Structural changes induced by electroconvulsive therapy are associated with clinical outcome

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Background: Electroconvulsive therapy (ECT) is the most effective treatment option for major depressive disorder, so understanding whether its clinical effect relates to structural brain changes is vital for current and future antidepressant research.

Objective: To determine whether clinical response to ECT is related to structural volumetric changes in the brain as measured by structural magnetic resonance imaging (MRI) and, if so, which regions are related to this clinical effect. We also determine whether a similar model can be used to identify regions associated with electrode placement (unilateral versus bilateral ECT).

Methods: Longitudinal MRI and clinical data (Hamilton Depression Rating Scale) was collected from 10 sites as part of the Global ECT-MRI research collaboration (GEMRIC). From 192 subjects, relative changes in 80 (sub)cortical areas were used as potential features for classifying treatment response. We used recursive feature elimination to extract relevant features, which were subsequently used to train a linear

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Introduction

Major depressive disorder is a leading cause of disability worldwide and one of the biggest challenges the field of mental health faces today [1]. High prevalence and the fact that up to a third of patients suffering from depression fail to respond to conventional pharmaco- or psychotherapy [2] has renewed scientific interest in electroconvulsive therapy (ECT), which achieves a fast antidepressant response in a majority of these treatment-resistant patients [3]. Understanding the mechanisms through which ECT achieves its remarkably strong clinical effect could provide critical biological markers to advance both established and emerging antidepressant therapies. To this end, the Global ECT-MRI Research Collaboration (GEMRIC) was founded to pool data from multiple sites to increase power and enable analyses that cannot be performed on smaller samples [4].

Over the past years an emerging body of literature has investigated ECT-related changes in brain structure and, to a lesser degree, function. A recent explorative GEMRIC analysis of structural change reported volumetric increases in 79 of 84 grey matter regions, which linked to electrode placement (uni- or bilateral) and number of ECTs, but not to clinical outcome [5]. While others have also observed widely distributed effects throughout the brain [6–10], several regions have been more consistently implicated as relevant to ECT’s antidepressant effects. Stimulated by translational studies on neurotrophic effects of ECT, medial temporal lobe structures including the hippocampus and amygdala have been subject to a number of investigations [7,11–13]. Nearly all these studies report significant volume increases after ECT, which has been confirmed through meta-analyses [14,15]. In a recent GEMRIC mega-analysis this increase in hippocampal volume after ECT was again related to both electrode placement and number of ECT sessions administered [16], but while translational and human studies have suggested a link between hippocampal volume and behavioral changes [17–21], no relation to treatment outcome was established. Furthermore, follow-up studies have found the increase in medial temporal lobe volume to be transient in nature [22,23]. Other areas of interest reported across multiple studies are the anterior cingulate cortex (ACC) [8,10,24,25], the insula [26,27] and the striatum [6,27,28]. Critically, all of these regions are also affected in patients suffering from depression, with recurrent or treatment-resistant patients being typically more affected [29–32].

So, although ECT induces prominent and widespread structural changes, it remains unclear whether these changes are related to its antidepressant properties [15,16,33]. A lack of reproducible links between structural changes and clinical efficacy of ECT could indicate that either treatment response to ECT is not related to any structural changes in the brain or that samples and methods used so far have been underpowered to detect a statistically and clinically relevant relationship. An important limitation here is that most studies have employed a univariate approach, attempting to link clinical improvement to structural change in a single region, while both depression and ECT are known to affect various interacting regions and circuits throughout the brain which makes it unlikely that response depends on changes in a single region [30,34]. To address this issue, we use the aforementioned GEMRIC dataset to investigate whether 1) patterns of structural changes in the brain induced by ECT are related to clinical response and 2) if so, which regions in these patterns are most relevant for treatment response. We employ multivariate discriminant analysis to test whether a model that can discriminate responders from non-responders on the basis of volumetric changes detected with structural MRI can be developed. Such a model provides both the flexibility of not needing strong prior assumptions on where clinically relevant effects happen as well as the appropriate multivariate linear framework allowing us to identify which regions contribute to ECT’s remarkable clinical effect.

Methods

Participants and neuroimaging data

We use data from the Global ECT-MRI Research Collaboration (GEMRIC), a multi-site initiative pooling clinical and neuroimaging data of ECT patients. Informed consent was obtained from all patients. For our analysis we use data from 10 GEMRIC sites for a total of 237 depressed subjects who had received either right unilateral or bilateral ECT (or both) with available imaging and clinical data (depression severity, either 17-item Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale converted to HAM-D through the method described by Heo et al. [35]). For a detailed description of GEMRIC including site-specific ECT procedures, image acquisition and common data processing methods, we refer to Oltedal et al. [4]. In short, the data includes patients with a depressive episode who were eligible to receive ECT, most typically after failure to respond to conventional psycho- and pharmacotherapy. There are some regional differences in ECT procedure used among the sites in our sample, including electrode placement which varies between right unilateral only, bilateral only or initial right unilateral with a switch to bilateral after non-response. For each subject, response was defined as a decrease of 50% or more on HAM-D score.

T1-weighted MRI volumes with a minimum resolution of 1.3 mm³ were acquired before and after ECT using either a 1.5T or 3T scanner. Imaging data were analyzed using a common pipeline. Images were corrected for scanner-specific gradient nonlinearity [36], registered to a common atlas and resampled to 1 mm³ resolution. FreeSurfer 5.3 was used to obtain measures of cortical and subcortical volumes [37–39]. Longitudinal change was estimated using Quarc [40], for a total of 80 longitudinal features per subject (see supplementary information for the full feature list). Due to the lack of robust clinically relevant effects found in ECT and the widespread effect ECT has on brain volume we did not select only regions-of-interest.

classifier. As a validation, the same was done for electrode placement. We report accuracy as well as the structural coefficients of regions included in the discriminative spatial patterns obtained.

Results: A pattern of structural changes in cortical midline, striatal and lateral prefrontal areas discriminates responders from non-responders (75% accuracy, p < 0.001) while left-sided mediotemporal changes discriminate unilateral from bilateral electrode placement (81% accuracy, p < 0.001).

Conclusions: The identification of a multivariate discriminative pattern shows that structural change is relevant for clinical response to ECT, but this pattern does not include mediotemporal regions that have been the focus of electroconvulsive therapy research so far.

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Analysis

80 different regions were tested for association with treatment response by means of a penalized Linear Discriminant Analysis (LDA). Because of sensitivity to outliers in feature selection, we excluded patients that were extreme outliers (>3 standard deviations) on any of the 80 imaging features for a final sample of 192 subjects. A leave-one-subject out design, using volume normalization and recursive feature elimination with internal cross-validation, provided 192 model estimates of features relevant for discrimination between responders and non-responders [41].

Due to the large number of features compared to the number of subjects in the smallest group, we observed high variance in the number of relevant brain areas selected at each fold. Consequently, to get a unique set of relevant features we removed features that were selected less than –1% of all models (2 models). To validate the quality of the set of selected brain areas, we used these remaining features to train a linear classifier (LDA, least squares fit with automatic shrinkage estimation) which provided us with the learned model accuracy. The performance of this model was then evaluated by means of permutation testing (1000 permutations, where within each iteration the labels are randomized and our model is tested against the “chance” model) [42]. Due to the large number of features in contrast to our smallest group (72 non-responders), we were unable to select features, train and test the model in independent samples. As such, while our sample is diverse and contains data from various research sites, the model accuracy is an indication of picking up relevant within-sample signal, rather than the estimated accuracy should it be applied to an out-of-sample dataset. Using both leave-one out and stratified 10-fold cross-validation gives insight into how the model accuracy changes based on a different split of the data.

Because we use a linear model, we can interpret the weights from the classifier by transforming them to structural coefficients as described by Haufe et al. [43]. This transform helps us discern weights that contribute to classification from those included to cancel noise that obscures the underlying relevant discriminative properties. These structural coefficients are more informative for the classification of interest the further they are from zero, while their sign indicates how values are indicative of belonging to one class over the other. These coefficients together make up a discriminative map that indicates regional predictive power for clinical improvement.

We used this analysis to detect which regions are related to treatment response to answer our main research question. To assess how our model is affected by variables that are inherently linked to treatment trajectory and effect, we also test the model taking into account age, sex, number of ECT sessions and electrode placement by regressing these variables out of the imaging data before training the classifier. We also test for site-differences by training the classifier excluding each site and predicting treatment response in the site left out. Finally, as an additional validation strategy for our analysis, we apply the same method to obtain a discriminative map for regions associated with site of electrode placement (defined as having received either right unilateral treatment only (RUL) versus bilateral treatment only or unilateral followed by bilateral treatment (BL)). All analyses were performed in python using the scikit-learn toolkit [44] and results were visualized using a template [45].

Results

Demographics

Key demographics are presented in Table 1. Notably, there is a clear treatment effect for ECT, which separates responders from non-responders, and these groups also differ in age (p < 0.001), but not sex or baseline clinical score. As expected, non-responders have a higher likelihood of receiving bilateral ECT, as a switch from unilateral to bilateral treatment is common practice after initial non-response. Within our sample 62.5% were responders and 61% received exclusively unilateral ECT while the other 39% received only bilateral ECT (n = 39) or switched to bilateral ECT after non-response to unilateral treatment (n = 36).

General effects

In line with earlier work [5], all features included in the analysis showed an average positive increase in volume, ranging from 0.2 to 5.1%. This increase is more pronounced in lateral and mediobasal temporal regions (amygdala, hippocampus, entorhinal cortex, temporal pole), while changes in parietal and occipital regions were relatively small (see Supplementary Table S1 for baseline and changes per region).

Feature selection and analysis

Treatment response

The feature selection procedure over 192 iterations selected on average 8.9 features (±2.4 features, median 8). 18 features were selected by more than 1% of all models (see Supplementary Table S2 for probabilities). Using these features, we trained a linear classifier (LDA), which performed with an accuracy of 75% to classify treatment response (sensitivity 84%, specificity 60%), which is significantly better than chance (p < 0.001; stratified 10-fold accuracy 72%, p < 0.001; split-half accuracy 66%, p < 0.001). Per-site accuracy scores are presented in Supplementary Table S3. The discriminative pattern remained significant after regressing out age, sex, number of ECT sessions and electrode placement (p < 0.001, Supplementary Table S4).

The relevant features, ranked by their structural coefficients [43], are presented in Fig. 1 and Table S5. From highest to lowest importance, the contributing regions are the right precuneus (0.27), right putamen (−0.26), left rostral ACC (−0.21), right supramarginal gyrus (0.17), left rostral middle frontal gyrus (−0.16), right caudal ACC (0.16), right rostral ACC (−0.11), left fusiform gyrus (0.11), left precuneus (0.11), left middle temporal cortex (−0.11), right supramarginal gyrus (0.09), right frontal pole (0.06), left entorhinal cortex (−0.06), right precentral cortex (−0.05), left banks of the superior temporal sulcus (−0.04), left isthmus cingulate (−0.02), left fusiform gyrus (0.02) and right parahippocampal cortex (0.01). The signs of the coefficients indicate that larger increases in volume in the bilateral precuneus, supramarginal gyrus and right caudal ACC are more indicative of being a responder to ECT, while larger increases in right putamen, left rostral middle frontal gyrus and rostral ACC are more indicative of being a non-responder.

As is evident by the discriminative map presented, while all regions add classification accuracy, some regions are highly relevant for discriminating responders from non-responders as represented in high absolute structural coefficients (right precuneus, right putamen, right supramarginal, left rostral ACC, left rostral middle frontal gyrus, right caudal ACC), while other regions are almost exclusively cancelling noise to uncover the relevant signal (structural coefficient close to zero: left fusiform gyrus, right parahippocampal cortex, left isthmus cingulate, left banks of the superior temporal sulcus, right precentral cortex).
Feature selection for electrode placement revealed 31 features of interest. The linear classifier trained using these features classified electrode placement with an accuracy of 81% (sensitivity 90%, specificity 68%, \( p < 0.001 \)). The full set of features and their structural coefficients are presented in Fig. 2 (and Supplementary Table S6). Most notably, the obtained discriminative map shows a strong contribution of left-sided regions known to be affected differently by electrode placement: the left amygdala (0.28), left hippocampus (0.21) and left entorhinal cortex (0.24). Larger changes in these regions are indicative of having received bilateral over unilateral ECT.

**Discussion**

Understanding the neural mechanisms underlying the most potent antidepressant treatment available is an important step towards advancing current and novel treatment strategies, as well as reducing stigma surrounding psychiatric disorders and their treatments. As such, information on whether structural changes in the brain are relevant for treatment response is a simple yet fundamental question that needs to be addressed. We show, by
means of training a linear classifier, that a pattern of structural changes in the brain is associated with clinical response to ECT. Regions identified as contributing to response are located in cortical midline, striatal and lateral prefrontal areas implicated in the pathophysiology of depression. In addition, we dissociate regions related to treatment response from those related to site of electrical stimulation by showing that the type of ECT used (unilateral or bilateral) can be identified by a discriminative map that incorporates unilateral medial temporal regions that are known to be affected by ECT [46]. Below, we will discuss the significance of these findings.

To interpret our results in the light of earlier work, it is important to distinguish that our multivariate model is not directly comparable with the majority of univariate analyses; none of the regions associated with treatment response or electrode placement does so independently. Instead, multivariate analysis takes the full pattern of structural changes into account and allows us to discriminate responders from non-responders. Furthermore it is able to discriminate bilateral from unilateral ECT which, given the clinical discussion on preference of unilateral versus bilateral stimulation, could aid in uncovering neuroimaging correlates of different approaches to ECT. In addition to the multivariate interpretation, the sign of the structural coefficients as derived from the feature weights relates to increases in volume, within the pattern as a whole, being either indicative of response (bilateral precuneus, supramarginal gyrus and right caudal ACC) or non-response (right putamen, rostral ACC, left rostral middle frontal gyrus).

We observe that the predominantly bilateral regions contributing significantly to classification of treatment response are consistent with other work indicating aberrant structure and/or function in cortico-limbic and cortico-striatal systems in depression. In fact, all of the discriminative regions have previously been demonstrated to show changed (mostly decreased) volume [29,30,32,47,48] and dysconnectivity within large-scale functional networks [49–52] in depression. Several of these regions are well established in the context of depression and warrant additional consideration here.

The precuneus is part of the posterior default mode network and is associated with self-related processing and episodic memory retrieval [53,54]. There is evidence of decreased volume in the precuneus in first-episode depression [55], and altered function or functional connectivity during rest [55–58] and self-related judgment [59]. Preliminary evidence also links changes in precuneus activity or network connectivity to treatment with antidepressants [60], psychotherapy [61] and ECT [56]. The anterior cingulate cortex is a core region within the anterior default mode network [62], showing decreased volume [29,30,32] and typically increased activation during rest in depressed patients [62,63], which has been suggested as a biomarker for treatment response to various forms of biological treatment up to deep brain stimulation [62,64]. Importantly, activity within the anterior cingulate cortex appears to be highly context-sensitive, in line with its function in self-referential emotional processing and the attribution of valence to external stimuli [65–67]. The left rostral middle frontal cortex
includes the dorsolateral prefrontal cortex and is part of the cognitive-executive network, a functional hub that exerts top-down cognitive control over cortical midline and limbic regions, a balance that has been shown to be dysfunctional in depression [68–70]. Antidepressant effects have been found in this region in response to antidepressants [71] and ECT [72], and left dorsolateral prefrontal cortex is currently the primary target for transcranial magnetic stimulation for depression. A recent study has also shown how various lesions in a brain circuit centered around the dorso- lateral prefrontal cortex link to depression [73]. Finally, the discriminative relevance of the putamen is consistent with reports of reduced putamen volume in depression [32,75] and the relevance of the striatum in the context of depression and as a potential marker for treatment response [64]. Taken together our finding that these regions, which are critical to our discriminative pattern, are already established as key depression hubs, potential biomarkers of treatment response, and/or the target for other neuromodulation techniques [74], gives further credence to our method detecting relevant response-related effects.

We also report that structural changes in the main regions under investigation in the context of ECT, the hippocampus and amygdala, are not included in the pattern associated with treatment response. This is in line with a lack of any reproducible findings linking volumetric changes in these regions to clinical effects in either depression or ECT [14,16]. One possible explanation is that not the hippocampus as a whole, but rather specific subfields within the hippocampus such as the dentate gyrus (or granule cell layer) are relevant for clinical response [75,76]. Medial temporal regions also appear differentially engaged by unilateral or bilateral ECT, as is evident by unilateral medial temporal changes being associated with electrode placement. Recent work within GEMRIC has shown how structural changes are affected by local electric fields [77], which could further explain differences between stimulation methods. This is consistent with differences in cortical volume [78], cerebral blood flow [11] and seizure propagation [79] between unilateral and bilateral ECT. More expansive engagement of medial temporal regions in bilateral ECT might be related to the higher occurrence of cognitive side-effects in bilateral versus unilateral ECT [80,81]. Overall, no single region was in itself predictive of treatment response or electrode placement at the level of the multivariate solution, corresponding to our current understanding of depression as a multi-systems level disorder encompassing large-scale brain networks and with the large-scale engagement of the brain in ECT [82]. As such, a multivariate approach appears more suitable to further conceptualize neuroimaging markers of antidepressant response.

In light of their expansiveness and the time frame of structural changes induced by ECT, there has been much discussion on their biological nature. While some have suggested they could be attributable to edema caused by the electrical stimulus itself, this notion is not supported by studies using T2-relaxometry to detect significant fluid shifts [12,83,84]. A prominent hypothesis posits that ECT combats depression by inducing neurotrophic effects [85], in line with volumetric decreases in depression [30,31]. Indeed, preclinical studies of ECT have found support for neurogenesis [18,86], angiogenesis [87], glial cell proliferation [88] and increased dendritic complexity and synaptogenesis [89]. Certainly, in ECT, neurogenesis is not the only factor at play as neurogenesis is slow compared to ECT-induced volume changes and is limited to the dentate gyrus and subventricular zone, while ECT-induced volume changes occur across the brain. In patients, support for neuroplastic effects is represented by increases in plasma and serum brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor after ECT [90,91] but while persistent depression has been associated with decreased peripheral BDNF, its prognostic value may be limited [92–94]. Furthermore, while volumetric increases after ECT become more pronounced as the number of ECT sessions increases, they revert back to pre-treatment levels after 6 [22,23,95] and 12 months [23]. Consistent with the lack of a clear relation of ECT-induced volumetric changes to clinical efficacy, their return to pre-treatment levels has not been found to be related to either relapse of depression or recovery from cognitive side-effects [22,23,95].

Taken together, it is likely that not one but multiple neuroplastic systems are engaged during and after ECT and operate on varying timescales to affect both short and longer-term changes in structure and function. How these neuroplastic changes can help to overcome depression is still largely unknown, but one possibility is that this forging or restoring of connections within large scale networks that are dysfunctional in depression helps to overcome depressogenic pathways. Better characterization of changes over time, as opposed to only before and after treatment, their relation to both response and relapse, and integration of structural and functional imaging could be beneficial in understanding these effects.

Despite our promising results there are some limitations that need addressing. While we use both a statistical and biological validation for the method used, we are still limited by trying to optimize covariance space of 80 features in a sample with 72 non-responders, which restricts us to selecting the relevant features and building the classifier using the same data while ideally those processes would be split. Although we validate our discriminative pattern by cross-validation and our methods by applying it to well-known unilateral effects (site of electrode placement), there is still a risk of overfitting the feature selection to our specific dataset. As such, accuracy of the model should be interpreted as indicative of within-sample performance; additional work should confirm whether this pattern holds in independent samples. Furthermore, the FreeSurfer parcellation, while robust and sufficiently validated, remains an average representation of more localized variations in structure. Finer grained parcellations could provide more insight into the areas identified in this paper here or areas whose relevance is now undervalued by their inclusion into a larger region, such as the dentate gyrus [75,76]. In addition, subject-specific information such as stimulation parameters other than electrode placement might also affect structural changes differently, which we were unable to take into account. Finally, while multivariate analyses are powerful in detecting relevant patterns, with an increase in the number of relevant regions their interactions become more complex to interpret.

**Conclusion and future**

In conclusion, we show that structural brain changes are indicative of treatment response to ECT, but not in the regions that are typically investigated (medial temporal areas). Instead, we observe this response to be related to cortical midline, striatal and lateral prefrontal areas implicated in the etiology of depression and its treatments. We show the power of collaborative efforts to tackle questions that would otherwise remain elusive and the power of explorative multivariate approaches when linking brain and behavior. Future studies could elaborate on our work, including replication in larger or independent samples, as well as integrating structural and functional data to reach a more comprehensive understanding of the mechanisms underlying antidepressant response.

**Declaration of competing interest**

The authors report no conflict of interest.
CRediT authorship contribution statement

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.02.020.

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