Volume Increase of the Dentate Gyrus Induced by Electroconvulsive Therapy Shedding Light on the Clinical Relevance of Plasticity in the Hippocampus

Takamiya, Akihiro; Nuninga, Jasper O.; Mandl, Rene C. W.; Sommer, Iris E. C.; Mimura, Masaru; Kishimoto, Taishiro

Published in:
Journal of ect

DOI:
10.1097/YCT.0000000000000630

A Role for Ketamine in Electroconvulsive Therapy

To the Editor:

Although electroconvulsive therapy (ECT) is more effective than other treatments used for severe major depression, it is associated with a high relapse rate in patients who do not receive continuation or maintenance pharmacotherapy or ECT. In addition, a subset of patients including those with longer duration of depressive episode, nonresponse to adequate medication trials, and comorbid borderline personality disorder may require an increased number of treatments during their index episode to obtain response. In addition, although ECT is safe and efficacious for geriatric depression, older age is associated with increased seizure threshold. Irrespective of when it is used in the treatment cycle, the generation of a generalized tonic-clonic seizure of sufficient duration is necessary for effective treatment. Previous research has demonstrated that up to 5% of patients have a short seizure or no seizure during their index course of ECT despite maximum stimulus intensity.[1] Strategies to augment or maintain seizure duration are thus of ongoing importance.[2]

Ketamine has been used as an alternate anesthetic agent for ECT. It has been shown to prolong seizure duration and induce a more intense seizure. Ketamine does not appear to enhance ECT response, and concerns surrounding more extended posttreatment disorientation, restlessness, blood pressure elevations, and recovery times have precluded its widespread adoption.[3,4]

Sheppard Pratt Hospital, Towson, a 259-bed not-for-profit hospital is the flagship inpatient facility of Sheppard Pratt Health System. They have been a high-volume provider of inpatient and outpatient ECT services averaging 3517 treatments annually over the past 5 years. During this time, we have had 9 patients receive ketamine anesthesia after being unable to generate an adequate or even any seizure with the use of other agents. The patients had an average age of 56.1 years (37–78 years), 6 were male and 3 female. Four carried diagnosis of major depression recurrent, 4 had bipolar 1 or 2 diagnoses, and 1 had schizoaffective disorder. All patients received treatment on a Thymatron System IV, pulse width of 1.0 milliseconds with titration to maximum stimulus charge of 504 mC. All patients received initial treatment with 1 mg/kg of methohexital with subsequent switch to etomidate for seizure duration of less than 25 seconds. Intravenous caffeine benzoate was added in all patients with doses ranging from 250 mg to 625 mg. Four patients had subsequent treatments with less than 25-second seizure duration, whereas in 5 patients no seizure was able to be generated. All patients were switched to ketamine anesthesia dosed at .8 to 1.0 mg/kg. Three patients were switched from right unilateral to bilateral electrode placement for clinical reasons prior to the initiation of ketamine. The pulse width was not altered in any patient in response to reduced seizure duration. In 5 of the patients, caffeine was continued although at a reduced dose. All patients were able to continue to receive effective ECT for an average of 44 additional treatments (range, 3–117). No patient required the addition of blood pressure medications, there were no complications requiring emergency room transfer, and anecdotally, there was no significant increase in recovery room time.

Our experience reinforces previous recommendations that a switch to ketamine anesthesia even with the concurrent use of intravenous caffeine benzoate to elicit a seizure of adequate duration is a safe and viable option for patients at any time during their ECT treatment course.[5]

Marc Zisselman, MD
Sheppard Pratt Health System
m.zisselman@comcast.net

William Zitzmann, MD
American Anethesiology

The authors have no conflicts of interest or financial disclosures to report.

REFERENCES

1. Krystal AD, Dean MD, Weiner RD, et al. ECT stimulus intensity: are present ECT devices too limited? *Am J Psychiatry.* 2000;157:963–967.
2. Datto C, Rai AK, Ilivicky HJ, et al. Augmentation of seizure induction in electroconvulsive therapy: a clinical reappraisal. *J ECT.* 2002;18:118–125.
3. Rasmussen KG, Ritter MJ. Some considerations of the tolerability of ketamine for ECT anesthesia. A case series and review of the literature. *J ECT.* 2014;30:283–286.
4. Rasmussen KG, Kung S, Lapid MI, et al. A randomized comparison of ketamine versus methohexital anesthesia in electroconvulsive therapy. *Psychiatry Res.* 2014;215:362–365.
5. Krystal AD, Weiner RD, Dean MD, et al. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. *J Neuropsychiatry Clin Neurosci.* 2003;15:27–34.

Volume Increase of the Dentate Gyrus Induced by Electroconvulsive Therapy
Shedding Light on the Clinical Relevance of Plasticity in the Hippocampus

Dear Editor:

While the underlying mechanisms of electroconvulsive therapy (ECT) remain unknown, volume increase in the hippocampus has been consistently reported[1–4] since the first study by Nordanskog et al[5] in the *Journal of ECT*. To date, the role of this volume increase, as well as whether it contributes to or is responsible for the effectiveness of ECT, is unclear. In this letter, we reanalyzed the data from a previous study,[3] replicating a recent finding,[4] showing that an increase in volume of the dentate gyrus (DG) is related to improvement in depressive symptoms. This replication sheds light on the relationship between volume increase and the clinical effect of ECT. Furthermore, we briefly discuss the importance of using sensitive statistical techniques to investigate the effectiveness of ECT.

The finding of ECT-induced hippocampal volume increase is consistent with multiple lines of evidence from animal studies, which have shown that electroconvulsive stimulation induced neuroplasticity in the hippocampus, including neurogenesis, synaptogenesis, gliogenesis, and angiogenesis, of which neurogenesis is the most robust finding.[6] Surprisingly, previous studies found no significant correlation between hippocampal volume change and clinical improvement,[1,2] yet the number of ECTs, electrode placement,[2] or even cognitive changes resulting from ECT[6] have been put forward as possible explanations of ECT-related hippocampal volume change. However, the hippocampus is a multilayer structure with each substructure comprising different functions. Therefore, analyzing the whole hippocampus might not

be accurate to detect a relationship between volume change and clinical improvement. Recent technological advances in neuroimage (post)processing enabled us to calculate volumes of each hippocampal subfield. Given the strong and robust finding of neurogenesis in the DG (possibly the only neurogenic region of adult human brain) after electroconvulsive stimulation in preclinical studies, several authors suggested that the volume increase of the hippocampus will selectively pertain to the DG.[3,4]

In our original study,[3] we reported that hippocampal volume increase induced by bilateral ECT was mostly driven from volume increase in the DG and that remitters showed larger volume increase in the right DG than nonremitters. However, we did not find a linear correlation between volume change in the right DG and change in Hamilton Depression Rating Scale (HAM-D) scores. Nuninga et al,[4] however, showed that the effect of ECT was specific to the DG by using a 7-T magnetic resonance imaging (MRI) and that volume changes in the DG were significantly correlated with change in HAM-D scores. One major difference between these 2 studies is the field strength (ie, 3 T vs 7 T) of MRI (increasing the accuracy of subfield delineation). In addition, Nuninga et al,[4] investigated the relationship between volume change of the DG and clinical effect with a repeated measures correlation (rmcorr),[7] whereas we used a simple linear correlation. Rmcorr accounts for nonindependence among observation and adjust for interindividual variability. Moreover, it evaluates intraindividual association between 2 measures, and parallel lines are fit to the data from each participant. The benefits of rmcorr include higher statistical power than simple correlation. Because of these advantages, rmcorr seems more suitable than simple linear correlation for data from a pre-ECT/post-ECT design. Therefore, we reanalyzed our data in collaboration with Nuninga et al[4] using the statistical package R (version 3.4.3) and rmcorr.

As a result, we now found a statistically significant negative correlation between HAM-D score and the right DG volume ($r = -0.46$; $P = 0.018$; 95% confidence interval, −0.72 to −0.07), but no significant result in the left DG ($r = -0.35$; $P = 0.076$; 95% confidence interval, −0.66 to 0.06). The negative correlation indicates that an increase in the DG volume is associated with a decrease in HAM-D score. We did not find any correlations between HAM-D score and the other subfields. Even though our data were from 3 T MRI scanner, our reanalyzed results are consistent with the previous study[4] and also support the hypothesis that neuroplasticity underlies the efficacy of ECT.[6]

Akihiro Takamiya, MD
Department of Neuropsychiatry
School of Medicine
Keio University
Tokyo, Japan
Center for Psychiatry and Behavioral Science
Tokyo, Japan

Jasper O. Nuninga, MSc
Department of Biomedical Sciences
of Cells and Systems
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands
Department of Psychiatry
UMC Utrecht Brain Center
University Medical Center Utrecht
Utrecht, The Netherlands

René C. W. Mandl, PhD
Department of Psychiatry
UMC Utrecht Brain Center
University Medical Center Utrecht
Utrecht, The Netherlands

Iris E. C. Sommer, MD, PhD
Department of Biomedical Sciences
of Cells and Systems
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Masaru Mimura, MD, PhD
Taishiro Kishimoto, MD, PhD
Department of Neuropsychiatry
School of Medicine
Keio University
Tokyo, Japan
tkishimoto@keio.jp

The authors have no conflicts of interest or financial disclosures to report.

REFERENCES

1. Takamiya A, Chung JK, Liang KC, et al. Effect of electroconvulsive therapy on hippocampal and amygdala volumes: systematic review and meta-analysis. *Br J Psychiatry.* 2018; 212:19–26.
2. Oltedal L, Narr KL, Abbott C, et al. Volume of the human hippocampus and clinical response following electroconvulsive therapy. *Biol Psychiatry.* 2018;84:574–581.
3. Takamiya A, Plitman E, Chung JK, et al. Acute and long-term effects of electroconvulsive therapy on human dentate gyrus. *Neuropsychopharmacology.* 2019;44: 1805–1811.
4. Nuninga JO, Mandl RCW, Boks MP, et al. Volume increase in the dentate gyrus after electroconvulsive therapy in depressed patients as measured with 7T. *Mol Psychiatry.* 2019. doi: 10.1038/s41380-019-0392-6.
5. Nordanskog P, Dahlstrand U, Larsson MR, et al. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J ECT.* 2010; 26:62–67.
6. Bouckaert F, Sienaert P, Obbels J, et al. ECT: its brain enabling effects: a review of electroconvulsive therapy-induced structural brain plasticity. *J ECT.* 2014;30:143–151.
7. Bakdash JZ, Marusich LR. Repeated measures correlation. *Front Psychol.* 2017;8. https://doi.org/10.3389/fpsyg.2017.00456.

Electroconvulsive Therapy With Chiari Malformation

To the Editor:

Chiari malformation, type I, defined as an elongation of the cerebellar tonsils and medulla oblongata through the foramen magnum, may be accompanied by syringomyelia or hydrocephalus.[1] Such conditions are thought to pose a risk during electroconvulsive therapy (ECT), as it induces increased intracranial pressure with the potential to cause herniation of the brain.[2] Actually, ECT can be safely and successfully administered to patients with Chiari malformation, type I.

CASE

A 35-year-old woman with recurrent major depressive disorder was admitted to an inpatient psychiatric unit because of suicidal ideation. She experienced a suboptimal response to several medication trials and therapies including partial hospitalization. An intensive outpatient program had yielded little progress. On admission, she reported depressed mood, anhedonia, regret, crying, low energy, and hypersomnia. This patient expressed thoughts of death with fantasies regarding suicide.

Chiari malformation, type I, was noted on computerized head tomogram during a routine pre-ECT evaluation. This was confirmed on magnetic resonance imaging. The cerebellar tonsils extended 19 mm below the foramen magnum, and there was an empty sella. The cervical spine was without evidence of syrinx.

Retrospectively, the patient described symptoms consistent with increased intracranial pressure including persistent headache and neck pain, especially with coughing or straining. However, after consultations with neurology and neurosurgery, ECT was deemed safe because there was no evidence of syringomyelia or hydrocephalus.