Retrograde amnesia following electroconvulsive therapy for depression: a propensity score analysis

Ana Jelovac, Sabine Landau, Gabriele Gusciute, Martha Noone, Keeva Kavanagh, Mary Carton, Cathal McCaffrey, Kelly McDonagh, Eimear Doody, Declan M. McLoughlin*

Author details: **Ana Jelovac**, PhD, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Sabine Landau**, PhD, Department of Biostatistics and Health Informatics, King's College London, London, United Kingdom; **Gabriele Gusciute**, BA, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Martha Noone**, PhD, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Keeva Kavanagh**, MPsychSc, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Mary Carton**, PhD, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Cathal McCaffrey**, MRCPsych, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Kelly McDonagh**, MSc, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Eimear Doody**, MRCPsych, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; **Declan M. McLoughlin**, PhD, MRCPI, MRCPsych, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland.

*__Corresponding author__: Declan McLoughlin, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, James Street, Dublin, D08 K7YW, Ireland

E-mail: d.mcloughlin@tcd.ie

Tel: +353 1 2493343

Short Report word count: 1200

Declaration of Interest: DMM has received speaker's honoraria from Mecta, Otsuka and Janssen, and an honorarium from Janssen for participating in an esketamine advisory board meeting. Other authors report no conflicts of interest.

Funding: This work was supported by Health Research Board grants TRA/2007/5, HPF/2010/17 and TRA/2007/5/R. The Health Research Board had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; review or approval of the manuscript, preparation of the manuscript, or the decision to submit the manuscript for publication. SL is supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust and the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Author Contributions: AJ, SL and DMM designed the study and drafted the manuscript. SL analysed the data. All authors interpreted the analyses and revised the manuscript for important intellectual content.

Data Availability: An application to St Patrick's Mental Health Services Research Ethics Committee with a study proposal is required for data sharing.

Summary

Retrograde amnesia for autobiographical memories is a commonly self-reported cognitive side effect of electroconvulsive therapy (ECT) but it is unclear to what extent objective performance differs between ECT-exposed and unexposed patients with depression. We investigated the association between exposure to brief-pulse (1.0 ms) bitemporal or high-dose right unilateral ECT and retrograde amnesia at short- and long-term follow-up compared to inpatient controls with moderate-to-severe depression without lifetime exposure to ECT receiving psychotropic pharmacotherapy and other aspects of routine inpatient care. In propensity score analyses, statistically significant reductions in autobiographical memory recall consistency were found in bitemporal and high-dose right unilateral ECT within days of an ECT course and three months following final ECT session. The reduction in autobiographical memory consistency was substantially more pronounced in bitemporal ECT. Retrograde amnesia for items recalled before ECT occurs with commonly utilised ECT techniques and may be a persisting adverse cognitive effect of ECT.

Introduction

Autobiographical retrograde amnesia is a commonly self-reported adverse cognitive effect of electroconvulsive therapy (ECT). Modifications in technique, including unilateral electrode placement and ultrabrief pulse stimulus, attenuate retrograde amnesia.[1] While the impact of ECT technique on autobiographical memory has been extensively documented, the extent to which autobiographical memory recall may be affected in ECT-exposed compared to ECT-unexposed patients with depression has received little attention. This is surprising, given the well-characterised autobiographical memory abnormalities in depression.[2] Demonstrations of retrograde amnesia in ECT-exposed patients compared to non-depressed healthy controls are confounded by effects of mood disorder itself on autobiographical memory. To disentangle the effect of ECT on memory from the effect of mood disorder, the more appropriate control group is patients with depression of similar severity not receiving ECT.

Early work examining retrograde amnesia as percentage loss of recall consistency of selected autobiographical memory items at post-ECT follow-ups relative to content recalled at pre-ECT baseline suggested that patients receiving bitemporal ECT exhibited worse recall consistency at end-of-treatment than non-ECT treated depressed controls.[3,4] Two small contemporary studies have compared ECT-exposed versus ECT-unexposed patients with depression. Patients receiving bifrontal ECT had reduced recall consistency at end-of-treatment and four-week follow-up compared to controls receiving isoflurane anaesthesia.[5] One randomised trial has compared autobiographical recall consistency following right unilateral ECT to a pharmacologically-treated control group with bipolar depression; percentage consistency scores were 72.9% vs. 80.8% at end-of-treatment [6] and 64.3% vs. 72.3% at six months after ECT,[7] respectively. Given the paucity of data quantifying retrograde amnesia in ECT patients compared to ECT-unexposed controls with depression, we aimed to examine the association between two commonly used forms of ECT and loss of autobiographical memory consistency.

Methods

Methods are detailed in Supplementary Material. ECT participants were recruited to the EFFECT-Dep Trial.[8] Adult (age ≥18) inpatients were eligible if meeting Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive episode (unipolar or bipolar) and scoring ≥21 on baseline 24-item Hamilton Depression Rating Scale (HAM-D). Exclusion criteria were: medical conditions rendering unfit for general anaesthesia; ECT in previous six months; history of schizophrenia, schizoaffective disorder or dementia; substance use disorder in previous six months; involuntary status or inability to consent.

Control participants took part in MEM-Dep[9] and AMBER-Dep[10] prospective cohort studies and were adult inpatients with major depressive episode meeting DSM-IV or ICD-10 criteria, scoring ≥21 on HAM-D. Exclusion criteria were: history of ECT; neurological or unstable medical condition; active Axis I comorbidity; substance use disorder in previous six months; and involuntary status or inability to consent.

All groups received psychotropic medications and other aspects of inpatient care. This study received St Patrick's Mental Health Services research ethics committee approval (Protocol 08/22). Informed consent requirements were waived for these secondary analyses of deidentified data.

Autobiographical memory was assessed using the Autobiographical Memory Interview–Short Form (AMI-SF)[11] at pre-ECT baseline, end-of-treatment (within days of final ECT) and three months after final ECT. Controls were retested at analogous time intervals: 1-2 months after baseline assessment (coinciding with test-retest interval in the ECT groups where patients received twice-weekly ECT) and three months after the second visit.

A propensity score stratification approach was used to control for measured confounding. Propensity scores were estimated for each comparison (right unilateral ECT vs. control, bitemporal ECT vs. control) at each timepoint (end-of-treatment, 3-month follow-up) using logistic regression models with seven putative confounders (age, gender, education, polarity, psychosis, baseline HAM-D and baseline AMI-SF score). Baseline covariate balance was considered adequate where (absolute) pooled within-strata standardised mean differences were <0.1. We estimated the average treatment effect on the treated (ATT); here, the difference in average population recall percentages

under ECT and control treatments for patients who later receive ECT. Odds ratios arising from binomial models were converted to percentage differences using *g*-computation. Sensitivity analyses were conducted to evaluate robustness of primary analyses to choice of analysis method and non-ignorable missingness.

Results

Baseline characteristics of 210 included patients are provided in Supplementary Table 1; Supplementary Table 2 shows that baseline covariates were successfully balanced after propensity score stratification. In primary analyses (Table 1; Supplementary Figure 1), AMI-SF percentage recall was significantly reduced in both ECT groups compared to ECT-unexposed depressed controls at end-of-treatment and three-month follow-up. Sensitivity analyses with alternative methods (Table 1) yielded similar ATT estimates, with reductions estimated at 7-10% for right unilateral ECT at 6x seizure threshold and 18-21% for bitemporal ECT at 1.5x seizure threshold. There was a 24-25% loss of autobiographical recall consistency at both follow-ups in depressed controls (Supplementary Table 3). Sensitivity analyses of non-ignorable missingness showed limited impact on ATT estimates (Supplementary Table 4).

Table 1

Discussion

We measured autobiographical memory consistency, an accepted measure of retrograde amnesia in the ECT field, in brief-pulse bitemporal ECT, high-dose right unilateral ECT and ECT-unexposed controls. Compared to a control group of inpatients with moderate-to-severe depression, both ECT techniques were associated with significantly increased loss of autobiographical memory consistency immediately following the course. The difference in autobiographical memory consistency between ECT groups and controls remained unattenuated in size and statistically significant at three-month follow-up, implying that retrograde amnesia for AMI-SF items is a persisting side-effect of ECT.

Differences between unilateral ECT and control groups at end-of-treatment and three months were similar to a randomised trial that found 7.9% difference at end-of-treatment and 8.0% at six-month follow-up in a substantially different patient population (all bipolar and younger).[6,7] An additional notable finding was that patients without exposure to ECT experienced substantial loss of autobiographical memory consistency over time. Consequently, when interpreting results of brain stimulation studies, the majority of which do not include a clinical control group, it is imperative to not misinterpret a within-group reduction in AMI-SF score as evidence of retrograde amnesia per se.

Brief-pulse bitemporal ECT, while falling out of favour at leading academic centres in North America, is in widespread use worldwide.[12] The reluctance to switch to high-dose right unilateral ECT is difficult to justify given equivalent antidepressant efficacy and significantly reduced retrograde amnesia.[8,13] Bitemporal ECT may result in faster reduction in depressive symptoms[14] which should be taken into consideration in scenarios where rapid response is required. However, for most ECT referrals for depression, this marginal benefit does not outweigh the markedly pronounced risk of retrograde amnesia. Ultrabrief pulse right unilateral ECT, not examined in the present study, results in even less retrograde amnesia than brief-pulse right unilateral ECT but this relative sparing of autobiographical memory may come at the expense of reduced efficacy.[15] Risks and benefits of bitemporal vs. alternative forms of ECT should be presented to patients during the informed consent process.

Limitations of this study include loss to three-month follow-up and single-centre design. Future work is needed to address the limited evidence on impact of antidepressant medications on autobiographical memory. Our findings apply to the respective regions of common support used to achieve covariate balance. These regions excluded some ECT patients who had a negligible probability of being included in the control group. Our inferences regarding ECT are, therefore, applicable to less severely ill subpopulations. This is expected, as brief-pulse ECT occupies a special place in the treatment of the most severely ill psychiatric patients with no proven alternative treatment of comparable efficacy.

References

1. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul* 2008; **1(2)**: 71-83.

2. Barry TJ, Hallford DJ, Takano K. Autobiographical memory impairments as a transdiagnostic feature of mental illness: A meta-analytic review of investigations into autobiographical memory specificity and overgenerality among people with psychiatric diagnoses. *Psychol Bull* 2021; **147(10)**: 1054-1074.

3. Calev A, Ben-Tzvi E, Shapira B, Drexler H, Carasso R, Lerer B. Distinct memory impairments following electroconvulsive therapy and imipramine. *Psychol Med* 1989; **19(1)**: 111-119.

4. Weiner RD, Rogers HJ, Davidson JR, Squire LR. Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci* 1986; **462**: 315-325.

5. Weeks HR, 3rd, Tadler SC, Smith KW, Iacob E, Saccoman M, White AT, et al. Antidepressant and neurocognitive effects of isoflurane anesthesia versus electroconvulsive therapy in refractory depression. *PLoS One* 2013; **8(7)**: e69809.

6. Kessler U, Schoeyen HK, Andreassen OA, Eide GE, Malt UF, Oedegaard KJ, et al. The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. *J Clin Psychiatry* 2014; **75(11)**: e1306-1313.

7. Bjoerke-Bertheussen J, Schoeyen H, Andreassen OA, Malt UF, Oedegaard KJ, Morken G, et al. Right unilateral electroconvulsive therapy does not cause more cognitive impairment than pharmacologic treatment in treatment-resistant bipolar depression: A 6-month randomized controlled trial follow-up study. *Bipolar Disord* 2018; **20(6)**: 531-538.

8. Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, et al. Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomized, non-inferiority trial. *Am J Psychiatry* 2016; **173(4)**: 408-417.

9. Semkovska M, Noone M, Carton M, McLoughlin DM. Measuring consistency of autobiographical memory recall in depression. *Psychiatry Res* 2012; **197(1-2)**: 41-48.

10. Whooley E, Gusciute G, Kavanagh K, McDonagh K, McCaffrey C, Doody E, et al. Reliable change indices and minimum detectable change for the Montreal Cognitive Assessment in

electroconvulsive therapy for depression. *J ECT* [Epub ahead of print] Jul 5 2024. Available from: https://doi:10.1097/YCT.0000000000001043

11. McElhiney MC, Moody BJ, Sackeim HA. *The Autobiographical Memory Interview Short From: manual for administration and scoring*. Department of Biological Psychiatry, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians & Surgeons, Columbia University, 2001.

12. Rohde P, Noorani R, Feuer E, Lisanby SH, Regenold WT. Electroconvulsive therapy across nations: a 2022 survey of practice. *J ECT* 2024; **40(2)**: 96-104.

13. Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med* 2017; **47(3)**: 518-530.

14. Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry* 2010; **196(3)**: 226-234.

15. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry* 2015; **76(9)**: e1092-1098.