Brief Report

Impact of Inflammation on Cognitive Functioning After Electroconvulsive Therapy in Older Patients with Depression with and Without White Matter Hyperintensities

Angela Carlier, M.D., Annemiek Dols, M.D., Ph.D., Mardien Oudega, M.D., Ph.D., Pascal Sienaert, M.D., Ph.D., Filip Bouckaert, M.D., Ph.D., Max L. Stek, M.D., Ph.D., Piet Eikelenboom, M.D., Ph.D., Eric van Exel, M.D., Ph.D.,1 Didi Rhebergen, M.D., Ph.D.1

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ABSTRACT

Objective: Should we treat older patients with depression with white matter hyperintensities (WMH) with electroconvulsive therapy (ECT)? WMH, inflammation, depression and cognitive functioning are suggested to be intertwined. Hence, this study investigates whether the association between inflammation and cognition is different in patients with depression with or without WMH.

Methods: Cognitive functioning was assessed using the Mini–Mental State Examination and after a course of ECT in 77 older patients with depression. Serum samples (C-reactive protein [CRP], interleukin-6 [IL-6], interleukin-10 [IL-10] and tumour necrosis factor–alpha [TNF-α]) and 3T magnetic resonance imaging were obtained prior to ECT. Results: An interaction effect was found for IL-10, but not for CRP, IL-6 or TNF-α. Conclusion: In general, the association between inflammatory markers and cognition in patients with...
depression treated with ECT is not different in patients with WMH compared to patients without WMH. (Am J Geriatr Psychiatry 2021; ■■:■■−■■)

Highlights

- What is the primary question addressed by this study?
- Do white matter hyperintensities alter the association between inflammatory markers and cognitive functioning in depressed patients treated with Electroconvulsive Therapy?
- What is the main finding of this study?
- In general, white matter hyperintensities do not alter the association between inflammatory markers and cognition in patients with depression treated with Electroconvulsive Therapy.
- What is the meaning of the finding?
- Older patients with white matter hyperintensities and inflammation are not more vulnerable to experiencing cognitive side effects after Electroconvulsive Therapy.

OBJECTIVES

Should we treat older patients with depression with white matter hyperintensities (WMH) with electroconvulsive therapy (ECT)? ECT is the most effective treatment for depression. However, practitioners are often reluctant to start ECT because of the risk of transient cognitive side effects after a course of ECT. Known factors associated with transient cognitive side effects include poor baseline cognitive functioning, smaller hippocampal volume, bilateral electrode placement and higher stimulus dose. Previously in this cohort with older patients with depression, more pronounced cognitive impairments were found in patients with severe WMH, and, a relationship was found between higher baseline levels of inflammatory markers and lower cognitive functioning before, during and after electroconvulsive therapy (ECT). In line with these findings, although still inconclusive, studies suggest an association between cognitive functioning and inflammation in both patients with depression and healthy controls. A potential underlying factor linking inflammation with cognition might be WMH as studies have found associations between WMH, cognitive functioning and depression, as well as between WMH and inflammation. For example, in post–operative delirium research, it was found that patients with pre-operative WMH had an increased risk of developing delirium, which is a disorder characterized by temporary profound changes in cognitive functioning, suggesting that a brain with WMH is more vulnerable to inflammation.

Here, we expand on our earlier findings and investigate whether, in older patients with depression, the association between inflammatory markers and cognitive functioning is different in patients with moderate to severe WMH compared to patients without WMH. For many practitioners, the cognitive side effects of ECT remain a concern. Hence, it is particularly interesting to explore the association between inflammatory markers and cognitive functioning during and directly after a course of ECT in older patients with depression. A better understanding of the underlying factors contributing to lower cognitive functioning may lead to potential targets for prevention.

METHODS

Study overview. Data were collected from 2 psychiatric hospitals, GGZ inGeest in the Netherlands, and the University Psychiatric Center KU Leuven in Belgium. All included patients were diagnosed with unipolar major depression, aged 55 years and older and referred for ECT. Excluded were patients with a history of major neurological illness including stroke...
and dementia. The study was approved by the Ethical Review Board of the Amsterdam University Medical Centre and subsequently by the ethical review board of the Leuven University Hospitals. Written consent was obtained from all participants. Here we present data from a subgroup (N = 77) from a previously described cohort study (N = 110).\textsuperscript{6} Attrition was not differential for age, sex, baseline depression severity, and baseline cognitive functioning. Patients received brief pulse ECT twice weekly according to Dutch guidelines. The median number of ECT administrations was 11.0 (interquartile range = 6.0). ECT was continued until a Montgomery Asberg Depression Rating Scale (MADRS) score of less than 10 was reached at 2 consecutive ratings or until no further improvement in clinical condition was seen after at least 6 unilateral and 6 firstly bilateral ECT sessions. Remission of depression and response to treatment were defined as a MADRS score of less than 10 and a decrease in MADRS score of at least 50%, respectively.

**Inflammatory Markers**

The selection of inflammatory markers is based on availability and findings on the relevance of these markers in studies to date. Serum cytokine and C-reactive protein (CRP) levels were measured prior to ECT. Interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor-alpha (TNF-\(\alpha\)) were determined using the Simoa Human Cytokine 3-Plex immunoassay. CRP was determined using the Cobas CRPHA kit. All determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit, and Amsterdam.

**Cognitive Functioning**

Cognitive functioning was screened using the Mini–Mental State Examination (MMSE, score range 0-30) during and directly after a course of ECT. In line with previous papers on this subject,\textsuperscript{2,7} during ECT was measured 3 weeks after start of treatment and after ECT was measured 1 week after the last ECT session.

**White Matter Hyperintensities**

Magnetic Resonance Imaging (MRI) was performed prior to ECT. Structural WMH were rated using the Age-Related White Matter Changes (ARWMC) scale as the sum score of 10 brain regions, subsequently ranked in 2 groups: 1) no or few structural white matter hyperintensities (WMH; score 0-9) and 2) moderate to severe WMH (score 10-30). All MRI images were rated by an independent neuroradiologist.

**Statistical analyses.** The distribution of characteristics across patients without structural WMH and patients with moderate to severe WMH were compared using the 2−tailed chi−square test for dichotomous variables and the Student t−test for continuous variables. The association between inflammatory markers and MMSE score was investigated using linear regression analyses. Interaction terms between whiter matter hyperintensities and inflammatory markers were examined. To provide the most complete extension of previous results, all analyses were repeated stratified even when interaction terms were non−significant (p < 0.05). Analyses were stratified for the presence of WMH (‘no structural WMH’ and ‘moderate to severe WMH’). Effect sizes (Cohen’s \(f^2\)) were calculated using delta \(R^2\). The \(R^2\) calculated in the fully adjusted model with predictor variable was subtracted from the \(R^2\) in the fully adjusted model without predictor variable to calculate delta \(R^2\). Effect sizes were interpreted as a small: \(f^2 = 0.02\), medium \(f^2 = 0.15\) or large \(f^2 = 0.30\) effects. All analyses were adjusted for age, sex, baseline depression severity, baseline cognitive functioning, and years of education, smoking, alcohol use and presence of cardiovascular diseases. Post hoc analysis excluding all patients that received bilateral ECT was performed as switching to bilateral electrode placement can result in decreased cognitive functioning after ECT. Results are reported as unstandardized \(B−\)coefficients with a 95% confidence interval (CI). A Bonferroni correction for multiple comparisons was used setting the statistical significance level at alpha=0.0125. Statistical analyses were performed using SPSS version 23.

**RESULTS**

The mean age of the sample was 72.9 years (SD = 8.4). Patients without structural WMH (N = 50) had a mean MMSE score of 24.2 (SD = 5.2) prior to ECT, 25.6 (SD = 4.6) during ECT and 26.8 (SD = 3.5) directly after a course of ECT. Patients with structural
WMH (N = 27) had mean MMSE score of 23.5 (SD = 5.1) prior to ECT, 24.1 (SD = 4.6) during ECT, and 25.0 (SD = 4.6) directly after a course of ECT. In total, 67.5% (52/77) of patients reached remission of depression and 79.2% (61/77) responded to ECT. Both remission and response rates did not differ between groups: Remission: X² (1) = 0.01, p = 0.9, Response: X² (1) = 0.13, p = 0.7.

The interaction effect between IL-10 and WMH was statistically significant, (IL-10: unstandardized B = -0.35; 95%CI=(-0.65 to -0.04). No interaction effects were found between CRP, IL-6, TNF-α and WMH. In fully adjusted linear regression analyses, stratified for presence of structural WMH, both IL-10 and TNF-α were significantly associated with lower cognitive functioning directly after a course of ECT in patients with WMH: IL-10: f² = 0.27, TNF-α: f² = 0.26, but not with cognitive functioning during ECT, IL-10: f² = 0.03, TNF-α: f² = 0.08, see Table 1. The association was not found for any of the inflammatory markers and cognitive functioning in patients without WMH and effect sizes were low (MMSE during ECT: CRP: f² = 0.01, IL-6: f² = 0.04, IL-10: f² = 0.15, TNF-α: f² = 0.02, MMSE directly after a course of ECT: CRP: f² = 0.04, IL-6: f² = 0.03, IL-10: f² = 0.11, TNF-α: f² = 0.01).

In post hoc analysis, patients that switched to bilateral ECT during treatment were excluded (N = 34). Results remained similar, although as a result of low numbers of patients, in patients with moderate to severe WMH (N = 19), the association between IL-10, TNF-α and cognitive functioning after ECT altered to a non-significant association, IL-10: unstandardized B = -4.11; 95%CI=(-8.37 – 0.16), TNF-α: unstandardized B= 3.45; 95%CI=(-7.32 – 0.42).

### Table 1. Linear Regression Analyses. Association Between Inflammatory Markers and Cognitive Functioning During (3 Weeks After the Start of ECT) and Directly After a Course of ECT Divided in Patients With No or Few Structural White Matter Hyperintensities (WMH) (N = 50) and Patients With Moderate to Severe WMH (N = 27), in Older Depressed Patients

<table>
<thead>
<tr>
<th></th>
<th>During ECTB (95% CI)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>After a course of ECTB (95% CI)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No structural WMH</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.06 (-0.67 – 0.80)</td>
<td>0.9</td>
<td>-0.18 (-0.75 – 0.39)</td>
<td>0.5</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.30 (-0.32 – 0.95)</td>
<td>0.3</td>
<td>-0.05 (-0.46 – 0.56)</td>
<td>0.8</td>
</tr>
<tr>
<td>IL-10</td>
<td>-2.95 (-5.71 to -0.19)</td>
<td>0.04</td>
<td>-1.17 (-3.37 – 1.02)</td>
<td>0.3</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.63 (0.85 – 2.11)</td>
<td>0.4</td>
<td>0.36 (-0.73 – 1.46)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Moderate to severe WMH</strong></td>
<td></td>
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</tr>
<tr>
<td>CRP</td>
<td>-0.38 (-1.05 – 0.28)</td>
<td>0.2</td>
<td>-0.60 (-1.34 – 0.15)</td>
<td>0.1</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.14 (-0.83 – 0.55)</td>
<td>0.7</td>
<td>-0.61 (-1.35 – 0.14)</td>
<td>0.1</td>
</tr>
<tr>
<td>IL-10</td>
<td>-3.19 (-8.43 – 2.05)</td>
<td>0.04</td>
<td>-2.11 (-6.43 – -1.79)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-1.74 (-3.39 to -0.08)</td>
<td>0.04</td>
<td>-2.57 (-4.05 – -1.08)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note. B is an unstandardized regression coefficient. The multivariate model is adjusted for age, sex, years of education, MMSE at baseline, depression severity at baseline, presence of cardiovascular disease, smoking and alcohol use.

<sup>a</sup>p-values for B-coefficients were derived using 2-tailed t-tests with df’s ranging from 8 to 20.

<sup>b</sup>statistical significance level at alpha = 0.0125 CI: Confidence Interval; CRP: C-reactive Protein; IL-6: Interleukin-6; IL-10: Interleukin-10; TNF-α: Tumour Necrosis Factor-alpha

### CONCLUSIONS

Previously, we suggested that ECT is more effective in patients with signs of inflammation (CRP levels 3 – 10 mg/L).<sup>8</sup> In addition, in the same cohort, we found that patients with higher levels of TNF-α, IL-10, and CRP prior to ECT showed lower cognitive functioning prior to, during and after a course of ECT in depressed older patients.<sup>2</sup> The aim of the present study was to investigate whether the association between cognitive functioning and inflammation is different for patients with or without WMH.

An interaction effect was found between WMH, the level of IL-10 prior to ECT and cognitive functioning after a course of ECT. No interaction effect was found for the other inflammatory markers. These findings suggest that, generally, WMH does not alter the association between inflammatory markers and cognitive functioning in patients with depression treated with ECT. In conclusion, our hypothesis that the association between cognitive functioning and inflammation is different in patients with WMH compared to patients without WMH could not be confirmed. Previous studies have found that patients with WMH experience lower cognitive functioning during ECT compared to patients without WMH,<sup>1,7,9</sup> however, in all patients cognitive functioning recovers towards baseline levels after ECT.<sup>1,7</sup> Moreover, patients with WMH have similar response and remission rates as patients without WMH,<sup>10</sup> therefore the presence of WMH does not oppose ECT. Limitations of this study are the use of the MMSE to measure cognitive functioning as it has a known ceiling effect, test – retest effects and it does not permit assessment of different cognitive domains. In addition, adjustment for cardiovascular diseases and smoking may have
caused an underestimation of the association between inflammation and cognitive functioning. Strengths of this study are the relatively large sample size and the statistical approach, that is, the use of linear regression analysis and effect sizes.

**DATA STATEMENT**

The data has not been previously presented orally or by poster at scientific meetings.

**AUTHOR CONTRIBUTIONS**


**CONFLICTS OF INTEREST/GRANT SUPPORT**

The authors report no conflicts with any concept discussed in this article. DR has received funding from ZonMW Programme 'Rational Pharmacotherapy' under grant agreement n°2016/15385/ZONMW. No conflicts of interest.

**References**