# Inflammation and Cognitive Functioning in Depressed Older Adults Treated With Electroconvulsive Therapy: A Prospective Cohort Study

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## ABSTRACT

***Objective:*** Despite the effectiveness of electroconvulsive therapy (ECT), patients and practitioners are often reluctant to start it due to the risk of transient cognitive side effects, particularly in older patients. Inflammatory processes may be associated with the occurrence of these effects. This study assessed whether inflammatory markers prior to ECT are associated with cognitive functioning in depressed patients treated with ECT.

***Methods:*** Between 2011 and 2013, 97 older patients (mean [SD] age = 73.1 [8.1] years) with severe unipolar depression (according to *DSM-IV*) referred for ECT were included. Mini-Mental State Examination (MMSE) scores were used to determine cognitive functioning prior to, weekly during, and in the first week after a course of ECT. Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) were assessed prior to ECT.

***Results:*** In fully adjusted models, there was an association between TNF-α and cognitive functioning (β = −1.05; 95% CI, −2.04 to −0.06; $f^2 = 0.06$). An association was also found between baseline levels of IL-10 and TNF-α and lower MMSE scores during ECT (IL-10: β = −2.08; 95% CI, −3.22 to −0.95; TNF-α: β = −0.65; 95% CI, −1.07 to −0.22). In addition, an association was found between baseline CRP and lower MMSE scores directly after a course of ECT (β = −0.51; 95% CI, −0.93 to −0.09; $f^2 = 0.10$). Associations with IL-6 did not reach significance.

***Conclusions:*** This study suggests that inflammatory processes are associated with lower cognitive functioning prior to ECT and predispose for further cognitive dysfunction during and after a course of ECT.

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Electroconvulsive therapy (ECT) is one of the most effective treatments for major depression, especially in older patients.[1] Despite its effectiveness, patients and practitioners are often reluctant to start ECT,[2] partly due to fear of memory impairment.[3,4] Indeed, several cognitive side effects with a range of manifestations and impact have been described, varying from postictal delirium[5,6] to retrograde amnesia.[7,8] In general, studies demonstrated that cognitive side effects are transient.[8–13] Meta-analyses described declined cognitive performance in the first 3 days after finishing a course of ECT and improved cognitive performance, back to baseline or beyond baseline levels, in the following 12 days.[8] Similarly, studies on long-term cognitive functioning, measured with a cognitive test battery 6 months after ECT, showed no decline in cognitive performance as compared to cognitive functioning prior to ECT.[14,15]

Nonetheless, transient cognitive side effects increase treatment burden by leading to worse daily functioning, higher care demands, poorer quality of life, and fear for ECT, which may result in a barrier and nonadherence to treatment.[3,4] Being able to give information on individual risk for cognitive side effects to patients and family members would help avoid premature discontinuation of ECT.[16–18] Moreover, strategies for minimizing cognitive side effects are being developed and include cognitive training[19] and administration of thyroid hormone,[20] erythropoietin,[21,22] and acetylcholinesterase inhibitors.[23,24] To further develop strategies that minimize cognitive side effects and to identify patients at risk, insight into the underlying pathophysiology of cognitive functioning during a course of ECT is needed.

Known patient characteristics associated with cognitive functioning during or directly after ECT include poor baseline cognitive functioning and smaller hippocampal volume.[9,25,26] Notably, no relation was found between age and cognitive

**Clinical Points**

- Electroconvulsive therapy (ECT) is extensively studied; however, it remains unclear how transient cognitive side effects arise during and after ECT treatment.
- Various baseline markers are associated with cognitive functioning prior to (tumor necrosis factor-α [TNF-α]), during (TNF-α and interleukin-10), and after (C-reactive protein) ECT.
- A proinflammatory profile prior to ECT is associated with cognitive dysfunction in depression.

functioning after ECT.[8,27] In addition, several factors related to ECT administration were negatively associated with cognitive functioning during ECT, including bilateral electrode placement, brief pulse width, and higher stimulus dose of ECT.[10,28–30]

The mechanisms by which change in cognitive functioning during and after a course of ECT may occur are largely unknown.[31] One hypothesis is that cognitive functioning after ECT is impacted by larger temporary ECT-induced changes in hippocampus volume.[32] Another hypothesis is that there is an analog with the pathogenesis of delirium: evidence from delirium research suggests that clinical factors such as inflammation, endocrine abnormalities, and oxidative stress can lead to transient disturbances in cognitive functioning by interacting with preexistent degenerative changes in the brain.[33,34] Studies have found a relationship between increased levels of peripheral inflammatory markers, postoperative delirium, and postoperative cognitive dysfunction.[35] We hypothesize that mechanisms comparable to those in in delirium influence cognitive functioning in depressed patients treated with ECT and that the extent of the preexistent inflammatory state of the depressed brain may further explain the variability in observed cognitive functioning prior to, during, and after ECT.

### Aims of the Study

This study aims to investigate whether an inflammatory profile relates to cognitive functioning prior to, during, and directly after a course of ECT. We hypothesize that higher levels of inflammatory markers are associated with lower cognitive functioning during and after ECT. The Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) multicenter study provides an excellent opportunity to examine the interplay between inflammatory markers and cognitive functioning in depressed persons. Previously, it was shown that low-grade inflammation has a favorable effect on treatment response, eg, moderately elevated C-reactive protein (CRP) levels were associated with increased remission rates in depressed patients treated with ECT.[36,37]

Serum levels of CRP, interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α)—biomarkers that, to our knowledge, have not yet been studied in relation to cognitive functioning during and after a course of ECT in a larger sample of older depressed patients—were chosen for further exploration.

## METHODS

### Study Sample

One hundred ten older (>55 years) patients were included in this naturalistic prospective cohort study. Patients were selected between January 2011 and December 2013 from an inpatient population, referred for ECT, from the Department of Old Age Psychiatry of GGZ inGeest, Amsterdam, the Netherlands, and University Psychiatric Center KU Leuven, Belgium.[38] Informed consent was obtained from all patients. The study protocol was approved by the ethical review boards of the Amsterdam UMC and UPC Leuven and adhered to the Declaration of Helsinki. The clinical trial was registered at www.ClinicalTrials.gov (identifier: NCT02667353). Diagnosis of severe unipolar depression according to *DSM-IV* was made by a psychiatrist and confirmed with the Mini-International Neuropsychiatric Interview (MINI).[39,40] Exclusion criteria were major neurologic illnesses, including prior diagnosis of dementia. Patients with missing serum cytokine or CRP values were excluded from analysis (n = 13). Attrition was not differential for age, sex, baseline depression severity, baseline cognitive functioning, or level of education.

### Assessments

Global cognitive functioning was screened with the Mini-Mental State Examination (MMSE; range, 0–30)[41] and was assessed prior to ECT, weekly during ECT, and 1 week after ECT. The outcome was defined as (1) the mean MMSE score 1 week prior to the course of ECT, (2) the course of weekly MMSE scores during treatment, and (3) the mean MMSE score 1 week after the course of ECT.

### Biomarkers

Selection of markers was based on their relevance in previous studies on inflammation and depression. CRP is most widely used as a clinical marker for inflammation.[42] Both IL-6 and TNF-α are widely used in psychiatric research as potential biomarkers involved in depression.[43–45] IL-10 is an anti-inflammatory cytokine[46] with strong deactivating properties of the inflammatory host response in case of excessive inflammation.[47] IL-10 is able to inhibit the production of proinflammatory cytokines such as IL-6 and TNF-α.[46] Serum samples were collected prior to ECT between 7:00 AM and 9:00 AM and were stored at −85°C until assayed. Analyses of inflammatory markers were performed as described previously.[36] In short, serum levels of CRP were determined with the High Sensitive (CRPhs) kit (Cobas CRPHA; Catalog No. 04628918 190). Serum levels of IL-6, IL-10, and TNF-α, were simultaneously determined using a 3-step multiplex digital immunoassay, the Simoa Human Cytokine 3-Plex A assay kit (Quanterix; Catalog No. 101160). Intra-assay and interassay reproducibility were 4.3% and 5.9% for IL-6, 3.9% and 5.3% for IL-10, and 4.2% and 5.3%

for TNF-α, respectively. All determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands.

### Characteristics

Depressive symptoms were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS; range, 0–60).[48] Remission was defined as a score < 10. Information on age, sex, inclusion site, the level of education in years, current smoking (yes/no), current alcohol use (yes/no), and somatic history including presence of cardiovascular diseases and the number of chronic diseases (cardiovascular disease, hypertension, chronic respiratory disease, diabetes mellitus, and arthrosis) were collected in a semistructured interview. Information on antidepressant and antipsychotic medication use during ECT and ECT characteristics including electrode placement and the total number of treatment sessions was collected during treatment.

### ECT Procedure

Brief pulse ECT was administered twice weekly using the Thymatron System IV (Somatics, LLC; maximum energy 200%, 1,008 mCoulombs) according to Dutch guidelines.[49] A titration protocol was used to determine the seizure threshold. Higher stimulus dose relative to seizure threshold is a risk factor for cognitive impairment[28]; therefore, all patients received a stimulus dose 6 times the seizure threshold for unilateral stimulation and 2.5 times the seizure threshold for bilateral stimulation. Seizure duration shorter than 20 seconds (motor activity) or 25 seconds (electroencephalographic activity) was considered inadequate, after which the dose was raised. Treatment was continued until remission was achieved or until there was no further improvement. Switch to bilateral stimulation (n = 31) was made when no clinical improvement occurred after 6 right unilateral treatments or when clinical condition worsened, ie, increased suicidality, dehydration, or an increased MADRS score. Psychotropic medications were tapered off within 2 weeks prior to ECT or were kept stable during the ECT course if necessary.

### Statistical Analysis

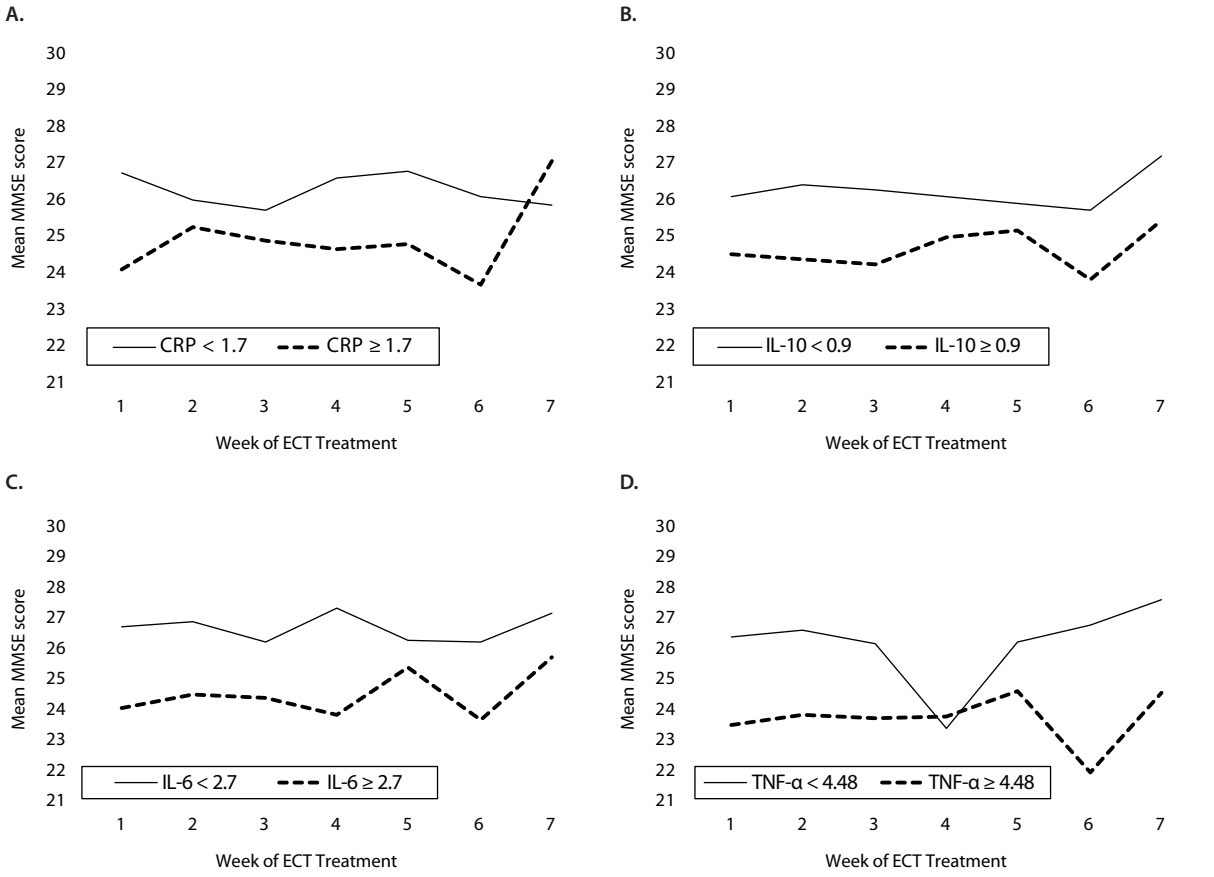
Baseline characteristics are reported as means with standard deviation (SD), median with interquartile range (IQR), and percentages. In post hoc analysis, differences between patients with low and high levels of TNF-α were tested using independent-samples *t* tests, Mann-Whitney *U* tests, and $\chi^2$ tests. Statistical significance was set at $P < .05$. Normality (of the residuals) was assessed by the visual exploration of the data. Outliers were excluded according to Q1–Q3 * IQR and Q3 + 3 * IQR to avoid bias as a result of acute infection (CRP: n = 7, IL-6: n = 6, IL-10: n = 4, TNF-α: n = 1). Dichotomized values of the biomarkers—using the median value as the cutoff—were used to draw figures and to compare MMSE values within low and high inflammation groups. The mean MMSE values prior to and directly after a course of ECT were analyzed using independent-samples *t* tests. We used a linear mixed model analysis to explore the association between biomarkers and longitudinal MMSE data (weekly scores) during treatment. The advantages of using a longitudinal mixed model instead of a linear regression analysis is that the former allows for correlation between repeated measures—that is, inclusion of weekly MMSE scores rather than a change score—and it allows for multivariate analyses. After week 7, most patients had finished ECT (84/97, 86.6%), and although mixed models are capable of processing missing values, the estimated models for week 8 and further are based on merely 13.3% of actual measures; therefore, we used solely the first 7 weeks of MMSE measures. Subsequently, linear regression analysis was used to estimate the association between CRP, IL-6, IL-10, and TNF-α with cognitive functioning prior to and directly after a course ECT. All analyses were adjusted for age, sex, baseline MADRS score, and baseline cognitive functioning. All analyses were adjusted for cardiovascular diseases, smoking, and alcohol use, as lifestyle factors can be associated with inflammation and/or cognition.[50–56] In the linear regression models, the Cohen $f^2$ was calculated from $\Delta R^2$ and was interpreted as a small ($f^2 = 0.02$), medium ($f^2 = 0.15$), or large ($f^2 = 0.30$) effect.[57] No correction for multiple testing was applied, as a clear a priori hypothesis was assessed.[58] The explained variance was estimated in multivariate analyses. Sensitivity and specificity were calculated. Switching to bilateral electrode placement can result in decreased cognitive

**Table 1. Baseline Characteristics of Older Depressed Patients Treated With ECT (n = 97)**

| Variable | Total |
|---|---|
| **Sociodemographic** | |
| Age, mean (SD), y | 73.1 (8.1) |
| Female, n (%) | 65 (67.0) |
| Level of education, median (IQR), y | 9.0 (3.0) |
| Inclusion site, Amsterdam/Leuven, n (% Amsterdam) | 54/43 (55.7) |
| MMSE baseline score, mean (SD) [n = 82] | 24.1 (5.1) |
| MMSE score after ECT, mean (SD) | 26.2 (3.8) |
| MADRS baseline score, mean (SD) | 33.8 (9.0) |
| **Somatic morbidity** | |
| Cardiovascular diseases, n (%) | 22 (22.7) |
| No. of chronic diseases, median (IQR) | 1.0 (2.0) |
| Current smoking, n (%) [total n = 82] | 21 (25.6) |
| Current alcohol use, n (%) [total n = 91] | 24 (26.4) |
| **ECT Characteristics** | |
| ECT sessions, median (IQR) | 11.0 (6.0) |
| Switch to bilateral ECT, n (%) | 29 (29.9) |
| Remission, n (%) | 64 (66.0) |
| Use of antidepressants, n (%) [total n = 82] | 15 (18.3) |
| Use of antipsychotics, n (%) [total n = 82] | 7 (8.5) |
| **Biomarkers**[a] | |
| CRP, median (IQR), mg/L [total n = 90] | 1.7 (3.9) |
| IL-6, median (IQR), pg/mL [total n = 91] | 2.7 (3.6) |
| IL-10, median (IQR), pg/mL [total n = 93] | 0.9 (0.6) |
| TNF-α, mean (SD), pg/mL [total n = 96] | 4.5 (1.7) |

[a]Serum concentrations.
Abbreviations: CRP = C-reactive protein, ECT = electroconvulsive therapy, IL-6 = interleukin-6, IL-10 = interleukin-10, IQR = interquartile range, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, TNF-α = tumor necrosis factor-α.

**Figure 1. Mean Weekly MMSE Scores During the First 7 Weeks of ECT in Depressed, Older Patients, Stratified for Low and High Levels of (A) CRP, (B) IL-10, (C) IL-6, and (D) TNF-α[a]**




[a]Serum concentration values for inflammatory markers are shown as follows: CRP: mg/L, IL-6: pg/mL, IL-10: pg/mL, TNF-α: pg/mL.
Abbreviations: CRP = C-reactive protein, ECT = electroconvulsive therapy, IL-6 = interleukin-6, IL-10 = interleukin-10, MMSE = Mini-Mental State Examination, TNF-α = tumor necrosis factor-α.

functioning during and after ECT[10]; therefore, post hoc analysis was performed excluding all patients that switched to bilateral ECT during treatment. To rule out an influence of improvement of depressive symptoms on the association between inflammatory markers and cognitive functioning, the interaction terms between inflammatory markers, remission, and change in MADRS score were examined post hoc. If interaction terms were significant ($P < .1$), analyses were repeated stratified. Multicollinearity was evaluated using Variance Inflation Factors (VIFs) in which a VIF > 2 indicates multicollinearity between covariates. Statistical analyses were performed using SPSS version 23 and STATA version 15.

## RESULTS

In total, 97 patients were included in the analysis. The mean (SD) age was 73.1 (8.1) years (Table 1). In total, 35.1% of patients (34/97) received bilateral ECT, of whom 88.2% (30/34) received it after 6 unilateral sessions. Overall, 22 patients received either antipsychotic or antidepressant medication.

**Table 2. Association Between Baseline Biological Markers and Cognitive Functioning in Linear Regression and Mixed Model Analyses in Older Depressed Patients Receiving ECT**

| Predictor Variable | Univariate β (95% CI) | *P* Value | Multivariate[a] β (95% CI) | *P* Value |
|---|---|---|---|---|
| Prior to Start of ECT | | | | |
| CRP | −0.41 (−0.79 to −0.02) | .04 | −0.30 (−0.77 to 0.16) | .2 |
| IL-6 | −0.29 (−0.59 to 0.01) | .1 | −0.18 (−0.62 to 0.26) | .4 |
| IL-10 | −1.29 (−3.51 to 0.94) | .3 | 0.08 (−2.48 to 2.62) | .9 |
| TNF-α | −1.02 (−1.78 to −0.26) | < .01 | −1.05 (−2.04 to −0.06) | .04 |
| During ECT | | | | |
| CRP | −0.33 (−0.60 to −0.06) | .02 | −0.18 (−0.42 to 0.06) | .1 |
| IL-6 | −0.22 (−0.43 to −0.00) | .05 | 0.10 (−0.06 to 0.26) | .2 |
| IL-10 | −2.85 (−4.44 to −1.26) | < .01 | −2.08 (−3.22 to −0.95) | < .01 |
| TNF-α | −0.69 (−1.13 to −0.24) | < .01 | −0.65 (−1.07 to −0.22) | < .01 |
| Directly After a Course of ECT | | | | |
| CRP | −0.30 (−0.58 to −0.02) | .04 | −0.51 (−0.93 to −0.09) | .02 |
| IL-6 | −0.15 (−0.39 to 0.08) | .2 | 0.06 (−0.30 to 0.43) | .7 |
| IL-10 | −1.98 (−3.64 to −0.33) | .02 | −1.84 (−3.82 to 0.14) | .1 |
| TNF-α | −0.44 (−0.91 to 0.04) | .1 | −0.57 (−1.40 to 0.25) | .2 |

[a]Adjusted for age, sex, depression severity at baseline, presence of cardiovascular disease, smoking, alcohol use, and MMSE score at baseline. Number of patients ranges from 58 to 94 because of missing data for some covariates.
Abbreviations: CRP = C-reactive protein, ECT = electroconvulsive therapy, IL-6 = interleukin-6, IL-10 = interleukin-10, MMSE = Mini-Mental State Examination, TNF-α = tumor necrosis factor-α.

### Cognitive Functioning Prior to a Course of ECT

The mean (SD) MMSE score at baseline was 24.1 (5.1) and was significantly lower in patients with higher levels of IL-6 ($t_{59.5} = 2.5$, $P = .02$) and TNF-α ($t_{46.2} = 3.2$, $P \leq .01$; Figure 1). In adjusted linear regression analysis, an association with a small to medium effect was found between higher levels of TNF-α at baseline and lower cognitive functioning prior to start of ECT ($f^2 = 0.06$; see Table 2). No significant association was found with CRP, IL-6, and IL-10, and effect sizes were small ($f^2 = 0.05$, 0.03, and 0.02, respectively). The fully adjusted model including TNF-α explained 14.8% of the variance of cognitive functioning prior to a course of ECT (adjusted $R^2 = 0.148$).

### Cognitive Functioning During ECT

Notably, a drop in MMSE score wass seen at week 4 of treatment only in patients with lower levels of TNF-α (Figure 1). In linear mixed model analysis including the first 7 weeks of ECT (adjusted for age, sex, depression severity, baseline MMSE scores, cardiovascular diseases, smoking, and alcohol use), higher levels of IL-10 and TNF-α were associated with lower MMSE scores (see Table 2).

### Cognitive Functioning Directly After a Course of ECT

The mean (SD) MMSE score directly after ECT was 26.2 (3.8) and was significantly lower in patients with higher levels of IL-6 ($t_{86} = 2.3$, $P = .03$). We found a significant association between higher levels of CRP at baseline and cognitive functioning directly after a course of ECT in adjusted linear regression analysis ($f^2 = 0.10$; see Table 2). The associations between the baseline cytokine levels and cognitive functioning after ECT were nonsignificant, and the sizes of the effect were small (IL-6: $f^2 < 0.01$, IL-10: $f^2 = 0.04$, TNF-α: $f^2 = 0.003$). The fully adjusted model including CRP explained 24.9% of the variance of cognitive functioning directly after a course of ECT (adjusted $R^2 = 0.249$).

In post hoc analysis, patients who switched to bilateral ECT during treatment were excluded. The results remained similar for findings during ECT. The results after ECT altered slightly; that is, in the multivariate models, the association between IL-10, TNF-α, and cognitive functioning altered to a significant association (TNF-α: $\beta = -1.18$; 95% CI, −1.48 to −0.88; $f^2 = 0.83$; IL-10: $\beta = -3.86$; 95% CI, −4.77 to −2.95; $f^2 = 0.87$). Values for sensitivity and specificity did not exceed 80% for any of the inflammatory markers. No multicollinearity was found between covariates (VIF < 2). No interaction effects were found between inflammatory markers and remission of depression or between CRP, IL-6, TNF-α, and change in MADRS score both during and after a course of ECT. The interaction effect between IL-10 and change in MADRS score was significant. However, in stratified analysis, similar results were found; that is, no significant association was found between baseline IL-10 level and cognitive functioning after a course of ECT. In post hoc analysis, similar remission rates were found between patients with low or high levels of TNF-α. Patients with higher levels of TNF-α were older and had more chronic diseases (see Supplementary Table 1.)

## DISCUSSION

In this naturalistic cohort, we investigated whether higher levels of inflammatory markers are related to cognitive functioning. We hypothesized that inflammatory markers such as CRP, IL-6, IL-10, and TNF-α would be associated with lower cognitive functioning in depressed patients treated with ECT. Previously, in this cohort it was shown that moderately elevated levels of CRP were associated with higher remission rates, whereas no association was found with IL-6, IL-10, and TNF-α levels.[36] Here, we found that (1) higher levels of TNF-α are associated with lower cognitive functioning prior to the start of ECT; (2) higher baseline levels of IL-10 and TNF-α are significantly associated with lower cognitive functioning during the first 7 weeks of ECT, even when controlling for baseline MMSE score; and (3) higher baseline levels of CRP are associated with cognitive functioning directly after a course of ECT. Patients with higher levels of CRP, IL-6, IL-10, and TNF-α only partially overlap. Our findings suggest that patients with higher levels of TNF-α in particular not only experience decreased cognitive functioning prior to the start of ECT but also are more vulnerable to lower cognitive functioning during a course of ECT.

### Cognitive Symptoms in Older Depressed Patients and Inflammation

This study is the first to examine inflammatory markers and cognition in patients treated with ECT. Our finding that patients with higher levels of TNF-α are more likely to experience lower cognitive functioning prior to ECT suggests that severe depression with inflammation is associated with cognitive symptoms. Why do inflammatory depressed patients experience lower cognitive functioning? An analogy with the pathophysiologic mechanism of delirium is proposed. Evidence from delirium research suggests that the presence of inflammation can lead to disturbances in cognitive functioning by interacting with preexistent degenerative changes in the brain and that peripheral inflammation can induce the release of inflammatory markers in the central nervous system.[33,35] In depression, the presence of low-grade peripheral inflammation in combination with degenerative changes (in older patients) or a preexistent inflammatory state of the brain may explain the variability in observed cognitive symptoms in depressed patients. Our findings are in line with those of other studies in which an association between higher levels of inflammatory markers and cognitive impairment in older, healthy or depressed subjects was found.[59–66] However, there are many conflicting reports showing a lack of association between inflammatory markers and cognitive impairment in older, healthy or depressed subjects.[67–69] An explanation for the inconsistency in these findings could be the different composition of participants under study—for example,

participants with less severe depressive symptoms—and different use of cognitive measures (global cognitive functioning scale versus specific cognitive domains). There are no comparable studies in older depressed patients treated with ECT. Our findings further strengthen the idea that cognitive functioning in older persons is influenced by an inflammatory process.

### Cognitive Side Effects of ECT and Inflammation

The mechanism by which cognitive side effects occur during and directly after a course of ECT is largely unknown. In contrast to our expectations, there was no decline in MMSE score at the group level during ECT. Our findings may suggest that depressed patients with higher levels of inflammatory markers are more vulnerable to lower cognitive functioning—although only small changes occurred—during and after a course of ECT. However, as this association was also found prior to ECT, it is difficult to arrive at any conclusions with regard to the effect of ECT on this association.

### Future Implications

Monitoring inflammatory processes to predict cognitive functioning in depressed patients prior to and after a course of ECT seems possible based on the current data. Although the sensitivity and specificity when using inflammatory markers to predict cognitive functioning were low, the percentage of variance explained by the multivariate model was 25%. Administration of anti-inflammatory medication during ECT can significantly reduce levels of TNF-α, as is shown in patients with bipolar depression.[70] If our findings are confirmed, such treatment strategies could be of additional value for improvement in cognitive functioning prior to, during, and after a course of ECT. Future investigations of the effect of anti-inflammatory treatment on cognitive functioning in depression are merited. Moreover, to further explore whether changes in inflammatory markers during ECT affect cognitive functioning during and after ECT, future studies should include longitudinal measurements of inflammatory markers. Just like in delirium research,[34] multiple pathways may be complementary in cognitive functioning in depressed patients. Therefore, a suggestion for future studies may be to combine inflammatory markers with other (imaging) biomarkers in developing a combined risk score for lower cognitive functioning during and after a course of ECT. In addition, to further explore whether changes in cognitive functioning are driven by specific cognitive domains, future studies should include more specific and sensitive neuropsychological instruments rather than solely the MMSE.

### Strengths and Limitations

Notably, the following strengths and limitations should be considered. The prospective study design allowed us to collect a substantial set of clinical data from which putative confounders were selected. We used the MMSE—widely used to measure global cognitive functioning—as a scale to measure cognitive functioning. It has shortcomings such as test-retest effects, a ceiling effect, and the lack of ability to assess specific cognitive domains, and it may lack sensitivity to detect small changes, especially in patients with vascular brain changes.[71–75] Despite the ceiling effect, we found a significant association between inflammatory markers and cognitive functioning, suggesting the effect may have been larger if we had used a more sensitive test. Moreover, one of the difficulties in investigating cognitive functioning during ECT is the influence of depression itself on cognitive performance. In this study, the influence of ECT on cognitive functioning may be underreported because of the synchronous improvement in depressive symptoms and cognition.[76] This study used pre-ECT inflammatory markers to investigate the association with cognitive functioning before, during, and after ECT. Including longitudinal inflammatory biomarkers would have allowed us to control for depression-related changes in inflammation. Also, it is to be determined whether the differences in weekly MMSE scores between patients with lower and higher levels of inflammatory markers (ranging from 0.5 to 2.5 points) are of clinical relevance to patients. No corrections for multiple testing were performed, which, although the analysis was all hypothesis driven, still may have affected the type I error of this study. Finally, other factors may have an impact on cognition such as anesthesia itself,[9] pulse width,[77] and stimulus dose of ECT.[28] To minimize the influence of these factors on our findings, all patients received equal ratios of stimulus dose relative to seizure threshold and all received brief pulse ECT.

### Conclusion

Previously low-grade inflammation was found to be associated with increased remission rates in our sample of 97 depressed older patients treated with ECT. This current study suggests that baseline inflammatory processes are associated with lower cognitive functioning prior to ECT (TNF-α) and predispose for (further) cognitive dysfunction during (TNF-α and IL-10) and after (CRP) a course of ECT. Future studies could provide more in-depth information on the role of inflammation on the cognitive symptoms of depression and the effectiveness of add-on anti-inflammatory treatment to improve these symptoms during an ECT course.

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# Supplementary Material

**Article Title:** Inflammation and Cognitive Functioning in Depressed Older Adults Treated With Electroconvulsive Therapy: A Prospective Cohort Study

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## List of Supplementary Material for the article

1. Table 1 — Group characteristics of older depressed patients with low (< 4.48 pg/ml) or high levels of TNF-α treated with ECT (*n* = 96).

## Disclaimer

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**Supplementary Table 1.** Group characteristics of older depressed patients with low (< 4.48 pg/ml) or high levels of TNF-α treated with ECT (*n* = 96).

| | Low TNF-α n = 56 | High TNF-α n = 40 | p-value |
|---|---|---|---|
| **Socio-demographics** | | | |
| Age, years, mean (SD) | 70.8 (7.7) | 76.4 (7.7) | <0.01 |
| Female, No. (%) | 36 (64.3) | 29 (72.5) | 0.4 |
| MMSE baseline, mean (SD), *n* = 81 | 25.5 (3.9) | 21.7 (5.9) | <0.01 |
| MMSE after ECT, mean (SD) | 26.8 (3.6) | 25.4 (4.0) | 0.1 |
| MADRS baseline, mean (SD) | 33.9 (8.1) | 33.7 (10.3) | 0.9 |
| Remission, No. (%) | 39 (69.6) | 25 (64.1) | 0.6 |
| **Somatic morbidity** | | | |
| Cardiovascular diseases, No (%) | 9 (16.4) | 13 (33.3) | 0.1 |
| No. of chronic diseases, median (IQR) | 1.0 (1.0) | 1.0 (1.0) | 0.02 |
| Current smoking, No. (%), *n* = 82 | 13 (30.2) | 8 (21.6) | 0.4 |
| Current alcohol use, No. (%), *n* = 91 | 15 (27.3) | 9 (25.7) | 0.9 |
| **ECT characteristics** | | | |
| ECT sessions, median (IQR) | 10.5 (6.0) | 11.5 (7.0) | 0.8 |
| Switch to bilateral ECT, No. (%) | 15 (26.8) | 14 (35.0) | 0.6 |
| Use of antidepressants, No. (%), *n* = 82 | 7 (16.3) | 8 (21.1) | 0.6 |
| Use of antipsychotics, No. (%), *n* = 82 | 3 (7.0 | 4 (10.5) | 0.6 |

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg depression rating scale, TNF-α = tumour necrosis factor- α