Clinical Relevance of Brain Changes After Electroconvulsive Therapy

Nuninga, Jasper O.; Mandl, Rene C. W.; Sommer, Iris E. C.

Published in:
Biological Psychiatry

DOI:
10.1016/j.biopsych.2020.04.030

Publication date:
2021

Biological Psychiatry

Clinical Relevance of Brain Changes After Electroconvulsive Therapy: Is There Really No Link at All?

To the Editor:

Recently, Ousdal *et al.* (1) reported widespread changes in cortical and subcortical volumes after electroconvulsive therapy (ECT). They reported that although the number of ECT sessions is associated with changes in multiple volumes in the brain, clinical response is not. While their analyses are sound and open up new research avenues, and their dataset is adequately powered, an important question remains.

Ousdal *et al.* (1) found that subcortical gray matter, cortical gray matter, and ventricle volume changed significantly compared with control subjects after ECT. Specifically, they showed that ECT induced significant volumetric increases in nearly all gray matter regions of interest (ROIs) (33 cortical [left and right] and 8 subcortical ROIs) except for the left and right cerebellar cortex (false discovery rate corrected). Furthermore, ventricle volume decreased significantly, while total white matter volume remained the same. The results of Ousdal *et al.* are an important milestone in showing that ECT is not related to harmful processes such as atrophy and cell necrosis, which would result in volume decreases.

However, an important question concerning the association between volumetric changes of the subcortical, cortical, and ventricle volumes and the clinical response (i.e., remission of depression) remains unanswered. Are these broadly distributed changes just an epiphenomenon of ECT, or are certain changes in specific ROIs related to the antidepressant effects of ECT? To this end, Ousdal *et al.* (1) analyzed the change in Montgomery–Åsberg Depression Rating Scale score (pre- and post-ECT) and volumetric change, while controlling for age, sex, site, baseline depression score, number of ECTs, number of ECTs squared, and the respective baseline volumes in a simple linear model. No significant associations between any of the 84 gray matter ROIs and change in Montgomery–Åsberg Depression Rating Scale score were found. In contrast, using ultra-high-field 7T magnetic resonance imaging, our group showed that the dentate gyrus (DG) of the hippocampus significantly increased in volume after 10 ECT sessions (2). Importantly, the increase in DG volume was related to the decrease in Hamilton Depression Rating Scale score, and baseline DG volume could predict clinical effect. Aside from the fact that we used ultra-high-field magnetic resonance imaging and subfield analysis, we also employed linear mixed modeling and repeated-measures correlation to investigate the effects of ECT. Repeated-measures correlation may be more sensitive in detecting a relationship between two variables in a repeated-measures design than the analysis of difference scores alone (3). Together with Takamiya *et al.* (4), we illustrated this point in a reanalysis of their data acquired with conventional 3T magnetic resonance imaging. In their original study, Takamiya *et al.* (5) showed that ECT significantly increased the volume of the DG, yet no associations were found to the antidepressant effect of ECT. However, when reanalyzing their results using a repeated-measures correlation, a significant association was found for the right DG with 3T data as well (4), thus replicating our 7T findings.

The results from the study of Takamiya *et al.* (4), mentioned above, raise the question of whether the data collected by Ousdal *et al.* (1) might also show significant associations between different ROIs and Montgomery–Åsberg Depression Rating Scale scores when analyzed the same way. Establishing a connection between specific changes in the brain, presumably the DG, and the antidepressant response of ECT is crucial for a better understanding of ECT as a treatment for severe depression. As cognitive side effects of ECT [albeit temporary (6)] remain a drawback for many patients, it is important to understand the exact mechanism of ECT in order to design new treatments with the same efficacy as ECT but without the associated side effects (7). Therefore, an important research avenue is to investigate whether the volumetric changes reported in the current study are associated with the cognitive side effects of ECT, and if these changes can be disentangled from the effects that add to the antidepressant properties of ECT.

Jasper O. Nuninga
René C.W. Mandl
Iris E.C. Sommer

Acknowledgments and Disclosures

This work was supported by an Apasia Grant from the Netherlands Organization for Scientific Research (to IECS).

We thank the Netherlands Organization for Scientific Research for the Aspasia Grant, allowing us to conduct the research mentioned in this paper.

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Biomedical Sciences of Cells and Systems (JON, IECS), University Medical Center Groningen, University of Groningen, Groningen; and Department of Psychiatry (JON, RCWM), University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, the Netherlands.

Address correspondence to Jasper O. Nuninga, M.Sc., at j.o.nuninga@umcutrecht.nl.

See also associated correspondence: https://doi.org/10.1016/j.biopsych.2020.05.031.

Received Mar 23, 2020; accepted May 27, 2020.

References

1. Ousdal OT, Argyelan M, Narr KL, Abbott C, Wade B, Vandenbulcke M, *et al.* (2020): Brain changes induced by electroconvulsive therapy are broadly distributed. Biol Psychiatry 87:451–461.
2. Nuninga JO, Mandl RCW, Boks MP, Bakker S, Somers M, Heringa SM, *et al.* (2020): Volume increase in the dentate gyrus after electroconvulsive therapy in depressed patients as measured with 7T. Mol Psychiatry 25:1559–1568.
3. Bakdash JZ, Marusich LR (2017): Repeated measures correlation. Front Psychol 8:456.

4. Takamiya A, Nuninga JO, Mandl RCW, Sommer IEC, Mimura M, Kishimoto T (2019): Volume increase of the dentate gyrus induced by electroconvulsive therapy. J ECT 35:e57–e58.
5. Takamiya A, Plitman E, Chung JK, Chakravarty M, Graff-Guerrero A, Mimura M, Kishimoto T (2019): Acute and long-term effects of electroconvulsive therapy on human dentate gyrus. Neuropsychopharmacology 44:1805–1811.
6. Nuninga JO, Claessens TFI, Somers M, Mandl R, Nieuwdorp W, Boks MP, *et al.* (2018): Immediate and long-term effects of bilateral electroconvulsive therapy on cognitive functioning in patients with a depressive disorder. J Affect Disord 238:659–665.
7. Nuninga JO, Mandl RCW, Sommer IEC (2020): The dentate gyrus in depression: Directions for future research [published online ahead of print Feb 17; correction published Apr 22]. Mol Psychiatry.