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Nikolaos Statharakos, Vasilios Savvidis, Taxiarchis Gravanis

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REVIEW

Towards Precision ECT: A systematic review of epigenetic biomarkers in treatment-resistant depression

Nikolaos Statharakos,^{1,2} Vasilios Savvidis,^{1,2} Taxiarchis Gravanis^{1,2}

1. *Adult Psychiatry, Papanikolaou Hospital, Thessaloniki, Greece*
2. *Psychiatric Hospital of Thessaloniki, Thessaloniki, Greece*

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ABSTRACT

Electroconvulsive therapy (ECT) remains one of the most effective treatments for patients with treatment-resistant major depressive disorder (TR-MDD). However, the biological mechanisms underlying its therapeutic effects are not yet fully understood. Epigenetic regulation has recently emerged as a promising field for elucidating the molecular underpinnings of ECT response. This systematic review aimed to identify and synthesize existing studies investigating epigenetic biomarkers associated with ECT outcomes in human populations. A systematic review was conducted in PubMed and Scopus for studies published between January 2015 and March 2025. The review adhered to PRISMA 2020 guidelines. Inclusion criteria were: (1) original, peer-reviewed studies; (2) investigation of ECT-induced effects on epigenetic markers; and (3) diagnosis of major depressive disorder. Extracted data included epigenetic targets, patient characteristics, ECT parameters, and clinical outcomes. Risk of bias and heterogeneity were taken into account in the synthesis. Eleven studies met the inclusion criteria, encompassing a total of 498 patients with TR-MDD. Across studies, 31 promising epigenetic biomarkers were identified, including genes involved in neuroplasticity, hypothalamic–pituitary–adrenal (HPA) axis regulation, inflammation, immune signaling, and non-coding RNAs. DNA methylation and microRNA (miRNA) expression were the most frequently studied mechanisms. No studies to date have investigated histone modifications in human subjects undergoing ECT. This systematic review provides preliminary evidence that epigenetic mechanisms—particularly DNA methylation and miRNA expression—may play a role in modulating response to ECT in patients with TR-MDD. While these findings offer important insights for clinical stratification and precision psychiatry, they are limited by small sample sizes and methodological variability. Larger, standardized, and longitudinal studies are needed to validate these initial findings and support translational applications.

KEYWORDS: Electroconvulsive therapy, treatment-resistant depression, epigenetics, biomarkers, precision psychiatry.

Corresponding Author: Nikolaos Statharakos, Adult Psychiatry, Papanikolaou Hospital, Papanikolaou blvd, 57 100, Exochi, Thessaloniki, Greece, Email: nicstath@gmail.com, nstathaa@auth.gr

Introduction

Electroconvulsive Therapy (ECT) is a noninvasive brain stimulation involving controlled induction of generalized seizures under anesthesia and muscle relaxation.¹ It has

demonstrated robust and consistent efficacy in the treatment of severe and treatment-resistant mood and psychotic disorders, including major depressive disorder (MDD), bipolar disorder, schizophrenia, and catatonia.² Among these, ECT remains the most effective intervention for severe MDD.¹ The procedure typically involves unilateral (sometimes bilateral) electrode placement over the non-dominant hemisphere to deliver an electrical stimulus that induces tonic-clonic seizures. There is a complex interplay between the stimulus parameters, including the position of electrodes, dosage, and waveform of electricity, and its efficacy.

ECT is rarely used as first-line therapy, except in an emergency where the person's life is at risk because of refusal to eat or drink, or in cases of attempted suicide.¹ Most patients fail one or more antidepressant medications before receiving ECT, and those who respond to ECT usually receive continuation pharmacotherapy.³⁻⁵ Regarding its effectiveness, in controlled studies, ECT has a response rate of 70% to 90%. However, in naturalistic population-based community-setting studies, ECT remission rates reach levels less than 50%.³⁻⁵ Despite its effectiveness, ECT is often underutilized due to persistent stigma and limited understanding of modern protocols.⁶

Even though several theories have been proposed for its mechanism of action, it remains poorly elucidated. Potential Mechanisms of action include a) altered activity of the monoamine neurotransmitter system, b) effect on neurotrophins, c) alteration in the concentration of inflammatory factors, d) epigenetic modifications, e) structural neuroplasticity, f) increased neuronal functional changes.⁷ Given the current lack of conclusive data, it is unlikely that any single biomarker will fully define a psychiatric disorder or account for the inherent heterogeneity of psychiatric diagnoses. Instead, it is more plausible that multiple biological mechanisms interact in complex and dynamic ways, collectively contributing to the treatment response.

Optimization of treatment strategies and enabling personalized medicine in the long term are a necessity. Currently, there is a lack of clinically useful biomarkers predictive of treatment response.⁸ Therefore, prospective indicators of ECT response are thus in great need. Although treatment resistance in MDD is a robust clinical predictor of poor response for most antidepressant strategies, including ECT, this might be related more to the depressive episode per se than to the intervention.

Regarding 'precision psychiatry', it is envisaged to bring a paradigm shift in clinical psychiatry through the process of integrating data from the complex nature of psychiatric diseases to give biomarkers that can enable more efficacious and personalized treatment strategies.⁹ Precision medicine initiative, as it applies to ECT, can be advanced through the study of epigenetics.¹⁰ Epigenetics comprises a highly increasing area of studies in psychiatry, especially in mood and psychotic disorders, because it acts as a link between environmental factors and the genome, enabling to deciphering of the complex interplay of factors and the nature of psychiatric disorders.¹¹ The novel field of epigenetic effects of ECT is increasingly studied as a key mechanism mediating the impact of environmental factors on brain function and thus enables the research to yield biomarkers.¹²

The individual genetic constitution provides a baseline for the vulnerability to certain diseases, but additional environmental factors are often necessary to provoke the onset. Epigenetics refers to the study of heritable phenotype alterations that do not involve alterations in the DNA sequences, or "the mitotically and meiotically heritable changes in gene expression that do not entail variation in the DNA sequence". Epigenetics is an evolving area of research, especially in psychiatry, due to the nature of psychiatric disorders, where genetic and environmental factors interact. Epigenetics mechanistically links life experiences with the structural DNA code, providing an opportunity to potentially study the effect of both at once.¹³ The three pillars of epigenetic mechanisms are a) DNA methylation,¹⁴⁻¹⁶ b) Histone Modifications,¹⁷ c) RNA interference with non-coding (nc) RNAs.^{7,18} These mechanisms

determine the transcriptional state by regulating the access to the DNA sequence of the transcriptional machinery.¹³ Environmental factors seem to influence and play a major role in psychiatric diseases according to the genetic profile of the patients. Epigenetics, being a link between environmental and internal factors, provides the opportunity to further understand this complex interplay of factors and increase the efficacy of treatment methods.¹⁹

The investigation of epigenetic effects induced by electroconvulsive therapy (ECT) offers a unique molecular perspective that integrates previously documented alterations in gene expression, cellular dynamics, neurocircuitry, and functional brain activity. A recent systematic review by Castro et al. (2023) synthesized human studies on epigenetic mechanisms related to ECT and identified nine studies, with the majority focusing on DNA methylation and microRNA expression.²⁰ Building on this foundation, the objective of the present systematic review is to comprehensively examine and synthesize the current literature on epigenetic biomarkers associated with ECT response in individuals diagnosed with treatment-resistant major depressive disorder (TR-MDD). Through a critical evaluation of existing studies, this review aims to identify potential molecular signatures that could inform future translational research and advance the development of precision psychiatry approaches in mood disorders. The review critically reassesses prior findings in light of recent methodological advancements, enabling a more nuanced and clinically actionable synthesis of the data. Thus, it not only updates the existing evidence base but also reorients the field toward precision-based interpretations of the epigenetic effects of ECT.

Methodology

This systematic review was conducted following the PRISMA 2020 guidelines²¹ (Figure 1). The aim was to identify, evaluate, and synthesize all relevant studies investigating the relationship between Electroconvulsive Therapy (ECT) response in TR-MDD and epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNA expression. A systematic literature search was performed in PubMed and Scopus from 2015 to 2025. The following Boolean queries were used:

- PubMed: (Electroconvulsive Therapy [MeSH Terms] OR Electroconvulsive Therapy [Title/Abstract] OR ECT[Title/Abstract]) AND (Epigenetics [MeSH Terms] OR Epigenetics [Title/Abstract] OR "non-coding RNA"[Title/Abstract] OR "Histone Modification"[Title/Abstract] OR Methylation [Title/Abstract])
- Scopus: TITLE-ABS-KEY ("Electroconvulsive Therapy" OR ECT) AND TITLE-ABS-KEY (epigenetics OR "non-coding RNA" OR "histone modification" OR methylation)

Additional studies were identified through manual screening of references in eligible articles. Eligible studies were peer-reviewed original research articles that examined the effects of ECT on epigenetic markers in humans diagnosed with MDD and were published in English. Exclusion criteria included animal studies, review articles, conference abstracts, opinion pieces, studies not directly involving ECT, and studies without reported epigenetic outcomes. All references were managed using Rayyan for deduplication and organization. Two reviewers independently screened titles and abstracts, followed by full-text reviews, with disagreements resolved by a third reviewer. Data extraction was conducted using a standardized form and included study characteristics, design, population/sample details, ECT protocol, epigenetic outcomes, and key findings. Due to the heterogeneity of study designs, no formal risk of bias tool was applied. However, potential sources of bias were considered narratively.

Results

This systematic review synthesized current evidence from eleven studies exploring the epigenetic mechanisms associated with electroconvulsive therapy (ECT) in patients with treatment-resistant major depressive disorder (TR MDD) (Table 1). The results provide converging but preliminary evidence that ECT may induce epigenetic changes—potentially

underlying therapeutic response and symptom improvement. Eight studies investigated the role of DNA methylation as a potential biomarker or mechanistic correlate of Electroconvulsive Therapy (ECT) response, while three studies explored the role of microRNAs (miRNAs) in the context of ECT, utilizing both discovery and validation approaches. In total, 31 promising epigenetic biomarkers were examined in the studies (Table 2).

ECT and DNA Methylation Findings

Epigenome-Wide and Genome-Wide Analyses

Carvalho Silva et al (2024) conducted a comprehensive epigenome-wide association study (EWAS) to identify methylation changes associated with clinical outcomes of ECT. Longitudinal analyses revealed differentially methylated probes (DMPs) and regions (DMRs) nominally associated with symptom improvement and response status, including genes such as ADARB1, FAM20C, IQCE, and SLC25A24. Female-specific analyses uncovered additional significant and trend-significant DMRs in genes implicated in psychiatric disorders (ZFP57, GAS7, ADORA2A), trauma exposure (RIPOR2), and immune regulation (TOLLIP, LAT, FAM30A). Although none of the findings survived false discovery rate correction, the results suggest potential biological pathways modulated by ECT, particularly in sex-specific contexts.²²

Similarly, Sirignano et al (2021), using a genome-wide DNA methylation approach, identified two differentially methylated genes, TNKS and FKBP5, surpassing the stringent genome-wide significance threshold, both of which have been previously implicated in stress-response regulation and psychiatric vulnerability.²³

Candidate Gene Methylation Studies

Several studies focused on targeted DNA methylation analysis of stress-related and neuroplasticity-associated genes. Maier et al. (2023) assessed methylation of NR3C1 (glucocorticoid receptor) and POMC, reporting lower baseline NR3C1 methylation in unmedicated depressed controls compared to both ECT-treated patients and healthy controls. ECT induced a reduction in methylation levels of both genes, with responders showing lower post-treatment NR3C1 methylation than non-responders.²⁴

Schurgers et al (2022) observed increased mRNA expression of BDNF, ERK1, and NR3C1 during ECT, with corresponding changes in DNA methylation, highlighting dynamic transcriptional regulation during treatment.²⁵ Similarly, Kleimann et al (2015) found that ECT remitters exhibited significantly lower methylation in BDNF promoter regions (particularly exon I), suggesting epigenetic modulation of neurotrophic signaling as a mechanism of ECT efficacy.²⁶

Moschny et al (2020) performed a genome-wide methylation screen and implicated several novel genes (RNF175, TBC1D14, TRERF1) in ECT response.²⁷ In a separate analysis, while no baseline methylation differences were observed in t-PA and PAI-1 between remitters and non-remitters, cell-type-specific methylation differences were noted, underscoring the relevance of immune cell heterogeneity in peripheral biomarkers.²⁸

In an independent replication study, Neyazi et al (2018) demonstrated higher p11 promoter methylation in ECT responders across two clinical cohorts, reinforcing the potential predictive utility of this locus in antidepressant response.²⁹

ECT and Non-Coding RNA Findings

Genome-Wide and Transcriptomic Analysis

Israel-Elgali et al (2021) conducted a genome-wide assessment of miRNA expression profiles before and after ECT in patients with TR MDD. While no statistically significant changes remained after correction for multiple comparisons, exploratory analyses revealed a potential

upregulation of miR-24-3p associated with ECT response, warranting further investigation in larger cohorts.³⁰

Gururajan et al (2016) examined baseline and post-treatment expression of let-7b and let-7c, two miRNAs implicated in neuroinflammation and synaptic plasticity. Although expression levels were reduced in patients relative to healthy controls at baseline, no significant changes were observed post-ECT, nor was there an association with treatment outcome.⁷

Targeted and Subtype-Specific miRNA Studies

Kolshus et al (2017) employed a discovery-validation framework to examine peripheral blood miRNA and VEGF-A (Vascular endothelial growth factor A) mRNA levels in MDD patients undergoing ECT. In individuals with psychotic depression, levels of miR-126-3p and miR-106a-5p were elevated at baseline and normalized following ECT, in parallel with reductions in VEGF-A. These changes were not observed in patients with non-psychotic depression, suggesting a potential subtype-specific epigenetic signature responsive to ECT.³¹

Discussion

Across eight studies, DNA methylation emerged as a frequently examined epigenetic marker, with several investigations identifying differentially methylated positions (DMPs) and regions (DMRs) before and after ECT. Notably, Carvalho Silva et al (2024), employing an epigenome-wide association approach, found DMPs and DMRs associated with symptom changes and clinical response, annotated in genes such as ADARB1, IQCE, FAM20C, and immune-related loci such as SLC25A24 and NLRP6. Although these findings did not survive false discovery rate correction, they highlight genes involved in transcriptional regulation, immune signaling, and stress response.²²

Several studies investigated candidate genes previously implicated in HPA axis regulation. Maier et al (2023) and Schurgers et al. (2022) both reported altered methylation in NR3C1, the gene encoding the glucocorticoid receptor. Maier et al. found that responders to ECT exhibited lower NR3C1 methylation post-treatment, suggesting normalization of stress-related epigenetic patterns.²⁴ Similarly, Schurgers et al observed increased NR3C1 mRNA and correlated DNA methylation changes during ECT, supporting functional relevance.²⁵

The BDNF gene, a critical gene for neuroplasticity, was also differentially methylated in responders. Kleimann et al (2015) found that ECT remitters had significantly lower BDNF promoter methylation (especially exon I),²⁶ whereas Schurgers et al additionally demonstrated an increase in BDNF mRNA expression, linked to methylation dynamics.²⁵ It has been previously suggested as a biomarker able to distinguish between healthy and depressed subjects.³² These findings support previous hypotheses that BDNF regulation may mediate ECT-induced neuroadaptive processes.

Other genome-wide or targeted studies identified novel epigenetic candidates: TNKS and FKBP5²³; RNF175, WSCD1, TRERF1;²⁷ and p11 (S100A10)²⁹ the latter showing higher promoter methylation among ECT responders in two independent samples. However, some methylation effects were found to be cell-type dependent,²⁸ highlighting the complexity of interpreting peripheral epigenetic data.

The role of non-coding RNAs, particularly microRNAs (miRNAs), was evaluated in three studies. The findings remain mixed and methodologically heterogeneous. Kolshus et al (2017) conducted a multi-phase investigation, identifying normalization of elevated miR-126-3p and miR-106a-5p levels post-ECT in patients with psychotic depression. These miRNAs are known to regulate VEGF-A, whose mRNA levels also decreased after treatment, indicating a possible coordinated epigenetic and transcriptomic response in specific depression subtypes.³¹ Although the present systematic review focused exclusively on studies involving patients with major depressive disorder (MDD), it is worth noting related work in other psychiatric

populations. A recent study by Saglam et al (2024) investigated peripheral microRNA expression in patients with schizophrenia undergoing ECT. The authors examined miRNA expression before and after ECT, identifying differential expression of miR-20a-5p and miR-598 in patients with schizophrenia relative to healthy controls.³² However, no statistically significant changes were observed post-treatment, echoing findings from some MDD studies where miRNA responses to ECT were similarly variable or inconclusive. These results underscore the methodological challenges and inter-individual variability inherent in miRNA biomarker research, and further support the need for larger, diagnosis-specific, and well-powered studies.

In contrast, Israel-Elgali et al (2021) reported no genome-wide significant changes in circulating miRNAs but observed an upregulation of miR-24-3p under less stringent statistical thresholds, suggesting potential sensitivity limitations in miRNA detection methodologies.³⁰ Gururajan et al (2016) similarly found reduced let-7b/c expression in TRD patients relative to controls, but no predictive or treatment-related changes, casting doubt on their utility as dynamic biomarkers of ECT response.⁷

The focus of research in the animal studies was to prove a well-established epigenetic effect of the electroconvulsive seizures (ECS), analogous to ECT in animal studies, in the brain of rodents, and provide the knowledge background and a stimulus for further research. The animal studies literature reveals that Electroconvulsive seizures have multiple epigenetic effects that are hypothesized to adjust the therapeutic effects of ECT. Based on the studies included in the de Jong et al review¹² and more recent studies^{29,34,35}, the epigenetic effects of ECS cover all the spectrum of epigenetic mechanisms and include increased histone acetylation in c-Fos, BDNF, and CREB genes; demethylation of BDNF promoter¹², ECS-induced HDAC2 upregulation and decreased H3 acetylation at Arc promoter³² significant decline in H3K9 acetylation in the hippocampus following chronic electroconvulsive seizure³⁵, p11 promoter and changes in the level of various hippocampal miRNAs.²⁹

Nonetheless, the results cannot be extrapolated to a clinical population of individuals with severe and/or chronic depression, and the results can be considered explorative due to the early phase of neuroepigenetic research and the lack of replication in most of the findings. In contrast to this viewpoint, the most recent animal study of Neyazi et al²⁹ managed to yield results in a proof-of-concept clinical trial. Utilizing a chronic mild stress model of MDD, the group obtained citalopram-resistant rats, and ECS was used. Besides, the group proposed cortical ECS as a more valid procedure to mimic ECT than auricular ECS. The results depict a higher p11 promoter methylation, which was also found in the first clinical trial and was then replicated in a second one. This translational study successfully validates the first biomarker reliably predicting the responsiveness to ECT.

Collectively, the evidence suggests that ECT is associated with measurable epigenetic modifications, primarily in DNA methylation and to a lesser extent in non-coding RNA expression. Genes involved in neuroplasticity (BDNF), HPA axis modulation (NR3C1, FKBP5), inflammation, and synaptic regulation appear to be central mediators. The heterogeneity of findings across studies reflects both the complexity of epigenetic regulation and the diversity of analytic strategies employed. No studies in humans concerning histone modifications were found, leading to the recommendation of future research.

Despite the promising insights presented, several limitations must be acknowledged. The included studies were heterogeneous in terms of sample size, ECT protocols, clinical populations, and methods used to assess epigenetic changes, limiting the comparability of findings. It is important to note that more research is needed before a reliable conclusion can be made, not only in terms of the reproducibility of the results in larger sample sizes. Most studies featured small cohorts and lacked replication, which increases the risk of false-positive results. Additionally, most of the studies did not report or control for key confounders such as medication status, comorbidities, or baseline inflammation, all of which may influence

epigenetic signatures. Formal risk of bias assessment was constrained by the variability in study design, but methodological limitations, such as the absence of blinding, small sample sizes, and lack of longitudinal follow-up, were common.

Furthermore, the reliance on peripheral blood as a proxy for brain-based changes introduces an additional layer of uncertainty, given the tissue specificity of epigenetic mechanisms. Due to ethical reasons, the most acceptable sample is peripheral blood, leading the focus of studies to shift in search of biomarkers that can be traced in the blood. However, since epigenetic changes are cell- and tissue-specific, there is a possibility for some results not to reflect the actual changes in the brain. Though DNA methylation varies between tissues, some inter-individual variations are reflected across the brain and blood in humans.³⁶

From a future perspective, further research is needed to lead to more conclusive results. We recommend research in a multi-omics approach for ECT effects and biomarkers, incorporating longitudinal designs, and considering cell-specific and brain-derived samples where feasible. Strategies that would enhance biomarker validity include adequately powered sample sizes and a priori hypotheses for the role of the markers of interest. Ideally, as stated in the studies choice of prior unmedicated patients will potentially yield more accurate results. Moreover, assessment of SNPs in cases of overlap with areas of interest can eliminate bias and potential influence in the results. Considering research for optimization of therapies for MDD, studies can be conducted for biomarkers for second-and third-line treatment of treatment-resistant MDD, including repetitive transcranial magnetic stimulation (rTMS). There is a plethora of molecular mechanisms involved in the pathophysiology of depression, which can be a target for epigenetic studies. Instances with evidence of epigenetic changes include serotonin transporter-regulating genes, glucocorticoid receptors, and GABA receptors.³⁷

Epigenetics is a promising type of novel biomarker for treatment response for ECT and could improve predictability when used in combination with more established predictors.³⁸ Epigenetic modifications across the genome represent orchestrated phenomena that modulate the transcriptional output of the genetic code. In this sense, identifying the aberrant changes in the epigenetic landscape associated with human disease and the factors promoting such alterations provides the potential for new biomarkers that contribute to clinical decisions. A patient's epigenetic profile may represent a measurable combination of genetic and clinical predictors that could have more prognostic value than either alone, potentially improving physician decision-making and patient experience.^{39,40}

Conclusion

This systematic review synthesized evidence from eleven studies investigating epigenetic mechanisms associated with electroconvulsive therapy (ECT) response in patients with treatment-resistant major depressive disorder (TR-MDD). Across these studies, a total of 31 promising epigenetic biomarkers were identified, including DNA methylation patterns in genes related to HPA axis regulation, neuroplasticity, inflammation, and immune modulation, as well as miRNAs. While the most consistently investigated mechanism was DNA methylation, a smaller number of studies explored non-coding RNAs, with no human studies addressing histone modifications. The findings suggest that epigenetic changes may play a mediating role in ECT-induced symptom improvement, reflecting underlying molecular adaptations to treatment. However, the overall body of evidence remains preliminary, due to limitations such as small sample sizes, heterogeneity in patient populations and methodologies, lack of replication, and reliance on peripheral blood samples rather than brain-derived tissue. The observed variability in epigenetic signatures across studies also highlights the complex, cell-type-specific nature of epigenetic regulation, which may limit generalizability. To strengthen the field and move toward clinical translation, future research should focus on well-powered, longitudinal studies with standardized protocols, integration of multi-omics approaches, and

consideration of sex-specific and cell-specific effects. Validation of these candidate biomarkers could pave the way for stratified treatment planning and more personalized applications of ECT in psychiatry. Epigenetics holds significant promise as a biomarker platform that could complement existing clinical predictors and enhance our understanding of individual variability in antidepressant response.

References

1. Deng ZD, Robins PL, Regenold W, et al. *Neuropsychopharmacology* 2024, 49:150-162, doi: 10.1038/s41386-023-01677-2
2. Kellner CH, Obbels J, Sienaert P. When to consider electroconvulsive therapy (ECT). *Acta Psychiatr Scand* 2020, 141:304-315, doi: 10.1111/acps.13134
3. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry* 1996, 153:985-992, doi:10.1176/ajp.153.8.985
4. Prudic J, Olfson M, Marcus SC, et al. Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry* 2004, 55:301-312, doi: 10.1016/j.biopsych.2003.09.015
5. Brus O, Cao Y, Gustafsson E, et al. Self-assessed remission rates after electroconvulsive therapy of depressive disorders. *Eur Psychiatry* 2017, 45:154-160, doi:10.1016/j.eurpsy.2017.06.015
6. Alevizos B, Sackeim HA, Fink M. Attitudes of Greek nonpsychiatrist physicians toward electroconvulsive therapy. *J ECT* 2005, 21:194-198
7. Gururajan A, Naughton ME, Scott KA, et al. MicroRNAs as biomarkers for major depression: A role for let-7b and let-7c. *Transl Psychiatry* 2016, 6:e862, doi: 10.1038/tp.2016.131
8. Jiang J, Wang J, Li C. Potential mechanisms underlying the therapeutic effects of electroconvulsive therapy. *Neurosci Bull* 2017, 33:339-347, doi:10.1007/s12264-016-0094-x
9. Khanra S, Khess CRJ, Munda SK. "Precision psychiatry": A promising direction so far. *Indian J Psychiatry* 2018, 60:373-374, doi: 10.4103/psychiatry.IndianJPsychiatry_203_18
10. Feng T, Youssef NA. Can epigenetic biomarkers lead us to precision medicine in predicting treatment response and remission for patients being considered for ECT?. *Psychiatry Res* 2020, 284:112659, doi: 10.1016/j.psychres.2019.112659
11. Keverne J, Binder EB. A review of epigenetics in psychiatry: Focus on environmental risk factors. *Med Genet* 2020, 32:57-64, doi:10.1515/medgen-2020-2004
12. De Jong JOZ, Arts B, Boks MP, et al. Epigenetic effects of electroconvulsive seizures. *J ECT* 2014, 30:152-159, doi:10.1097/YCT.0000000000000141
13. Rasool M, Malik A, Naseer MI, et al. The role of epigenetics in personalized medicine: Challenges and opportunities. *BMC Genomics* 2015, 8:S5, doi:10.1186/1755-8794-8-S1-S5
14. Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology* 2013, 38:23-38, doi:10.1038/npp.2012.112
15. Jin SG, Wu X, Li AX, et al. Genomic mapping of 5-hydroxymethylcytosine in the human brain. *Nucleic Acids Res* 2011, 39:5015-5024, doi:10.1093/nar/gkr120
16. Spiers H, Hannon E, Schalkwyk LC, et al. 5-Hydroxymethylcytosine is highly dynamic across human fetal brain development. *BMC Genomics* 2017, 18:1-14, doi:10.1186/s12864-017-4091-x
17. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res* 2011, 21:381-395, doi:10.1038/cr.2011.22
18. Djupedal I, Ekwall K. Epigenetics: Heterochromatin meets RNAi. *Cell Res* 2009, 19:282-295, doi:10.1038/cr.2009.13

19. Nicoglou A, Merlin F. Epigenetics: A way to bridge the gap between biological fields. *Stud Hist Philos Sci C* 2017, 66:73-82, doi:10.1016/j.shpsc.2017.10.002
20. Castro SCC, Bicca C, Bicca B, et al. A systematic mini-review of epigenetic mechanisms associated with electroconvulsive therapy in humans. *Front Hum Neurosci* 2023, 17:1143332, doi:10.3389/fnhum.2023.1143332
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an Updated Guideline for Reporting Systematic Reviews. *Br Med J* 2021, 372:71
22. Carvalho Silva R, Martini P, Hohoff C, et al. Unraveling epigenomic signatures and effectiveness of electroconvulsive therapy in treatment-resistant depression patients: a prospective longitudinal study. *Clin Epigenetics* 2024, 16:93, doi:10.1186/s13148-024-01704-z
23. Sirignano L, Frank J, Kranaster L, et al. Methylome-wide change associated with response to electroconvulsive therapy in depressed patients. *Transl Psychiatry* 2021, 11:347, doi:10.1038/s41398-021-01474-9
24. Maier HB, Moschny N, Eberle F, et al. DNA methylation of POMC and NR3C1-1F and its implication in major depressive disorder and electroconvulsive therapy. *Pharmacopsychiatry* 2023, 56:64-72, doi:10.1055/a-2034-6536
25. Schurgers G, Walter S, Pishva E, et al. Longitudinal alterations in mRNA expression of the BDNF neurotrophin signaling cascade in blood correlate with changes in depression scores in patients undergoing electroconvulsive therapy. *Eur Neuropsychopharmacol* 2022, 63:60-70, doi:10.1016/j.euroneuro.2022.07.183
26. Kleimann A, Kotsiari A, Sperling W, et al. BDNF serum levels and promoter methylation of BDNF exon I, IV and VI in depressed patients receiving electroconvulsive therapy. *J Neural Transm* 2015, 122:925-928, doi:10.1007/s00702-014-1336-6
27. Moschny N, Zindler T, Jahn K, et al. Novel candidate genes for ECT response prediction – a pilot study analyzing the DNA methylome of depressed patients receiving electroconvulsive therapy. *Clin Epigenetics* 2020, 12:1-16, doi:10.1186/s13148-020-00891-9
28. Moschny N, Jahn K, Bajbouj M, et al. DNA methylation of the t-PA gene differs between various immune cell subtypes isolated from depressed patients receiving electroconvulsive therapy. *Front Psychiatry* 2020, 11:571, doi:10.3389/fpsy.2020.00571
29. Neyazi A, Theilmann W, Brandt C, et al. P11 promoter methylation predicts the antidepressant effect of electroconvulsive therapy. *Transl Psychiatry* 2018, 8:77, doi:10.1038/s41398-017-0077-3
30. Israel-Elgali I, Hertzberg L, Shapira G, et al. Blood transcriptional response to treatment-resistant depression during electroconvulsive therapy. *J Psychiatr Res* 2021, 141:92-103, doi:10.1016/j.jpsychires.2021.06.039
31. Kolshus E, Ryan KM, Blackshields G, et al. Peripheral blood microRNA and VEGFA mRNA changes following electroconvulsive therapy: implications for psychotic depression. *Acta Psychiatr Scand* 2017, 136:594-606, doi:10.1111/acps.12821
32. Fuchikami M, Morinobu S, Segawa M, et al. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. *PLoS One* 2011, 6:e23881, doi:10.1371/journal.pone.0023881
33. Usta Saglam NG, Duz MB, Salman Yilmaz S, et al. Comparison of microRNA expression levels in patients with schizophrenia before and after electroconvulsive therapy. *Psychiatr Genet* 2024, 34:79-85, doi:10.1097/YPG.0000000000000371
34. Dyrvig M, Gøtzsche CR, Woldbye DPD, et al. Epigenetic regulation of Dnmt3a and Arc gene expression after electroconvulsive stimulation in the rat. *Mol Cell Neurosci* 2015, 67:137-143, doi:10.1016/j.mcn.2015.06.011

35. Pusalkar M, Ghosh S, Jaggar M, et al. Acute and chronic electroconvulsive seizures (ECS) differentially regulate the expression of epigenetic machinery in the adult rat hippocampus. *Int J Neuropsychopharmacol* 2016, 19:1-11, doi:10.1093/ijnp/pyw040
36. Davies MN, Volta M, Pidsley R, et al. Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. *Genome Biol* 2012, 13:R43, doi:10.1186/gb-2012-13-6-r43
37. Kular L, Kular S. Epigenetics applied to psychiatry: Clinical opportunities and future challenges. *Psychiatry Clin Neurosci* 2018, 72:195-211, doi:10.1111/pcn.12634
38. Yao Z, McCall WV, Essali N, et al. Precision ECT for major depressive disorder: A review of clinical factors, laboratory, and physiologic biomarkers as predictors of treatment response. *Pers Med Psychiatry* 2019, 17-18:23-31, doi:10.1016/j.pmip.2019.07.001
39. Lockwood LE, Su S, Youssef NA. The role of epigenetics in depression and suicide: A platform for gene-environment interactions. *Psychiatry Res* 2015, 228:235-242, doi:10.1016/j.psychres.2015.05.071
40. Alladi CG, Etain B, Bellivier F, et al. DNA methylation as a biomarker of treatment response variability in serious mental illnesses: A systematic review focused on bipolar disorder, schizophrenia, and major depressive disorder. *Int J Mol Sci* 2018, 19:3026, doi:10.3390/ijms19103026

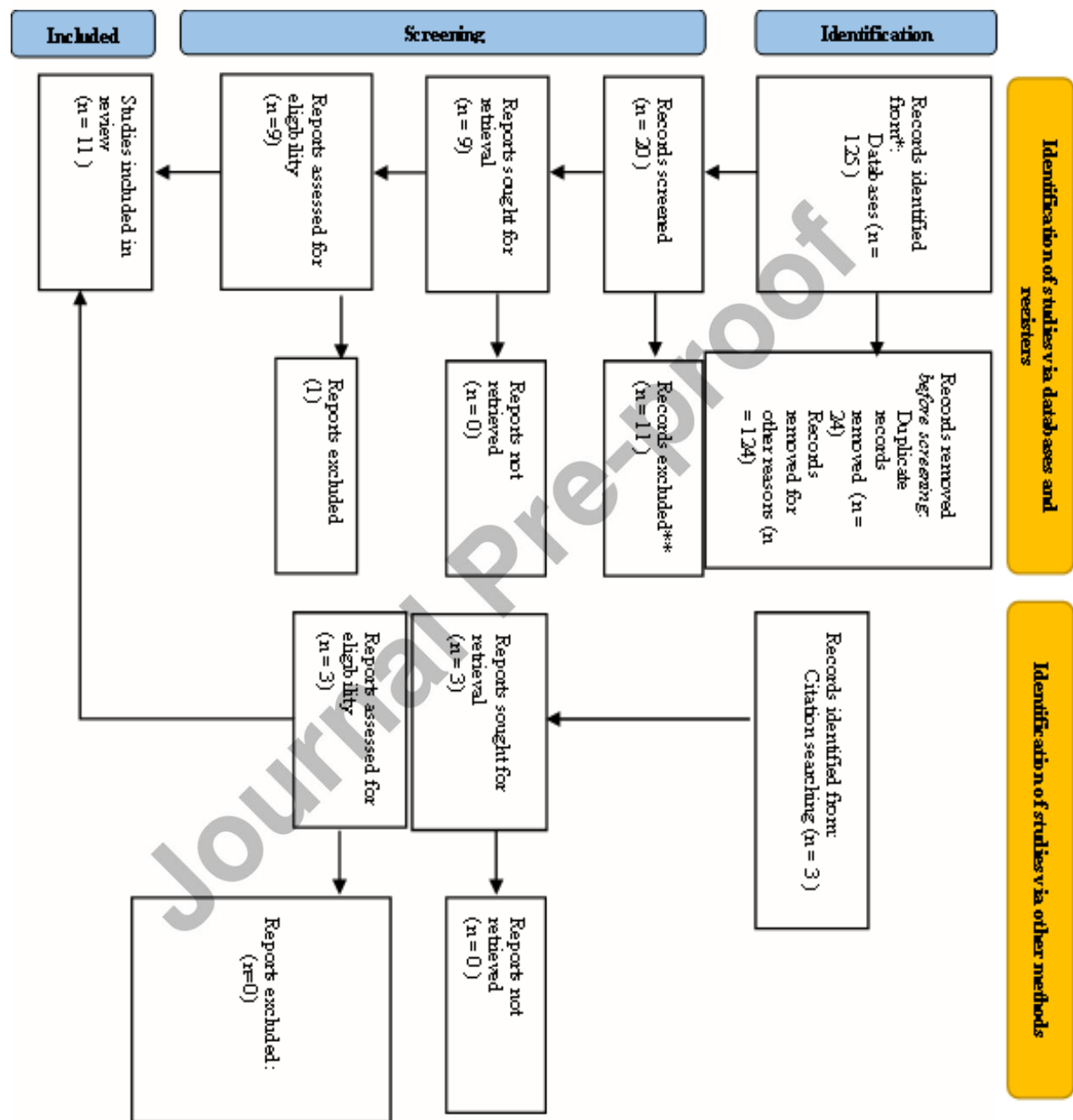


Figure 1. PRISMA flow diagram

Table 1. Key findings of the included studies

Author (Year)	N (ECT pts)	Biomarker / Epigenetic Target	ECT Protocol	Concomitant Medication	Outcome Scale	Key Findings
Kleimann et al. 2015	11	BDNF promoter (exons I, IV, VI) methylation; serum BDNF	Thymatron IV; 3 ECT sessions/week over 3, 5 weeks.	medications including antidepressants (n=10), antipsychotics (n=9) remained unchanged	MADRS Score ≤12	Lower baseline exon I methylation predicted remission; no serum BDNF change

Gururajan et al. 2016	24	miRNA transcriptome (let-7b, let-7c)	bi-weekly brief-pulse bitemporal ECT (not specified further)	Usual antidepressants continued	MADRS ≥ 50 % decrease	let-7b/c lower vs controls but neither predicted or changed with ECT
Kolshus et al. 2017	16 miRNA cohort; 37 miRNA validation cohort; 97 VEGF-A cohort	miR-126-3p, miR-106a-5p; VEGF-A mRNA	hand-held electrodes on the Spectrum 5000M device; Two group, parallel, double-blind randomised controlled non-inferiority trial comparing high-dose R-unilateral with standard-dose bitemporal ECT; 2 times/week	Mixed; psychotic subgroup often on antipsychotics	HDRS, BPRS-5	Psychotic depression showed elevated miRNAs & VEGF-A; normalised post-ECT. No miRNA changes in non-psychotic depression.
Neyazi et al. 2018	76 (11 Proof of Concept + 65 replication)	p11 (S100A10) promoter methylation	Not specified	medication remained unchanged	MADRS ≥ 50 % decrease	Higher baseline p11 methylation robustly predicted response
Moschny et al. 2020a	17	Genome-wide DNA methylation	Thymatron IV; R-unilateral 3 times/weekly up to 4 weeks followed by maintenance ECTs applied only once a week.	medication remained unchanged	MADRS ≥ 50 % decrease	8 novel CpGs (RNF175, RNF213, etc.) associated with response
Moschny et al. 2020b	first cohort (n = 59) second group (n = 28)	t-PA (PLAT) & PAI-1 (SERPINE1) DNA methylation (cell-sorted)	Ultra-brief pulse devices [Mecta 5000Q and Thymatron IV]; R-unilateral; 3 times/week up to 4 weeks	medication remained unchanged	HAM-D or MADRS ≥ 50 % decrease was interpreted as response, ≤ 7 HAM-D or ≤ 10 MADRS as remission.	Strong cell-type methylation differences; no global ECT effect
Sirignano et al. 2021	34	Differentially methylated CpG sites, Genome-wide DNA methylation	Thymatron IV; unilateral stimulation with the possibility to change to bilateral stimulation at the discretion of the ECT supervisor; 2-3 times/week	Not specified	HDRS-17 Δ or ≥ 50 %	CpG in TNKS ($q < 0.05$) & FKBP5 were differentially methylated above stringent statistical threshold, related to response
Israel-Elgali et al. 2021	17	miRNA & mRNA transcriptome	hand-held electrodes ; unilateral; 2 times/week	Compared with SSRI & ketamine groups	HAM-D24 ≥ 50 % decrease and a score	$\uparrow$ FKBP5, $\downarrow$ ITGA2B, $\uparrow$ miR-24-3p

					≤16 at the end of treatment	unique to ECT responders
Schurgers et al. 2022	19	mRNA (BDNF, ERK1, NR3C1) & DNA methylation	ThymatronR System IV device; bitemporal electrode position; 2 times/week mean sessions = 6.1 (3-11)	Benzodiazepines were stopped before the first ECT session. Other medications including antidepressants remained unchanged.	MADRS ≥50 % decrease	mRNA ↑ for BDNF, ERK1, NR3C1; correlated with DNA methylation levels.
Maier et al. 2023	31	NR3C1-1F & POMC DNA methylation	Thymatron IV; unilateral; 3times/week up to 10 (±4) sessions	Registry patients on standard medication	MADRS ≥50 % decrease	Responder baseline lower NR3C1 methylation; both genes demethylated acutely
Carvalho Silva et al. 2024	32	EPIC EWAS	Thymatron DG ;Bilateral brief-pulse; 3times/week for 4 weeks	medication remained unchanged	MADRS ≥50 % decrease	Identified multiple DMPs and DMRs related to symptom variation and response, eg. CYB5B, PVRL4, ADARB1, IQCE, SLC25A24. Female-specific DMRs involved psychiatric, trauma-related, and immune-related genes (e.g., ZFP57, POLD4, H19). Pathway analysis highlighted transcriptional, growth, and immune processes.

Table 2. Promising epigenetic biomarkers of ECT response

Epigenetic Mechanism	Biomarker
DNA Methylation (candidate genes)	NR3C1, POMC, BDNF (exon I, IV, VI), FKBP5, TNKS, SLC25A24, ADARB1, FAM20C, IQCE, RNF175, RNF213, TRERF1, TBC1D14, WSCD1, TOLLIP, LAT, FAM30A, ZFP57, GAS7, ADORA2A, RIPOR2, t-PA, PAI-1, p11 (S100A10, promoter methylation), VEGF-A (mRNA)
microRNAs (miRNAs)	let-7b, let-7c, miR-126-3p, miR-106a-5p, miR-24-3p

ΑΝΑΣΚΟΠΗΣΗ

Με κατεύθυνση την Ηλεκτροσπασμοθεραπεία Ακριβείας: Συστηματική ανασκόπηση επιγενετικών δεικτών απόκρισης στη φαρμακοανθεκτική κατάθλιψη

Νικόλαος Σταθαράκος,^{1,2} Βασίλειος Σαββίδης,^{1,2} Ταξιάρχης Γραβάνης,^{1,2}

1. Ψυχιατρική Ενηλίκων, ΓΝΘ «Γ.Παπανικολάου», Θεσσαλονίκη, Ελλάδα

2. Ψυχιατρικό Νοσοκομείο Θεσσαλονίκης, Θεσσαλονίκη, Ελλάδα

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ΠΕΡΙΛΗΨΗ

Η ηλεκτροσπασμοθεραπεία (ΗΣΘ) αποτελεί μία από τις πιο αποτελεσματικές θεραπείες για ασθενείς με φαρμακοανθεκτική μείζονα καταθλιπτική διαταραχή. Ωστόσο, οι βιολογικοί μηχανισμοί που διέπουν την θεραπευτική της δράση παραμένουν εν μέρει αδιευκρίνιστοι. Η επιγενετική ρύθμιση έχει αναδειχθεί πρόσφατα ως ένας υποσχόμενος τομέας για την κατανόηση της μοριακής βάσης της απόκρισης στην ΗΣΘ. Σκοπός αυτής της συστηματικής ανασκόπησης ήταν η καταγραφή και σύνθεση των υπαρχουσών μελετών που διερευνούν επιγενετικούς βιοδείκτες σχετιζόμενους με τα θεραπευτικά αποτελέσματα της ΗΣΘ σε ανθρώπινους πληθυσμούς. Διενεργήθηκε συστηματική ανασκόπηση στις βάσεις δεδομένων PubMed και Scopus για μελέτες που δημοσιεύτηκαν μεταξύ Ιανουαρίου 2015 και Μαρτίου 2025, σύμφωνα με τις οδηγίες PRISMA 2020. Κριτήρια ένταξης αποτέλεσαν: (1) πρωτότυπες, αξιολογημένες από ομότιμους εργασίες· (2) διερεύνηση των επιδράσεων της ΗΣΘ σε επιγενετικούς δείκτες· και (3) διάγνωση μείζονος καταθλιπτικής διαταραχής. Απόσπασμα δεδομένων αφορούσε τους επιγενετικούς στόχους, τα χαρακτηριστικά των ασθενών, τις παραμέτρους της ΗΣΘ και τα κλινικά αποτελέσματα. Ελήφθησαν υπόψη ο κίνδυνος μεροληψίας και η ετερογένεια των μελετών. Έντεκα μελέτες πληρούσαν τα κριτήρια ένταξης, περιλαμβάνοντας συνολικά 498 ασθενείς με TR-MDD. Στο σύνολο των μελετών εντοπίστηκαν 31 υποσχόμενοι επιγενετικοί βιοδείκτες, που σχετίζονται με τη νευροπλαστικότητα, τη ρύθμιση του άξονα ΥΥΕ (υποθαλάμου-υπόφυσης-επινεφριδίων), τη φλεγμονή, την ανοσιακή σηματοδότηση και τα μη κωδικά RNAs. Οι πιο συχνά μελετημένοι μηχανισμοί ήταν η μεθυλίωση του DNA και η έκφραση microRNA (miRNA). Καμία μελέτη σε ανθρώπους δεν εξέτασε τροποποιήσεις ιστονών. Η παρούσα συστηματική ανασκόπηση παρέχει προκαταρκτικά ευρήματα που υποστηρίζουν τον ρόλο των επιγενετικών μηχανισμών—ιδίως της μεθυλίωσης του DNA και της έκφρασης miRNA—στη ρύθμιση της ανταπόκρισης στην ΗΣΘ σε ασθενείς με TR-MDD. Αν και τα ευρήματα αναδεικνύουν υποψήφιους βιοδείκτες για κλινική ταξινόμηση και ψυχιατρική ακριβείας, οι μικροί πληθυσμοί δειγμάτων και η μεθοδολογική ετερογένεια περιορίζουν τη γενίκευση. Απαιτούνται μεγαλύτερες, τυποποιημένες και προοπτικές μελέτες για την επικύρωση και περαιτέρω αξιοποίηση αυτών των πρώιμων δεδομένων.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Ηλεκτροσπασμοθεραπεία, φαρμακοανθεκτική κατάθλιψη, επιγενετική, βιοδείκτες, ψυχιατρική ακριβείας.

Επιμελητής συγγραφέας: Νικόλαος Σταθαράκος, Ψυχιατρική Ενηλίκων, ΓΝΘ «Γ.Παπανικολάου», Λεωφόρος Παπανικολάου, Εξοχή, 57100, Θεσσαλονίκη, Ελλάδα, Email: nicstath@gmail.com, nstathaa@auth.gr