

The Immune System and Electroconvulsive Therapy for Depression

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Background: Electroconvulsive therapy (ECT) remains the most effective and fast-acting treatment option for several psychiatric conditions, including treatment-resistant depression. Although ECT has been in use for 75 years, the mechanism of action is unknown. There is emerging evidence that modulation of the hypothalamic-pituitary-adrenal axis may mediate, in part, the therapeutic action of ECT. A growing body of evidence points to links between disturbances in the immune system and depression. However, the impact of ECT on immune functioning and the possible role of alterations in the immune system as a mechanism of action of ECT remain elusive.

Objectives: To provide a literature overview on the effects of ECT on the immune system.

Methods: Relevant articles and abstracts in English were retrieved from PubMed/Medline using search terms related to ECT, inflammation, and immune system. The results of studies examining ECT-induced changes in immune functioning as well as the degree to which these represent possible mechanisms mediating the therapeutic action of ECT were summarized.

Results: Our search identified only a limited number of studies. The findings suggest that a single session of ECT induces an acute, transient immune activation, whereas repetitive ECT treatment results in long-term down-regulation of immune activation. However, inconsistency in findings and methodological issues, including sample size and lack of consideration of confounding factors affecting cytokine concentrations, precludes definitive conclusion.

Conclusions: To elucidate the possible role of immunological changes mediating the effect of ECT, more prospective controlled studies with larger sample sizes are required.

Key Words: ECT, depression, mechanism, inflammation, cytokine, immunology

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Electroconvulsive therapy (ECT) remains the most effective treatment option for several psychiatric conditions and is mainly used in treatment-resistant depression.¹ The mechanism of action of ECT remains unknown. A complex network of effects on different neurotransmitter, neurohormone, and neurotrophic systems may play a role.^{2–6} Numerous studies show

that the release of hormones associated with the hypothalamic-pituitary-adrenal (HPA) axis, for example, prolactin, adrenocorticotropin, arginine vasopressin, growth hormone, and neuropeptide Y, is altered by ECT.^{4,7} The HPA axis, thus, is one of the most extensively studied pathways underlying ECT. Although the findings of these studies are not always consistent, most report normalization of HPA-axis deregulation, as measured by the dexamethasone suppression test, after successful ECT treatment, supporting the role of the HPA axis in mediating the therapeutic effects of ECT.^{7,8}

An intriguing factor that has received relatively little attention in the search for the biological mechanism of ECT is the immune system. A growing body of evidence shows that disturbances in certain aspects of the immune system are involved in the pathogenesis of depression.^{9,10} In addition, antidepressants have immunomodulating properties, and, vice versa, interventions that restore normal immune functioning can have antidepressant effects. It is therefore plausible to consider a role of immune pathways in the mechanism of action of ECT. In this review, we first provide a brief summary on the immune-related pathways that are proposed to underlie the pathogenesis of depression, and discuss the impact of ECT on the immune system in relation to its mechanism of action.

DEPRESSION AND THE IMMUNE SYSTEM

Approximately 3 decades ago, evidence accumulated that major depression was accompanied by signs of mild immunosuppression, mainly in the form of lower proliferative responses of lymphocytes and reduced activity of natural killer (NK) cells.¹¹ However, when knowledge on regulation of immune functioning increased, it became clear that depressed patients had increased levels of inflammatory mediators and activated immune cells. In the early 1990s, Robert Smith first coined the macrophage theory of depression, based on an extensive synthesis of the available literature at the time, stating that a heightened activity of the innate immune system was causally related to major depression.¹² Today, the notion that the proinflammatory state in depressed patients contributes to etiology, pathogenesis, and course of the disease is widely researched, based on several lines of evidence: (1) large-scale epidemiological studies and meta-analyses have consistently found increased levels of proinflammatory mediators, in particular C-reactive protein,^{13,14} interleukin-6 (IL-6),^{14,15} IL-1¹⁴, and tumor necrosis factor α (TNF- α)¹⁵ in depressed patients; (2) therapies using proinflammatory cytokines, that is, interferon- α (IFN- α) for hepatitis C infection, evoke depressive symptoms and clinical depression in a sizeable number of patients^{16,17}; (3) mood disorders have a high rate of comorbidity with somatic diseases associated with chronic inflammation, for example, diabetes mellitus, cardiovascular illness, and autoimmune diseases such as Crohn disease and rheumatoid arthritis.⁹ In addition, prolonged psychological stress, a well-established risk factor for depression, has been associated with a shift toward a proinflammatory state.^{9,10} There is also some evidence that polymorphisms in immune genes are associated with major

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depression.¹⁸ To what degree these genetic factors, possibly in interaction with adverse environmental exposures such as chronic stress, represent true vulnerability for depression remains to be determined.

Several mechanistic pathways of how peripheral inflammation affects the neurobiological circuits of affect regulation have been described.^{9,19,20} For example, proinflammatory cytokines increase the catabolism of tryptophan through the kynurenine pathway, leading to decreased availability of tryptophan (the precursor for serotonin synthesis) and to accumulation of neurotoxic metabolites, that is, 3-hydroxykynurenine and quinolinic acid, in the brain.²¹ In addition, proinflammatory cytokines stimulate the HPA axis and impair glucocorticoid receptor function, resulting in HPA-axis deregulation and prolonged increases in circulating stress hormones,²² further contributing to a neurotoxic environment in the central nervous system. This neurotoxic challenge disturbs neurotransmitter homeostasis and neuronal growth factor synthesis and finally perturbs the normal functioning of the neuronal circuits of the limbic system.²³

If inflammatory processes indeed are causally related to major depression, it is tempting to speculate that antidepressants have anti-inflammatory properties or that successful alleviation of symptoms during therapy would be associated with decreases in immune activation. Immune-modulating effects of antidepressants have been described.^{24,25} Recent meta-analyses indicated that treatment with antidepressants reduces the levels of proinflammatory cytokines^{26,27} and C-reactive protein.²⁷ It remains inconclusive, however, whether these reductions are associated with clinical improvement; it has been suggested that heterogeneity in findings may be due in part to differential effects of various types of antidepressants on circulating cytokine levels.²⁸ Another factor affecting heterogeneity may be that patients displaying chronic inflammation represent a depression subgroup with special clinical characteristics.²⁹ For example, it has been suggested that patients with increased inflammation markers respond more poorly to antidepressants and have a more chronic course of the disease,^{30,31} which is in agreement with recent findings that anti-inflammatory interventions alleviate depressive symptoms in this subset of patients.^{32,33}

Taken together, the findings indicate a possible role for chronic inflammation in depression, which may influence the success of antidepressant therapy, including ECT. We will therefore review studies that examined the effects of ECT on immune functioning.

THE IMPACT OF ECT ON THE IMMUNE SYSTEM

Table 1 summarizes the characteristics of clinical studies investigating the impact of ECT on immune parameters. These studies concentrated on both the acute immunological effects after a single ECT session and effects after repeated ECT sessions (reaching sufficient clinical improvement to discontinue ECT) on different immune parameters. The main immune parameters reported were measures of cellular immune function (lymphocyte subpopulations and NK cell activity) and levels of circulating cytokines.

Acute Effects of Electroconvulsive Seizure

Several studies focusing on the acute effect of ECT on NK cell activity indicate an increment in NK cell activity within minutes after ECT administration.^{34,36,39} Interleukin-6 activity was increased after a single session of ECT.³⁵ Fluitman et al⁴³ likewise demonstrated that a single session of ECT was associated with increased production of IL-6, IL-10, and TNF- α by

monocytes after lipopolysaccharide stimulation, and decreased production of IFN- γ by T cells after CD2/CD28 stimulation. After the correction of the cytokine response by number of producing cells, changes in IL-6 and IFN- γ still remained statistically significant.⁴³ Additionally, acute increase in the total number of leukocytes, monocytes, granulocytes, and NK cells, returning to baseline levels 30 minutes after the stimulus, was also demonstrated in this study.⁴³ After a single session of ECT, plasma IL-1 β and IL-6 concentrations increased over the following 3-hour time point, returning to baseline concentrations in 24 hours.⁴² Other studies have focused on markers of glial activity, that is, S100B, in association with ECT-induced cognitive impairment. S100B, a calcium-binding protein expressed by astrocytes and oligodendrocytes, has various functions in neuronal survival and apoptosis, and may be elevated in cerebrospinal fluid (CSF) and serum of patients with depression.⁴⁵ Electroconvulsive therapy has been associated with an increase in serum S100B concentrations 1 and 3 hours after the ECT session,⁴¹ whereas another study found no change in S100B after ECT.³⁸

Long-Term Effects of ECT

In addition to these studies investigating short-term effects of a single ECT session on the immune system, several studies focused on long-term effects after the end of the ECT treatment. In one of the earliest clinical trials, repetitive ECT sessions reduced both phytohemagglutinin and concanavalin A–induced lymphocyte blastogenesis.³⁴ Another study demonstrated that ECT resulted in immune system activation evidenced by enhancement in the number of lymphocytes expressing activation antigens (CD25 and CD38) after completion of treatment.³⁶ Whereas ECT increases NK cell activity acutely, repeated ECT treatments did not show substantial changes in NK cell activity after completion of the ECT treatment.^{36,39,43} Hestad et al showed that depression-related increases in TNF- α concentrations before administration of ECT decreased during the ECT treatment period and reached a level comparable to that in healthy controls at the end of the study, whereas TNF- α concentrations during the study period remained stable in patients who received only drug treatment.⁴⁰ A recent study measuring an extensive array of cytokines by cytokine membrane techniques showed a decrease in the signal intensities of IL-5 and eotaxin-3, which are both proinflammatory cytokines involved in chronic inflammatory diseases such as asthma, 24 hours after the completion of a 12-session ECT treatment.⁴⁴ Although decreased eotaxin-2 and TNF- β were also observed, these changes failed to reach statistical significance. Furthermore, in the same study, reverse transcription polymerase chain reaction method revealed an increase in TNF- β .⁴⁴ Fluitman et al⁴³ demonstrated that ECT had an acute effect on immune parameters (TNF- α , IL-6, IL-10, IFN- γ , IL-4, and total number of immune cells), whereas repeated ECT (11 sessions) did not have an additive effect on these changes. Several studies show that serum and cerebrospinal fluid S100B concentrations are not influenced by ECT.^{37,38,41} Higher baseline S100B concentration was associated with poorer working memory performance after ECT but also with less subjective cognitive impairment and less depression at follow-up.⁴¹ The authors argued that the negative association between baseline S100B concentrations and working memory performance further implicates possible frontal lobe involvement in the cognitive effects of ECT. There is no alteration in S100B expression after chronic electroconvulsive shock (ECS) administration in mice.⁴⁶ Other animal studies have provided further evidence that repeated ECS for 10 consecutive days in normal rats may down-regulate the immune system

TABLE 1. Characteristics of the Clinical Studies

Reference	Study Population	ECT Procedure	Immune Measures	Measurement Time Points
Albrecht et al, ³⁴ 1985	12 MDD, 3 BD (6 treated with only ECT (unmedicated), 2 treated with only Li, 7 treated with only TCA)	Not provided	T-cell analysis in lymphocyte culture: T3, T4, T8, T11, T4/8 by cytofluorograph	At weeks 3 and 6
Kronfol et al, ³⁵ 1990	8 patients with affective disorders	Not provided	Plasma IL-6 activity	Before and 10 minutes after single session
Fischler et al, ³⁶ 1992	10 MDD (6 unmedicated, 4 medicated)	BL, 3×/week (3–16 sessions), methohexital or etomidate or propofol	PBMC analysis: CD2, CD3, CD4, CD8, CD14, CD16, CD21, CD25, CD38, CD71, HLA-DR by FACSTAR flow cytometer, NK cell activity	Before and 15 and 60 minutes after each session
Zachrisson et al, ³⁷ 2000	7 MDD, 2 BD-II (8 medicated, 1 unmedicated)	RUL, 3×/week (6 sessions), methohexital	CSF (tau, NLF, S100B) by ELISA and CSF/serum albumin ratio	Before the first session, and 1 day after the last session
Agelink et al, ³⁸ 2001	8 MDD, 6 SP (all unmedicated except 6 received occasional lorazepam)	BL, 2-day intervals (3–12 sessions), propofol	Serum NSE, S100B by RIA	Before and 6, 24, and 48 hours after the first to third session, and 24 hours after the fourth, fifth, sixth, and last session.
Kronfol et al, ³⁹ 2002	13 MDD (medication status not provided)	RUL, methohexital	NK cell activity	Before; 30, 10, and 3 min; and 3, 10, 30, and 60 minutes after each session
Hestad et al, ⁴⁰ 2003	12 MDD, 1 Dysrhythmia, 2 BD (medicated), 8 MDD (not receiving ECT), 15 healthy controls (sex and age matched)	RUL, 3×/week (4–18 sessions), sodium pentothal	Plasma TNF-α by ELISA	1 hour before and 1 hour after the first, fourth, and last session, and 24 hours and 1 week after the last session
Arts et al, ⁴¹ 2006	12 MDD or BD (medicated)	BL, 2×/week (4–8 sessions), etomidate	Serum S100B by ILMA	Before and 1 and 3 hours after each ECT session
Lehtimäki et al, ⁴² 2008	9 MDD (medicated) 8 healthy controls	BL, propofol or methohexital	Plasma IL-1β, IL-1RA, IL-6 by ELISA	Before and 1, 3, 6, and 24 hours after single session
Fluitman et al, ⁴³ 2011	12 MDD (unmedicated)	RUL (4), BL (2), RUL + BL (6), 2×/week methohexital	TNF-α, IL-6, IL-10, IFN-γ, IL-4 in stimulated whole blood cultures by ELISA, NK cell activity, plasma cortisol by HPLC, ACTH by ECLL, number of leukocytes, granulocytes, NK cells, CD3+ cells, B cells by FACS Calibur flow cytometer	Before and 5, 15, 30 minutes after the first, fifth, and 11th session

Rotter et al,⁴⁴ 2013 15 MDD (medicated) RUL, 2 × to 3 ×/week (12 sessions), etomidate or methohexital Serum NEG, Angiotensin, BDNF, BLC, BMP-4, BMP-6, CK β 8-1, CNTF, EGF, eotaxin, eotaxin-2, eotaxin-3, FGF-6, FGF-7, FGF-3 ligand, fractalkine, GCP-2, GDNF, GM-CSF, I-309, IGFBP-1, IGFBP-2, IGFBP-4, IGF-1, IL-10, IL-13, IL-15, IL-16, IL-α, IL-β, IL-1m, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, Leptin, LIGHT, MCP-1, MCP-2, MCP-3, MCP-4, M-CSF, MDC, MIG, MIP-10, MIP-3α, NAP-2, NT-3, PARC, PDGF-BB, PN-γ, RANTES, SCF, SDF-1, TA/RC, TGF-β1, TGF-β3, TNF-α, TNF-β by cytokine membrane-based antibody array; and quantitative RT-PCR

Before: 1 hour after the first, sixth, and 12th session; and 24 hours after the 12th session

ACTH indicates adrenocorticotrophic hormone; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BL, bilateral electrode placement; BLC, B lymphocyte chemoattractant; BMP, human bone morphogenetic protein; CD, cluster of differentiation; CK, chemokine; CNTF, ciliary neurotrophic factor; CSF, cerebrospinal fluid; ECLI, electrochemiluminescence immunoassay; EGF, epidermal growth factor; ELISA, enzyme-linked immunosorbent assay; FGF, fibroblast growth factor; GCP, granulocyte chemotactic peptide; GDNF, glial cell-derived neurotrophic factor; GM-CSF, granulocyte macrophage colony stimulating factor; HLA, human leukocyte antigens; HPLC, high-performance liquid chromatography; I-309, CC chemokine ligand 1; IFN, interferon; IGF, insulinlike growth factor; IGFBP, insulinlike growth factor binding protein; IL, interleukin; ILMA, immunoluminometric assay; Li, lithium; LIGHT, lymphotaxin, inducible expression, competes with HSV glycoprotein D for HVEM, a receptor expressed on T-lymphocytes; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MDC, macrophage-derived chemoattractant; MDD, major depressive disorder; MIG, monokine induced by gamma-interferon; MIP, macrophage inflammatory protein; NAP, neutrophil-activating protein-2; NFL, neurofilament; NSE, neuron-specific enolase; NT, neurotrophic factor; PARC, pulmonary and activation-regulated chemokine; PBMC, peripheral blood mononuclear cell; PDGF-BB, platelet-derived growth factor; PN, pneumocytes; RANTES, regulated upon activation normal T-cell expressed, and presumably secreted; RIA, radioimmunoassay; RT-PCR, real-time quantitative reverse transcriptase polymerase chain reaction; RUL, right unilateral electrode placement; SCF, stromal cell factor; SDF, stromal cell-derived factor; SP, schizodepressive psychosis; TA/RC, thymus and activation-regulated chemokine; TCA, tricyclic antidepressant; TGF, transforming growth factor.

with attenuation of nitric oxide synthesis by the peritoneal macrophages assessed 24 hours after the last session.^{47,48}

CONCLUSIONS AND FUTURE WORK

Taken together, only a limited number of studies have addressed functioning of the immune system in relation to ECT for depression. These studies mainly focused on peripheral markers of the immune system in humans, and their findings suggest that ECT induces a transient immune activation immediately after a single ECT session, whereas repeated ECT may down-regulate immune activation. However, it is difficult to reach firm conclusions owing to inconsistencies in the scarce data available on this topic. Moreover, the findings cannot be taken as evidence for a role of immune moderation in the mechanism of action of ECT in the treatment of depression since none of the studies provides evidence for criteria associated with causality, with the possible exception of temporal order. Additionally, several methodological issues should be considered when interpreting these findings. First, the most common limitation of these human studies is the small sample size, with risk of a type II statistical error especially when measuring multiple immune markers. Second, small sample size also limits further post hoc analyses, and, more importantly, hinders the consideration of potential confounding factors such as age, sex, concomitant medication, and body mass index, all of which may influence immune markers.⁴⁹ For example, with the exception of one study, all of the human studies consisted of patients who were on psychotropic medications. As explained before, nearly all psychotropic medications, especially antidepressants, have an effect on immune markers, and it has been argued that down-regulation of an activated immune system in depression after treatment with psychotropics may play a therapeutic role.²⁴ Therefore, distinguishing the impact of ECT from that of psychotropics on immune markers is fundamental to elucidate possible ECT-regulated immune pathways. Although it is impossible to extract the net effect of ECT from the current studies, it is reasonable to speculate that changes in immune parameters are likely due to the ECT, as most patients were on stable medication for extensive periods. In this regard, it should be noted that ECT is usually administered to patients who are refractory to antidepressants, the group of patients particularly displaying chronic inflammation.^{30,31} Additionally, differentiating the immunological changes in responders and nonresponders may also be informative. Finally, some factors inherent to the ECT procedure may also hamper a clear interpretation of the studies, that is, electrode placement, stimulus intensity and frequency, and seizure duration (which all may have different effects on the immune system), as well as the use of anesthetics, which is known to influence immune markers, although recent evidence is scarce.^{50,51}

Although some of these limitations can and should be considered in the design of future studies, such as sample size and confounding factors (age, sex, and body mass index), some of them, for example, concurrent medication use and anesthesia, are quite difficult or even impossible to eliminate. Here, animal studies investigating the effects of ECS on the immune system can be quite useful to understand the differential effects. To date, however, the effects of ECS on immune functioning have only been studied in healthy animals. Animal models of treatment-resistant depression may provide a better basis for understanding the working mechanism of ECT, especially when they also display an altered immune status.

The literature search revealed ECT-induced cognitive impairment in association with possible immunological pathways, which have not been investigated thoroughly, with the exception

of S100B. Growing evidence suggests immune-mediated pathological pathways underlie the cognitive impairment related to numerous neuropsychiatric diseases such as Alzheimer disease. Furthermore, cytokines such as IL-1 β , IL-6, and TNF- α have been associated with cognitive decline and dementia in both cross-sectional and prospective population studies.⁵² Given the transient effects of ECT on cognition, particularly memory, it would be intriguing to investigate whether ECT-induced cognitive problems are related to immune changes.⁵³

In conclusion, substantial evidence implicates a role for a disturbed immune system in depression. Whereas the current data also indicate that ECT evokes differential immune responses, inconsistencies in published studies and lack of replication prevent us from making a solid statement on the role of the immune system in the mechanism of action of ECT. To further elucidate this topic, more prospective studies investigating a broad set of immune markers in large samples achieving sufficient statistical power allowing to control for confounders and to perform post hoc analyses are required. Additionally, research should be carried out to elucidate the association between immune dysregulation and ECT-induced cognitive impairment, which may lead to a better understanding of the mechanism of action of ECT.

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