Rewiring the Brain

Insights into Electroconvulsive and Magnetic Stimulation Therapies and Their Impact on Cognition and Neural Processing

Doctoral thesis

to obtain a doctorate (PhD)

from the Faculty of Medicine

of the University of Bonn

Maximilian Philippe Detlef Kiebs

From Berlin, Germany

2025

Written with authorization of

the Faculty of Medicine of the University of Bonn

First Reviewer: Prof. Dr. Dr. René Hurlemann

Second Reviewer: Prof. Dr. Ulrich Ettinger

Day of oral examination: 04.04.2025

From the Department of Psychiatry and Psychotherapy

Director: Prof. Dr. Alexandra Philipsen

Table of Contents

List of abbreviations

BT	Bitemporal
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
DLPFC	Dorsolateral Prefrontal Cortex
ECT	Electroconvulsive Therapy
GEMRIC	Global ECT-MRI Research Collaboration
ICD-10	Int. Statistical Classification of Diseases and Related Health Problems
iTBS	intermittent Theta-Burst Stimulation
L-DLPFC	Left Dorsolateral Prefrontal Cortex
LPC	Lateral Parietal Cortex
mC	Millicoulomb
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
MST	Magnetic Seizure Therapy
OTS	One Touch Stockings of Cambridge Task
RUL	Right Unilateral
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TRD	Treatment-Refractory Depression
VLMT	Verbal Learning Memory Task

1. Abstract

Depressive disorders are a group of debilitating and at times life-threatening diseases affecting millions of individuals worldwide. They interfere with most aspects of everyday life, such as social behavior, affective experiences, and cognition. As our understanding of the disorder increases, available treatments change or are being refined. Five studies are presented that address the effect of brain stimulation treatment on cognitive performance (Studies 1 and 2), altered processing of touch as a measure of social reward (Study 3), a novel and individualized parieto-hippocampal target for intermittent theta-burst stimulation (iTBS; Study 4), and a composition of clinical trials investigating non-invasive brain stimulation for treatment refractoriness (Study 5) in patients with major depressive disorder (MDD). Contrary to expectations, the results of study 1 suggest a positive impact of increasing electroconvulsive therapy (ECT) treatments on verbal fluency performance in the bitemporally treated group while a decrease in performance was observed in the right-unilaterally treated group. As we found no evidence of cognitive impairment associated with bitemporal electrode placement in any cognitive domain, we recommend a standardized battery of robust cognitive measures with strong psychometrics and minimal subject burden to facilitate multisite investigation. As digital tracking of all ECT data has recently become available, we also present research on the role of treatment stimulus charge on cognitive performance. As hypothesized, we show that increased stimulus charge predicts decreased delayed memory performance after ECT treatment, independent of age and number of treatments applied. Comparison of this effect with other cognitive domains assessed indicates that this finding is specific to delayed memory recall (Study 2). However, this result should be replicated in a larger sample. As depressive disorders are well known to impede social functioning, we show that the perceived pleasantness of social touch is decreased in patients with depression when compared to healthy controls and that their neural processing is altered (Study 3). These effects indicate altered reward-dependent processing of social touch in MDD. Moreover, in the context of personalizing depression treatments, a novel target for iTBS is evaluated for its clinical potential (Study 4). After individual selection of a target in the parietal cortex most strongly functionally connected to the hippocampus, antidepressant iTBS treatment was augmented with this

novel parieto-hippocampal stimulation. Although we found no stronger clinical response in patients randomized to receive the novel target stimulation, increased functional connectivity between the hippocampus and the dorsolateral-prefrontal cortex was significant. This finding may be clinically relevant in conditions associated with prefrontal-hippocampal dysconnectivity. Lastly, by reexamining the study composition of a meta-analysis investigating the efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression, we showed that most trials include only patients with higher levels of treatment-refractoriness (Study 5). In light of the different compositions of clinical trials regarding this characteristic between evidence-based treatment options, more studies investigating the potential of repetitive transcranial magnetic stimulation in patients with lower degrees of treatment refractoriness are needed.

2. Introduction and aims with references

Depression is a complex and varied condition that does not present the same way in every person. Similar to conditions such as rashes or heart disease, depression has many forms and can appear differently from one individual to another. Although there is a core group of commonly associated symptoms, each person's experience is distinct. As a result, our understanding of depression and the methods used to treat it are constantly changing and adapting. However, several core features of depression are indeed identified across geographies and cultures with variations of the disease having been described since the Ayurveda healing traditions in South Asia (see Fig. 1). Even though the concept has undergone substantial transformation, some descriptions such as low spirits, sadness, and dejection have been used throughout human history to describe the experiences associated with this phenomenon (Herrman et al. 2022). Based on shared descriptors such as these, formal definitions of clinical depression have led to a number of criteria used to diagnose the disorder today (e.g. depressed mood most of the day, reduction of energy, or decrease in activity). When patients are classified into these categories, the dramatic global prevalence of depressive disorders becomes evident. They are among the top ten non-communicable causes of disease-adjusted life-years[1] worldwide, with a global 12-month prevalence of 4-5 % (Marx et al. 2023; Vollset et al. 2024). This number translates to more than 250 million people currently living with the disease worldwide (World Health Organization 2024). In addition to debilitating symptoms, depressive disorders are associated with a twofold increase in mortality, due not only to an increased risk of suicide, but also to physical and substance-related illnesses as well as disease-promoting lifestyle factors (Chesney et al. 2014; Laursen et al. 2016).

Disease classification systems, such as the DSM-V or ICD-10, are currently irreplaceable for determining prevalence or quickly establishing a diagnosis. However, defining clinical depression in an individual can be challenging because the condition encompasses a wide range of physical and mental conditions, meaning that the

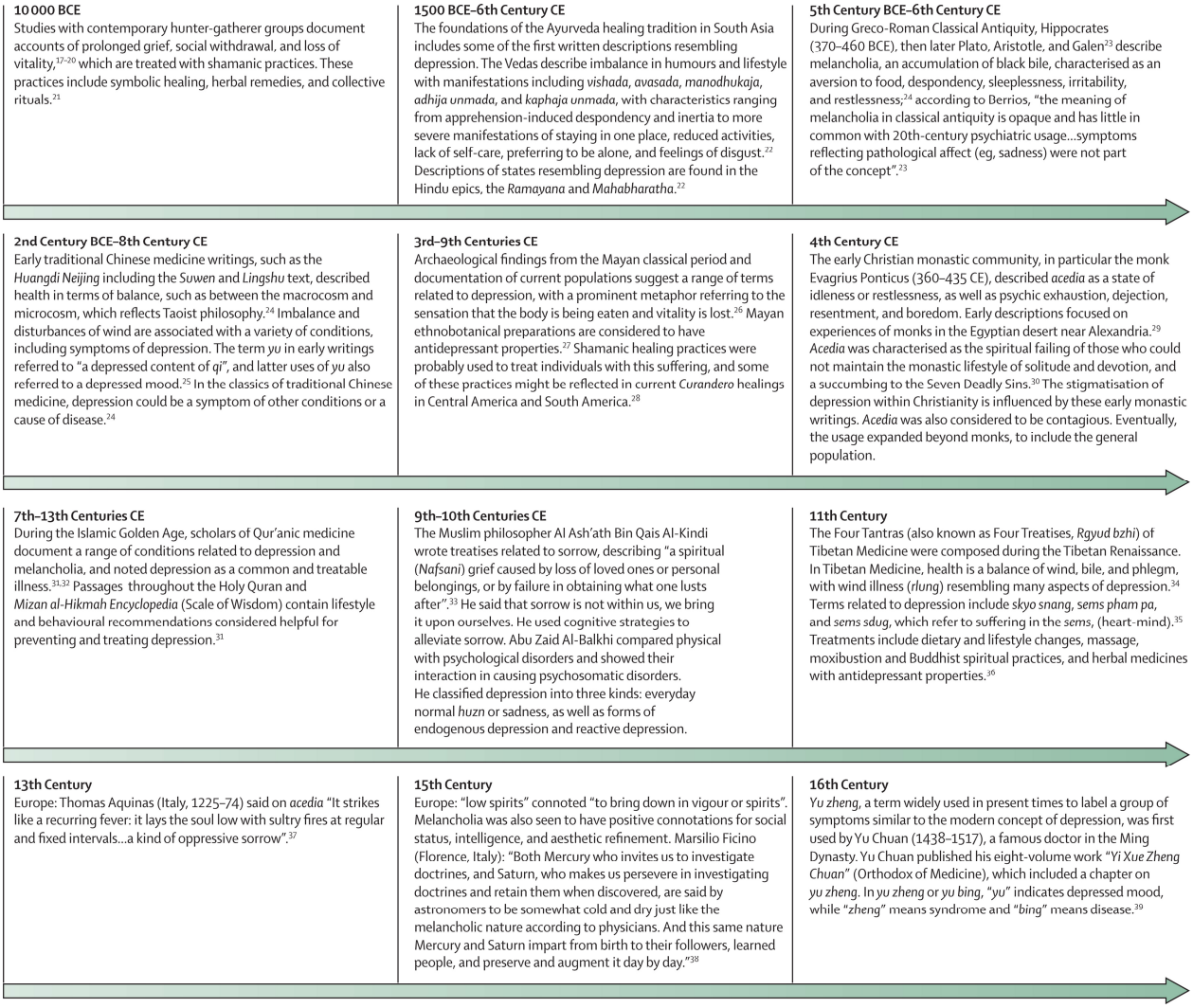
[1] DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population

symptoms of patients diagnosed with depression today can vary widely (Monroe and Anderson 2015). This heterogeneity can theoretically lead to two patients diagnosed with major depressive disorder not sharing a single symptom (Fried 2017a; Fried 2017b; Monroe and Anderson 2015). As a result, it has been proposed to study individual symptoms rather than diagnoses, to study associations among symptoms rather than sum scores of rating scales, and to personalize the treatments (Fried 2017a). The currently used treatments can be thought of as a stepped care approach, with most patients being treated via psycho- and pharmacotherapy (Tab. 1). Both forms of treatment are evidence based and have been shown to be effective in randomized controlled trials (Cipriani et al. 2018; Cuijpers et al. 2021). Treatment-refractory depression, usually defined by the failure to respond to two different classes of pharmacotherapy, and severe symptoms may be treated by electroconvulsive therapy (ECT) (McIntyre et al. 2023). A treatment that exerts its effect through the weekly induction of seizures by means of very brief electric currents.

Table 1 | Stepped care for MDD (from Marx et al., 2023)

Levels of care	Indication and clinical actions	Setting
1	All suspected presentations of depression and subthreshold depressive symptoms: diagnostic and risk assessment, psychoeducation on lifestyle factors (for example, diet, sleep, substance use, exercise), and psychological strategies (e.g. stress management, relaxation), active monitoring or watchful waiting	Self-care, general practitioner or community services
2	Mild to moderate depressive symptoms: psychotherapy, lifestyle approaches (for example, exercise), pharmacological treatment	General practitioner or community services
3	Moderate depressive symptoms: psychotherapy, lifestyle approaches (for example, exercise), pharmacological treatment, transcranial magnetic stimulation and transcranial direct current stimulation can all be considered	Specialist service
4	Treatment-resistant depression and/or severe depressive symptoms; risk of harm to self or others; risk of physical impairment, psychotic symptoms: biological and non-biological treatment for treatment-resistant MDD (for example, electroconvulsive therapy), crisis services and inpatient care, until the level of care can be stepped down	Specialist service or inpatient care depending on circumstance

Transcranial repetitive magnetic (rTMS) and direct current (tDCS) stimulation are alternative treatments which may be applied to therapy-refractory patients after failure of conventional therapies (Mutz et al. 2019a, see Fig. 2 for a description of the brain stimulation methods used or investigated in psychiatry). Even though all these treatments are efficacious, only few personalized treatment options exist to date and the effects of a treatment on specific symptoms remain not well understood.



(Figure 1 continues on next page)

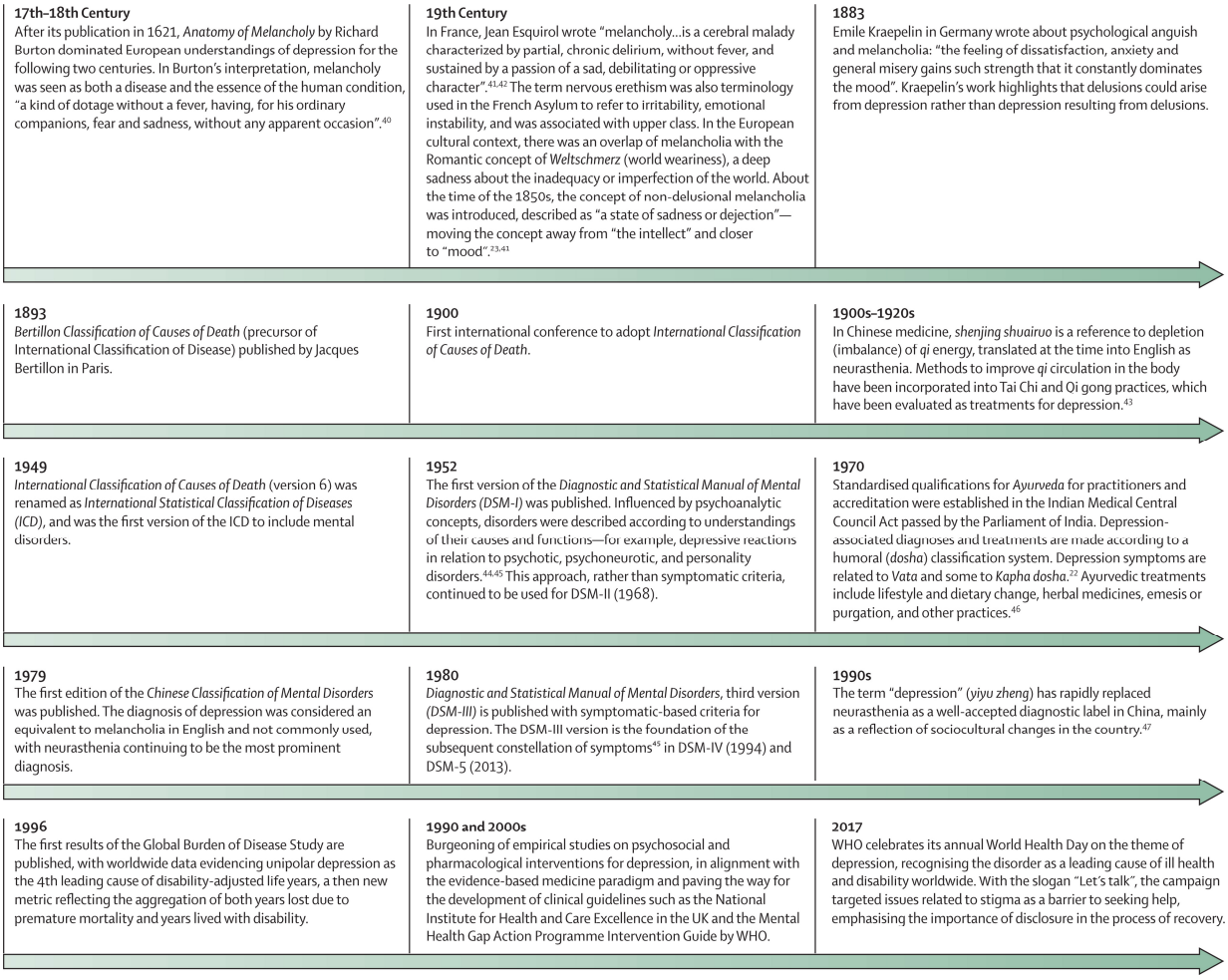


Figure 1. Historical timeline of depression across the ages (reprinted from The Lancet, Herrman et al., 2022, with permission from Elsevier)

This is specifically true for one debilitating symptom of depression, which is defined as an almost daily occurrence of diminished ability to think or concentrate, or indecisiveness. These cognitive effects of depression have not been the focus of research for a long time (Perini et al. 2019). Hence, it is not surprising that these symptoms have later been found to persist as residual symptoms in many patients and most commonly used pharmacological agents are not as effective for cognitive symptoms as for symptoms of mood (Colwell et al. 2022; Miskowiak and Petersen 2019). Yet, modulating cognitive functions is particularly relevant in depression research, as cognitive deficits are commonly observed alongside affective and vegetative symptoms in patients with Major Depressive Disorder (MDD) (Burt et al. 1995; Rock et al. 2014; Snyder 2013; Veiel 1997; Zakzanis et al. 1998). Both rTMS and tDCS have been widely utilized in research to explore and influence cognitive and psychomotor functions. When

targeted at the left dorsolateral prefrontal cortex (DLPFC), evidence suggests that both methods can enhance attention, working memory, and psychomotor speed in healthy individuals (Brunoni and Vanderhasselt 2014; Miniussi and Ruzzoli 2013). Numerous studies have explored the impact of non-invasive brain stimulation techniques on cognitive functions in individuals with MDD. ECT, for instance, has been found to enhance cognitive domains such as processing speed, working memory, and various aspects of executive function (Semkovska and McLoughlin 2010). However, ECT is also associated with potential negative effects on memory, including both retrograde and anterograde amnesia (Lisanby et al. 2000; Payne and Prudic 2009; Sackeim 2014). Thus, concerns persist among patients and healthcare providers regarding the risk of cognitive impairment following brain stimulation therapies, especially in the case of ECT (Payne and Prudic 2009). Recent meta-analyses of randomized controlled trials have indicated that prefrontal rTMS may improve cognitive skills such as psychomotor speed, visual scanning, and set-shifting abilities (Martin et al. 2017). In contrast, an earlier review reported limited evidence of cognitive enhancement across psychiatric conditions following rTMS (Martin et al. 2016). Notably, rTMS is generally not associated with significant cognitive side effects post-treatment (Lefaucheur et al. 2020; Lefaucheur et al. 2014). Magnetic Seizure Therapy (MST), another form of non-surgical brain stimulation, appears to enhance certain memory and executive functions and may be associated with fewer unwanted cognitive side effects compared to ECT (Cretaz et al. 2015; Kayser et al. 2015). Meanwhile, some studies have reported that tDCS can improve cognitive control in patients with MDD (Wolkenstein and Plewnia 2013). However, a recent meta-analysis using individual patient data found no consistent evidence that tDCS provides cognitive benefits beyond its effects on mood improvement (Martin et al. 2018). In summary, while these non-invasive brain stimulation methods hold promise for cognitive enhancement in MDD, their effects can vary widely. This underscores the need for comprehensive evaluation to better inform clinical practice beyond antidepressant efficacy (Kiebs et al. 2019).

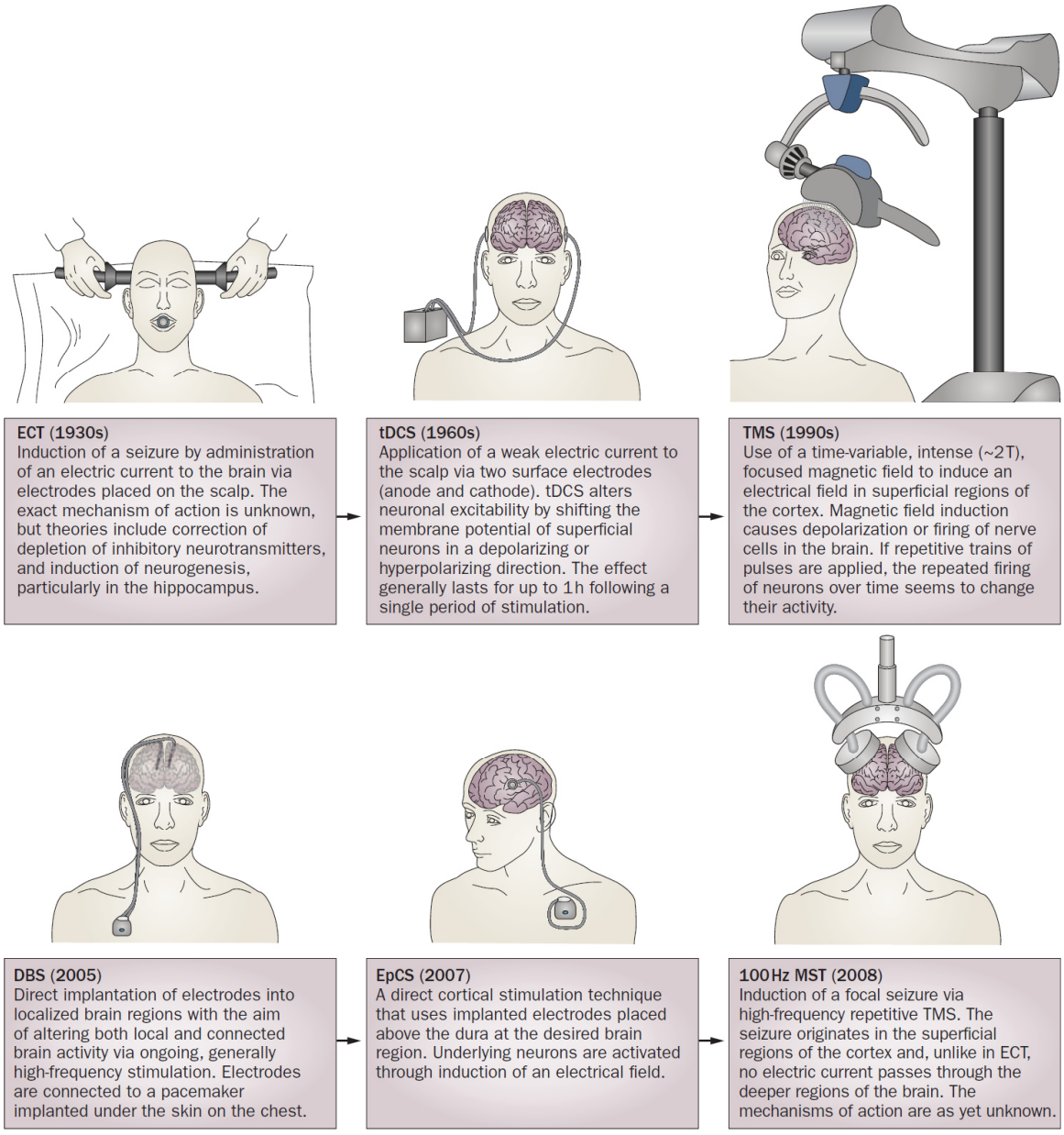


Figure 2. Timeline of introduction of brain stimulation techniques. Abbreviations: DBS, deep brain stimulation; ECT, electroconvulsive therapy; EpCS, epidural cortical stimulation; MST, magnetic seizure therapy; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation. From Hoy & Fitzgerald (2010), https://doi.org/10.1038/nrneurol.2010.30. Reproduced with permission from Springer Nature.

Consequently, research investigating the cognitive effects of ECT in an international, multicentric data set is presented. Secondly, research on the role of stimulus dose on cognitive performance is presented (Studies 1 and 2).

As mentioned, it has been proposed to study specific symptoms of depression and how they are affected by treatment. Specifically, during the COVID-19 pandemic, social distancing measures resulted in an absence of social touch, which has been linked to increased anxiety and loneliness (von Mohr et al. 2021). One of the debilitating symptoms of depressive disorders is the impairment in social functioning (Kupferberg et al. 2016). As social touch has been proposed to be inherently rewarding, the neural processing of social touch presents an opportunity to investigate the role of social reward in depressed patients, which has only been investigated in virtual social feedback tasks (Hertenstein et al. 2006; Hsu et al. 2015; Morrison et al. 2010; Olino et al. 2015). In this sense, the third objective of this work was to investigate whether reward network activity is altered in response to social touch in patients suffering from MDD (Study 3).

Personalization of mental health treatments is increasingly emerging as a promising approach for improving treatment outcomes, particularly for heterogeneous disorders (Perna et al., 2024). Since more than 10 years it has been established that targeting the L-DLPFC with rTMS leads to a clinically relevant antidepressant response (Cotovio et al. 2023; Mutz et al. 2019b). Traditionally, rTMS targets have been limited to areas close to the surface of the scalp as the intensity of the magnetic field decreases exponentially as the distance from the source increases. In addition, conventional rTMS coil placement strategies, such as the “5 cm rule”, Beam F3, and most magnetic resonance imaging (MRI) neuronavigation methods, are all landmark-based (e.g. 5 cm anterior to the motor cortex) and therefore not personalized. Approaches that attempt to personalize treatment typically use individual fMRI data from patients to pinpoint specific superficial cortical areas that are functionally linked to deeper brain structures, which are beyond the direct reach of TMS. By targeting these accessible cortical regions, it is possible to indirectly influence deeper brain structures through top-down propagation of stimulation effects (Eldaief et al. 2023; Fox et al. 2013; Wang et al. 2014). As such, they allow for more individualized treatment and examination of the therapeutic potential of stimulating brain regions beyond the DLPFC, which have been relatively underexplored (Downar and Daskalakis 2013; Nestor and Blumberger 2020; Schutter and Van Honk 2005; Siddiqi et al. 2020). This network-based approach facilitates the targeting of alternative brain regions for antidepressant interventions, with the hippocampus emerging as a compelling candidate due to its central role in the neural circuitry involved in MDD

(Nestler et al. 2002). Research has consistently shown that hippocampal volume loss is a common feature in MDD patients, and this reduction is linked to a longer duration of illness as well as poorer response to treatment (Caetano et al. 2004; Fu et al. 2013; MacQueen and Frodl 2011). Based on findings such as these, further research is presented here, in which commonly used theta-burst TMS over the L-DLPFC was augmented with a personalized rTMS target within the lateral parietal cortex (LPC), which is functionally connected to the hippocampus (Study 4).

Lastly, by reexamining the studies included in a meta-analysis regarding the efficacy of non-invasive brain stimulation as a treatment for MDD, we present data suggesting that practically all evidence for TMS in depressive disorders is based on trials comprising treatment-refractory patients (TRD; Mutz et al. 2018; Study 5). This is understandable for any novel treatment, as there could possibly be unanticipated side effects altering the relative risk-to-benefit ratio. Interestingly, most of the evidence for pharmacological interventions is from trials excluding TRD patients and well-performed trials with this group of patients are rare (Cipriani et al. 2018; Furukawa et al. 2011; Maj et al. 2020; Zimmerman et al. 2020). This has led to dramatic differences in the characteristics of patients enrolled in brain stimulation and pharmacological treatment trials. To this end, the fifth line of research presented here examined the inclusion of TRD patients in clinical trials of non-invasive brain stimulation with respect to their outcomes.

2.1 Research Aims

The overall aim was to investigate the effect of treatments on specific symptoms and to explore the potential for personalization. To this end, five studies were conducted to examine specific symptoms of MDD (Study 1, Study 2, Study 3), personalization and a novel target for iTBS treatment (Study 4), and patient characteristics in clinical trials (Study 5). The following research questions were addressed in depressed patients:

(1) Is the cognitive performance worse in patients after ECT than in healthy controls, and is bitemporal (BT) electrode placement associated with the greatest cognitive impairment?

(2) Is a higher mean stimulus energy, measured in millicoulomb (mC) and calculated as mean charge across the ECT series, independent of the total number of ECT sessions and higher age, predictive of greater cognitive impairment following an ECT series?
(3) Do MDD patients perceive social touch as less comfortable and 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?
(4) Does parieto-hippocampal stimulation compared to sham stimulation as an add-on to active DLPFC stimulation improve cognitive performance, modulate both hippocampal functional connectivity and memory-related functional hippocampus activity, and increase the therapeutic effect of iTBS on depressive symptoms?
(5) How many trials included in a recent meta-analysis regarding the efficacy of non-invasive brain stimulation as a treatment for MDD reported the level of treatment refractoriness of the included patients, and which inclusion criteria regarding TRD were used in most of the trials?

All presented research was conducted in accordance with the Declaration of Helsinki (2013), and the studies were approved by the institutional review board of the Medical Faculty of the University of Bonn (Ref.-Nr. 092/1 & Ref.-Nr. 254/17).

2.2 References

Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 2014; 86: 1–9

Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol Bull 1995; 117(2): 285–305

Caetano SC, Hatch JP, Brambilla P, Sassi RB, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. Psychiatry Research: Neuroimaging 2004; 132(2): 141–147

Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014; 13(2): 153–160

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet 2018; 391(10128): 1357–1366

Colwell MJ, Tagomori H, Chapman S, Gillespie AL, Cowen PJ, Harmer CJ, Murphy SE. Pharmacological targeting of cognitive impairment in depression: recent developments and challenges in human clinical research. Transl Psychiatry 2022; 12(1): 484

Cotovio G, Ventura F, Rodrigues Da Silva D, Pereira P, Oliveira-Maia AJ. Regulatory Clearance and Approval of Therapeutic Protocols of Transcranial Magnetic Stimulation for Psychiatric Disorders. Brain Sciences 2023; 13(7): 1029

Cretaz E, Brunoni AR, Lafer B. Magnetic Seizure Therapy for Unipolar and Bipolar Depression: A Systematic Review. Neural Plast 2015; 521398: 1-9

Cuijpers P, Quero S, Noma H, Ciharova M, Miguel C, Karyotaki E, Cipriani A, Cristea IA, Furukawa TA. Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. World Psychiatry 2021; 20(2): 283–293

Downar J, Daskalakis ZJ. New Targets for rTMS in Depression: A Review of Convergent Evidence. Brain Stimulation 2013; 6(3): 231–240

Eldaief MC, McMains S, Izquierdo-Garcia D, Daneshzand M, Nummenmaa A, Braga RM. Network-specific metabolic and haemodynamic effects elicited by non-invasive brain stimulation. Nat Ment Health 2023; 1(5): 346–360

Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. NeuroImage 2013; 66: 151–160

Fried EI. Moving forward: how depression heterogeneity hinders progress in treatment and research. Expert Rev Neurother 2017a; 17(5): 423–425

Fried EI. The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. J Affect Disord 2017b; 208: 191–197

Fu CHY, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiology of Disease 2013; 52: 75–83

Furukawa TA, Akechi T, Shimodera S, Yamada M, Miki K, Watanabe N, Inagaki M, Yonemoto N. Strategic use of new generation antidepressants for depression: SUN(^_^)D study protocol. Trials 2011; 12: 116

Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, Furukawa TA, Kessler RC, Kohrt BA, Maj M, McGorry P, Reynolds CF, Weissman MM, Chibanda D, Dowrick C, Howard LM, Hoven CW, Knapp M, Mayberg HS, Penninx BWJH, Xiao S, Trivedi M, Uher R, Vijayakumar L, Wolpert M. Time for united action on depression: a Lancet-World Psychiatric Association Commission. Lancet 2022; 399(10328): 957–1022

Hertenstein MJ, Verkamp JM, Kerestes AM, Holmes RM. The communicative functions of touch in humans, nonhuman primates, and rats: a review and synthesis of the empirical research. Genet Soc Gen Psychol Monogr 2006; 132(1): 5–94

Hoy KE, Fitzgerald PB. Brain stimulation in psychiatry and its effects on cognition. Nat Rev Neurol 2010; 6(5): 267–275

Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Walker SJ, Mickey BJ, Koeppe RA, Langenecker SA, Zubieta J-K. It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. Mol Psychiatry 2015; 20(2): 193–200

Kayser S, Bewernick BH, Matusch A, Hurlemann R, Soehle M, Schlaepfer TE. Magnetic seizure therapy in treatment-resistant depression: clinical, neuropsychological and metabolic effects. Psychological Medicine 2015; 45(05): 1073–1092

Kiebs M, Hurlemann R, Mutz J. Cognitive effects of non-surgical brain stimulation for major depressive disorder: protocol for a systematic review and meta-analysis. BMJ Open 2019; 9(2): e023796

Kupferberg A, Bicks L, Hasler G. Social functioning in major depressive disorder. Neuroscience & Biobehavioral Reviews 2016; 69: 313–332

Laursen TM, Musliner KL, Benros ME, Vestergaard M, Munk-Olsen T. Mortality and life expectancy in persons with severe unipolar depression. J Affect Disord 2016; 193: 203–207

Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen J-P, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clin Neurophysiol 2020; 131(2): 474–528

Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D. Evidence-based guidelines on the therapeutic use of

repetitive transcranial magnetic stimulation (rTMS). Clinical Neurophysiology 2014; 125(11): 2150–2206

Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. Arch. Gen. Psychiatry 2000; 57(6): 581–590

MacQueen G, Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 2011; 16(3): 252–264

Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, Demyttenaere K, McIntyre RS, Widiger T, Wittchen H-U. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry 2020; 19(3): 269–293

Martin DM, McClintock SM, Forster J, Loo CK. Does Therapeutic Repetitive Transcranial Magnetic Stimulation Cause Cognitive Enhancing Effects in Patients with Neuropsychiatric Conditions? A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Neuropsychol Rev 2016; 26(3): 295–309

Martin DM, McClintock SM, Forster JJ, Lo TY, Loo CK. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with depression: A systematic review and meta-analysis of individual task effects. Depress Anxiety 2017; 34(11): 1029–1039

Martin DM, Moffa A, Nikolin S, Bennabi D, Brunoni AR, Flannery W, Haffen E, McClintock SM, Moreno ML, Padberg F, Palm U, Loo CK. Cognitive effects of transcranial direct current stimulation treatment in patients with major depressive disorder: an individual patient data meta-analysis of randomised, sham-controlled trials. Neurosci. Biobehav. Rev. 2018; 90:137-145

Marx W, Penninx BWJH, Solmi M, Furukawa TA, Firth J, Carvalho AF, Berk M. Major depressive disorder. Nat Rev Dis Primers 2023; 9(1): 44

McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH, Ly-Uson J, Mansur RB, McAllister-Williams RH, Murrough JW, Nemeroff CB, Nierenberg AA, Rosenblat JD, Sanacora G, Schatzberg AF, Shelton R, Stahl SM, Trivedi MH, Vieta E, Vinberg M, Williams N, Young AH, Maj M. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023; 22(3): 394–412

Miniussi C, Ruzzoli M. Transcranial stimulation and cognition. Handb Clin Neurol 2013; 116: 739–750

Miskowiak KW, Petersen CS. Neuronal underpinnings of cognitive impairment and -improvement in mood disorders. CNS Spectr. 2019; 24(1): 30–53

von Mohr M, Kirsch LP, Fotopoulou A. Social touch deprivation during COVID-19: effects on psychological wellbeing and craving interpersonal touch. R Soc Open Sci 2021; 8(9): 210287

Monroe SM, Anderson SF. Depression: The Shroud of Heterogeneity. Curr Dir Psychol Sci 2015; 24(3): 227–231

Morrison I, Löken LS, Olausson H. The skin as a social organ. Exp Brain Res 2010; 204(3): 305–314

Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. Neuroscience & Biobehavioral Reviews 2018; 92: 291–303

Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ 2019a; : l1079

Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ 2019b; : l1079

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of Depression. Neuron 2002; 34(1): 13–25

Nestor SM, Blumberger DM. Mapping Symptom Clusters to Circuits: Toward Personalizing TMS Targets to Improve Treatment Outcomes in Depression. AJP 2020; 177(5): 373–375

Olino TM, Silk JS, Osterritter C, Forbes EE. Social Reward in Youth at Risk for Depression: A Preliminary Investigation of Subjective and Neural Differences. Journal of Child and Adolescent Psychopharmacology 2015; 25(9): 711–721

Payne NA, Prudic J. Electroconvulsive Therapy Part I: A Perspective on the Evolution and Current Practice of ECT. J Psychiatr Pract 2009; 15(5): 346–368

Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat 2019; 15: 1249–1258

Perna G, Caldirola D, Schatzberg AF, Nemeroff CB. Advancements, challenges and future horizons in personalized psychiatry. World Psychiatry 2024; 23(3): 460–461

Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychological Medicine 2014; 44(10): 2029–2040

Sackeim HA. Autobiographical Memory and Electroconvulsive Therapy: Do Not Throw Out the Baby. The Journal of ECT 2014; 30(3): 177–186

Schutter DJLG, Van Honk J. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. Journal of Psychiatry and Neuroscience 2005; 30(2): 91–97

Semkovska M, McLoughlin DM. Objective Cognitive Performance Associated with Electroconvulsive Therapy for Depression: A Systematic Review and Meta-Analysis. Biological Psychiatry 2010; 68(6): 568–577

Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation. AJP 2020; 177(5): 435–446

Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. Psychological Bulletin 2013; 139(1): 81–132

Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 1997; 19(4): 587–603

Vollset SE, Ababneh HS, Abate YH, Abbafati C, Abbasgholizadeh R, Abbasian M, Abbastabar H, Abd Al Magied AHA, Abd ElHafeez S, Abdelkader A, Abdelmasseh M, Abd-Elsalam S, Abdi P, Abdollahi M, Abdoun M, Abdullahi A, Abebe M, Abiodun O, Aboagye RG, Abolhassani H, Abouzid M, Aboye GB, Abreu LG, Absalan A, Abualruz H, Abubakar B, Abukhadijah HJJ, Addolorato G, Adekanmbi V, Adetunji CO, Adetunji JB, Adeyeoluwa TE, Adha R, Adhikary RK, Adnani QES, Adzigbli LA, Afrashteh F, Afzal MS, Afzal S, Agbozo F, Agodi A, Agrawal A, Agyemang-Duah W, Ahinkorah BO, Ahlstrom AJ, Ahmad A, Ahmad F, Ahmad MM, Ahmad S, Ahmad S, Ahmed A, Ahmed A, Ahmed H, Ahmed S, Ahmed SA, Akinosoglou K, Akkaif MA, Akrami AE, Akter E, Al Awaidy S, Al Hasan SM, Al Mosa AS, Al Ta'ani O, Al Zaabi OAM, Alahdab F, Alajlani MM, Al-Ajlouni Y, Alalalmeh SO, Al-Aly Z, et al. Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the Global Burden of Disease Study 2021. The Lancet 2024; 403(10440): 2204–2256

Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, Hermiller MS, Voss JL. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 2014; 345(6200): 1054–1057

Wolkenstein L, Plewnia C. Amelioration of Cognitive Control in Depression by Transcranial Direct Current Stimulation. Biological Psychiatry 2013; 73(7): 646–651

World Health Organization. Depressive disorder (depression) [Internet]. 2024 [cited 2024]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression

Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11(3): 111–119

Zimmerman M, Balling C, Chelminski I, Dalrymple K. Applying the inclusion/exclusion criteria in placebo-controlled studies to a clinical sample: A comparison of medications. J Affect Disord 2020; 260: 483–488

3. Publications

Publication overview:

Kiebs M, Farrar DC, Yrondi A, Cardoner N, Tuovinen N, Redlich R, Dannlowski U, Soriano-Mas C, Dols A, Takamiya A, Tendolkar I, Narr KL, Espinoza R, Laroy M, van Eijndhoven P, Verwijk E, van Waarde J, Verdijk J, Maier HB, Nordanskog P, van Wingen G, van Diermen L, Emsell L, Bouckaert F, Repple J, Camprodon JA, Wade BSC, Donaldson KT, Oltedal L, Kessler U, Hammar Å, Sienaert P, Hebbrecht K, Urretavizcaya M, Belge JB, Argyelan M, Baradits M, Obbels J, Draganski B, Philipsen A, Sartorius A, Rhebergen D, Ousdal OT, Hurlemann R, McClintock S, Erhardt EB, Abbott C. Electroconvulsive therapy and cognitive performance from the Global ECT MRI Research Collaboration. Journal of Psychiatric Research 2024; 179: 199–208. DOI: https://doi.org/10.1016/j.jpsychires.2024.09.013

Rummel L, Göke K, Philipsen A, Hurlemann R, **Kiebs M**. Role of Stimulus Dose on Neuropsychological Functioning after Electroconvulsive Therapy in Patients with Major Depressive Disorder. Frontiers in Psychiatry 2024; 15: 1443270. DOI: https://doi.org/10.3389/fpsyt.2024.1443270

Mielacher C, Scheele D, **Kiebs M**, Schmitt L, Dellert T, Philipsen A, Lamm C, Hurlemann R. Altered reward network responses to social touch in major depression. Psychological Medicine 2024; 54(2): 308–316. DOI: https://doi.org/10.1017/S0033291723001617

Mielacher C, Schultz J, **Kiebs M,** Dellert T, Metzner A, Graute L, Högenauer H, Maier W, Lamm C, Hurlemann R. Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder. Personalized Medicine in Psychiatry 2020; 23–24: 100066. DOI: https://doi.org/10.1016/j.pmip.2020.100066

Kiebs M, Hurlemann R, Mutz J. Repetitive transcranial magnetic stimulation in non-treatment-resistant depression. The British Journal of Psychiatry 2019; 215(2): 445–446. DOI: https://doi.org/10.1192/bjp.2019.75

3.1 Publication 1: Electroconvulsive therapy and cognitive performance from the Global ECT MRI Research Collaboration

Journal of Psychiatric Research 179 (2024) 199–208

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Electroconvulsive therapy and cognitive performance from the Global ECT MRI Research Collaboration

Maximilian Kiebs [a,b,**], Danielle C. Farrar [c], Antoine Yrondi [d,e], Narcis Cardoner [f,g,h], Noora Tuovinen [i], Ronny Redlich [j,k,l], Udo Dannlowski [k], Carles Soriano-Mas [m,h,n], Annemiek Dols [o,p], Akihiro Takamiya [q,r], Indira Tendolkar [s], Katherine L. Narr [t], Randall Espinoza [t], Maarten Laroy [q], Philip van Eijndhoven [s], Esmée Verwijk [u,v,w], Jeroen van Waarde [x], Joey Verdijk [x], Hannah B. Maier [y], Pia Nordanskog [z,aa], Guido van Wingen [ab,ac], Linda van Diermen [ad,ae], Louise Emsell [q,af], Filip Bouckaert [q,af], Jonathan Repple [ag,ah], Joan A. Camprodon [ai], Benjamin S.C. Wade [ai], K. Tristan Donaldson [ai], Leif Oltedal [aj,ak], Ute Kessler [al,am], Åsa Hammar [an,ao,ap], Pascal Sienaert [aq], Kaat Hebbrecht [aq], Mikel Urretavizcaya [ar,as,h], Jean-Baptiste Belge [at], Miklos Argyelan [au,av], Mate Baradits [av], Jasmien Obbels [aq], Bogdan Draganski [aw,ax], Alexandra Philipsen [b], Alexander Sartorius [ay], Didericke Rhebergen [p,az], Olga Therese Ousdal [ba], René Hurlemann [a], Shawn McClintock [bb], Erik B. Erhardt [bc], Christopher C. Abbott [c,*]

[a] Department of Psychiatry and Psychotherapy, School of Medicine and Health Sciences, University of Oldenburg, Oldenberg, Germany
[b] Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany
[c] Department of Psychiatry and Behavioral Sciences, University of New Mexico School of Medicine, Albuquerque, NM, USA
[d] Service de Psychiatrie et de Psychologie Médicale, Centre Expert Dépression Résistante FondaMental, CHU de Toulouse, Hôpital Purpan, ToNIC Toulouse NeuroImaging Centre, Toulouse, France
[e] Université de Toulouse, INSERM, UPS, Toulouse, France
[f] Sant Pau Mental Health Research Group, Institut d'Investigació Biomèdica Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[g] Department of Psychiatry and Forensic Medicine, School of Medicine Bellaterra, Universitat Autònoma de Barcelona, Barcelona, Spain
[h] Network Center for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[i] Department of Psychiatry, Psychotherapy, Psychosomatics and Medical Psychology, Division of Psychiatry I, Medical University of Innsbruck, Innsbruck, Austria
[j] Department of Psychology, University of Halle, Germany
[k] Institute of Translational Psychiatry, University of Muenster, Germany
[l] Halle-Jena-Magdeburg, German Center for Mental Health (DZPG), Germany
[m] Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Spain
[n] Department of Social Psychology and Quantitative Psychology, Institute of Neurosciences, Universitat de Barcelona - UB, Barcelona, Spain
[o] Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
[p] Department of Psychiatry, Amsterdam UMC location, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[q] Department of Neurosciences, Neuropsychiatry, Leuven Brain Institute, KU Leuven, Leuven, Belgium
[r] Hills Joint Research Laboratory for Future Preventive Medicine and Wellness, Keio University School of Medicine, Tokyo, Japan
[s] Department of Psychiatry, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands
[t] Departments of Neurology and Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA
[u] Department of Psychology, Brain and Cognition, University of Amsterdam, Amsterdam, the Netherlands
[v] Department of Medical Psychology, UMC Amsterdam, Amsterdam, the Netherlands
[w] ECT-Department, Parnassia Psychiatric Institute, The Hague, the Netherlands

* Corresponding author. Psychiatric Neuromodulation, SOM - Psychiatry & Behavioral Sciences, Domenici Center for Health Sciences Education (DOMCTR), Bldg. 200 1, University of New Mexico, MSC09 5030 Albuquerque, NM, 87131, USA.
** Corresponding author. Department of Psychiatry and Psychotherapy, School of Medicine and Health Sciences, University of Oldenburg, Hermann-Ehlers-Str. 7, D-26160, Bad Zwischenahn, Germany.
E-mail addresses: m.kiebs@uol.de (M. Kiebs), CAbbott@salud.unm.edu (C.C. Abbott).

https://doi.org/10.1016/j.jpsychires.2024.09.013
Received 24 May 2024; Received in revised form 3 September 2024; Accepted 9 September 2024
Available online 18 September 2024

[x] Department of Psychiatry, Rijnstate, Arnhem, the Netherlands
[y] Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany
[z] Center for Social and Affective Neuroscience (CSAN), Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[aa] Department of Psychiatry in Linköping, Linköping, Sweden
[ab] Department of Psychiatry, Amsterdam UMC location, University of Amsterdam, Amsterdam, the Netherlands
[ac] Amsterdam Neuroscience Amsterdam, the Netherlands
[ad] Department of Psychiatry, University Hospital of Liège, Liege, Belgium
[ae] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, the Netherlands
[af] Geriatric Psychiatry, University Psychiatry Center (UPC), KU Leuven, Leuven, Belgium
[ag] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University Frankfurt, Frankfurt, Germany
[ah] Institute for Translational Psychiatry, University of Münster, Münster, Germany
[ai] Division of Neuropsychiatry and Neuromodulation, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[aj] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[ak] Mohn Medical Imaging and Visualization Centre, Department of Radiology, Haukeland University Hospital, Bergen, Norway
[al] Department of Psychiatry, Haukeland University Hospital, Bergen, Norway
[am] University of Bergen, Bergen, Norway
[an] Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway
[ao] Department of Clinical Sciences Lund, Psychiatry, Faculty of Medicine, Lund University, Lund, Sweden
[ap] Office for Psychiatry and Habilitation, Psychiatry Research Skåne, Skåne, Sweden
[aq] Academic Center for ECT and Neuromodulation (AcCENT), Department of Neurosciences, Neuropsychiatry, University Psychiatry Center (UPC), KU Leuven, Leuven, Belgium
[ar] Neurosciences Group - Psychiatry and Mental Health, Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Spain
[as] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona, Barcelona, Spain
[at] Department of Psychiatry, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[au] Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, NY, USA
[av] Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, NY, USA
[aw] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[ax] Neurology Department, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[ay] Department of Psychiatry and Psychotherapy, Central Institute of Mental Health (CIMH), Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany
[az] GGZ Central, Mental Health Institute, Amersfoort, the Netherlands
[ba] Department of Biomedicine, Faculty of Medicine, University of Bergen, Norway
[bb] Division of Psychology, Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA
[bc] Department of Mathematics and Statistics, University of New Mexico, Albuquerque, NM, USA

ARTICLE INFO

Keywords:
Electroconvulsive therapy
Depression
Cognition
Neuropsychology

ABSTRACT

The Global ECT MRI Research Collaboration (GEMRIC) has collected clinical and neuroimaging data of patients treated with electroconvulsive therapy (ECT) from around the world. Results to date have focused on neuroimaging correlates of antidepressant response. GEMRIC sites have also collected longitudinal cognitive data. Here, we summarize the existing GEMRIC cognitive data and provide recommendations for prospective data collection for future ECT-imaging investigations. We describe the criteria for selection of cognitive measures for mega-analyses: Trail Making Test Parts A (TMT-A) and B (TMT-B), verbal fluency category (VFC), verbal fluency letter (VFL), and percent retention from verbal learning and memory tests. We performed longitudinal data analysis focused on the pre-/post-ECT assessments with healthy comparison (HC) subjects at similar timepoints and assessed associations between demographic and ECT parameters with cognitive changes. The study found an interaction between electrode placement and treatment number for VFC ($F(1,107) = 4.14$, $p = 0.04$). Higher treatment was associated with decreased VFC performance with right unilateral electrode placement. Percent retention showed a main effect for group, with post-hoc analysis indicating decreased cognitive performance among the HC group. However, there were no significant effects of group or group interactions observed for TMT-A, TMT-B, or VFL. We assessed the current GEMRIC cognitive data and acknowledge the limitations associated with this data set including the limited number of neuropsychological domains assessed. Aside from the VFC and treatment number relationship, we did not observe ECT-mediated neurocognitive effects in this investigation. We provide prospective cognitive recommendations for future ECT-imaging investigations focused on strong psychometrics and minimal burden to subjects.

1. Introduction

Electroconvulsive therapy (ECT) has potent antidepressant effects with high response and remission rates (UK ECT Review Group, 2003). Sixty to eighty percent of individuals with treatment-resistant depression have rapid improvement or remission of depressive symptoms (Weiner and Reti, 2017). ECT is cost effective and reduces hospital readmission, suicide risk, and 1-year all-cause mortality (Kaster et al., 2021; Rhee et al., 2021; Ross et al., 2018; Slade et al., 2017). ECT is also medically safe and not associated with increased severe medical events (Kaster et al., 2021). Despite ECT's efficacy and safety, less than 1% of individuals diagnosed with major depressive disorder (MDD) receive ECT (Rhee et al., 2020; Wilkinson et al., 2018, 2021).

ECT is often utilized as a treatment of last resort because of stigma and risk of cognitive side effects (Slade et al., 2017). The cognitive adverse effects of ECT are transient but may mitigate clinical improvement (Alexopoulos et al., 2005; Chakrabarti et al., 2010; Kiosses and Alexopoulos, 2005; Kiosses et al., 2001; Porter et al., 2008; Rajagopal et al., 2013) and limit the use of ECT (Sackeim, 2017; Slade et al., 2017). While right unilateral (RUL) ultrabrief pulse ECT results in less cognitive impairment relative to bitemporal (BT) brief pulse (Lisanby, 2007; Sackeim, 2017; Semkovska et al., 2016), both still produce moderate to large (Cohen's $d = -0.53$ to -0.83) adverse cognitive effects (Tor et al., 2015). Key adverse cognitive effects include amnesia, executive dysfunction, and verbal dysfluency (Abbott et al., 2020; Lisanby et al., 2020; Loef et al., 2024; McClintock et al., 2011; Semkovska and McLoughlin, 2010; Vasavada et al., 2017a, 2017b). Current research demonstrates the return to pre-ECT baseline levels for most cognitive

domains in the weeks following an acute ECT series (Nuninga et al., 2018; Semkovska and McLoughlin, 2010; Vasavada et al., 2017a, 2017b). Autobiographical memory, which has numerous measurement challenges, may persist for up to six months (Martin et al., 2015; Semkovska and McLoughlin, 2013, 2014). The mechanisms and anatomic locations underlying cognitive adverse effects remain largely unknown (Bolwig, 2014; Singh and Kar, 2017).

The Global ECT MRI Research Collaboration (GEMRIC) was developed to combine longitudinal neuroimaging data from ECT studies across sites and institutions to investigate ECT's mechanism of action (Oltedal et al., 2017). GEMRIC utilizes a common analysis pipeline to combine ECT-imaging datasets from different study sites for mega-analyses. The increased power of the larger sample sizes associated with the GEMRIC database has examined structural and functional changes associated with ECT. Important findings to date from GEMRIC include ECT-mediated volumetric changes (Oltedal et al., 2018; Ousdal et al., 2020), relationships between electric field strength and volumetric changes (Argyelan et al., 2019), and volumetric changes associated with treatment response (Argyelan et al., 2023; Mulders et al., 2020).

Here, we assess GEMRIC cognitive measures across all sites. We describe the demographic information of the GEMRIC patient and healthy comparison subjects (HC) who have longitudinal cognitive data. We assess the cognitive changes associated with each electrode placement (RUL, BT, bifrontal [BF], and left anterior right temporal [LART]) relative to the HC sample. We hypothesize that BT electrode placement would be associated with the most cognitive impairment. We then make prospective cognitive assessment recommendations for future GEMRIC sites to facilitate the study of neuroanatomic mechanisms underlying ECT cognitive impairment.

2. Methods

2.1. Participant selection

We included all subjects from the GEMRIC database with a diagnosis of MDD or bipolar disorder type I or II with most recent episode depressed, and with longitudinal (pre-/post-ECT) neurocognitive data. We also included HC with longitudinal neurocognitive data. Exclusion criteria for individuals diagnosed with MDD or bipolar disorder consisted of the following: 1) bipolar disorder diagnosis without specification of current episode; 2) less than four ECT treatments; 3) pre-ECT 17-item Hamilton Rating Scale for Depression (HAM-D) total score less than 19; or 4) unspecified electrode placement. As per GEMRIC regulations, informed consent was locally obtained from all sites in addition to the approval of the Regional Ethics Committee South-East in Norway (2018/769 The GEMRIC study).

2.2. Depression ratings

All sites used either the 17-item HAM-D or Montgomery-Asberg Depression Rating Scale (MADRS) to assess depression severity with each imaging assessment (Hamilton, 1960; Montgomery and Asberg, 1979). We converted MADRS to HAM-D with an established scale conversion (Heo et al., 2007). Response was defined as $\geq$ 50% improvement post-ECT in comparison to pre-ECT HAM-D (Husain et al., 2004).

2.3. Cognitive data

Thirteen sites contributed data with 34 neuropsychological measures at four time points: pre-, mid-, post-, and follow-up ECT (Supplemental Table 1: GEMRIC cognitive data from all sites). Due to heterogeneity of represented cognitive domains and available data for multisite analysis, selection of cognitive measures was based on the following consensus criteria: 1) uniform data collection; 2) cognitive domain known to be impacted by ECT (e.g., memory, verbal fluency); and 3) large number of participants. As a result, five tests were selected for this analysis: Trail-Making Tests Part A (TMT-A) and B (TMT-B) (Reitan and Wolfson, 1985), letter (VFL) and category verbal fluency (VFC) (Lezak, 2012), and percent retention from verbal declarative memory tests (percent retention) (Table 1: Neurocognitive measures). Verbal learning and memory tasks included the Rey Auditory Verbal Learning Test (Lezak, 2012), California Verbal Learning Test-2nd Edition (Delis et al., 2000), and Hopkins Verbal Learning Test-Revised (Brandt and Benedict, 2001). The verbal memory tests were combined into one memory score by their percent retention score defined as *Delayed recall/Last learning trial*. The percent retention score reduces the possibility of over-estimating memory function from immediate and delayed free recall scores (Clark et al., 2010). Notably, only three sites measured autobiographical memory with two different tests: two sites used the Autobiographical Memory Interview – Short Form, and one site used the autobiographical fluency task (Dritschel et al., 1992; McElhiney et al., 2001). Therefore, this analysis did not include autobiographical memory (see Future Directions).

2.3.1. Electroconvulsive therapy

32% of participants underwent treatment using a MECTA versus 68% using a THYMATRON device. ECT procedures were site specific and included different devices: MECTA (MECTA Corporation, Tualatin, Oregon) or Thymatron (Somatics LLC, Venice, Florida, USA); electrode placements: BT, RUL, LART, or BF; pulse widths: 0.3–1.0 ms; and dosing methods: seizure titration or demographically informed. Treatment number was also site-specific with either fixed treatment or variable ECT endpoints. Sites had variable timing of the cognitive-imaging assessments: pre-, mid-, post-ECT, and follow-up (>1-month post-ECT) assessments. For this investigation, we focused on the pre-/post-ECT cognitive outcomes to maximize subject number. Post-ECT neuropsychological assessment was done within one week after the last ECT treatment across sites.

2.4. Analysis

GEMRIC data release 3.2 (DOI: 10.17605/OSF.IO/YP2G, link: https://osf.io/yp2g4/) was used for the analysis of pre-post change of the five neuropsychological outcomes (Table 1). Clinical response was defined as $\geq$ 50% change. To minimize group comparisons, RUL- and LART-ECT-Placements were grouped together (RUL). Many sites started with RUL and included a BT contingency in the context of RUL non-

Table 1
Neurocognitive assessment synthesis across Global ECT MRI Research Collaboration (GEMRIC) sites.

Neurocognitive Test	Domain	Metric	Direction of effect[a]	Number of sites
Trail-Making Test Part A	Processing speed/ attention	Seconds	Negative	8
Trail-Making Test Part B	Executive function	Seconds	Negative	7
Verbal Fluency Semantic	Language function	N words	Positive	7
Verbal Fluency Letter	Language function	N words	Positive	5
Rey Auditory Verbal Learning Test Hopkins Verbal Learning Test-Revised California Verbal Learning Test, Second Edition	Verbal learning and memory	% retention	Positive	3

[a] Positive signifies higher values represent enhanced neuropsychological performance, while lower values indicates diminished performance. Vice versa for negative direction of effect.

response or worsening clinical condition. These subjects were grouped as BT. Due to heteroskedasticity between the patient and HC groups, we applied square-root transformations to TMT and VF scores. Linear models assessed group differences (RUL, BT, and HC) between percent differences relative to baseline ("%diff") in neurocognitive outcomes ($100 \times (Post - PreECT)/PreECT$). All models were adjusted for demographic and clinical characteristics (age, sex, education, site, number of ECT treatments, pre-post HAM-D % change). To retain as many observations as possible, missing HAM-D and values for the HC group were imputed using each site's mean. In patients, we imputed missing HAM-D (RUL n = 1, BT n = 3) and education values using the mice package (Version: 3.14 van Buuren and Groothuis-Oudshoorn, 2011). For each neuropsychological measure, a full model was fit and then reduced with best-subset selection for the ECT covariates (electrode placement and treatment number) using Akaike Information Criterion (AIC) (Akaike, 1974), but main effects for treatment group, age, sex, education, site and number of treatments were retained for all models. Model fit assumptions on the residuals are equal variance and normality, which were both assessed visually; however, results are robust to violations of the model distributional assumption (Schielzeth et al., 2020). VFC, VFL, and percent-retention had two outliers and were removed. The restricted maximum-likelihood (REML) adjusted least-squares mean difference estimates are reported (Lenth, 2023). In the case of significant main effects or interactions between model covariates and outcomes, post-hoc comparisons were calculated to elucidate direction of effect. Reported results are averaged across all other covariates. Multiple testing was controlled for via the false-discovery rate using the method of Benjamini and Hochberg (1995). All analyses were performed in R (Version 4.1.3; R Core Team, 2023). Plots were made using raincloud plots (Allen et al., 2019) and gghalves (https://github.com/erocoar/gghalves). Tables 1 and 2 were made using gtsummary (Sjoberg et al., 2021). R code of the analysis is available upon request.

Table 2
Patient group demographics.

Group	RUL or LART	BT	HC	p-value[a]
Total *n*	115	42	39	
Age: years (± SD)	50 (15)	54 (9)	45 (15)	0.031
Sex: Male/Female	52/63	17/25	16/23	0.847
Diagnosis: Unipolar/bipolar	105/10	42/0	–	<0.05
Pre-ECT HAM-D-17 (± SD)	26 (5)	26 (5)	1 (1)	<0.001
Antidepressant response (%)[b]	59%	83%	–	0.004
Treatment number (± SD)	12 (5)	13 (5)	0 (0)	<0.001
No. of previous ECT[c,d]	0.6 (2.1)	1.8 (0.3)	–	0.0138
No. of depressive episodes[c,d]	6.3 (11.4)	3 (2.1)	–	0.040
Episode duration (month, (± SD)[d]	18.4 (42.9)	19.3 (25.7)	–	0.896
Age first treatment (± SD)[d]	34.6 (13.9)	40.4 (9.24)	–	0.077
Education				
Grade 6 or less	4 (3.5%)	1 (2.4%)	0 (0%)	
Grade 7–12 (without graduating high school)	12 (10%)	11 (26%)	0 (0%)	
Graduated high school	12 (10%)	2 (4.8%)	4 (10%)	
Part college or university	16 (14%)	4 (9.5%)	2 (5.1%)	
Graduated 2-year college (associate degree)	15 (13%)	10 (24%)	11 (28%)	
Graduated 4-year college (bachelor degree)	24 (21%)	8 (19%)	10 (26%)	
Part graduate or professional school	5 (4.3%)	3 (7.1%)	6 (15%)	
Completed graduate or professional school	27 (23%)	3 (7.1%)	6 (15%)	

[a] Kruskal-Wallis rank sum test; Welch two sample *t*-test, Pearson's Chi-squared test; Fisher's exact test.
[b] Clinical response was defined as ≥ 50% change.
[c] Median.
[d] Data not available for full sample (No. previous ECT = 51; No. dep. Episodes = 90; Dur. Episode = 99, Age first Treatment = 55).

3. Results

3.1. Demographics and clinical characteristics

A total of 197 patients (11 study sites) and 39 HC subjects (3 study sites) had longitudinal clinical and neurocognitive data. We excluded patients with fewer than 4 four treatments (n = 1), a baseline HAM-D total score of less than 19 (n = 27), unknown electrode placement (n = 2), or unspecified bipolar disorder episode (n = 10). The remaining patients received ECT as a treatment for MDD (n = 147) or bipolar disorder I or II disorder most recent episode depressed (n = 10). The final sample included 157 patients (88 female, mean age = 51.2 years ± 13.8 SD) and 39 HC subjects (23 female, mean age = 44.6 years ± 15.2).

115 subjects received RUL (includes 2 subjects with LART), and 42 subjects received BT subjects (includes 25 subjects who transitioned from RUL). RUL received 12.3 ± 5.3 treatments and BT received 13.4 ± 5.4. In both groups, the pre-ECT HAMD total score was 26 ± 5 with a significantly higher response rate in the BT group (83%) than in the RUL group (59%, $p = 0.0045$). RUL and BT did not differ in mean age, sex, pre-ECT HAM-D-17, treatment number, education, or diagnosis (all $p > 0.1$). Both patient groups were significantly older compared to the HC group ($p = 0.031$), but HC and patient groups did not differ in sex-ratio ($p > 0.1$) (Table 2: Patient and HC demographics). The raw neurocognitive data and subject number for each test are presented in Table 3.

3.2. Analysis of change in neuropsychological performance

AIC reduced the main effect and interaction variables to the following: site, age, sex, education, antidepressant response (% change in HAM-D), treatment number, ECT placement (RUL, BT, and HC) or "group", treatment number-group interaction, sex-group interaction, and age-group interaction.

3.3. Verbal fluency category

VFC had a group-treatment number interaction (F(1,107) = 4.14, p = 0.04). Post-hoc analysis revealed that increased treatment number resulted in improved VFC performance in the BT group (β = 0.85, 95% CI [−0.12, 1.82]). In contrast, increased treatment number resulted in decreased VFC performance in the RUL group (β = −0.37, 95% CI [−1.11, 0.36]). The difference in slope between BT and RUL was significant ($\beta_{diff} = -1.23$, p = 0.04).

3.4. Percent retention

The main effect for group (RUL and HC) was significant for percent retention (F(1,81) = 4.35, p = 0.04). Post-hoc analysis revealed that

Table 3
Summary of neuropsychological results (pre-/post-ECT or longitudinal change).

Measure		RUL	BT	HC
Trail-Making Test Part A	N	76	36	23
	Δ seconds (± SD)	−2 ± 18	−3 (22)	−3 (16)
Trail-Making Test Part B	N	75	30	23
	Δ seconds (± SD)	−4 (21)	3 (34)	−2 (17)
Verbal Fluency Semantic	N	61	38	23
	Δ word number (± SD)	−2 (15)	6 (17)	−1 (7)
Verbal Fluency Letter	N	26	32	23
	Δ word number (± SD)	−3 (16)	1 (27)	6 (17)
Percent Retention	N	60	0	31
	Δ percent recall (± SD)	2 (26)	NA	0 (20)

mean performance in HC decreased by −20.4% (95% CI [−38, −2.74]) relative to an increase in mean performance in RUL by 11.95% (95% CI [1.54, 21.5]). BT subjects did not have percent retention data.

3.5. Trail-making tests, verbal fluency letter, and other main effects

All other neuropsychological measures (TMT-A, TMT-B, VFL) showed no main effects for group or group interactions (all $p > 0.05$). VFC had sex differences ($F(1,107) = 4.24$, $p = 0.04$) with males performing 5.9 %diff better after treatment than females ($t(1, 107) = 2.1$, p

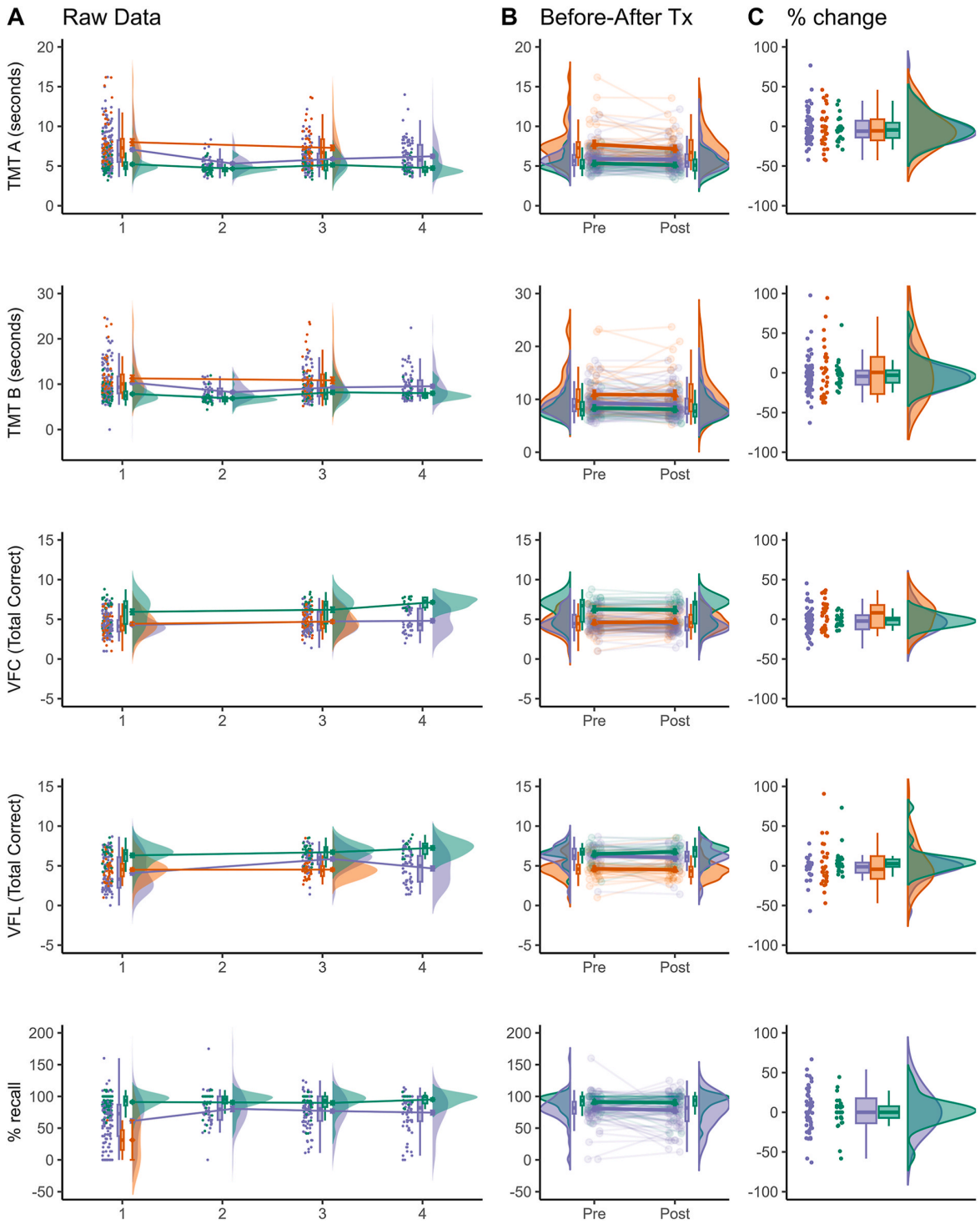


Fig. 1. A. Available raw data for the following time points for RUL (includes LART), BT, and HC data: 1) pre-ECT; 2) mid-ECT; 3) post-ECT (within one-week of finishing series); and 4) follow-up ECT (>1-month post-ECT). The focus of this investigation is pre- and post-ECT cognitive measures. B. Pre-/post-ECT trajectories of square-root transformed values. C. Percent change (pre-/post-ECT) change of square-root transformed data. Shown are half-violin data distributions, mean (SD), and histograms.

= 0.04). TMT-A also had sex differences ($F(1,120) = 4.34, p = 0.03$) with males performing 7.3 %diff worse than females ($t(1, 120) = 2.1$, $p = 0.03$). TMT-A ($F(7,120) = 2.12$, $p = 0.04$) and percent retention ($F(2,81) = 3.12$, $p = 0.04$) demonstrated site differences. ECT treatment number was not significant any of the models.

Statistical results are summarized in Figs. 1 and 2 and Table 3. When controlling for multiple testing via false discovery rate, none of the effects remained significant ($p_{adj} > 0.1$; Fig. 2B).

4. Discussion

We assessed five neurocognitive outcomes (TMT-A, TMT-B, VFL, VFC, and percent recall) from the GEMRIC database. We focused on pre-/post-ECT neurocognitive measures that had the most consistent administration across the study sites to maximize the sample sizes for each measure. Our sample size was robust from 91 subjects (60 patients and 31 HC) with percent retention to 135 subjects (112 patients and 23 HC) with TMT-A. Each cognitive measure included HC subjects with longitudinal testing for comparative normative data. The larger sample allowed us to investigate and correct for seven covariates (group, age, sex, education, site, number of ECT treatments, pre-post HAM-D % change) and interactions for each neurocognitive measure. Our results demonstrated a group (RUL, BT, and HC) and treatment number interaction for VFC (impaired VFC performance with increased RUL treatment number) and a group main effect for percent retention. Post-hoc analysis with percent retention revealed that the group main effect was related to a decreased HC performance and therefore deemed spurious (see Supplemental Fig. 1). Overall, we found no significant effect of group or group interactions for TMT-A, TMT-B, or VFL.

Our main result agrees with previous knowledge that VFC is adversely impacted by ECT and may be sensitive to electrode placement. A meta-analysis focused on RUL cognitive performance with ultrabrief pulse width demonstrated large effect sizes with VFC (Cohen's d = −0.98) (Semkovska et al., 2011). Although our results were not significant for VFL likely due to a smaller RUL sample, a multi-site RUL investigation has demonstrated moderate effect size (Cohen's d = −0.39) for longitudinal pre-/post-ECT changes in VFL (Lisanby et al., 2020). Another longitudinal RUL ECT neurocognitive investigation compared differences in amplitude-mediated changes in cognitive performance (Abbott et al., 2021). In this study, the primary cognitive outcome was focused on percent retention, which was stable throughout the ECT series. A secondary analysis revealed impairment in both VFL and VFC. Another large study (n = 634) demonstrated large effect sizes for post-ECT impairment in VFL and VFC (Loef et al., 2024). Further research is needed, but the RUL electric field geometry may transiently impact frontal-temporal circuitry associated with verbal fluency (Baldo et al., 2006). Focal Electrically Administered Seizure Therapy (FEAST), nonconvulsive electrotherapy (NET), hybrid ECT, and magnetic seizure therapy represent novel treatment modalities that may reduce the impact on frontal-temporal circuitry and preserve verbal fluency performance (Deng et al., 2024; Nahas et al., 2013; Regenold et al., 2015; Zhang et al., 2022).

Contrary to our hypotheses, we did not observe impairment with BT for any cognitive domain. This result is in stark contrast to prior research showing larger cognitive impairment with BT electrode placement (Kolshus et al., 2018; Martin et al., 2020). A meta-analysis demonstrated the largest effect sizes for word list delayed recall (Semkovska and McLoughlin, 2010). Our sample size was relatively modest for the BT group. A range of 30–38 BT subjects had TMT and VF data, but no BT subjects had percent retention data (Table 3). Dosing patterns (seizure titration vs. demographically based), charge, and treatment frequency (twice vs. thrice weekly) are additional variables that may have influenced these results and will be a focus of future investigations. Given the limitations of the available dataset discussed below, we hesitate to draw definitive conclusions regarding the absence of ECT-mediated neurocognitive effects for the BT subjects. However, BT did demonstrate improved efficacy relative to RUL, which is consistent with past research demonstrating faster and improved response rates with BT relative to RUL and BF (Kellner et al., 2010).

We acknowledge several limitations necessary for result interpretation. First, we had significant site differences in neurocognitive performance in TMT-A and percent retention. ECT administration and study protocols were site specific and therefore have variable patterns of subject selection (e.g., we excluded 27 subjects with a pre-ECT HAM-D-17 < 19), ECT devices, parameters, and standard operating procedures. Despite our relatively large sample size, we were unable to assess

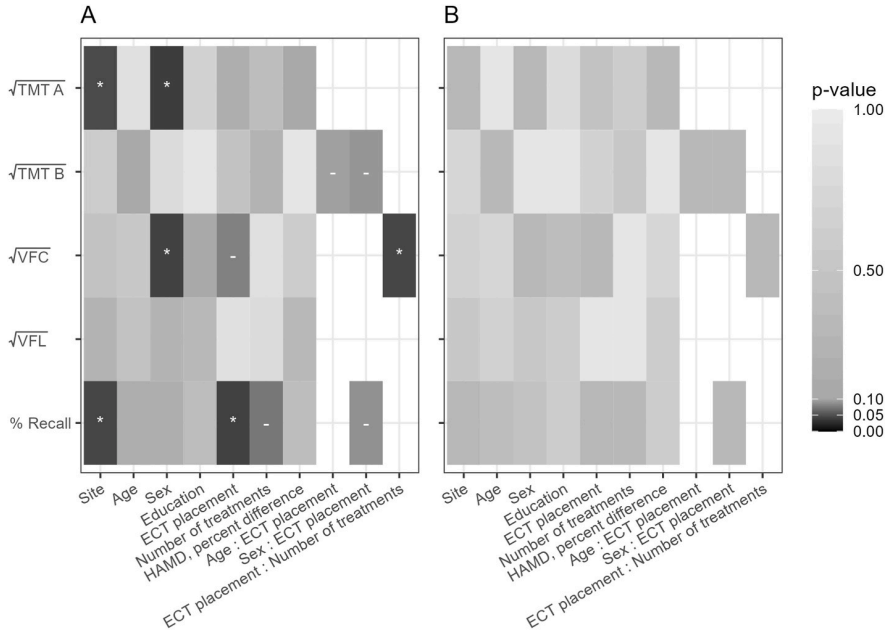


Fig. 2. Summary of p-values for all possible effects for the five neurocognitive measures. p-value stars indicate: p > 0.10 = blank; p < 0.10 = "-"; p < 0.05 = "*". Panel A is uncorrected p-values, and Panel B includes corrected p-values.

neurocognitive differences with all the site-specific variables in ECT administration. These factors contributed to significant data variability and decreased statistical power to detect longitudinal changes in cognitive performance. Second, neurocognitive assessment protocols were study- and site-specific. Some sites had a limited emphasis on collection of cognitive data and excluded important neurocognitive domains such as verbal learning and memory or autobiographical memory. The inclusion of only five cognitive measures included across multiple sites represents a significant limitation of this investigation. Third, we used education as a proxy for intelligence quotient. Longitudinal cognitive performance should include measures of premorbid intelligence, which was unavailable in the current GEMRIC database (Camprodon-Boadas et al., 2024). Fourth, percent recall may bias the pre-ECT results as poor performing subjects on list learning trials may recall a larger percentage of words. Furthermore, the pre-post change of the five neuropsychological outcomes may have been more susceptible to regression towards the mean as opposed to a different statistical analysis (repeated measures analysis of variance with baseline cognitive measure included as a covariate). Given the significant limitations of this dataset, we hesitate to draw definitive conclusions regarding the absence of ECT-mediated neurocognitive effects with four of the five tests used in this investigation and highlight the need for harmonized neurocognitive assessment protocols and procedures.

4.1. ECT neurocognitive battery for GEMRIC

The GEMRIC Clinical and Cognitive Work Group, comprised of an interdisciplinary team of experts in neuropsychiatry and clinical neuropsychology across the globe, has provided recommendations for prospective data collection for ECT-imaging investigations. The goal is to increase uniform neurocognitive data collection procedures across sites to improve measurement of the cognitive changes that occur with ECT. The selected tests met the following objectives: cognitive domains 1) sensitive to cognitive effects of ECT; 2) ease of administration; 3) minimal cost; 4) available in multiple languages; and 5) established reliability and validity; 6) availability of normative data; and 7) minimization of subject burden.

The recommended neurocognitive domains and tests are listed in Table 4. TMT-A, TMT-B, VFL, VFC, and RAVLT were included in our retrospective analysis. The RAVLT is available in several different languages with standardized administration and normative data. The Symbol Digit Modality Test (SDMT) is an easy-to-administer test to assess psychomotor processing speed, attention, and incidental learning (Strauss et al., 2006). This test is highly sensitive to cognitive impairment and includes multiple forms with normative data to minimize practice effects. Digit span backward (DSB) assesses working memory (Weschler, 1997). The Test of Premorbid Function (TOPF) estimates premorbid intellectual ability (Wechsler, 2009). The Montreal Cognitive Assessment (MoCA), a measure of global cognitive function that is sensitive to gross neurocognitive abnormalities, screens for preexisting cognitive impairment (Nasreddine et al., 2005; Rossetti et al., 2011) and can be used to examine global cognitive functioning changes after ECT. The GEMRIC Clinical and Cognitive Work Group also recommends pre-/post-ECT assessments at a minimum with emphasis on additional time points: mid-ECT (before electrode placement switch) and follow-up assessments (1-, 3- and 6-month post-ECT).

The GEMRIC Clinical and Cognitive Work Group evaluated several different autobiographical memory tests. The Autobiographical Memory Interview (AMI) strengths include published administration and scoring manual, validation in an amnestic and ECT samples, and controls for retention time interval and encoding age (Kho et al., 2006; Kopelman, 1989; Kopelman et al., 1989, 1990; O'Connor et al., 2010; Sienaert et al., 2010; Stoppe et al., 2006). This test is licensed and copyrighted and must be purchased. The AMI has a long administration time (~90 min) testing recollections over multiple time epochs. The use of a specific or multiple AMI time epochs as a standalone instrument has not been validated for longitudinal assessments. The Autobiographical Memory Test (AMT) is efficient (approximately 15 min for entire test), available in the public domain, and validated in depression and ECT samples (Deng et al., 2024; Raes et al., 2008; Williams and Broadbent, 1986; Williams and Scott, 1988). However, the AMT does not control for retention time interval or encoding age and does not measure consistency of autobiographical memory over time. The Columbia University Autobiographical Memory Interview – Short Form (CAMI-SF) is relatively easy to administer, has an administration and scoring manual, and was designed to assess changes in autobiographical memory consistency related to ECT (McElhiney et al., 1997). However, the CAMI-SF is sensitive to test-retest interval, does not control for encoding age, can have lengthy administration time (up to 30–45 min for baseline assessment), and there have been concerns regarding its validity, including ecological validity, as the CAMI-SF tests the accuracy of baseline memory recall (Semkovska and McLoughlin, 2013). Given the limitations of the available autobiographical memory tests, the GEMRIC Work Group recommended that each site include their autobiographical memory test of choice.

Adoption of the standardized cognitive testing battery recommended in this text by participating GEMRIC studies can help provide a harmonized and comprehensive dataset that can be used to answer many questions still outstanding in ECT treatment, including the nature and course of cognitive changes experienced during acute ECT treatment, the neurobiological correlates and underlying mechanism of these changes, and the impact of ECT parameters such as pulse width, amplitude, electrode placement, treatment number contribute to these changes, and how to integrate cognitive assessment in clinical practice. This will allow for refinement of ECT treatment parameters to make mechanism-based adjustments to minimize adverse cognitive effects while preserving the unparalleled efficacy of ECT.

Acknowledgments and disclosures

We thank all GEMRIC member sites for contributing data and

Table 4
Prospective GEMRIC neurocognitive battery.

Domain	Neurocognitive measures	Duration
Processing speed	Symbol Digit Modality Test (SMDT)	~3 min
Attention	Trail Making Test Part A (TMT-A)	~3 min
Language function	Verbal Letter Fluency (VFL), Category Fluency (VFC)	~8 min
Memory - verbal	Rey Auditory Verbal Learning Test (RAVLT)	~40 min (inclusive of a 20–30 min delay period during which other tests can be administered)
Memory - autobiographical	Autobiographical Memory Test (AMT)	~15 min
	Autobiographical Memory Interview (AMI)	~90 min
	Columbia University Autobiographical Memory Interview – Short Form (CAMI-SF)	~40 min
Executive function	Trail Making Test Part B (TMT-B)	~6 min
Working memory	Digit Span Backwards (DSB)	~10 min
Premorbid IQ	Test of Premorbid Functioning (TOPF)	~5 min
Global cognitive function	Montreal Cognitive Assessment (MoCA, version 8.1)	~10 min

especially Leif Oltedal, Leila Frid, and Hauke Bartsch for their continuing support and effort for ECT multisite research. Our strongest gratitude goes to the patients and participants who generously dedicated their time and effort to this research.

Funding sources

MK (Förderung Klinische Studien [2021-FKS-12] of University Hospital Bonn), CA (NIH/NIMH R33MH125126, R01MH128692), EE (NIH/NIMHR33MH125126, R01MH128692**),** AY (grant from the Délégation Régionale à la Recherche Clinique des Hôpitaux de Toulouse "2015"), NC (PI21/01756), NT (intramural funding program of the Medical University Innsbruck for young scientists MUI-START, Project, 2023-1-3), RR (German Research Foundation [DFG grant RE4458/1-1] and by the Federal Ministry of Education and Research [BMBF] German Center for Mental Health [DZPG, BMBF grant 01 EE2305C]), CSM (PI19/01171 from the Carlos III Health Institute), AT (Fellowship of Astellas Foundation for Research on Metabolic Disorders [2023], the Uehara Memorial Foundation [2024], and the FWO [1283524N]), IT (several grants from the Dutch research organisation [ZONMW]), KLN (NIH/NIMH R01MH128690), RE (NIH/NIMH R01MH128690), HBM (PRACTIS-Clinician Scientist Program of Hannover Medical School, funded by the Deutsche Forschungsgemeinschaft [DFG, German Research Foundation, ME3696/3-1] – Project-ID 413617135), LO (Western Norway Regional Health Authority grant #912238), MA (R21MH119616), BD (Swiss National Science Foundation [project grants Nr. 32003B_135679, 32003B_159780, 324730_192755 and CRSK-3_190185], ERA_NET iSEE project, the Swiss Personalised Health Network SACR project, the Donase and the Leenaards Foundations). All other authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Maximilian Kiebs: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Danielle C. Farrar:** Writing – review & editing, Writing – original draft. **Antoine Yrondi:** Writing – review & editing. **Narcis Cardoner:** Writing – review & editing. **Noora Tuovinen:** Writing – review & editing. **Ronny Redlich:** Writing – review & editing. **Udo Dannlowski:** Writing – review & editing. **Carles Soriano-Mas:** Writing – review & editing. **Annemiek Dols:** Writing – review & editing. **Akihiro Takamiya:** Writing – review & editing. **Indira Tendolkar:** Writing – review & editing. **Katherine L. Narr:** Writing – review & editing. **Randall Espinoza:** Writing – review & editing. **Maarten Laroy:** Writing – review & editing. **Philip van Eijndhoven:** Writing – review & editing. **Esmée Verwijk:** Writing – review & editing. **Jeroen van Waarde:** Writing – review & editing. **Joey Verdijk:** Writing – review & editing. **Hannah B. Maier:** Writing – review & editing. **Pia Nordanskog:** Writing – review & editing. **Guido van Wingen:** Writing – review & editing. **Linda van Diermen:** Writing – review & editing. **Louise Emsell:** Writing – review & editing. **Filip Bouckaert:** Writing – review & editing. **Jonathan Repple:** Writing – review & editing. **Joan A. Camprodon:** Writing – review & editing. **K. Tristan Donaldson:** Writing – review & editing. **Leif Oltedal:** Writing – review & editing, Software, Resources. **Ute Kessler:** Writing – review & editing. **Åsa Hammar:** Writing – review & editing. **Pascal Sienaert:** Writing – review & editing. **Kaat Hebbrecht:** Writing – review & editing. **Mikel Urretavizcaya:** Writing – review & editing. **Jean-Baptiste Belge:** Writing – review & editing. **Miklos Argyelan:** Writing – review & editing. **Mate Baradits:** Writing – review & editing. **Jasmien Obbels:** Writing – review & editing. **Bogdan Draganski:** Writing – review & editing. **Alexandra Philipsen:** Writing – review & editing. **Alexander Sartorius:** Writing – review & editing. **Didericke Rhebergen:** Writing – review & editing. **Olga Therese Ousdal:** Writing – review & editing. **René Hurlemann:** Writing – review & editing. **Shawn McClintock:** Writing – review & editing, Writing – original draft. **Erik B. Erhardt:** Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis. **Christopher C. Abbott:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

HBM part in educational events sponsored by Livanova and Rovi. RH has received consulting and speaker fees from Boehringer Ingelheim International GmbH, Janssen-Cilag GmbH and ROVI GmbH in the last three years. All other authors report no biomedical financial interests or potential conflicts of interest with this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.09.013.

References

Abbott, C.C., Quinn, D., Miller, J., Ye, E., Iqbal, S., Lloyd, M., Jones, T.R., Upston, J., Deng, Z., Erhardt, E., McClintock, S.M., 2020. Electroconvulsive therapy pulse amplitude and clinical outcomes. Am. J. Geriatr. Psychiatr. 29 (2), 166–178.

Abbott, C.C., Quinn, D., Miller, J., Ye, E., Iqbal, S., Lloyd, M., Jones, T.R., Upston, J., Deng, Z., Erhardt, E., McClintock, S.M., 2021. Electroconvulsive therapy pulse amplitude and clinical outcomes. Am. J. Geriatr. Psychiatr. 29 (2), 166–178.

Akaike, H., 1974. A new look at the statistical model indentification. IEEE Transactions on Automic Control 19 (6), 716–723.

Alexopoulos, G.S., Kiosses, D.N., Heo, M., Murphy, C.F., Shanmugham, B., Gunning-Dixon, F., 2005. Executive dysfunction and the course of geriatric depression. Biol. Psychiatr. 58, 204–210.

Allen, M., Poggiali, D., Whitaker, K., Marshall, T.R., van Langen, J., Kievit, R.A., 2019. Raincloud plots: a multi-platform tool for robust data visualization. Wellcome Open Res 4, 63.

Argyelan, M., Deng, Z.D., Ousdal, O.T., Oltedal, L., Angulo, B., Baradits, M., Spitzberg, A. J., Kessler, U., Sartorius, A., Dols, A., Narr, K.L., Espinoza, R., van Waarde, J.A., Tendolkar, I., van Eijndhoven, P., van Wingen, G.A., Takamiya, A., Kishimoto, T., Jorgensen, M.B., Jorgensen, A., Paulson, O.B., Yrondi, A., Peran, P., Soriano-Mas, C., Cardoner, N., Cano, M., van Diermen, L., Schrijvers, D., Belge, J.B., Emsell, L., Bouckaert, F., Vandenbulcke, M., Kiebs, M., Hurlemann, R., Mulders, P.C., Redlich, R., Dannlowski, U., Kavakbasi, E., Kritzer, M.D., Ellard, K.K., Camprodon, J. A., Petrides, G., Malhotra, A.K., Abbott, C.C., 2023. Electroconvulsive therapy-induced volumetric brain changes converge on a common causal circuit in depression. Mol. Psychiatr. 29, 229–237.

Argyelan, M., Oltedal, L., Deng, Z.D., Wade, B., Bikson, M., Joanlanne, A., Sanghani, S., Bartsch, H., Cano, M., Dale, A.M., Dannlowski, U., Dols, A., Enneking, V., Espinoza, R., Kessler, U., Narr, K.L., Oedegaard, K.J., Oudega, M.L., Redlich, R., Stek, M.L., Takamiya, A., Emsell, L., Bouckaert, F., Sienaert, P., Pujol, J., Tendolkar, I., van Eijndhoven, P., Petrides, G., Malhotra, A.K., Abbott, C., 2019. Electric field causes volumetric changes in the human brain. Elife 8, 1–20.

Baldo, J.V., Schwartz, S., Wilkins, D., Dronkers, N.F., 2006. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. J. Int. Neuropsychol. Soc. : JINS 12 (6), 896–900.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. 57 (1), 289–300.

Bolwig, T.G., 2014. Neuroimaging and electroconvulsive therapy: a review. J. ECT 30 (2), 138–142.

Brandt, J., Benedict, R., 2001. Hopkins Verbal Learning Test-Revised: Professional Manual. PAR, Florida.

Camprodon-Boadas, P., De Prisco, M., Rabelo-da-Ponte, F.D., Sugranyes, G., Clougher, D., Baeza, I., Torrent, C., Castro-Fornieles, J., Tosetti, Y., Vieta, E., de la Serna, E., Amoretti, S., 2024. Cognitive reserve and cognition in mood disorders: a systematic review and meta-analysis. Psychiatr. Res. 339, 116083.

Chakrabarti, S., Grover, S., Rajagopal, R., 2010. Electroconvulsive therapy: a review of knowledge, experience and attitudes of patients concerning the treatment. World J. Biol. Psychiatr. 11 (3), 525–537.

Clark, J.H., Hobson, V.L., O'Bryant, S.E., 2010. Diagnostic accuracy of percent retention scores on RBANS verbal memory subtests for the diagnosis of Alzheimer's disease and mild cognitive impairment. Arch. Clin. Neuropsychol. 25 (4), 318–326.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 2000. California Verbal Learning Test, second ed. The Psychological Corporation, San Antonio, TX.

Deng, Z.D., Luber, B., McClintock, S.M., Weiner, R.D., Husain, M.M., Lisanby, S.H., 2024. Clinical outcomes of magnetic seizure therapy vs electroconvulsive therapy for major depressive episode: a randomized clinical trial. JAMA Psychiatr. 81 (3), 240–249.

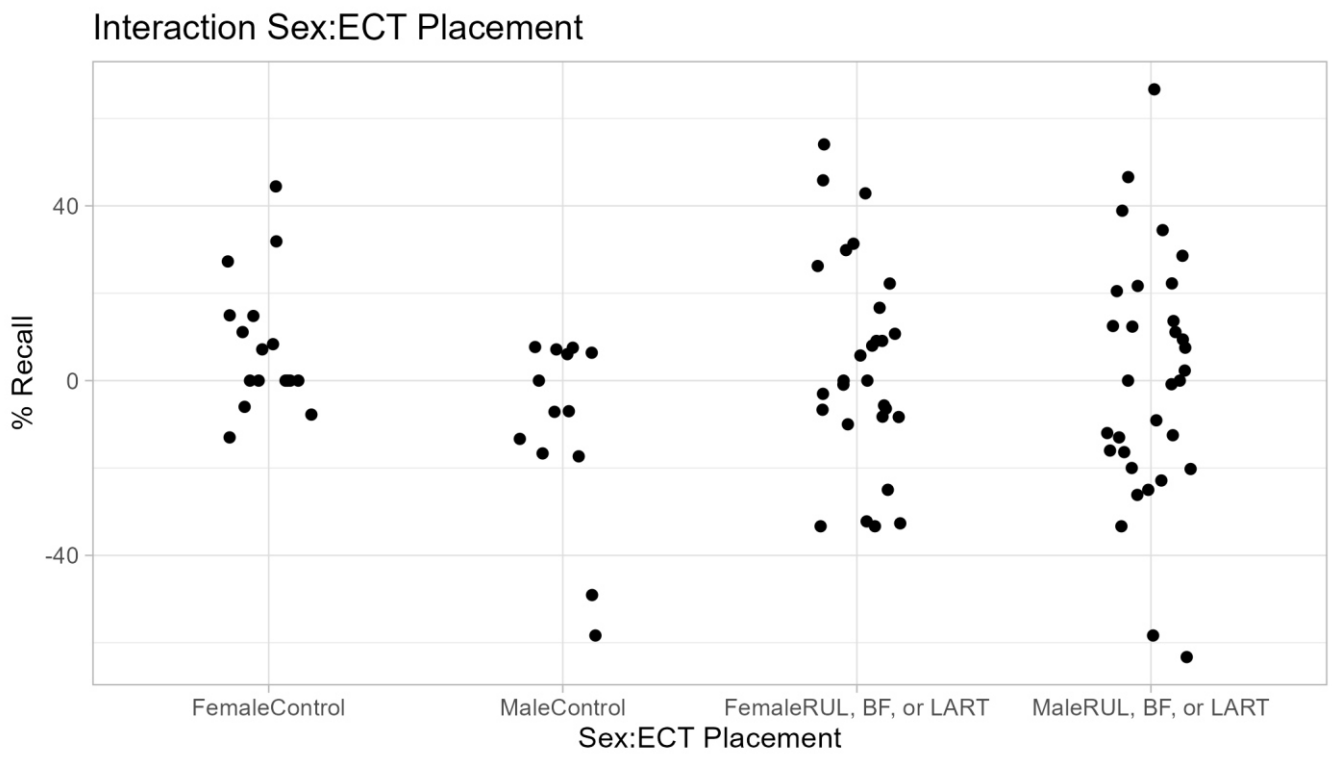
Dritschel, B.H., Williams, J.M., Baddeley, A.D., Nimmo-Smith, I., 1992. Autobiographical fluency: a method for the study of personal memory. Mem. Cognit. 20 (2), 133–140.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (1), 56–62.
Heo, M., Murphy, C.F., Meyers, B.S., 2007. Relationship between the Hamilton depression rating scale and the montgomery-asberg depression rating scale in depressed elderly: a meta-analysis. Am. J. Geriatr. Psychiatr. 15 (10), 899–905.
Husain, M.M., Rush, A.J., Fink, M., Knapp, R., Petrides, G., Rummans, T., Biggs, M.M., O'Connor, K., Rasmussen, K., Litle, M., Zhao, W., Bernstein, H.J., Smith, G., Mueller, M., McClintock, S.M., Bailine, S.H., Kellner, C.H., 2004. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. J. Clin. Psychiatr. 65 (4), 485–491.
Kaster, T.S., Vigod, S.N., Gomes, T., Sutradhar, R., Wijeysundera, D.N., Blumberger, D. M., 2021. Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study. Lancet Psychiatr. 8 (8), 686–695.
Kellner, C.H., Knapp, R., Husain, M.M., Rasmussen, K., Sampson, S., Cullum, M., McClintock, S.M., Tobias, K.G., Martino, C., Mueller, M., Bailine, S.H., Fink, M., Petrides, G., 2010. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br. J. Psychiatry 196 (3), 226–234.
Kho, K.H., VanVreeswijk, M.F., Murre, J.M., 2006. A retrospective controlled study into memory complaints reported by depressed patients after treatment with electroconvulsive therapy and pharmacotherapy or pharmacotherapy only. J. ECT 22 (3), 199–205.
Kiosses, D.N., Alexopoulos, G.S., 2005. IADL functions, cognitive deficits, and severity of depression: a preliminary study. Am. J. Geriatr. Psychiatr. 13, 244–249.
Kiosses, D.N., Klimstra, S., Murphy, C., Alexopoulos, G.S., 2001. Executive dysfunction and disability in elderly patients with major depression. Am. J. Geriatr. Psychiatr. 9, 269–274.
Kolshus, E., Jelovac, A., McLoughlin, D.M., 2018. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials - CORRIGENDUM. Psychol. Med. 48 (4), 703–704.
Kopelman, M.D., 1989. Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. Neuropsychologia 27 (4), 437–460.
Kopelman, M.D., Wilson, B.A., Baddeley, A.D., 1989. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. J. Clin. Exp. Neuropsychol. 11 (5), 724–744.
Kopelman, M.D., Wilson, B.A., Baddeley, A.D., 1990. The Autobiographical Memory Interview. Pearson Assessment, London, England.
Lenth, R., 2023. Emmeans: estimated marginal means, aka least-squares means_. https://CRAN.R-project.org/package=emmeans.
Lezak, M.D., 2012. Neuropsychological Assessment, fifth ed. Oxford University Press, Oxford ; New York.
Lisanby, S.H., 2007. Electroconvulsive therapy for depression. N. Engl. J. Med. 357, 1939–1945.
Lisanby, S.H., McClintock, S.M., Alexopoulos, G., Bailine, S.H., Bernhardt, E., Briggs, M. C., Cullum, C.M., Deng, Z.D., Dooley, M., Geduldig, E.T., Greenberg, R.M., Husain, M.M., Kaliora, S., Knapp, R.G., Latoussakis, V., Liebman, L.S., McCall, W.V., Mueller, M., Petrides, G., Prudic, J., Rosenquist, P.B., Rudorfer, M.V., Sampson, S., Teklehaimanot, A.A., Tobias, K.G., Weiner, R.D., Young, R.C., Kellner, C.H., Group, C.P.W., 2020. Neurocognitive effects of combined electroconvulsive therapy (ECT) and venlafaxine in geriatric depression: phase 1 of the PRIDE study. Am. J. Geriatr. Psychiatr. 28 (3), 304–316.
Loef, D., van Eijndhoven, P., van den Munckhof, E., Hoogendoorn, A., Manten, R., Spaans, H.P., Tendolkar, I., Rutten, B., Nuninga, J., Somers, M., van Dellen, E., van Exel, E., Schouws, S., Dols, A., Verwijk, E., 2024. Pre-treatment predictors of cognitive side-effects after treatment with electroconvulsive therapy in patients with depression: a multicenter study. J. Affect. Disord. 349, 321–331.
Martin, D., Katalinic, N., Hadzi-Pavlovic, D., Ingram, A., Ingram, N., Simpson, B., McGoldrick, J., Dowling, N., Loo, C., 2020. Cognitive effects of brief and ultrabrief pulse bitemporal electroconvulsive therapy: a randomised controlled proof-of-concept trial. Psychol. Med. 50 (7), 1121–1128.
Martin, D.M., Galvez, V., Loo, C.K., 2015. Predicting retrograde autobiographical memory changes following electroconvulsive therapy: relationships between individual, treatment, and early clinical factors. Int. J. Neuropsychopharmacol. 18 (12).
McClintock, S., Staub, B., Husain, M., 2011. The effects of electroconvulsive therapy on neurocognitive function in elderly adults. Ann. Long Term Care: Clinical Care Aging 19 (3), 32–38.
McElhiney, M.C., Moody, B.J., Sackeim, H., 2001. Manual for Administration and Scoring the Columbia University Autobiographical Memory Interview—Short Form, Version 3. New York State Psychiatric Institute, New York.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Mulders, P.C.R., Llera, A., Beckmann, C.F., Vandenbulcke, M., Stek, M., Sienaert, P., Redlich, R., Petrides, G., Oudega, M.L., Oltedal, L., Oedegaard, K.J., Narr, K.L., Magnusson, P.O., Kessler, U., Jorgensen, A., Espinoza, R., Enneking, V., Emsell, L., Dols, A., Dannlowski, U., Bolwig, T.G., Bartsch, H., Argyelan, M., Anand, A., Abbott, C.C., van Eijndhoven, P.F.P., Tendolkar, I., 2020. Structural changes induced by electroconvulsive therapy are associated with clinical outcome. Brain Stimul. 13 (3), 696–704.
Nahas, Z., Short, B., Burns, C., Archer, M., Schmidt, M., Prudic, J., Nobler, M.S., Devanand, D.P., Fitzsimons, L., Lisanby, S.H., Payne, N., Perera, T., George, M.S., Sackeim, H.A., 2013. A feasibility study of a new method for electrically producing seizures in man: focal electrically administered seizure therapy [FEAST]. Brain Stimul. 6 (3), 403–408.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53 (4), 695–699.
Nuninga, J.O., Claessens, T.F.I., Somers, M., Mandl, R., Nieuwdorp, W., Boks, M.P., Bakker, S., Begemann, M.J.H., Heringa, S., Sommer, I.E.C., 2018. Immediate and long-term effects of bilateral electroconvulsive therapy on cognitive functioning in patients with a depressive disorder. J. Affect. Disord. 238, 659–665.
O'Connor, D.W., Gardner, B., Eppingstall, B., Tofler, D., 2010. Cognition in elderly patients receiving unilateral and bilateral electroconvulsive therapy: a prospective, naturalistic comparison. J. Affect. Disord. 124 (3), 235–240.
Oltedal, L., Bartsch, H., Sorhaug, O.J., Kessler, U., Abbott, C., Dols, A., Stek, M.L., Ersland, L., Emsell, L., van Eijndhoven, P., Argyelan, M., Tendolkar, I., Nordanskog, P., Hamilton, P., Jorgensen, M.B., Sommer, I.E., Heringa, S.M., Draganski, B., Redlich, R., Dannlowski, U., Kugel, H., Bouckaert, F., Sienaert, P., Anand, A., Espinoza, R., Narr, K.L., Holland, D., Dale, A.M., Oedegaard, K.J., 2017. The Global ECT-MRI Research Collaboration (GEMRIC): establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. Neuroimage Clin 14, 422–432.
Oltedal, L., Narr, K.L., Abbott, C., Anand, A., Argyelan, M., Bartsch, H., Dannlowski, U., Dols, A., van Eijndhoven, P., Emsell, L., Erchinger, V.J., Espinoza, R., Hahn, T., Hanson, L.G., Hellemann, G., Jorgensen, M.B., Kessler, U., Oudega, M.L., Paulson, O. B., Redlich, R., Sienaert, P., Stek, M.L., Tendolkar, I., Vandenbulcke, M., Oedegaard, K.J., Dale, A.M., 2018. Volume of the human Hippocampus and clinical response following electroconvulsive therapy. Biol. Psychiatr. 84 (8), 574–581.
Ousdal, O.T., Argyelan, M., Narr, K.L., Abbott, C., Wade, B., Vandenbulcke, M., Urretavizcaya, M., Tendolkar, I., Takamiya, A., Stek, M.L., Soriano-Mas, C., Redlich, R., Paulson, O.B., Oudega, M.L., Opel, N., Nordanskog, P., Kishimoto, T., Kampe, R., Jorgensen, A., Hanson, L.G., Hamilton, J.P., Espinoza, R., Emsell, L., van Eijndhoven, P., Dols, A., Dannlowski, U., Cardoner, N., Bouckaert, F., Anand, A., Bartsch, H., Kessler, U., Oedegaard, K.J., Dale, A.M., Oltedal, L., Gemric, 2020. Brain changes induced by electroconvulsive therapy are broadly distributed. Biol. Psychiatr. 87 (5), 451–461.
Porter, R., Heenan, H., Reeves, J., 2008. Early effects of electroconvulsive therapy on cognitive function. J. ECT 24 (1), 35–39.
Raes, F., Sienaert, P., Demyttenaere, K., Peuskens, J., Williams, J.M., Hermans, D., 2008. Overgeneral memory predicts stability of short-term outcome of electroconvulsive therapy for depression. J. ECT 24 (1), 81–83.
Rajagopal, R., Chakrabarti, S., Grover, S., 2013. Satisfaction with electroconvulsive therapy among patients and their relatives. J. ECT 29 (4), 283–290.
Regenold, W.T., Noorani, R.J., Piez, D., Patel, P., 2015. Nonconvulsive electrotherapy for treatment resistant unipolar and bipolar major depressive disorder: a proof-of-concept trial. Brain Stimul. 8 (5), 855–861.
Reitan, R., Wolfson, D., 1985. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press.
Rhee, T.G., Olfson, M., Sint, K., Wilkinson, S.T., 2020. Characterization of the quality of electroconvulsive therapy among older medicare beneficiaries. J. Clin. Psychiatr. 81 (4).
Rhee, T.G., Sint, K., Olfson, M., Gerhard, T., S, H.B., Wilkinson, S.T., 2021. Association of ECT with risks of all-cause mortality and suicide in older medicare patients. Am. J. Psychiatr. 178 (12), 1089–1097.
Ross, E.L., Zivin, K., Maixner, D.F., 2018. Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA Psychiatr. 75 (7), 713–722.
Rossetti, H.C., Lacritz, L.H., Cullum, C.M., Weiner, M.F., 2011. Normative data for the Montreal cognitive assessment (MoCA) in a population-based sample. Neurology 27 (77), 1272–1275.
Sackeim, H.A., 2017. Modern electroconvulsive therapy: vastly improved yet greatly underused. JAMA Psychiatr. 74 (8), 779–780.
Schielzeth, H., Dingemanse, N., Nakagawa, S., Westneat, D., Allegue, H., Teplitsky, C., Reale, D., Dochtermann, N., Garamszegi, L., Araya-Ajoy, Y., 2020. Robustness of linear mixed-effects models to violations of distributional assumptions. Methods Ecol. Evol. 11 (9), 1141–1152.
Semkovska, M., Keane, D., Babalola, O., McLoughlin, D.M., 2011. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. J. Psychiatr. Res. 45 (6), 770–780.
Semkovska, M., Landau, S., Dunne, R., Kolshus, E., Kavanagh, A., Jelovac, A., Noone, N., Carton, M., Lambe, S., McHugh, C., McLoughlin, D.M., 2016. Bitemopral versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomized, non-inferiority trial. Am. J. Psychiatr. 173 (4), 408–417.
Semkovska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol. Psychiatr. 68 (6), 568–577.
Semkovska, M., McLoughlin, D.M., 2013. Measuring retrograde autobiographical amnesia following electroconvulsive therapy: historical perspective and current issues. J. ECT 29 (2), 127–133.
Semkovska, M., McLoughlin, D.M., 2014. Retrograde autobiographical amnesia after electroconvulsive therapy: on the difficulty of finding the baby and clearing murky bathwater. J. ECT 30 (3), 187–188. ; discussion 189-190.
Sienaert, P., Vansteelandt, K., Demyttenaere, K., Peuskens, J., 2010. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. J. Affect. Disord. 122 (1–2), 60–67.

Singh, A., Kar, S.K., 2017. How electroconvulsive therapy works?: understanding the neurobiological mechanisms. Clin Psychopharmacol Neurosci 15 (3), 210–221.
Sjoberg, D.D., Whiting, K., Curry, M., Lavery, J.A., Larmarange, J., 2021. Reproducible summary tables with the gtsummary package. R Journal 13, 570–580.
Slade, E.P., Jahn, D.R., Regenold, W.T., Case, B.G., 2017. Association of electroconvulsive therapy with psychiatric readmissions in US hospitals. JAMA Psychiatr. 74 (8), 798–804.
Stoppe, A., Louza, M., Rosa, M., Gil, G., Rigonatti, S., 2006. Fixed high-dose electroconvulsive therapy in the elderly with depression: a double-blind, randomized comparison of efficacy and tolerability between unilateral and bilateral electrode placement. J. ECT 22 (2), 92–99.
Strauss, E., Sherman, E.M.S., Spreen, O., Spreen, O., 2006. A Compendium of Neuropsychological Tests : Administration, Norms, and Commentary, third ed. Oxford University Press, Oxford ; New York.
Tor, P.-C., Bautovich, A., Wang, M.-J., Martin, D., Harvey, S.B., Loo, C., 2015. A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. J. Clin. Psychiatr. 76 (9), e1092–e1098.
UK ECT Review Group, 2003. Efficacy and safety of electroconvulsive therapy in depressive disorder: a systematic review and meta-analysis. Lancet 361, 799–808.
van Buuren, S., Groothuis-Oudshoorn, K., 2011. mice: multivariate imputation by chained equations in R. J. Stat. Softw. 45 (3), 1–67.
Vasavada, M.M., Leaver, A., Njau, S., Joshi, S.H., Ercoli, L., Hellemann, G., Narr, K.L., Espinoza, R., 2017a. Short- and long-term cognitive outcomes in patients with major depression treated with electroconvulsive therapy. J. ECT 33 (4), 278–285.
Vasavada, M.M., Leaver, A.M., Njau, S., Joshi, S.H., Ercoli, L., Hellemann, G., Narr, K.L., Espinoza, R., 2017b. Short- and long-term cognitive outcomes in patients with major depression treated with electroconvulsive therapy. J. ECT 33 (4), 278–285.
Wechsler, D., 2009. Test of Premorbid Functioning. The Psychological Corporation, San Antonio, TX.
Weiner, R.D., Reti, I.M., 2017. Key updates in the clinical application of electroconvulsive therapy. Int. Rev. Psychiatr. 29 (2), 54–62.
Weschler, D., 1997. Weschler Memory Scale-III. Psychological Corporation, San Antonio, TX.
Wilkinson, S.T., Agbese, E., Leslie, D.L., Rosenheck, R.A., 2018. Identifying recipients of electroconvulsive therapy: data from privately insured Americans. Psychiatr. Serv. 69 (5), 542–548. Washington, D.C.
Wilkinson, S.T., Kitay, B.M., Harper, A., Rhee, T.G., Sint, K., Ghosh, A., Lopez, M.O., Saenz, S., Tsai, J., 2021. Barriers to the implementation of electroconvulsive therapy (ECT): results from a nationwide survey of ECT practitioners. Psychiatr. Serv. 72 (7), 752–757. Washington, D.C.
Williams, J.M., Broadbent, K., 1986. Autobiographical memory in suicide attempters. J. Abnorm. Psychol. 95 (2), 144–149.
Williams, J.M., Scott, J., 1988. Autobiographical memory in depression. Psychol. Med. 18 (3), 689–695.
Zhang, J.Y., Xu, S.X., Zeng, L., Chen, L.C., Li, J., Jiang, Z.Y., Tan, B.J., Gu, C.L., Lai, W.T., Kong, X.M., Wang, J., Rong, H., Xie, X.H., 2022. Improved safety of hybrid electroconvulsive therapy compared with standard electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind, parallel-group pilot trial. Front. Psychiatr./Frontiers Res. Foundat. 13, 896018.

Supplemental Material: Electroconvulsive therapy and cognitive performance from the Global ECT MRI Research Collaboration

Supplemental Table 1: GEMRIC cognitive data from all sites

Cognitive Test	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Site 12	Site 13	Total
Trail Making Test - Part A	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			*x*	*x*	*11*
Verbal Fluency - Semantic	*x*	*x*		*x*	*x*	*x*	*x*	*x*		*x*		*x*	*x*	*10*
Verbal Fluency - Letter		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			*x*	*x*	*10*
Trail Making Test - Part B	*x*	*x*		*x*	*x*	*x*	*x*	*x*	*x*			*x*	*x*	*10*
Digit Span (Wechlser Adult Intelligence Scale - Revised)		x	x	x	x			x	x			x		7
Mini Mental State Examination						x	x	x	x	x				5
Rey Osterrieth Complex Figure Test		x			x		x		x	x				5
Rey Auditory Verbal Learning Test*					*x*	*x*	*x*	*x*					*x*	*5*
Digit Sympbol Coding (Wechlser Adult Intelligence Scale - Revised)		x		x				x			x			4
Stroop Test					x		x	x	x					4
Wechsler Abbreviated Scales of Intelligence		x							x			x		3
Montreal Cognitive Assessment			x								x			2
Continuous Performance Test - II (Conner's)		x					x							2
Autobiographical Memory Interview - Short Form		x						x						2
Hopkins Verbal Learning			*x*								*x*			*2*
Brief Visuospatial Memory Test - Revised			x									x		2
National Reading Test for Adults*					x					x				2
Repeatable Battery for Assessment of Neuropsychological Status	x													1
California Verbal Learning Test II		*x*												*1*
Wisconsin Card Sorting Test		x												1
Color Word Interference Test (Delis Kaplan Executive Function System)		x												1
Tower Test		x												1
Grooved Pegboard Test		x												1
Brief Boston Naming Test			x											1
Block Design				x										1
Clock Test						x								1
NLV (IQ)							x							1
Wechsler Memory Scale							x							1
N-Back								x						1
Wide Range Achievement Test								x						1
Logic Memory Subtest I (Wechlser Memory Scale)									x					1
Logic Memory Subtest II (Wechlser Memory Scale)									x					1
Autobiographical Fluency Test										x				1
RLRI 16 (French Word List)												x		1



Supplemental Figure 1. Our results demonstrated a group (RUL, BT, and HC) main effect for percent recall ($F(1,81) = 4.35$, $p = 0.04$) and a non-significant sex-group interaction ($F(1,81) = 2.99$, $p = 0.09$). Post-hoc analysis revealed that mean performance in HC decreased by -20.4% (95% CI [-38, -2.74]) relative to an increase in mean performance in RUL by 11.95% (95% CI [1.54, 21.5]). We therefore concluded that the main effect for group was related to HC % recall cognitive performance and not related to ECT.

3.2 Publication 2: Role of Stimulus Dose on Neuropsychological Functioning after Electroconvulsive Therapy in Patients with Major Depressive Disorder

frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 26 September 2024
DOI 10.3389/fpsyt.2024.1443270

OPEN ACCESS

EDITED BY
Zhi-De Deng,
National Institute of Mental Health (NIH), United States

REVIEWED BY
Jeroen Antonius Van Waarde,
Rijnstate Hospital, Netherlands
Jean-Baptiste Belge,
University of Antwerp, Belgium

*CORRESPONDENCE
Maximilian Kiebs
m.kiebs@uol.de

RECEIVED 03 June 2024
ACCEPTED 09 September 2024
PUBLISHED 26 September 2024

CITATION
Rummel L, Göke K, Philipsen A, Hurlemann R and Kiebs M (2024) Role of stimulus dose on neuropsychological functioning after electroconvulsive therapy in patients with major depressive disorder.
Front. Psychiatry 15:1443270.
doi: 10.3389/fpsyt.2024.1443270

Role of stimulus dose on neuropsychological functioning after electroconvulsive therapy in patients with major depressive disorder

Lea Rummel[1,2], Katharina Göke[3], Alexandra Philipsen[2], René Hurlemann[1] and Maximilian Kiebs[1,2]*

[1]Department of Psychiatry and Psychotherapy, School of Medicine & Health Sciences, University Hospital Oldenburg, Oldenburg, Germany, [2]Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany, [3]Institute of Medical Science, University of Toronto, Toronto, ON, Canada

Introduction: Electroconvulsive therapy (ECT) is the most effective treatment for patients suffering from treatment-resistant depression but its use is often limited by the concern for cognitive side effects. This study examines the effect of ECT on autobiographical and verbal memory compared to a healthy control group and the impact of the mean stimulus dose on cognition after ECT.

Methods: Autobiographical and verbal memory were assessed in depressed patients and healthy controls before the first and within one week after the last ECT treatment. Neuropsychological testing included the Autobiographical Memory Interview, the Verbal Learning and Memory Test and five tests from the Cambridge Neuropsychological Test Automated Battery. The mean charge delivered across the ECT series and the total number of sessions were examined in relationship to cognitive impairment after ECT using a multiple regression model.

Results: Autobiographical memory was significantly impaired after ECT treatment compared to healthy controls. Baseline scores were lower for depressed patients on all cognitive domains. Improvements in performance after ECT were found on tests for executive functions and working memory. Effects of the mean charge delivered on cognitive functioning after ECT were heterogeneous across cognitive domains but significant for verbal retrograde memory.

Conclusion: ECT led to autobiographical memory impairment. The relationship between mean charge delivered and cognitive performance is heterogeneous across different cognitive domains and requires further research. Significant effects of the mean charge delivered were found without a significant difference in cognitive functioning compared to a healthy control group.

KEYWORDS

electroconvulsive therapy, neuropsychology, treatment dose, charge, depression, cognition

1 Introduction

Electroconvulsive therapy (ECT) is currently the most effective treatment for treatment-refractory depression (TRD). In comparison to pharmacotherapy or other forms of brain stimulation, ECT yields higher response and remission rates, even in more severely ill patients (1–4). ECT involves an (ultra-) brief electrical current being passed through the brain via electrodes to induce a generalized seizure while the patient is under general anesthesia. Despite its long history, the underlying mechanism of antidepressant action of ECT remains unclear and is still under investigation (5, 6).

Although haven itself proven safe for patients across the adult life span including elderly patients (7, 8), as well as tolerable and highly efficient for TRD, ECT is still associated with stigma (9–11).

Adverse effects during or right after a treatment session include nausea, headaches, muscle or jaw pain (12–14). However, part of the stigma is due to the undesirable cognitive effects associated with the treatment (9, 15). Whereas some authors claim that ECT does not cause significant neuropsychological impairment, which is more likely to be a depressive phenomenon (16), others are more cautious (17, 18).

As one of the most critical cognitive adverse effects, several studies showed a significant decline of retrograde autobiographical memory immediately after ECT treatment and up to six months after the last treatment (17, 19–21). Additionally, other neuropsychological domains that might be affected by ECT treatment include processing speed, attention, verbal fluency, visual memory and executive functions (22–24).

Verwijk et al. found that ECT results in a loss of autobiographical memory and impairment of verbal fluency, anterograde verbal and non-verbal memory immediately after brief pulse right unilateral RUL-ECT. A reduction of processing speed as well as an impairment of working memory were found to a lesser extent (21, 24). Subjectively, memory worsening following ECT was found to be reported only by a minority of patients (25). Often, subjective memory complaints are strongly correlated with depression severity, rather than objective cognitive impairment and improve after ECT treatment (26–29). Nuninga et al. (30) also found transient adverse cognitive effects for verbal memory and learning as well as verbal fluency following bilateral ECT, but no persisting impairments. However, it has been shown that ECT can cause a significant impairment of autobiographical memory persisting up to three months after the procedure (20, 31). Semkovska and McLoughlin (23) found that cognitive abnormalities associated with ECT are mainly limited to the first three days posttreatment, and some domains, including processing speed and working memory, showed improvement 15 days post ECT. For visual and visuospatial memory, significant impairments during and within one week after ECT were found, which mostly resolved when testing one month after the last ECT treatment (22).

In light of these heterogeneous findings, predicting the occurrence and understanding the origin and nature of the neurocognitive effects of ECT remain a challenge. Apart from individual patient characteristics, bilateral electrode placement as well as longer pulse-width predict stronger cognitive impairment after ECT (29, 32–37). Furthermore, increased frequency of ECT treatments was also associated with more cognitive side effects (38, 39). Regarding the impact of electrical dose, studies have found that a higher dosage relative to individual seizure threshold predicted stronger cognitive side effects rather than the absolute electrical dose administered, however, the antidepressant effect of ECT also increased with dosage (40–45). For instance, fixed high dose stimulation was associated with reduced autobiographical memory and longer time to reorientation compared to titrated moderately suprathreshold stimulation (40). Sackeim et al. showed that RUL high dosage stimulation was twice as effective as low dose stimulation (34). More recent studies showed that lowered ECT stimulus doses were associated with less subjective memory worsening and better verbal learning without compromising efficacy, but this association was only detectable up to three days after the final ECT treatment (25, 46).

This study examines the effects of ECT on autobiographical and verbal memory in comparison to a healthy control group. Additionally, the study aims to determine the extent to which cognitive impairment can be predicted by the mean electrical charge delivered across the ECT series and the total number of ECT sessions. Firstly, it was hypothesized that there would be significant differences in autobiographical and delayed verbal memory tests between depressed patients and healthy controls and that memory performance scores decrease following ECT treatment. Additional cognitive domains were included for exploratory purposes. Secondly, it was hypothesized that a higher mean stimulus energy, measured in milli Coulomb (mC) and calculated as mean charge across the ECT series, rather than the total number of ECT sessions, would be associated with greater cognitive impairment following an ECT series.

2 Materials and methods

2.1 Subjects

Data were collected from adult patients who received ECT treatment from January 2018 to December 2019 at the University Hospital Bonn (clinicaltrials.gov: NCT03490149). The indication for ECT treatment was made by the treating psychiatrist for patients with a clinical diagnosis of a unipolar or bipolar depressive disorder and who failed to respond to treatment with at least two antidepressant medications. Patients were excluded from the study in case of heart disease, certain neurological conditions, diagnosed hearing loss, thyroid dysfunction, prior treatment with at least one ECT within the last three months and a history of treatment with deep brain stimulation. In terms of psychiatric disorders, patients with the following diagnoses were excluded: secondary or substance-induced depression, psychotic disorders, generalized anxiety disorder, panic disorder or social phobia.

The sample of this study consisted of 21 patients and 19 control participants, matched to the therapy group in terms of gender and age. All participants gave written, informed consent to take part in the study.

2.2 ECT

Brief pulse ECT treatments were administered twice weekly with a constant current apparatus (Thymatron IV). For anesthesia, propofol (1-2 mg/kg) and succinylcholine (1 mg/kg) were used. Prior to treatment, all patients received positive pressure ventilation with 100% oxygen. Seizure threshold was determined individually during the first ECT session for all patients (44), and the therapeutic dosage was set to at least four times initial seizure threshold. In case of insufficient seizures, the energy was raised accordingly and the stimulation was repeated, with a maximum of three stimulations in a single session. All treatment related data was collected using the longitudinal data collection tool GENET-GPD (47).

2.3 Neuropsychological testing

All neuropsychological tests were administered by trained personnel before starting an ECT series and within one week after finishing the series. Clinical improvement was assessed using the 21-item Hamilton Rating Scale for Depression (HAMD) (48).

The following tests were used in order to evaluate different aspects of cognitive functioning after ECT treatment: Verbal Learning and Memory Test (VLMT), Autobiographical Memory Interview – Short Form (AMI-SF). Exploratively, five tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used for assessment of other cognitive domains.

2.3.1 VLMT

The VLMT is based on the Auditory Verbal Learning Test (AVLT), originally developed by Rey (49, 50). This standardized German version is frequently used for the assessment of verbal declarative memory (51). Subjects are read a list of 15 words on five successive trials with a free-recall task after each trial. Next, a distraction list is presented as interference with consecutive recall. The subjects are then asked to recall as many words as possible from the original list. This is repeated after 30 minutes. The primary variables of interest were the VLMT total score (recall sum across five successive trials), and the VLMT delay score (free recall after 30 min. delay).

2.3.2 AMI

The AMI-SF (52) quantifies the extent of retrograde amnesia for autobiographical events following an ECT course. The test consists of six different parts, each covering different aspects of autobiographical memory (family member, travel, New Years, birthday, employment, physical illness). Amnesia scores are calculated by dividing the post-treatment scores by the baseline scores and multiplying the result by 100 in order to obtain a percentage.

2.3.3 CANTAB

Exploratively, five different tests were chosen from CANTAB, which provides a rapid and non-invasive method of cognitive assessment that is increasingly used in examining cognitive effects after ECT (22, 53, 54). Advantages of the CANTAB tests are their efficiency, their highly standardized and digital administration and the automated response recording with millisecond precision (55). Below, each test used is summarized briefly.

- Delayed Matching to Sample (DMS) is a test for visual memory. The subject is shown a visual pattern made up of four sub-elements. Simultaneously or after a brief delay (4 or 12 s), four choice patterns are presented on a screen and the subject is instructed to touch the pattern that matches the sample previously shown. The subject is given a total correct score, expressed as a percentage.
- One Touch Stockings of Cambridge (OTS) assesses executive function, working memory and planning. The subject is presented with two displays containing three colored balls. The balls in the lower display must be moved one at a time in order to copy the pattern shown in the upper display with increasing complexity. The subject is given a score, representing the mean number of choices needed for the correct pattern.
- Rapid Visual Information Processing (RVP) is a test of visual sustained attention. The subjects are presented with digits from two to nine, appearing in a box on the computer screen at the rate of 100 digits per minute. Subjects are requested to detect a target sequence of three digits. The subject is given a total score (total hits).
- Spatial Working Memory (SWM) tests the subject's ability to retain spatial information and to manipulate remembered items in working memory. The subject is shown a number of colored boxes, in which the subject should find one blue "token". The number of boxes presented on the screen is gradually increased from three to eight boxes, as well as changing color and position of the boxes. The subjects must touch each box until one opens with a blue token inside. This is repeated for the next blue token. An error occurs when touching a box in which a blue token has already been found. The subject is given a total error score.
- Pattern Recognition Memory (PRM) is a test of visual pattern recognition memory in a two-choice forced discrimination paradigm. Firstly, the subject is presented with a series of 12 colored visual patterns, each pattern presented for three seconds. In the following recognition phase, the subject must choose between a pattern they have already seen and a novel pattern. The score for each subject is expressed as a total correct score.

2.4 Statistical analysis

To analyze cognitive impairment following a series of RUL-ECT in comparison to a healthy control group, a linear mixed model was used for each neuropsychological test including the variables timepoint, group and age as main effects. Effects of timepoint, group and their interaction were examined. The distribution of variances was assessed visually. In order to examine the association

between stimulus energy across ECT treatment and cognitive performance, the mean charge delivered across all ECT sessions in the series was calculated for each patient. Mean charge delivered, number of ECT sessions and age were included as independent variables in a multiple regression model, with absolute change scores of cognitive measures as dependent variable. Pearson correlations were calculated respectively. All raw scores were z-transformed prior to analysis, which was performed in R statistics 4.2.3 (56). Multiple testing was controlled for via the false-discovery rate using the method of Benjamini and Hochberg (57).

3 Results

3.1 Participant characteristics

Demographics and clinical characteristics are reported in Table 1. Depressed patients and healthy controls showed no significant differences regarding sex, age and education. Depressed patients had a significant higher body mass index ($p = 0.016$).

TABLE 1 Participant Characteristics.

Variable	N	Patients, N = 21[1]	Controls, N = 19[1]	p-value[2]
Sex	40			0.5
m		9 (43%)	10 (53%)	
w		12 (57%)	9 (47%)	
Age	40	48 (37, 56)	43 (33, 56)	0.5
BMI	36	30 (24, 34)	24 (22, 26)	0.016
Education[3]	36			0.5
2		0 (0%)	1 (5.3%)	
3		3 (18%)	3 (16%)	
4		2 (12%)	0 (0%)	
5		7 (41%)	5 (26%)	
6		0 (0%)	2 (11%)	
7		5 (29%)	7 (37%)	
8		0 (0%)	1 (5.3%)	
Diagnosis	40			
F31.4		5 (23.8%)	0 (0%)	
F32.2		1 (4.8%)	0 (0%)	
F33.2		14 (66.6%)	0 (0%)	
F33.3		1 (4.8%)	0 (0%)	
NA		0 (0%)	19 (100%)	
Duration of depressive episode [month]	17	13 (9, 22)	NA	
Number of depressive episodes	36	7.0 (3.0, 10.0)	0.0 (0.0, 0.0)	
Age at first treatment	18	30 (22, 40)	NA	
HAMD total score	40	20 (17, 22)	0 (0, 2)	
Mean charge delivered [mC]	21	330.69 (232.27, 421.10)	NA	
Number of ECT sessions	21	11.86 (10, 13)	NA	

[1]n (%); Median (IQR).
[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.
[3]2 = grade 7-12 (without graduating high school); 3 = graduated high school; 4 = part college or university; 5 = graduated 2-year college (Associates Degree); 6 = graduated 4-year college (Bachelor Degree); 7 = part graduate or professional school; 8 = completed graduate or professional school.

3.2 Efficacy of ECT treatment

Efficacy of the ECT treatment was assessed by comparing the mean HAMD score before and after ECT treatment. The mean HAMD score decreased significantly after a course of ECT from 19.73 ± 4.05 to 6.6 ± 4.37 ($p < 0.01$).

3.3 Longitudinal effects patients vs. controls

3.3.1 AMI and VLMT

In comparison to healthy participants, depressed patients scored significantly lower on the AMI-SF at both timepoints ($p < 0.01$) and the scores also decreased significantly after ECT treatment compared to before treatment ($p < 0.01$; see Figure 1). The mixed model found a significant interaction effect between group and timepoint ($p < 0.01$) and no significant effect of age on the AMI score ($p = 0.53$).

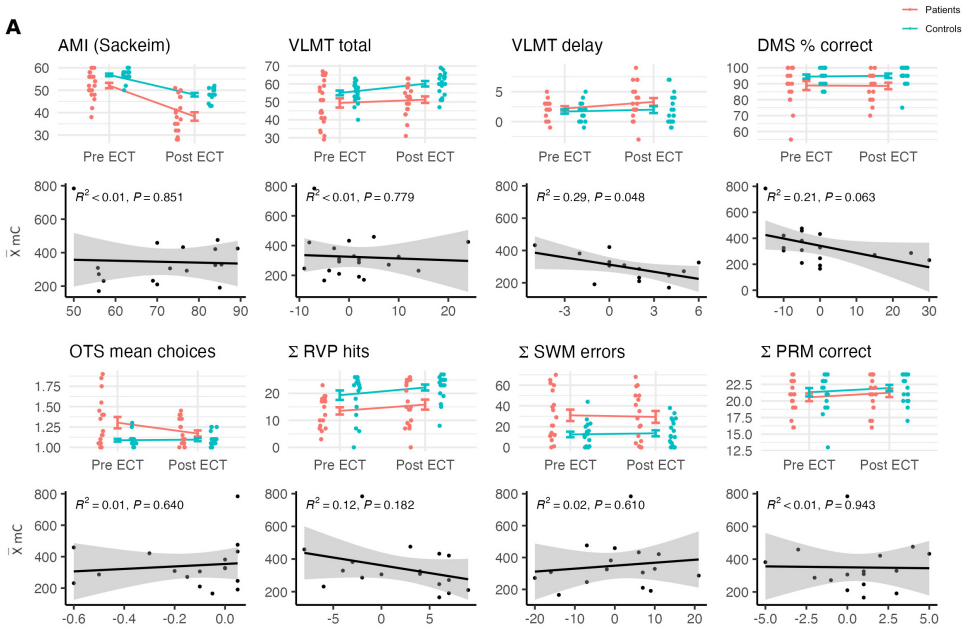
For the VLMT variables, the linear mixed model found a significant difference in performance between patients and healthy control participants for all tested variables (all $p < 0.05$) as well as a significant effect of the timepoint for VLMT total score ($p < 0.01$). No significant interaction effect was found for either VLMT variable (all $p > 0.01$). Performance on the VLMT was negatively influenced by the age of the participants (all $p < 0.01$).

3.3.2 CANTAB

In the DMS task, depressed patients scored significantly lower than healthy controls ($p = 0.01$). However, there was no significant difference between initial baseline scores and subsequent tests after ECT treatment ($p = 0.93$) and no significant interaction effect was found between group and timepoint ($p = 0.8$) as well as no age effect ($p = 0.44$).

In the OTS task, depressed patients needed significantly more choices for the correct result in comparison to healthy control participants ($p < 0.01$), but their scores improved significantly after ECT ($p = 0.03$). The mixed model found a significant interaction effect between group and timepoint ($p = 0.01$). However, the model also found a significant effect for age ($p = 0.01$).

For visual processing, the depressed group had significantly fewer hits in total compared to the healthy group ($p < 0.01$). The linear mixed model found a significant difference in total scores



B

Neuropsych. task	Beta (95% CI)	Value	Standard Error	t value	p value
AMI (Sackeim)					
Number of Sessions		0.23	0.29	0.78	0.45
Mean charge		-0.01	0.27	-0.05	0.96
Age		-0.18	0.31	-0.6	0.56
VLMT total					
Number of Sessions		0.19	0.25	0.75	0.46
Mean charge		-0.01	0.24	-0.03	0.98
Age		0.37	0.23	1.59	0.13
VLMT delay					
Number of Sessions		0.39	0.27	1.45	0.18
Mean charge		-1.08	0.42	-2.55	0.03
Age		0.28	0.25	1.13	0.28
DMS percent correct					
Number of Sessions		-0.11	0.24	-0.46	0.66
Mean charge		-0.5	0.24	-2.06	0.06
Age		0.32	0.26	1.24	0.24
OTS mean choices to correct					
Number of Sessions		0.03	0.23	0.15	0.88
Mean charge		0.15	0.22	0.69	0.5
Age		-0.69	0.24	-2.93	0.01
PRM number correct					
Number of Sessions		-0.57	0.24	-2.38	0.03
Mean charge		-0.26	0.24	-1.08	0.3
Age		-0.4	0.24	-1.63	0.13
RVP total hits					
Number of Sessions		-0.1	0.26	-0.38	0.71
Mean charge		-0.35	0.25	-1.39	0.19
Age		-0.39	0.27	-1.46	0.17
SWM total errors					
Number of Sessions		-0.14	0.29	-0.49	0.63
Mean charge		0.05	0.29	0.16	0.88
Age		0.31	0.29	1.07	0.31

FIGURE 1
(A) Above, comparison between patient and control group for performance on each neuropsychological test before and after ECT treatment. Below, Pearson´s correlational analyses between the mean charge delivered (mC) and the change in performance from before to after ECT treatment on each neuropsychological test and their respective p values. **(B)** Results from the multiple regression model for each neuropsychological test conducted in the analysis. Data were z-transformed prior to the analysis. Components of the regression model include the mean charge delivered across the ECT series (mC), age and total number of ECT sessions. Beta value (including the 95% confidence interval), standard error, t value and p value were added for each factor respectively. Beta values were pseudo-log transformed for visualization purposes using the ggallin package (58).

before and after ECT series ($p < 0.01$), also indicating an improvement after the ECT series. There was no significant interaction effect between group and timepoint detectable in the model ($p = 0.78$).

In the SWM task, depressed patients made significantly more errors in total compared to the healthy control group ($p < 0.01$), but there was no significant difference before and after ECT series ($p = 0.79$). There was also no significant interaction effect between group

and timepoint detectable in the model (p = 0.74). However, the linear mixed model found a significant negative impact of the participants´ age on the performance on the SWM task (p < 0.01).

For the PRM task, there were no significant effects for group or timepoint as well as no interaction effect or age effect detectable (all p > 0.01).

3.4 Role of treatment charge

3.4.1 AMI and VLMT

The mean charge delivered across all patients was 330.69 mC (SD = 140.47) as reported in Table 1. On average, the patients received a mean total of 11.86 ECT sessions (SD = 2.15). For the AMI score, including a total of 17 patients in the analysis due to incomplete post-treatment testing, the multiple regression model found no significant effect of the mean charge on the AMI score (p = 0.96). A significant negative effect of the mean charge delivered in the ECT series on verbal memory was found for the VLMT delay score (p = 0.03), but not for the VLMT total score (p = 0.98). Due to missing follow-up data, only 14 patients could be included in the analysis for the VLMT delay score, whereas 20 patients were included for the VLMT total score. Age and the number of ECT sessions had no significant impact on either variable (p > 0.1).

3.4.2 CANTAB

Exploratively, multiple regression models were also calculated for the five CANTAB variables. A higher mean charge influenced the performance on the DMS test, with lower overall percent correct in comparison to lower mean charge, although this trend was not significant (p = 0.06). A multiple regression model calculated for the total errors in the DMS task found a significant effect of mean charge (p = 0.01), indicating that a higher mean charge was associated with more errors on the task. Age and the number of ECT sessions had no significant impact on cognitive performance (p > 0.1). For the OTS task, a higher mean charge had no significant impact on the mean choices to correct score (p = 0.5). As already mentioned in the ANOVA analysis, the model detected a significant influence of age on the test score (p = 0.01). The multiple regression model also found a significant impact of the mean charge on the mean latency to first choice score (p = 0.04). In the RVP task, the model did not find a significant impact of the mean charge on the total hits in the task (p = 0.19), but the total misses score was found to be significantly influenced by the mean charge delivered over the ECT course with more misses when a higher mean charge had been applied (p = 0.02). The number of ECT sessions had no significant impact on either variable (p > 0.1). No significant effects were found for the SWM task, indicating that performance on the SWM task was significantly influenced by neither the mean charge delivered nor the number of ECT sessions (p > 0.1). A significant effect for the number of sessions was found for the PRM task (p = 0.03), whereas no significant effect was detected for the mean charge delivered (p = 0.3). Age had no significant impact on performance in the PRM task (p > 0.1). Because not every CANTAB test was completed by each patient, four patients were not included in the analysis of the DMS, OTS and RVP tasks and five patients in the analysis of the SWM and PRM tasks, respectively. After correcting for multiple testing, using the method of Benjamini and Hochberg (57), no significant results were found anymore.

4 Discussion

This study examined cognitive performance on autobiographical and verbal memory tests before and after ECT treatment compared to a healthy control group. As expected, ECT did lead to short-term impairments in autobiographical memory compared to healthy controls. A significant decline in AMI scores before and after ECT treatment compared to a healthy control group was shown. These results are supported by a number of studies that also found autobiographical memory impairment shortly after ECT treatment (19–21, 30). Moreover, depressed patients had significantly lower AMI scores than healthy controls across both timepoints, indicating that major depressive disorder (MDD) is associated with memory dysfunction, which is also in line with previous research (59–61). Contrary to our expectations, this study found no verbal memory impairments after ECT treatment. Still, baseline scores were significantly lower in the depressed group. In a similar study, Verwijk et al. found transiently disrupted verbal memory immediately after brief-pulse ECT (21). Biedermann et al. even found significant improvement of verbal memory after ECT treatment (62).

To explore other cognitive domains and their dependency on ECT treatment, five CANTAB tests were included in the exploratory analysis. Those tests focused on executive functions and planning, visual information processing, spatial working memory and visual pattern recognition memory. For all tests, except the PRM task, baseline scores were significantly lower in the depressed group. This is in line with previous research showing moderately impaired memory as well as executive functions and working memory for depressed patients (59, 60, 63). Tests for working memory and executive functions may not be impaired by ECT treatment, but rather dependent on the age of the participants and performance even improved significantly after ECT treatment for the OTS and RVP task (23, 64).

Although it is widely established that ECT causes significant cognitive side effects, there are remaining questions on how these cognitive side effects are influenced by technical ECT parameters. It is known that ultra-brief pulse ECT as well as unilateral ECT are associated with fewer cognitive side effects, but no or only a slight decline in efficacy compared to brief-pulse or bilateral ECT (4, 29, 35, 43, 65–67). This study focused on the impact of the mean charge delivered across the RUL-ECT series as well as the total number of RUL-ECT sessions on autobiographical and verbal memory function after RUL-ECT treatment. In the literature, it has been described that a fixed high dose stimulation (403 mC) was associated with impaired autobiographical memory and longer time to reorientation, compared to titrated moderately suprathreshold (2.25 x) stimulation, but with higher efficacy (40).

Not the absolute electrical dosage but rather the degree to which dosage exceeds threshold is related to the magnitude of acute cognitive impairments after ECT (42).

The results from this study, using the empiric titration method with RUL-ECT at least four times initial seizure threshold, implicate that a higher mean charge delivered across an ECT series may in fact predict stronger cognitive side effects, but these findings are heterogeneous across different cognitive domains. As expected, a higher mean charge across the RUL-ECT series predicted a lower VLMT delay score, but not a lower VLMT total score or lower AMI score. Moreover, a higher mean charge was associated with lower scores on the DMS task as well as on the RVP task, although these trends were not significant. In line with results from Kirov et al., the number of previous ECT sessions had no significant impact on cognitive deficits after ECT, with the exception of the PRM task (68).

This study highlights the importance of interpreting studies cautiously when they lack a healthy control group. Significant effects of the mean charge delivered on cognitive performance were found even when there was no significant difference in cognitive functioning compared to a healthy control group, which for instance applies to the VLMT delay score.

Due to the small sample size, the reported results have to be considered as rather preliminary but they serve as a guide for future studies with larger sample sizes focusing on the how the stimulus dose might predict cognitive performance after ECT.

In clinical settings, monitoring specific stimulation parameters in combination with potential cognitive side effects after ECT treatment might be useful. Future research should continue with predicting side effects after ECT in different cognitive domains based on different technical parameters. More research is needed to distinguish specific cognitive impairments following ECT from depressive phenomena and age-related decline in cognitive functioning. Understanding the nature of the cognitive side effects after ECT and looking for specific predictors is essential in further improving ECT practice and in diminishing residual stigma.

4.1 Limitations

The results of this study are limited by the sample size and the large number of tests that were assessed for each participant, although some were added for explorative reasons only. Furthermore, neuropsychological testing was conducted within the week after completion of the RUL-ECT series. This study is not able to differentiate whether cognitive side effects vary depending on how much time has passed after the last ECT session. Moreover, possible effects from the anesthetic dose on the mean charge delivered were not included in the analysis. There was no evaluation of subjective cognitive impairments after ECT. The extensive and potentially overwhelming neuropsychological testing may have influenced performance and missing data in depressed patients. Although focusing on less studied neuropsychological domains is highly relevant, it may be preferable to focus on fewer tests, including the VLMT delay task.

5 Conclusion

RUL-ECT was associated with significant autobiographical memory impairment in this study. The relationship between mean charge delivered and cognitive performance has been heterogeneous across different cognitive domains and requires further research. Significant effects of the mean charge delivered were found without a significant difference in cognitive functioning compared to a healthy control group, specifically for the VLMT delay score.

Data availability statement

Restrictions apply to the datasets: The datasets presented in this article are not readily available because local data protection laws. Requests to access the datasets should be directed to the University Hospital Bonn. Summary data will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethical Review Board of the Medical Faculty-University Bonn. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LR: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. KG: Formal analysis, Visualization, Writing – original draft, Writing – review & editing. AP: Funding acquisition, Supervision, Writing – review & editing. RH: Funding acquisition, Supervision, Writing – review & editing. MK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. MK received a grant of University Hospital Bonn (Förderung Klinische Studien [2021-FKS-12]). This research received no other specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgments

We would like to thank all patient and control participants for their time and effort. We would also like Luisa Wiedemann, Jessica

Warnusz and Max von Bargen for their effort in collecting the data. Special thanks are extended to Ralf Berninger for his valuable technical comments and technical support regarding Thymatron® System IV stimulation device. We are also highly grateful for Jesse Pavels development and continuing development of the ECT data collection tool GPD.

Conflict of interest

Author RH received speaker or advisor honoraria from Atheneum, Boehringer Ingelheim, Janssen and Rovi.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kellner CH, Kaicher DC, Banerjee H, Knapp RG, Shapiro RJ, Briggs MC, et al. Depression severity in electroconvulsive therapy (ECT) versus pharmacotherapy trials. *J ECT*. (2015) 31:31–3. doi: 10.1097/YCT.0000000000000135

2. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ*. (2019) 364:l1079. doi: 10.1136/bmj.l1079

3. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J ECT*. (2004) 20:13–20. doi: 10.1097/00124509-200403000-00004

4. ECT Review Group. Efficacy UK. and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. (2003) 361:799–808. doi: 10.1016/S0140-6736(03)12705-5

5. Espinoza RT, Kellner CH. Electroconvulsive therapy. *N Engl J Med*. (2022) 386:667–72. doi: 10.1056/NEJMra2034954

6. Oltedal L, Bartsch H, Sørhaug OJE, Kessler U, Abbott C, Dols A, et al. The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. *NeuroImage: Clin*. (2017) 14:422–32. doi: 10.1016/j.nicl.2017.02.009

7. Geduldig ET, Kellner CH. Electroconvulsive therapy in the elderly: new findings in geriatric depression. *Curr Psychiatry Rep*. (2016) 18:40. doi: 10.1007/s11920-016-0674-5

8. Dominiak M, Antosik-Wójcińska AZ, Wojnar M, Mierzejewski P. Electroconvulsive Therapy and Age: Effectiveness, Safety and Tolerability in the Treatment of Major Depression among Patients under and over 65 Years of Age. *Pharm (Basel)*. (2021) 14:582. doi: 10.3390/ph14060582

9. Chakrabarti S, Grover S, Rajagopal R. Electroconvulsive therapy: A review of knowledge, experience and attitudes of patients concerning the treatment. *World J Biol Psychiatry*. (2010) 11:525–37. doi: 10.3109/15622970903559925

10. Payne NA, Prudic J. Electroconvulsive therapy: Part I. A perspective on the evolution and current practice of ECT. *J Psychiatr Pract*. (2009) 15:346–68. doi: 10.1097/01.pra.0000361277.65468.ef

11. Sackeim HA. Modern electroconvulsive therapy: vastly improved yet greatly underused. *JAMA Psychiatry*. (2017) 74:779–80. doi: 10.1001/jamapsychiatry.2017.1670

12. Andrade C, Arumugham SS, Thirthalli J. Adverse effects of electroconvulsive therapy. *Psychiatr Clin North Am*. (2016) 39:513–30. doi: 10.1016/j.psc.2016.04.004

13. Datto CJ. Side effects of electroconvulsive therapy. *Depress Anxiety*. (2000) 12:130–4. doi: 10.1002/1520-6394(2000)12:3<130::AID-DA4>3.0.CO;2-C

14. Devanand DP, Fitzsimons L, Prudic J, Sackeim HA. Subjective side effects during electroconvulsive therapy. *Convuls Ther*. (1995) 11:232–40.

15. Rose D, Fleischmann P, Wykes T, Leese M, Bindman J. Patients' perspectives on electroconvulsive therapy: systematic review. *BMJ*. (2003) 326:1363. doi: 10.1136/bmj.326.7403.1363

16. Brodaty H, Berle D, Hickie I, Mason C. Side effects" of ECT are mainly depressive phenomena and are independent of age. *J Affect Disord*. (2001) 66:237–45. doi: 10.1016/s0165-0327(00)00314-1

17. Sackeim HA. Autobiographical memory and electroconvulsive therapy: do not throw out the baby. *J ECT*. (2014) 30:177–86. doi: 10.1097/YCT.0000000000000117

18. Sterling P. ECT damage is easy to find if you look for it. *Nature*. (2000) 403:242–2. doi: 10.1038/35002188

19. Fraser LM, O'Carroll RE, Ebmeier KP. The effect of electroconvulsive therapy on autobiographical memory: a systematic review. *J ECT*. (2008) 24:10–7. doi: 10.1097/YCT.0b013e3181616c26

20. Napierała M, Bodnar A, Chlopocka-Wozniak M, Permoda-Osip A, Rybakowski J. Electroconvulsive therapy and autobiographical memory in patients with treatment-resistant depression. *Psychiatr Pol*. (2019) 53:589–97. doi: 10.12740/PP/85787

21. Verwijk E, Comijs HC, Kok RM, Spaans H-P, Stek ML, Scherder EJA. Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review. *J Affect Disord*. (2012) 140:233–43. doi: 10.1016/j.jad.2012.02.024

22. Falconer DW, Cleland J, Fielding S, Reid IC. Using the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess the cognitive impact of electroconvulsive therapy on visual and visuospatial memory. *Psychol Med*. (2010) 40:1017–25. doi: 10.1017/S0033291709991243

23. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry*. (2010) 68:568–77. doi: 10.1016/j.biopsych.2010.06.009

24. Tsourtos G, Spong J, Stough C. The effects of electro-convulsive therapy on the speed of information processing in major depression. *J Affect Disord*. (2007) 103:263–6. doi: 10.1016/j.jad.2007.01.026

25. Brus O, Nordanskog P, Båve U, Cao Y, Hammar Å, Landén M, et al. Subjective memory immediately following electroconvulsive therapy. *J ECT*. (2017) 33:96–103. doi: 10.1097/YCT.0000000000000377

26. Brakemeier E-L, Berman R, Prudic J, Zwillenberg K, Sackeim HA. Self-evaluation of the cognitive effects of electroconvulsive therapy. *J ECT*. (2011) 27:59–66. doi: 10.1097/YCT.0b013e3181d77656

27. Coleman EA, Sackeim HA, Prudic J, Devanand DP, McElhiney MC, Moody BJ. Subjective memory complaints prior to and following electroconvulsive therapy. *Biol Psychiatry*. (1996) 39:346–56. doi: 10.1016/0006-3223(95)00185-9

28. Prudic J, Peyser S, Sackeim HA. Subjective memory complaints: a review of patient self-assessment of memory after electroconvulsive therapy. *J ECT*. (2000) 16:121–32. doi: 10.1097/00124509-200006000-00004

29. Vann Jones S, McCollum R. Subjective memory complaints after electroconvulsive therapy: systematic review. *BJPsych Bull*. (2019) 43:73–80. doi: 10.1192/bjb.2018.45

30. Nuninga JO, Claessens TFI, Somers M, Mandl R, Nieuwdorp W, Boks MP, et al. Immediate and long-term effects of bilateral electroconvulsive therapy on cognitive functioning in patients with a depressive disorder. *J Affect Disord*. (2018) 238:659–65. doi: 10.1016/j.jad.2018.06.040

31. Blomberg M, Semkovska M, Kessler U, Erchinger VJ, Oedegaard KJ, Oltedal L, et al. A longitudinal comparison between depressed patients receiving electroconvulsive therapy and healthy controls on specific memory functions. *Biol Psychiatry*. (2020) 87:S355–6. doi: 10.1016/j.biopsych.2020.02.912

32. Prudic J. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. *J ECT*. (2008) 24:46–51. doi: 10.1097/YCT.0b013e31815ef238

33. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med*. (1993) 328:839–46. doi: 10.1056/NEJM199303253281204

34. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. (2000) 57:425–34. doi: 10.1001/archpsyc.57.5.425

35. Spaans H-P, Kho KH, Verwijk E, Kok RM, Stek ML. Efficacy of ultrabrief pulse electroconvulsive therapy for depression: a systematic review. *J Affect Disord*. (2013) 150:720–6. doi: 10.1016/j.jad.2013.05.072

36. Tor P-C, Bautovich A, Wang M-J, Martin D, Harvey SB, Loo C. A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry*. (2015) 76:e1092–1098. doi: 10.4088/JCP.14r09145

37. Weiner RD, Rogers HJ, Davidson JR, Squire LR. Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci*. (1986) 462:315–25. doi: 10.1111/j.1749-6632.1986.tb51266.x

38. Lerer B, Shapira B, Calev A, Tubi N, Drexler H, Kindler S, et al. Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. *Am J Psychiatry*. (1995) 152:564–70. doi: 10.1176/ajp.152.4.564

39. McAllister DA, Perri MG, Jordan RC, Rauscher FP, Sattin A. Effects of ECT given two vs. three times weekly. *Psychiatry Res*. (1987) 21:63–9. doi: 10.1016/0165-1781(87)90063-1

40. McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry*. (2000) 57:438–44. doi: 10.1001/archpsyc.57.5.438

41. Peterchev AV, Rosa MA, Deng Z-D, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. *J ECT*. (2010) 26:159–74. doi: 10.1097/YCT.0b013e3181e48165

42. Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S. Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry*. (1987) 22:249–68. doi: 10.1016/0006-3223(87)90144-2

43. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul*. (2008) 1:71–83. doi: 10.1016/j.brs.2008.03.001

44. Sackeim HA, Devanand DP, Prudic J. Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. *Psychiatr Clin North Am*. (1991) 14:803–43. doi: 10.1016/S0193-953X(18)30271-5

45. Sinclair JE, Fernie G, Bennett DM, Reid IC, Cameron IM. Assessing the association between electrical stimulation dose, subsequent cognitive function and depression severity in patients receiving bilateral electroconvulsive therapy for major depressive disorder. *J ECT*. (2016) 32:159–63. doi: 10.1097/YCT.0000000000000321

46. Semkovska M, Keane D, Babalola O, McLoughlin DM. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psychiatr Res*. (2011) 45:770–80. doi: 10.1016/j.jpsychires.2010.11.001

47. Freundlieb N, Schneider E, Brühl A, Kiebs M. GENET-GPD: A documentation tool to digitally collect longitudinal ECT treatment data and associated biosignals. *Brain Stimulation*. (2023) 16:1173–5. doi: 10.1016/j.brs.2023.07.053

48. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

49. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol*. (1941) 28:286–340.

50. Ray A. *L'examen clinique en psychologie*. Presse Universitaires de France, Paris (1964).

51. Helmstaedter C, Durwen HF. VLMT: Verbaler Lern- und Merkfähigkeitstest: Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. [VLMT: A useful tool to assess and differentiate verbal memory performance. *Schweizer Archiv für Neurologie Neurochirurgie und Psychiatr*. (1990) 141:21–30.

52. McElhiney M, Moody B, Sackeim H. *The autobiographical memory interview-short form*. New York: New York State Psychiatric Institute (1997).

53. Fernie G, Bennett DM, Currie J, Perrin JS, Reid IC. Detecting objective and subjective cognitive effects of electroconvulsive therapy: intensity, duration and test utility in a large clinical sample. *Psychol Med*. (2014) 44:2985–94. doi: 10.1017/S0033291714000658

54. Maric NP, Stojanovic Z, Andric S, Soldatovic I, Dolic M, Spiric Z. The acute and medium-term effects of treatment with electroconvulsive therapy on memory in patients with major depressive disorder. *Psychol Med*. (2016) 46:797–806. doi: 10.1017/S0033291715002287

55. Luciana M. Practitioner Review: Computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). *J Child Psychol Psychiatry*. (2003) 44:649–63. doi: 10.1111/1469-7610.00152

56. R Core Team. *R: A language and environment for statistical computing* (2023). Available online at: https://www.R-project.org/. (accessed November 11, 2023).

57. Benjamini Y, Hochberg Y. Controlling the false discovery rate - A practical and powerful approach to multiple testing. *J R Statist Soc Ser B*. (1995) 57:289–300. doi: 10.2307/2346101

58. Pav SE. *ggallin: grab bag of "ggplot2" Functions* (2017). Available online at: https://cran.r-project.org/web/packages/ggallin/ (Accessed December 15, 2023).

59. Luo W, Luo L, Wang Q, Li Y, Zhang Y, Hu Y, et al. Disorder-specific impaired neurocognitive function in major depression and generalized anxiety disorder. *J Affect Disord*. (2022) 318:123–9. doi: 10.1016/j.jad.2022.08

60. Pan Z, Park C, Brietzke E, Zuckerman H, Rong C, Mansur RB, et al. Cognitive impairment in major depressive disorder. *CNS Spectr*. (2019) 24:22–9. doi: 10.1017/S1092852918001207

61. Vasavada MM, Leaver AM, Njau S, Joshi SH, Ercoli L, Hellemann G, et al. Short- and long-term cognitive outcomes in patients with major depression treated with electroconvulsive therapy. *J ECT*. (2017) 33:278–85. doi: 10.1097/YCT.0000000000000426

62. Biedermann SV, Bumb JM, Demirakca T, Ende G, Sartorius A. Improvement in verbal memory performance in depressed in-patients after treatment with electroconvulsive therapy. *Acta Psychiatr Scand*. (2016) 134:461–8. doi: 10.1111/acps.12652

63. Trivedi MH, Greer TL. Cognitive dysfunction in unipolar depression: implications for treatment. *J Affect Disord*. (2014) 152–154:19–27. doi: 10.1016/j.jad.2013.09.012

64. Takagi S, Takeuchi T, Yamamoto N, Fujita M, Furuta K, Ishikawa H, et al. Short- and long-term evaluation of cognitive functions after electroconvulsive therapy in a Japanese population. *Psychiatry Clin Neurosci*. (2018) 72(2):95–102. doi: 10.1111/pcn.12614

65. Dominiak M, Antosik-Wójcińska AZ, Goetz Z, Sikorska O, Stefanowski B, Gorostiza D, et al. Efficacy, safety and tolerability of formula-based unilateral vs bilateral electroconvulsive therapy in the treatment of major depression: A randomized open label controlled trial. *J Psychiatr Res*. (2021) 133:52–9. doi: 10.1016/j.jpsychires.2020.12.002

66. Kellner CH, Tobias KG, Wiegand J. Electrode placement in electroconvulsive therapy (ECT): A review of the literature. *J ECT*. (2010) 26:175–80. doi: 10.1097/YCT.0b013e3181e48154

67. Loo CK, Katalinic N, Smith DJ, Ingram A, Dowling N, Martin D, et al. A randomized controlled trial of brief and ultrabrief pulse right unilateral electroconvulsive therapy. *Int J Neuropsychopharmacol*. (2014) 18:pyu045. doi: 10.1093/ijnp/pyu045

68. Kirov GG, Owen L, Ballard H, Leighton A, Hannigan K, Llewellyn D, et al. Evaluation of cumulative cognitive deficits from electroconvulsive therapy. *Br J Psychiatry*. (2016) 208:266–70. doi: 10.1192/bjp.bp.114.158261

3.3 Publication 3: Altered reward network responses to social touch in major depression

Psychological Medicine

cambridge.org/psm

Altered reward network responses to social touch in major depression

Clemens Mielacher[1], Dirk Scheele[1,2], Maximilian Kiebs[1], Laura Schmitt[1], Torge Dellert[3], Alexandra Philipsen[4], Claus Lamm[5] and René Hurlemann[1,2,6]

[1]Research Section Medical Psychology, Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany; [2]Department of Psychiatry, School of Medicine & Health Sciences, University of Oldenburg, Bad Zwischenahn, Germany; [3]Institute of Medical Psychology and Systems Neuroscience, University of Münster, Münster, Germany; [4]Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany; [5]Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria and [6]Research Center Neurosensory Science, University of Oldenburg, Oldenburg, Germany

Original Article

Cite this article: Mielacher C, Scheele D, Kiebs M, Schmitt L, Dellert T, Philipsen A, Lamm C, Hurlemann R (2024). Altered reward network responses to social touch in major depression. *Psychological Medicine* **54**, 308–316. https://doi.org/10.1017/S0033291723001617

Received: 21 February 2022
Revised: 6 March 2023
Accepted: 15 May 2023
First published online: 5 June 2023

Keywords:
fMRI; major depression; reward; social touch

Corresponding author:
Clemens Mielacher;
Email: cmielach@mailbox.org

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, 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.

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) ($n = 47$)		
HDRS-17			
Baseline	17.26 (5.63)	0.23 (0.58)	<0.001
After treatment	10.21 (5.78)		<0.001
Improvement (in percent)	40.40 (28.67)		
Response (yes/no)	23/30		
BDI-II			
Baseline	33.34 (8.75)	2.76 (3.27)	<0.001
After treatment	19.28 (10.80)		<0.001
Improvement (in percent)	41.70 (28.25)		
4 weeks after treatment1	22.28 (11.59) ($n = 50$)		<0.001
8 weeks after treatment1	23.73 (10.80) ($n = 49$)		<0.001
12 weeks after treatment1	24.37 (9.97) ($n = 46$)		<0.001
CTQ	45.08 (16.26)	29.68 (4.6)	<0.001
STAI	63.68 (7.08)	29.44 (4.69)	<0.001

Abbreviations: BDI-II, Beck Depression Inventory; HDRS, 17-item Hamilton Depression Rating Scale; STAI, State-Trait Anxiety Inventory.
Values are given as frequencies or as means (s.d.). 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.
1BDI-II Follow-up measurements are compared to baseline scores. The significance threshold was set at $p < 0.05$.

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

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

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. online 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 et al., 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 analog 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 images with blood-oxygen-level-dependent 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; TE_{fast} = 4.76 ms; TE_{slow} = 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 ⩾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 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).

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

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 $p < 0.001$. Peak-level p values were then family-wise error (FWE) corrected for multiple comparisons and $p < 0.05$ 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 labeling atlas 3 (Rolls, Huang, Lin, Feng, & Joliot, 2020). The peak-level threshold for significance was set to $p < 0.05$, 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 $p < 0.05$, and p values were Bonferroni-adjusted if appropriate (p_{corr}). 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. online 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 ($F_{(2.59,\ 134.89)} = 36.82$, $p < 0.001$, $\eta_p^2 = 0.42$) 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 ($F_{(1,\ 92)} = 99.46$, $p < 0.001$, $\eta_p^2 = 0.52$) and group ($F_{(1,\ 92)} = 7.12$, $p = 0.009$, $\eta_p^2 = 0.07$, 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 ($t_{(92)} = 3.06$, $p_{corr} = 0.012$, $d = 0.64$) but not slow touch ($t_{(92)} = 0.79$, $p_{corr} > 0.999$, $d = 0.16$).

The analysis comparing responders and non-responders also revealed a significant main effect of speed ($F_{(1,\ 51)} = 70.86$, $p < 0.001$, $\eta_p^2 = 0.58$) 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 ($t_{(89.88)} = 4.89$, $p < 0.001$, $d = 0.97$), while no difference was found between responders and non-responders ($t_{(51)} = 0.08$, $p = 0.936$, $d = 0.02$).

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. online 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 *v.* post treatment) in the bilateral nucleus accumbens [peak MNI coordinates (x, y, z): −6, 16, −4; $F_{(1,\ 89)} = 15.59$, $p_{FWE} = 0.010$, $\eta_p^2 = 0.14$; MNI: 4, 14, −2; $F_{(1,\ 89)} = 11.68$, $p_{FWE} = 0.041$, $\eta_p^2 = 0.11$; shown in Fig. 2a] and in the bilateral caudate nucleus (MNI: − 14, 20, 12; $F_{(1,\ 89)} = 21.88$, $p_{FWE} = 0.005$, $\eta_p^2 = 0.19$; MNI: 10, 10, 14; $F_{(1,\ 89)} = 21.64$, $p_{FWE} = 0.006$, $\eta_p^2 = 0.20$; 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; $F_{(1,\ 89)} = 19.23$, $p_{FWE} = 0.016$, $\eta_p^2 = 0.18$). Post-hoc tests revealed decreased responses to fast touch in patients compared to controls at baseline ($t_{(89)} = 3.06$, $p_{corr} = 0.036$, $d = 0.65$) but not after treatment ($t_{(89)} = 0.38$, $p_{corr} > 0.999$, $d = 0.08$).

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; $F_{(1,\ 49)} = 17.86$, $p_{FWE} = 0.039$, $\eta_p^2 = 0.26$, 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; $F_{(1,\ 49)} = 20.01$, $p_{FWE} = 0.022$, $\eta_p^2 = 0.30$, shown in Fig. 3b) showed that non-responders exhibited reduced activation during slow touch compared to responders ($t_{(49)} = 3.75$, $p_{corr} = 0.002$, $d = 1.06$), but not during fast touch ($t_{(49)} = 0.01$, $p_{corr} > 0.999$, $d < 0.01$). For the interaction of speed, time and group, we found two significant clusters in the right putamen (MNI: 32, −2, −8; $F_{(1,\ 49)} = 19.33$, $p_{FWE} = 0.032$, $\eta_p^2 = 0.28$; MNI: 30, −6, 10; $F_{(1,\ 49)} = 18.20$, $p_{FWE} = 0.046$, $\eta_p^2 = 0.27$). Post-hoc tests revealed no significant effects after Bonferroni correction (all $p_{corr} > 0.05$). See online 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. online Supplement).

Discussion/conclusion

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

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

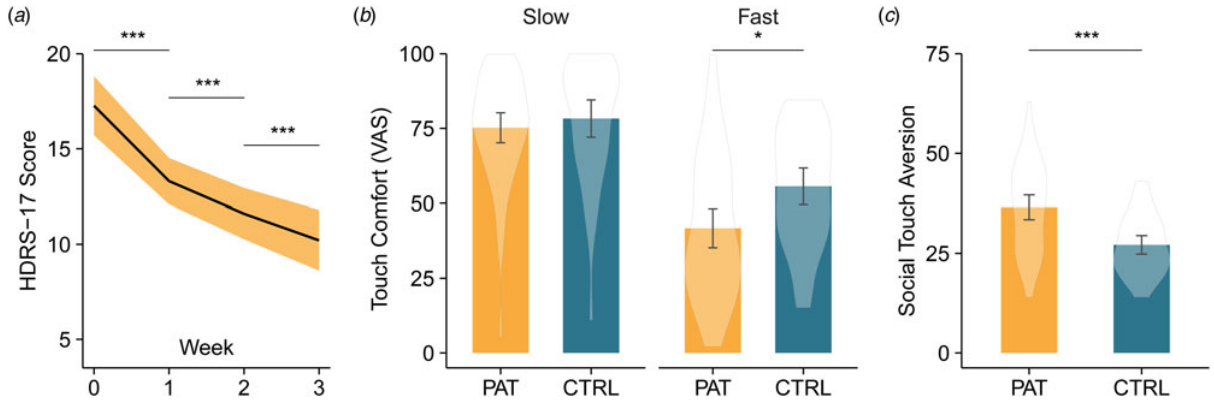


Figure 1. Depression symptom severity as measured by Hamilton Depression Rating Scale (HDRS-17) scores decreased over the treatment course (a). Patients rated fast but not slow touch as significantly less comfortable than controls (b). At baseline patients reported a higher aversion to social touch than 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 analog scale. $*p < 0.05$, $***p < 0.001$.

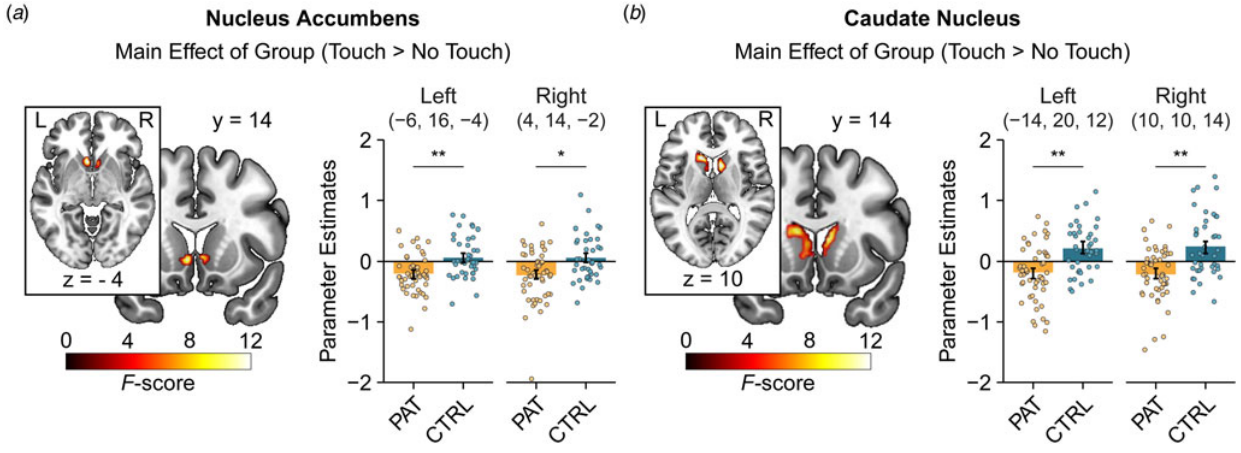


Figure 2. Patients exhibited decreased neural responses to social touch in the bilateral nucleus accumbens (a) and caudate nucleus (b) across time (i.e. before and after treatment) compared with healthy controls. Significant clusters are displayed at a peak-level threshold of $p < 0.05$ uncorrected. Parameter estimates are displayed for peak voxels. Error bars indicate 95%-confidence intervals. Abbreviations: CTRL, controls; PAT, patients. $*p < 0.05$, $**p < 0.01$.

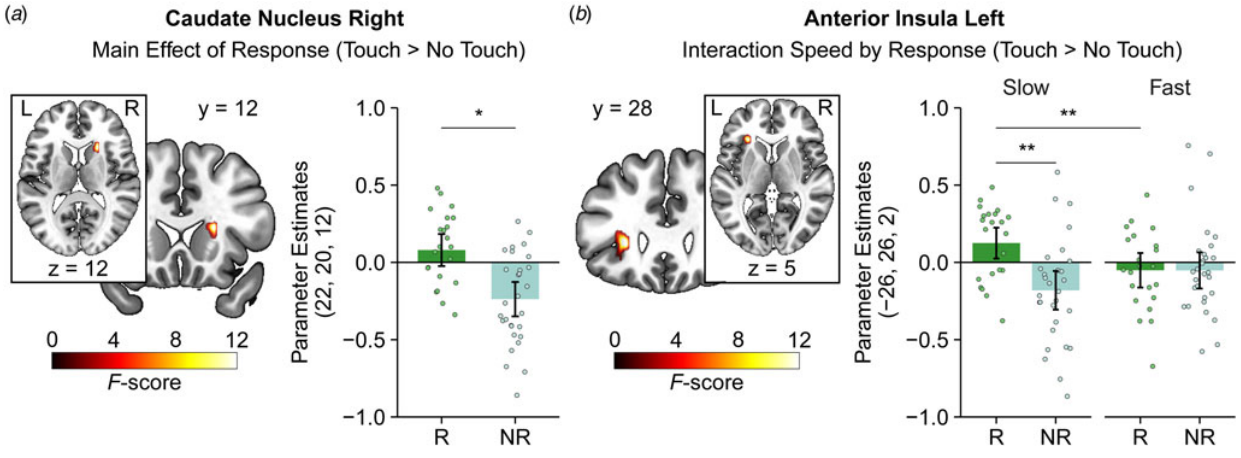


Figure 3. Treatment responders exhibited heightened neural responses to social touch in the right caudate nucleus across time compared with non-responders (a). Responses to slow touch in the left anterior insula were increased in responders across time compared with non-responders (b). Significant clusters are displayed at a peak-level threshold of $p < 0.05$ 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. $*p < 0.05$, $**p < 0.01$.

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

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, & de 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

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

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.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001617

Acknowledgements. The authors thank Paul Jung for his programming assistance as well as Anna Metzner, Lara Graute and Lea Köster for their help with data acquisition.

Financial support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict 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.

References

Achterbergh, L., Pitman, A., Birken, M., Pearce, E., Sno, H., & Johnson, S. (2020). The experience of loneliness among young people with depression: A qualitative meta-synthesis of the literature. *BMC Psychiatry*, *20*(1), 415. https://doi.org/10.1186/s12888-020-02818-3.

Alkire, D., Levitas, D., Warnell, K. R., & Redcay, E. (2018). Social interaction recruits mentalizing and reward systems in middle childhood. *Human Brain Mapping*, *39*(10), 3928–3942. https://doi.org/10.1002/hbm.24221.

Arnold, M. M., Müller-Oerlinghausen, B., Hemrich, N., & Bönsch, D. (2020). Effects of psychoactive massage in outpatients with depressive disorders: A randomized controlled mixed-methods study. *Brain Sciences*, *10*(10), 676. https://doi.org/10.3390/brainsci10100676.

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., & Simmons, W. K. (2014). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological Psychiatry*, *76*(3), 258–266. https://doi.org/10.1016/j.biopsych.2013.11.027.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*(3), 588–597. https://doi.org/10.1207/s15327752jpa6703_13.

Bell, R. A., Daly, J. A., & Gonzalez, M. C. (1987). Affinity-maintenance in marriage and its relationship to women's marital satisfaction. *Journal of Marriage and the Family*, *49*(2), 445. https://doi.org/10.2307/352313.

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132.

Boehme, R., Hauser, S., Gerling, G. J., Heilig, M., & Olausson, H. (2019). Distinction of self-produced touch and social touch at cortical and spinal cord levels. *Proceedings of the National Academy of Sciences*, *116*(6), 2290–2299. https://doi.org/10.1073/pnas.1816278116.

Calati, R., Ferrari, C., Brittner, M., Oasi, O., Olié, E., Carvalho, A. F., & Courtet, P. (2019). Suicidal thoughts and behaviors and social isolation: A narrative review of the literature. *Journal of Affective Disorders*, *245*, 653–667. https://doi.org/10.1016/j.jad.2018.11.022.

Conradi, H. J., Ormel, J., & de Jonge, P. (2011). Presence of individual (residual) symptoms during depressive episodes and periods of remission: A 3-year prospective study. *Psychological Medicine*, *41*(6), 1165–1174. https://doi.org/10.1017/S0033291710001911.

Croy, I., Geide, H., Paulus, M., Weidner, K., & Olausson, H. (2016). Affective touch awareness in mental health and disease relates to autistic traits – An explorative neurophysiological investigation. *Psychiatry Research*, *245*, 491–496. https://doi.org/10.1016/j.psychres.2016.09.011.

Crucianelli, L., & Ehrsson, H. H. (2023). The role of the skin in interoception: A neglected organ? *Perspectives on Psychological Science*, *18*(1), 224–238. https://doi.org/10.1177/17456916221094509.

Davidovic, M., Jönsson, E. H., Olausson, H., & Björnsdotter, M. (2016). Posterior superior temporal sulcus responses predict perceived pleasantness of skin stroking. *Frontiers in Human Neuroscience*, *10*, 432. https://doi.org/10.3389/fnhum.2016.00432.

DGPPN, BÄK, KBV, & AWMF. (2015). *S3–Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Langfassung*, 2. *Auflage* [Text/pdf]. Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN); Bundesärztekammer (BÄK); Kassenärztliche Bundesvereinigung (KBV); Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). https://doi.org/10.6101/AZQ/000364.

Dichter, G. S., Felder, J. N., Petty, C., Bizzell, J., Ernst, M., & Smoski, M. J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological Psychiatry*, *66*(9), 886–897. https://doi.org/10.1016/j.biopsych.2009.06.021.

Dichter, G. S., Kozink, R. V., McClernon, F. J., & Smoski, M. J. (2012). Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. *Journal of Affective Disorders*, *136*(3), 1126–1134. https://doi.org/10.1016/j.jad.2011.09.048.

Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *NeuroImage*, *61*(3), 677–685. https://doi.org/10.1016/j.neuroimage.2012.04.005.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry*, *64*(3), 327–337. https://doi.org/10.1001/archpsyc.64.3.327.

Elmer, T., & Stadtfeld, C. (2020). Depressive symptoms are associated with social isolation in face-to-face interaction networks. *Scientific Reports*, *10*(1), 1444. https://doi.org/10.1038/s41598-020-58297-9.

Flores, L. E. J., Alarcón, G., Eckstrand, K. L., Lindenmuth, M., & Forbes, E. E. (2022). Interpersonal context and desired emotional closeness in neural response to negative visual stimuli: Preliminary findings. *Brain and Behavior*, *12*(1), e2438. https://doi.org/10.1002/brb3.2438.

Fuchs, T. (2001). Melancholia as a desynchronization: Towards a psychopathology of interpersonal time. *Psychopathology*, *34*(4), 179–186. https://doi.org/10.1159/000049304.

Fuchs, T., & Schlimme, J. E. (2009). Embodiment and psychopathology: A phenomenological perspective. *Current Opinion in Psychiatry*, *22*(6), 570–575. https://doi.org/10.1097/YCO.0b013e3283318e5c.

Gazzola, V., Spezio, M. L., Etzel, J. A., Castelli, F., Adolphs, R., & Keysers, C. (2012). Primary somatosensory cortex discriminates affective significance in social touch. *Proceedings of the National Academy of Sciences*, *109*(25), E1657–E1666. https://doi.org/10.1073/pnas.1113211109.

Geugies, H., Mocking, R. J. T., Figueroa, C. A., Groot, P. F. C., Marsman, J.-B. C., Servaas, M. N., … Ruhé, H. G. (2019). Impaired reward-related learning signals in remitted unmedicated patients with recurrent depression. *Brain*, *142*(8), 2510–2522. https://doi.org/10.1093/brain/awz167.

Groenewold, N. A., Opmeer, E. M., de Jonge, P., Aleman, A., & Costafreda, S. G. (2013). Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neuroscience & Biobehavioral Reviews*, *37*(2), 152–163. https://doi.org/10.1016/j.neubiorev.2012.11.015.

Gulledge, A. K., Gulledge, M. H., & Stahmannn, R. F. (2003). Romantic physical affection types and relationship satisfaction. *The American Journal of Family Therapy*, *31*(4), 233–242. https://doi.org/10.1080/01926180390201936.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(1), 56–62.

Harshaw, C. (2015). Interoceptive dysfunction: Toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychological Bulletin*, *141*, 311–363. https://doi.org/10.1037/a0038101.

Hertenstein, M. J., Verkamp, J. M., Kerestes, A. M., & Holmes, R. M. (2006). The communicative functions of touch in humans, nonhuman primates, and rats: A review and synthesis of the empirical research. *Genetic, Social,*

and General Psychology Monographs, *132*(1), 5–94. https://doi.org/10.3200/MONO.132.1.5-94.

Höflich, A., Michenthaler, P., Kasper, S., & Lanzenberger, R. (2019). Circuit mechanisms of reward, anhedonia, and depression. *International Journal of Neuropsychopharmacology*, *22*(2), 105–118. https://doi.org/10.1093/ijnp/pyy081.

Holvast, F., Burger, H., de Waal, M. M. W., van Marwijk, H. W. J., Comijs, H. C., & Verhaak, P. F. M. (2015). Loneliness is associated with poor prognosis in late-life depression: Longitudinal analysis of the Netherlands study of depression in older persons. *Journal of Affective Disorders*, *185*, 1–7. https://doi.org/10.1016/j.jad.2015.06.036.

Hopko, D. R., Lejuez, C. W., Ruggiero, K. J., & Eifert, G. H. (2003). Contemporary behavioral activation treatments for depression: Procedures, principles, and progress. *Clinical Psychology Review*, *23*(5), 699–717. https://doi.org/10.1016/S0272-7358(03)00070-9.

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Walker, S. J., … Zubieta, J.-K. (2015). It still hurts: Altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Molecular Psychiatry*, *20*(2), 193–200. https://doi.org/10.1038/mp.2014.185.

Insel, T. R. (2003). Is social attachment an addictive disorder? *Physiology & Behavior*, *79*(3), 351–357. https://doi.org/10.1016/S0031-9384(03)00148-3.

Izuma, K., Saito, D. N., & Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron*, *58*(2), 284–294. https://doi.org/10.1016/j.neuron.2008.03.020.

Jakubiak, B. K., & Feeney, B. C. (2017). Affectionate touch to promote relational, psychological, and physical well-being in adulthood: A theoretical model and review of the research. *Personality and Social Psychology Review*, *21*(3), 228–252. https://doi.org/10.1177/1088868316650307.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Kawamichi, H., Sugawara, S. K., Hamano, Y. H., Makita, K., Kochiyama, T., & Sadato, N. (2016). Increased frequency of social interaction is associated with enjoyment enhancement and reward system activation. *Scientific Reports*, *6*(1), 24561. https://doi.org/10.1038/srep24561.

Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G. A., Brotman, M. A., Leibenluft, E., … Stringaris, A. (2018). Reward processing in depression: A conceptual and meta-analytic review across fMRI and EEG studies. *American Journal of Psychiatry*, *175*(11), 1111–1120. https://doi.org/10.1176/appi.ajp.2018.17101124.

Kim, B. J., & Kihl, T. (2021). Suicidal ideation associated with depression and social support: A survey-based analysis of older adults in South Korea. *BMC Psychiatry*, *21*, 409. https://doi.org/10.1186/s12888-021-03423-8.

Kreuder, A.-K., Scheele, D., Wassermann, L., Wollseifer, M., Stoffel-Wagner, B., Lee, M. R., … Hurlemann, R. (2017). How the brain codes intimacy: The neurobiological substrates of romantic touch: The neurobiological substrates of romantic touch. *Human Brain Mapping*, *38*(9), 4525–4534. https://doi.org/10.1002/hbm.23679.

Kupferberg, A., Bicks, L., & Hasler, G. (2016). Social functioning in major depressive disorder. *Neuroscience & Biobehavioral Reviews*, *69*, 313–332. https://doi.org/10.1016/j.neubiorev.2016.07.002.

Lamm, C., Silani, G., & Singer, T. (2015). Distinct neural networks underlying empathy for pleasant and unpleasant touch. *Cortex*, *70*, 79–89. https://doi.org/10.1016/j.cortex.2015.01.021.

Laurent, H. K., & Ablow, J. C. (2012). A cry in the dark: Depressed mothers show reduced neural activation to their own infant's cry. *Social Cognitive and Affective Neuroscience*, *7*(2), 125–134. https://doi.org/10.1093/scan/nsq091.

Law, R. W., & Sbarra, D. A. (2009). The effects of church attendance and marital status on the longitudinal trajectories of depressed mood among older adults. *Journal of Aging and Health*, *21*(6), 803–823. https://doi.org/10.1177/0898264309338300.

Löken, L. S., Wessberg, J., Morrison, I., McGlone, F., & Olausson, H. (2009). Coding of pleasant touch by unmyelinated afferents in humans. *Nature Neuroscience*, *12*(5), 547–548. https://doi.org/10.1038/nn.2312.

Luoto, K. E., Lindholm, L. H., Paavonen, V., Koivukangas, A., Lassila, A., Leinonen, E., & Kampman, O. (2018). Behavioral activation versus treatment as usual in naturalistic sample of psychiatric patients with depressive symptoms: A benchmark controlled trial. *BMC Psychiatry*, *18*(1), 238. https://doi.org/10.1186/s12888-018-1820-x.

Maier, A., Gieling, C., Heinen-Ludwig, L., Stefan, V., Schultz, J., Güntürkün, O., … Scheele, D. (2019). Association of childhood maltreatment with interpersonal distance and social touch preferences in adulthood. *American Journal of Psychiatry*, *177*(1), 37–46. https://doi.org/10.1176/appi.ajp.2019.19020212.

May, A., Stewart, J., Paulus, M., & Tapert, S. (2014). The effect of age on neural processing of pleasant soft touch stimuli. *Frontiers in Behavioral Neuroscience*, *8*, 52. https://doi.org/10.3389/fnbeh.2014.00052.

McCabe, C., Cowen, P. J., & Harmer, C. J. (2009). Neural representation of reward in recovered depressed patients. *Psychopharmacology*, *205*(4), 667–677. https://doi.org/10.1007/s00213-009-1573-9.

McCabe, C., Mishor, Z., Cowen, P. J., & Harmer, C. J. (2010). Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological Psychiatry*, *67*(5), 439–445. https://doi.org/10.1016/j.biopsych.2009.11.001.

McFarquhar, M. (2019). Modeling group-level repeated measurements of neuroimaging data using the univariate general linear model. *Frontiers in Neuroscience*, *13*, 352. https://doi.org/10.3389/fnins.2019.00352.

McGlone, F., Olausson, H., Boyle, J. A., Jones-Gotman, M., Dancer, C., Guest, S., & Essick, G. (2012). Touching and feeling: Differences in pleasant touch processing between glabrous and hairy skin in humans: Pleasant touch on glabrous and hairy skin. *European Journal of Neuroscience*, *35*(11), 1782–1788. https://doi.org/10.1111/j.1460-9568.2012.08092.x.

McGlone, F., Wessberg, J., & Olausson, H. (2014). Discriminative and affective touch: Sensing and feeling. *Neuron*, *82*(4), 737–755. https://doi.org/10.1016/j.neuron.2014.05.001.

Meltzer, H., Bebbington, P., Dennis, M. S., Jenkins, R., McManus, S., & Brugha, T. S. (2013). Feelings of loneliness among adults with mental disorder. *Social Psychiatry and Psychiatric Epidemiology*, *48*(1), 5–13. https://doi.org/10.1007/s00127-012-0515-8.

Morrison, I., Löken, L. S., & Olausson, H. (2010). The skin as a social organ. *Experimental Brain Research*, *204*(3), 305–314. https://doi.org/10.1007/s00221-009-2007-y.

Muise, A., Giang, E., & Impett, E. A. (2014). Post sex affectionate exchanges promote sexual and relationship satisfaction. *Archives of Sexual Behavior*, *43*(7), 1391–1402. https://doi.org/10.1007/s10508-014-0305-3.

Ng, T. H., Alloy, L. B., & Smith, D. V. (2019). Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. *Translational Psychiatry*, *9*(1), 1–10. https://doi.org/10.1038/s41398-019-0644-x.

Nummenmaa, L., Tuominen, L., Dunbar, R., Hirvonen, J., Manninen, S., Arponen, E., … Sams, M. (2016). Social touch modulates endogenous μ-opioid system activity in humans. *NeuroImage*, *138*, 242–247. https://doi.org/10.1016/j.neuroimage.2016.05.063.

Olino, T. M., Silk, J. S., Osterritter, C., & Forbes, E. E. (2015). Social reward in youth at risk for depression: A preliminary investigation of subjective and neural differences. *Journal of Child and Adolescent Psychopharmacology*, *25*(9), 711–721. https://doi.org/10.1089/cap.2014.0165.

Papalini, S., Lange, I., Bakker, J., Michielse, S., Marcelis, M., Wichers, M., … Schruers, K. (2019). The predictive value of neural reward processing on exposure therapy outcome: Results from a randomized controlled trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 339–346. https://doi.org/10.1016/j.pnpbp.2019.02.002.

Paulus, M. P., & Stein, M. B. (2010). Interoception in anxiety and depression. *Brain Structure and Function*, *214*(5–6), 451–463. https://doi.org/10.1007/s00429-010-0258-9.

Pechtel, P., Dutra, S. J., Goetz, E. L., & Pizzagalli, D. A. (2013). Blunted reward responsiveness in remitted depression. *Journal of Psychiatric Research*, *47*(12), 1864–1869. https://doi.org/10.1016/j.jpsychires.2013.08.011.

Poldrack, R. A. (2006). Can cognitive processes be inferred from neuroimaging data? *Trends in Cognitive Sciences*, *10*(2), 59–63. https://doi.org/10.1016/j.tics.2005.12.004.

Redcay, E., Dodell-Feder, D., Pearrow, M. J., Mavros, P. L., Kleiner, M., Gabrieli, J. D. E., & Saxe, R. (2010). Live face-to-face interaction during

fMRI: A new tool for social cognitive neuroscience. *NeuroImage*, *50*(4), 1639–1647. https://doi.org/10.1016/j.neuroimage.2010.01.052.

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., & Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience and Biobehavioral Reviews*, *65*, 21–35. https://doi.org/10.1016/j.neubiorev.2016.03.004.

Röhricht, F., Papadopoulos, N., & Priebe, S. (2013). An exploratory randomized controlled trial of body psychotherapy for patients with chronic depression. *Journal of Affective Disorders*, *151*(1), 85–91. https://doi.org/10.1016/j.jad.2013.05.056.

Rolls, E. T., Huang, C.-C., Lin, C.-P., Feng, J., & Joliot, M. (2020). Automated anatomical labelling atlas 3. *NeuroImage*, *206*, 116189. https://doi.org/10.1016/j.neuroimage.2019.116189.

Sailer, U., Hausmann, M., & Croy, I. (2020). Pleasantness only? *Experimental Psychology*, *67*(4), 224–236. https://doi.org/10.1027/1618-3169/a000492.

Scheele, D., Kendrick, K. M., Khouri, C., Kretzer, E., Schläpfer, T. E., Stoffel-Wagner, B., … Hurlemann, R. (2014). An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. *Neuropsychopharmacology*, *39*(9), 2078–2085. https://doi.org/10.1038/npp.2014.78.

Schrader, G. D. (1997). Does anhedonia correlate with depression severity in chronic depression? *Comprehensive Psychiatry*, *38*(5), 260–263. https://doi.org/10.1016/S0010-440X(97)90057-2.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(20), 22–33.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spijker, J., Bijl, R. V., Graaf, R. D., & Nolen, W. A. (2001). Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatrica Scandinavica*, *103*(2), 122–130. https://doi.org/10.1034/j.1600-0447.2001.103002122.x.

Strauss, T., Rottstädt, F., Sailer, U., Schellong, J., Hamilton, J. P., Raue, C., … Croy, I. (2019). Touch aversion in patients with interpersonal traumatization. *Depression and Anxiety*, *36*(7), 635–646. https://doi.org/10.1002/da.22914.

Visentini, C., Cassidy, M., Bird, V. J., & Priebe, S. (2018). Social networks of patients with chronic depression: A systematic review. *Journal of Affective Disorders*, *241*, 571–578. https://doi.org/10.1016/j.jad.2018.08.022.

von Mohr, M., Kirsch, L. P., & Fotopoulou, A. (2021). Social touch deprivation during COVID-19: Effects on psychological wellbeing and craving interpersonal touch. *Royal Society Open Science*, *8*(9), 210287. https://doi.org/10.1098/rsos.210287.

Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D. A., Sienaert, P., … Claes, S. (2014). Dimensions in major depressive disorder and their relevance for treatment outcome. *Journal of Affective Disorders*, *155*, 35–41. https://doi.org/10.1016/j.jad.2013.10.020.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., & Johnson, S. (2018). Associations between loneliness and perceived social support and outcomes of mental health problems: A systematic review. *BMC Psychiatry*, *18*(1), 156. https://doi.org/10.1186/s12888-018-1736-5.

Weinberg, A., & Shankman, S. A. (2017). Blunted reward processing in remitted melancholic depression. *Clinical Psychological Science*, *5*(1), 14–25. https://doi.org/10.1177/2167702616633158.

Wilhelm, F. H., Kochar, A. S., Roth, W. T., & Gross, J. J. (2001). Social anxiety and response to touch: Incongruence between self-evaluative and physiological reactions. *Biological Psychology*, *58*(3), 181–202. https://doi.org/10.1016/s0301-0511(01)00113-2.

Woods, A., Solomonov, N., Liles, B., Guillod, A., Kales, H. C., & Sirey, J. A. (2021). Perceived social support and interpersonal functioning as predictors of treatment response among depressed older adults. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *29*(8), 843–852. https://doi.org/10.1016/j.jagp.2020.12.021.

Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., & Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*, *151*(2), 531–539. https://doi.org/10.1016/j.jad.2013.06.039.

Zimmermann, K., Kendrick, K. M., Scheele, D., Dau, W., Banger, M., Maier, W., … Becker, B. (2019). Altered striatal reward processing in abstinent dependent cannabis users: Social context matters. *European Neuropsychopharmacology*, *29*(3), 356–364. https://doi.org/10.1016/j.euroneuro.2019.01.106.

https://doi.org/10.1017/S0033291723001617 Published online by Cambridge University Press

Supplementary Material for

Altered reward network responses to social touch in major depression

Clemens Mielacher*, Dirk Scheele, Maximilian Kiebs, Laura Schmitt, Torge Dellert, Alexandra Philipsen, Claus Lamm, René Hurlemann

* Corresponding author: Clemens Mielacher

Email: cmielach@mailbox.org

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, Hall, Zelaya, Williams, & Mehta, 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; $F_{(1, 89)} = 17.80$, $p_{FWE} = .024$, $\eta_p^2 = 0.17$). We also found main effects of speed in the left nucleus accumbens (MNI: -6, 6, −4; $F_{(1, 89)} = 12.97$, $p_{FWE} = .030$, $\eta_p^2 = 0.13$) and the left posterior insula (MNI: -34, 2, 12; $F_{(1, 89)} = 25.94$, $p_{FWE} = .001$, $\eta_p^2 = 0.22$), 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; $F_{(1, 89)} = 20.25$, $p_{FWE} = .009$, $\eta_p^2 = 0.19$; MNI: 34, -20, 20; $F_{(1, 89)} = 17.63$, $p_{FWE} = .025$, $\eta_p^2 = 0.17$) 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; $F_{(1, 49)} = 19.14$, $p_{FWE} = .029$, $\eta_p^2 = 0.29$) and the left (MNI: -36, 0, 12; $F_{(1, 49)} = 21.78$, $p_{FWE} = .012$, $\eta_p^2 = 0.32$) and right posterior insula (MNI: 36, -16, 22; $F_{(1, 49)} = 27.13$, $p_{FWE} = .002$, $\eta_p^2 = 0.37$). 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 Figures

Figure S1

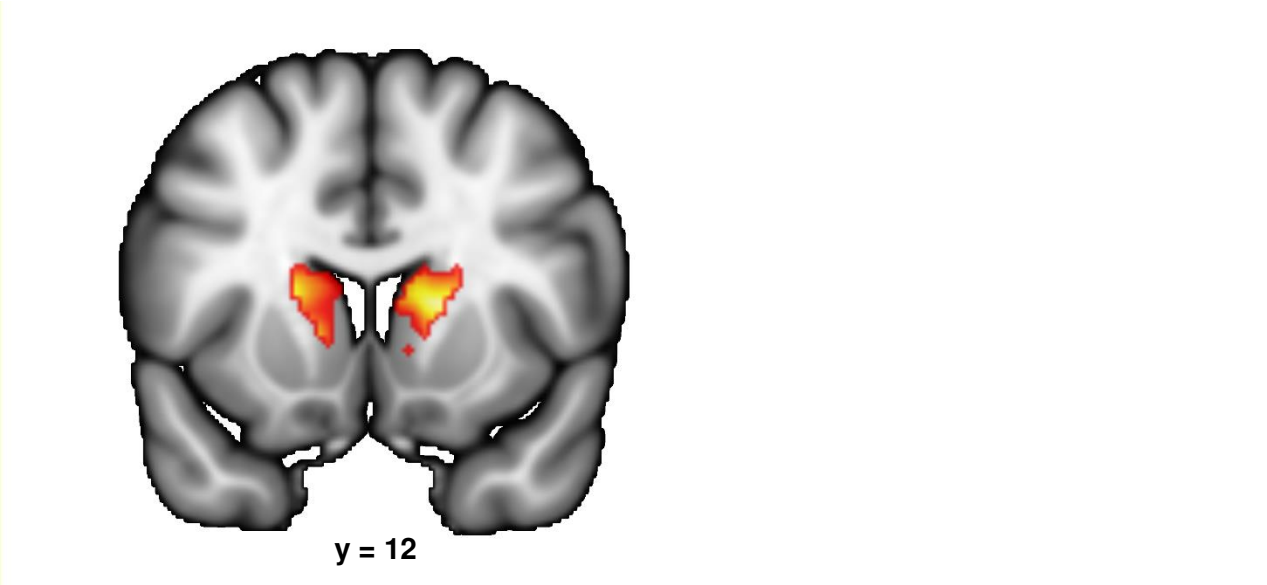


Fig. S1. Controls exhibited increased neural responses to social touch compared to the no touch control condition in the bilateral caudate nucleus across time (i.e. before and after treatment). Significant clusters are displayed at a peak-level threshold of $p < .05$ uncorrected.

Supplementary Tables

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
STAI baseline	61.96 (7.92)	65.00 (6.18)	0.122

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)

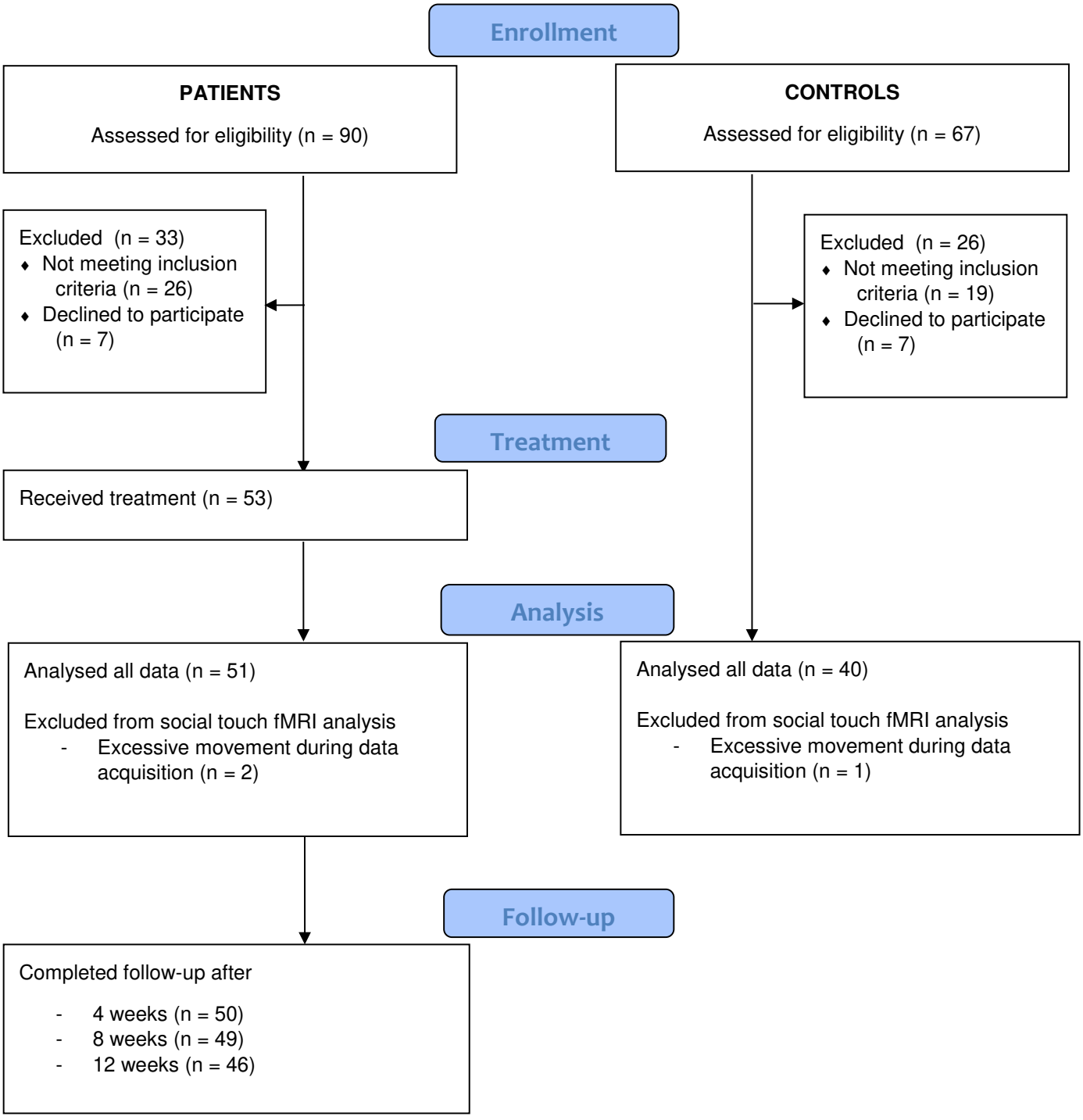
Region	Right/left	Cluster size (voxels)	*t*-score	MNI Coordinates x	y	z	*p*-value
Touch > No Touch							
Insula	L	14977	15.30	-40	-4	8	< 0.001
Postcentral Gyrus	L		14.18	-64	-22	22	< 0.001
Supramarginal Gyrus	L		13.72	-56	-22	18	< 0.001
Supramarginal Gyrus	R	9303	13.56	52	-28	24	< 0.001
Supramarginal 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



References

Caceres, A., Hall, D. L., Zelaya, F. O., Williams, S. C. R., & Mehta, M. A. (2009). Measuring fMRI reliability with the intra-class correlation coefficient. *NeuroImage*, *45*(3), 758–768. https://doi.org/10.1016/j.neuroimage.2008.12.035

Cicchetti, D. V. (1994). Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. *Psychological Assessment*, *6*(4), 284–290.

Hamilton, M. (1960). A Rating Scale for Depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(1), 56–62.

Hayes, A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression Based Approach*. New York: Guildford.

Maier, A., Gieling, C., Heinen-Ludwig, L., Stefan, V., Schultz, J., Güntürkün, O., … Scheele, D. (2019). Association of Childhood Maltreatment With Interpersonal Distance and Social Touch Preferences in Adulthood. *American Journal of Psychiatry*, appi.ajp.2019.19020212. https://doi.org/10.1176/appi.ajp.2019.19020212

Mielacher, C., Schultz, J., Kiebs, M., Dellert, T., Metzner, A., Graute, L., … Hurlemann, R. (2020). Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder. *Personalized Medicine in Psychiatry*, *23–24*, 100066. https://doi.org/10.1016/j.pmip.2020.100066

Portney, L. G., & Watkins, M. P. (2009). *Foundations of Clinical Research: Applications to Practice*. Pearson/Prentice Hall.

Strobach, T., & Huestegge, L. (2017). Evaluating the Effectiveness of Commercial Brain Game Training with Working-Memory Tasks. *Journal of Cognitive Enhancement*, *1*(4), 539–558. https://doi.org/10.1007/s41465-017-0053-0

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.1037//0022-3514.54.6.1063

3.4 Publication 4: Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder

New Journal and we have not received input yet 23–24 (2020) 100066

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.sciencedirect.com/journal/personalized-medicine-in-psychiatry

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

Clemens Mielacher [a,*], Johannes Schultz [b,c], Maximilian Kiebs [a,e], Torge Dellert [d], Anna Metzner [a], Larissa Graute [a], Hanna Högenauer [e], Wolfgang Maier [e], Claus Lamm [f], René Hurlemann [a,e,g,h]

[a] Division of Medical Psychology, Medical Faculty, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
[b] Institute of Experimental Epileptology and Cognition Research, Medical Faculty, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
[c] Center for Economics and Neuroscience, University of Bonn, Nachtigallenweg 86, 53127 Bonn, Germany
[d] Institute of Medical Psychology and Systems Neuroscience, University of Münster, Von-Esmarch-Str. 52, 48149 Münster, Germany
[e] Department of Psychiatry, Medical Faculty, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
[f] Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods, Faculty of Psychology, University of Vienna, Liebiggasse 5, 1010 Vienna, Austria
[g] Department of Psychiatry, School of Medicine & Health Sciences, University of Oldenburg, Hermann-Ehlers-Str. 7, 26160 Bad Zwischenahn, Germany
[h] Research Center Neurosensory Science, University of Oldenburg, Carl-von-Ossietzky-Str. 9-11, 26111 Oldenburg, Germany

ARTICLE INFO

Keywords:
Depression
iTBS
fMRI
Functional connectivity
Hippocampus

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.

1. 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

* Corresponding author at: Division of Medical Psychology, Medical Faculty, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany.
E-mail address: cmielach@mailbox.org (C. Mielacher).

https://doi.org/10.1016/j.pmip.2020.100066

Available online 20 November 2020

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	0.481
Age (years)	40.28 (12.65)	43.59 (11.45)	42.28 (12.99)	0.754
Education (years)	16.69 (7.59)	14.06 (3.06)	16.58 (4.43)	0.278
Duration of current depressive episode (years)	4.01 (5.39)	3.09 (3.29)	6.46 (9.22)	0.289
Number of depressive episodes [a]	3.57 (3.40)	3.28 (2.52)	2.72 (2.60)	0.701

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).

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.

2. Methods and materials

2.1. 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.

2.2. 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. Fig. 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 inter-session interval = 2.7 h, range = 1.5 to 6.5 h). 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). 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.

2.3. 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 inter-train 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

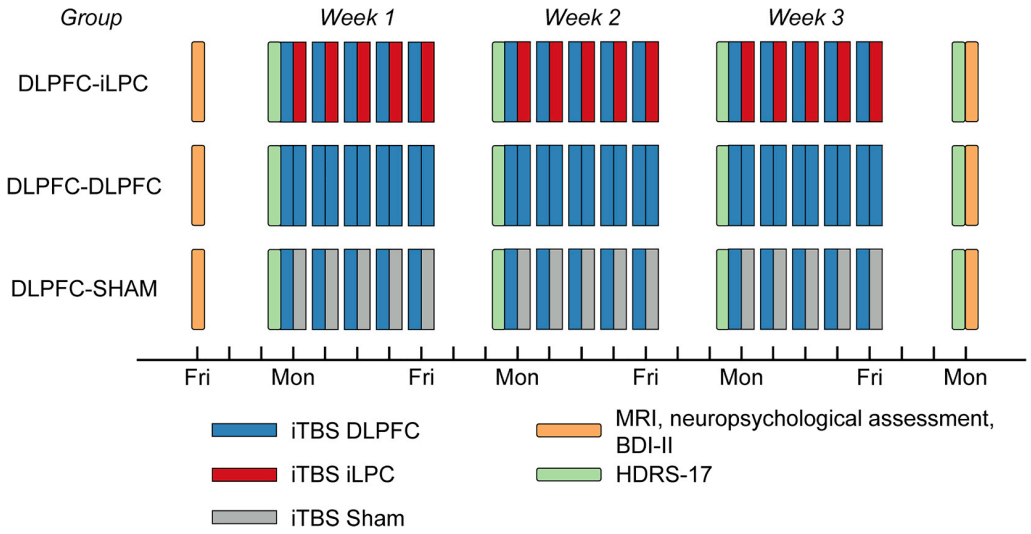


Fig. 1. Study design. Patients received two daily stimulation sessions, one over the left dorsolateral prefrontal cortex (DLPFC), the other depending on group affiliation. Follow-up Beck Depression Inventory (BDI-II) scores were acquired 4, 8 and 12 weeks after the treatment phase (not depicted). HRDS-17,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

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.

2.4. 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).

2.5. 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).

2.6. 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 $p_{\text{uncorrected}} < 0.05$ and a cluster threshold of $p_{\text{FWE}} < 0.05$.

2.7. 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.

2.8. 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.

2.9. 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 $p_{FWE} < 0.05$. 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.

3. Results

3.1. Clinical and neuropsychological results

HDRS-17 scores (pre-treatment 17.21 ± 5.59, post-treatment 10.19 ± 5.79, $F_{(1,52)} = 91.06$, $p < .001$, $\eta_p^2 = 0.64$) and BDI-II scores (pre-treatment 33.45 ± 8.83, post-treatment 18.87 ± 11.11, $F_{(1,52)} = 87.05$, $p < .001$, $\eta_p^2 = 0.63$) improved across groups after treatment. A significant group effect ($F_{(2,49)} = 3.60$, $p = .035$, $\eta_p^2 = 0.13$) 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, $t_{(33)} = 2.41$, $p = .020$, $d = 0.84$); Fig. 2A) when controlling for pre-treatment scores. No group differences were found for BDI-II at the end of the treatment course ($F_{(2,49)} = 0.46$, $p = .632$; Fig. 2B) or at any of the follow-up measurements (all p's > 0.701), 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 ($F_{(1,52)} = 9.24$, $p = .004$, $\eta_p^2 = 0.15$), RVP ($F_{(1,52)} = 19.97$, $p < .001$, $\eta_p^2 = 0.28$) and SWM ($F_{(1,52)} = 4.21$, $p = .045$, $\eta_p^2 = 0.08$) 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: $F_{(2,49)} = 1.33$, $p = .275$).

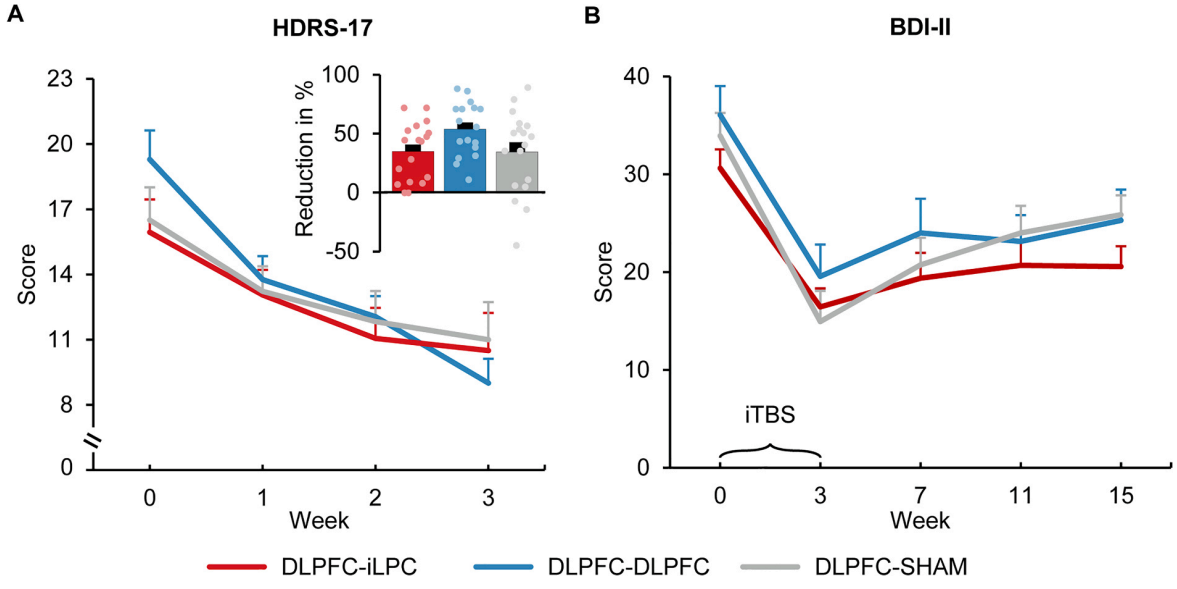


Fig. 2. Change in depression symptom severity over time. (A) Patients in the DLPFC-DLPFC group showed better outcomes in the Hamilton Depression Rating Scale (HDRS-17) than patients in the other groups when controlling for baseline scores. (B) No group differences were found for Beck Depression Inventory (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.

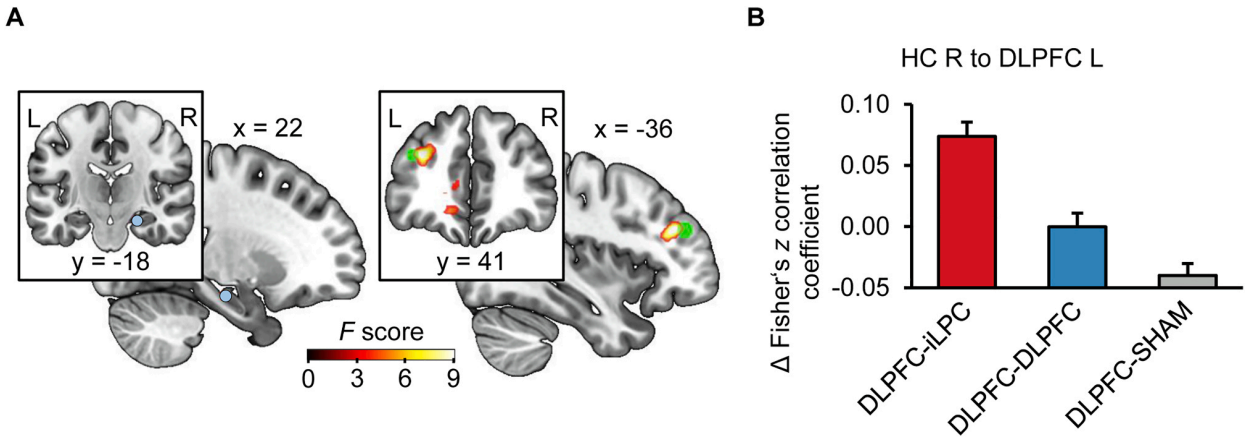


Fig. 3. Whole-brain resting-state functional connectivity of right hippocampus (HC). (A) Exploratory seed-to-voxel analysis revealed a significant group effect on change of functional connectivity between the right hippocampus seed (3-mm sphere; blue) and a prefrontal cluster topographically close to 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. 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, $p_{FWE} = 0.041$, Fig. 3A). Post-hoc tests revealed a stronger increase in connectivity in the DLPFC-iLPC group than in the DLPFC-

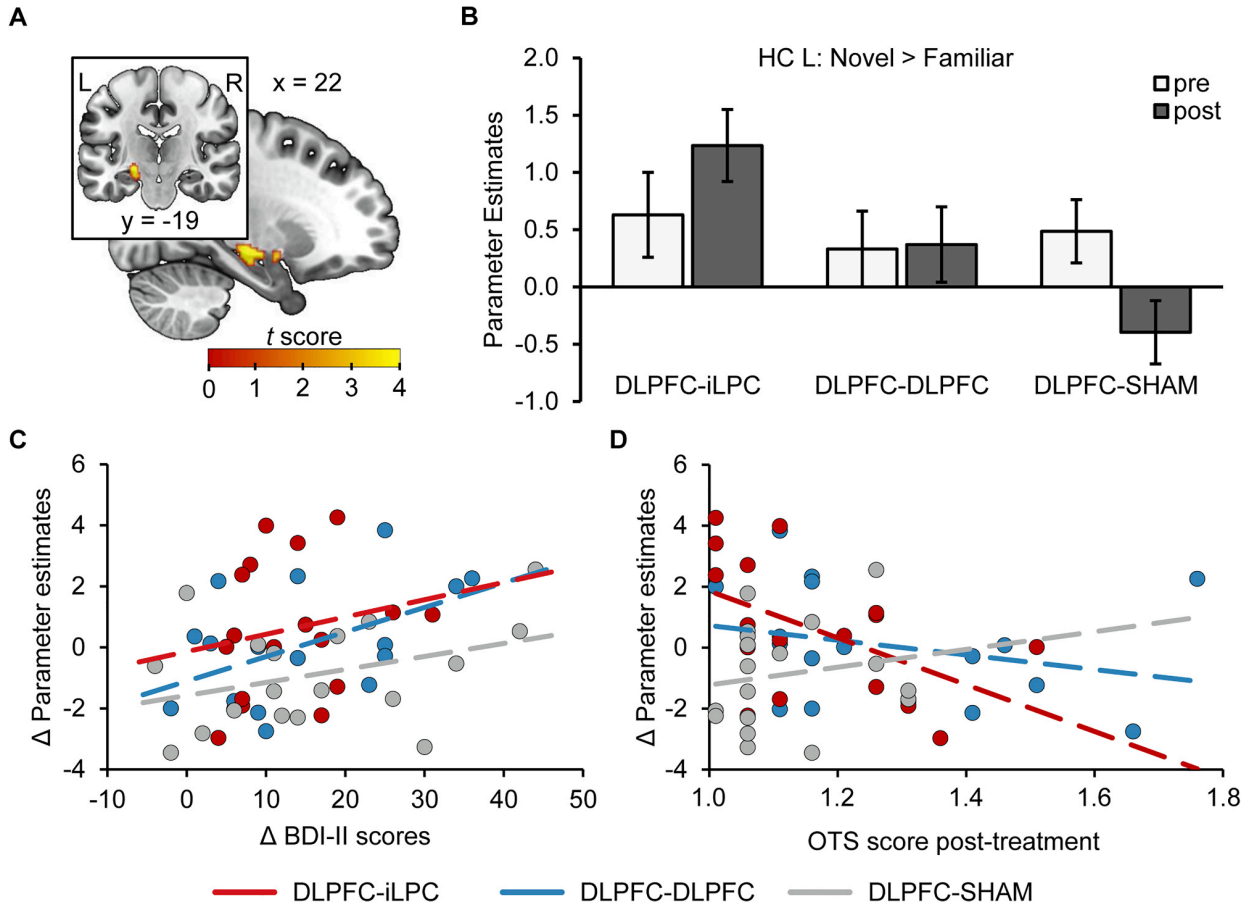


Fig. 4. fMRI results from the encoding task. (A) A leave-one-subject-out approach was used to define subject-independent regions of interest (ROIs) in the hippocampus (HC) (displayed is an exemplary ROI). (B) After treatment, patients in the DLPFC-iLPC group showed a greater increase in hippocampal response 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.

DLPFC ($t_{(33)} = 4.57, p < .001, d = 1.59$) and DLPFC-SHAM group ($t_{(34)} = 7.46, p < .001, d = 2.56$; Fig. 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 > 0.372). Analysis across groups, however, revealed a significant decrease of functional connectivity between iLPC and ipsilateral hippocampus both in the left ($F_{(1,52)} = 68.12, p < .001, \eta_p^2 = 0.57$) and right hemisphere ($F_{(1,52)} = 142.22, p < .001, \eta_p^2 = 0.73$). 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.

3.3. 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 ($F_{(2,48)} = 11.80, p = .002, \eta_p^2 = 0.23$; Fig. 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: $0.37 \pm 1.36, p = .049$; DLPFC-SHAM: $-0.39 \pm 1.17, p < .001$; Fig. 4B). No group differences were present in the retrieval task (p's > 0.107) 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 ($r_{(52)} = 0.29, p = .041$; Fig. 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: $r_{(18)} = 0.17, p = .494$; Fig. 4D).

4. 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 inter-session interval of 2–3 h, 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.

CRediT authorship contribution statement

Clemens Mielacher: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft. **Johannes Schultz:** Conceptualization, Methodology, Software, Writing - review & editing. **Maximilian Kiebs:** Investigation, Writing - review & editing. **Torge Dellert:** Investigation, Writing - review & editing. **Anna Metzner:** Investigation. **Larissa Graute:** Investigation. **Hanna Högenauer:** Investigation, Writing - review & editing. **Wolfgang Maier:** Resources, Writing - review & editing. **Claus Lamm:** Methodology, Writing - review & editing, Supervision. **René Hurlemann:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2020.100066.

References

[1] Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6. https://doi.org/10.1016/j.neuron.2004.12.033.

[2] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, Knyahnytska Y, Kennedy SH, Lam RW, Daskalakis ZJ, Downar J. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391(10131):1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.

[3] Berlim MT, McGirr A, Rodrigues dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 2017;90:102–9. https://doi.org/10.1016/j.jpsychires.2017.02.015.

[4] Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen J-P, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 2020;131(2):474–528. https://doi.org/10.1016/j.clinph.2019.11.002.

[5] Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ 2019;364:l1079. https://doi.org/10.1136/bmj.l1079.

[6] Schutter DJLG, van Honk J. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. J Psychiatry Neurosci JPN 2005;30:91–7.

[7] Deng Z-D, Lisanby SH, Peterchev AV. Electric field depth–focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimulation 2013;6(1):1–13. https://doi.org/10.1016/j.brs.2012.02.005.

[8] Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A. Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. Proc Natl Acad Sci 2011;108(52):21229–34. https://doi.org/10.1073/pnas.1113103109.

[9] Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. NeuroImage 2013;66:151–60. https://doi.org/10.1016/j.neuroimage.2012.10.082.

[10] Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, Hermiller MS, Voss JL. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 2014;345(6200):1054–7. https://doi.org/10.1126/science:1252900.

[11] Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34(1):13–25. https://doi.org/10.1016/S0896-6273(02)00653-0.

[12] MacQueen G, Frodl T. The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 2011;16(3):252–64. https://doi.org/10.1038/mp.2010.80.

[13] Caetano SC, Hatch JP, Brambilla P, Sassi RB, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. Psychiatry Res: Neuroimag 2004;132(2):141–7. https://doi.org/10.1016/j.pscychresns.2004.08.002.

[14] Fu CHY, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiol Dis 2013;52:75–83. https://doi.org/10.1016/j.nbd.2012.05.008.

[15] Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, Leaver A, Woods RP, Narr KL. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. Biol Psychiatry 2016;79(4):282–92. https://doi.org/10.1016/j.biopsych.2015.02.029.

[16] Oltedal L, Narr KL, Abbott C, Anand A, Argyelan M, Bartsch H, Dannlowski U, Dols A, van Eijndhoven P, Emsell L, Erchinger VJ, Espinoza R, Hahn T, Hanson LG, Hellemann G, Jorgensen MB, Kessler U, Oudega ML, Paulson OB, Redlich R, Sienaert P, Stek ML, Tendolkar I, Vandenbulcke M, Oedegaard KJ, Dale AM. Volume of the human hippocampus and clinical response following electroconvulsive therapy. Biol Psychiatry 2018;84(8):574–81. https://doi.org/10.1016/j.biopsych.2018.05.017.

[17] Cullen KR, Westlund MK, Klimes-Dougan B, Mueller BA, Houri A, Eberly LE, Lim KO. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry 2014;71(10):1138. https://doi.org/10.1001/jamapsychiatry.2014.1087.

[18] Ge R, Torres I, Brown JJ, Gregory E, McLellan E, Downar JH, Blumberger DM, Daskalakis ZJ, Lam RW, Vila-Rodriguez F. Functional disconnectivity of the hippocampal network and neural correlates of memory impairment in treatment-resistant depression. J Affect Disord 2019;253:248–56. https://doi.org/10.1016/j.jad.2019.04.096.

[19] Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 2015;72(6):603. https://doi.org/10.1001/jamapsychiatry.2015.0071.

[20] Chin Fatt CR, Jha MK, Cooper CM, Fonzo G, South C, Grannemann B, Carmody T, Greer TL, Kurian B, Fava M, McGrath PJ, Adams P, McInnis M, Parsey RV, Weissman M, Phillips ML, Etkin A, Trivedi MH. Effect of intrinsic patterns of functional brain connectivity in moderating antidepressant treatment response in major depression. AJP 2020;177(2):143–54. https://doi.org/10.1176/appi.ajp.2019.18070870.

[21] Abbott CC, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, et al. Hippocampal structural and functional changes associated with electroconvulsive therapy response. Transl Psychiatry 2014;4:e483–e483. https://doi.org/10.1038/tp.2014.124.

[22] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805–9. https://doi.org/10.1126/science.1083328.

[23] Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, Almeida OFX, Sousa N. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol Psychiatry 2009;14(8):764–73. https://doi.org/10.1038/mp.2008.119.

[24] Battaglia FP, Benchenane K, Sirota A, Pennartz CMA, Wiener SI. The hippocampus: hub of brain network communication for memory. Trends Cogn Sci 2011;15:310–8. https://doi.org/10.1016/j.tics.2011.05.008.

[25] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014;44(10):2029–40. https://doi.org/10.1017/S0033291713002535.

[26] Squire LR. Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem 2004;82(3):171–7. https://doi.org/10.1016/j.nlm.2004.06.005.
[27] Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 2003;54(7):693–702. https://doi.org/10.1016/S0006-3223(03)00634-6.
[28] Hermiller MS, Karp E, Nilakantan AS, Voss JL. Episodic memory improvements due to noninvasive stimulation targeting the cortical–hippocampal network: a replication and extension experiment. Brain Behav 2019;9(12). https://doi.org/10.1002/brb3.1393.
[29] Kim S, Nilakantan AS, Hermiller MS, Palumbo RT, VanHaerents S, Voss JL. Selective and coherent activity increases due to stimulation indicate functional distinctions between episodic memory networks. Sci Adv 2018;4(8):eaar2768. https://doi.org/10.1126/sciadv.aar2768.
[30] Nilakantan AS, Mesulam M-M, Weintraub S, Karp EL, VanHaerents S, Voss JL. Network-targeted stimulation engages neurobehavioral hallmarks of age-related memory decline. Neurology 2019;92(20):e2349–54. https://doi.org/10.1212/WNL.0000000000007502.
[31] Hermiller MS, VanHaerents S, Raij T, Voss JL. Frequency-specific noninvasive modulation of memory retrieval and its relationship with hippocampal network connectivity. Hippocampus 2018;29:595–609. https://doi.org/10.1002/hipo.23054.
[32] Tambini A, Nee DE, D'Esposito M. Hippocampal-targeted theta-burst stimulation enhances associative memory formation. J Cognit Neurosci 2018;30(10):1452–72. https://doi.org/10.1162/jocn_a_01300.
[33] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–33.
[34] Strobach T, Huestegge L. Evaluating the effectiveness of commercial brain game training with working-memory tasks. J Cogn Enhanc 2017;1(4):539–58. https://doi.org/10.1007/s41465-017-0053-0.
[35] Holzer M, Padberg F. Intermittent theta burst stimulation (iTBS) ameliorates therapy-resistant depression: a case series. Brain Stimulat 2010;3(3):181–3. https://doi.org/10.1016/j.brs.2009.10.004.
[36] Van Breukelen GJP. ANCOVA versus change from baseline had more power in randomized studies and more bias in nonrandomized studies. J Clin Epidemiol 2006;59(9):920–5. https://doi.org/10.1016/j.jclinepi.2006.02.007.
[37] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23(1):56–62. https://doi.org/10.1136/jnnp.23.1.56.
[38] Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. 1996.
[39] Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2(3):125–41. https://doi.org/10.1089/brain.2012.0073.
[40] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012;72(7):595–603. https://doi.org/10.1016/j.biopsych.2012.04.028.
[41] Becker B, Wagner D, Koester P, Bender K, Kabbasch C, Gouzoulis-Mayfrank E, Daumann J. Memory-related hippocampal functioning in ecstasy and amphetamine users: a prospective fMRI study. Psychopharmacology 2013;225(4):923–34. https://doi.org/10.1007/s00213-012-2873-z.
[42] Daumann J, Fischermann T, Heekeren K, Henke K, Thron A, Gouzoulis-Mayfrank E. Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. Psychopharmacology 2005;180(4):607–11. https://doi.org/10.1007/s00213-004-2002-8.
[43] Esterman M, Tamber-Rosenau BJ, Chiu Y-C, Yantis S. Avoiding non-independence in fMRI data analysis: leave one subject out. NeuroImage 2010;50(2):572–6. https://doi.org/10.1016/j.neuroimage.2009.10.092.
[44] Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MFS. Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. J Neurosci 2011;31(48):17669–79. https://doi.org/10.1523/JNEUROSCI.1513-11.2011.
[45] Johnen VM, Neubert F-X, Buch ER, Verhagen L, O'Reilly JX, Mars RB, et al. Causal manipulation of functional connectivity in a specific neural pathway during behaviour and at rest. ELife 2015;4:e04585. https://doi.org/10.7554/eLife.04585.
[46] Plewnia C, Rilk AJ, Soekadar SR, Arfeller C, Huber HS, Sauseng P, Hummel F, Gerloff C. Enhancement of long-range EEG coherence by synchronous bifocal transcranial magnetic stimulation. Eur J Neurosci 2008;27(6):1577–83. https://doi.org/10.1111/j.1460-9568.2008.06124.x.
[47] Santarnecchi E, Momi D, Sprugnoli G, Neri F, Pascual-Leone A, Rossi A, Rossi S. Modulation of network-to-network connectivity via spike-timing-dependent noninvasive brain stimulation. Hum Brain Mapp 2018;39(12):4870–83. https://doi.org/10.1002/hbm.24329.
[48] Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. Nat Neurosci 2000;3(S11):1178–83. https://doi.org/10.1038/81453.
[49] Bähner F, Meyer-Lindenberg A. Hippocampal–prefrontal connectivity as a translational phenotype for schizophrenia. Eur Neuropsychopharmacol 2017;27(2):93–106. https://doi.org/10.1016/j.euroneuro.2016.12.007.
[50] Alemany-González M, Gener T, Nebot P, Vilademunt M, Dierssen M, Puig MV. Prefrontal–hippocampal functional connectivity encodes recognition memory and is impaired in intellectual disability. Proc Natl Acad Sci USA 2020;117(21):11788–98. https://doi.org/10.1073/pnas.1921314117.
[51] Li M, Long C, Yang L. Hippocampal-Prefrontal circuit and disrupted functional connectivity in psychiatric and neurodegenerative disorders. Biomed Res Int 2015;2015:1–10. https://doi.org/10.1155/2015/810548.
[52] Shallice T, Broadbent DE, Weiskrantz L. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 1982;298:199–209. https://doi.org/10.1098/rstb.1982.0082.
[53] Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990;28(10):1021–34. https://doi.org/10.1016/0028-3932(90)90137-D.
[54] Newman SD, Carpenter PA, Varma S, Just MA. Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. Neuropsychologia 2003;41(12):1668–82. https://doi.org/10.1016/S0028-3932(03)00091-5.
[55] Owen AM, Doyon J, Petrides M, Evans AC. Planning and spatial working memory: a positron emission tomography study in humans. Eur J Neurosci 1996;8:353–64. https://doi.org/10.1111/j.1460-9568.1996.tb01219.x.
[56] Knight MJ, Baune BT. Executive function and spatial cognition mediate psychosocial dysfunction in major depressive disorder. Front Psychiatry 2018;9. https://doi.org/10.3389/fpsyt.2018.00539.
[57] Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014;44(2):225–39. https://doi.org/10.1017/S0033291713000512.
[58] Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, Loo C, Thase ME, Demitrack MA, George MS. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. J Clin Psychiatry 2008;69(3):441–51. https://doi.org/10.4088/JCP.v69n0315.
[59] McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, Avery D, Anderson BS, Nahas Z, Zarkowski P, Sackeim HA, George MS. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. Depress Anxiety 2011;28(11):973–80. https://doi.org/10.1002/da.20885.

Supplementary Material for

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

Clemens Mielacher*, Johannes Schultz, Maximilian Kiebs, Torge Dellert, Anna Metzner, Larissa Graute, Hanna Högenauer, Wolfgang Maier, Claus Lamm, René Hurlemann

* Corresponding author: Clemens Mielacher
Email: cmielach@mailbox.org

1 Supplementary Methods

1.1 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.

1.2 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.

1.3 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 [1].

1.4 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 [2] 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.

1.5 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.

1.6 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.

1.7 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, [3]). Subsequently, the residual data were band-pass filtered at a frequency between 0.01 and 0.1 Hz.

1.8 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 [4], 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).

1.9 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.

2 Supplementary Results

2.1 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).

2.2 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).

2.3 Group blinding

Patients' assumptions regarding whether they had received active or sham iTBS at S2 were correct above chance ($\chi^2_{(1)} = 7.46$, $p = .009$, $\varphi = 0.38$). However, only patients who received active or sham stimulation of the DLPFC ($\chi^2_{(1)} = 5.00$, $p = .041$, $\varphi = 0.20$) 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.

3 Supplementary References

[1] Awiszus F. On relative frequency estimation of transcranial magnetic stimulation motor threshold. Clin Neurophysiol 2012;123:2319–20. https://doi.org/10.1016/j.clinph.2012.04.014.

[2] Lundqvist D, Flykt A, Öhman A. The Karolinska Directed Emotional Faces – KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet, ISBN 91-630-7164-9. 1998.

[3] Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage 2007;37:90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042.

[4] Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 2005;25:1325–35. https://doi.org/10.1016/j.neuroimage.2004.12.034.

Supplementary Figures and Tables

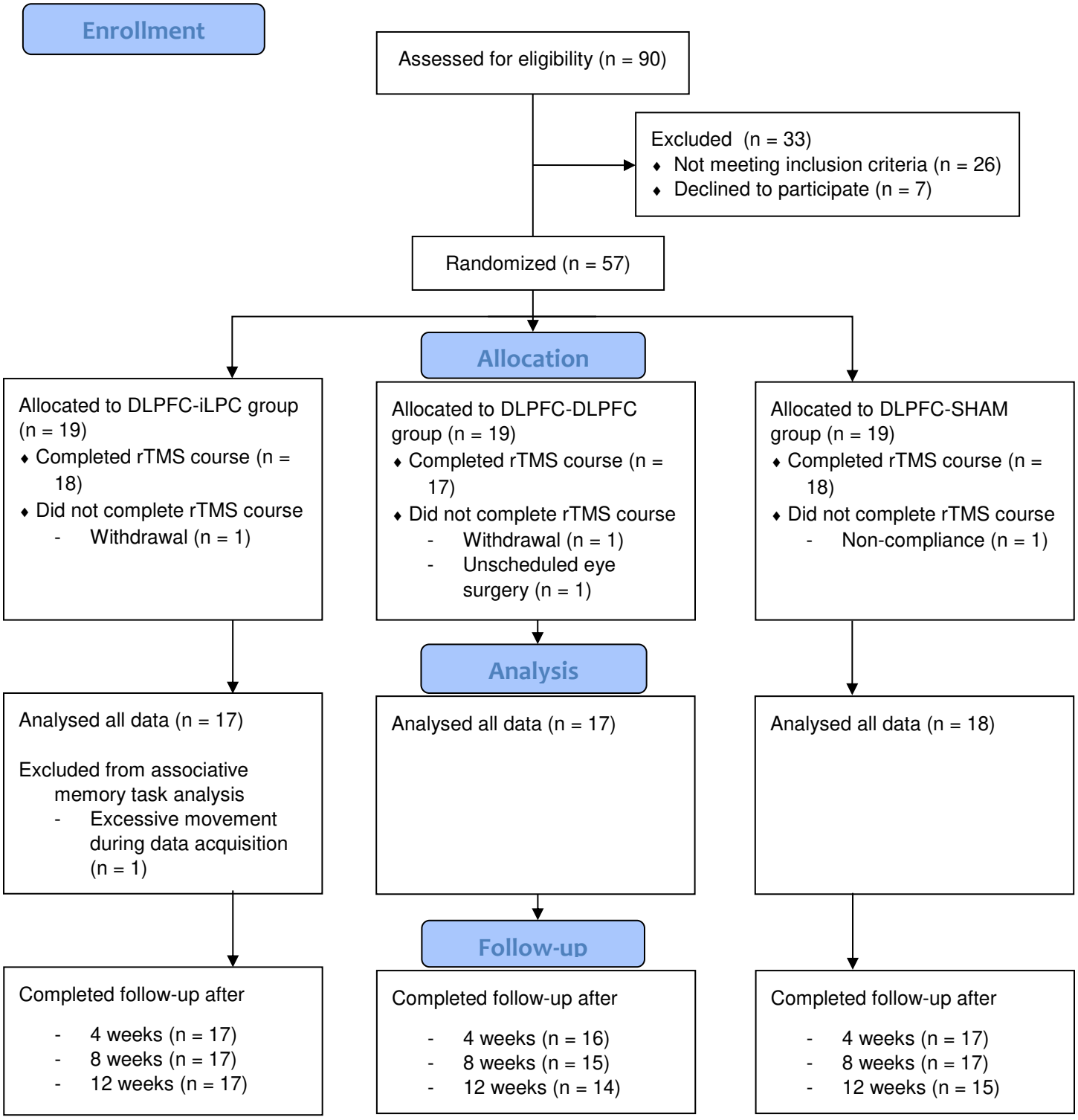


Figure S1. CONSORT diagram.

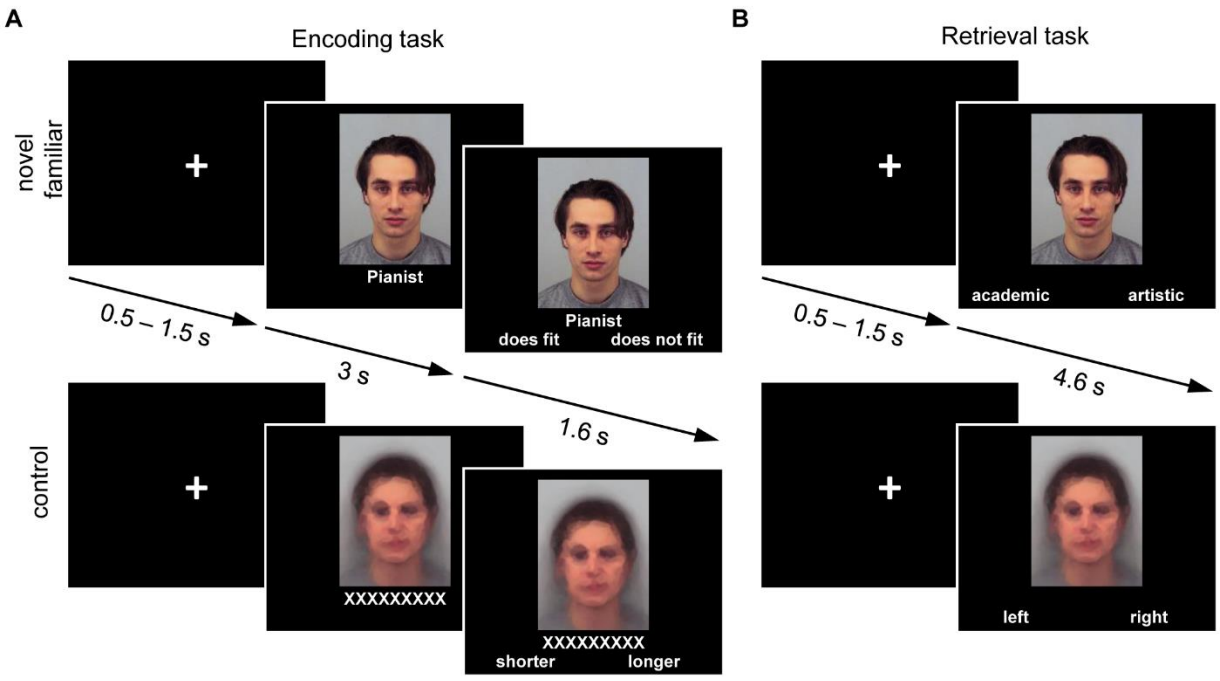


Figure S2. Experimental design of the associative memory task. **(A)** In the encoding task, four blocks of four stimuli were presented for the novel, familiar and control conditions. Subjects were tasked with memorizing the stimuli pairs and indicated whether they felt face and profession were a fit (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).

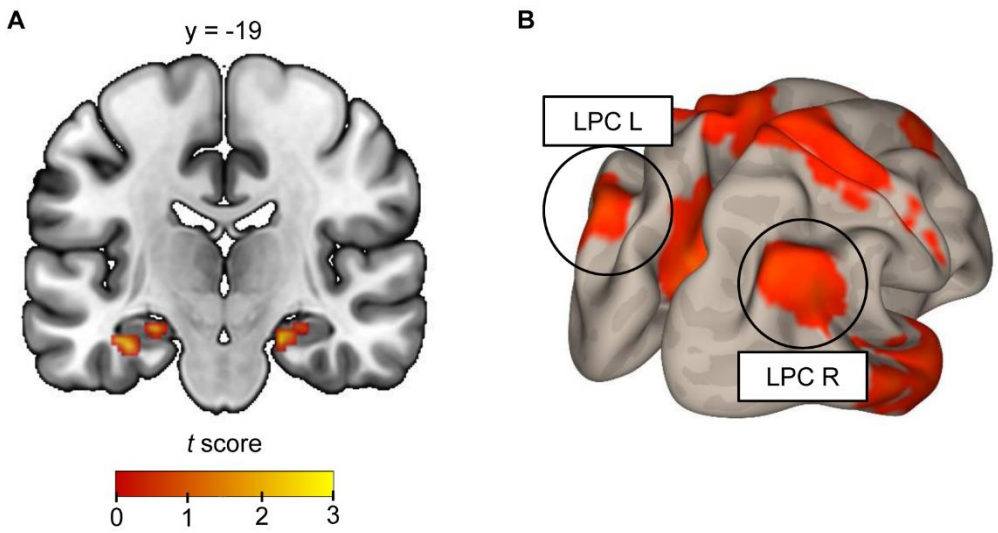


Figure S3. Results from the pre-study to determine HC targets and LPC mask. **(A)** Group-level neural activation in the left and right HC during the encoding task ([novel > familiar)] based on which HC targets were selected. **(B)** Functional connectivity analysis of bilateral HC seed revealed significant 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				Right iLPC			
	MNI coordinates				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
	-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-	-54	-68	+22	0.43	+38	-68	+50	0.27
SHAM	-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

3.5 Publication 5: Repetitive transcranial magnetic stimulation in non-treatment-resistant depression

BJPsych | The British Journal of Psychiatry (2019)
215, 445–446. doi: 10.1192/bjp.2019.75

Editorial

Repetitive transcranial magnetic stimulation in non-treatment-resistant depression

Maximilian Kiebs, René Hurlemann and Julian Mutz

Summary

Repetitive transcranial magnetic stimulation (rTMS) has been investigated as treatment for major depressive episodes since the early 1990s. Using data from a recent meta-analysis, we show that most patients included in randomised trials display relatively high degrees of treatment resistance. This might have unfavourably biased the clinical reputation of rTMS.

Declaration of interests

M.K. has received a lecture fee from Innomed Medizintechnik in 2017 and 2018.

Keywords

Transcranial magnetic stimulation; treatment resistance; depression; rTMS; medication-naive.

Maximilian Kiebs (pictured) is pursuing a PhD concerning neuromodulation through non-invasive brain stimulation in depression and the prediction of undesired effects of electroconvulsive therapy at the Medical Psychology Department of the University Hospital Bonn. **Professor René Hurlemann** is Head of the Medical Psychology Division and Vice Head of the Psychiatry Department at the University Hospital Bonn with a focus on developing innovative neuromodulatory and neuroendocrine therapies. **Julian Mutz** is a doctoral researcher at the Institute of Psychiatry, Psychology & Neuroscience at King's College London. His research focuses on brain stimulation in mood disorders, evidence synthesis and prediction of healthy ageing.

Current treatment modalities for people with treatment-resistant depression include repetitive transcranial magnetic stimulation (rTMS). rTMS uses electromagnetic fields, generated by a coil that is placed over the patient's head, to depolarise superficial neurons which potentially leads to prolonged modulation of neural activity. Meta-analyses of randomised clinical trials support the antidepressant efficacy of rTMS and find the treatment to be generally well tolerated by patients, e.g.[1]. Common undesired effects are limited to transient headaches, dizziness and mild discomfort at the site of stimulation. Countries including Australia, Brazil, Canada, Israel and the USA have approved rTMS as second-line treatment for major depressive disorder (MDD), while others have included rTMS in their guidelines for good clinical practice (e.g. Finland, Germany, Serbia, UK). Initially thought of as a less-invasive alternative to electroconvulsive therapy, rTMS has been investigated primarily in people with treatment resistance. Staging models define levels of treatment resistance by the number of failed pharmacological interventions at adequate duration and dosage, with more failed antidepressant trials – which sometimes include class switching and augmentation – reflecting higher degrees of treatment resistance.

In a recent meta-analysis, we examined the antidepressant efficacy and acceptability of several non-invasive brain stimulation techniques for the treatment of unipolar and bipolar depression.[2] Of the 42 randomised sham-controlled trials ($N = 1703$ patients) that investigated rTMS without co-initiation of another treatment, only three trials ($n = 49$ patients) recruited exclusively patients who were not treatment resistant. To the best of our knowledge, no randomised controlled trial has investigated the antidepressant efficacy of rTMS without co-initiation of pharmacotherapy in patients with medication-naive and/or first-onset depression. This highlights an important gap in the literature.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which enrolled 4041 outpatients with nonpsychotic depression, has shown that remission rates decline with each successive treatment step. In STAR*D, the first-line remission rate was 36.8% compared with 13% after the fourth treatment step. We found that only 5% of the studies ($n = 41$ patients) that were included in our meta-analysis and reported on the level of treatment resistance used an inclusion criterion of at least one failed medication trial. The majority of trials (64%; $n = 702$ patients) required participants to have failed at least two pharmacological treatments. Moreover, 33% of all participants included in this analysis stem from two trials that recruited patients with one to four failed antidepressant trials.

Given this empirical background, it seems evident that (a) there is a lack of trials investigating rTMS as a treatment for medication-naive nonpsychotic MDD and (b) that most studies to date primarily recruited patients with high degrees of treatment resistance, reflecting its historical roots as a potential therapeutic alternative to electroconvulsive therapy. This has unfavourably biased the clinical reputation of rTMS, leading many clinicians to believe that rTMS is a less powerful treatment modality for nonpsychotic MDD. Although the need for treatment alternatives in people with treatment resistance is considerable, it is also clear from our observations that the patient population included in randomised clinical trials of rTMS represents a group characterised by one of the most reliable clinical predictors of poor response to treatment: treatment resistance. Several studies have indicated lower degrees of treatment resistance to be a reliable predictor of increased response to rTMS, e.g.[3]. As some people do not tolerate pharmacotherapy due to undesired effects – including sexual dysfunction, weight gain and insomnia – we contend that trials with participants showing lower degrees of treatment resistance are needed. We also suggest that studies ought to investigate the comparative efficacy of rTMS and standard first-line pharmacological treatments, similar to the work comparing transcranial direct current stimulation with escitalopram.

Current barriers to a more widespread use of rTMS are the need for specialised equipment and infrastructure, associated costs, as well as the duration and labour intensity of treatment (typically administered 5 days a week for 4–6 weeks), with high-frequency rTMS requiring up to 37.5 min per treatment session. However, Blumberger *et al*[4] have recently shown in a large randomised trial including 414 participants that a 3 min theta-burst stimulation protocol is not statistically inferior to 37.5 min of high-frequency rTMS. This advance in reduced treatment duration could represent a key step in bringing non-invasive brain stimulation to a wider group of people with MDD. A more

https://doi.org/10.1192/bjp.2019.75 Published online by Cambridge University Press

widespread use of rTMS may be considered, especially for groups in which antidepressant pharmacodynamics may be cause for concern, e.g. during pregnancy or breastfeeding, in adolescents or in the context of somatic contraindications (e.g. pre-existing liver damage).

rTMS was first introduced in 1985 and studies in MDD have been conducted since the early 1990s, with rTMS receiving Food and Drug Administration approval for treatment-resistant depression in 2008. Although the decision to extend any treatment to a new patient population demands careful evaluation, findings to date suggest that rTMS has very few undesired effects. Moreover, although this finding cannot be extrapolated to treatment-naive patients, evidence from health-economic modelling suggests that rTMS may be cost-effective compared to pharmacotherapy in a non-treatment-resistant population.[5] Since future research may facilitate the accessibility of rTMS through portable devices or community care providers, we conclude that it is important to conduct clinical trials that investigate rTMS in less treatment-resistant and/or medication-naive patients with depression.

Maximilian Kiebs, PhD Student, Division of Medical Psychology, Department of Psychiatry, University of Bonn Medical Center, Germany; **René Hurlemann**, Head, Division of Medical Psychology; and Vice Head, Department of Psychiatry, University of Bonn Medical Center, Germany; **Julian Mutz**, Doctoral Researcher, Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

Correspondence: Julian Mutz, Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, Memory Lane, Camberwell, London SE5 8AF, UK. Email: julian.mutz@gmail.com.

First received 6 Sep 2018, final revision 11 Feb 2019, accepted 2 Mar 2019

Acknowledgements

We thank Professor Cynthia H.Y. Fu from the University of East London and the two anonymous reviewers for their helpful comments on an earlier draft of this paper.

References

1 Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ* 2019; **364**: l1079.

2 Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neurosci Biobehav Rev* 2018; **92**: 291–303.

3 Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* 2009; **34**: 522–34.

4 Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet* 2018; **391**: 1683–92.

5 Voigt J, Carpenter L, Leuchter A. Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure for major depressive disorder in newly diagnosed patients – A lifetime analysis. *PLoS ONE* 2017; **12**: e0186950.

https://doi.org/10.1192/bjp.2019.75 Published online by Cambridge University Press

4. Discussion with references

The research presented here aimed to investigate the effect of ECT on cognitive performance (Study 1), the role of treatment charge on cognitive performance (Study 2), the effect of social touch on reward processing (Study 3), the effect of individualized theta-burst stimulation on hippocampal activity (Study 4), and the composition regarding treatment refractoriness in clinical trials investigating non-invasive brain stimulation treatments (Study 5).

Specifically, as there is concern among clinicians and patients regarding negative effects of ECT on cognition, we investigated performance in five cognitive tasks from the Global ECT MRI Research Collaboration (GEMRIC), which has amassed clinical and neuroimaging data from ECT-treated patients worldwide (Oltedal et al. 2017). In study 1, we showed that electrode placement and treatment number impacted verbal fluency category (VFC), but contrary to our hypothesis, no significant effects were found for other cognitive measures. This finding does align with large studies and meta-analytical data showing VFC to be sensitive to the treatments' electrode position (Loef et al. 2024; Semkovska and McLoughlin 2010). Contrary to our expectations, we found no evidence of cognitive impairment associated with bitemporal (BT) electrode placement across any domain. This outcome sharply diverges from previous studies, which have consistently reported more pronounced cognitive deficits linked to BT electrode configurations (Kolshus et al. 2017; Martin et al. 2020). One potential explanation may be the relatively small sample size of patients with data on cognitive tasks after bitemporal treatment in the current GEMRIC dataset (Oltedal 2021). Critically, for fluency and trail making the sample size ranged between 30-38 and there is currently no data available for bitemporally treated patients on memory recall and autobiographical memory. Future data collection should fill this gap, as not only are memory deficits at the center of ongoing scientific debate, but the fear of experiencing them can lead to refusal or discontinuation of much-needed treatment (Obbels et al., 2017). Notably, while objective memory tends to improve more frequently than it declines when evaluated before and after treatment, most patients reported that ECT had a negative impact on their memory when asked to reflect on their experiences (Eggleston and Porter 2020; Sackeim 2014; Semkovska et al. 2012; Sigström et al. 2020; Vann Jones and McCollum 2019). To

advance and facilitate the collection of cognitive measures alongside clinical and neuroimaging data, participating GEMRIC sites should use robust cognitive measures with strong psychometrics and minimal subject burden by adopting the standardized cognitive test battery recommended here. This may help to provide a harmonized and comprehensive dataset which can be used to answer many unanswered questions in ECT treatment.

In addition to the effect of electrode configuration, the second study aimed to investigate the role of stimulus charge on cognitive performance after ECT. As hypothesized, we found that right unilateral (RUL) ECT was associated with marked autobiographical memory impairment and mean charge had a significant effect on Verbal Learning Memory Task (VLMT) delay score. However, there was no significant difference in overall cognitive function when compared to a healthy control group in the VLMT delay score and there was no association of mean charge with worsening autobiographical memory. Of the neuropsychological tasks included for exploratory analyses, only the One Touch Stockings of Cambridge Task (OTS), which assesses executive function, working memory, and planning, showed significant improvement of patient performance compared to the control sample. Apart of VLMT delay, no other neuropsychological task performance could be predicted from the treatments mean charge. As digital monitoring of the treatments technical parameters has only recently become possible, this study serves as a guide for selecting the task to be applied in investigating the role of seizure induction on post-treatment cognitive effects (Freundlieb et al. 2023). Still, it should be noted that the small sample size impairs the generalizability of these findings, which will have to be replicated in a larger cohort. In addition, the study does not provide an answer to how the charge and its respective electric field lead to impaired memory performance in the brain. As there is mixed evidence that ECT-induced hippocampal enlargement is associated with decreased memory performance, a larger GEMRIC sample should replicate such findings (Argyelan et al. 2021; Nordanskog et al. 2014; van Oostrom et al. 2018).

It has been suggested that not only treatment effects and sum scores of illness symptoms, but also individual symptoms should be further investigated. Thus, the third study aimed to determine whether the experience and neural processing of social touch

is altered in patients with MDD. As hypothesized, individuals with MDD showed greater aversion to interpersonal touch, found it less pleasurable, and showed reduced neural activation within the brain's reward circuitry compared to healthy individuals. Notably, we observed reduced responses to social touch in the nucleus accumbens, caudate nucleus, and putamen. Unexpectedly, the differences in neural activity within the nucleus accumbens and caudate nucleus remained unchanged even after treatment response. This finding suggests that reduced pleasure derived from social touch may contribute to the social isolation in patients suffering from MDD and that this effect may be rooted in an altered reward-associated processing of social stimuli in the brain. Nevertheless, diminished striatal activation in MDD does not definitively indicate that social touch is less rewarding (Poldrack 2006). Striatal activation could alternatively reflect cognitive biases or the perceived significance of social touch. Further research is needed to elucidate the precise mechanisms underlying reduced comfort ratings and processing of social touch in MDD.

To further investigate the personalization of treatments for MDD, we presented research regarding a novel and individualized target for iTBS (Study 4). By individually locating the region in the lateral parietal cortex (LPC) where the functional connectivity shows the greatest positive correlation to the hippocampus during an associative memory task, we assumed to be able to modulate hippocampal functional connectivity, improve cognitive performance, and enhance the antidepressant effect of iTBS. It was shown that stimulation of the novel parieto-hippocampal target compared with standard L-DLPFC target did lead to an increased hippocampus-DLPFC connectivity and a greater hippocampal activation during encoding. Additionally, there was a stronger association between hippocampal activity during encoding and improved performance on a spatial planning task. However, no significant difference was found between the sham and LPC add-on in terms of associative memory or clinical symptoms. Unexpectedly, seed-to-voxel analysis revealed no significant group effect on change of functional connectivity between the right hippocampus seed and the LPC-target. However, exploratory analysis revealed a significant change in functional connectivity between the right hippocampus seed and a prefrontal cluster topographically close to the DLPFC stimulation target potentially stemming from effects similar to bifocal stimulation. Although clinical symptoms did not improve in parallel with this effect, the findings point to a promising

avenue for future research focused on increasing connectivity in individuals with disorders in which prefrontal-hippocampal disconnection has been described, such as schizophrenia, memory disorders, and other conditions (Alemany-González et al. 2020; Bähner and Meyer-Lindenberg 2017; Li et al. 2015).

Finally, who is treated with TMS for the symptoms of MDD? Evidence from clinical trials comparing TMS to sham suggests that most patients whose symptoms have failed at least two prior pharmacological treatments are included in such studies. Only 5% of randomized controlled trials included in our supporting analysis involved patients who had not responded to at least one antidepressant. We found no studies in which patients received TMS as a first-line treatment or in a non-TRD population. Conversely, in most trials investigating the efficacy of pharmacological agents, only non-treatment refractory patients are included (Cipriani et al. 2018). Given that treatment refractoriness has been shown to be a negative predictor of treatment response across different types of treatment, this marked difference in inclusion criteria may have negatively impacted the clinical perception of rTMS, causing many clinicians to view it as a less effective treatment option for nonpsychotic MDD (Kautzky et al. 2019; Rush et al. 2006; Trevizol et al. 2020; Turkoz et al. 2023). As rTMS has proven to be an effective treatment in treatment-refractory depression, further research should investigate its potential as a first-line treatment and its competitive efficacy compared to currently used first-line treatments such as escitalopram regarding clinical symptoms and undesired effects (Mutz et al. 2019; O'Sullivan et al. 2024).

4.1 Limitations

The studies presented have several limitations that must be considered when interpreting the results. In study 1, significant differences exist regarding neurocognitive performance as well as variability in ECT administration protocols by site. Differences in subject selection, ECT devices, and procedures between sites introduced variability that we could not fully account for, potentially reducing our ability to detect longitudinal changes in cognitive performance. In addition, neurocognitive assessment protocols varied across sites, with some excluding key cognitive measures such as verbal learning and most sites not contributing autobiographical memory data. We also used education as a proxy for intelligence, which may not accurately capture premorbid cognitive abilities. In addition, we could not account for the time between the cognitive task and the last ECT. Although this was restricted to a maximum of one week, many cognitive effects have been shown to return to baseline in this time frame (Semkovska and McLoughlin 2010). These factors limit the strength of our conclusions regarding the absence of significant ECT-mediated cognitive effects. Standardized assessment protocols and larger samples are needed to reduce data variability in future studies.

Study 2 had several limitations, including a small sample size and the large number of neuropsychological assessments administered, some of which were exploratory in nature. In addition, we did not consider the effect of anesthetic dosage on ECT charge or assessed participants' subjective experience of cognitive impairment. The extensive test battery may have overwhelmed participants, potentially influencing their performance and contributing to incomplete data. Although the study explored understudied cognitive domains, a more focused approach with fewer tests, such as prioritizing the VLMT delay task, may yield stronger results in the future.

In study 3, although activation of the reward network during touch was consistent with some studies in healthy controls, other studies have not consistently shown such activation, suggesting that the rewarding aspects of social touch are not always clear. The highly standardized MRI environment, which may induce anxiety in patients with MDD, may limit the generalizability of our findings. Future studies should use more naturalistic social touch paradigms and include other reward related tasks to determine

whether the observed effects in MDD are specific to social touch or extend to non-rewarding stimulation.

Although study 4 used an innovative stimulation approach, it was limited by a small sample size and a high number of analyses. Variability in concomitant pharmacotherapy and the inclusion of participants with anxiety disorders may have introduced confounders that make it difficult to examine stimulation-dependent effects beyond doubt. Larger studies with more controlled conditions are needed to validate these findings. As the sample size of study 2 is rather small, these effects should be replicated in a larger sample as well.

Finally, study 5 only examined the inclusion criteria of randomized controlled trials. Non-randomized cohort or open label studies may have included patients with lesser degrees of treatment refractoriness. In addition, the analysis focused solely on the studies inclusion criteria. As only very few studies report the actual number of failed treatment attempts, it became clear that more thorough reporting standards regarding the patient's clinical background may be needed in the future.

4.2 Outlook for future research

While the studies presented primarily examined the effects of non-invasive brain stimulation on clinical, cognitive, and neural outcomes, most of the studies have in common that they were enabled by technological advances. Whether it's the use of large multi-site data collaborations (Study 1), the use of novel data collection software (Study 2), or the investigation of neural effects to guide symptom-specific treatments (Study 3) or improve their efficacy (Study 4). However heterogeneous the research projects may be in detail, they share a common goal. To identify clinical or neural patterns shared by individuals that could be used to reduce specific symptoms or better balance clinical and side effects. Depression is perhaps the most dramatic example of why this personalized approach to treatment is needed. Since symptom heterogeneity can mean that two patients may not even share a single symptom, we can expect that a. treatment options will have very different effects on each individual case and b. the neural effects associated with the disease may be very different between individuals due to symptom heterogeneity. Individual characteristics such as disability, employment status, age,

functional impairment, baseline depression, and outcome expectancy have been shown to be differentially associated with persistence of depressed mood or anxiety symptoms after treatment (Delgadillo et al., 2016). In addition, recent evidence suggests that identifying individuals who will derive the most clinical benefit or the least adverse effects from specific treatments could improve the effectiveness of psychological care or rTMS treatment (Cash et al., 2021; Delgadillo et al. 2021). However, most treatment guidelines do not provide differential/stratified treatment guidance, but rather a usual or stepped care approach for all patients with the same condition (Baune et al. 2024). This may be due to the complex longitudinal datasets and analyses required to develop stratified treatment guidance algorithms. Advancing a personalized approach to mental health will require robust developments in statistical modeling to unravel the intricate interactions of biological and clinical data, as well as the creation of digital, measurement-based tools to assess diagnosis, monitor treatment progress, evaluate response, and map disease trajectories (Baune 2020). Thus, it has been argued that the success of personalized psychiatry rests on technological advances (Perna et al., 2018).

The studies presented here provide a glimpse of what more personalized treatments might look like in the future. However, they all involve individual technological advances rather than collecting all potentially relevant patient data and feeding it into large, global repositories. Study 1 makes use of a highly digitized and global database of clinical, cognitive, and neural data, but the cognitive data shared by the globally dispersed sites are so heterogeneous that only a comparatively small sample remains when examining the tasks shared by most sites. Digital recording of ECT technical parameters has been shown to play a role in adverse cognitive effects (Study 2). However, these data are rarely collected by any of the centers and are not shared within GEMRIC. Until recently, there was no international data collaboration for rTMS, and data sets large enough to investigate personalized treatments are scarce. Therefore, larger and more naturalistic datasets of brain imaging and treatment-related data are needed to develop individualized treatment decision support tools. While there are a number of databases worldwide that focus on psychiatric disorders, very few contain longitudinal treatment data (Tanaka et al. 2024). The GEMRIC collaboration, combined with the recommendation for harmonized prospective data collection based on transparent scientific aspects, may provide a template for a process to achieve such datasets.

4.3 Conclusion

In summary, five studies examined specific symptoms and treatment effects that are common to many patients treated for depressive disorders. Brain stimulation treatments tend to be complex, and treatment administration as well as the data collected can vary considerably between sites. To this end, large cohorts such as GEMRIC need to guide which data are collected prospectively, as only homogeneously collected data sets provide the basis for robust multisite analyses. We have proposed such a battery for international multisite collaboration with a focus on strong psychometrics and minimal subject burden. In conclusion, the evidence for ECT effects on cognitive function underscores the importance of considering stimulus dose and neuropsychological outcomes. Altered reward network responses to social touch in MDD revealed key neural differences that may influence affective states in these patients. Individualized theta burst stimulation was demonstrated to modulate hippocampal activity and connectivity, potentially offering a personalized approach to future treatments. In addition, findings on repetitive transcranial magnetic stimulation (rTMS) suggest a research gap in non-treatment-refractory depression and encourage further exploration of its use in broader clinical populations. Together, these studies highlight the need for continued research to refine brain stimulation therapies, optimize their efficacy, and minimize cognitive side effects.

4.4 References

Alemany-González M, Gener T, Nebot P, Vilademunt M, Dierssen M, Puig MV. Prefrontal–hippocampal functional connectivity encodes recognition memory and is impaired in intellectual disability. Proceedings of the National Academy of Sciences 2020; 117(21): 11788–11798

Argyelan M, Lencz T, Kang S, Ali S, Masi PJ, Moyett E, Joanlanne A, Watson P, Sanghani S, Petrides G, Malhotra AK. ECT-induced cognitive side effects are associated with hippocampal enlargement. Transl Psychiatry 2021; 11(1): 516

Bähner F, Meyer-Lindenberg A. Hippocampal–prefrontal connectivity as a translational phenotype for schizophrenia. European Neuropsychopharmacology 2017; 27(2): 93–106

Baune BT. Chapter 1 - What is personalized psychiatry and why is it necessary? In: Baune BT, editor. Personalized Psychiatry 2020. p. 1–2.

Baune BT, Fromme SE, Kiebs M, Hurlemann R. Klinisches Management der therapieresistenten Depression. Nervenarzt 2024; 95(5): 416–422

Cash RFH, Cocchi L, Lv J, Wu Y, Fitzgerald PB, Zalesky A. Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. Hum Brain Mapp 2021; 42(13): 4155–4172

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet 2018; 391(10128): 1357–1366

Delgadillo J, Ali S, Fleck K, Agnew C, Southgate A, Parkhouse L, Cohen ZD, DeRubeis RJ, Barkham M. Stratified Care vs Stepped Care for Depression: A Cluster Randomized Clinical Trial. JAMA Psychiatry 2022; 79(2): 101–108

Delgadillo J, Moreea O, Lutz W. Different people respond differently to therapy: A demonstration using patient profiling and risk stratification. Behaviour Research and Therapy 2016; 79: 15–22

Eggleston K, Porter R. Subjective memory impairment after electroconvulsive therapy – potentially modifiable? BJPsych open 2020; 6(3): e38

Freundlieb N, Schneider E, Brühl A, Kiebs M. GENET-GPD: A documentation tool to digitally collect longitudinal ECT treatment data and associated biosignals. Brain Stimulation 2023; 16(4): 1173–1175

Kautzky A, Dold M, Bartova L, Spies M, Kranz GS, Souery D, Montgomery S, Mendlewicz J, Zohar J, Fabbri C, Serretti A, Lanzenberger R, Dikeos D, Rujescu D, Kasper S. Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. Acta Psychiatrica Scandinavica 2019; 139(1): 78–88

Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. Psychol Med 2017; 47(3): 518–530

Li M, Long C, Yang L. Hippocampal-Prefrontal Circuit and Disrupted Functional Connectivity in Psychiatric and Neurodegenerative Disorders. BioMed Research International 2015; 2015(1): 810548

Loef D, van Eijndhoven P, van den Munckhof E, Hoogendoorn A, Manten R, Spaans H-P, Tendolkar I, Rutten B, Nuninga J, Somers M, van Dellen E, van Exel E, Schouws S, Dols A, Verwijk E. Pre-treatment predictors of cognitive side-effects after treatment with electroconvulsive therapy in patients with depression: A multicenter study. J Affect Disord 2024; 349: 321–331

Martin D, Katalinic N, Hadzi-Pavlovic D, Ingram A, Ingram N, Simpson B, McGoldrick J, Dowling N, Loo C. Cognitive effects of brief and ultrabrief pulse bitemporal electroconvulsive therapy: a randomised controlled proof-of-concept trial. Psychological Medicine 2020; 50(7): 1121–1128

Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ 2019; : l1079

Nordanskog P, Larsson MR, Larsson E-M, Johanson A. Hippocampal volume in relation to clinical and cognitive outcome after electroconvulsive therapy in depression. Acta Psychiatr Scand 2014; 129(4): 303–311

Obbels J, Verwijk E, Bouckaert F, Sienaert P. ECT-Related Anxiety: A Systematic Review. The Journal of ECT 2017; 33(4): 229

Oltedal L. Data release 3.2. 2021 [cited 2023]; Available from: https://osf.io/yp2g4/

Oltedal L, Bartsch H, Sørhaug OJE, Kessler U, Abbott C, Dols A, Stek ML, Ersland L, Emsell L, van Eijndhoven P, others. The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. NeuroImage: Clinical 2017; 14: 422–432

Perna G, Grassi M, Caldirola D, Nemeroff CB. The revolution of personalized psychiatry: will technology make it happen sooner? Psychol. Med. 2018; 48(5): 705–713

van Oostrom I, van Eijndhoven P, Butterbrod E, van Beek MH, Janzing J, Donders R, Schene A, Tendolkar I. Decreased Cognitive Functioning After Electroconvulsive Therapy Is Related to Increased Hippocampal Volume: Exploring the Role of Brain Plasticity. J ECT 2018; 34(2): 117–123

O'Sullivan SJ, Buchanan DM, Batail J-MV, Williams NR. Should rTMS be considered a first-line treatment for major depressive episodes in adults? Clin Neurophysiol 2024; 165: 76–87

Poldrack RA. Can cognitive processes be inferred from neuroimaging data? Trends in Cognitive Sciences 2006; 10(2): 59–63

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163(11): 1905–1917

Sackeim HA. Autobiographical Memory and Electroconvulsive Therapy: Do Not Throw Out the Baby. The Journal of ECT 2014; 30(3): 177–186

Semkovska M, McLoughlin DM. Objective Cognitive Performance Associated with Electroconvulsive Therapy for Depression: A Systematic Review and Meta-Analysis. Biological Psychiatry 2010; 68(6): 568–577

Semkovska M, Noone M, Carton M, McLoughlin DM. Measuring consistency of autobiographical memory recall in depression. Psychiatry Research 2012; 197(1–2): 41–48

Sigström R, Nordenskjöld A, Juréus A, Clements C, Joas E, Pålsson E, Landén M. Long-term subjective memory after electroconvulsive therapy. BJPsych Open 2020; 6(2): e26

Tanaka SC, Kasai K, Okamoto Y, Koike S, Hayashi T, Yamashita A, Yamashita O, Johnstone T, Pestilli F, Doya K, Okada G, Shinzato H, Itai E, Takahara Y, Takamiya A, Nakamura M, Itahashi T, Aoki R, Koizumi Y, Shimizu M, Miyata J, Son S, Aki M, Okada N, Morita S, Sawamoto N, Abe M, Oi Y, Sajima K, Kamagata K, Hirose M, Aoshima Y, Hamatani S, Nohara N, Funaba M, Noda T, Inoue K, Hirano J, Mimura M, Takahashi H, Hattori N, Sekiguchi A, Kawato M, Hanakawa T. The status of MRI databases across the world focused on psychiatric and neurological disorders. Psychiatry and Clinical Neurosciences 2024; 78: 563–579

Trevizol AP, Downar J, Vila-Rodriguez F, Thorpe KE, Daskalakis ZJ, Blumberger DM. Predictors of remission after repetitive transcranial magnetic stimulation for the treatment of major depressive disorder: An analysis from the randomised non-inferiority THREE-D trial. EClinicalMedicine 2020; 22: 100349

Turkoz I, Nelson JC, Wilkinson ST, Borentain S, Macaluso M, Trivedi MH, Williamson D, Sheehan JJ, Salvadore G, Singh J, Daly E. Predictors of response and remission in patients with treatment-resistant depression: A post hoc pooled analysis of two acute trials of esketamine nasal spray. Psychiatry Research 2023; 323: 115165

Vann Jones S, McCollum R. Subjective memory complaints after electroconvulsive therapy: systematic review. BJPsych Bull 2019; 43(2): 73–80

5. Acknowledgements

For as long as I can remember, my mother has been by my side, guiding me and fighting for my future, which must have been very hard and exhausting at times. Without her, I would not have made this journey to write these last lines of my thesis. This thesis and all my gratitude for everything you have done for me belongs to you. This thesis is for you. I am so grateful and happy to have chosen and being able to choose to be a scientist. Even though there have been many hardships and it really feels like almost every day a new problem arises for every problem solved, most days I cannot believe how much I enjoy what I do. Doing research with students, teaching, coming up with new things and ways to find out new things, feeling the gratitude and appreciation of patients or people interested in our research. My own daily escape room that I never want to escape. I am here because of you.

Still, there have been others who have believed in me and let me know that they feel I am on the right track. My father always believed in me, I know that, and I thank you for that. Some of those late evenings with pasta secondo la ricetta della casa were really helpful in getting back on track. Discussing current politics, sharing our objection to all Nazi, ultra right-wing attitudes and any kind of backwards conservatism. Those times were an anchor in the endless vastness of possibilities of what to do with my life. You have been a guide and a pillar of strength all these years.

Since my first day at university, things were really different from school. I had a strong feeling of having arrived, sometimes it even felt like a second home. Most of this is due to the wonderful and amazing people I encountered at the different universities I attended. Most recently, my Ph.D. supervisor René Hurlemann has repeatedly put his trust in me. Although this must have been difficult at times, he never wavered and even gave me a future in academia when many research results were still on the horizon. Even after having had several disagreements, not only has he never been in any way resentful or vindictive, I never felt that his confidence in my abilities was in question, even when I questioned it myself. Thank you for supporting me all these years, thank you for having and supporting a shared vision. Quitting a PhD project after 7 months of work, moving to Bonn and starting all over again often felt questionable, but it turned out to be one of the best decisions of my life (I have to thank my mother again for supporting

me in this decision, even though it meant losing her beloved Kiel). René, thank you! I would also like to thank Prof. Dr. Alexandra Philipsen for giving me the freedom and support to also continue our research in Bonn.

I believe that working at this level of independence, to be able to do research in my own way and time was only possible because of my extraordinary educators. The first and foremost scientific teacher and role model, to whom I am extremely grateful, is Dr. Thorsten Albrecht, Postdoc at the Department of Experimental Psychology in Göttingen and my "master". Thorsten, I have learned so much from you, and this knowledge, integrity, and way of approaching research and teaching has been my guide and aid at many points in my career. Even in difficult times we have kept in touch and I am so proud to call you my friend. It is strange to have your role model as a friend, but Nautibar has surely helped a lot with that. I know you don't really like this kind of praise, so I hope you'll never read these lines, but if you ever do: sorry not sorry. I would also like to mention Prof. Dr. Uwe Mattler, who taught me so many skills, one of which will always stand out: Integrity. I learned a great deal regarding sustainable ways to do research from you and benefited a lot from your in-depth feedback. I still remember your detailed, point-by-point feedback regarding my master's thesis defense. This and your other feedback helped me so much on my way. Generally speaking, studying psychology in Göttingen turned out to be one of the best decisions I ever made. There were so many people who helped me through difficult times and paved the way for me to become a researcher. A job I never thought I would do, but one I now enjoy so much. I like to thank Björn Albrecht, who taught me so much about neuroscience and provided me with many theoretical as well as practical lab skills. Without Franziska Niemeyer and her tutoring for the rather difficult Statistics I & II of Prof. Willi Hager, in addition to her work as a private tutor (which I desperately needed), I don't think I would have made it this far. Thank you very much. I would also like to thank my friends who believed in me and assured me that I "had to" go into research, even though their confidence surprised me most times. Julian Mutz was the most insistent that I stay in academia. As he is perhaps the most focused, effective, and organized researcher I have ever met, this means a lot. It has been a great pleasure to work with you all these years. Thank you for encouraging me to stay in academia and for being a close personal friend. Marie Coenjaerts has also consistently encouraged me to stay in science and I thank you so much for that. Before

he became as busy as he is today, Gunnar Gutsche was also a strong motivator for me to go into research. Discussing science in the BarRacuda in the middle of the night was a real pleasure. Even at times when I questioned my choices or our current academic system, talking science with people has always let me regain confidence. Clemens Mielacher, I am so thankful that you were always up for discussion, visions and shared research. More recently, I am extremely grateful for the scholarly exchange with Benjamin Selaskowski, who was not only one of the few people to express his appreciation for some of my earlier work, but also to develop a shared vision. Every time we talk, every time we discuss research, I am reminded of what I enjoy about this work. Even though we work in a higher education system where being a "good teacher" not only has practically no rewarding effects on a young researcher's career, but is even used as a well-known euphemism for being a bad researcher at some top universities, teaching has always been a real pleasure for me, and I think this has a lot to do with Reinhart Wolff, Professor of Theory and History of Pedagogy during my time at the Alice-Salomon University in Berlin. I have never again attended a more captivating lecture then the ones held by you, Prof. Reinhart Wolff. I am very grateful.

Not only because of Prof. Wolff, the Alice-Salomon University (ASH) was truly a place where I felt at home (probably too much at times). The people I met, the knowledge I gained there. None of the self-questioning moments about starting a full course in psychology after having already spent over three years at ASH will ever come close to how I have grown as an individual during my time at this institution. Although we are no longer in contact, Tobias Berger is a good friend and a source of my first real critical thinking, my life would be not the same without you. Thank you for always asking the right questions and letting me into your life. I will never forget it. I remember it vividly. My time in Bonn would not have been the same without my colleague Marcel Schulze who is so much more than a colleague. Above and beyond any fantastic research or philosophical controversies we have had, at times it felt as if you were the only one actually happy to see me in Bonn. I cannot adequately express here how much I enjoy having you as friend.

To all of my other friends who did not directly support this research and instead have rather been fairly annoying by repeatedly asking, most times at the very first sight of me, when my thesis would be finished, I thank you very much for your strong interest in my

work. Without you, this process may have been quicker, but surely much less enjoyable. As I remember so many fantastic moments we shared together, as always, I really hope to see you soon.
Finally, I remember my fellow-student in Göttingen Alexandra Wehrmann. A truly wonderful, kind and good-natured soul who was brutally killed on the island of Juist in 2013. Alexandra, with whom I gave student presentations only a short time before she became a victim of femicide: I will never forget you, and I am sure I speak for all my fellow students in Göttingen: You will always be in our thoughts.

5.1 Acknowledgements (deutsche Sprache)

Solange ich mich erinnern kann, war meine Mutter an meiner Seite, kämpfte für meine Zukunft und war meine Beraterin, was manchmal sehr schwierig und anstrengend gewesen sein muss. Ohne sie hätte ich diese Reise nicht geschafft. Diese Arbeit und meine ganze Dankbarkeit für alles, was Du für mich getan hast, gehört Dir. Diese Arbeit ist für Dich. Ich bin so dankbar und glücklich, dass ich den Beruf des Wissenschaftlers gewählt habe und wählen konnte. Auch wenn es viele Schwierigkeiten gab und ich wirklich fast jeden Tag das Gefühl habe, dass für jedes gelöste Problem ein neues auftaucht, kann ich an den meisten Tagen trotzdem kaum glauben, wie viel Spaß mir meine Arbeit macht. Mit Studierenden zu forschen, zu lehren, neue Wege zu finden, neue Dinge zu entdecken, die Dankbarkeit und Wertschätzung von Patienten oder Menschen zu spüren, die sich für unsere Forschung interessieren. Mein eigener täglicher Escape Room, aus dem ich nie entkommen möchte. Ich bin deinetwegen hier.

Aber es gab auch andere, die an mich geglaubt und mir oft zu verstehen gegeben haben, dass sie annehmen, dass ich auf dem richtigen Weg bin. Mein Vater hat immer an mich geglaubt, das weiß ich, und dafür danke ich Dir. Einige dieser späten Abende mit Pasta secondo la ricetta della casa waren wirklich hilfreich, um wieder auf den richtigen Weg zu kommen. Unsere Diskussionen über Politik, unsere Einigkeit in der Ablehnung aller Nazis, rechtsradikaler Einstellungen und jeder Form von rückwärtsgewandtem

Konservatismus. Diese Abende waren ein Anker im scheinbar endlosen Meer der Möglichkeiten. Du warst mir in all diesen Jahren ein Wegweiser und eine Stütze.

Seit meinem ersten Tag an der Universität war alles anders als in der Schule. Ich hatte das starke Gefühl, angekommen zu sein. Manchmal fühlte es sich sogar wie ein zweites Zuhause an. Das liegt vor allem an den wunderbaren und außergewöhnlichen Menschen, die ich an den verschiedenen Universitäten kennengelernt habe. Vor allem mein Doktorvater René Hurlemann hat mir immer wieder sein Vertrauen geschenkt. Auch wenn es schwierig war, hat er nie gezögert und mir auch dann noch eine Zukunft in der Wissenschaft gegeben, als viele Forschungsergebnisse noch in weiter Ferne lagen. Selbst nach etlichen Meinungsverschiedenheiten war er nie nachtragend oder rachsüchtig, ich hatte nie das Gefühl, dass sein Vertrauen in meine Fähigkeiten in Frage gestellt war, auch wenn ich es selbst in Frage stellte. Danke für die Unterstützung in all den Jahren und für unsere gemeinsame Vision. Ein Promotionsprojekt nach 7 Monaten Arbeit abzubrechen, nach Bonn zu ziehen und von vorne anzufangen, erfüllte mich nicht selten mit Sorge, aber es hat sich als eine der besten Entscheidungen meines Lebens herausgestellt (an dieser Stelle möchte ich noch einmal meiner Mutter danken, dass sie mich bei dieser Entscheidung unterstützt hat, auch wenn es bedeutete, ihr geliebtes Kiel darüber zu verlieren). René, vielen Dank! Ich möchte mich auch bei Prof. Dr. Alexandra Philipsen dafür bedanken, dass sie mir den Freiraum und die Unterstützung gegeben hat, unsere Forschung auch in Bonn fortzusetzen.
Ich glaube, dass ich diesen Grad an Unabhängigkeit, um auf meine eigene Weise und zu meiner eigenen Zeit zu forschen, nur dank meiner außergewöhnlichen Lehrer:innen erreichen konnte. Mein wichtigster wissenschaftlicher Lehrer und persönliches Vorbild, dem ich sehr dankbar bin, ist Thorsten Albrecht, Postdoc in der Abteilung für Experimentelle Psychologie in Göttingen und mein "Meister". Thorsten, ich habe so viel von Dir gelernt, deine Integrität und deine Art zu forschen und zu lehren, haben mich an vielen Stellen meiner Karriere geleitet und mir geholfen. Auch in schwierigen Zeiten sind wir in Kontakt geblieben, und ich bin stolz darauf, Dich meinen Freund nennen zu dürfen. Es ist seltsam, sein Vorbild zum Freund zu haben, aber die Nautibar hat dabei sehr geholfen. Ich weiß, dass Du diese Art von Anerkennung nicht wirklich magst, also hoffe ich, dass Du diese Zeilen nie lesen wirst, aber falls doch: sorry not sorry. Ich möchte

auch Prof. Dr. Uwe Mattler erwähnen, der mir so viele Fähigkeiten beigebracht hat, von denen eine immer hervorstechen wird: Integrität. Ich habe von Ihnen viel über belastbare Forschung gelernt und von Ihrem ausführlichen Feedback profitiert. Ich erinnere mich noch gut an Ihr detailliertes, Punkt für Punkt ausgearbeitetes Feedback bezüglich der Verteidigung der Masterarbeit. Dieses und Ihre anderen Feedbacks haben mir auf meinem Weg sehr geholfen.

Alles in allem war das Psychologiestudium in Göttingen eine der besten Entscheidungen, die ich je getroffen habe. Es gab so viele Menschen, die mir durch schwierige Zeiten geholfen und mir den Weg in die Forschung geebnet haben. Ein Beruf, von dem ich nie gedacht hätte, dass ich ihn einmal ausüben würde, der mir jetzt aber so viel Freude bereitet. Ich möchte mich bei Björn Albrecht bedanken, der mir so viel über Neurowissenschaften beigebracht und viel praktisches Laborwissen vermittelt hat. Ohne Franziska Niemeyer und ihre Nachhilfe für die recht schwierigen Statistik I und II Vorlesungen von Prof. Willi Hager, zusätzlich zu ihrer Arbeit als Tutorin (welche ich dringend brauchte), wäre ich nicht so weit gekommen. Vielen Dank! Ich möchte mich auch bei meinen Freunden bedanken, die an mich geglaubt haben und mir versichert haben, dass ich in die Forschung gehen "muss", auch wenn mich ihr Vertrauen oft überrascht hat. Julian Mutz war derjenige, der am meisten darauf bestanden hat, dass ich in der Wissenschaft bleibe. Da er vielleicht der fokussierteste, effizienteste und am besten organisierte Forscher ist, den ich je kennengelernt habe, bedeutet mir dieses Kompliment sehr viel. Es war und ist ein großes Vergnügen, all die Jahre mit Dir zusammenzuarbeiten. Danke, dass du mich ermutigt hast, in der Wissenschaft zu bleiben, und dass Du ein enger persönlicher Freund bist. Auch Marie Coenjaerts hat mich immer wieder ermutigt, in der Wissenschaft zu bleiben, und dafür danke ich auch Dir sehr. Gunnar Gutsche war, bevor er so viel zu tun hatte wie heute, ein großer Motivator für mich, in die Wissenschaft zu gehen. Es war eine wahre Freude, mitten in der Nacht im BarRacuda über Forschung zu diskutieren. Auch in Zeiten, in denen ich meine Entscheidungen oder unser derzeitiges akademisches System in Frage gestellt habe, hat mir das Gespräch mit anderen Wissenschaftler:innen immer wieder neue Zuversicht gegeben. Clemens Mielacher, ich bin Dir sehr dankbar, dass Du immer offen warst für Diskussionen, Visionen und gemeinsame Forschung. In jüngster Zeit bin ich sehr dankbar für den wissenschaftlichen Austausch mit Benjamin Selaskowski, der nicht

nur als einer der wenigen seine Wertschätzung für einige meiner früheren Arbeiten zum Ausdruck gebracht hat, sondern auch eine gemeinsame Vision entwickelt hat. Jedes Mal, wenn wir uns unterhalten, jedes Mal, wenn wir über Forschung sprechen, werde ich daran erinnert, was mir an dieser Arbeit gefällt.

Obwohl wir in einem Hochschulsystem arbeiten, in dem ein "guter Lehrer" zu sein nicht nur so gut wie keine Auswirkungen auf die Karriere eines jungen Forschers hat, sondern an einigen Spitzenuniversitäten sogar als geflügeltes Wort für einen schlechten Forscher verwendet wird, habe ich immer sehr gerne unterrichtet, und ich glaube, das hat viel mit Reinhart Wolff zu tun, Professor für Theorie und Geschichte der Pädagogik während meiner Zeit an der Alice-Salomon-Hochschule in Berlin. Ich habe nie wieder so fesselnde Vorlesungen gehört wie Ihre. Dafür bin ich Ihnen sehr dankbar.

Nicht nur wegen Prof. Wolff war die Alice Salomon Hochschule (ASH) ein Ort, an dem ich mich wirklich zu Hause gefühlt habe (vielleicht manchmal ein bisschen zu viel wie Hause). Die Menschen, die ich dort getroffen habe, das Wissen, das ich dort erworben habe. Keiner der Momente, in denen ich gezweifelt habe, ob ich nach mehr als drei Jahren an der ASH ein Vollstudium der Psychologie hätte beginnen sollen, wird jemals an die Entwicklung herankommen, die ich als Person während meiner Zeit an der ASH gemacht habe. Obwohl wir keinen Kontakt mehr haben, ist Tobias Berger ein guter Freund und die Quelle meines ersten wirklich kritischen Denkens, mein wissenschaftliches Leben wäre nicht dasselbe ohne Dich. Danke, dass Du die richtigen Fragen gestellt hast und mich an Deinem Leben hast teilhaben lassen. Das werde ich nie vergessen. Meine Zeit in Bonn wäre nicht die gleiche ohne meinen Kollegen Marcel Schulze, der so viel mehr ist als ein Kollege. Neben all den fantastischen Forschungsdebatten oder philosophischen Kontroversen, hatte ich manchmal das Gefühl, dass Du der Einzige warst, der sich wirklich gefreut hat, wenn ich nochmal in Bonn aufgetaucht bin. Ich kann hier nicht angemessen ausdrücken, wie schön es ist, Dich als Freund zu haben. Allen anderen Freunden, die diese Forschungsarbeit nicht direkt unterstützt haben, sondern sich eher durch ständiges Nachfragen, wann denn meine Doktorarbeit fertig sei, hervorgetan haben, danke ich herzlich für ihr großes Interesse an meiner Arbeit. Ohne Euch wäre dieser Prozess vielleicht schneller, aber sicher weniger episch verlaufen. Ich erinnere mich an so viele tolle Momente, die wir gemeinsam erlebt haben und hoffe wie immer, Euch alle bald wiederzusehen.

Schließlich erinnere ich mich an meine Kommilitonin Alexandra Wehrmann aus Göttingen. Eine wirklich wunderbare, freundliche und gute Seele, die 2013 auf Juist brutal umgebracht wurde. Alexandra: Ich werde Dich nie vergessen und bin mir sicher, dass ich damit im Namen aller unserer Kommiliton:innen in Göttingen spreche: Du wirst immer in unseren Gedanken sein.