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DISSERTATION

Neurostructural targets and predictors of response to interventional antidepressant treatment

Neurostrukturelle Ziele und Prädiktoren für das Ansprechen auf interventionelle antidepressive Therapien

zur Erlangung des akademischen Grades Medical Doctor – Doctor of Philosophy in Medical Neurosciences (MD/PhD in Medical Neurosciences)

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von

Ana Lucía Herrera Meléndez

aus Tampico, Mexiko

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LIST OF ABBREVIATIONS

ACC anterior cingulate cortex 14

CBT cognitive behavioral therapy 12

CHB Charité–Universitätsmedizin Berlin 15

C-SVM linear kernel support vector machine 17

ECT electroconvulsive therapy 9

EMA European Medicines Agency 9

FDA Food and Drug Administration 9

FWHM full width at half maximum 16

GLM general linear model 33

GMV gray matter volume 14

GWAS genome-wide association studies 12

HAMD Hamilton Depression Rating Scale 15

MADRS Montgomery-Asberg Depression Rating Scale 15

MDD Major depressive disorder 8

MRI magnetic resonance imaging 13

MVPA multivariate pattern analysis 17

MVPC multivariate pattern classification 17

NAc Nucleus Accumbens 17

NIBS non-invasive brain stimulation 9

NMDA N-methyl-D-aspartate 10

PCB percent change from baseline 15

PFC dorsolateral prefrontal cortex 14

rACC rostral anterior cingulate cortex 19

ROI region of interest 14

SD standard deviation 19

ABSTRACT

The high variability in remission rates highlights the importance of optimizing treatment response in depression. Interventional psychiatry treatments are an option for patients who have been unable to achieve remission with established therapies. Their efficacy could be further improved by identifying subgroups of individuals more likely to respond based on specific features. Moreover, interventional therapies could boost classical behavioral interventions. The aim of the present dissertation was to investigate antidepressant-response predictors to interventional psychiatry techniques and the potential of neuromodulation to enhance the effect of psychotherapy while providing a better understanding of the neural mechanisms and treatment-related effects on brain structure.

In the first study we used voxel-based morphometry to investigate structural predictors of response in 33 depressed patients treated with a single sub-anesthetic ketamine infusion. We found that greater baseline gray matter volume (GMV) of the bilateral rostral anterior cingulate cortex (rACC) significantly predicts symptom reduction after ketamine. It could be speculated that ketamine acts by enhancing a well-preserved rACC, thus promoting adaptive self-referential processing and cognitive control. In the second study, we applied multivariate pattern analysis techniques to baseline data of 71 patients treated with ECT. sMRI-based classification of ECT responders and non-responders reached an accuracy of 69 %, with a cluster in the right anterior parahippocampal gyrus (aPHCr) contributing the most to the classification. A post-hoc regression-based prediction analysis on continuous symptom improvements showed a significant relationship between smaller GMV on the aPHCr and treatment response. These results are in line with previous reports that ECT acts by promoting neurogenesis in temporal structures. Finally, we conducted a double-blind, placebo-controlled randomized clinical trial to investigate whether the efficacy of cognitive behavioral therapy (CBT) can be enhanced by concurrent transcranial direct current stimulation (tDCS). We set three groups: 53 patients to CBT alone, 48 to CBT+tDCS, and 47 to CBT+sham-tDCS. The interventions showed to be safe and reduced depressive symptoms with a significant effect over time. However, we found no significant interactions between group and time.

The findings suggest structural predictors may be specific to treatment mechanisms (such as enhancing well-preserved structures or facilitating neurogenesis). A better understanding of these would enable the design of further synergistic interventions that target specific neurobiological

processes. Using a combination of clinical variables, functional brain imaging, laboratory data, and genetic data, it may be possible to gain a systematic understanding of treatment effects.

ZUSAMMENFASSUNG

Die hohe Variabilität der Remissionsraten fordert eine Optimierung der Behandlungswirkung bei Depressionen. Interventionelle psychiatrische Behandlungen sind eine Option für Patienten, bei denen klassischen Therapien keine Remission bewirkt. Ihre Wirksamkeit könnte durch die Ermittlung von Personengruppen, die aufgrund ihrer Merkmale eher ansprechen, verbessert werden. Auch könnten interventionelle Therapien wiederum die klassischen kognitiven Interventionen verstärken. Das Ziel der vorliegenden Dissertation war, Prädiktoren einer Antidepressiv-Wirkung für interventionelle Psychiatrietechniken und das Potenzial der Neuromodulation zur Wirkungsverstärkung der Psychotherapie zu untersuchen und ein besseres Verständnis der neuronalen Mechanismen und der Auswirkungen der Behandlung auf die Gehirnstruktur zu gewinnen.

Die erste Studie untersuchte mit voxel-basierter Morphometrie strukturelle Response-Prädiktoren bei 33 depressiven Patienten nach Gabe einer subanästhetischen Ketamin-Infusion. Ein größeres Volumen der grauen Substanz (GMV) des bilateralen rostralen anterioren cingulären Kortex (rACC) konnte eine Symptomreduktion nach Ketamin signifikant vorhersagen. Möglicherweise wirkt Ketamin durch Verstärkung eines gut erhaltenen rACC und fördert adaptive selbstreferenzielle Verarbeitung sowie kognitive Kontrolle. Die zweite Studie wendete multivariate Musteranalyseverfahren auf Ausgangsdaten von 71 mit EKT behandelte Patienten an. Die sMRI-basierte Klassifizierung von EKT-Respondern und Nicht-Respondern erreichte eine Genauigkeit von 69 %. Ein Cluster im rechten anterioren parahippocampalen Gyrus (aPHCr) trug am meisten zur Klassifizierung bei. Eine regressionsbasierte Post-hoc-Vorhersageanalyse zur kontinuierlichen Symptomverbesserung zeigte eine signifikante Korrelation zwischen einer geringeren GMV im aPHCr und einer kontinuierlichen Symptomverbesserung. Diese Ergebnisse passen zu früheren Berichten, wonach die EKT die Neurogenese temporaler Strukturen fördert. Schließlich wurde eine doppelblinde, placebokontrollierte, randomisierte klinische Studie durchgeführt, zu untersuchen, ob die Wirksamkeit der kognitiven Verhaltenstherapie (CBT) durch gleichzeitige transkranielle Gleichstromstimulation (tDCS) verbessert werden kann. Es gab 3 Gruppen: 53 Patienten nahmen an CBT allein, 48 an CBT+tDCS und 47 an CBT+sham-tDCS teil. Die Interventionen führten zu einer signifikanten Reduktion der depressiven Symptome. Wir fanden jedoch keine signifikanten Interaktionen zwischen Gruppe und Zeit.

Die Ergebnisse deuten darauf hin, dass strukturelle Prädiktoren spezifisch für die Behandlungsmechanismen sein können. Eine Kombination aus klinischen Variablen,

funktioneller Bildgebung des Gehirns, Labordaten und genetischen Daten könnte ein systematisches Verständnis der Behandlungseffekte ermöglichen, um weitere synergistische Interventionen zu entwickeln, die auf spezifische neurobiologische Prozesse abzielen.

I. SYNOPSIS

1. INTRODUCTION

While there are many effective treatments for major depressive disorder (MDD), there is considerable clinical response heterogeneity. Unfortunately, relatively little progress has been made in improving the efficacy of established therapies. In general, it is accepted that antidepressant treatment will fail to achieve remission in approximately one out of three patients (Rush et al., 2006). Furthermore, a high percentage of patients don't or only partially respond to psychological interventions, are unable to fully recover following treatment or show high relapse rates (Dedoncker et al., 2021; Steinert et al., 2014).

Although there is no universally accepted definition of treatment-resistant depression (TRD), the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) define TRD once two antidepressant products of different pharmacological classes, used for a sufficient amount of time and at adequate dose have been unsuccessful. Despite adequate treatment, not attaining remission poses a serious challenge to clinicians and patients alike. The symptoms of treatment-resistant depression are accompanied by poor social function, decreased physical health, suicidal thoughts, and increased medical care utilization (Jaffe et al., 2019). Moreover, the overall healthcare costs and productivity loss of TRD are almost twice as high as those with MDD (Jaffe et al., 2019).

Increasing diagnostic and therapeutic advances have led to the emergence of interventional therapies, which are a natural progression when standard treatments fail and patients become resistant to treatment (Williams et al., 2014). The term interventional psychiatry was originally proposed for invasive and non-invasive brain stimulation techniques. However, it also extends to novel pharmacological interventions (e.g. esketamine or ketamine administration), surgical procedures (e.g. deep brain stimulation, vagus nerve stimulation), enhanced psychotherapy (e.g. psychedelic-assisted) and complex digital interventions (e.g. cognitive control training during brain stimulation) (Padberg et al., 2022). The present dissertation investigated three of these techniques: electroconvulsive therapy (ECT) subanesthetic ketamine administration and tDCS-augmented psychotherapy.

Non-invasive brain stimulation (NIBS) is a technique which allows transcranial modulation of specific brain areas and large-scale networks linked to them (Boes et al., 2018a). ECT is the most effective and evidence-based NIBS technique (Brakemeier et al., 2014; Merkl et al., 2009; Merkl et

al., 2011; Stippl et al., 2020). ECT has been consistently found to be more effective at treating depression symptoms than simulated ECT, placebo, and pharmacotherapy, according to meta-analyses conducted over the past three decades (Pinna et al., 2018). Historically, the adverse cognitive effects of ECT and the propensity for relapse were the two main limitations that would restrict its use. Both limitations have been considerably addressed in recent years, optimizing several parameters such as electrode placement, pulse width, and pulse shape. Modern ECT is performed under general anesthesia and usually administered as unilateral ultra-brief pulse stimulation. This approach reduces cognitive side effects while delivering meaningful efficacy (Sackeim, 2017).

Another NIBS technique, transcranial direct current stimulation (tDCS), has drawn attention due to its ease of use and good tolerability (Herrera-Melendez et al., 2020). Stimulation involves low amplitude direct current (usually ≤2 mA) flowing between electrodes placed on the scalp. The anode (i.e. the positively charged electrode) has shown to locally increase cortical excitability; on the other hand, an inhibitory effect is observed through the cathode (i.e. negatively charged electrode). In other words, tDCS alters the rate and timing of neuronal firing instead of directly initiating action potentials. Excitation and inhibition are achieved by shifting membrane potentials to depolarization and hyperpolarization, respectively, and these effects persist after stimulation.

Besides optimizing electrical neurostimulation, there have been considerable efforts to establish psychopharmacological interventions beyond serotonergic, noradrenergic, and dopaminergic pathways. A major drawback of classical antidepressants is the relatively slow onset of their therapeutic effect, with symptoms improving only after weeks or months. A paradigm of "initiation and adaptation" states that antidepressants initially act on substrates that are upstream of the targets that are ultimately responsible for antidepressant action. This delays the action of therapeutic agents. In this regard, it has been proposed that the glutamatergic system is responsible for mediating this delayed adaptive response, and that targeting it directly would provide rapid antidepressant effects (Zarate et al., 2006). Indeed, antagonists of the glutamate N-methyl-D-aspartate (NMDA) receptor demonstrated antidepressant-like effects in animal models and clinical studies. Specifically, the dissociative anesthetic and NMDA-receptor antagonist ketamine has moved forward in its clinical application as an antidepressant.

Like ECT and other NIBS, ketamine administration requires a particular setting due to the special indication and possible acute adverse reactions. It is dispensed in a controlled manner and is only intended for use under the direct supervision of a physician. There are two optical stereoisomers in ketamine: S(+) and R(−)-ketamine. As well as being available in racemic and enantiopure forms,

ketamine can be administered intravenously over 40 minutes with a subanesthetic dose for the treatment of TRD (Andrade, 2017). The FDA has approved the intranasal formulation of s-ketamine (also called esketamine) for alleviating symptoms of TRD in 2019, which may lead to the increasing use of s-ketamine intranasal applications (Mahase, 2019).

Unfortunately, despite its therapeutic potential, not all patients benefit from these treatments. ECT response rates in TRD are high; nonetheless, they oscillate between 60 – 80 % (Haq et al., 2015). There have also been a number of studies examining the clinical effects of tDCS with statistically significant effects, however their clinical relevance is moderate. (Berlim et al., 2013; Herrera-Melendez et al., 2020). Additionally, approximately half of patients respond poorly to ketamine will require another therapeutic trial with a different antidepressant (Zheng et al., 2020). The implementation of targeted approaches could help overcome those barriers. In this regard, clinicians should be able to optimize patients' selection by identifying subgroups of individuals more likely to respond based on specific features.

In the absence of a reliable test that can predict with a fairly high degree of certainty whether a particular patient will respond to a specific antidepressant treatment, it is difficult to make prognostications. This is particularly important as current medical practices are driven by personalized medicine (Hood and Friend, 2011). Although there are promising approaches (Drysdale et al., 2017), personalized therapies have not been established (Fernandes et al., 2017), in part due to the complexity of psychiatric phenotypes (Arslan, 2015). Consequently, for each patient, the most appropriate treatment can currently only be found by trial and error. Each therapeutic approach must be used for a reasonable amount of time to assess whether or not the patient responds, a method that could result in a prolonged series of multiple trials. If we could predict well in advance that an intervention is likely to be (un)successful in an individual patient with a reasonable degree of certainty, we could improve treatment effectiveness and reduce disease burden significantly.

1.1. Enhancing treatment response by modulation of neurostructural targets

It is generally thought to be a temporary facilitation of behavior in the cortex under the target electrode by positive anodal currents, while negative cathodal currents inhibit behavior (Nitsche et al., 2008). In light of this, it is crucial to consider the neuroanatomical correlates of the targeted symptoms when selecting electrode placement. In clinical trials, dorsolateral prefrontal cortex (DLPFC) has been mainly targeted as the main neurostructural target since studies suggest

it is a key dysfunctional node in brain networks involved in depression pathophysiology (Grimm et al., 2008). The results of previous research demonstrate that tDCS with electrodes placed over the DLPFC is capable to enhance cognitive control in healthy individuals (Feeser et al., 2014) and in patients with MDD (Wolkenstein and Plewnia, 2013). Cognitive control is a fundamental process involved in goal-directed behavior. Regardless of whether the situation is novel, unclear, or a combination of both, it is necessary to select an appropriate response when motivational conflicts are present. This function is impaired in patients with depression (Grahek et al., 2019). Psychotherapy promotes cognitive flexibility and control, utilizing for example metaphors and behavioral experiments. Particularly, cognitive behavioral therapy (CBT) has a strong empirical evidence in the treatment of depression. A central premise of CBT is that inaccurate beliefs and maladaptive information processing (which lead to repetitive negative thinking) are crucial factors in the development of depression (Driessen and Hollon, 2010). By correcting maladaptive thinking, both acute distress and the risk of recurrence of symptoms can be reduced (Beck, 1979). Interestingly, studies involving small groups of patients with MDD showed that tDCS over the DLPFC enhances the effects of cognitive therapies (Segrave et al., 2014; Welch et al., 2019).

1.2. TREATMENT RESPONSE BIOMARKERS

The severity of MDD, the length and frequency of episodes, the presence of associated anxiety disorders, and the age at which the disorders occur are among the clinical variables that are known to modulate its response to treatment (Kraus et al., 2019). Unfortunately, no biological or objective predictor has been proven to be sufficient clinically useful and practical to guide the selection of appropriate therapy.

An alternative approach to identify optimal treatments is to work backwards from treatment response to the pre-treatment state. Such approach relies not in identifying the exact underlying biology of the syndrome; it intends to find biomarkers associated with specific action mechanisms. This method may provide information on the neurobiology of the disease, but its actual value relies on improving treatment outcomes. It is imperative to distinguish between diagnostic biomarkers and therapy-response biomarkers. Diagnostic biomarkers identify specific conditions, whereas treatment-response biomarkers identify subgroups of patients within a complex disease that are most likely to receive benefit from specific treatments (or not) (Kapur et al., 2012). Predictive biomarkers do not guarantee benefit. Rather, they suggest to healthcare professionals who might respond and for whom other more suitable treatments should be sought and help exclude patients from getting a therapy that they will not benefit from.

Many efforts have been made to link the effectiveness of antidepressant therapy to various types of biomarkers. Genetic and epigenetic characteristics have been studied in genome-wide association studies (GWAS) and in single nucleotide polymorphisms (SNPs) (Lin and Chen, 2008; Lisoway et al., 2018). However, metanalyses agree that the results are heterogeneous and inconsistent (Howard et al., 2019). The translation of markers into clinical practice is another fundamental problem. This process is subject to a number of limitations, including the difficulty of integrating expertise and additional effort into clinical practice on a daily basis. One limitation is the fact that acquiring and analyzing data requires expertise and additional efforts. By utilizing materials obtained during routine clinical examinations, It may be possible to overcome this limitation. Patients receiving specialized treatment undergo a series of tests in order to exclude contraindications and to guarantee the safety of the procedure. In this respect, structural magnet Resonance Imaging (sMRI) is often performed as part of the baseline clinical testing, making it a promising tool to develop biological biomarkers.

1.3. NEUROIMAGING IN MDD

Structural abnormalities are often linked to the development of a disease, but can also be the consequence of it. These abnormalities may contribute to particular symptoms and lead to a particular course of illness. As a result of cell loss, pathological changes in the brain manifest themselves as atrophy, which sMRI can detect. Two traditional methods of evaluating structural atrophy on magnetic resonance imaging (MRI) are visual assessment by experienced radiologists and manual measurements of structures that may be of interest. They do, nevertheless, depend on the user's expertise or the quality of an atlas, and they do not provide details regarding local changes within regions. On the other hand, in recent years, automated procedures have allowed the processing of large amounts of data. In this way, it is possible to manage large amounts of images without the need for subjective visual evaluation or the need for time consuming manual measures.

One of such automated techniques is voxel-based morphometry (VBM). A gray matter segmentation of a T1-weighted image is first performed to obtain a typical VBM image for a subject. The partial volume estimation image of the gray matter is then non-linearly registered to a template, with each voxel having a number between zero and one representing the fraction of gray matter in the voxel. A perfect registration would result in the loss of all valuable information. Consequently, the registered image is smoothed after being modulated based on how much the local volume had to expand or contract in order to be registered. As a result, a VBM image may be used to estimate the amount of grey matter in a given area in relation to the template. VBM images from the same cohort may be compared voxel-by-voxel to see if the volume of gray matter

in each voxel differs across groups or in relation to a variable of interest. Studies comparing VBM analyses to visual or manual measurements of specific structures have found good correspondence between the two methods, despite the difficulty in establishing the biological validity of VBM experiments (Whitwell, 2009). Furthermore, quantitative studies have concluded that MRI-measured gray matter volume changes correlate to changes in the cellular constituents of gray matter, bolstering the biological validity of VBM measurements (Kassem et al., 2012).

Gray matter volume (GMV) reduction in areas involved in emotion processing such as the hippocampus, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (PFC), and basal ganglia is a well-replicated result in neuroimaging studies (Arnone et al., 2012; Bora et al., 2012; Koolschijn et al., 2009; Schmaal et al., 2017). Brain imaging has also shed light on the effects of treatment on brain structure and predictors of response (Chen et al., 2007; Colle et al., 2016; Jung et al., 2014; Korgaonkar et al., 2015; Li et al., 2010; Liao et al., 2013; MacQueen et al., 2008; Phillips et al., 2015; Samann et al., 2013). Specifically, higher pre-treatment GMV of the hippocampus (Colle et al., 2016; Liao et al., 2013; MacQueen et al., 2008; Samann et al., 2013), the ACC (Chen et al., 2007; Phillips et al., 2015; Samann et al., 2013), the PFC (Chen et al., 2007; Korgaonkar et al., 2015; Li et al., 2010; Liao et al., 2013; Samann et al., 2013), as well as lower GMV of temporal areas (Li et al., 2010; Samann et al., 2013) have been associated with response to antidepressant medication. In contrast, ECT outcome and hippocampal volume seem to be negatively correlated (Cao et al., 2018; Gryglewski et al., 2019; Joshi et al., 2016). Early increases in ACC thickness following ECT (Pirnia et al., 2016), as well as a higher baseline GMV of the subgenual anterior cingulate cortex (sgACC) are associated with a better outcome (Redlich et al., 2016).

Despite the interesting and consistent results obtained by the univariate methods used in these analyses, these methods have several limitations that must be taken into account. It is important to note that region of interest (ROI) methods are confined to predefined brain regions and cannot capture distributed gray matter deviation patterns across the brain. On the other hand, VBM requires brain averaging and cannot be used to capture individual differences. Considering that this information is derived by group-level inferences, it is not possible to use this information to make decisions about individual patients. Multivariate pattern recognition techniques offer the ability to make individual inferences and are ideal for use in medical decision making.

Against this background it is hypothesized that variations in brain structure explain differences in treatment response. As such, structural measurements could then be used as objective, reliable predictors of response allowing tailored interventions to be selected based on the information provided by these biomarkers.

2. OBJECTIVES

In this dissertation we explored neural structures assessed by sMRI as potential treatment response biomarkers to two interventional therapies of depression: a subanesthetic ketamine infusion (study 1, (Herrera-Melendez et al., 2021)) and ECT (study 2, (Gartner et al., 2021)). Furthermore, we took the results from previous investigations pointing the DLPFC as a key structure in the pathophysiology of depression and used tDCS to modulate its function during psychotherapy in a proof-of-concept clinical trial (study 3, (Aust et al., 2022)).

The first study analyzed structural imaging data obtained from 33 patients with TRD at two centers before and 24 hours after a single ketamine treatment. We examined brain structural predictors of rapid symptom improvement at the ROI and whole-brain levels and sought out macroscopic changes in gray matter using voxel-based morphometry.

On the second retrospective investigation we analyzed the predictive power of clinical and sMRI pre-treatment data of 71 patients treated with ECT by applying multivariate pattern analysis techniques.

On the third study we compared the efficacy of tDCS over the DLPFC combined with CBT to that of CBT plus sham-tDCS and to that of CBT alone in a multicenter, double blind, placebo-controlled clinical trial. We hypothesized that tDCS over the DLPFC would enhance clinical response to CBT and would be therefore superior to CBT plus sham-tDCS and to CBT alone.

3. GENERAL METHODOLOGY

This section provides an overview of the methodology employed in this dissertation. A more detailed description can be found in the attached original publications. Research was conducted according to the latest version of the Declaration of Helsinki and was approved by the Institutional Review Board of Charité–Universitätsmedizin Berlin (CHB) (study 1, 2 and 3), the Ethics Committee of University of Zurich (UZH) in study 2, as well as the Ethics Committee of the University Hospitals involved in study 3 (Munich, Tübingen, Leipzig, Freiburg, Mannheim).

3.1 CLINICAL ASSESSMENT

Depression severity was evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). Patients recruited at UZH in study 1 were evaluated

with the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1980). We homogenized clinical scores across sites using a previously published equivalence table (Leucht et al., 2018). To measure changes in depressive symptoms, we assessed the percent change from baseline (PCB) using the following formula: baseline score − follow-up score /baseline score x 100. In order to be considered a responder, a patient's PCB had to reach 50%.

For study 2, the documented medical evaluation of individual responses to ECT included in the discharge summary was compared to the MADRS score in order to ensure that the response was not influenced by other treatment shortly following the last ECT session. Therefore, in cases of obvious inconsistencies, the patients' response was classified according to the hospital discharge summary.

In study 3 the inclusion criteria was a total HAMD score of 15 or higher. Of note, the primary outcome was the change in MADRS scores from baseline to week 6 after intervention, followed by follow-ups at 18 and 30 weeks. Secondary end points included treatment response rates (≥50% reduction in MADRS), as well as remission rates (e.g. <10 Pts. in MADRS). Other secondary end points were changes in self-rated depression severity (Beck Depression Inventory–II, (Beck et al., 1996)), anhedonia (Snaith-Hamilton Pleasure Scale–Depression, (Snaith et al., 1995)), and health-related quality of life (ShortForm-36, mental health, (Ware, 1992)).

3.2 Magnetic Resonance Imaging

3.2.1. Data Acquisition.

Study 1: At CHB the images were obtained on a 3T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) using a standard quadrature head coil. Subjects at UZH were measured on a Philips Achieva TX 3-T scanner. Study 2: Data was acquired on either a 1.5T scanner (Magnetom Aera, Siemens Healthineers, Erlangen) or a 3T scanner (Magnetom Skyra, Siemens Healthineers, Erlangen), both equipped with a 20-channel head/neck surface coil.

3.2.2. Preprocessing.

The Computational Anatomy Toolbox was used to preprocess all structural MRI data (CAT12, C. Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany). T1-weighted images were segmented into GM, WM and CSF after adjusting for field inhomogeneities (Ashburner and Friston, 2005). Non-linear normalization used the Diffeomorphic Anatomical Registration Using Exponentiated Lie Algebra (Ashburner and Friston, 2007). All images were evaluated for artifacts and went through an automated quality inspection procedure. A Gaussian kernel with an isotropic full width at half maximum (FWHM)

of 8 mm was used to smooth the normalized gray matter maps. We used the default longitudinal segmentation pipeline implemented in the Computational Anatomy Toolbox to carry out the follow-up analysis in study 1.

3.2.3. VOXEL BASED MORPHOMETRY. The VBM analysis in study 1 was also performed with the CAT12 toolbox implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). The volume of each region of interest was estimated by applying an automated brain parcellation algorithm. The measurements obtained using this method have been found to be reliable and reproducible. (Khlif et al., 2019; Yamagishi et al., 2017). The Hammers brain atlas was used to generate anatomical ROIs (Hammers et al., 2003). Preliminary ROI selection for study 1 was based on previous literature findings of gray matter structures associated with treatment response (Abdallah et al., 2015; Niciu et al., 2018) and volumetric changes (Abdallah et al., 2017) after a single subanesthetic ketamine infusion. These areas were the bilateral hippocampus, bilateral ACC and bilateral Nucleus Accumbens (NAc). To control for between-subject variation in intracranial size, each ROI was expressed as a ratio of total intracranial volume (TIV), which was calculated by adding up the volumes of gray matter, white matter and cerebrospinal fluid partitions.

3.2.4. MULTIVARIATE PATTERN ANALYSIS. In neuroimaging, multivariate pattern analysis (MVPA) refers to the use of machine learning algorithms on magnetic resonance images. The objective is to extract information from multiple voxel values while taking into account their interaction in order to conduct classification and regression tasks. The input features are either the whole image or a part of it so that the pipeline includes a feature selection or extraction strategy. Feature selection is a well-known machine learning strategy that aims to infer a subset of the original feature space that is more relevant for the task of interest. After applying MVPA, one or more patterns of activity consisting of a set of features will be determined as the most relevant for classification or mostly associated to a continuous prediction target (regression). In study 2, the classification task was to distinguish responders from non-responders, while the regression task corresponded to the reduction of symptom severity.

As part of Study 2, a multivariate pattern classification (MVPC) based on a linear kernel support vector machine (C-SVM) was used for the prediction task of determining whether patients would respond to electroconvulsive therapy. Voxel values of the preprocessed whole-brain structural images after masking were used as input features for the classifier. The sMRI-based analysis pipeline included a feature selection step based on the fScore metric. The fScore metric provided

an estimation of the features' discriminative power in relation to the class label, considering the classifier's performance quality. We refer to the proposed approach as SVM-fScore as it uses an SVM with a linear kernel and a feature selection strategy based on F-scores. The performance of the classifier was tested with a leave-one-out cross validation due to the limited sample size. Fivefold cross validation was used to select the C-SVM parameter and percentage of selected features. Based on the averages of all cross-validation folds, we constructed the following classification weight maps. To identify regions most important for classification, five percent of the highest classification weights were retained. 500 voxels were set as the threshold for significant clusters. Classifier performance was evaluated based on accuracy, sensitivity, and specificity. The statistical significance of the classification accuracy was determined using a permutation test of 1000 repetitions.

We conducted a multivariate linear regression analysis to predict continuous symptom improvement based on MADRS score changes. We used a pipeline similar to that used for classification to replace SVMs with linear regressions and determine F-value using F-test. Cross-validation with leave-one-out was used to reduce the mean squared error. We selected features using inner 5-fold cross-validation only from the training data. A total of 54 patients with MADRS scores clearly correlated with ECT were included in this analysis. A FSL Harvard-Oxford Atlas anatomical mask was used for the regression analysis post-hoc, corresponding to the anterior right parahippocampal gyrus (aPHCr). Machine learning analyses were performed in Python (Python 3.6.4) using the Nilearn library (v0.4.2). Figure 1 illustrates the MVPA pipeline.

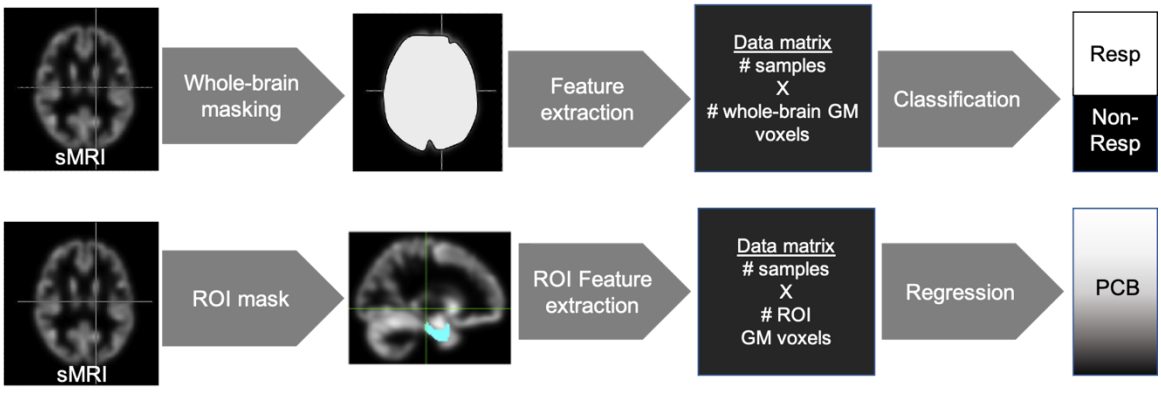

Figure 1. Pipelines for the classification and regression analyses. The smoothed, modulated, whole-brain gray matter volume images served as input. Upper row: steps in the classification analysis. Whole-brain masking followed by feature extraction using SVM-fScore with a resulting SVM-based classification using responders and non-responders as class labels. Lower row: steps in the post-hoc regression analysis. Masking using an anatomical mask of the right anterior parahippocampal gyrus followed by feature extraction corresponding to gray matter voxels in the ROI mask with a resulting linear regression to predict the symptom percentage change from baseline (PCB). Modified from (Gartner et al., 2021).

4. STUDY DESIGN, POPULATION AND MAIN RESULTS

4.1. STUDY 1. STRUCTURAL PREDICTORS OF RAPID ANTIDEPRESSANT RESPONSE TO KETAMINE (HERRERA-MELENDEZ ET AL., 2021)

4.1.1. PARTICIPANTS AND DESIGN. We recruited 33 patients with TRD at two sites: Charité University Hospital Berlin (CHB) and University Hospital Zurich (UZH). 23 patients were included at CHB (12 females, mean age: 49.13, SD 12.2) and 10 patients at UZH (6 females, mean age: 42.1 SD 12.9). Neither age ($t(31) = 1.42$, $P = 0.85$) or sex distribution ($\chi 2$ (21, N=33) = 18.79, $P = 0.59$) between patients at both sites were significantly different. Medication included selective serotonin reuptake inhibitors (SSRIs) (N = 7), serotonin and norepinephrine reuptake inhibitors (SNRIs) (N = 8), tri-/tetracyclic antidepressants (N = 4), antiepileptics (N = 3), atypical antipsychotics (N = 9), benzodiazepines (N = 6), and melatonin (N = 3). Baseline MRI measurements were taken up to 24 hours prior to ketamine administration.

4.1.2. TREATMENT. The procedure at CHB and the procedure at UZH was performed based on clinical practice at both locations. 0.5 mg/kg of racemic ketamine at CHB and 0.25 mg/kg of S-ketamine at UZH was administered intravenously over 40 minutes.

4.1.3. CLINICAL RESULTS. The average baseline MADRS score was 25.8 (SD 5.9). After 24 h the average MADRS score was 17.4 (SD 6.3). 30.3% of patients were considered to be responders. Baseline MADRS scores did not differ between responders and non-responders ($t(31) = 0.81$, $P = 0.29$). There was no significant difference regarding depression severity at baseline or symptom improvement ($t(31) = -0.91$, $P = 0.36$) between both sites.

4.1.4. WHOLE-BRAIN ANALYSIS RESULTS. There was a positive association between symptom improvement and GMV of the bilateral rostral anterior cingulate cortex (rACC)

(x= 2, y= 34, z=10) at baseline (T = 3.42, P < 0.05 cluster level corrected, extent = 319 voxels; Figure 2). No other significant clusters were observed. The whole-brain follow-up explorative analysis revealed no changes in GMV 24 h after the infusion.

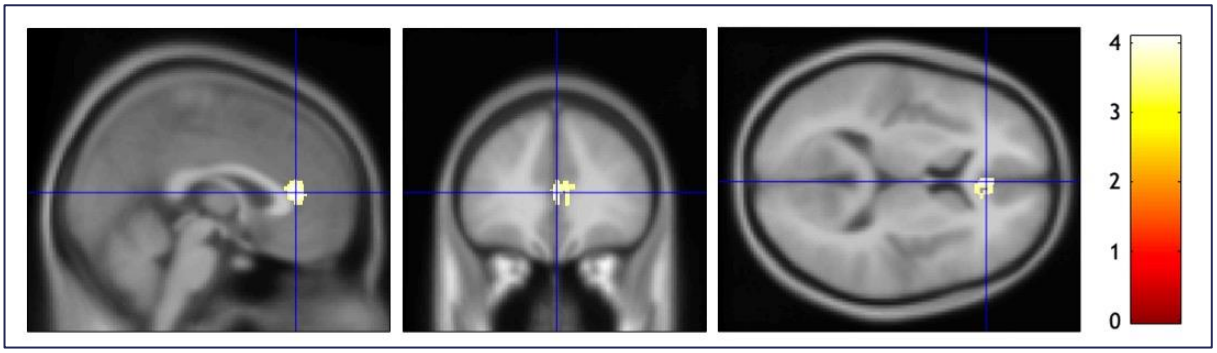

Figure 2. Cluster within the bilateral rostral ACC positively associated with the reduction of depressive symptoms 24 h after ketamine infusion (MNI coordinates x= 2, y= 34, z=10; T = 3.42, P < 0.05 cluster level corrected, extent = 319 voxels). Modified from (Herrera-Melendez et al., 2021).

4.1.5. ROI ANALYSIS RESULTS. A significant positive correlation was observed between baseline GMV of the right anterior cingulate and symptom improvement (r = 0.57 P < 0.006, Bonferroni-corrected) (Figure 3). The left anterior cingulate also showed a positive association, however, did not survive correction for multiple comparisons (r = 0.45 P = 0.01, Bonferroni-corrected). Baseline GMV of bilateral hippocampus (right, r = .10, P = .62; left, r = .15, P = .47) or bilateral NAc (right, r = .87, P = .68; left, r = .084, P = .68) was not significantly associated with symptom reduction. GMV of the right ACC differed between responders and non-responders at baseline, though without surviving correction for multiple comparisons (F (1,27) = 4.53, P = 0.04). There was no significant difference between responders and non-responders on the left ACC (F(1,27) = .708, P = .40), bilateral hippocampus (right: F(1,27) = 1.825, P = .18; left: F(1,27) = 2.404, P = .13) and bilateral NAc (right: F(1,27) = .215, P = .64; left: F(1,27) = .643, P = .429) at baseline.

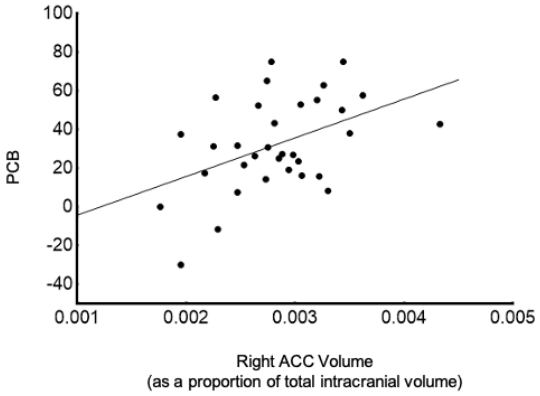

Figure 3. Association between right anterior cingulate cortex (ACC) and symptom improvement or percentage change from baseline (PCB). Modified from (Herrera-Melendez et al., 2021).

4.2. Study 2. Structural predictors of response to electroconvulsive therapy (Gartner et al., 2021)

4.2.1. Participants and design. In study 2, we retrospectively analyzed data from 71 patients (41 female, age: M = 50.7, SD = 17.6, age range: 19 - 90) who had been diagnosed with a major affective disorder and underwent ECT during the period 2012 – 2018 at CHB. Recurrent major depressive disorder was the most frequent primary diagnosis (66%), although there were other affective disorders as well (F32 - 14%, F31 - 13%, F25 - 4%, F34 - 3%). We did not implement any additional exclusion criteria related to medication intake, age groups, or psychiatric and somatic conditions in order to reflect regular clinical practice. All patients underwent an MRI scan to check for structural anomalies and other potential contraindications before the first ECT.

4.2.2. Treatment. The treatment regimen consisted of Ultrabrief Pulse Right Unilateral ECT (Thymatron IV system, Somatics Inc.) performed three times a week. ECT was initially administered over a 12-session period. Additional ECT sessions were administered to patients who displayed a partial response. A patient's treatment was discontinued if there was no relevant improvement.

4.2.3. Clinical results. The mean MADRS score at baseline was 29.6 (SD 6.4). The average PCB was 47.1 (SD 27.5). 39 patients (54.9%) were classified as responders. Furthermore, there was no difference in sex distribution ($\chi 2$ (1, N=71) = 1.43, P = 0.33) presence of psychotic symptoms ($\chi 2$ (1, N=71) = 0.20, P = 0.77), duration of current episode (t(53) = .77, P = 0.44), number of ECTs, (t(69) = 1.35, P = 0.19), and baseline MADRS score (t(61) = .78, P = 0.44) between responders and non-responders.

4.2.4. CLASSIFICATION RESULTS. On 71 patients, the SVM-fScore was evaluated, with 39 patients responding to the treatment and 32 patients not responding to it. According to the binary classifier, structural magnetic resonance images provided adequate signal and information to distinguish responders from non-responders (permutation test: P = 0.002). Method accuracy was 69.01%, sensitivity was 66.67%, and specificity was 71.87 %. SVM-fScore correctly identified 26 out of 39 responders and 23 out of 32 non-responders. According to the classification weight maps, the right anterior parahippocampal gyrus (aPHCr) was the most important GMV region for determining ECT response. (Figure 4).

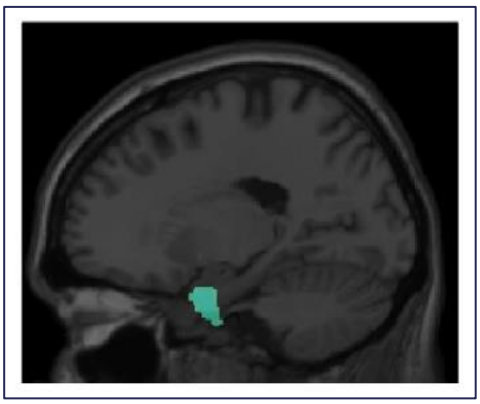

Figure 4. Classification weight map. Blue color depicts a cluster of the most contributing weights in the right anterior parahippocampal gyrus (aPHCr; MNI coordinates: x = 18, y = 0, z = -30; extent: 573 voxels). Modified from (Gartner et al., 2021).

We also used clinical predictors as input features for the SVM-fScore, either univariate or multivariate. Age, psychotic symptoms, and depression severity were not statistically significant predictors. Overall, the classifier predicted the majority class (responders), suggesting that clinical variables cannot provide meaningful information for meaningful separation. Following the clinical predictor classification, a confirmatory analysis found no differences in psychotic symptoms, age, or depression severity between ECT respondents and non-responders.

4.2.5. REGRESSION RESULTS. An anatomical mask of the aPHCr was used to perform a multivariate regression analysis to predict PCB (Figure 5). 54 patients that had clear MADRS scores, as mentioned in the clinical assessment method section, were included in this analysis. The results showed that the predicted PCB on aPHCr and the corresponding true PCB have a positive significant correlation (r = 0.36, P = 0.007). This finding suggests that the signal in the aPHCr region's GMV values, is significantly associated to PCB after ECT.

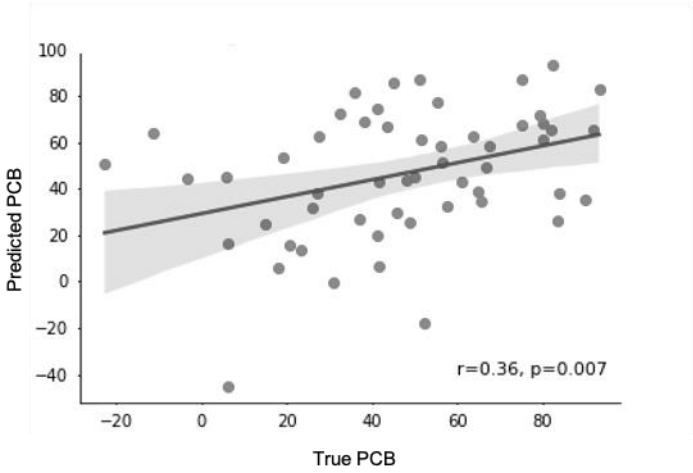

Figure 5. Regression results on aPHCr region. Predicted symptom percentage change from baseline (PCB) versus true PCB with a linear regression fit. Gray area is a confidence interval for the slope parameter. Modified from (Gartner et al., 2021).

4.3. Study 3. Enhancing Cognitive Behavioral Therapy with Transcranial Direct Current Stimulation over the DLPFC (Aust et al., 2022)

4.3.1. Randomization and blinding. In a 1:1:1 ratio, patients were randomly assigned to receive either CBT+tDCS (group 1), CBT+sham-tDCS (group 2), or CBT alone (group 0). In order to reduce group effects, patients who received active or sham-tDCS attended the same CBT group. The tDCS conditions were blinded to therapists, raters, and patients until the end of the study.

4.3.2. Participants. In study 3, 210 patients aged 20 to 65 with MDD (single or recurrent episode) and a HAMD score ≤15 were assessed for eligibility (Table 1). The duration of the current depressive episode was limited to five years, so severe cases were included. It was required that patients be either medication-free or on a stable dose of SSRIs and/or mirtazapine at least four weeks before inclusion. 148 patients were randomly assigned to the three study arms (group 1: CBT+tDCS N=48; group 2: CBT+sham-tDCS N=47; group 0: CBT alone N=53). A total of N=126 completed the study (group 1: N=43; group 2: N=42; group 0: N=41). The study flow diagram depicts the details (Figure 6).

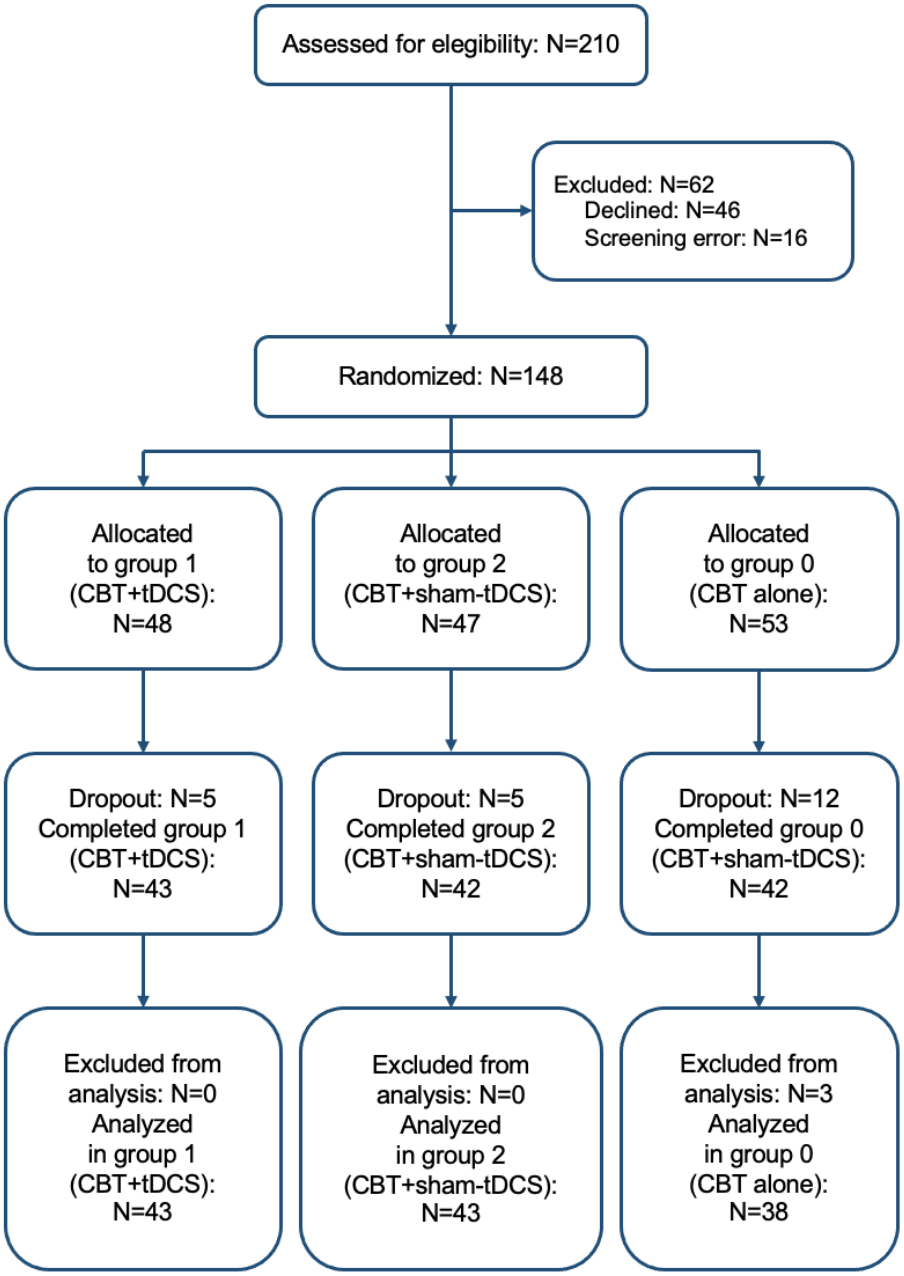

Figure 6. Study Flow Diagram according to CONSORT standards

TABLE 1. Patient characteristics according to treatment arm (Intention to treat sample N=148)

	Group 1: N=48 CBT + tDCS	Group 2: N=47 CBT + sham-tDCS	Group 0: N=53 CBT alone	p
Age at inclusion (years)	42.7±12.7	39.0±14.8	41.5±13.6	n.s.
Female sex	52.1% (N=25)	59.6% (N=28)	67.9% (N=36)	p<.005
Years of education	11.4	11.9	11.2	n.s.
Number of previous episodes (incl. current)	3.8±4.7	5.0±6.8	4.3±3.9	n.s.
Duration of current episode (months)	21.3±15.9	16.6±15.2	12.2±11.9	p< .01
ATHF score	1.5±2.7	2.4±2.6	1.5±2.5	n.s.
SSRI/Mirtazapine intake	33.3% (N=16)	51.1% (N=24)	32.1% (N=17)	p< .001
Baseline scores:				
- **HDRS-21**	- 20.3±4.2	- 21.0±4.3	- 20.5±4.3	- n.s.
- **MADRS**	- 22.9±6.7	- 23.1±5.5	- 23.0±7.2	- n.s.
- **BDI-II**	- 29.0±8.2	- 29.9±10.9	- 26.0±10.6	- n.s.
Any comorbid psychiatric disorder	29.2% (N=14)	27.7% (N=13)	49.1% (N=26)	p< .001
Employed in the past three months	64.6% (N=31)	70.2% (N=33)	60.4% (N=32)	p< .001

Means ± standard deviations are shown if not otherwise specified. Group differences were detected via one way ANOVA with "group" as factor. Post-hoc tests were Bonferroni-corrected. Chi-Square-Tests were used for nonparametric group comparisons (Modified from (Aust et al., 2022).

4.3.3. COGNITIVE BEHAVIORAL THERAPY. We adopted a CBT-oriented psychotherapeutic approach based on established, empirically validated guidelines (Beck et al., 1996; McCullough, 2003). During the six-week program, 12 sessions lasted 100 minutes each. Each session consisted of six patients and two psychotherapists. Detailed descriptions of each group session, video clips demonstrating key therapeutic techniques and a guide for dealing with difficult situations were compiled into a manual for psychotherapists so that group CBT could be implemented throughout all study sites.

4.3.4. TRANSCRANIAL DIRECT CURRENT STIMULATION. After the introductory round, stimulators were activated, if assigned. In terms of the technical setup, it was designed to follow previous tDCS studies and the DepressionDC multicenter trial (Padberg et al., 2017). The stimulation intensity was set at 2mA with the anode over F3 and the cathode over F4, using EEG 10-20 as a guide. During the monitoring process, an electrode positioning system was used to ensure standardized electrode placement. In the sham-tDCS condition, stimulation was only applied for a short period of time during the ramp-in and ramp-out phases, using small portable devices (neuroConn GmbH, Ilmenau, Germany). Stimulations lasted for 30 minutes with 30 seconds ramp-in and ramp-out phases. After each stimulation session, technical supervisors controlled stimulation log data with the aim of continuously monitoring stimulation efficacy (as described in (Kumpf et al., 2021). An effective stimulation sessions percentage was also calculated.

4.3.5. TOLERABILITY AND SAFETY. CRQ (Comfort Rating Questionnaire; (Palm et al., 2014) was used to assess the tolerability of stimulation. It was required to document and report adverse and severe adverse events within 24 hours. All relevant safety data was presented to an external Safety Monitoring Board every year.

4.3.6. STATISTICAL ANALYSES. A researcher who was blind to the study group assignment was responsible for the analysis of the primary and secondary outcome data for both studies. We calculated linear mixed models for intention-to-treat (ITT) and per-protocol (PP) samples. It was determined that missing values would be replaced by the last observation carried forward method. The variables “group”, “time” as well as their interaction were used to predict post-treatment MADRS scores at weeks 6, 18 and 30. We calculated logistic multilevel models in order to examine whether type of treatment was associated with increased likelihood of a clinically relevant response or remission. For the purpose of specifying efficacy, Cohen's d was calculated for both ITT and PP samples. A t-test statistic was used to analyze the differences between groups in terms of tolerability and safety.

4.3.7. PRIMARY OUTCOMES. There was a significant reduction in MADRS scores of 6.5 points (95%CI: 3.82; 9.14) across all treatment arms in the ITT analysis (regardless of the intervention type). Cohen's d was -.90 (95%CI: -1.43; -.50) which indicates a strong time effect. Groups 1 and 2 were not significantly different from the control group, and neither was group x time significantly different from the control group, as shown by the estimated additive effects of stimulation or sham-stimulation (groups 1 and 2) compared to CBT alone (group 0), which remained under statistical significance (Figure 7). The PP sample showed stronger a MADRS score reduction of 9.0 points (95%CI: 6.28; 11.62) and a Cohen's d of -1.37 (95%CI: -2.17; -.86), meaning a stronger pre-post effects. However, neither group nor interaction effect was statistically significant. Follow-up MADRS scores did not change the results of the study (Cohen's d week 18 = -1.01; Cohen's d week 30 = -.78).

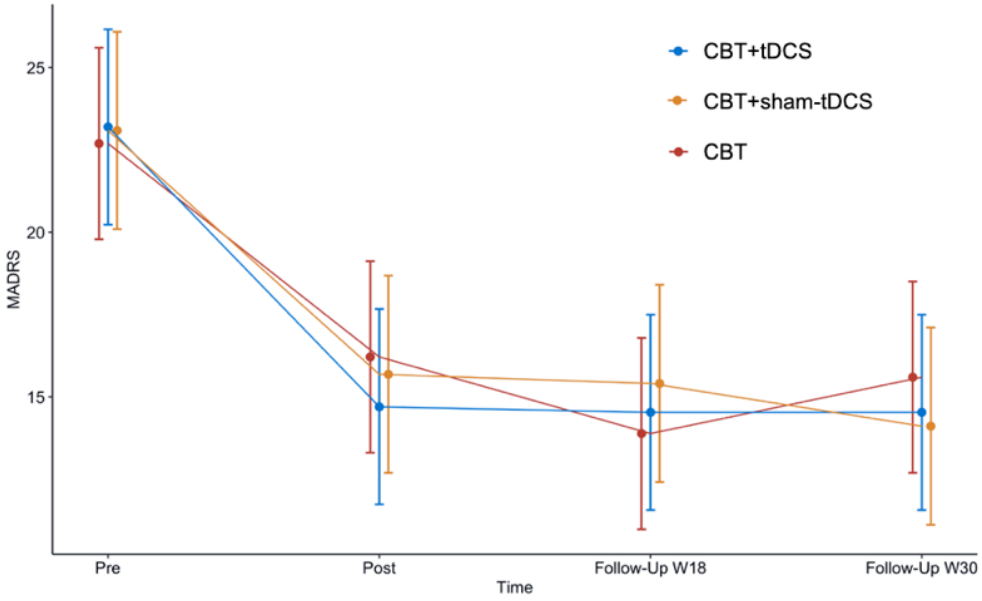

Figure 7. The error bars represent 95%CIs. CBT, cognitive behavioral therapy; tDCS, transcranial direct current stimulation. (Modified from (Aust et al., 2022))

4.3.8. SECONDARY OUTCOMES. 40 out of 45 patients in the ITT sample were in remission (27.0%) and 45 had a treatment response (30.4%). According to a logistic multilevel model, remission or response as a function of group did not appear to be associated with a higher likelihood of remission. In regards to all secondary outcomes (BDI-II, SHAPS-D, SF-36), we found no significant differences among groups and no significant interactions between groups and time, although patients significantly improved on all measures regardless of the group they were enrolled (Table 2).

Table 2. Primary, secondary and exploratory outcomes according to treatment arm (intention-to-treat sample N=148)

	Group 1: CBT + tDCS	Group 2: CBT + sham-tDCS	Group 0: CBT alone
Remission	N=15 (34.9%)	N=11 (26.2%)	N=14 (34.1%)
Response (incl. remitted patients)	N=15 (34.9%)	N=13 (31.0%)	N=17 (41.5%)
MADRS			
pre	22.9±6.7	23.1±5.5	23.0±7.2
post*	14.4±6.9	15.7±7.3	16.6±8.8
week 18*	14.2±8.0	15.4±8.6	14.2±8.3
week 30*	14.2±9.4	14.1±8.6	15.9±9.3
BDI-II			
pre	29.0±8.2	29.9±10.9	26.0±10.6
post*	18.3±10.6	18.4±10.4	17.5±9.9
week 18*	15.6±9.9	17.7±12.7	14.5±8.0
week 30*	16.3±13.8	16.2±13.9	15.6±9.7
SHAPS-D			
pre	23.9±6.8	24.7±8.3	26.0±7.0
post	25.5±8.1	28.4±8.3	26.1±9.1
week 18*	28.8±6.4	28.9±8.2	29.5±7.0
week 30*	30.2±8.2	29.1±8.4	30.2±6.6
SF-36 mental health			
pre	14.6±3.2	14.3±4.0	15.3±4.5
post*	16.6±4.5	16.5±4.1	17.5±4.8
week 18*	17.1±4.0	16.5±4.3	17.6±4.1
week 30*	18.3±6.0	18.6±4.7	19.1±4.4

Means ± standard deviations are shown if not otherwise specified. (*****) refers to a significant difference to baseline score ("pre") in the ITT-sample irrespective of treatment arm (all tests $p < .001$, Bonferroni-correction applied). Measures with significant pre-post differences in the ITT-sample are printed in bold. Additional pre-post data are reported in the supplement.

4.3.8. BLINDING EFFICACY AND TOLERABILITY. In the comparison of active versus sham intervention arm, patients receiving stimulation (groups 1 and 2) were not able to get a correct guess about which arm of treatment they were assigned. We concluded that blinding worked effectively as the correct assignment rate was below chance (39%). The self-reported adverse effects during and after stimulation were not significantly different between groups 1 and 2. The trial did not report any severe adverse events (e.g., no new onset of mania or hypomania, no suicide attempts or completions, or hospitalizations). 16.2% of all randomized patients reported 25 adverse events. There were five events (20%) related to or possibly related to tDCS (active tDCS: three events [local pain at the stimulation site], sham-tDCS: two events [local pain at the stimulation site and dizziness]). These are all considered to be typical tDCS side effects.

5. DISCUSSION

5.1. GMV OF THE ACC ASSOCIATES WITH RAPID ANTIDEPRESSANT RESPONSE TO KETAMINE

The findings from study 1 further support the growing body of evidence that the rACC plays a crucial role in depression. The bilateral rACC showed a positive association with rapid symptom improvement at both the whole-brain and ROI levels. Individuals with a higher GMV showed a greater reduction in depression scores 24 hours after the ketamine infusion.

The rACC complements a vital mood-regulating network, which controls visceral and autonomic responses to stressors and assigns emotional valence to internal and external stimuli through connections with limbic, paralimbic, and subcortical structures (amygdala, brain stem, ventral striatum, thalamus, insula, hippocampal, and orbitofrontal cortex) (Pizzagalli, 2010). In MRI (Bora et al., 2020) and post-mortem studies (Chana et al., 2003; Cotter et al., 2001) reduced GM volume of the rACC is a well replicated finding. This has also been associated with depression severity (Boes et al., 2018b; Leung et al., 2009), attentional biases against negative stimuli (Leung et al., 2009), and the capacity to downregulate negative (but not positive) emotions (Boes et al., 2018b; Leung et al., 2009). Activity in the rACC enables adaptive self-referential processing, resulting in a reconfiguration of the interaction between the default mode network and the task-positive network involving the dorsolateral PFC and dorsal ACC (e.g. the ACC 'cognitive subdivision'). This reconfiguration would enforce cognitive regulation (Pizzagalli, 2010).

Neurobiological processes responsible for gray matter degradation in the rACC are still not fully understood. Chronic stress, such as that experienced by patients with depression, induces dendritic

atrophy of glutamatergic cells, , spine loss, dendritic atrophy and decreases GABAergic interneuron markers (Fogaça and Duman, 2019). Chronic stress is likely to disrupt the delicate balance between excitatory and inhibitory regulation, given the presence of abundant GABAergic interneurons in the ACC and their major inhibitory function (Zhou et al., 2018). A glutamatergic pyramidal neuron would be disinhibited if NMDA receptors in GABAergic interneurons are blocked with ketamine, resulting in a glutamate rush, which promotes activity-dependent synaptic plasticity and alleviates depressive symptoms (Duman et al., 2016; Fogaça and Duman, 2019). The glutamate release induced by ketamine is detectable for an hour before levels return to normal (Moghaddam et al., 1997). However, this glutamate burst can also produce activity-dependent long-term changes.

The correlation between a greater pre-treatment volume of the rACC and a better ketamine treatment outcome suggests that maintaining the volume of this region that is involved in emotional and motivational processing is crucial for antidepressant treatment success. One possible interpretation is that, rather than normalizing gray matter volume, successful ketamine treatment may result in a relative normalization of the rACC connectivity pattern to other limbic regions, which would require a less compromised structure.

In animal models of depression, ketamine reversed spine density loss in the medial PFC (Sarkar and Kabbaj, 2016; Zhang et al., 2019) and hippocampus (Zhang et al., 2019) already three hours after administration. Nevertheless, the restoration of dendritic spines by ketamine appears to be only partial, and spine loss persists after treatment, regardless of improvement in depression-related behaviors (Moda-Sava et al., 2019). The lack of visible changes after 24 hours may be due to this reason. It can also be argued that measuring GMV changes after 24 hours may be too early to detect significant macroscopic changes. GMV changes 45 min after a ketamine infusion have been correlated with increased regional blood flow (Höflich et al., 2017). Converging results of structural and functional MRI studies linking the rACC to the treatment response could be then explained by an increase in regional blood flow. Using arterial spin labeling in conjunction with structural MRI, for example, may provide further insight into this topic.

5.2. GMV OF THE APHC PREDICTS ANTIDEPRESSANT RESPONSE TO ECT

In study 2, we followed a machine learning approach to evaluate and compare the predictive power of response to ECT from routine sMRI scans and clinical data. Using binary pattern classification for the analysis of structural images, we were able to achieve an accuracy of 69%. As determined by the analysis of classification weight maps, a region of the right aHPC was

the most significant contributor to the classification task. An anatomical mask of this area on the right aHPC was used to predict PCB using a multivariate regression analysis. According to our results, ECT was more likely to be successful in patients with a smaller rather than a larger GMV in this region.

The classification results showed to be highly significant based upon permutation testing, but the clinical benefit of accuracy within this range remains to be determined. In a previous study, ECT responders were classified with an accuracy of 78% (Redlich et al., 2016). Our study, on the other hand, examined a larger and more heterogeneous sample of MDD patients than the mentioned investigation, which included 23 patients. The inclusion of patients with different affective diagnoses, medication, and scanning protocols ultimately results in more data variance. In this respect, our results are encouraging, as they demonstrate that structural images which contain uncontrolled sources of variance (as occurs in daily clinical practice) are capable of predicting significant outcomes.

This study adds to the body of literature examining GMV of temporal structures and treatment response prediction in depression. There is considerable and generally homogenous evidence in the literature that higher hippocampal GMV predicts a positive response to antidepressant medication (Enneking et al., 2019); consequently, decreased hippocampal GMV is generally associated with an unfavorable response to antidepressants (Stratmann et al., 2014; Zaremba et al., 2018). Surprisingly, for ECT, the findings point in the opposite direction. A higher hippocampal GMV is negatively (Cao et al., 2018; Gryglewski et al., 2019; Joshi et al., 2016) or not associated (Tendolkar et al., 2013) with the antidepressant response. These previous reports are in line with our finding that patients with less GMV in temporal structures are more likely to respond to treatment. A possible interpretation is that ECT promotes neurogenesis of temporal structures (Phillips et al., 2015) so that patients with a higher pre-treatment GMV are less likely to benefit from treatment-induced increases in temporal volume.

Unlike previous studies, we found no significant predictive power in univariate and multivariate analyses of established clinical predictors such as age, psychotic symptoms, or depression severity. As our cohort had relatively small baseline clinical differences between responders and non-responders, it is possible that the resulting small effect sizes are inefficient for making individual predictions.

5.3. DLPFC MODULATION DURING COGNITIVE BEHAVIORAL THERAPY

A randomized, double-blind, placebo-controlled clinical trial was conducted to compare tDCS-augmented CBT for major depression to two control conditions (CBT with and without sham-tDCS). The antidepressant effect across the groups showed no significant differences. There was a significant reduction in depressive symptoms regardless of the treatment arm with similar response and remission rates over the course of treatment. Combined with CBT, tDCS was well tolerated, with no significant adverse effects reported.

Perhaps the lack of superiority of tDCS-augmented CBT can be attributed to the fact that we took preliminary findings of individual cognitive control tasks being enhanced by tDCS and translated them into a complex group-psychotherapy setting. Thus, synchronization between state-dependent stimulation and behavioral interventions may not have been adequate (Weigand et al., 2013; Bortoletto et al., 2015). Even though tDCS-augmented CBT failed to show any clinical advantage over the control conditions, the study provides useful guidelines for future research on neuromodulatory-behavioral interventions. TDCS combined with psychotherapeutic approaches targeting cognitive control may be a promising experimental approach in the future. (Callesen et al., 2020). Furthermore, individual sessions may prove to be more effective than group sessions in the sense that patients' thought processes may be easier to guide than in a group setting. We may also be able to gain a better understanding of the effects of tDCS on cognitive control by concentrating on the improvement of individual symptom clusters (e.g. core depression, sleep, anxiety or cognitive symptoms) rather than on the change in total depression scores (Siddiqi et al., 2020). This approach would also facilitate the conduct of transdiagnostic research.

5.4. NEUROSTRUCTURAL TREATMENT TARGETS AND RESPONSE PREDICTORS: THE UNDERLYING MECHANISM OF ACTION

The investigation of treatment biomarkers provides insight into the relationship between brain anatomy and pathological processes as well as into the mechanisms of action involved. In this regard, our findings show that predictors could differ depending on the mechanism of action of the treatment.

Neuroimaging investigation of neurobiological biomarkers of depression led to the development of the imbalance hypothesis of MDD. According to this hypothesis, there is a relative hypoactivity in the left DLPFC and relative hyperactivity in the right DLPFC, which would lead to prefrontal asymmetry (Grimm et al., 2008; Rogers et al., 2004). NIBS techniques for depression specifically target this region and baseline differences among individuals may account for some of the inconsistencies in clinical response to prefrontal tDCS. In fact, previous research showed that

prefrontal gray matter volume at baseline is associated with response to tDCS (Bulubas et al., 2019) and that baseline activity of the same region predicts response to subsequent tDCS plus CBT (Nord et al., 2019). The modulation of the antidepressive response to prefrontal-tDCS by individual variations in gray matter structure is a topic that should be further explored.

Considering that the aHPC is one of the most important structural markers for predicting response to ECT, it is plausible that this stimulation technique has a neuromodulatory effect. By reducing neurodegeneration processes in temporal areas, effective antidepressant treatment may have a neurobiological impact on depressive disorder. An abnormal neuronal architecture might be a signature of a premorbid state, or it could also be acquired as a result of illness and contribute to the occurrence of residual symptoms or even influence the course of the disease. The nervous system is provided with a compensatory capacity for structural aberrations. In the event that these capacities are exceeded, neural network dysfunction may appear and manifest itself as neuropsychiatric symptoms on a behavioral level. ECT can help restore optimal brain function.

Ketamine, on the other hand, would reveal another target of action. This NMDA-receptor antagonist could act by inhibiting glutamate ion channels on GABAergic neurons, with a resulting glutamate surge and increased activity of the cingulate cortex. The rACC may facilitate adaptive self-referential processing and cognitive control by reconfiguring the interactions between the default mode network and the task positive network.

5.5. Outlook of neuroanatomic markers in depression research

The analysis of neuroimaging data through the general linear model (GLM) is a well-established procedure. However, it has some disadvantages. First, the GLM treats each voxel independently and their interactions are not taken into account. Secondly, there is no consensus when choosing the method to correct for multiple comparisons. Multivariate approaches, such as MVPC, were initially proposed to overcome those two major limitations. The influence and composition of a particular brain region cannot, however, be determined by such machine learning techniques. They instead illustrate how GMV patterns at the whole-brain level interact with response to treatment. The accuracy of pattern classification could likely be improved by focusing on relevant structures from univariate predictive biomarker studies. Hence, both methods would be complementary to one another.

Another issue that needs to be considered is response dichotomization. In study one and two, the statistical power was greater when using a continuous symptom improvement- (e.g., PCB) rather than a binomial-approach (e.g., responders vs non-responders). In fact, it might be more useful in

a clinical setting to approach response prediction from a regression perspective. Clinical practitioners would then be given a range of predicted symptom improvement rather than a yes or no answer. These considerations call for a further investigation of regression-based prediction approaches.

Despite still being in the proof-of-concept phase, response prediction has high potential for application in clinical practice. In the near future, it could be incorporated into the decision-making algorithm followed by clinicians. Given that the evaluation of structural neuroimaging data is already part of the routine medical evaluation in many in- and outpatient psychiatric services, an implementation of sMRI-based response prediction appears feasible for the clinical setting. Furthermore, combining large datasets with clinical variables, structural and functional imaging, laboratory, and genetic data could lead to a systematic understanding of treatment effects and to a more precise prediction of treatment response and the development of treatment targets.

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II. STATUTORY DECLARATION

"I, Ana Lucía Herrera Meléndez, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "*Neurostructural targets and predictors of response to interventional antidepressant treatment*" *(Neurostrukturelle Ziele und Prädiktoren für das Ansprechen auf interventionelle antidepressive Therapien),* independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

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Date and signature

III. DECLARATION OF CONTRIBUTION TO THE PUBLICATIONS

Herrera-Melendez AL, Stippl A, Aust S, Scheidegger M, Seifritz E, Heuser-Collier I, Otte C, Bajbouj M, Grimm S, Gartner M. 2021. Gray matter volume of rostral anterior cingulate cortex predicts rapid antidepressant response to ketamine. Eur Neuropsychopharmacol 43, 63-70.

> Contribution in detail: Ana Herrera-Melendez performed ketamine infusions at Charité Universitaetsmedizin Berlin. She collected clinical data directly from patients and clinical records. She scanned patients on the Siemens 3T Scanner at the Center for Cognitive Neuroscience Berlin. She worked on the study design. She performed MRI preprocessing, statistical analysis, results interpretation, and produced the figures (Figure 1 and 2). She wrote the entire manuscript and performed revisions prior to publication with assistance of her supervisors.

Gartner M, Ghisu E, **Herrera-Melendez AL,** Koslowski M, Aust S, Asbach P, Otte C, Regen F, Heuser I, Borgwardt K, Grimm S, Bajbouj M. 2021. Using routine MRI data of depressed patients to predict individual responses to electroconvulsive therapy. Exp Neurol 335, 113505.

> Contribution in detail: Ana Herrera-Melendez conducted electroconvulsive therapy on part of the patient cohort. She also retrospectively collected part of the clinical and MRI data based on patients' records. She was in charge of MRI preprocessing and aided in results interpretation and revised all drafts of the manuscript before submission.

Aust S, Brakemeier EL, Spies J, **Herrera-Melendez AL**, Kaiser T, Fallgatter A, Plewnia C, Mayer SV, Dechantsreiter E, Burkhardt G, Strauss M, Mauche N, Normann C, Frase L, Deuschle M, Bohringer A, Padberg F, Bajbouj M. 2022. Efficacy of Augmentation of Cognitive Behavioral Therapy With Transcranial Direct Current Stimulation for Depression: A Randomized Clinical Trial. JAMA Psychiatry 79, 528-537.

> Contribution in detail: Ana Herrera-Melendez applied the direct current stimulation devices before each psychotherapy session. She assessed possible acute adverse effects before each session. Herrera-Melendez aided in patient recruiting and acquired clinical data. She was also involved in the revision of the manuscript.

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Signature, date and stamp of first supervising university professor

Signature of doctoral candidate

IV. Journal Summary List (ISI Web of Knowledge) and print version of publication 1.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"PSYCHIATRY"** Selected Category Scheme: WoS
Gesamtanzahl: 214 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	World Psychiatry	5,426	34.024	0.014100
2	Lancet Psychiatry	4,887	18.329	0.022100
3	JAMA Psychiatry	10,894	15.916	0.055560
4	PSYCHOTHERAPY AND PSYCHOSOMATICS	3,892	13.744	0.005800
5	AMERICAN JOURNAL OF PSYCHIATRY	43,025	13.655	0.036370
6	MOLECULAR PSYCHIATRY	20,353	11.973	0.049290
7	BIOLOGICAL PSYCHIATRY	43,122	11.501	0.053320
8	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,660	8.272	0.030730
9	SCHIZOPHRENIA BULLETIN	17,794	7.289	0.025590
10	BRITISH JOURNAL OF PSYCHIATRY	25,101	7.233	0.022570
11	NEUROPSYCHOPHARMACOLOGY	25,672	7.160	0.039090
12	ADDICTION	19,945	6.851	0.032100
13	Epidemiology and Psychiatric Sciences	1,217	6.402	0.003830
14	JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY	19,942	6.391	0.019370
15	BRAIN BEHAVIOR AND IMMUNITY	14,533	6.170	0.025700
16	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	19,072	6.129	0.023100
17	PSYCHOLOGICAL MEDICINE	25,176	5.641	0.038080
18	JOURNAL OF ABNORMAL PSYCHOLOGY	15,807	5.519	0.014930
19	Translational Psychiatry	7,313	5.182	0.024860
20	AUSTRALIAN AND NEW ZEALAND JOURNAL OF PSYCHIATRY	7,078	5.000	0.008330

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	BIPOLAR DISORDERS	5,143	4.936	0.006760
22	DEPRESSION AND ANXIETY	8,537	4.935	0.014490
23	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	3,293	4.899	0.004540
24	Journal of Behavioral Addictions	1,642	4.873	0.004340
25	ACTA PSYCHIATRICA SCANDINAVICA	13,340	4.694	0.010630
26	SCHIZOPHRENIA RESEARCH	22,220	4.569	0.029410
27	CURRENT OPINION IN PSYCHIATRY	4,030	4.483	0.006280
28	EUROPEAN NEUROPSYCHOPHARMACOLOGY	7,488	4.468	0.015500
29	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	10,674	4.315	0.012400
30	JOURNAL OF PSYCHOPHARMACOLOGY	6,460	4.221	0.010120
31	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,551	4.207	0.012320
32	CNS DRUGS	4,602	4.192	0.007190
33	JOURNAL OF AFFECTIVE DISORDERS	30,314	4.084	0.052950
34	CANADIAN JOURNAL OF PSYCHIATRY-REVUE CANADIENNE DE PSYCHIATRIE	5,658	4.080	0.006390
35	WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY	2,429	4.040	0.004200
36	JOURNAL OF CLINICAL PSYCHIATRY	19,074	4.023	0.019900
37	PSYCHONEUROENDOCRINOLOGY	16,809	4.013	0.028150
38	EUROPEAN PSYCHIATRY	5,610	3.941	0.008420
39	CNS SPECTRUMS	2,368	3.940	0.003340
40	PSYCHOSOMATIC MEDICINE	12,747	3.937	0.009630
41	JOURNAL OF PSYCHIATRIC RESEARCH	15,180	3.917	0.020850
42	Current Psychiatry Reports	4,050	3.816	0.009260

With a Rank of 28 out of 214, European Neuropsychopharmacology is in the top 25% of the Psychiatry journals.

Herrera-Melendez AL, Stippl A, Aust S, Scheidegger M, Seifritz E, Heuser-Collier I, Otte C, Bajbouj M, Grimm S, Gartner M. 2021. Gray matter volume of rostral anterior cingulate cortex predicts rapid antidepressant response to ketamine. Eur Neuropsychopharmacol 43, 63-70.

https://doi.org/10.1016/j.euroneuro.2020.11.017

V. Journal Summary List (ISI Web of Knowledge) and print version of publication 2.

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS
Gesamtanzahl: 271 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	42,809	33.654	0.055400
2	NATURE NEUROSCIENCE	62,933	20.071	0.144390
3	BEHAVIORAL AND BRAIN SCIENCES	9,395	17.333	0.008170
4	TRENDS IN COGNITIVE SCIENCES	27,705	15.218	0.036050
5	JOURNAL OF PINEAL RESEARCH	10,537	14.528	0.009430
6	NEURON	95,056	14.415	0.199640
7	ACTA NEUROPATHOLOGICA	21,908	14.251	0.040740
8	TRENDS IN NEUROSCIENCES	20,011	12.891	0.021220
9	Annual Review of Neuroscience	13,215	12.547	0.012740
10	MOLECULAR PSYCHIATRY	22,227	12.384	0.054730
11	Nature Human Behaviour	2,457	12.282	0.014190
12	BIOLOGICAL PSYCHIATRY	44,016	12.095	0.053910
13	BRAIN	53,282	11.337	0.067050
14	SLEEP MEDICINE REVIEWS	8,077	9.613	0.013000
15	Molecular Neurodegeneration	4,933	9.599	0.011840
16	PROGRESS IN NEUROBIOLOGY	12,791	9.371	0.011250
17	FRONTIERS IN NEUROENDOCRINOLOGY	4,491	9.059	0.007050
18	ANNALS OF NEUROLOGY	37,304	9.037	0.044120
19	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	28,873	8.330	0.051900
20	Neurology-Neuroimmunology & Neuroinflammation	2,232	7.724	0.008400
21	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,992	7.500	0.005960

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
22	Neurobiology of Stress	1,055	7.197	0.003840
23	NEUROPSYCHOPHARMACOLOGY	26,281	6.751	0.040680
24	npj Parkinsons Disease	662	6.750	0.002500
25	BRAIN BEHAVIOR AND IMMUNITY	16,285	6.633	0.028560
26	Brain Stimulation	6,537	6.565	0.015580
27	NEUROSCIENTIST	5,188	6.500	0.007220
28	Acta Neuropathologica Communications	4,070	6.270	0.014730
29	CURRENT OPINION IN NEUROBIOLOGY	14,959	6.267	0.028730
30	Alzheimers Research & Therapy	3,876	6.116	0.011650
31	Neurotherapeutics	4,998	6.035	0.009520
32	GLIA	14,220	5.984	0.017250
33	NEUROIMAGE	102,632	5.902	0.125360
34	Annual Review of Vision Science	601	5.897	0.003700
35	Molecular Autism	2,510	5.869	0.007450
36	Journal of Neuroinflammation	13,709	5.793	0.025870
37	Translational Stroke Research	2,274	5.780	0.004520
38	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,492	5.681	0.024230
39	JOURNAL OF NEUROSCIENCE	167,114	5.673	0.181170
40	BRAIN PATHOLOGY	5,308	5.568	0.007020
41	Translational Neurodegeneration	1,030	5.551	0.002790
42	NEURAL NETWORKS	14,065	5.535	0.018910
43	PAIN	37,753	5.483	0.035730

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
44	Multiple Sclerosis Journal	11,792	5.412	0.019460
45	BIPOLAR DISORDERS	4,838	5.410	0.006610
46	Dialogues in Clinical Neuroscience	3,842	5.397	0.005280
47	Biological Psychiatry-Cognitive Neuroscience and Neuroimaging	1,361	5.335	0.005880
48	NEUROBIOLOGY OF DISEASE	17,200	5.332	0.023770
49	Brain Connectivity	2,431	5.263	0.005180
50	Journal of Parkinsons Disease	2,244	5.178	0.005810
51	CEREBRAL CORTEX	30,815	5.043	0.056030
52	Developmental Cognitive Neuroscience	3,177	4.966	0.010180
53	CEPHALALGIA	11,053	4.868	0.011970
54	NEUROPSYCHOLOGY REVIEW	3,114	4.840	0.004050
55	SLEEP	22,296	4.805	0.024610
56	JOURNAL OF HEADACHE AND PAIN	3,898	4.797	0.007600
57	PSYCHONEUROENDOCRINOLOGY	19,287	4.732	0.027100
58	JOURNAL OF NEUROSCIENCE RESEARCH	13,098	4.699	0.010490
59	EXPERIMENTAL NEUROLOGY	20,154	4.691	0.020070
60	Molecular Brain	2,785	4.686	0.006510
61	Current Neuropharmacology	4,178	4.668	0.006280
62	JOURNAL OF PAIN	10,887	4.621	0.015040
63	JOURNAL OF PHYSIOLOGY-LONDON	50,045	4.547	0.037090
64	EUROPEAN JOURNAL OF NEUROLOGY	11,015	4.516	0.017330
65	MOLECULAR NEUROBIOLOGY	15,297	4.500	0.031350

With a Rank of 59 out of 271, Experimental Neurology is in the top 25% of the Neuroscience journals.

Gartner M, Ghisu E, **Herrera-Melendez AL,** Koslowski M, Aust S, Asbach P, Otte C, Regen F, Heuser I, Borgwardt K, Grimm S, Bajbouj M. 2021. Using routine MRI data of depressed patients to predict individual responses to electroconvulsive therapy. Exp Neurol 335, 113505.

https://doi.org/10.1016/j.expneurol.2020.113505

VI. JOURNAL SUMMARY LIST (ISI WEB OF KNOWLEDGE) AND PRINT VERSION OF PUBLICATION 3.

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,
Selected Categories: **"PSYCHIATRY"** Selected Category
Scheme: WoS
Gesamtanzahl: 156 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	World Psychiatry	9,619	49.548	0.020030
2	Lancet Psychiatry	14,839	27.083	0.036240
3	JAMA Psychiatry	19,105	21.596	0.052990
4	AMERICAN JOURNAL OF PSYCHIATRY	48,206	18.112	0.031970
5	PSYCHOTHERAPY AND PSYCHOSOMATICS	6,123	17.659	0.006750
6	MOLECULAR PSYCHIATRY	28,622	15.992	0.046220
7	BIOLOGICAL PSYCHIATRY	50,155	13.382	0.045540
8	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	37,094	10.154	0.026380
9	BRITISH JOURNAL OF PSYCHIATRY	30,003	9.319	0.019160
10	SCHIZOPHRENIA BULLETIN	21,642	9.306	0.023290
11	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	25,273	8.982	0.021190
12	JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY	25,046	8.829	0.017190
13	Evidence-Based Mental Health	1,201	8.141	0.003220
14	NEUROPSYCHOPHARMACOLOGY	30,856	7.853	0.034600
15	PSYCHOLOGICAL MEDICINE	34,876	7.723	0.038850
16	BRAIN BEHAVIOR AND IMMUNITY	24,161	7.217	0.026930
17	Clinical Psychological Science	3,811	7.169	0.010420
18	Epidemiology and Psychiatric Sciences	2,571	6.892	0.005580
19	Journal of Behavioral Addictions	4,024	6.756	0.008100
20	BIPOLAR DISORDERS	6,185	6.744	0.007510

With a Rank of 3 out of 156, JAMA Psychiatry is in the top 25% of the Psychiatry journals.

Aust S, Brakemeier EL, Spies J, Herrera-Melendez AL, Kaiser T, Fallgatter A, Plewnia C, Mayer SV, Dechantsreiter E, Burkhardt G, Strauss M, Mauche N, Normann C, Frase L, Deuschle M, Bohringer A, Padberg F, Bajbouj M. 2022. Efficacy of Augmentation of Cognitive Behavioral Therapy With Transcranial Direct Current Stimulation for Depression: A Randomized Clinical Trial. JAMA Psychiatry 79, 528-537.

https://doi.org/10.1001/jamapsychiatry.2022.0696

VII. CURRICULUM VITAE

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

VIII. COMPLETE LIST OF PUBLICATIONS

Aust S, Brakemeier EL, Spies J, **Herrera-Melendez AL**, Kaiser T, Fallgatter A, Plewnia C, Mayer SV, Dechantsreiter E, Burkhardt G, Strauß M, Mauche N, Normann C, Frase L, Deuschle M, Böhringer A, Padberg F, Bajbouj M. 2022. Efficacy of Augmentation of Cognitive Behavioral Therapy With Transcranial Direct Current Stimulation for Depression: A Randomized Clinical Trial. JAMA Psychiatry doi: 10.1001/jamapsychiatry.2022.0696. Epub ahead of print. (Impact factor: 21.596)

Herrera-Melendez AL, Acquarone D, Kreutz R. 2021. Cases of exposure to disinfectants from children under 6 years of age in Germany during the COVID-19 pandemic. Dtsch Arztebl Int 118, 300-301. (Impact factor: 5.594)

Stippl A, Scheidegger M, Aust S, **Herrera-Melendez AL,** Bajbouj M, Gartner M, Grimm S. 2021. Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. J Psychiatr Res 136, 402-8. (Impact factor: 4.791)

Herrera-Melendez AL, Stippl A, Aust S, Scheidegger M, Seifritz E, Heuser-Collier I, Otte C, Bajbouj M, Grimm S, Gartner M. 2021. Gray matter volume of rostral anterior cingulate cortex predicts rapid antidepressant response to ketamine. Eur Neuropsychopharmacol 43, 63-70. (Impact factor: 4.468)

Gartner M, Ghisu E, **Herrera-Melendez AL,** Koslowski M, Aust S, Asbach P, Otte C, Regen F, Heuser I, Borgwardt K, Grimm S, Bajbouj M. 2021. Using routine MRI data of depressed patients to predict individual responses to electroconvulsive therapy. Exp Neurol 335, 113505. (Impact factor: 4.691)

Herrera-Melendez AL, Bajbouj M, Aust S, 2020. Application of Transcranial Direct Current Stimulation in Psychiatry. Neuropsychobiology 79, 372-383. (Impact factor: 2.328)

Fan Y, Borchardt V, von During F, Leutritz AL, Dietz M, **Herrera-Melendez AL,** Bajbouj M, Li M, Grimm S, Walter M. 2019. Dorsal and Ventral Posterior Cingulate Cortex Switch Network Assignment via Changes in Relative Functional Connectivity Strength to Noncanonical Networks. Brain Connect 9, 77-94. (Impact factor: 5.263)

Bajbouj M, Aust S, Spies J, **Herrera-Melendez AL,** Mayer SV, Peters M, Plewnia C, Fallgatter AJ, Frase L, Normann C, Behler N, Wulf L, Brakemeier EL, Padberg F. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. 2018. Eur Arch Psychiatry Clin Neurosci 268, 797-808. (Impact factor: 3.192)

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