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THOUGHT LEADERS INVITED REVIEW

Rethinking the impact and management of electroconvulsive therapy session number in depression

Yang Ji[1,#], Hao Zheng[2,#], Yue Wu[3], Kai Wang[2,4,5,6], and Yanghua Tian[2,4,5,6]

Electroconvulsive therapy (ECT) has been an essential treatment for severe depressive disorder, utilizing electrical current to induce generalized seizures under anesthesia. Session is one of the core parameters of ECT, yet critical knowledge gaps persist regarding its quantitative relationships with clinical outcomes and neurobiological mechanisms, while lacking consensus on optimal stopping rules. This narrative review focused on the impact of ECT session on depression improvement, memory impairment, seizure duration, and biomarkers, representing antidepressant efficacy, cognitive safety, neurophysiological processes and mechanisms of ECT. Building on multidimensional analyses, we propose a novel response-guided sequential strategy that tailors ECT sessions and sequential treatments through individual therapeutic responses, optimizing early antidepressant effects while avoiding ineffective or excessive sessions. Comprehensive mapping of ECT session effects in clinical will establish predictive frameworks for ECT response optimization, catalyzing a paradigm shift from empirical to algorithmic depression therapeutics.

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Introduction

Electroconvulsive therapy (ECT) is one of the oldest surviving biological forms of neurostimulation for severe or medication-resistant depression in which brief and generalized seizures were induced by electrical current (1). Its origins date back to the advent of modern biological psychiatry in 1938. Over time, a series of refinements encompassing electrode placement, pulse width, muscle relaxants, and anesthetics have significantly enhanced its efficacy and safety profile while concurrently reducing side effects (Figure 1). Presently, ECT is administered under meticulous medical and psychiatric supervision and remains a well-established acute treatment option for depression. It produces response rates of 60%–80%, surpassing those of alternative antidepressant therapies (2, 3). Despite its propensity to induce cognitive impairment, ECT is widely used in clinical settings, with approximately 1 million people receiving ECT annually. However, fundamental questions regarding ECT remain unanswered. A primary concern for patients undergoing ECT pertains to the number of sessions deemed necessary and appropriate for their condition.

ECT is a treatment modality that relies on a series of sessions. Most national guidelines recommend a course of 6 to 12 sessions over 2 to 4 weeks, typically resulting in the alleviation of depressive symptoms (4, 5). The total number of sessions is determined by the ECT team, depending on patient's the severity of depression and clinical response. However, there are doubts regarding these sessions. On one hand, the recommended number of sessions is based more on clinical experience than on scientific evidence. Due to the widespread and longstanding acceptance of ECT, there is a tendency to believe accumulated clinical impressions as if they were incontrovertible facts. On the other hand, the number of treatment sessions varies widely among clinics and psychiatrists owing to inconsistent standards, with some patients receiving a higher than average number of ECT sessions (6). In academic terms, the outcomes of ECT are influenced by the number of sessions, which researchers may overlook (7). Moreover, any efforts to improve ECT, such as the calculation of dose delivery, exploration of electrode configurations, selection of anesthetics, and utilization of electromagnetic energy in magnetic seizure therapy, are closely intertwined with the determination of the number of treatment sessions (Figure 2) (8, 9). In summary, irrespective of patient-specific considerations, scientific research rigor, or technological development demands, the number of sessions remains a pivotal parameter and avenue for advancement in ECT. Therefore, it is crucial to understand the patterns of ECT sessions comprehensively. This is a guidance for clinicians and reassurance for patients seeking credible treatment options.

In this narrative review, our focus lies on exploring the impact of the number of ECT sessions. First, from a clinical perspective, we discuss the trajectories of depression improvement and memory impairment during ECT, as these factors constitute key cognitive variables crucial for understanding the effect of ECT (Figure 3) (10). Subsequently, we delve into the evolving trend in epileptic seizure duration, a parameter believed to be pivotal for achieving a successful antidepressant outcome through ECT from a methodological standpoint (11). Furthermore, we analyzed longitudinal studies involving hematological and magnetic resonance imaging (MRI) assessments during ECT to investigate how the brain responds to increasing ECT sessions (12). Additionally, the sequential treatment strategy combines different intervention methods to maximize the advantages of each therapy and reduce the side effects or residual symptoms of a single treatment, offering a promising approach for improving depressive disorder outcomes (13). Therefore, we propose an innovative ECT optimization framework, the ECT response-guided sequential strategy, which beyond conventional protocol extensions, instead developing dynamic sequential treatment plans based on individualized ECT response trajectories. We hope this systems-level evidence and model will motivate future research, ultimately leading to a comprehensive understanding and facilitating more effective ECT practices.

[1]Department of Neurology, the Second Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [2]Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [3]Department of Psychology and Sleep Medicine, the Second Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [4]Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei 230032, China; [5]The College of Mental Health and Psychological Sciences, Anhui Medical University, Hefei 230032, China; [6]Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health, Hefei 230032, China

[#]These authors contributed equally to the manuscript

Corresponding Author: Yanghua Tian, PhD; Department of Neurology, The First Affiliated Hospital of Anhui Medical University Hefei 230022, China. Phone: +86-551-62922328; E-mail: ayfytyh@126.com

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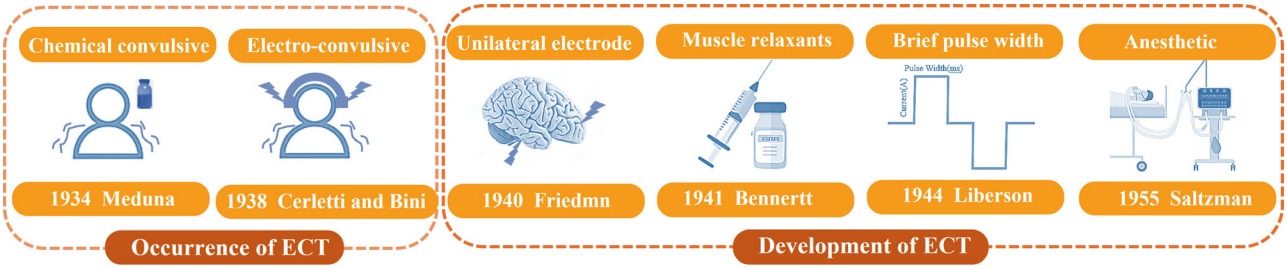

Figure 1. The historical milestone for the evolution of ECT. ECT originated from chemical drug induced epilepsy and gradually developed into modern ECT in terms of electrode placement, muscle relaxants, pulse width, and anesthetic parameters.

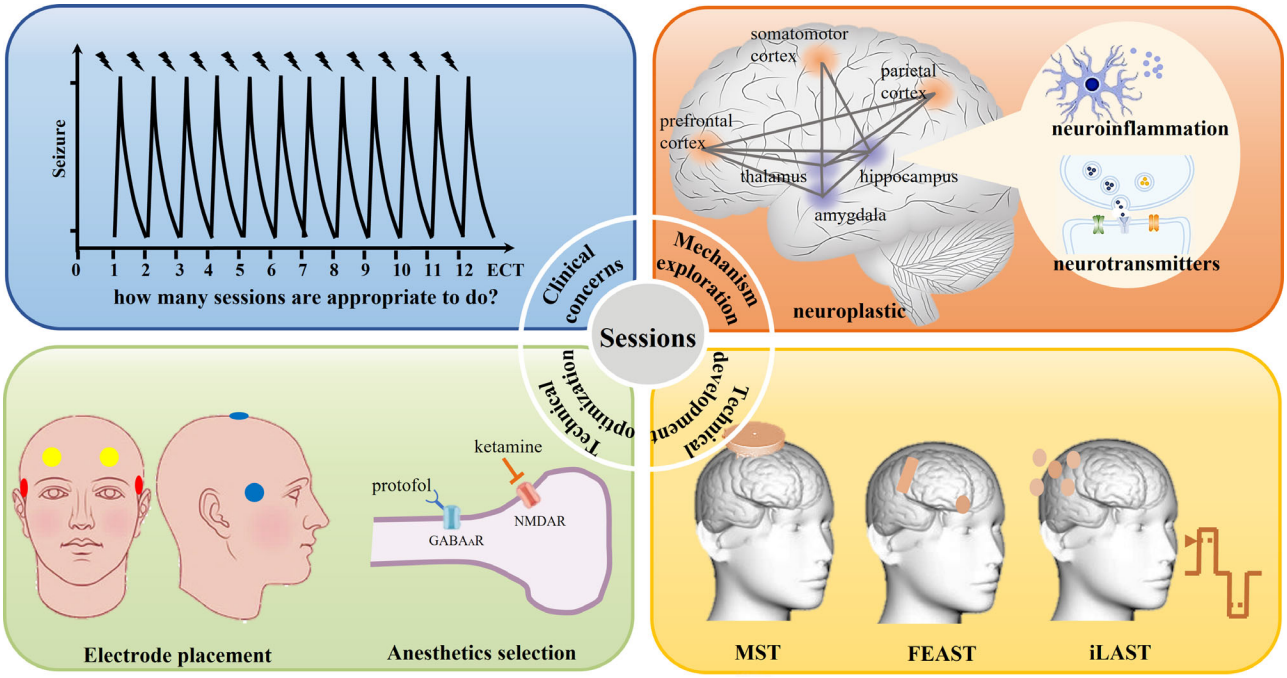

Figure 2. The central role of ECT sessions. The central role of ECT sessions in clinical problem, mechanism exploration, technical optimization, and technical development. MST, magnetic seizure therapy; FEAST, focal electrically administered seizure therapy; iLAST, individualized low amplitude seizure therapy.

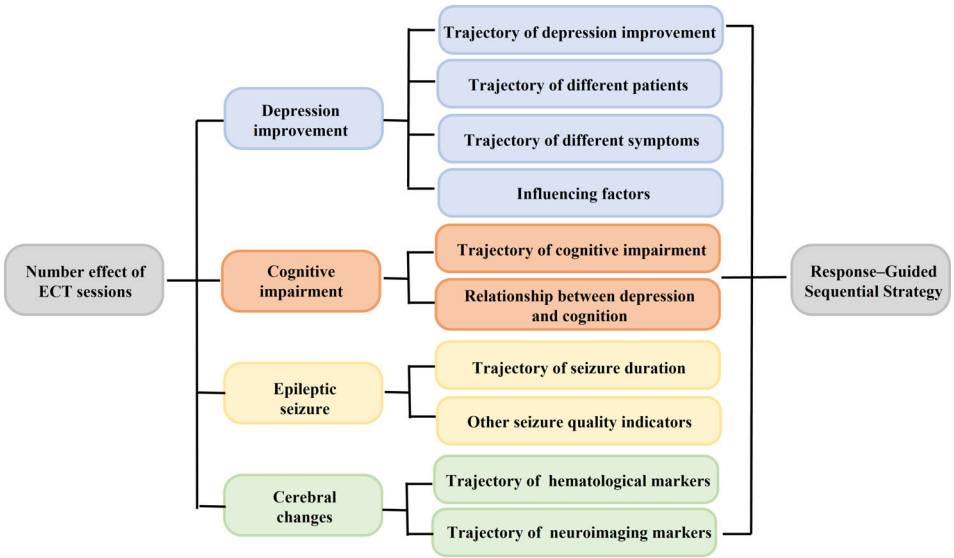

Figure 3. The conceptual framework of this review. The discussion framework of this review based on the effects of ECT sessions.

Search Strategies and Selection Criteria

Evidence for this narrative review was identified through searches of PubMed, Cochrane Library, Embase, ClinicalTrials.gov and relevant references in those articles with the search terms: "electroconvulsive therapy" AND ("depression" OR "depressive") AND ("session" OR "course" OR "trajectory") AND ("response" OR "remission") AND ("cognitive" OR "cognition") AND ("seizure") AND ("hematological" OR "biomarker") AND ("neuroimaging" OR "MRI") AND ("sequential treatment"). Articles published in English up to October 31, 2024 were included.

Trajectory of Depressive Improvement

Depression is a common and disabling psychiatric disease accompanied by high suicide attempts (14, 15). Although ECT has significant advantages over antidepressants in efficacy and course, clinicians and patients seek clarity regarding the pace at which clinically meaningful benefits manifest, which defined as either achieving remission (i.e., an asymptomatic state) or response (i.e., a $>$ 50% reduction in baseline symptoms severity), or reaching a plateau (i.e., no change in depression score). For example, what is the extent of depression improvement after each ECT session? when does the response or remission onset? What is the discrepancy in the speed of remission across different dimensions of depression? Which situations have a more rapid response following ECT?

Investigators have documented a nonlinear antidepressant response pattern over ECT. the Consortium for Research in ECT (CORE) conducted significant research in this field, gathering Hamilton Rating Scale for Depression (HRSD) scores after each ECT in 576 patients (16, 17). Their findings revealed a notable decrease in the mean HRSD score by 25.8% after the first session, 39% after the second session, and 49.3% after the third sessions. It was observed that the median time to first response was typically three ECT sessions, with remission achieved after approximately four additional ECT sessions, demonstrating an early improvement trajectory. Other studies have similarly reported rapid effects of ECT in comparable populations. In the Prolonging Remission in Depressed Elderly (PRIDE), involving 185 geriatric depressed patients received right unilateral ECT, the mean decrease of HRSD scores in the first three ECT sessions were 24.5%, 35%, and 42.7%, respectively (18). Additionally, Rodger *et al.* reported the change in HRSD score between first and third session was six times greater than the remaining sessions (19). Overall, the trajectory of depressive improvement during ECT appears to be swift in the early stages, leveling off in the later stage, reflecting the relatively rapid response to ECT.

While average trajectories offer valuable insights, substantial individual differences remain in the speed of response to ECT. Clinical case reports have described varied response patterns, including rapid response after one session and delayed improvement following 10 sessions (20, 21). A large prospective cohort study reported that 12.6% of patients responded after the first session, whereas 5.9% showed no response throughout the treatment course (16). Another study found that 40% patients recovered with two to four ECT sessions, 40% with five to eight sessions, and only 20% required nine to 12 sessions (22). To better characterize the variability, researchers have applied data-driven methods to identify distinct response subgroups. Latent class analysis of 156 consecutive patients identified five distinct trajectories of depressive symptoms, including rapid improvement (25%), moderate improvement (30.12%), slow improvement (19.23%), slow improvement with delayed onset (11.54%), and no improvement (12.82%) (23). Similarly, growth mixture modeling in 239 patients identified three patient groups consisting of rapid response group (16.74%), slow response group (76.15%), and nonremit group (7.11%) (24). Taken together, these studies underscore the heterogeneity in ECT response trajectories. Recognizing and accounting for these variations may help guide individualized treatment duration, optimize outcomes, and reduce unnecessary exposure to prolonged ECT courses.

As widely acknowledged, depression is a heterogeneous disease characterized by multiple distinct symptom clusters, including mood, anxiety, somatic, insomnia symptoms, and suicidal ideation, among others (25). When treating depression, it is essential to recognize that not all symptoms improve at the same rate or degree (26). Relying solely on total scores of depressive symptom severity to define responses may lack detection of resolved and residual symptoms. Some studies have suggested that suicidal ideation respond quickly to ECT (27), hence proposing suicide risk as an indication for ECT. In contrast, a study involving 89 older persons with depression found that while all dimensions showed rapid and significant improvement, the mood dimension demonstrated the highest rate of improvement compared to suicidal dimensions (28). These results are consistent due to the differing proportions of each dimension in the HRSD scale; for example, the suicidal dimension comprised only one item. Considering the covariation of symptoms over time, a dynamic time warping analysis of 68 participants showed that improvements in somatic symptoms and suicidal ideation preceded those in mood symptoms (29). In conclusion, the temporal trajectories of symptom clusters vary, and it remains debatable which sets of symptoms are most effectively and rapidly targeted.

In addition to subgroup analyses of response trajectories, several studies have investigated predictors of early and delayed responses to ECT. Notably, patients with bipolar depression, psychotic features, and higher depression severity at baseline showed a more rapid response after ECT (24, 30). There is evidence that among initial responders, patients with unipolar depression require an average of six treatments to meet the response criteria. In contrast, patients with bipolar depression meet the response criteria after four treatments (30). In the CORE study, patients with psychosis had an average percentage change in HRSD of 64% compared to 56% for nonpsychotic groups after the fifth ECT (31). Additionally, a regression model demonstrated that baseline HRSD scores were significantly associated with a rapid response. Other clinical characteristics also affect response speed. Treatment-resistant depression (TRD) is often associated with slower improvement, while comorbid personality disorders are linked to a higher likelihood of nonresponse (23). In contrast, first-episode depression does not appear to significantly influence response speed (23). The role of age in response speed is inconsistent and complex. While some studies indicate that elderly patients experience faster remission than younger patients (32), another study reported that elderly patients with depression require more ECT treatments than adults (33). This discrepancy arises from various factors interfering with the analysis of the independent role of age. Regarding the ECT technique, response speed is associated with electrode placement (34). Kellner *et al.* observed a decrease of 44% in HRSD scores after the first session of right unilateral ECT, 48% for bifrontal ECT, and 51% for bitemporal ECT (35). Despite growing insights into potential predictors, systematic evidence on the temporal dynamics of ECT response remains scarce, as most meta-analyses emphasize overall outcomes (36, 37). Future studies should investigate how clinical and technical factors shape response trajectories, to support more personalized and effective ECT protocols.

Trajectory of Cognitive Impairment

Cognitive impairment is a frequent adverse effect of ECT among patients, which can be divided into memory-related and nonmemory cognitive impairment (38). Memory-related issues include disorientation, anterograde amnesia and retrograde amnesia. Nonmemory cognitive impairment involves decreased attention, processing speed, and executive function (39). National guidelines recommend the cognitive impact of ECT should be monitored on an ongoing basis. However, in clinical practice, key questions remain unanswered: when does the cognitive impairment occur? Does the trajectory of cognitive impairment worsen or improve over time? What is the relationship between depressive symptoms and cognitive impairment?

Cognitive deficits emerge early in ECT (40). A prospective follow-up study found that 62% of patients with depression reported subjective memory deficits after the first ECT session, a figure that increased with subsequent ECT sessions (41). Although these deficits typically resolve after all modified ECT sessions are completed, 34% of the deficits may last for 6 months or longer (42). Notably, disorientation commonly surfaced immediately after the second ECT session and was more pronounced after the fifth ECT session (43). However, these results are somewhat subjective due to the nonspecific learning effects associated with cognitive measurement tools, hindering accurate assessment post-ECT. To address

these limitations, some researchers have adopted strategies such as employing multiple parallel sets of tests or reducing the frequency of measurements. Viswanath *et al.* applied a short cognitive-related battery in 30 inpatients and they found that objective cognitive deficits such as verbal memory, autobiographic memory, and psychomotor speed progressively deteriorated from the first to the third to the sixth ECT session (44). However, this study lacked a baseline assessment. Another study compared a new electroconvulsive therapy cognitive assessment (ECCA) tool with the classic Montreal Cognitive Assessment (MoCA). It indicated that ECCA scores were significantly decreased across the three testing points, whereas MoCA scores did not vary significantly (45). An intensive longitudinal follow-up of associative memory at five timepoints found that memory impairment occurred after the first ECT and worsened during subsequent ECT treatments (46). It is important to note that cognitive deficits are influenced by factors such as age, education level, and medications, including anesthetics and antidepressants. For instance, older individuals with lower education levels tend to experience more severe cognitive impairment (46), while substances like propofol, low-dose ketamine, and lithium may have potential cognitive-protective effects (47–49). In summary, cognitive impairment occurs early during ECT and may accumulate throughout the treatment course, implying the importance of understanding the optimal number of ECT sessions to mitigate unnecessary cognitive damage.

Emotion and cognition constitute the two main elements of neuropsychology (50). Despite ECT induces rapid improvement in depressive symptoms alongside cumulative cognitive impairment, the relationship between depression and cognitive function remains unclear. Clinical perspectives suggest that cognitive impairment might aid depressive remission by enabling patients to forget distressing memories (51). Bai *et al*. found that negative memory impairment was more severe than positive memory impairment and correlated with symptom relief (10). Conversely, depressive remission can enhance certain cognitive functions, such as increased subjective initiative (39, 52). From a neurophysiological perspective, the seizures induced by ECT, especially those aimed at enhancing efficacy, are often linked to cognitive side effects. For instance, compared to ultra-brief pulse width, brief pulse width has proven to be more efficacious regarding symptom reduction but resulting in more pronounced cognitive side effects (53). Right unilateral ECT typically yields milder and less persistent cognitive effects but slower response rates compared to bilateral ECT due to reduced stimulation of the left temporal lobe (54). Additional research suggests that hippocampal changes caused by ECT are involved in both depressive improvement and cognitive impairment (55). In conclusion, while emotion and cognition are closely connected, the exact nature of this relationship, the role of epileptic seizures, and the whole-brain alterations need further investigation. Before clarifying these questions, regular monitoring of both depressive symptoms and cognitive function during ECT is essential to help clinicians decide the optimal time to end treatment.

Seizure Trajectory

The objective of ECT is to induce generalized seizures, leveraging neurological changes that counteract those seen in epilepsy and psychiatric disorders. Various studies indicate that the effectiveness of ECT stems from generalized seizures surpassing the therapeutic benefits of noninvasive brain stimulation without convulsions (56). A typical ECT stimulus comprises a series of pulses ranging 100–1000, each lasting 0.25 to 1.0 ms, and an electrical silence of 6 to 16 ms between pulses, ultimately producing a seizure lasting 20 to 60 s (57). Despite its widespread use, several questions regarding ECT-induced seizures persist in clinical practice. For instance, how can the seizure quality be evaluated? What range is considered optimal? How does seizure quality change with an increase in the number of ECT sessions? And what is the relationship between seizure quality and therapeutic and cognitive outcomes?

Seizure duration has long been investigated as an important intermediate variable in determining dose–response properties due to its measurability through movement or electroencephalography (EEG). Evidence suggests an inverse correlation between the number of treatments and seizure duration (58). Rasimas *et al*. conducted a review of the course of ECT in 519 patients, and they found that seizure duration experienced the most significant drop between the first and second treatments, with a slight further increase thereafter (59). Similarly, a 17-year retrospective cohort study conducted at a single center, which enrolled 3648 patients receiving 32,879 courses of ECT treatments, reported a reduction in mean seizure duration across the course, with the greatest decrease in duration over the first three sessions (60). Research suggests that the reduction in seizure duration during ECT may be associated with an increased seizure threshold, shifts in the brain's inhibitory-excitatory balance, and adjustments in treatment parameters such as dosage (61–63). However, the potential implications of shorter seizures on the antidepressant properties of ECT remains controversial. A cohort study involving 6998 patients finding that patients with an EEG seizure duration of 60 to 69 s from the first ECT session had the highest remission rates compared to those with a seizure duration of less than 20 s (64), which suggests declining seizure duration signals treatment resistance. In contrast, other studies have indicated that higher electrical charges are associated with shorter seizure durations and higher remission rates (60). Some observational studies have also found no association between seizure duration and treatment response (65), which may simply reflect normal physiological adaptation. It is important to note that the current conflicting evidence on seizure duration and ECT outcomes largely stems from overreliance on first-session data, which fails to account for the process of change that unfolded over the treatment course. Moreover, there is no consensus regarding the minimum seizure duration required for ECT. Despite this, clinicians often endeavor to lengthen seizures in patients experiencing short seizure durations, with concerns that excessively brief seizures may be clinically ineffective (59). In summary, seizure duration as a pragmatic but incomplete guide shows an early decline during ECT, while further research is needed to clarify its relationship with clinical outcomes.

In addition to seizure duration, several ictal parameters derived using more complex algorithms based on the amplitude of the ictal EEG have been developed to assess seizure quality. These parameters include the average seizure energy index (ASEI), postictal suppression index (PSI), and seizure quality index (SQI), among others (66, 67). The ASEI and PSI are computed directly from the ECT device, the ASEI by multiplying the mean integrated amplitude with the seizure duration and the PSI by dividing the mean amplitude after seizure termination by the mean amplitude obtained during seizure. On the other hand, the SQI refers to the summed score of five different seizure domains, including duration, inhibition, amplitude, sympathetic activation, and interhemispheric coherence, at the second ECT session, to predict clinical outcomes (67). However, despite the existence of these parameters, there is a notable gap in research exploring the changing trends of these indicators during each ECT treatment and their relationship with clinical improvement and cognitive side effects. In addition, several factors can potentially affect variations in seizure quality, such as anesthetic use, stimulus dosage, electrode positioning, time of seizure induction, and medication, among others (62). Therefore, these variables must be combined or controlled to determine the trajectory of changes in seizure quality. Overall, the assessment of seizure quality during each ECT treatment session holds direct and significant clinical implications. Adjusting these indicators within defined limits makes it feasible to ensure session adequacy and, therefore, enhance the likelihood of a favorable clinical outcome.

Trajectories of Hematological and Neuroimaging Markers

Understanding the mechanisms of treatment responses is paramount for improving depression outcomes. However, due to its spatially unfocused nature, the neural mechanisms underlying the clinical response to ECT remain uncertain (68). Various hypotheses have been proposed to explain the effect of ECT, including neurotransmitter, neuroendocrine, neuroinflammation, and neuroplastic changes (12). For instance, monoamine neurotransmitter systems, such as norepinephrine, and inhibitory neurotransmitter systems, such as gamma-aminobutyric acid (GABA), have been discussed as potential mediators of therapeutic response in ECT (11). Additionally, ECT triggers the release of neurotrophic factors, adrenocorticotrophic hormones, and inflammatory mediators, including

interleukin-6, and cortisol (69). Moreover, ECT brings about widespread changes in the structure and function of the brain, attributed to neuroplastic effects (70). Although these effects are easy to detect, challenges persist in research on ECT-induced neurological effects. For example, questions arise regarding the temporal relationship between these neurological changes following ECT and the treatment effects. Moreover, there is a need to understand the internal relationship among these factors and determine which of these changes may be related to the antidepressant and amnesic effects or incidental phenomena.

Most existing studies have investigated neural alterations before and after ECT, which is the total effect of multiple ECT sessions, resulting in key changes being masked (71, 72). However, few studies have focused on the time course and processes of neural effects during ECT treatment. Regarding hematological markers, a longitudinal study spanning nine visits during the ECT period indicated that serum brain-derived neurotrophic factor (BDNF) levels increased after each ECT session yet showed no significant association with treatment response (73). Similarly, an exploratory study evaluated the acute endocrine effects and found that levels of cortisol and norepinephrine were significantly elevated after the first ECT session and fall back to baseline after the course of ECT (74). Another study by Göteson *et al*. investigated alterations in the serum proteome of 309 patients before and after the first ECT session and before the sixth ECT session, revealing findings related to signal transduction; however, none of the studied protein biomarkers were associated with the clinical response to ECT (75). In addition, no significant changes were found in white blood cell, proinflammatory cytokine/neurotrophin ratios, and plasma vascular endothelial growth factor levels over the course of ECT (76). In essence, on a finer time scale, the hematological markers associated with nutritional factors, inflammation, and endocrine function exhibit transient surges, potentially attributed to the stress induced by ECT.

In particular, because MRI is relatively safe without ionizing radiation, it has enabled repeated scanning of patients at various intervals to track the longitudinal trajectories of structural and functional cerebral changes during ECT. The majority of imaging studies are acquired before, mid and after treatment and focused on the hippocampus and the amygdala. Shantanu *et al.* scanned 43 patients with major depression at three timepoints: before ECT, after the second session, and within 1 week of completing the ECT series, and found progressive increases in hippocampal and amygdala volumes, which were associated with symptom improvement (7). Smaller baseline hippocampal volume predicted greater clinical response. Similarly, another longitudinal study of 14 patients, with MRI assessments conducted before ECT, after the fifth or sixth session, and at treatment completion, demonstrated a trend toward increased hippocampal volume across sessions. A large association analysis between MRI data and the number of ECT sessions from the Global ECT-MRI Research Collaboration (GEMRIC) reported a 0.28% linear increase in hippocampal volume after each ECT session (77–79). Marta *et al*. further examined hippocampal metabolites and amygdala functional connectivity across an acute course of bitemporal ECT including pretreatment, after the first and ninth sessions, and 15 days posttreatment, identifying sequential changes in neuroinflammatory markers and limbic network activity (80). These findings support the role of ECT-induced neuroplasticity in the hippocampus and amygdala in mediating clinical improvement in depression. Beyond the hippocampus–amygdala complex, longitudinal changes of gray matter volume or cortical thickness in the thalamus, putamen, and anterior cingulate cortex, as well as fractional amplitude of low-frequency fluctuations in the subgenual cingulate cortex and activation intensities within auditory networks have also been reported during ECT course. A summary of the longitudinal neuroplastic effects of ECT is provided in Table 1. Taken together, ECT appears to affect a broad range of brain regions, aligning with the distribution of electric field strength; however, its core neurobiological mechanisms remain unresolved (81). Moreover, findings from longitudinal studies suggest that ECT may induce brain changes at an early stage, consistent with the rapid clinical response. Nevertheless, the dynamic impact of ECT

Table 1. Longitudinal trajectories of neuroplastic effects during ECT in patients with depression[a]

Brain region	Analysis indicators	Timepoints during ECT	Longitudinal trajectory of neuroplastic effect	Correlation with outcome
Hippocampus (7, 80, 106)	Volume	Three timepoints (ECT0, ECT2 or ECT5, ECT endpoint)	Increase between each timepoint[a]	Relate to the clinical response
	Metabolite concentrations	Four timepoints (ECT0, ECT1, ECT9, ECT endpoint)	Decrease in NAA/Cr ratio and increase in Glx/Cr ratio at ECT9	Relate to the left hippocampus volume change
Amygdala (7, 82)	Volume	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between each timepoint	Relate to the clinical response
	Functional connectivity	Four timepoints (ECT0, ECT1, ECT9, ECT endpoint)	FC with lSgACC decreased between ECT1 and ECT9; FC with rDLPFC increased at ECT9	NA
Thalamus (83)	T2 relaxation Times	Three timepoints (ECT0, ECT1, ECT2)	Increase between each timepoint	Relate to the verbal anterograde memory impairment
Putamen (84)	Volume	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	NA
Anterior cingulate cortex (85)	Thickness	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	Relate to the clinical response
Limbic and paralimbic cortex (85)	Thickness	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	Not relate to the clinical response
Subgenual cingulate cortical (80)	fALFF	Three timepoints (ECT0, ECT1, ECT endpoint)	Decrease between each time point	A trend level correlation with clinical response
Auditory networks (86)	Activation intensities	Three timepoints (ECT0, ECT8, ECT endpoint)	Decrease between ECT0 and ECT 8, increase at ECT endpoint	Relate to the clinical response

[a]Changes during ECT are summarized qualitatively due to lack of reported effect sizes in original studies.
Note: ECT0 = prior to ECT; ECT1 = after the first ECT; ECT2 = after the second ECT; ECT5 = after the fifth ECT; ECT8 = after the eighth ECT; ECT9 = after the ninth ECT; ECT endpoint = after the entire ECT; fALFF = fractional amplitude of low-frequency fluctuations; NA = no data.

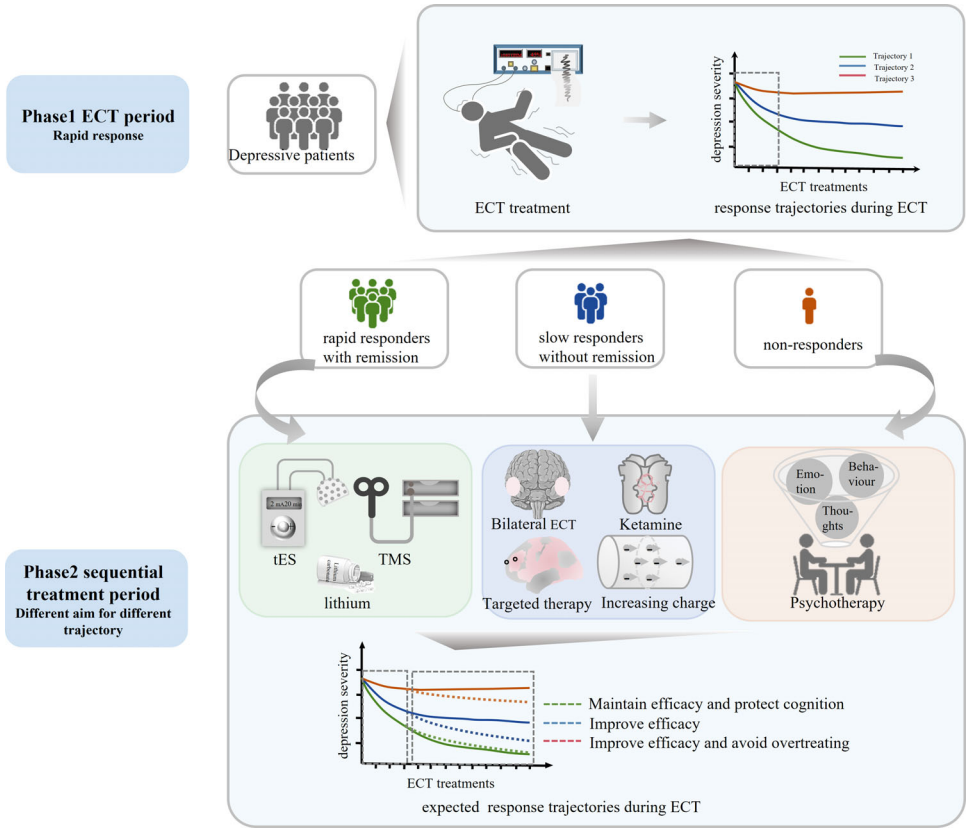

Figure 4. ECT response–guided sequential strategy. This strategy comprises two phases. In the initial phase, the goal is to exploit the advantage of ECT in rapidly inducing mood improvement and then to sequential reasonable treatment measures according to the response trajectories of different patients for maintaining efficacy and protect cognition, improving efficacy, and avoid overtreating. tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation.

sessions on brain structure and function remains unclear, as most studies include only a limited number of observation timepoints, typically three or four. Notably, although longitudinal designs rely on self-comparisons, stimulation parameters, medications, and individual traits may still confound imaging findings, yet their effects remain insufficiently studied due to limited data. Therefore, further longitudinal studies using multidimensional imaging markers across more timepoints or even throughout ECT while controlling for potential confounding factors, are needed to generate a comprehensive profile of neuroplastic changes over time and their relationship to therapeutic outcomes (80–86).

The mechanism behind the early and rapid response to ECT remains elusive, with the microscopic changes in the brain that accompany these responses are still under speculation. Studies in rodents suggest that even a single ECT session can have profound effects, including the activation of the immune system and neurotransmitter increase. Hippocampal neurogenesis, which is thought to be involved in the therapeutic effects of ECT, was significantly increased in single electroconvulsive seizures in a rat model, consistent with the increased hippocampal volume shown by neuroimaging (87). However, some researchers argue that the induction of neurogenesis or an increase in gray matter volume takes time and may not occur acutely (20). Integrating insights from micro-level biology, meso-level imaging, and macro-cognitive levels at multiple timepoints could provide a clearer understanding of how the number of ECT sessions affect outcomes and further clarify the rapid onset mechanism of ECT.

ECT Response–guided Sequential Strategy

Although multiple treatment options are available for depression, no single treatment approach can fully and safely address the complexity of the disorder (13). In recent years, sequential treatment strategies, which combine different interventions in a staged and adaptive manner, have gained increasing attention (88). This approach aims to maximize the benefits of each treatment at a specific stage while minimizing the side effects and risk of treatment resistance that can develop from long-term use of a single treatment modality (89, 90). Therefore, a sequential treatment strategy is a meaningful shift in clinical thinking, allowing the selection of appropriate alternative treatment options based on the patient's response to the first course of treatment (91). In an ideal scenario, the primary objective of an initial ECT course is to treat the current episode while minimizing cognitive impairment. The number of sessions plays an important role in the clinical effects of ECT. Through our literature review, we have identified a discernible pattern in both depression alleviation and memory impairment throughout the course of ECT. Initially, depression tends to improve rapidly with successive ECT sessions, followed by a slower rate of improvement, while memory impairment tends to accumulate gradually. This supports the view that it may not be necessary to perform ECT so many times. Therefore, managing ECT sessions and sequencing to other treatments may be an effective way to improve outcomes (88, 92). The notable advantage of ECT lies in its swift antidepressant effect during the early stages, which is unmatched by other treatment modalities. However, as treatment progresses, the cognitive and economic burdens tend to escalate (93). In light of these considerations, we propose a new treatment strategy in which ECT should be terminated early once the optimal benefit-to-risk ratio is achieved, and then the patient should be transitioned to other safer treatments rather than persisting until complete remission. Notably, the response trajectories of ECT vary among patients with depression. Therefore, we outline an ECT response–guided sequential strategy to provide tailored sequential treatments for different response trajectories (Figure 4).

Based on the previously described speed of improvement and treatment outcomes, patients undergoing ECT can generally be categorized into three clusters: rapid responders with remission, slow responders

without remission, and nonresponders. Rapid responders with remission are those who improve quickly in the early stages of ECT. Although continued ECT can lead to remission, it may increase the risk of memory impairment. For these patients, sequential use of portable and safe noninvasive brain stimulation (NIBS) or lithium after an ECT-induced response helps consolidate the treatment effects while reducing cognitive damage (94). NIBS is an emerging therapy that modulates neuronal activity through physical stimulation, such as electricity, with the advantages of safety, portability, precise regulation, and cognitive enhancement, which is recommended by the FDA for the treatment of depression (95, 96). Sequential application of NIBS after ECT may not only further alleviate depressive symptoms through targeted modulation of specific brain regions, but also help prevent cognitive impairment caused by excessive ECT, protect cognition-related brain areas, promote cognitive recovery, and provide a home-based option that is more acceptable to patients (97–99). An adequately powered exploratory efficacy study is currently underway to provide definitive evidence of NIBS following ECT (100). Slow responders without remission are those who show a slow response in the early stages of ECT and experience no further clinical improvement in the later stages. This may be due to poor neural plasticity or insufficient precision of ECT (101). Augmentation strategies that lengthen seizure duration, such as applying bilateral ECT or increasing the electrical dosage, may improve efficacy, but at the expense of cognitive impairment (58). Alternatively, switching strategies may be considered, replacing ECT with fast-acting treatments such as ketamine, an N-methyl-D-aspartate antagonist, which has demonstrated rapid antidepressant effects and has been found to be noninferior to ECT (102). In addition, supplementation strategy using personalized neuromodulation therapies shows considerable promise in addressing individualized residual symptoms that may persist after ECT, such as anhedonia or somatic complaints. These symptoms are often not fully resolved by standard ECT protocols and may require targeted interventions tailored to specific neural circuits or symptom clusters, thereby complementing the antidepressant effects of ECT and enhancing overall recovery (103). The third group, a small subset of patients, showed minimal clinical response to ECT and were labeled nonresponders. The reason for poor efficacy is often due to the co-occurrence of personality disorders, making these patients more suitable for targeted psychotherapy or thought training (104). In summary, this response-guided sequential treatment strategy consists of two phases: an initial phase leveraging the rapid antidepressant effects of ECT, followed by tailored follow-up interventions based on individual response trajectories, such as maintenance, augmentation, switching, or supplementation, to optimize clinical outcomes while minimizing cognitive burden and overtreatment.

Although the theoretical foundation and indirect evidence supporting the sequential treatment strategy are compelling, further rigorous testing in future studies is essential. A key challenge lies in accurately characterizing individual ECT response trajectories and determining optimal sequential treatment approaches. Emerging evidence suggests that baseline predictors, including clinical characteristics (e.g., age, depression subtype, treatment resistance) and neuroimaging markers (e.g., hippocampal volume), may help forecast these trajectories and subsequent treatments, with further refinement of predictions achievable by integrating dynamic data, such as symptom reduction rates and biological changes during early treatment sessions (105). However, the reliable biomarkers and clinical features to guide transition decisions require investigation and validation in future studies. Another critical issue is determining the appropriate time to transition from ECT to subsequent interventions. Ideally, the cut-off point for ECT should be based on achieving optimal levels of neuroplasticity and disruption, providing a sufficient antidepressant response with minimal side effects (70). On average, responsive patients may require 3 to 4 ECT sessions to reach this critical point, while nonresponders should discontinue ECT, as it may no longer be suitable for them. It is important to note that this sequential strategy primarily addresses the acute treatment phase and does not replace the need for long-term consolidation, which is typically maintained with pharmacotherapy. Nevertheless, tailoring sequential treatment strategies based on ECT response trajectories holds significant potential for improving clinical outcomes, particularly by offering greater flexibility and safety in addressing challenging conditions such as TRD. We strongly encourage future clinical trials to further explore and validate this approach, ultimately enhancing understanding and improving treatment outcomes.

Conclusions

ECT, as a well-established neuromodulation technique, plays an important role in the treatment of severe depression. This review summaried the impact of ECT sessions on multiple therapeutic domains, including depression improvement, memory impairment, epileptic seizure time, and biological markers and highlighted the rapid early antidepressant effects of ECT alongside the cumulative risk of cognitive burden, underscoring the importance of managing treatment session. Taking into account the individual variability in treatment response, we proposed a response-guided sequential strategy that sequence other interventions based on distinct clinical trajectories to optimize outcomes. Although this approach remains hypothetical, it offers a testable framework that may generate new clinical trials and treatment options. We hope this review provides a conceptual and evidence-informed foundation to support individualized ECT decision-making and inspire future work in this field.

Author Contributions

Y.J. and Y.T. conceived and designed the review. Y.J. and H.Z. conducted the literature search. Y.J. and Y.W. created all the figures and tables. Y.J. wrote the first draft of the manuscript. W.K. and Y.T. critically revised the manuscript. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text, and approve the content and submission of the study.

Corresponding author: Professor Y.T. is responsible for all aspects of the work and for the submission process.

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Author Disclosures

The authors have confirmed that no conflict of interest exists.

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