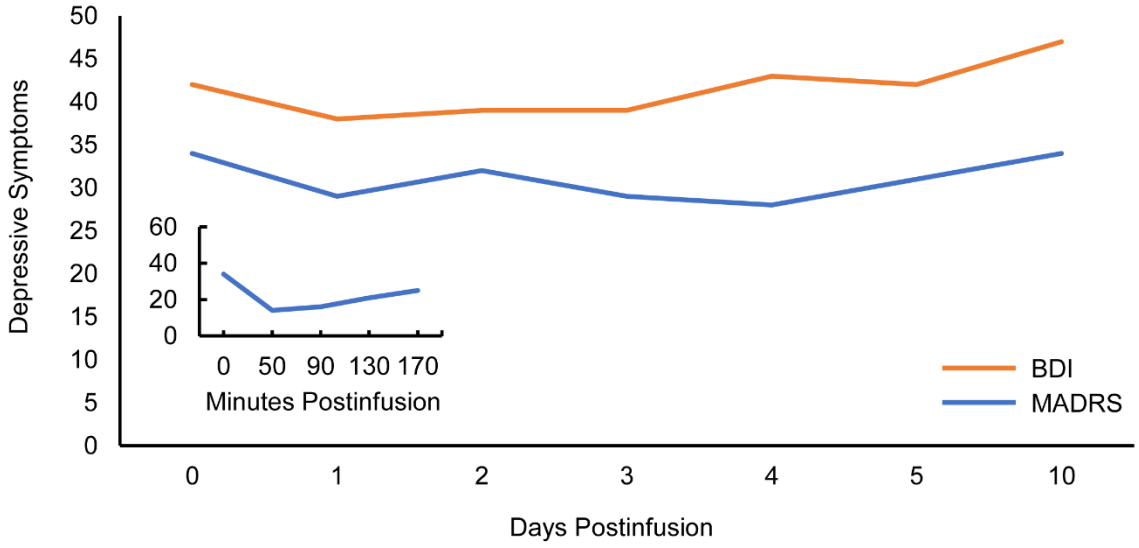
Note: Several medications were prescribed in parallel. The duration of treatments varied over the course of three years (2015-2018), but the minimum durations were in accordance with current guidelines (58).

Figure S1.



Normalized coronal anatomical T1-weighted magnetic resonance images of patient AM's amygdala lesion in the years 2010 and 2018. Anatomical inspection of patient AM's scans reveals complete bilateral destruction of the basolateral amygdala with minor sparing in anterior amygdaloid and ventral cortical amygdaloid regions at a rostral level and central amygdaloid nucleus and the amygdalo-hippocampal transition zone at more caudal levels. Notably, her lesion has remained stable over this time period and has not progressed into other regions of the brain.

Figure S2.



Depressive symptoms were assessed for five consecutive days and 10 days after a second subanesthetic i.v. dose (0.25 mg/kg) of ketamine in a patient with severe depression despite bilateral amygdala damage. Clinician-evaluated depressive symptoms were reduced after the ketamine infusion, but the magnitude of this antidepressant effect was smaller than the effect observed after the first infusion with a large ketamine dose (0.5 mg/kg). The inlay display changes in the clinician-rated depressive symptoms in the 170 minutes after the ketamine infusion.

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Chapter 5.

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Improving therapy outcome prediction in major depression using multimodal functional neuroimaging: A pilot study

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ABSTRACT

Mounting evidence emphasizes the usefulness of imaging biomarkers for predicting therapy outcome in major depressive disorder (MDD), in particular building on functional imaging studies of task-based responses to emotional face stimuli and resting state-related connectivity patterns. To explore the possibility that prediction accuracy even in small patient samples would significantly gain from integrating data from different imaging modalities, we acquired functional neuroimaging data both at-rest and during exposure to emotional faces from 21 MDD patients before and 7 weeks after treatment-as-usual, as well as from 20 age- and gender-matched control participants assessed at similar intervals. As expected, MDD patients showed disturbed pre-treatment responses to emotional faces, including left amygdala hyperactivation. Therapeutic outcome correlated with pre-treatment activation, with subgenual cingulate response to emotional faces yielding best results (r values ranging from .4 to .66). A support vector machine classifier trained on task-based or resting-state data predicted responder status, with the right dorsolateral prefrontal cortex connectivity pattern yielding best accuracy (88.9%). Crucially, combining task-based with resting-state data increased prediction accuracy by 6.5 to 7.7 percentage points on average. From this pilot study, we conclude that multimodal functional imaging has the potential of improving therapy outcome prediction even in small MDD sample sizes, resulting in about one additional correct classification every 15 patients. The present results inform future studies which are needed to consolidate imaging approaches as a means of establishing precision medicine in psychiatry.

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric conditions, currently the leading cause of disability in the US for people 15 to 44 years old (1), and predicted to be among the 21st century's most burdensome diseases [1,2]. As remission of depressive symptoms occurs in only one-third of MDD patients after the first antidepressant trial and unsuccessful treatments prolong suffering, development of predictive biomarkers of therapeutic outcome is at the center-stage of current psychiatry research [3-6]. Thanks to its increasing availability in university hospitals, functional neuroimaging is a promising tool in that endeavor [3,7-9], with methodological advances moving towards personalized treatments based on direct pre-treatment measures of neural and behavioral response in MDD [4].

Current neurocircuitry models of MDD emphasize disturbed functional connectivity of fronto-striatal and limbic regions [10-16], with deficient emotion regulation functionality assumed to lie at the core of the pathophysiology of MDD [3]. Emotion regulation engages, among other regions, the amygdala and divisions of the medial prefrontal cortex (mPFC), in particular the subgenual part of the anterior cingulate cortex (sgACC) [10,11,13,15,17-19]. The amygdala is a primary hub for early (<100 ms) assessment of social and emotional stimuli [20-23], and patients with MDD consistently exhibit reduced top-down regulatory interactions between mPFC and amygdala, resulting in increased amygdala responses to negative stimuli [12,24,25]. In particular, the processing of emotional faces [12,21,22] reliably shows activation abnormalities in patients with MDD [26] while controlling for higher-order cognitive processing. In addition, there is accruing evidence that amygdala responses to emotional face stimuli inform treatment outcome prediction in MDD [7,8,27]. Another informative brain region in this regard is the aforementioned sgACC, which contributes to automatic behavioral control and recognition of emotional states, reciprocally communicates with the amygdala, and shows abnormal responses and connectivity signatures in MDD patients [3,10,11,13,15,19,26,28-30]. sgACC pre-treatment hyperactivity normalizes after cognitive, pharmacological and electric stimulation therapy [13,31-33], and is predictive of therapy outcome [11,17,34-37]: the greater the sgACC pre-treatment response to emotional faces (particularly negative emotions), the greater the likelihood of improvement resulting from pharmaco- or psychotherapy [3,8].

In contrast to task-based neuroimaging, resting-state paradigms allow to investigate at the same time multiple distributed areas that seem to be functionally and anatomically connected, including the default mode network (DMN), the dorsal attention network (DAN), the executive control network (ECN), and the salience network (SN) [38-40]. Advantageously for investigations of MDD, resting-state connectivity is less susceptible to the confounding influence of task-relevant cognitive impairments typical of MDD than task-based paradigms. Several networks show altered resting-state signatures in MDD [3,9,15,41-43], with a recent study of over a thousand MDD patients identifying four distinct neurophysiological subtypes defined by specific patterns of dysconnectivity in limbic and fronto-striatal circuits [16]. Notably, those patterns were predictive of the response to transcranial magnetic stimulation (TMS) [16]; similarly, another study revealed that connectivity between nodes of the SN and the DMN was predictive of the outcome of psychotherapy [9].

Aims of the study

The aims of this pilot study were (1) to replicate previous findings relating brain responses to disease severity and treatment outcome using correlation approaches [11,17,34-37] and (2) to explore the possibility that combining data from multiple neuroimaging modalities (namely, task-based and resting-state data) has the

potential of improving classification-based therapeutic outcome prediction in MDD [3].

Material and methods

Participants

Functional imaging data were obtained pre- and post-treatment (7-weeks intervals on average) from 21 patients with MDD, and at comparable intervals from 20 age- and sex-matched healthy participants (Table 1). Patients were recruited from August 5, 2013, to January 9, 2015. All patients met DSM-IV criteria for unipolar major depressive disorder (MDD), diagnosed by structured clinical interview for DSM IV [44] conducted by specialist physicians of the University Medical Center in Bonn, and were under treatment according to current guidelines for MDD for the duration of the present study (56) and received selective serotonin reuptake inhibitors (N = 11), Alpha2-receptor-antagonists (N = 6), atypical antipsychotics (N = 5), and group behavioral therapy (N = 16). Exclusion criteria for patients were suicidal ideation, psychotic symptoms and MRI contraindications; for healthy participants, exclusion criteria were any lifetime axis I or II psychiatric disorder and any past or current psychoactive medication. This study was conducted according to the principles of the Declaration of Helsinki 2008 and approved by the local Institutional Review Board (IRB). In accordance with the guidelines of the ethics committee, the study procedures were fully explained prior to the participants providing written informed consent.

Criteria for response

Study outcome used for the correlation analyses was % change in Beck's Depression Index (BDI) (58) as a result of treatment, and study outcome used for classification analyses was treatment response, defined as a $\geqslant$ 50% decrease from the baseline BDI scores.

Task-based fMRI experimental paradigm

We employed short-duration presentation of emotional faces, a paradigm previously used in several MDD studies [7,12,24,45]. Stimuli consisted in pictures of faces expressing fear, anger, sadness, disgust, happiness, and no emotion (neutral), selected from the Karolinska Directed Emotional Faces [46]. These stimuli were presented near the threshold of conscious awareness by presenting an emotional face picture very briefly (33 ms), followed immediately by a neutral face picture from the same actor presented for 800 ms. Individual characteristics (e.g. hair) were covered using a mask with the same colour as the background, leaving an oval aperture for the facial features. The inter-stimulus interval varied between 5.5 and 7.5 s (uniform distribution). In each fMRI run, nine stimuli were presented for each emotion in an event-related design; participants underwent 4 runs of about 6 min duration each. Previous psychophysical tests have shown that with this presentation schedule, emotional faces are close to or below the subliminal threshold for discrimination according to signal detection criteria, i.e. most individual participants cannot detect the emotional face stimulus nor discriminate the facial expression [47]. As the aim of this experiment was to measure the response in emotion-related brain regions to emotional face stimuli, participants were asked to report the gender of the face stimuli, a task that focused their attention on the face but was irrelevant to the research question. Stimulus presentation and response collection was implemented using Presentation software (Neurobehavioral Systems, Albany, CA), liquid crystal display video goggles (Nordic NeuroLab, Bergen, Norway) and a custom MRI-compatible response box.

In line with previous studies [21], participants were asked after the experiment whether they had noticed any abnormalities about the face stimuli presented, to ensure that the emotional faces presented were below the subjective level of awareness. These interviews revealed that 3 patients and 2 control participants had, in some trials, perceived 2 faces presented in rapid

succession, one of which displayed an emotion. To ascertain that these participants did not drive the reported effects, we repeated the analysis after omitting these participants' data but observed no substantial changes in the results. In order to evaluate if the information perceived during the task was sufficient for recognition of the presented emotions, a sample of 12 patients repeated the experiment after the fMRI scan at measurement time 2 (i.e. post-treatment or equivalent) and attempted to categorize the face stimuli into six categories (five emotions plus neutral; i.e., a six-alternative forced choice task). Classification performance was not different from chance (mean % correct: 17.5; standard deviation: 3.4; t-test vs. chance: $t(11)=0.85$, $p=0.41$), indicating that the masking procedure prohibited conscious emotion recognition.

MRI data acquisition

MRI data were acquired using a 1.5 Tesla Avanto MRI system (Siemens, Erlangen, Germany) equipped with a 12-channel standard head coil at the Life & Brain Centre, Bonn. Imaging data were collected for each participant and measurement point (pre- and post-treatment for participants with MDD, and at similar time intervals for control participants), and consisted in four task-based runs with 119 to 127 functional images each and one resting-state run (5.75 minutes, 115 volumes, eyes closed) obtained using a T2*-weighted gradient-echo planar image (EPI) sequence (voxel size = 3 x 3 x 3 mm; TR = 3000 ms; TE = 45 ms; flip angle = 90°; FoV = 192 mm; matrix size = 64 x 64; 35 slices; interleaved slice order with interslice gap of 1 mm). Slices were oriented parallel to the intercommissural plane (AC-PC line). Subsequently, a high-resolution structural image was acquired using a T1-weighted 3D MRI sequence (voxel size = 1 x 1 x 1 mm; TR = 1660 ms; TE = 3.09 ms; flip angle = 15°; matrix size = 256 × 256, no interslice gap). Participants wore earplugs and foam padding was used to reduce head motion.

Task-based fMRI data analysis

The fMRI data were preprocessed and processed using SPM12 software from the Wellcome Trust Centre for Neuroimaging (www.fil.ion.ucl.ac.uk/spm) running in MATLAB R2015A (The MathWorks, Natick, MA). Preprocessing followed standard procedures as in our previous studies [48]. In brief, after discarding the first 5 images to ascertain that T1-equilibration artefacts were eliminated from the time-series, images were motion-corrected using realignment, the anatomical T1 image was co-registered with the aligned functional images, spatially normalized to the Montreal Neurological Institute (MNI) standard space using a two-step procedure including segmentation of the T1-image and application of the resulting transformation parameters to the functional time-series, resampled at a 3x3x3mm resolution, and finally smoothed by convolution with a 8-mm full width at half maximum 3D Gaussian kernel [49]. Preprocessed fMRI data were analyzed using the general linear model (GLM) framework implemented in SPM12, following a 2-step mixed-effects analysis, as is common in SPM for group analyses [50]. The first step used a fixed-effects model to analyze individual data sets, and the second step used a random-effects model to analyze the group aggregate of individual results, described under "whole-brain analysis", below. For the fixed-effects model, a temporal high-pass filter with a cutoff of 128 s was used to remove low-frequency signal drifts and an autoregressive model (AR 1 + white noise) was used to estimate serial correlations in the data. A masking threshold level of 0.2 was used to determine voxel inclusion in the analysis. Following that, a linear combination of regressors in a design matrix was fitted to the task-based data to produce beta estimates [51], which represent the contribution of a particular regressor to the data. The GLM applied to the individual data sets contained separate regressors of interest for each experimental condition (i.e. faces expressing fear, anger, sadness, disgust, happiness and no emotion). These

regressors were created by modeling the onset and duration of each stimulus as a series of delta functions representing probable neural events, this time-series was then convolved with the canonical hemodynamic response function (HRF, implemented as a sum of 2 gamma functions in SPM12) to yield predictions of changes in BOLD signal evoked by the stimuli. The design matrix further included a constant term, and 6 realignment parameters (yaw, pitch, and roll and X-, Y-, and Z-axis translation terms, obtained during motion correction) used to model movement-related artefacts not eliminated during realignment (e.g., spin-history effects). 3D parameter estimate maps for each of our experimental conditions (i.e. faces expressing fear, anger, sadness, disgust, happiness and no emotion) were produced for each participant and measurement session (i.e. one per scanning day) and used to calculate contrast maps (see second-level analyses, below).

Resting-state fMRI data analysis

Resting-state data were analysed using the CONN toolbox for SPM (68), including default preprocessing settings such as slice-time correction, unwarping, denoising using a band-pass filter [0.008 – 0.09 Hz] and smoothing with a 8-mm full width at half maximum 3D Gaussian kernel. We ran both whole-brain correlation analyses using regions-of-interest (ROIs; see below) as seeds, and seed-to-seed correlation analyses for each subject and measurement point. Seeds were anatomically-defined ROIs relevant in the pathophysiology of depression. They included left and right subgenual cingulate (sgACC, Brodmann Area 25) and left and right amygdala (entire Amygdala, defined using the Anatomy toolbox version 2.1 [52,53]), as well as several regions identified in analyses of the brain at rest, identified using 5mm-diameter spheres centered on coordinates previously published and used in an MDD study [9,40]: left and right intraparietal sulcus (MNI coordinates: [-41 -39 45; 44 -39 45], part of the dorsal attention network = DAN), left and right dorsolateral prefrontal cortex ([-32 45 30; 32 45 30], executive control network = ECN), left and right anterior insula and dorsal anterior cingulate cortex ([-41 3 6; 41 3 6; 0 21 36], salience network = SN), medial prefrontal cortex and precuneus ([-1 54 27; 0 -52 27], default-mode network = DMN). Whole-brain correlation maps were Fischer-Z transformed, compared across participant groups and measurements, and used in correlation analyses with disease severity or treatment effects. Seed-to-seed data were compared across participant groups and measurements and used in correlation analyses with disease severity or treatment effects and for patient classification analyses.

Whole-brain group (second-level) analysis

Single-subject parameter maps (task-based data) or Fischer-transformed correlation maps (resting state data) of MDD participants MDD and controls, for both measurement points, were smoothed with a Gaussian kernel imported separately into SPM12's full-factorial analysis of variance (ANOVA) model to evaluate group statistics (second-level analysis; random effects). For task-based data, effects assessed in each voxel of the brain were the response to emotional faces overall (all emotions vs. neutral), and the response to each type of emotional face (i.e. fear, anger, sadness, disgust, happiness each contrasted with neutral) assessed within regions showing differences in the response to emotional faces overall. For the resting-state data, we assessed the connectivity between each seed region and the whole brain. SPM12 uses the Greenhouse–Geisser correction for nonsphericity in the data. The results were controlled for multiple comparisons by using a whole-brain, voxel-wise family-wise error correction (pFWE = 0.05). Locations of peak activation were defined using MNI coordinates.

Region-of-interest analysis of task-based fMRI data

We further analysed task-based responses in bilateral amygdalae and subgenual cingulate

regions (anatomically-defined, see resting-state analysis above). Parameter estimates for each ROI were extracted from all voxels included in the GLM analysis and averaged across voxels. Parameter estimates in clusters that showed hyper- or hypo-activation in response to emotional faces in patients vs. controls (see Results) were extracted and processed in the same fashion. The resulting summary parameter estimates were then compared across conditions, participant groups and measurements and used in correlation and classifier analyses. ROIs were identical across all participants.

Treatment outcome prediction: classification procedure

To predict responder status (responder / non-responder) we employed libsvm [54] (available at http://www.csie.ntu.edu.tw/~cjlin/libsvm), a commonly-used implementation of a support vector machine (SVM) run within MATLAB R2015A on a MacPro (late 2013 model) 3.7 GHz Quad-Core Intel Xeon E5 with 64 GB 1866 MHz DDR3 RAM. The type of SVM used was C-SVM.

Features were, for the task-based data, the parameter estimates ("Beta" values calculated in SPM) of the response to each kind of emotional face, averaged across voxels of each ROI, and for the resting-state data, the connectivity (r) values obtained between a given ROI and the other ROIs of interest. The reason for evaluating responses to emotions separately in the task-based data and evaluating connectivity profiles separately by ROI for the resting-state data is that for task-based data neural responses to different emotions were found to be differently predictive of treatment outcome in previous work and combining task-based data across ROI yielded robust classification findings, while many ROIs were candidates for connectivity changes between patients and controls based on the resting-state data. All features were normalised to values between 0 and 1. There was no missing data.

Parameters were either at default values (free parameter of the Gaussian radial basis function g = 1/number of features; tolerance of termination criterion = 0.001) or were systematically assessed: the parameter for the soft margin cost function C was varied (values of 1, 2, 3, 5, 10 and 20 were tested), and 4 kernel types (linear, polynomial, radial basis function, sigmoid) were tested. At this optimization stage, all resulting combinations of kernel and C value were tested in a grid search, performance values (raw accuracy) for all conditions of each modality (task-based or resting-state) were averaged, and the combination yielding the highest average performance was identified: polynomial kernel with C = 1. This kernel and C = 1 were then used to compare classifier performance across conditions and data types. Classifier performance was evaluated using a leave-one-patient-out cross-validation scheme: data from all but one patient were used to train the classifier (labels were responder and non-responder), and correct categorization (as responder or non-responder) of the patient not used during training by the trained classifier was considered a correct response. This procedure was repeated N times, where N = number of patients, yielding a classification accuracy score (N correct classifications / N patients). Significance of the classification accuracy score in each condition was assessed using permutation statistics [55,56]: the actual accuracy scores were compared to a reference distribution of accuracy values observed under the null hypothesis that the data features had no systematic relation to the patient's responder status. This distribution was built by repeating the leave-one-patient-out cross-validation scheme described above 10'000 times, each time shuffling the patients' labels (responder or non-responder) anew during classifier training. The *p*-value of a classification accuracy score was then the fraction of the distribution of accuracy values under the null hypothesis that was greater than, or equal to, the accuracy score actually observed using the correct labels. *P* values resulting from this procedure were corrected for multiple comparisons

across conditions using the Holm-Bonferroni procedure [57].

Results

Treatment response

Changes in BDI and HAMD scores in patients as a result of treatment are presented in Table 1. We found a significant decline from pre-treatment to post-treatment, a clinically meaningful response [58]. Out of our 21 patients, there were 7 responders based on BDI criteria.

Task-based hyper- and deactivations in patients pre-treatment

One cortical brain region showed higher activity during the presentation of emotional faces (contrast: all emotions > neutral faces) in patients pre-treatment (compared to both patients post-treatment and controls; conjunction contrast): the right postcentral gyrus [MNI coordinates: 50 -22 60; Z = 4.84; cluster size 689 voxels / 12 voxels survived voxel-wise p<0.05 FWE threshold]. Cortical brain regions with lower activity in patients pre-treatment (compared to both patients post-treatment and controls) were left inferior frontal gyrus [-36 21 12; Z = 5.72; 70 / 15 voxels], two locations in left middle frontal gyrus [-42 18 42; Z = 5.62; 152 / 31 voxels and -30 30 34; Z = 4.7; 86 / 2 voxels], precuneus [-8 -54 52; Z = 4.7; 204 / 2 voxels], and right posterior middle temporal sulcus [50 -50 2; Z = 4.77; 80 / 2 voxels]. These results are shown in Figure 1A.

BOLD response to emotional faces in amygdala and subgenual cingulate ROIs

As expected, we found an increased response to emotional compared to neutral faces in the left amygdala in MDD at T1 compared with controls, which normalized after therapy (3-way ANOVA with factors measurement timepoint, subject type and emotion; interaction between measurement timepoint and subject type: $F(1,189)$ = 11.80, p < 0.001; Figure 1B). There was no significant effect of emotion or interaction between

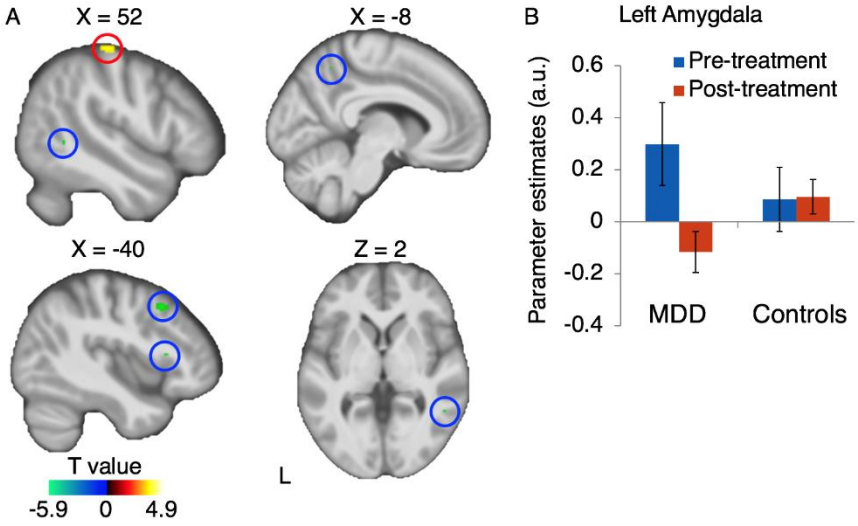

Figure 1. Abnormal neural response to emotional faces in MDD. A: left inferior and middle frontal gyrus, precuneus and right posterior middle temporal sulcus show decreased (green, blue circles) and right postcentral gyrus shows increased (yellow, red circles) BOLD responses during presentation of emotional faces compared to neutral faces, in patients pre-treatment compared to both patients post-treatment and controls (conjunction contrast). Results are shown here rendered on the average structural scan of all participants, and are thresholded at p < 0.05 corrected for family-wise errors (FWE) resulting from multiple comparisons across all voxels of the brain. X and Z values indicate the position of the slice in MNI coordinate space. B: Left amygdala showed an increased response to emotional compared to neutral faces in MDD pre-treatment compared with controls; this response decreased after therapy.

emotion and subject type or measurement point. Activation in subgenual cingulate cortex (sgACC) did not significantly vary with subject type, measurement timepoint or emotions.

Correlations between BOLD response to emotional faces and pre-treatment disease severity or treatment outcome

Next, we examined whether the BOLD signal in regions showing abnormal responses to emotional faces in patients and in the anatomically-defined amygdala and subgenual cingulate regions correlated with disease severity and therapy response in patients. The aim of this analysis was to replicate previous similar findings [11,17,34-37]. While correlations between disease severity and activation were not significant, we did find significant correlations between the effects of therapy (% BDI change) and pre-therapy activations in several ROIs (Table 2). Interestingly, different regions showed significant correlations depending on the BOLD contrast used, as follows. Using the BOLD response to neutral faces, we found significant positive correlations in left IFG and precuneus, and negative correlations in right postcentral gyrus and right amygdala; using the BOLD response to the emotional faces, we found significant positive correlations in precuneus for sad faces only. None of these correlations survived correction for multiple comparisons, in contrast to the strong positive correlations we obtained with bilateral subgenual cingulate regions' responses to all emotions. When we subtracted the response to neutral faces from the response to emotional faces, we found negative correlations for one or more emotions in all regions we investigated (of which only two survived corrections for multiple comparisons), except in the amygdala and subgenual cingulate regions. In the amygdala, we found strong positive correlations for several emotions, many of which survived correction for multiple tests, while in the subgenual cingulate, we found positive correlations for several emotions that did not survive multiple comparisons (Table 2).

Functional connectivity based on resting-state data

A whole-brain search for correlations between resting-state activity in our regions of interest for connectivity analyses and all voxels of the brain revealed that compared with healthy controls, patients showed before treatment a reduced connectivity between the right subgenual cingulate (sgACC) and the right middle frontal

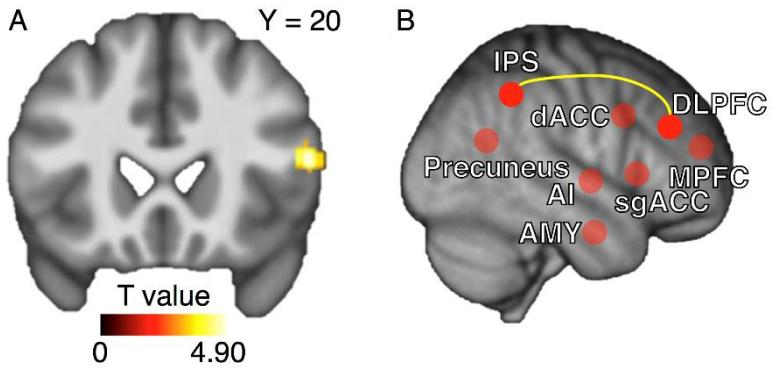

Figure 2. Results of resting-state functional connectivity analyses. A: Before treatment, patients showed a reduced resting-state functional connectivity between the right subgenual cingulate (sgACC) and the right middle frontal gyrus compared with healthy controls (conventions as in Figure 1). B: Therapy resulted in a reduction of resting-state connectivity between seeds in right dorsolateral prefrontal cortex and right intraparietal sulcus in patients. Red dots are projections on the right hemispheric surface of the location of connectivity seeds included in the analysis. IPS = intraparietal sulcus; dACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; MPFC = medial prefrontal cortex; AI = anterior insula; sgACC = subgenual anterior cingulate cortex; AMY = amygdala.

gyrus [54 20 14; Z = 4.86; cluster size 25 voxels] (Figure 2). However, in the conjunction contrast comparing patients pre-treatment to both patients post-treatment and controls, no significant results were found. There was no significant correlation between BDI or change in BDI during treatment on one hand and connectivity between resting-state activity in our regions of interest and all other regions of the brain on the other hand. Systematic pairwise seed-to-seed correlation analyses between regions of interest revealed that patients' functional connectivity between right DLPFC and right IPS was significantly reduced as a result of therapy ($t(20)$ = 5.745, p_{corr} = 0.01, 2-sample t-test with Holm-Bonferroni correction for multiple comparisons). There was no difference in seed-to-seed connectivity between patients and controls and no correlation between seed-to-seed connectivity and pre-treatment BDI or change in BDI as a result of treatment.

Prediction of responder status: comparing classifier performance based on data of one imaging modality or combined across imaging modalities

Finally, we addressed the main aim of this study: we assessed whether responder status (i.e. whether a patient responded to treatment or not) could be predicted based on the task-based activations evoked by each emotion (combined activation across ROIs), the resting-state data (pattern of seed-to-seed connectivity for each seed tested), or a combination of task-based and resting-state data. Results (Table 3) show that prediction was indeed possible, that prediction based on task-based data tended to be better (69.4 vs 59% correct, a non-significant difference: $t(17)$ = 1.60, p < 0.13), and importantly, that supplementing the data of one kind with the best data of the other kind yielded significant improvements of 6.5 percentage points for task-based data ($t(5)$ = 3.79, p < 0.02) and 7.7 percentage points for resting-state data ($t(12)$ = 2.47, p < 0.03). Thus, combining imaging modalities yields one additional correct identification every 15 patients.

Discussion

The aim of the present pilot study was to explore the potential of combining data from different functional neuroimaging modalities to predict treatment response in MDD. Specifically, we tested the hypothesis that prediction performance could be improved by combining task-based and resting-state neuroimaging data. We replicated previous findings by showing that treatment response can be related to activation differences across patients and could be predicted both from task-based and resting-state data. Crucially, we demonstrate that integrating these two modalities increases prediction accuracy, resulting in about one additional correct classification every 15 patients.

Comparing neural responses in patients pre-treatment against their post-treatment activations as well as against controls, we found increased responses to emotional faces in right postcentral gyrus and the left amygdala, and decreased responses in left inferior and middle frontal gyrus, precuneus, and right posterior middle temporal sulcus. Except for the postcentral gyrus, these regions have all been associated with emotional responses, emotion recognition, and emotion regulation [59], and most have previously been shown to abnormally respond to emotional stimuli in mood disorders [3,26,29]. The effects of therapy correlated very well with the following aspects of these activations: (a) pre-treatment response to neutral faces in precuneus, left inferior frontal gyrus, right amygdala and right parietal cortex; (b) the response to emotional faces in subgenual cingulate; and (c) the differential response to emotional vs. neutral faces in most of these regions. In general, in regions deactivated in patients pre-therapy compared to post-therapy and compared to controls, responses correlated negatively with therapy outcome. Our results thus confirm the vast previous findings

indicating that MDD therapy outcomes correlate with neural responses to neutral and emotional stimuli [3,8]. However, our results reveal a contrast between findings in regions responding to emotional faces compared to findings in subgenual cingulate: in the former regions, the highest correlations with therapy outcome were obtained using a differential response (response to emotional faces minus response to neutral faces, thus removing responses to the face per se), and the emotion with best results varied across regions; while in the subgenual cingulate, the response to emotional faces allowed extremely robust prediction results (positive correlations) using the response to each of the emotions (Table 2). The latter finding concords very well with previous reports of subgenual cingulate activity being predictive of therapy outcome [11,17,34-37], in particular with the common finding that greater activity relates to greater improvement [3,8]. Our results are thus in line with previous findings reporting that task-based activation correlates with therapy outcome.

Analysis of the resting-state data revealed reduced connectivity between the right subgenual cingulate and the right middle frontal gyrus in patients compared to controls. This finding is consistent with a large body of literature demonstrating abnormalities in the emotion regulation network in MDD, particularly connectivity between subgenual cingulate and other prefrontal regions [3,10,11,13,15,19,26,28-30]. Further, therapy resulted in reduction of seed-to-seed connectivity between right DLPFC and right IPS in MDD patients. These data confirm previous findings of abnormal seed-to-seed connectivity in MDD [15,41-43], specifically about connectivity between dorsolateral prefrontal and inferior parietal cortex [60], and findings indicating that therapy leads to changes in connectivity [61-63]. While therapy outcome can be predicted from changes in resting-state connectivity [9,16,62], our data have not yielded such results, most probably due to the relatively small sample of patients included in the study.

Using a common Support Vector Machine (SVM) algorithm, we could predict patients' response status with an accuracy of up to 88.9% based on neuroimaging data. Prediction using task-based data was on average 10 percentage points higher than prediction based on resting-state data, but the highest prediction scores were obtained using the latter. Interestingly, significant prediction from task-based data could be obtained only using the response to happy faces, while significant prediction from resting-state data could be obtained only from the connectivity pattern originating in the left intraparietal sulcus or the left dorsolateral prefrontal cortex. While our analysis is based on a small sample of patients and the classification accuracies we report are thus likely to be inflated [64], our findings suggest that results based on only one kind of neuroimaging data are more variable across patient subsamples than results based on multiple kinds of data. Combining the best-predicting resting-state data with the task-based data significantly improved accuracy, enabling significant prediction using the data of all emotional faces. While the complementary manipulation of combining the best-predicting task-based data with the resting-state data again also significantly improved accuracy overall, the number of seeds yielding significant prediction results was left unchanged (N = 2 seeds), and four seeds even showed decreased accuracy, indicating that the classifier relied on non-informative data features. These results suggest that the best method to achieve significant prediction is to supplement task-based data with the resting-state connectivity pattern of the left dorsolateral prefrontal cortex.

In our present data, clinically important, task-based prediction of therapy outcome could be obtained only using the response to happy faces; with the subgenual cingulate cortex' response to happy faces eliciting the strongest associations with clinical outcome. Differences in

the ability to emotionally process positive facial expressions have crucial implications for the therapeutic relationship [65] and the possibility to capitalize on social reinforcements [66], both of which are essential ingredients of depression therapy [67].

We must acknowledge several limitations of our pilot study, which suggest that the preliminary results presented here should be taken with caution. First, the patient sample from which the data where acquired was very small (N=21), heterogeneous in age, disease severity and duration, outcome, treatment protocol and recruited from only one site. Second, several aspects of the analysis may be optimized in future work. While we used a valid classification procedure relying on simple leave-one-patient-out cross-validation, this approach has recently been shown to yield artificially high accuracies in small samples [64,68]. Notably, as we optimised the parameters and tested the model using the same dataset, higher accuracies may have occurred by chance or through classifier overfitting. Recent developments such as nested cross-validation [69] have demonstrated higher reliability and show great promise for further investigations aiming to uncover the most relevant variables for accurate treatment outcome prediction. Further particularities of our analyses should be mentioned, for example the fact that we did not use the same number of ROIs for the analysis of task-based and resting-state data (comparing accuracies based on the different kinds of data was not an aim of our study), and the fact that using balanced accuracy rather than raw accuracy may be a better option for analysing classes of unequal sizes. The small sample size and these methodological details may be the reason why we observed large variations in prediction accuracy across conditions (task-based: 44.4 to 88.9%, resting-state-based: 61.1 to 77.8%). This variation might be due to genuine differences in information content regarding outcome across regions or to noisy data. For this reason, we did not expand too much on the differences across conditions. Our aim was to evaluate if combining modalities improves prediction accuracy irrespective of the number of ROIs contributing to each modality, and we have considered the conditions as that many tests allowing address this question. The results are coherent: accuracy for each modality can be improved by adding data from the other modality.

Another important aspect of this study is that we have only attempted to predict treatment outcome in general and not outcomes for different treatments. This second aspect is necessary to reach the ultimate goal of the present research, which is to provide recommendations for specific treatments for individual patients. Some successes have already been achieved in this direction [e.g. 70]. Our present work shows that combining multiple neuroimaging modalities improves outcome prediction; future work combining clinical data and different kinds of neuroimaging data may prove promising in order to identify the best treatment option for each individual.

Regarding the practical value of our approach, we must admit that acquiring MRI data is expensive in comparison to collecting clinical questionnaires. However, MRI scanners are nowadays quite widely available, data analysis is largely user-independent (especially for routine anatomical scans but also for simple functional paradigms), and crucially, the technique measures neurobiological variables rather than subjective mental states. The latter aspect allows to apply the technique even to patients incapable of reliable introspection or affected by mutism due to severe MDD. Future developments in the neuropsychopathology of MDD may provide more precise constraints on the brain regions to consider for outcome prediction, further improving prediction performance. Therefore, despite its costs, we believe that MRI-based outcome prediction is a useful avenue to pursue.

In summary, our study confirms the usefulness of neuroimaging in the prediction of therapy outcome of MDD and the benefits of acquiring several kinds of longitudinal neuroimaging data. Our findings demonstrate that in the prediction of treatment response, task-based and resting-state neuroimaging modalities are complementary rather than redundant [8]. Critically, our findings may inform future studies evaluating if combining neuroimaging data can help to formulate personalized treatment recommendations, thereby minimizing unnecessary treatment and the associated suffering and health care costs. This strategy may be an important step in the process of establishing precision medicine in psychiatry.

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Conflict of Interest

The authors declare no conflict of interest.

Table 1. Demographics of participants and clinical scores

	MDD N=21		Controls N=20		
	Mean (SD)	Range	Mean (SD)	Range	p
Sex (M/F)	14/7	-	11/9	-	0.44
Age (years)	37.5 (13.5)	19-62	37.4 (13.7)	19-59	0.92
Education (years)	15.2 (2.8)	11-22	16.4 (2.6)	13-23	0.20
N major episodes	2.82 (2.6)	0-10	0	0	-
Duration of current episode (months)	10.8 (12.2)	1-48	-	-	-
T1-T2 interval (days)	46.8 (9.6)	33-63	53.1 (17.3)	39-70	0.23
Pre-treatment BDI	31.8 (10.2)	9-54	2.8 (3.2)	0-10	<0.001
Post-treatment BDI	19 (11.6)	2-39	-	-	-
Improvement BDI	38.1% (35.5)	-44-95	-	-	<0.001
Pre-treatment HAMD	19.4 (8.7)	8-44	0.7 (1.1)	0-4	<0.001
Post-treatment HAMD	10.9 (5.6)	2-25	-	-	-
Improvement HAMD	35.0% (43.8)	-100-89	-	-	<0.001

Column p indicates p values of a chi-square test (sex) or two-sample t-tests comparing values in patients and controls, or, for “Improvement” data, comparing patients’ pre-treatment vs. post-treatment values.

Table 2. Correlations between activation and clinical improvement

Activation evoked by each kind of face						
	Neutral	Angry	Disgusted	Fearful	Happy	Sad
MFG left	0.15	0.01	0.08	0	0.02	0.08
DLPFC left	0.06	*0.01*	0.00	*0.10*	*0.01*	*0.04*
IFG left	0.39*	0.13	0.21	0.03	0.21	0.06
pMTG right	0.16	*0.05*	*0.03*	0	0.01	0
Precuneus	0.42*	0.26	0.13	0.02	0.25	0.26*
Postcentral right	*0.29**	0.08	0	*0.04*	*0.12*	0.04
Amygdala left	*0.25*	0.06	*0.02*	0	0.06	0.03
Amygdala right	*0.29**	0.02	*0.12*	*0.05*	0.01	0
sgACC left	0	0.43*	0.53**	0.66**	0.59**	0.59**
sgACC right	0	0.40*	0.45*	0.61**	0.65**	0.53**
Activation difference between each kind of emotional face and the neutral face						
		Angry	Disgusted	Fearful	Happy	Sad
MFG left	-	*0.30**	*0.16*	*0.42**	*0.27**	*0.14*
DLPFC left	-	*0.17*	*0.19*	*0.29**	*0.17*	*0.28**
IFG left	-	*0.40**	*0.33**	*0.29**	*0.13*	*0.23*
pMTG right	-	*0.37**	*0.51***	*0.25*	*0.15*	*0.32**
Precuneus	-	*0.23*	*0.30**	*0.48***	*0.10*	*0.05*
Postcentral right	-	0.23	0.30*	0.12	0.06	0.24
Amygdala left	-	0.58**	0.17	0.63**	0.49**	0.43*
Amygdala right	-	0.53**	0	0.04	0.31*	0.17
sgACC left	-	0.34*	0.19	0.25	0.38*	0.31*
sgACC right	-	0.23	0.11	0.23	0.40*	0.29

Variance in BDI change (range: 0-1) explained by activation in amygdalae, subgenual cingulate cortex and clusters showing abnormal response to the emotional faces in patients, as a function of the emotion of the face presented. MFG = middle frontal gyrus; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; pMTG = posterior middle temporal gyrus; sgACC = subgenual anterior cingulate cortex. * = $p < 0.05$ (uncorrected), ** = $p < 0.05$ (Holm-Bonferroni-corrected). Values in italic indicate a negative correlation. Correlations were calculated either using the response evoked by each kind of face stimuli (top half), or after subtracting the response evoked by neutral face stimuli from the response evoked by emotional faces (bottom half).

Table 3. Treatment outcome prediction using task-based activation data

Name of condition	*Accuracy (%)*	*Accuracy combined with best resting-state data (%)*	*Improvement % points*
Neutral	66.7	77.8*	11.1**
Angry	72.2	77.8*	5.6
Disgusted	61.1	72.2*	11.1**
Fearful	72.2	72.2*	0
Happy	77.8*	83.3**	5.5
Sad	66.7	72.2*	5.5**
Mean (CI)	69.4 (5.8)	75.9 (4.5)	6.5 (4.2)
Prediction using resting-state connectivity data			
Name of condition	*Accuracy (%)*	*Accuracy combined with best task-based data (%)*	*Improvement % points*
MPFC	44.4	66.7	22.3**
Precuneus	50	66.7	16.7**
dACC	55.6	61.1	5.5**
AI left	50	55.6	5.6**
AI right	61.1	55.6	-5.5
DLPFC left	88.9**	83.3**	-5.6
DLPFC right	77.8	72.2	-5.6
IPS left	83.3*	77.8	-5.5
IPS right	50	72.2	22.2**
Amygdala left	55.6	77.8*	22.2**
Amygdala right	61.1	66.7	5.6*
sgACC left	38.9	55.6	16.7**
sgACC right	50	55.6	5.6*
Mean (CI)	59.0 (15.3)	66.7 (9.6)	7.7 (11.2)

Results of a classifier (SVM, see Methods) predicting treatment responder status of one patient based on the task-based and/or resting-state data of the other patients, as a function of the emotion of the face or the seed of the resting-state fMRI connectivity. Values indicate average improvement in percentage points. * = $p < 0.05$; ** = $p < 0.001$. P values are corrected for multiple comparisons using the Holm-Bonferroni method. CI = confidence interval. MPFC = medial prefrontal cortex; dACC = dorsal anterior cingulate cortex; AI = anterior insula; DLPFC = dorsolateral prefrontal cortex; IPS = intraparietal sulcus; sgACC = subgenual cingulate.

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Chapter 6.

General Discussion

Summary of research

MDD is a complex mental disorder characterized by affective, cognitive, social, and neural impairments. The work presented in this thesis aims to deepen our understanding of MDD using fMRI and to explore potential implications for treatment. The first study, described in Chapter 2, examined the neural processing of social touch as an indicator of social reward in individuals with MDD and the effects of antidepressant therapy. Results revealed altered neural responses to social touch in several nodes of the reward network, including the nucleus accumbens (NAcc) and caudate nucleus. These effects were found across pre- and post-treatment measures, suggesting persistent dysfunctional processing of social touch. This is consistent with findings in patients with anhedonia, which also persists after other symptoms have abated (Conradi et al., 2011) and has been linked to impaired reward experience (Höflich et al., 2019). The second study presented in Chapter 3 examined the efficacy of non-invasive brain stimulation in the treatment of MDD by targeting individualized parietal stimulation sites functionally connected to the hippocampus. Although augmenting left DLPFC stimulation with parieto-hippocampal stimulation had no additive clinical benefit for patients with MDD, this novel stimulation approach did enhance encoding-related activation in the hippocampus. Furthermore, functional connectivity between the hippocampus and the DLPFC increased after stimulation. These results demonstrate the methodological feasibility of functional connectivity-guided stimulation, which may help improve cognitive symptoms in MDD. The third study, described in Chapter 4, examined the effects of intravenous ketamine in a patient with treatment-resistant MDD and bilateral amygdala lesions. Ketamine administration led to rapid improvement in depressive symptoms, suggesting that a functioning amygdala may not be necessary for the development of MDD or for ketamine's antidepressant mechanism of action. Resting-state fMRI scans revealed increased connectivity between the SAN and DMN in this patient compared to a group of controls with MDD at baseline, which temporarily decreased after treatment. This study sheds light on the therapeutic potential of ketamine in disrupting negative self-referential biases associated with DMN hyperactivity and provides insight into its mechanism of action in MDD. The fourth study presented in Chapter 5 focuses on the prediction of treatment outcome in patients with MDD using multimodal functional imaging approaches. Neural responses to emotional faces and connectivity patterns in the

DLPFC at baseline were associated with treatment response. Integration of task-based and resting-state fMRI data improved the accuracy of predicting treatment outcome. These findings support the potential of multimodal functional imaging as a tool for precision medicine in the treatment of MDD.

Although each study examines different aspects of MDD and uses different methodologies, all four studies examine neural processing in individuals with MDD. Using fMRI, these studies provide insight into the neurobiological underpinnings of MDD and shed light on specific neural impairments associated with the disorder. In addition, the presented studies converge on several key themes. First, these studies all conceptualize MDD as a network disorder and aim to investigate how it affects connected brain regions, intrinsic networks, and functional connectivity patterns through analysis of task-based activation and resting-state functional connectivity. Second, they each explore the potential implications of their findings for the treatment of MDD. The studies examine the effect of antidepressant therapy, innovative interventions, and the potential for personalized treatment approaches to improve treatment outcomes and identify novel strategies to address the symptoms and neural dysfunction of MDD. Third, all studies encompass an examination of the cognitive aspects of the disorder, as cognitive symptoms are a prevalent characteristic of MDD. They focus on impairments associated with reward processing, encoding and memory, emotional face processing, and negative self-referential biases. By elucidating these cognitive dimensions, the studies contribute to a comprehensive understanding of MDD beyond mere mood disturbance. In summary, the studies presented collectively provide valuable insights into the neurobiological mechanisms underlying MDD and offer potential avenues to improve treatment for individuals afflicted with this debilitating disorder.

Scientific contributions and implications for treatment

In summary, my research advances our understanding of the pathophysiology of depression and suggests opportunities for improving existing and new approaches for treating MDD through four key contributions.

Social reward processing in MDD. First, my work emphasizes the social facets of reward processing that have been understudied in MDD patients. Although the reward circuit has been studied extensively, few investigations have utilized social stimuli, which is concerning due to the critical role of social anhedonia. The present work is the first to investigate the neural underpinnings of the processing of social touch as a metric of social reward in MDD. Patients with MDD commonly experience less pleasure or reward from social interactions, even with loved ones. This diminished sensitivity to social rewards may lead to social withdrawal and isolation, which can exacerbate symptoms by reducing opportunities for positive experiences. These social impairments can continue for as long as three years following recovery (Rhebergen et al., 2010)

and are associated with unemployment and disability (Rizvi et al., 2015). As outlined in Chapter 2 and consistent with prior research (Dunlop & Nemeroff, 2007; McCabe et al., 2010), conventional antidepressants are ineffective in treating dysfunctional reward processing, highlighting the importance of alternative treatments to SSRIs for alleviating reward-related symptoms in MDD. For instance, psychotherapeutic interventions, like behavioral activation therapy and body-based interventions discussed in Chapter 2, may be beneficial in addressing impaired reward and social touch processing. Additionally, positive affect therapy is a suitable treatment for addressing impaired reward sensitivity (Craske et al., 2019). Potential pharmacological interventions include kappa opioid receptor antagonists (Krystal et al., 2020; Pizzagalli et al., 2020) and potassium channel modulators (Costi et al., 2021, p. 202). Notably, ketamine has been found to decrease self-reported anhedonia in patients with MDD (Rodrigues et al., 2020) and modify activation and connectivity within the reward system (Lally et al., 2014; Mkrtchian et al., 2021). These observations are intriguing when considering the findings presented in Chapter 4, which indicate that ketamine enhances activation in the SAN, a network closely linked to the reward system. Future studies should investigate the therapeutic potential of ketamine in treating anhedonia.

Functional connectivity-guided rTMS. Second, my research provides evidence for a new method of rTMS target selection. Chapter 3 illustrates that when applied to parieto-hippocampal pathways this approach enhanced neural activity and functional connectivity in the distal target, the hippocampus. This result supports the feasibility of the approach and is consistent with prior research (Wang et al., 2014). While our study did not find that parieto-hippocampal stimulation resulted in clinical improvement for patients with MDD, it may offer significant clinical benefit for patients with memory or cognitive symptoms, like mild cognitive impairment (MCI).

Besides targeting parieto-hippocampal pathways, future studies on MDD patients should implement functional connectivity-guided targeting to modulate other subsurface brain regions that have previously been inaccessible through non-invasive brain stimulation. Candidate targets can be identified through studies utilizing deep brain stimulation (DBS), which has been experimentally used for treatment-resistant depression. One of the most commonly studied targets for DBS is the sgACC (Mayberg et al., 2005). Evidence supporting the targeting of sgACC through rTMS comes from an fMRI study that showed stronger anticorrelations between a site of DLPFC stimulation and sgACC being associated with better clinical outcomes after rTMS (Fox et al., 2012). Preliminary evidence indicates that computing individualized DLPFC stimulation sites based on functional connectivity to the sgACC could improve treatment outcomes (Cash et al., 2021).

We also found that this stimulation approach enhanced functional connectivity between the directly stimulated DLPFC and the indirectly modulated hippocampus. As discussed in Chapter 3,

this could facilitate purposeful modulations of functional connectivity in patients with conditions associated with prefrontal-hippocampal dysconnectivity, or even other dysfunctional pathways. Thus, future studies could investigate the use of functional connectivity-guided rTMS in patients with schizophrenia (Bähner & Meyer-Lindenberg, 2017) or memory disorders (Alemany-González et al., 2020).

Targeting the reward network. Integrating these insights, future studies should employ rTMS to target the striatum through functional connectivity in order to alleviate reward-related symptoms. So far, there have been limited efforts to target the striatum, despite the need for treatments that specifically modulate the reward system. A possible striatal target for functional-connectivity guided rTMS is the NAcc, which has been effectively modulated by DBS (Bewernick et al., 2010). Because the ventral striatum is functionally and structurally connected to various prefrontal and parietal regions (Cauda et al., 2011; Kroemer et al., 2022), and because prior studies have found functional DLPFC-NAcc connectivity is a predictor of rTMS treatment outcome (Du et al., 2018), the DLPFC may also serve as a promising and accessible cortical stimulation site for individualized functional connectivity-guided NAcc stimulation.

Altered caudate nucleus activation in patients with MDD, as described in Chapter 2, indicate another potentially viable striatal target. PET studies have shown increased dopamine release in the caudate nucleus following rTMS of the DLPFC (Ko et al., 2008; Strafella et al., 2001), suggesting a functional pathway that may be suitable for targeted stimulation. Therefore, future research should investigate whether individualized non-invasive brain stimulation of frontostriatal pathways can alleviate otherwise persisting reward-related symptoms such as anhedonia.

Personalized psychiatry. Finally, my thesis contributes to the highly topical field of precision medicine in two ways. Personalized medicine in psychiatry utilizes patient-specific data to optimize treatment selection and implementation. Treatment selection algorithms allocate individuals into subpopulations that have been shown to respond to specific treatments. These subpopulations may be characterized by patterns of sociodemographic and clinical factors, genetics, or neuroimaging biomarkers. Our findings add to the foundation of this field by examining the effectiveness of neuroimaging biomarkers in predicting clinical outcomes. At present, MRI scans are commonly used for differential diagnoses in routine clinical practice. This readily available data ought to be utilized in treatment planning for patients. While we did not differentiate between specific interventions, treatment-specific biomarkers have been proposed for rTMS (Drysdale et al., 2016) and ketamine (Rong et al., 2018), as well as for more conventional treatments such as psychotherapy (Crowther et al., 2015), SSRIs (Lanzenberger et al., 2012), and ECT (Moreno-Ortega et al., 2019). Future research should combine different neuroimaging modalities, as shown by our research, to identify patterns that correspond with response to particular treatments. Integrating these findings to develop treatment selection algorithms is a challenging

task. However, it offers an opportunity to minimize the number of failed treatment attempts and shorten the trial-and-error phase of selecting and evaluating suitable treatments.

Additionally, this thesis describes a method for delivering personalized rTMS based on individual functional connectivity patterns. Although rTMS has proven to be a useful treatment for MDD, it is possible that its true efficacy has been underestimated due to common heuristics used to identify the DLPFC stimulation site. These targeting methods fail to adequately account for the technique's high focality and frequently miss the intended target area (Herwig et al., 2001). My research adds to the existing body of evidence, along with previous studies that utilized functional connectivity to identify personalized rTMS targets (Fox et al., 2013; Wang et al., 2014). Nevertheless, much of the existing research has been primarily aimed at demonstrating the feasibility of these methods. Therefore, comparative research is necessary to evaluate the effectiveness of standard targeting procedures in contrast to those guided by personalized functional connectivity.

Limitations

The work presented in this thesis contributes to the understanding of the neural pathophysiology of MDD and its treatment, yet there are some limitations that should be considered in future research.

A first limitation relates to the sample sizes of these studies. In particular, the samples in Chapters 3 and 5 were relatively small, which underscores the preliminary nature of the findings. This is a common issue in elaborate clinical fMRI studies (Button et al., 2013), especially those using longitudinal study designs. Future studies should replicate these findings in larger samples to ensure robustness and increase statistical power.

A second limitation concerns the naturalistic antidepressant treatment used in the studies described in Chapters 2, 3, and 5. Although treatment-as-usual reflects clinical reality, it complicates the interpretation of the fMRI findings. Psychotropic medications inherently affect neurochemical processes in the brain, and, therefore, any data obtained with functional neuroimaging techniques. This is particularly problematic when medication cannot be kept stable between measurements in a longitudinal study design, as was the case in the studies presented in this thesis. Given the wide variety of medications used to treat MDD and the limited understanding of their neural effects, it is nearly impossible to adequately model and subsequently control for their effects in statistical analyses. Thus, even though there is evidence that psychotropic medications for mood disorders have no significant effect on fMRI measures (Phillips et al., 2008), it should be assumed that differences attributed to treatment may be confounded by changes in psychotropic medication unrelated to clinical improvement.

Finally, it should be noted, that this doctoral project has undergone some changes since its inception. While the initial proposal for this thesis had a strong focus on non-invasive brain stimulation, the project had to be modified due to several circumstances, in particular a longer than planned data collection phase of the main study (described in Chapter 3) due to difficulties with patient recruitment, and thus it was not possible to conduct the follow-up study as planned. Therefore, the present thesis takes a broader view and addresses research questions from different areas of depression research employing various experimental paradigms (social touch, memory, and emotional faces tasks) and analysis approaches (tasked-based and resting-state fMRI).

Conclusion

The present thesis illuminates the pathophysiology and treatment of MDD from multiple perspectives. It is among the first works to address the significance of social reward in MDD and to highlight the persistent alterations in the reward-network. Furthermore, it shows how functional connectivity data can be used to modulate subsurface brain regions using non-invasive brain stimulation in MDD patients and discusses how this approach opens the door to several new potential targets for treatment of brain-related disorders beyond MDD. It also demonstrates how different fMRI data can be combined to predict patients' response to antidepressant treatment accurately. Lastly, this thesis describes the intriguing case of a patient who developed severe, treatment-resistant MDD in the absence of a functional amygdala and illustrates how ketamine affected her intrinsic brain networks and improved her depressive symptoms. Based on the findings of my research, I suggest a tailored intervention using non-invasive brain stimulation to target the brain's reward system, specifically the striatum, to alleviate reward-related symptoms in MDD. Further investigation is needed, but this approach represents a notable step toward more refined treatment strategies. While there are still countless intriguing and unanswered questions in the field of MDD research, this thesis addresses some understudied areas of depression research and demonstrates that MDD is a complex, multifaceted condition beyond traditional notions of mood disorders. It contributes novel insights to the existing body of research on the understanding of MDD and lays the groundwork for the development of more targeted and effective antidepressant interventions.

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Appendix

1. General Abstract

Despite decades of research into the neurobiology of major depressive disorder (MDD) and the development of a range of treatments, many questions remain unanswered and many patient needs unmet. This thesis consists of four studies using functional magnetic resonance imaging to address research questions from different areas of depression research. The first study examined the neural processing of social touch as an indicator of social reward in MDD. Patients showed reduced activation in the reward network, including the nucleus accumbens, caudate nucleus, and putamen, during social touch compared to healthy controls, both before and after antidepressant therapy. These findings suggest a persistent dysfunctional processing of social touch in MDD, which may contribute to social withdrawal. The second study used functional connectivity-guided repetitive transcranial magnetic stimulation in the treatment of MDD. Although targeting the hippocampus by stimulating individually mapped parietal cortex sites did not improve clinical symptoms, it increased functional connectivity and encoding-related activation of the hippocampus, demonstrating the feasibility of functional connectivity-guided stimulation of subsurface targets. The third study presented the case of a woman with treatment-resistant MDD and bilateral amygdala lesions. Ketamine administration resulted in rapid and significant improvement in depressive symptoms. Changes in functional connectivity were observed in large-scale brain networks, including the default mode, frontoparietal, and salience networks. This case suggests that a functioning amygdala is not necessary for the development of MDD or the mechanism of action of ketamine. The fourth study examined the integration of multimodal imaging data to predict treatment outcome in MDD. The combination of task-based and resting-state functional imaging modalities improved predictive accuracy, highlighting the potential of multimodal imaging for precision medicine in psychiatry. These findings are integrated and further discussed in the concluding discussion chapter in terms of their potential to inform more effective and targeted treatment. In summary, this thesis provides valuable insights into the neurobiological mechanisms underlying MDD and offers potential avenues for improving the treatment of individuals with this debilitating disorder.

2. Zusammenfassung

Trotz jahrzehntelanger Forschung zur Neurobiologie der Depression und der Entwicklung verschiedener Behandlungsmethoden bleiben viele Fragen unbeantwortet und viele Bedürfnisse von Betroffenen unerfüllt. Die vorliegende Arbeit umfasst vier Studien, in denen mittels funktioneller Magnetresonanztomographie Forschungsfragen zur Pathophysiologie und Therapie der Depression untersucht wurden. Die erste Studie untersuchte die neuronale Verarbeitung von sozialer Berührung als Indikator für soziale Belohnung bei Depression. Soziale Berührungen führten bei erkrankten Personen im Vergleich zur gesunden Kontrollgruppe zu einer verminderten Aktivierung des Belohnungsnetzwerks, darunter des Nucleus accumbens, des Nucleus caudatus und des Putamen, sowohl vor als auch nach antidepressiver Behandlung. Diese Ergebnisse deuten auf eine anhaltende dysfunktionale Verarbeitung sozialer Berührungen bei Depressionen hin, die sozialen Rückzug begünstigen kann. In einer weiteren Studie wurden auf Basis individueller funktioneller Konnektivitätsdaten Stimulationsziele für die Behandlung mit repetitiver transkranieller Magnetstimulation bestimmt. Obwohl die indirekte Stimulation des Hippocampus durch die Stimulation parietaler Ziele keine antidepressiven Effekte zeigte, erhöhte sie die funktionelle Konnektivität und die aufgabenbasierte Aktivierung des Hippocampus, was für die Möglichkeit der Anwendung konnektivitätsbasierter Stimulation bei anderen subkortikalen Zielen spricht. Die dritte Studie beschreibt den Fall einer Frau mit einer therapieresistenten depressiven Episode und bilateralen Amygdalaläsionen. Eine Behandlung mit Ketamin führte zu einer raschen und deutlichen Verbesserung der depressiven Symptomatik. Darüber hinaus zeigten sich Veränderungen in neuronalen Netzwerken, wie dem Default Mode Network, dem frontoparietalen Netzwerk und dem Salienznetzwerk. Dieser Fall zeigt, dass weder für die Entwicklung einer Depression noch für den Wirkmechanismus von Ketamin eine intakte Amygdala erforderlich ist. Die vierte Studie untersuchte die Integration multimodaler Bildgebungsdaten zur Vorhersage des Behandlungserfolgs bei Depression. Die Kombination von aufgabenbasierten Bildgebungsdaten und funktionellen Konnektivitätsdaten verbesserte die Vorhersagegenauigkeit und verdeutlicht das Potenzial der multimodalen Bildgebung für die Präzisionsmedizin in der Psychiatrie. Eine abschließende Diskussion führt die vorliegenden Ergebnisse zusammen und diskutiert deren Implikationen für eine effektivere und gezieltere Depressionsbehandlung. Diese Arbeit liefert wertvolle Einblicke in die neurobiologischen Mechanismen der Depression und zeigt mögliche Wege zur Behandlungsoptimierung auf.

3. Curriculum Vitae

Mag. CLEMENS MIELACHER

Professional experiences

Since 2023	**Clinical psychologist**, Department of Psychiatry, Klinikum Wels-Grieskirchen, Austria
2022 – 2023	**Clinical psychologist**, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria
2015 – 2021	**Research associate**, Section for Medical Psychology, Department of Psychiatry and Psychotherapy, University Hospital Bonn, Germany
2013	**Internship**, Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Austria
2012	**Internship**, Department of Psychosomatic Medicine, Charité Berlin, Germany
2012	**Internship**, Department of Psychiatry, Otto-Wagner-Spital, Vienna

Education

Since 2021	**Training in Clinical Psychology**, Austrian Academy for Psychology, Vienna, Austria
Since 2016	**PhD candidate in Psychology**, Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Austria
2018	Clinical TMS course
2008 – 2015	**Diploma degree in Psychology**, University of Vienna, Austria, *passed with distinction*
2013	**Erasmus student**, University of Copenhagen, Denmark

2023 **Mielacher C**, Scheele D, Kiebs M, Schmitt L, Dellert T, Philipsen A, Lamm C, Hurlemann R (2023) Altered reward network responses to social touch in major depression. *Accepted for publication in* Psychological Medicine; doi: https://doi.org/10.1101/2021.11.25.21266854

2021 Hebel T, Grözinger M, Landgrebe M, Padberg F, Schecklmann M, Schlaepfer T, Schönfeldt-Lecuona C, Ullrich H, Zwanzger P, Langguth B; And the DGHP Consensus Group, Bajbouj M, Bewernick B, Brinkmann K, Cordes J, Di Pauli J, Eichhammer P, Freundlieb N, Hajak G, Höppner-Buchmann J, Hurlemann R, Kamp D, Kayser S, Kis B, Kreuzer PM, Kuhn J, Lammers M, Lugmayer B, **Mielacher C**, Nickl-Jockschat T, Nunhofer C, Palm U, Poeppl TB, Polak T, Sakreida K, Sartorius A, Silberbauer C, Zilles-Wegner D (2021) Evidence and expert consensus based German guidelines for the use of repetitive transcranial magnetic stimulation in depression. The World Journal of Biological Psychiatry 23 (1): 1-36

2020 **Mielacher C**, Schultz J, Kiebs M, Dellert T, Metzner A, Graute L, Högenauer H, Maier W, Lamm C, Hurlemann R (2020) Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder. Personalized Medicine in Psychiatry 23: 100066

Kiebs M, Hurlemann R, **Mielacher C** (2020) Repetitive Transkranielle Magnetstimulation in der Depressionsbehandlung. internistische praxis 63: 120-129

Kaut O, **Mielacher C**, Hurlemann R, Wüllner U (2020) Resting-state fMRI reveals increased functional connectivity in the cerebellum but decreased functional connectivity of the caudate nucleus in Parkinson's disease. Neurological Research 42: 62 – 67

Pfabigan DM, **Mielacher C**, Dutheil F, Lamm C (2020) ERP Evidence Suggests That Confrontation with Deterministic Statements Aligns Subsequent Other- and Self-Relevant Error Processing. Psychophysiology 57 (8): e13556.

2019 Scheele D, Zimbal S, Feinstein JS, Delis A, Neumann C, **Mielacher C**, Philipsen A, Hurlemann R (2019) Treatment-resistant depression and ketamine response in a patient with bilateral amygdala damage. The American Journal of Psychiatry 176: 982 – 986

2018 Schultz J, Becker B, Preckel K, Seifert M, **Mielacher C**, Conrad R, Kleiman A, Maier W, Kendrick KM, Hurlemann R (2018) Improving therapy outcome prediction in major depression using multimodal functional neuroimaging - a pilot study. Personalized Medicine in Psychiatry 11 - 12: 7 - 15

2015 **Mielacher C**, Scheele D, Hurlemann R (2015) Experimental and therapeutic neuromodulation of emotion and social cognition using non-invasive brain stimulation. Der Nervenarzt 86: 1500 – 1507

Conference contributions

2020 *International Conference on Non-Invasive Brain Stimulation, Baden-Baden, Germany*. **Poster:** Mielacher C., Schultz J., Kiebs M., Dellert T., Metzner A., Graute L., Högenauer H., Maier W., Lamm C., Hurlemann R. Individualized theta-burst stimulation of parietal-hippocampal functional connectivity in patients with major depressive disorder.

2019 *International Brain Stimulation Conference, Vancouver, Canada*. **Poster:** Mielacher C., Kiebs M., Dellert T., Metzner A., Högenauer H., Schultz J., Lamm C., Hurlemann R. Once daily versus twice daily theta-burst stimulation in the treatment of major depression disorder.

2018 *Kongress der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung, Berlin, Germany*. **Talk:** Mielacher C. TMS als Therapie bei psychischen Erkrankungen.

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It has been a while since I started this adventure that has finally culminated in the form of this thesis. It has been a journey with many highs and occasional lows, but I am very grateful for all the experiences I have had and the people who have accompanied me along the way.

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