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Neurocognitive Effects of Combined Electroconvulsive Therapy (ECT) and Venlafaxine in Geriatric Depression: Phase 1 of the PRIDE Study

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ABSTRACT

Objective: There is limited information regarding the tolerability of electroconvulsive therapy (ECT) combined with pharmacotherapy in elderly adults with major depressive disorder (MDD). Addressing this gap, we report acute neurocognitive outcomes from Phase 1 of the Prolonging Remission in Depressed Elderly (PRIDE) study. **Methods:** Elderly adults (age ≥ 60) with MDD received an acute course of 6 times seizure threshold right unilateral ultrabrief pulse (RUL-UB) ECT. Venlafaxine was initiated during the first treatment week and continued throughout the study. A comprehensive neurocognitive battery was administered at baseline and 72 hours following the last ECT session. Statistical significance was defined as a two-sided *p*-value of less than 0.05. **Results:** A total of 240 elderly adults were enrolled. Neurocognitive performance acutely declined post ECT on measures of psychomotor and verbal processing speed, autobiographical memory consistency, short-term verbal recall and recognition of learned words, phonemic fluency, and complex visual scanning/cognitive flexibility. The magnitude of change from baseline to end for most neurocognitive measures was modest. **Conclusion:** This is the first study to characterize the neurocognitive effects of combined RUL-UB ECT and venlafaxine in elderly adults with MDD and provides new evidence for the tolerability of RUL-UB ECT in an elderly sample. Of the cognitive domains assessed, only phonemic fluency, complex visual scanning, and cognitive flexibility qualitatively declined from low average to mildly impaired. While some acute changes in neurocognitive performance were statistically significant, the majority of the indices as based on the effect sizes remained relatively stable. (Am J Geriatr Psychiatry 2019;

■■:■■-■■)

INTRODUCTION

Consequences of major depressive disorder (MDD) in elderly adults include neurocognitive sequelae,¹ suicide,² and increased all cause morbidity and mortality.³ In many cases, elderly adults receive little to no benefit from antidepressant therapies including pharmacotherapy,⁴ psychotherapy,⁵ and repetitive transcranial magnetic stimulation,⁶ or require rapidly acting intervention, and thus are prescribed electroconvulsive therapy (ECT).⁷

While ECT has been found to be effective in the elderly with high response and remission rates,⁸ concern about neurocognitive adverse effects limits its acceptance, particularly for seniors with age-related cognitive decline or dementia. Short-term neurocognitive effects of ECT include decreased processing speed, attention, learning and memory, working memory, and executive function.⁹ A recent systematic review found the neurocognitive adverse effects of ECT in elderly adults to be transient and to occur

mainly around the interictal and postictal periods and persist up to one month.¹⁰ However, other research suggests that ECT administered with bitemporal electrode configuration and brief pulse stimuli and is associated with retrograde amnesia for autobiographical memory consistency that can persist for up to 6 months.¹¹ The majority of this research has focused on mixed-age adult populations, with limited information specifically regarding elders.¹²

While the mechanisms of the neurocognitive effects of ECT remain unknown,^{13,14} ECT parameters including charge, stimulus waveform, and electrode configuration play significant roles. Different combinations of ECT parameters have differential effects on the electric field induced in the brain, and therefore may exert different effects on underlying neurocircuitry.¹⁵ The combination of dose-titrated, ultrabrief pulse width, and right unilateral electrode configuration (RUL-UB) relative to the combination of brief pulse width and bitemporal electrode configuration can have fewer neurocognitive adverse effects relative to other ECT dosages and configurations with efficacy

that approaches conventional brief pulse bilateral ECT.^{16,17}

We present the acute neurocognitive outcomes of elderly adults with MDD treated with combined ECT and venlafaxine in Phase 1 of the Prolonging Remission in Depressed Elderly (PRIDE) study.¹⁸ We hypothesized that elderly adults with MDD would tolerate RUL-UB ECT well, and have fewer cognitive adverse effects than typically reported with brief pulse RUL and bitemporal ECT.

METHOD

Study Design Overview

The PRIDE study methods have been described elsewhere.¹⁸ Briefly, this was a multicenter, randomized trial of an individualized symptom-titrated algorithm-based longitudinal ECT (STABLE) protocol combined with venlafaxine (VLF) and lithium (Li) to improve long-term outcomes of elderly adults with MDD. In Phase 1, patients received an acute course of RUL-UB ECT 3× weekly combined with VLF. In Phase 2, those who remitted during Phase 1 were randomized to receive pharmacotherapy (VLF and Li) alone or the combined modalities (pharmacotherapy and STABLE) for 6 months.

The study sites included: Columbia University/New York State Psychiatric Institute, Duke University School of Medicine, Medical College of Georgia/Augusta University, Icahn School of Medicine at Mount Sinai (Clinical Coordinating Center), Mayo Clinic, Medical University of South Carolina (data management and statistical coordinating center), New York Presbyterian/Weill Cornell Medical Center, University of Texas Southwestern Medical Center, Wake Forest University Medical Center, Zucker Hillside Hospital/Northwell Health System. The institutional review board at each study site approved the study protocol.

Study Sample

Patients were recruited over a 6-year period from clinical referrals for ECT at the enrolling sites. Inclusion criteria included in- or outpatients, age ≥ 60 , DSM-IV-TR diagnosis of unipolar major depressive episode, and 24-item Hamilton Rating Scale for

Depression (HRSD₂₄) total score ≥ 21 . Exclusion criteria included bipolar disorder, schizoaffective disorder, dementia, substance abuse/dependence in last 6 months, active general medical or neurological conditions that would affect cognitive function or treatment outcome, contraindications to Li or VLF, or failure to respond to an adequate trial of Li + VLF, or ECT in the current episode. All patients provided written informed consent to participate in the study.

Electroconvulsive Therapy and Medication Procedures

Medication Washout and Concomitant Medications

Patients discontinued psychotropic medications within 1 week of starting Phase 1. Rescue medication (lorazepam up to 3 mg/day or equivalent) was provided as needed for agitation, anxiety, or insomnia.

Electroconvulsive Therapy

ECT was provided 3 sessions per week with RUL electrode placement using a Somatics Thymatron System IV (Somatics, LLC, Lake Bluff, IL) with an ultrabrief pulse width of 0.25 ms and current of 900 mA or a MECTA SPECTRUM (MECTA Corporation, Portland, OR) device with an ultrabrief pulse width of 0.3 ms and current of 800 mA. Dose titration to determine seizure threshold was conducted at the first ECT session. Subsequent treatments were administered at six times individual seizure threshold.

The average seizure threshold during the titration procedures for the overall sample was 30.5 (SD = 14.3) millicoulombs. The average number of ECT sessions to produce remission was 7.32 (SD = 3.52) for the overall sample, 7.30 (SD = 3.03) for remitters, 12.36 (SD = 1.04) for nonremitters, and 5.51 (SD = 3.31) for drop-outs (see Kellner et al.¹⁸ for comprehensive details on the ECT treatment).

Medication

Open-label VLF was started 1–5 days prior to ECT or up to 2 days after the first treatment at an initial dosage of 37.5 mg po, increased by 37.5 mg every 3 days or as tolerated, with a target dose of 225 mg qD.

*Neurocognitive Effects of ECT and Venlafaxine in Geriatric Depression***Clinical Assessment Procedures**

Diagnosis was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (study years 1 and 2) or the Mini-International Neuropsychiatric Interview (MINI) (years 3–6). The change in diagnostic instrument was made to minimize patient burden. Depressive symptoms were assessed with the HRSD₂₄ and suicidal ideation with the Beck Scale for Suicide Ideation (BSS). Raters were trained to criteria via in-person and video interactive sessions.

Neurocognitive Assessment Procedures

The study assessed multiple cognitive domains including attention and processing speed, verbal fluency, verbal learning and memory, autobiographical memory consistency, and executive functions. The neuropsychological instruments were: Autobiographical Memory Interview-Short Form (AMI-SF),¹⁹ California Verbal Learning Test-II (CVLT-II),²⁰ Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency (Condition 1: Letter Fluency) Test,²¹ Dementia Rating Scale-2nd Edition Initiation Perseveration Index (DRS-2 IP),²² Stroop Color and Word Test,²³ and Trail Making Test Parts A and B (TMT A and B). Each neuropsychological instrument, with the exception of the TMT A and AMI-SF, had an alternate form. With the exception of the AMI-SF, all neuropsychological variable raw scores were converted into demographic-adjusted scores. Global cognitive function was assessed with the Mini Mental State Examination (results were previously reported)¹⁸ and premorbid intellectual ability was estimated with the Wechsler Test of Adult Reading (WTAR).²⁴ Patients completed the neurocognitive battery at baseline and within 72 hours following the last ECT session. Testers at all sites were trained to criteria via in-person and video interactive training sessions following the neuropsychological instrument procedure manual. For longitudinal quality control, the electronic database was range validated to automatically detect errors and alert the study site to correct errors. Every 4 months, a random sample of data was examined for scoring accuracy.

Statistical Analysis*Descriptive analyses*

Descriptive statistics were used to characterize the demographic, neurocognitive, and clinical features of the study sample (n = 240) who met selection criteria

and began Phase 1. Means and standard deviations are presented for continuous variables, and frequency distributions are presented for discrete variables. Pearson correlation coefficients and corresponding 95% confidence intervals (CI) around the correlation coefficient were computed to describe the association between baseline neurocognitive variables and initial depression severity (HRSD₂₄ total score).

Missing data

The percent of missing data for baseline, end of Phase 1 and change from baseline for the neurocognitive outcomes were determined. Clinical and cognitive differences between completers (remitters and nonremitters) and noncompleters (dropouts) were described using means and standard deviations or frequency distributions for each outcome category. Multiple imputations to impute missing neurocognitive data were incorporated into the estimation and inferential procedures (see section below).²⁵

Estimation and Inferential analyses

Ninety-five percent CI and paired *t*-tests obtained using multiple imputation procedure for missing data were used, respectively, to estimate the change from baseline to end of Phase 1 and determine if the change was statistically significant for each neurocognitive outcome.

First, as part of the multiple imputation procedure, logistic regression, with the dichotomous-dependent variable missing/not missing, was used to identify the variables predictive of missing values for the neurocognitive variables. The multiple imputation process was then carried out using the Markov Chain Monte Carlo (MCMC) method to obtain 100 completed data subsets for the neurocognitive variables. Variables included in the imputation model were outcome status (remitter, nonremitter, dropout), age, baseline and last observed HRSD₂₄ total score, sex, education, baseline and last observed MMSE total raw score, and number of ECT sessions in Phase 1. Next, in the multiple imputation procedure, results were combined across the 100 imputed subsets for final estimation of change from baseline (raw effect size) using 95% CI and inference using paired *t*-tests. Raw effect sizes were converted to standardized effect sizes (z-scores, Cohen's *d*) by dividing by the raw change from baseline standard deviation.

Electric Field Modeling

Following the recommendations of the National Institute of Mental Health (NIMH) to report electric field models for noninvasive neuromodulation therapy dosage^{26,27} and since the study employed ECT stimulators from two different manufacturers that operated at slightly different pulse current amplitudes and pulse widths, we compared the difference in the induced electric field in the brain. An anatomically realistic head model was constructed from magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) data from one of the study subjects (62-year-old male at the Zucker Hillside Hospital study site). The subject was scanned in a 3T GE Signa HDxt scanner. T1-weighted MRI was acquired using a spoiled gradient recalled echo (SPGR) sequence (repetition time = 7.83 ms, echo time = 3.02 ms, voxel size = 0.9375 × 0.9375 × 1 mm³, flip angle = 8°, 216 coronal slices). DTI was acquired using a spin echo planar sequence (repetition time = 14,000 ms, echo time = 75.5 ms, voxel size = 0.9375 × 0.9375 × 2.5 mm³, flip angle = 90°). Diffusion sensitizing gradients were applied along 31 non-collinear directions with a *b*-value of 1,000 s/mm². The finite element head model was constructed using SimNIBS 2.0.1.²⁸

The head model consisted of five tissue compartments: skin, skull, cerebrospinal fluid, gray matter, and white matter, with assigned isotropic conductivities of 0.465 S m⁻¹, 0.010 S m⁻¹, 1.654 S m⁻¹, 0.276 S m⁻¹, and 0.126 S m⁻¹, respectively.²⁹ White matter anisotropy was incorporated based on conductivity tensors derived from DTI using a volume normalized mapping approach.³⁰ We simulated the RUL ECT electrode placement with stimulus current amplitude of 800 mA or 900 mA, corresponding to the outputs of the MECTA spECTrum 5000Q and Somatics Thymatron System IV devices, respectively. We computed the distribution of the electric field strength relative to a pulse waveform specific neural activation threshold, E/E_{th} .³¹

RESULTS

Demographic and Baseline Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of the sample (n = 240, age range 60–91)

TABLE 1. Baseline Sociodemographic and Clinical Characteristics of Participants in a Study of ECT and Venlafaxine in Geriatric Depression

Baseline Characteristics	Total Sample (N = 240)	
	Mean	SD
Continuous		
Age (years)	69.9	7.6
Education (years) ^a	14.5	3.3
Hamilton Depression Rating Scale (24 item) total score	31.2	7.3
Mini-Mental State Examination total score ^a	27.5	2.4
Wechsler Test of Adult Reading Full Scale IQ score ^j	106.0	10.2
Clinical Global Impression severity score ^a	5.3	0.9
Psychiatric hospitalizations ^b	2.4	3.4
Cumulative Illness Rating Scale for Geriatrics score ^c	8.6	4.2
Number of previous antidepressant medications ^d	2.4	1.6
Categorical	N	%
Sex: Female	138	57.5
Race: White	228	95.0
Ethnicity: Hispanic ^e	9	3.8
Recurrent depressive episode	210	87.5
Depressive subtype		
Atypical ^a	5	2.1
Melancholic ^a	141	59.0
Psychotic	28	11.7
Beck Scale for Suicide Ideation, % with score of 0 ^f	105	52.0
Family history of psychiatric illness ^g	160	68.7
Family history of mood disorder ^h	143	61.9
Family history of major depressive disorder ⁱ	136	59.1
Family history of bipolar disorder ^j	33	14.3

^a Data missing for 1 subject (0.4%).

^b Data missing for 11 subjects (4.6%).

^c Data missing for 3 subjects (1.3%).

^d Data missing for 34 subjects (14.2%).

^e Data missing for 2 subjects (0.8%).

^f Data missing for 38 subjects (15.8%).

^g Data missing for 7 subjects (2.9%).

^h Data missing for 9 subjects (3.8%).

ⁱ Data missing for 10 subjects (4.2%).

^j Data missing for 32 subjects (13.3%).

who entered and completed Phase 1 of the PRIDE Study. Slightly over half of the participants were female, 95% were White, and the average years of education was 14.5 years (SD = 3.3). As typical of patients referred for ECT, most (87.5%) had recurrent MDD and a family history of psychiatric illness (68.7%) and MDD (59.1%). The current major depressive episode was severe (HRSD₂₄ total score = 31.2 (SD = 7.3) and most (59%) subjects had melancholic features.

Neurocognitive Effects of ECT and Venlafaxine in Geriatric Depression

Baseline Neurocognitive Performance

Baseline neurocognitive values are shown in Table 2. The sample had an estimated premorbid intellectual ability WTAR Full Scale IQ in the average range. Mean global cognitive function MMSE total score was in the intact range. Mean demographic adjusted scores for the neurocognitive variables ranged from average to mildly impaired. Simple visual scanning/psychomotor processing speed (TMT-A) and phonemic fluency (D-KEFS Letter Fluency) were average. Complex visual scanning/psychomotor processing speed and cognitive flexibility (TMT-B) and initiation/perseveration (DRS-2) were low average, but response inhibition (Stroop Color-Word) was mildly impaired. On the CVLT-II, verbal learning, and immediate free recall and recognition of learned words were low average, but delayed free recall was mildly impaired. On average, the participants

recalled approximately 83% of information to autobiographical questions.

Relationship Between Baseline Depression Severity and Neurocognitive Performance

At baseline, depression severity as rated on the HRSD₂₄ was negatively associated with global cognitive function ($r = -0.14$, 95% CI: -0.26 to -0.01 , $p = 0.04$), color naming processing speed ($r = -0.18$, 95% CI: -0.30 to -0.04 , $p = 0.01$), autobiographical memory recall ($r = -0.29$, 95% CI: -0.40 to -0.16 , $p < 0.0001$), verbal learning ($r = -0.17$, 95% CI: -0.30 to -0.03 , $p = 0.02$), delayed free recall of learned words ($r = -0.18$, 95% CI: -0.31 to -0.04 , $p = 0.01$), and initiation/perseveration ($r = -0.19$, 95% CI: -0.32 to -0.04 , $p = 0.007$). Though statistically significant, the correlations were relatively weak. Details for the full neurocognitive battery are provided in Table S1 in the online supplemental data.

TABLE 2. Neurocognitive Test Results Before and After Treatment With Electroconvulsive Therapy and Venlafaxine Obtained from Paired *t*-Test^a

Neurocognitive Test	Baseline		End		Raw Effect Size (Change From Baseline)		Standardized Effect Size		DF ^c	p Value ^c
	Mean	SD	Mean	SD	Mean	95% Confidence Interval	Cohen's d ^b	T-statistic ^c		
	Autobiographical Memory Interview-Short Form (AMI-SF)									
Total score	50.3	7.4	37.2	10.5	-13.1	-14.2, -11.9	-1.43	-22.10	158.7	<0.0001
California Verbal Learning Test – II (CVLT-II)										
Trial 1-5 total recall T-score	41.6	12.1	40.5	12.1	-1.1	-2.9, 0.6	-0.08	-1.28	155.0	0.20
Short delay free recall z-score	-0.9	1.2	-1.2	1.2	-0.3	-0.4, -0.1	-0.20	-3.17	146.9	0.002
Long delay free recall z-score	-1.1	1.6	-1.3	1.2	-0.2	-0.4, 0.0	-0.10	-1.58	143.3	0.12
Recognition discrimination z-score	-0.7	1.2	-1.1	1.4	-0.4	-0.6, -0.2	-0.22	-3.44	138.6	0.0008
Delis-Kaplan Executive Function System (D-KEFS)										
Letter fluency scaled score	8.6	4.4	7.1	3.6	-1.5	-2.0, -1.0	-0.39	-6.08	146.3	<0.0001
Dementia Rating Scale-2nd Edition (DRS-2)										
Initiation/perseveration index scaled score	7.8	3.3	7.3	3.5	-0.4	-0.9, 0.1	-0.11	-1.74	165.4	0.08
Stroop Color and Word Test (Stroop)										
Word T-score	33.7	12.3	30.8	10.9	-2.9	-4.4, -1.4	-0.24	-3.73	138.1	0.0003
Color T-score	29.5	12.3	30.3	11.6	0.7	-0.8, 2.3	0.06	0.92	142.3	0.36
Color-word T-score	39.5	10.6	38.2	10.5	-1.4	-2.8, -0.0	-0.12	-1.92	136.8	0.06
Trail making test										
Part A scaled score	8.1	2.7	7.1	3.0	-0.9	-1.4, -0.5	-0.27	-4.17	114.4	<0.0001
Part B scaled score	7.6	3.5	6.5	3.1	-1.1	-1.7, -0.5	-0.23	-3.63	80.1	0.0005

Notes: SD, standard deviation; DF, degrees for freedom.

^a Baseline, end, and change from baseline means and standard deviations (sd) for neurocognitive variables were obtained using a multiple imputation procedure with Markov Chain-Monte Carlo (MCMC) method and 100 imputations for missing data [SAS (v9.4) statistical software (SAS Proc MI and Proc MIAnalyze)]. Variables included in the imputation model were outcome status (remitter, nonremitters, dropout), age, baseline and last observed HRSD₂₄ total score, sex, education, baseline and last observed MMSE total raw score, and number of ECT sessions in Phase 1.

^b Cohen's d was calculated as the raw change from baseline divided by raw change from baseline standard deviation.

^c The t-statistic, degrees of freedom (df), and p value were for paired *t*-test incorporated into the multiple imputation procedure described in footnote a above.

Change in Neurocognitive Performance After Combined ECT and Venlafaxine

The percent of missing data for the analysis of change from baseline for the neurocognitive outcomes ranged from 27.1% to 50.8%, which is a limitation of the study. The frequency and percent of missing data for each of the variables and the comparison of demographic and baseline clinical and neurocognitive measures for completers (remitters and nonremitters) and noncompleters (dropouts) are presented in Tables S2 and S3 in the online supplemental data.

After an acute course of RUL-UB ECT combined with venlafaxine, most neurocognitive variable scores significantly decreased (Table 2). Specifically, performance significantly decreased on neuropsychological measures of simple visual scanning/psychomotor (paired *t*-test, $t = -4.17$, $df = 114.4$, $p < 0.0001$) and verbal processing speed (paired *t*-test, $t = -3.73$, $df = 138.1$, $p = 0.0003$), autobiographical memory consistency (paired *t*-test, $t = -22.1$, $df = 158.7$, $p < 0.0001$), short-term free recall (paired *t*-test, $t = -3.17$, $df = 146.9$, $p = 0.002$) and recognition (paired *t*-test, $t = -3.44$, $df = 138.6$, $p = 0.0008$) of learned words, phonemic fluency (paired *t*-test, $t = -6.08$, $df = 146.3$, $p < 0.0001$), and complex visual scanning and cognitive flexibility (paired *t*-test, $t = -3.63$, $df = 80.1$, $p = 0.0005$). However, in terms of qualitative changes (as based on the analyzed demographic-adjusted neurocognitive scores) from baseline to end, performance across most neurocognitive variables remained relatively stable as based on the effect sizes and ranged from intact/average to mildly impaired, reflecting little clinical effect on cognitive function. Verbal learning and delayed free recall of learned words, and initiation/perseveration ability showed no significant change from baseline to end of the acute course. The results were similar when analyses were repeated using the observed (nonimputed) data.

Electric Field Model

The spECTrum and Thymatron devices deliver rectangular pulses with pulse widths of 0.3 ms and 0.25 ms, respectively. Based on a first-order neuronal response model³¹ with a transmembrane time constant of 196 μs ,³² the estimated electric field threshold, E_{th} , for robust neural activation is 28.4 V m^{-1} for

0.3 ms pulse width and 30.2 V m^{-1} for 0.25 ms pulse width. The stimulation strength (E/E_{th}) is shown on the cortical surface (Fig. 1B) and the mid-coronal slice (Fig. 1C) for both the spECTrum and Thymatron devices. The Thymatron, relative to the spectrum, provides stronger stimulation by approximately 5% (Fig. 1D). For both devices, median E/E_{th} for the right hemisphere was approximately 1.7 times stronger than that in the left hemisphere. Of note, both stimulators deliver comparable electric fields strengths that exceed the threshold for neuronal depolarization by approximately fourfold for the right hemisphere, and by over twofold for the left hemisphere. As shown in Figure 1C, RUL ECT stimulates the right and left hemisphere at field strengths above threshold for neuronal depolarization. Both devices induced electric fields above the threshold for neuronal depolarization in the medial temporal lobe, with the field being greater on the right relative to the left side.

DISCUSSION

We found that the acute neurocognitive effects of RUL-Ultra-Brief ECT in an elderly sample were mild and less severe in magnitude than those typically reported with brief pulse RUL, bitemporal, or bifrontal (BF) ECT.³³ Some neurocognitive measures showed modest changes after ECT (e.g., delayed free recall of learned words, processing speed). For those measures that statistically significantly declined post ECT (autobiographical memory consistency, short-term free recall and recognition of learned words, phonemic fluency, processing speed, and visual scanning and cognitive flexibility), the degree of decline was clinically modest, with small relative differences from baseline as based on the effect sizes, and some measures fell into the mildly impaired range. It should also be noted that with the autobiographical memory consistency metric (AMI-SF), as opposed to the other neurocognitive measures, research has found that there is typically a decrease in consistency scores over a time period equivalent to an index ECT course even in non-ECT depressed subjects, so that a significant consistency decrease does not necessarily imply a neurocognitive impairment.^{34,35} Indeed, the AMI-SF has been critiqued due to its sensitivity to time,³⁶ which was substantiated in a recent study that found adult inpatients with severe depression treated

FIGURE 1. Electroconvulsive therapy electric field model.

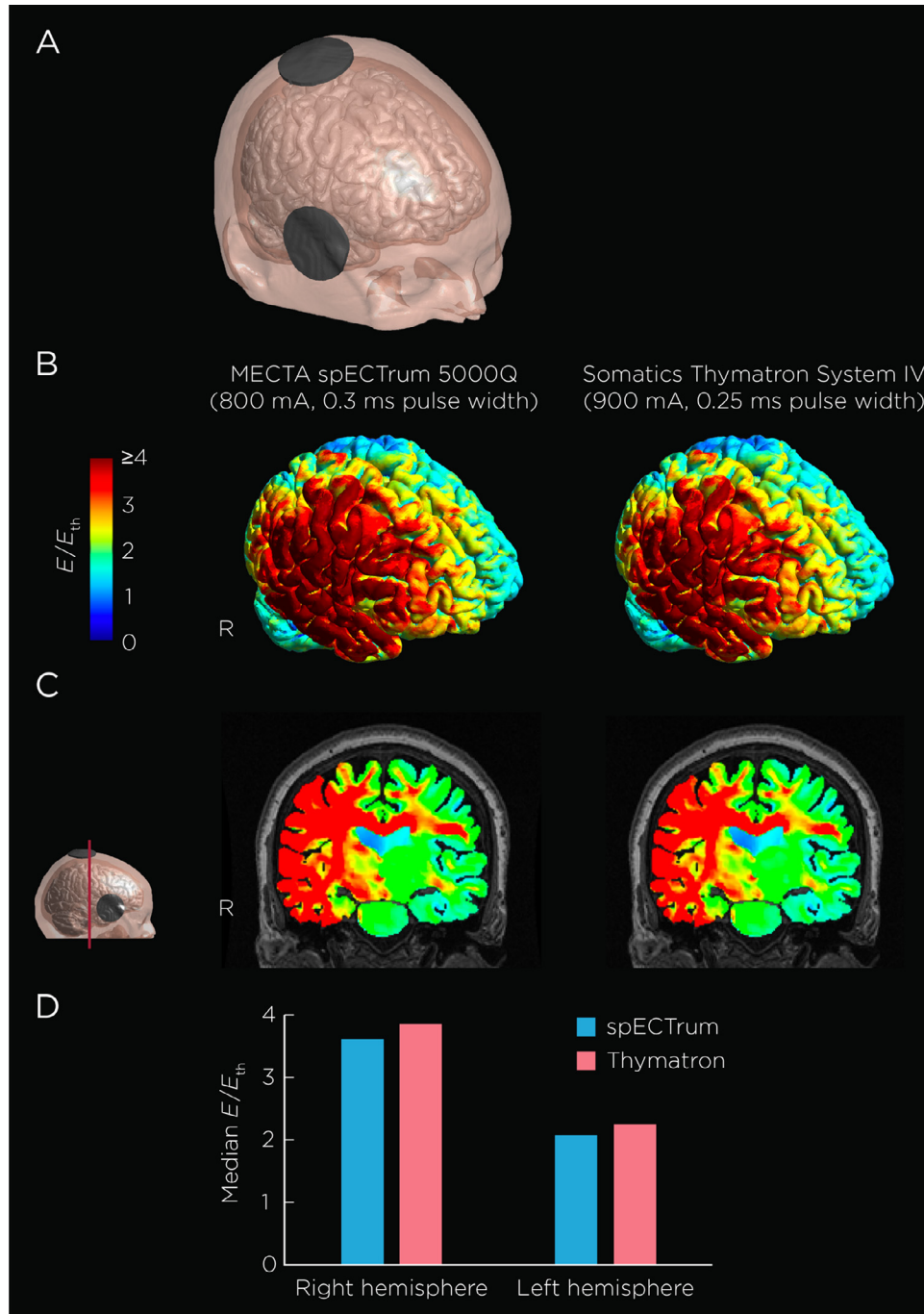


Figure 1 shows an anatomically realistic head model constructed from magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) data of one healthy, 62-year-old, male subject. (A) Head model showing the right unilateral ECT electrode placement. (B) Stimulation strength (electric field magnitude relative to neural activation threshold, E/E_{th}) on the cortical surface induced the MECTA spECTrum 5000Q and Somatics Thymatron System IV devices. (C) Coronal view of the field distribution. (D) Median E/E_{th} in the right and left hemispheres.

with or without ECT showed similar decreased autobiographical recall, which was explained by an effect of time.³⁷ Also, the decrease in autobiographical memory consistency as observed in this acute testing may be less during long-term follow-up as based on prior research.^{17,38} As there was no comparator group, the study was unable to clarify the independent effect of time and condition and their interaction on autobiographical memory consistency. In no case were mean post-ECT neurocognitive scores indicative of severe cognitive impairment (as based on a score that is two standard deviations below demographic-matched or population normative data³⁹), despite using a comprehensive neurocognitive battery sensitive to ECT-induced cognitive changes. We found weak and clinically nonsignificant associations between baseline depression severity and neurocognitive function, which extend prior findings in a mixed-age adult depressed cohort⁴⁰ into the elderly.

The finding that RUL-UB ECT, combined with venlafaxine, is tolerable in elderly patients with MDD is important because depression is a leading cause of disability, all cause morbidity, and suicide among the elderly. While ECT is highly effective in this age group in treating depression, preventing suicide, and improving quality of life,⁴¹ concerns regarding its neurocognitive side effects represent a barrier to its effective use, particularly among the elderly who are at increased risk of age-related cognitive decline and dementia. Making ECT more cognitively tolerable can minimize and remove barriers to its effective use in patients who could benefit from the treatment.

Some elderly patients may show no change or even possible improvement in global cognitive function following RUL-UB ECT, as the cognitive impairments associated within the baseline MDD episode resolve.^{42,43} However, the mechanism(s) of action underlying changes in neurocognitive function remains unclear and may be moderated by multiple variables including demographic (e.g., age, premorbid intellectual ability) and clinical (e.g., preexisting cognitive impairment) factors.¹³ There is mixed information whether preexisting cognitive impairment is a risk factor for greater ECT-associated cognitive adverse effects,⁴⁴ though there is consistent evidence that high intellectual functioning is a protective factor.⁴⁵ The study cohort had generally intact cognitive abilities and high premorbid intellectual ability at baseline, which could have helped to mitigate the

severity of ECT-induced adverse cognitive effects. If depressive relapse risk is increased by cognitive impairment (as has been hypothesized regarding autobiographical memory specificity),⁴⁶ then reducing cognitive side effects could benefit long-term outcomes.

Given that age increases seizure threshold, and that ECT was dosed at six times above seizure threshold, it was unknown whether these higher dosages needed to effectively treat elderly patients with RUL-UB ECT would show comparable levels of tolerability as seen with RUL-UB ECT in younger patients. It was therefore important to demonstrate that this form of ECT, when given at dosages adequate to ensure efficacy in the elderly, was also tolerable from a neurocognitive perspective. Of note, seizure thresholds with ultrabrief pulse ECT are substantially lower than those seen with brief pulse ECT, enhancing ability to effectively treat patients. In line with this observation, 85% of patients had a generalized tonic-clonic seizure on the first step of the seizure threshold titration protocol, indicating that the initial dose may have been higher than needed to induce a seizure. Despite this limitation, tolerability was excellent and suggests that even with high doses of RUL-UB ECT, adverse cognitive effects were mild.⁴¹

The study design did not allow one to discern the relative contributions of venlafaxine and RUL-UB ECT, or anesthetic agent to the neurocognitive outcomes. For example, the combination of RUL ECT and venlafaxine was found to possibly worsen ECT-associated cognitive adverse effects in other research.⁴⁷ However, that study was limited by study-site effects. A systematic review suggested that antidepressant agents, including venlafaxine, could have possible benefits in reducing cognitive difficulties in MDD.⁴⁸ However, there are mixed findings regarding the cognitive effects associated with pharmacotherapeutic agents such as venlafaxine as one large scale study (the International Study to Predict Optimized Treatment-Depression (iSPOT-D)) found no cognitive benefits,⁴⁹ but another large scale study found that duloxetine had positive global cognitive effects in elderly adults.⁵⁰ Regarding anesthesia regimens, some evidence across the adult lifespan has suggested that unique anesthetic agents may have differential effects on cognitive outcomes after ECT.^{51–53} Further research is warranted to clarify the cognitive effects of combined

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ECT and antidepressant medications, as well as specific anesthetic agents.

Unique strengths of this study in comparison with other research on the acute neurocognitive effects of ECT include the exclusive focus on the elderly, a study cohort with high years of education and estimated intellectual ability that is generalizable to other ECT study cohorts,⁵⁴ the use of RUL-UB ECT, the use of standardized neurocognitive measures with demographic-referenced scores, and the use of electric field simulation to demonstrate that the two different ECT devices used were similar in delivered dose. The narrower pulse width used by the Thymatron (0.25 ms, compared to 0.3 ms used by the spECTrum) is compensated by an increase in current pulse amplitude (900 mA, compared to 800 mA used by the spECTrum). The changes in neurocognitive function after RUL-UB ECT plus venlafaxine are consistent with a recent study of RUL-UB ECT in a young to mid-adult (i.e., 40.7 years) aged cohort (54) with demographic-adjusted neurocognitive data, and are relatively less severe than those reported with brief-pulse RUL and BF ECT in elderly adults^{33,55} with nondemographic-adjusted neurocognitive data. Interestingly, our study found that RUL-UB ECT plus venlafaxine had little effect on delayed verbal recall of information. While this finding is in contrast to prior evidence,⁹ it is consistent with other research studies that have employed a challenging verbal learning and memory measure in which the words are semantically encodable.⁵⁴

While RUL-UB ECT reduced the typical cognitive side effect burden seen with ECT, it did not completely eliminate it. Future work to improve ECT technique is warranted to further reduce and optimally eliminate such cognitive side effects. We showed in [Figure 1](#) that even with RUL-UB ECT, both ECT devices induced electric field strengths multiple-fold above the minimum threshold necessary to stimulate neurons. Recent work has begun to explore whether reducing the field strength by lowering ECT pulse amplitude, or via magnetic induction, could lower side effects while retaining efficacy.^{56,57} Low amplitude ECT⁵⁸ and magnetic seizure therapy (MST)⁵⁹ have yet to be systematically examined in the elderly.

Although the head model included in this work was from an ECT patient in the study, a single head model cannot account for interindividual variability

in the induced field distribution. A prior modeling study suggested that advanced age-related atrophy can significantly affect the induced electric field characteristics;⁶⁰ sex differences in head diameter, scalp and skull thicknesses can also contribute to variability. The electric field simulation presented here illustrated the general pattern of electric field distribution induced in the brain by RUL-UB ECT, and demonstrated that both ECT devices produced similar stimulation strength. Future studies should explore the relationships among the electric field distribution, clinical and functional outcomes, and underlying biological and neurophysiological markers,^{61–63} using patient specific head models from a larger sample.

In conclusion, using well-standardized neurocognitive measures, we demonstrated a high degree of tolerability and low degree of acute neurocognitive adverse effects in elderly adults with MDD. Our results support the tolerability and antidepressant efficacy of RUL-UB ECT in combination with venlafaxine in late-life depression.

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