Brain Stimulation 17 (2024) 588–590

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Synaptic density changes following electroconvulsive therapy: A longitudinal pilot study with PET-MR ^{11}C-UCB-J imaging in late-life depression

ARTICLE INFO

Keywords
Electroconvulsive therapy
Magnetic resonance imaging
Positron emission tomography
Neuroplasticity
Synaptic plasticity
Mood disorders

Dear Editor,

Electroconvulsive therapy (ECT) is an effective treatment for late-life depression (LLD), but its exact mechanism is not fully understood. The neuroplasticity hypothesis suggests that ECT works by inducing seizures that lead to neurotrophic effects crucial for its success [1]. Supporting the neuroplasticity hypothesis, preclinical research shows that electroconvulsive stimulation (ECS) enhances neurotrophic factors, promotes neurogenesis, boosts synaptogenesis, axonal sprouting, dendritic growth, and spine density, and alters synaptic circuitry in the hippocampus [2]. These changes, particularly in the hippocampus and prefrontal cortex, are believed to underlie ECT's mood-improving effects [3]. However, the translation of these preclinical findings to human ECT treatment remains to be verified. Clinical studies provide limited direct evidence for the neuroplasticity hypothesis, mostly relying on indirect measures such as MRI scans to show ECT's effect on increasing gray matter volume (GMV) [4]. The exact molecular mechanisms behind these structural changes and their relationship to the effectiveness of ECT are not well understood. Furthermore, there is no consensus on whether the increase in GMV observed in humans after ECT directly correlates with the neuroplastic changes seen in animal models subjected to ECS.

In vivo PET imaging of synaptic density has been advanced by new leviteracetam-based radioligands that target synaptic vesicle protein 2A (SV2A) with high affinity [5]. SV2A, a key presynaptic vesicle membrane protein, is consistently found across almost all brain synapses [6]. Due to its SV2A affinity and distribution volume, the ^{11}C-UCB-J tracer, serves as a reliable marker for assessing synaptic density in vivo [5]. With this tracer now available for human use, researchers can directly observe changes in synaptic density in patients receiving ECT.

This study aimed to validate preclinical synaptogenesis findings after ECS by utilizing in vivo synaptic density imaging, to detect ECT induced synaptogenesis in patients with late life depression (LLD). The primary goal was to assess whether an increase in GMV, detected through T1-weighted MRI, correlates with a concomitant increase in synaptic density, as measured by ^{11}C-UCB-J PET, following an acute series of ECT. A secondary aim was to explore the relationship between changes in synaptic density induced by ECT and the treatment's effectiveness.

Patients with LLD were recruited for the L3D-Study [7] (NCT03849417) at the Department of Old Age Psychiatry, KU Leuven, Belgium. Brain imaging was conducted using a GE Signa 3T PET-MR scanner. For longitudinal GMV analysis, Voxel-Based Morphometry (VBM) via the Computational Anatomy Toolbox 12 (CAT12) was used, employing a General Linear Model to detect within-subject changes. Statistical significance for VBM was set at $p < 0.001$ (voxel level) and corrected to $p < 0.01$ (cluster level), with significant clusters serving as the volume of interest for the subsequent ^{11}C-UCB-J analysis.

Off-scanner PET processing utilized custom MATLAB scripts (available at https://github.com/THOMVDC/PSYPET), to produce standardized uptake value ratio (SUVR) images. This process involved mapping the neuromorphometrics atlas VOI delineation onto each SUV image for accurate segmentation of the centrum semiovale, used as the reference region for SUVR calculations [8]. To account for potential partial volume effects due to expected GMV differences, a region-based voxel-wise partial volume correction algorithm was applied [9]. The mean SUVR within clusters of GMV change, identified through VBM analysis, was then further analyzed.

The study included 17 patients that were eligible for ECT, however, only 10 patients completed the longitudinal arm. These 10 participants were predominantly female (9 females and 1 male), and had an average age of 73 years. The range of ECT sessions varied from 9 to 11 prior to post-ECT assessment and all participants received right unilateral ECT only. The post-ECT scans were on average conducted within 2 days and 17 hours after the last ECT session. From a therapeutic perspective, the response rate to ECT in this cohort was 70 %, with 60 % achieving remission (MADRS <10). The VBM analysis of these patients revealed significant GMV changes post-ECT, including substantial increases in GMV in specific brain regions (Fig. 1a). The identified cluster overlapped with part of the right temporal pole, medial temporal gyrus, parahippocampus, inferior temporal gyrus, and the left supramarginal gyrus. No significant clusters of GMV decrease were detected. On average, no significant changes in ^{11}C-UCB-J uptake were detected in

https://doi.org/10.1016/j.brs.2024.04.020
Received 9 April 2024; Accepted 30 April 2024
Available online 1 May 2024

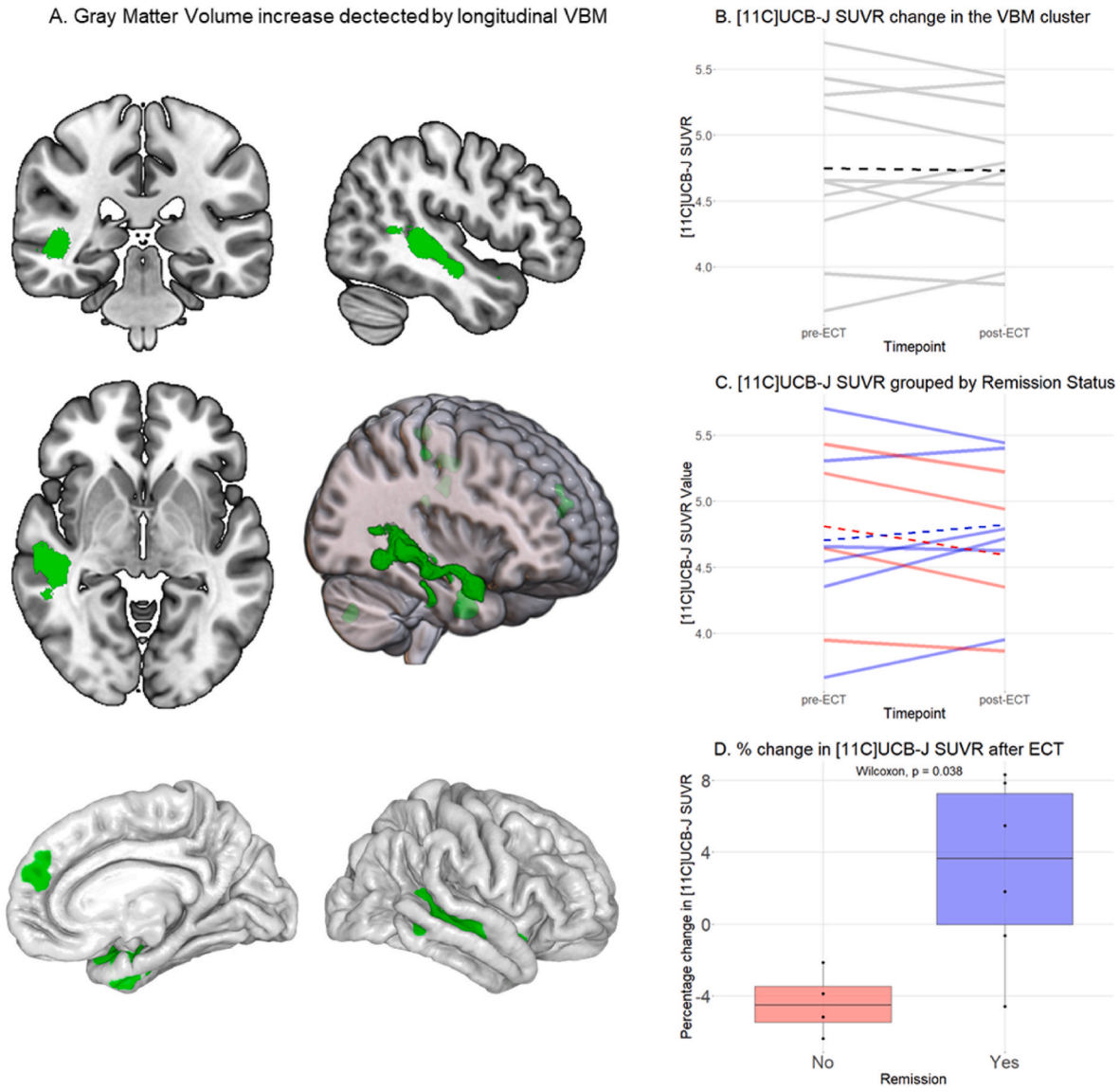

Fig. 1. **A.** GMV increase detected by longitudinal VBM on high-resolution 3D BRAVO T1-weighted MR images, depicted on coronal, axial and sagittal slices in MNI space. Green colored areas showed a significant increase in GMV following ECT. **B.** Plot of ^{11}C-UCB-J SUVR values from pre-to post-ECT for each subject. The black dashed line is the mean SUVR value in the VBM identified GMV increase cluster over time (Paired Wilcoxon signed rank exact test, w = 29, p = 0.92). **C.** plot of the ^{11}C-UCB-J SUVR values from pre-to post-ECT colored by remission status after ECT (MADRS <10). The dashed lines represent the mean change for patients achieving remission (blue) and not achieving remission (red) by the end of the study protocol. **D.** Boxplot of percentage of change in ^{11}C-UCB-J SUVR values from pre-to post-ECT grouped by remission status. There was a significant difference in percentage of ^{11}C-UCB-J SUVR change in the VBM GMV cluster based on remission status post-ECT (Wilcoxon Rank Sum Exact Test, w = 2, p = 0.038).

the VBM-identified GMV cluster (Paired Wilcoxon signed rank exact test, w = 29, p = 0.92) (Fig. 1b), indicating that the increases in GMV were not associated with changes in ^{11}C-UCB-J uptake in these regions. The changes in ^{11}C-UCB-J uptake varied depending on the clinical outcome after ECT (Fig. 1c). There was a significant difference in the percentage of ^{11}C-UCB-J SUVR change in the VBM-identified GMV cluster based on remission status at the time of the post-ECT assessment (Wilcoxon Rank Sum Exact Test, w = 2, p = 0.03) (Fig. 1d). In remitted patients, there was an increase in mean ^{11}C-UCB-J SUVR in the VBM-identified GMV increase cluster. In contrast, those who did not reach remission displayed a decrease of ^{11}C-UCB-J SUVR in that same VBM cluster.

This pilot study marks a pioneering effort to longitudinally assess synaptic density changes in vivo in ECT patients using PET-MR imaging, which confirmed increased GMV post-ECT but found no concomitant increase in synaptic density via ^{11}C-UCB-J PET. An important factor to consider is the temporal window of our measurement post-ECT. In our study, the average interval between the final ECT session and the follow-up ^{11}C-UCB-J PET scan was 2 days and 17 hours, potentially missing the acute phase of synaptic changes as indicated by ECS. Conversely, a recent study using similar SV2A-PET methodology reported SSRI associated synaptic plasticity after 3–5 weeks, suggesting a longer interval may be required to detect synaptogenesis post-ECT [10]. Further, the immediate clinical impact of these findings is limited by the small sample size and absence of a control group. However, the use of ^{11}C-UCB-J PET as a new in vivo marker of synaptic plasticity is a promising technique to bridge the gap between preclinical and clinical research on neuroplasticity following ECT. Future studies should aim to integrate molecular, structural and functional assessments to investigate the link between ECT, neuroplasticity and therapeutic efficacy.

CRediT authorship contribution statement

Maarten Laroy: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **Thomas Vande Casteele:** Data curation, Investigation, Software, Writing – review & editing. **Margot Van Cauwenberge:** Data curation, Investigation, Writing – review & editing. **Michel Koole:** Methodology, Writing – review & editing. **Patrick Dupont:** Methodology, Software, Writing – review & editing. **Stefan Sunaert:** Writing – review & editing. **Jan Van den Stock:** Writing – review & editing. **Pascal Sienaert:** Writing – review & editing. **Koen Van Laere:** Conceptualization, Methodology, Resources, Writing – review & editing. **Mathieu Vandenbulcke:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Louise Emsell:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Filip Bouckaert:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was supported by the Research Foundation Flanders (FWO) project G0C0319 N (M. Vandenbulcke, F. Bouckaert, L. Emsell), KU Leuven C24/18/095 (M. Vandenbulcke, F. Bouckaert, J. Van den Stock, L. Emsell) and KU Leuven Sequoia Fund. M. Laroy is an aspirant researcher for the Research Foundation Flanders (FWO, grant no. 1168821 N).

K. Van Laere is an advisory board member of Cerveau-Lantheus and has performed contract research through KU Leuven. All other authors have no competing interests to declare.

Acknowledgements

We thank Kwinten Porters, Jef Van Loock, Radiopharmacy UZ Leuven (Kim Serdons and team) for their assistance with regard to the PET imaging. This study was supported by the Research Foundation Flanders (FWO) project G0C0319 N (M. Vandenbulcke, F. Bouckaert, L. Emsell), KU Leuven C24/18/095 (M. Vandenbulcke, F. Bouckaert, J. Van den Stock, L. Emsell) and KU Leuven Sequoia Fund. M. Laroy is an aspirant researcher for the Research Foundation Flanders (FWO, grant no. 1168821 N).

References

[1] Bolwig TG. How does electroconvulsive therapy work? Theories on its mechanism. Can J Psychiatr 2011;56(1):13–8.
[2] Bouckaert F, Sienaert P, Obbels J, Dols A, Vandenbulcke M, Stek M, et al. ECT: its brain enabling effects: a review of electroconvulsive therapy-induced structural brain plasticity. J ECT 2014;30(2):143–51.
[3] Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol Psychiatr 2009;14(8):764–73. 39.
[4] Ousdal OT, Brancati GE, Kessler U, Erchinger V, Dale AM, Abbott C, et al. The neurobiological effects of electroconvulsive therapy studied through magnetic resonance: what have we learned, and where do we go? Biol Psychiatr 2022;91(6):540–9.
[5] Finnema SJ, Nabulsi NB, Eid T, Detyniecki K, Lin SF, Chen MK, et al. Imaging synaptic density in the living human brain. Sci Transl Med 2016;8(348):348ra96.
[6] Nabulsi NB, Mercier J, Holden D, Carre S, Najafzadeh S, Vandergeten MC, et al. Synthesis and preclinical evaluation of 11C-UCB-J as a PET tracer for imaging the synaptic vesicle glycoprotein 2A in the brain. J Nucl Med 2016;57(5):777–84.
[7] Emsell L, Laroy M, Van Cauwenberge M, Vande Casteele T, Vansteelandt K, Van Laere K, et al. The Leuven late life depression (L3D) study: PET-MRI biomarkers of pathological brain ageing in late-life depression: study protocol. BMC Psychiatr 2021;21(1):64.
[8] Michiels L, Mertens N, Thijs L, Radwan A, Sunaert S, Vandenbulcke M, et al. Changes in synaptic density in the subacute phase after ischemic stroke: a (11)C-UCB-J PET/MR study. J Cerebr Blood Flow Metabol 2022;42(2):303–14.
[9] Mertens N, Michiels L, Vanderlinden G, Vandenbulcke M, Lemmens R, Van Laere K, et al. Impact of meningeal uptake and partial volume correction techniques on [(18)F]MK-6240 binding in aMCI patients and healthy controls. J Cerebr Blood Flow Metabol 2022;42(7):1236–46.
[10] Johansen A, Armand S, Plaven-Sigray P, Nasser A, Ozenne B, Petersen IN, et al. Effects of escitalopram on synaptic density in the healthy human brain: a randomized controlled trial. Mol Psychiatr 2023;28(10):4272–9.

Maarten Laroy*, Thomas Vande Casteele
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium

Margot Van Cauwenberge
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium
Department of Neurology, University Hospitals Leuven, B-3000, Leuven, Belgium

Michel Koole
KU Leuven, Leuven Brain Institute, Department of Imaging and Pathology, Nuclear Medicine, B-3000, Leuven, Belgium

Patrick Dupont
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Laboratory for Cognitive Neurology, B-3000, Leuven, Belgium

Stefan Sunaert
KU Leuven, Leuven Brain Institute, Department of Imaging and Pathology, Translational MRI, B-3000, Leuven, Belgium
Department of Radiology, University Hospitals Leuven, B-3000, Leuven, Belgium

Jan Van den Stock
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium
Geriatric Psychiatry, University Psychiatric Centre KU Leuven, B-3000, Leuven, Belgium

Pascal Sienaert
KU Leuven, Department of Neurosciences, Academic Centre for ECT and Neuromodulation, B-3000, Leuven, Belgium

Koen Van Laere
Department of Nuclear Medicine and Molecular Imaging, University Hospitals Leuven, B-3000, Leuven, Belgium

Mathieu Vandenbulcke
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium
Geriatric Psychiatry, University Psychiatric Centre KU Leuven, B-3000, Leuven, Belgium

Louise Emsell
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium
KU Leuven, Leuven Brain Institute, Department of Imaging and Pathology, Translational MRI, B-3000, Leuven, Belgium
Geriatric Psychiatry, University Psychiatric Centre KU Leuven, B-3000, Leuven, Belgium

Filip Bouckaert
KU Leuven, Leuven Brain Institute, Department of Neurosciences, Neuropsychiatry, B-3000, Leuven, Belgium
Geriatric Psychiatry, University Psychiatric Centre KU Leuven, B-3000, Leuven, Belgium

* Corresponding author.
E-mail address: maarten.laroy@kuleuven.be (M. Laroy).