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# Differential Effects of Electroconvulsive Therapy in the Treatment of Major Depressive Disorder

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**Keywords**
Electroconvulsive therapy · Major depressive disorder · Antidepressant efficacy · Neurobiological markers of ECT response

**Abstract**
***Background/Aims/Methods:*** Electroconvulsive therapy (ECT) is still one of the most potent treatments in the acute phase of major depressive disorder (MDD) and particularly applied in patients considered treatment resistant. However, despite the frequent and widespread use of ECT for >70 years, the exact neurobiological mechanisms underlying its efficacy remain unclear. The present review aims to describe differential antidepressant and cognitive effects of ECT as well as effects on markers of neural activity and connectivity, neurochemistry, and inflammation that might underlie the treatment response and remission. ***Results:*** Region- specific changes in brain function and volume along with changes in concentrations of neurotransmitters and neuroinflammatory cytokines might serve as potential biomarkers for ECT outcomes. ***Conclusions:*** However, as current data is not consistent, future longitudinal investigations should combine modalities such as MRI, MR spectroscopy, and peripheral physiological measures to gain a deeper insight into interconnected time- and modality-specific changes in response to ECT.


Major depressive disorder (MDD) is a highly prevalent psychiatric disorder that pervades all socioeconomic classes. As a leading cause of medical disability, it has a huge negative impact on public health and productivity [1, 2]. In 2016, it ranked among the top 10 causes of medical conditions in all but 4 countries [3, 4]. Existing pharmacological therapies for MDD have a delayed onset of action and, even though standard antidepressant treatments are often effective, about 30% of patients suffering from MDD do not respond sufficiently to established pharmacological or psychotherapeutic treatments [5]. After nonresponse to 2 adequate treatments, a patient is described as having a treatment-resistant depression, which is associated with illness chronicity, a reduced quality of life, and a higher risk for suicide [6]. Especially for those patients, electroconvulsive therapy (ECT) is a recommended treatment strategy [7, 8]. It has response rates of 60–80%, making it one of the most potent and rapidly acting treatments for affective disorders [7].

During ECT, an electrical current is administered to the brain through the scalp, which provokes a therapeutic seizure. Usually, a series of ECTs (i.e., 9–12) is applied over several weeks [8]. ECT is effective in the treatment of uni- and bipolar depression but also other psychiatric disorders such as catatonia, mania, or schizophrenia [9–11]. Although international guidelines exist, there is no

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uniform global utilization regarding ECT provision, which results in a high variability between different countries and regions [12]. A general decline in utilization is observable in America, whereas an increase seems to be occurring in China [13]. Regarding ECT administration in Western countries, the majority of patients are older women with MDD, whereas in Asian countries younger men with schizophrenia constitute the majority [12]. Here we will focus on a description of the differential effects of ECT that might underlie the treatment response and remission in MDD.

Despite the frequent and widespread use of ECT for >70 years, the exact neurobiological mechanisms underlying its efficacy remain unclear. It seems to exert its antidepressant effect through its impact on regional brain structure and function via different neurotransmitter systems, inflammatory processes, and neurogenesis [8]. In a broader sense, understanding the therapeutic effects of ECT may also shed more light on the pathophysiological causes of severe depression and the mechanisms of action of effective treatments, and it might be the fundament for approaches aimed at individualizing therapy strategies.

## Parameters Predicting and Influencing the Antidepressant ECT Response

Investigations of clinical predictors of the ECT response have found that patients with depressive episode durations of <1 year or without a failed adequate antidepressant medication trial in the current episode most likely respond to ECT [14]. It has been suggested that ECT should be considered as the primary treatment strategy in special cases of depression requiring fast relief, such as severe psychotic depression and severe depression with psychomotor retardation, suicidality, or persistent food refusal [15]. Bipolar disorder, sex, age at onset, and the number of previous episodes were no significant predictors of response, whereas older age and psychotic features were weakly associated with a response to ECT. Additionally, it has been described that long-lasting mixed bipolar episodes and lifetime comorbidity with obsessive-compulsive disorder can predict a lack of response to ECT [16]. Increased ECT efficacy has mainly been observed in psychotic depression and patients who previously responded to ECT [17].

Specific epigenetic methylation patterns [18] and genotypes [19] might possibly predict the ECT response, although existing data exhibit large amounts of contradictions, requiring further investigations with larger sample sizes in order to draw final conclusions.

Although ECT is well tolerated and usually associated with improvement in patients' quality of life, functioning, and wellbeing, there are complaints about side effects such as cognitive deficits, headaches, and disorientation [20]. Particularly verbal episodic memory seems to be more disturbed by ECT than visual episodic memory. Processing speed, spatial problem solving, and global cognition demonstrate small impairments in comparison to baseline, while working memory does not seem to be affected. These cognitive deficits are mainly limited to the first 3 days after ECT and seem to be resolved within 2 weeks [21]. Accordingly, it has recently been confirmed that ECT does not lead to significant long-term memory impairments but rather to significant improvement 1 month after treatment, correlating with clinical improvement [22]. Thus, faced with the side effects of pharmacotherapy such as weight gain, sexual dysfunction, drug interactions, and discontinuation symptoms [23, 24], ECT has been proven to be beneficial not only due to the speed of recovery but also due to the short duration of the emerging side effects.

The efficacy and cognitive side effects of ECT seem to be influenced by parameters such as the positioning of electrodes, pulse width, and electrical dosage [25, 26]. There is evidence that right unilateral ECT at a high dosage is as effective as bilateral ECT but is accompanied by less cognitive side effects. When comparing different stimulus intensities (4×, 7×, and 10× above the seizure threshold), higher-intensity dosages seem to be associated with more cognitive side effects. Lower stimulus intensities, such as 4× to 7×, have demonstrated efficacies comparable to 10× without causing as many side effects [26]. A comparison of brief versus ultrabrief right unilateral ECT found the brief version to be more efficacious in terms of symptom reduction, simultaneously requiring fewer treatment sessions but leading to greater cognitive side effects [27].

Despite the relatively rapid and profound antidepressant effect of ECT in MDD, post-ECT relapse is frequent, especially if no maintenance treatment is supplied [28]. Since the relapse rates of ECT in patients with MDD amount to approximately 50% after 6–12 months, maintenance treatment involving ECT or pharmacotherapy should be carefully chosen and adapted according to the individual history [29]. The combination of acute ECT and pharmacotherapy followed by the combination of ECT and medication as maintenance therapy in uni- and bipolar depression is associated with lower relapse rates

than pharmacotherapy alone [30]. Recently, a third maintenance alternative in terms of cognitive-behavioral group therapy plus pharmacotherapy has been stated to be more effective and tolerable than pharmacotherapy alone or in conjunction with ECT [31].

Overall, ECT is a safe, well-tolerated treatment that provides a substantial long-term benefit and relapse prevention for a meaningful proportion of patients with severe MDD [32]. Even if a considerable proportion of patients experiences relapse, ECT remains one of the most effective antidepressant therapies [33].

### Volumetric and Functional Brain Changes after ECT

Significant volume increases after ECT that correlated with clinical improvement and might indicate that neurotrophic effects could be a part of the ECT mechanism of action were found in the anterior cingulate cortex (ACC) [34]. Moreover, a significant volume increase in both the hippocampus and the amygdala has been observed after ECT [35–38]. Surprisingly, even though the number of ECT sessions and the electrode placement influenced the extent and laterality of the hippocampal volume increase, no association with clinical outcome has been observed [39]. Similarly, an increase in temporomesial gray matter volume, mainly in the amygdala and the hippocampus, was not correlated with clinical change [40].

Brain volume might also be used as a prognostic biomarker. Accordingly, recent research has reported that a larger ACC volume prior to ECT is linked to treatment success [41]. Looking at limbic brain areas, it has been observed that larger pretreatment amygdala volume predicts better ECT response, whereby left amygdala volume seems to have a greater predictive value than right amygdala volume. Hippocampal volume on the other hand shows no independent predictive value [42].

Changes in resting-state network connectivity, referring to temporal correlating activity fluctuations between neuronal units, have been shown to interact with ECT treatment response. Dorsomedial prefrontal areas as well as ACC resting-state networks have been found to possibly predict the treatment outcome for individual patients [43]. A region in the medial prefrontal cortex defined as the dorsal nexus (DN) shows increased depression-associated functional connectivity (FC) with other networks implicated in different aspects of MDD [44]. Hence, it was suggested that reducing the increased connectivity of the DN might play a critical role in reducing the depressive symptomatology and thus represents a potential therapeutic target. This hypothesis is supported by recent findings in healthy subjects showing that also ketamine decreases the FC of the DN [45, 46]. A decreased FC between the DN and prefrontal areas such as the dorsolateral prefrontal cortex (DLPFC) might reflect restored aspects of emotional functioning while simultaneously contributing to the cognitive side effects of ECT [47].

Among the most consistent findings in depressive patients are alterations in resting state functional activation and connectivity in the pregenual ACC (pgACC), a region relevant for emotional processing and the establishment of mood states [48]. The pgACC is part of the default mode network [49], where activation is typically suppressed during the performance of cognitive or emotional tasks. The projection of the pgACC to the amygdala forms an important affective neurocircuitry for mood regulation since it allows for downregulation of the amygdala [50]. Overactivation of this affective processing network, in combination with a failing modulatory influence from prefrontal areas, may also contribute to the negative affective bias in MDD [51, 52]. Depressed patients show greater responses to negative stimuli in the amygdala [53], while reductions in pathologically exaggerate amygdala activation [54, 55] and changes in FC between pgACC and the amygdala [56] have been linked to psychopharmacological treatment. Successful ECT has been associated with decreased cerebral blood flow and glucose metabolism in the ACC and amygdala [57, 58].

Testing early versus later ECT effects on the FC might be a feasible way to detect clinical predictors. Thereby, evidence indicates that an early intralimbic FC decrease predicts a later increase in the limbic-prefrontal FC, which in turn predicts the ECT response [59]. Along those lines, future studies might focus on restoration of dysfunctional activation and connectivity patterns within and between prefrontal-limbic circuits, as these might potentially serve as treatment predictors [60, 61].

### Changes in Neurotransmission after ECT

Data from preclinical and clinical investigations suggests a key role of glutamate (Glu) in the pathophysiology of depression [62]. There is converging evidence for reduced levels of Glu and glutamine (Gln) in the pgACC [63, 64] and unchanged left DLPFC Glu concentrations [65, 66]. A reduced negative BOLD response during emotional processing in the pgACC has been related to reduced

Gln concentrations in this region and might be particularly pronounced in highly anhedonic patients [63].

ECT leads to alterations of glutamatergic neurotransmission, which seem to be crucially involved in its antidepressant efficacy [7, 67]. While some studies have reported increased Glx levels in the DLPFC and the ACC [67, 68] after ECT, others could not replicate these findings [66]. This might be due to the fact that the authors distinguished between Glu and Gln concentrations rather than using Glx, i.e., the combined values of these neurotransmitters.

Similarly conflicting results have been reported with regard to the hippocampus, where one recent study reported an association between hippocampal Glx increase and ECT response in treatment-resistant depression patients [69], although these results could not be confirmed by another report investigating uni- and bipolar patients with severe depression [38]. Altogether, glutamatergic brain metabolism emerges as an essential component in ECT efficacy but discrepancies in findings remain regarding the exact mechanism.

Also, diminished γ-aminobutyric acid (GABA) levels in the CSF and plasma, as well as a decreased GABA concentration in the frontal cortex, have been reported in MDD [70]. Accordingly, increased serum levels as well as occipital GABA concentrations have been observed after ECT [60, 61].

A growing body of evidence indicates that the ECT antidepressant response is also influenced by the 2 major amine systems associated with affective disorders, i.e., dopamine and serotonin [7]. Recent animal studies have indicated an increase in D2 receptor binding and dopamine-induced synaptic potentiation after ECT [71, 72]. Corroborating genetic and imaging data from human studies on ECT effects have reported increased serotonergic and mesocorticolimbic dopaminergic neurotransmission on various levels, starting from release over receptor binding up to signal transmission [7]. Also plasma (not only brain serotonin levels) has been reported to be increased after ECT [73].

As the different neurotransmitter systems involved in the antidepressant efficacy of ECT are interconnected via a complex network of signal transducing pathways, future studies could greatly benefit from more longitudinal multimodal designs involving measurement of different neurotransmission systems simultaneously.

Table 1 gives an extensive overview of neuroimaging studies on ECT effects.

### Effects of ECT on Inflammatory Processes

Inflammatory cytokines are of growing interest in depression research, as a significant subgroup of patients with mood disorders exhibits increased inflammation that is supposed to impact Glu metabolism. MDD patients show increased levels of cytokines such as IL-6, IL-1β, TNF-α, and CRP as well as a higher neutrophil/lymphocyte ratio. Bipolar patients show an additional increase in the platelet/lymphocyte ratio by which means these markers can be useful detectors of affective disorder related inflammation [74, 75]. Strikingly, a third of the depressive patient population shows increased cytokine levels even in the absence of a medical illness. Depression is more closely associated with inflammatory diseases than with noninflammatory ones and a higher baseline inflammation has been linked to a decreased antidepressant treatment response [76]. On the other hand, low-grade inflammation at baseline predicts a better ECT response in old patients [77], and this it is unclear whether this link exists for all ages.

The application of ECT in turn has been observed to first result in a transient immune activation, whereby repeated treatment rather induces long-term downregulation of the immune system [78]. Specifically, clinical improvement during ECT is accompanied by a gradual and significant decline in TNF-α, eventually reaching levels comparable with those in healthy controls. This decline could not be observed in depressed patients without ECT, who showed elevated TNF-α levels throughout the study period [79]. Inflammatory processes impact the majority of the mechanisms in Glu neurotransmission, including multiple cellular effects for instance on astrocytes and microglia, mediating Glu release as well as reuptake mechanisms [80]. This might indicate that inflammation can also serve as a biomarker for an altered Glu metabolism in depression as it may represent a pathophysiological pathway by which inflammation has an impact on the brain to influence behavior [81]. Glu released by astrocytes has preferential access to NMDA receptors that in turn decrease brain-derived neurotrophic factor (BDNF) and increase excitotoxicity [82, 83]. The result might be a decrease in neuroplasticity and neurogenesis that contributes to the loss of function and volume particularly in the prefrontal cortex [75].

In an animal model, electroconvulsive shocks but not pharmacological treatment normalized both the depressive-like behavioral impairments and the BDNF-related molecular alterations [84]. In patients, several studies

**Table 1.** Overview of neuroimaging studies on ECT effects

| Study | Subjects, *n* | Diagnosis | Study design | Rating scales | Main result |
|---|---|---|---|---|---|
| Ota et al. [34] | 15 | MDD | sMRI before and after ECT for GMV comparison | HAMD | GMV increase in the medial and inferior temporal cortices and the right ACC correlating with clinical response |
| Sartorius et al. [35] | 18 | MDD | sMRI before and after ECT for GMV comparison | HAMD | GMV increase in the temporal lobe, the hippocampus, and the amygdala following ECT; no correlation of GMV with clinical outcome |
| Tendolkar et al. [36] | 15 | MDD | sMRI before and after ECT analyzing hippocampus/amygdala volume | HAMD | Hippocampus and amygdala volume increase following ECT |
| Dukart et al. [37] | 19 vs. 15 | MDD and BD | Longitudinal sMRI at 3 different ECT time points (before and 3 and 6 months after), examining local anatomical effects attributable to ECT in patients vs. controls | HAMD | GMV increase following ECT only in the right hemisphere, restricted to the hippocampus, the amygdala, the anterior temporal pole, the insula, and the subgenual cortex |
| Jorgensen et al. [38] | 19 | MDD | Longitudinal sMRI, DTI, and MRS at 3 time points over the course of ECT to investigate volume, diffusivity, and metabolite changes in the hippocampus and other brain regions over the course of ECT | HAMD | Hippocampal and amygdala volume increase; DLPFC volume decrease; DTI revealed a reduced anisotropy and diffusivity of the hippocampus following ECT; no ECT-related brain metabolite changes; no imaging measures correlated with clinical outcome |
| Oltedal et al. [39] | 281 | MDD | sMRI before and after ECT examining hippocampal volume changes related to the ECT dosage in patients vs. healthy controls | MADRS + equated HAMD | Number of ECT and electrode placement impact the extent and laterality of hippocampal enlargement; no correlation with clinical outcome |
| Sartorius et al. [40] | 92 | MDD | sMRI before and after ECT to investigate GMV changes in patients vs. healthy controls | No rating scale | Longitudinal GMV increase occurs in the temporal lobe regions following ECT; within the specific region of interest, sign increases of GMV in the hippocampus and the amygdala; no correlation with clinical outcome |
| Redlich et al. [41] | 24 vs. 23 | MDD | sMRI obtained before and after ECT, about 6 weeks apart. Samples of ECT and medicated MDD patients compared to healthy controls | HAMD | A larger pretreatment subgenual cingulate volume is linked to ECT response |
| Ten Doesschate et al. [42] | 53 | MDD | sMRI before ECT examining the predictive value of amygdala and hippocampal volumes for ECT efficacy | MADRS | A larger pretreatment amygdala volume predicts more effective ECT |
| Van Waarde et al. [43] | 45 | MDD | rsfMRI before ECT investigating whether rs FC can predict treatment outcomes for individual patients | MADRS | DMPFC or ACC FC before ECT predicts MDD recovery with high sensitivity rates |
| Perrin et al. [47] | 9 | MDD | fMRI before and after ECT examining FC | MADRS | FC decrease in the left DLPFC correlating with clinical outcome |
| Beall et al. [52] | 6 | MDD | rsfMRI and fMRI during an affective working memory task before and after ECT examining ECT-induced cortical activation patterns | HAMD | An orbitofrontal activity decrease is associated with ECT response. FC increase of ACC to the right DLPFC and PCC before ECT |
| Redlich et al. [54] | 24 vs. 23 | MDD | fMRI during processing of emotional faces obtained before and after ECT, about 6 weeks apart. Samples of ECT and medicated MDD patients compared to healthy controls | HAMD | A decrease in amygdala activity to sad faces is associated with clinical improvement in the ECT sample |
| Nobler et al. [57] | 10 | MDD | PET before and after ECT examining regional cerebral metabolic rate for glucose | HAMD | Decreased regional cerebral glucose metabolism after ECT in the frontal and parietal cortex, the ACC, the PCC, and the left temporal cortex |

**Table 1** (continued)

| Study | Subjects, *n* | Diagnosis | Study design | Rating scales | Main result |
|---|---|---|---|---|---|
| Segawa et al. [58] | 10 | MDD | PET before and after ECT examining changes in rCBF | HAMD | rCBF in the left frontopolar gyrus, the left amygdala, the globus pallidus, the nucleus accumbens, and the left superior temporal gyrus correlates with clinical response |
| Cano et al. [59] | 15 | MDD | rsfMRI longitudinal intralimbic and limbic-prefrontal network connectivity study at 4 time points over the course of ECT in patients vs. healthy controls | HAMD | During early ECT sessions, an intralimbic FC decrease predicts a later increase in the limbic-prefrontal FC, which predicts clinical improvement at the end of the ECT course |
| Sanacora et al. [61] | 8 | MDD | MRS before and after ECT to examine cortical GABA concentrations | HAMD | Increase in the occipital cortex GABA concentration following ECT |
| Merkl et al. [66] | 25 | MDD | MRS before and after ECT to determine different metabolite concentrations in patients vs. healthy controls | HAMD | Baseline Glu and NAA levels are decreased in the cingulum of MDD patients; a high Glu level at baseline predicts a greater treatment response; responders show increased NAA levels after ECT and decreased NAA levels in the left DLPFC |
| Pfleiderer et al. [67] | 17 | MDD | MRS before and after ECT to assess the effect of successful ECT on Glx levels in the ACC in patients vs. healthy controls | MADRS | MDD patients exhibit reduced Glx levels in the left ACC that normalize in ECT responders until they no longer differ from age-matched controls |
| Michael et al. [68] | 12 | MDD | MRS of left DLPFC before and after ECT in patients vs. healthy controls | MADRS | In the left DLPFC of MDD patients pre-ECT Glx levels are reduced and correlate negatively with MDD severity; in ECT responders Glx levels increase until they no longer differ from age-matched controls |
| Kobayashi et al. [69] | 12 | MDD | Longitudinal sMRI and MRS at 4 time points over the course of ECT investigating changes in GMV and hippocampal metabolite concentrations in patients compared to healthy controls | HAMD | MTL and pgACC volume increase following ECT; a left MTL volume increase is associated with a hippocampal NAA decrease, a hippocampal Glx increase, and clinical improvement |

sMRI, structural magnetic resonance GMV, gray matter volume; HAMD, Hamilton Rating Scale for Depression; GM, gray matter; BD, bipolar disorder; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; MADRS, Montgomery-Asberg Depression Rating Scale; rsfMRI, resting-state functional magnetic resonance imaging; rs, resting state; FC, functional connectivity; DMPFC, dorsomedial prefrontal cortex; fMRI, functional magnetic resonance imaging; PCC, posterior prefrontal cortex; PET, position emission tomography; rCBF, regional cerebral blood flow; NAA, N-acetyl-aspartate; MTL, medial temporal lobe.

have observed increased serum or plasma BDNF levels after ECT [85], whereas others have found unaltered or decreased levels [86]. The difference in outcomes may be due to the fact that increases in peripheral BDNF levels may only reach their maximum 1 week to 1 month after the completion of ECT [87].

An investigation of the association of cytokine levels with Glu concentrations in distinct brain regions at several time points would help to elucidate whether inflammation might serve as a biomarker for altered Glu metabolism in MDD, with changes in cytokine levels associated with corresponding alterations in Glu concentrations reflecting or even predicting an ECT response.

## Summary and Outlook

ECT is still one of the most potent and rapidly acting treatments for MDD. However, the efficacy and cognitive side effects of ECT seem to be influenced by parameters such as the positioning of electrodes, pulse width, and electrical dosage. While findings are still conflicting and far from conclusive, it seems that ECT exerts its antidepressant effect through its impact on regional brain structure and function via different neurotransmitter systems, inflammatory processes, and neurogenesis. With regard to brain structure, volume increases in the ACC, the amygdala, and the hippocampus after ECT are of particular research interest; however, these increases are not nec-

essarily linked to clinical improvement. On the other hand, the pretreatment volume of the ACC and the amygdala has been linked to the ECT antidepressant response. Changes in functional activation and connectivity associated with ECT mainly concern key components of prefrontal-limbic circuits, such as the ACC, the dorsomedial and lateral prefrontal cortex, and the amygdala. Recent evidence indicates that early versus later ECT effects on functional connectivity might serve as clinical predictors. Glutamatergic neurotransmission plays a critical role in the pathophysiology of MDD, and changes in prefrontal and hippocampal Glu concentrations have been related to the ECT antidepressant response, while the regional and temporal specificity and the predictive value of these changes remain unclear. Furthermore, the effects of ECT on GABA, serotonine, and dopamine have been reported. Finally, increased levels of cytokines have been described in MDD patients and recent evidence suggests that inflammation is linked to altered glutamatergic neurotransmission. Clinical improvement during ECT is accompanied by a significant decline in inflammatory markers.

In order to better understand the antidepressant effects of ECT, future studies should apply multimodal approaches and investigate markers of neural activity and connectivity, neurochemistry, and inflammation simultaneously and at multiple time points. This might allow determination of which cognitive, neuronal, and immunological alterations are crucial for an antidepressant response and might be used for response prediction. More generally, this would also shed more light on the pathophysiological causes of MDD and the mechanisms of action of an effective treatment.

## Statement of Ethics

The authors have no ethical conflicts to declare.

## Disclosure Statement

The authors have no conflicts of interests to declare.

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## Author Contributions

A.S. and F.N.K. wrote this paper. M.B. contributed to the section on clinical data. S.G. contributed to the section on neurobiological data and cowrote this paper.

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