RESEARCH ARTICLE

Alpha tACS Improves Cognition and Modulates Neurotransmission in Dementia with Lewy Bodies

Alberto Benussi, MD,[1,2] Valentina Cantoni, PhD,[3] Jasmine Rivolta, MSc,[3] Nicola Zoppi, MD,[2,4] Maria Sofia Cotelli, MD,[3,5] Marta Bianchi, MD,[5] Maria Cotelli, PhD,[6] and Barbara Borroni, MD[2,3*]

[1]*Neurology Unit, Department of Medical, Surgical, and Health Sciences, University of Trieste, Trieste, Italy*
[2]*Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*
[3]*Cognitive and Behavioural Neurology Unit, Department of Continuity of Care and Frailty, ASST Spedali Civili di Brescia, Brescia, Italy*
[4]*Department of Neurology, San Jacopo Hospital, Pistoia, Italy*
[5]*Neurology Unit, Valle Camonica Hospital, Brescia, Italy*
[6]*Neuropsychology Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*

ABSTRACT: Background: Dementia with Lewy bodies (DLB) is characterized by a marked shift of electroencephalographic (EEG) power and dominant rhythm, from the α toward the θ frequency range. Transcranial alternate current stimulation (tACS) is a non-invasive brain stimulation technique that allows entrainment of cerebral oscillations at desired frequencies.
Objectives: Our goal is to evaluate the effects of occipital α-tACS on cognitive functions and neurophysiological measures in patients with DLB.
Methods: We conducted a double-blind, randomized, sham-controlled, cross-over clinical trial in 14 participants with DLB. Participants were randomized to receive either α-tACS (60 minutes of 3 mA peak-to-peak stimulation at 12 Hz) or sham stimulation applied over the occipital cortex. Clinical evaluations were performed to assess visuospatial and executive functions, as well as verbal episodic memory. Neurophysiological assessments and EEG recordings were conducted at baseline and following both α-tACS and sham stimulations.
Results: Occipital α-tACS was safe and well-tolerated. We observed a significant enhancement in visuospatial abilities and executive functions, but no improvement in verbal episodic memory. We observed an increase in short latency afferent inhibition, a neurophysiological marker indirectly and partially dependent on cholinergic transmission, coinciding with an increase in α power and a decrease in Δ power following α-tACS stimulation, effects not seen with sham stimulation.
Conclusions: This study demonstrates that occipital α-tACS is safe and enhances visuospatial and executive functions in patients with DLB. Improvements in indirect markers of cholinergic transmission and EEG changes indicate significant neurophysiological engagement. These findings justify further exploration of α-tACS as a therapeutic option for DLB patients. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: α frequency; cholinergic transmission; dementia with Lewy bodies; EEG; transcranial alternate current stimulation

Dementia with Lewy bodies (DLB) is recognized as the second most common neurodegenerative dementia after Alzheimer's disease (AD), accounting for 10% to 15% of all cases.[1] Early and prominent degeneration in the basal forebrain contributes significantly to the deficit in cholinergic neurotransmission, which is believed

***Correspondence to:** Prof. B. Borroni, Department of Clinical and Experimental Sciences, P.le Spedali Civili 1, 25123, Brescia, Italy; E-mail: bborroni@inwind.it

Relevant conflicts of interest/financial disclosures: There were no conflicts of interest relevant to this study to declare.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding agencies: A.B. was partially supported by Fondazione Cariplo (grant no: 2021-1516), and by the Fondation pour la Recherche sur Alzheimer. M.C. has been supported by the Italian Ministry of Health (Ricerca Corrente).

Received: 5 May 2024; **Revised:** 8 July 2024; **Accepted:** 24 July 2024

Published online 13 August 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29969

to underpin many of the cognitive and neuropsychiatric symptoms of the disease.[2-4] Despite its prevalence and the significant impact on patients, current therapeutic options are largely symptomatic, focusing on cognitive, psychiatric, and motor symptoms, thereby underscoring the critical need for exploring novel, disease-modifying treatment modalities.

A distinguishing feature of DLB is its electroencephalographic (EEG) profile. Typically, the brain's electrical activity in healthy individuals shows a dominance of α frequency oscillations (8–12 Hz) during relaxed wakefulness, particularly in the occipital region. In contrast, patients with DLB exhibit a marked shift from α toward θ (4–7 Hz) and Δ (1–3 Hz) frequencies.[5-7] This alteration in EEG patterns correlates with the degree of cognitive impairment and is an established supportive biomarker for DLB.[8]

Brain oscillations play a crucial role in various cognitive processes, including attention, memory, and consciousness. The α rhythm, in particular, is associated with cognitive performance, and its disruption is linked to the cognitive deficits observed in DLB.[9-11] Hence, restoring or enhancing α oscillatory activity through neuronal entrainment presents as a compelling therapeutic intervention in DLB, potentially ameliorating some of its cognitive symptoms.

Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation technique that applies a sinusoidal alternating electric current through the scalp, which can entrain neuronal firing patterns to its desired frequency.[12] This technique offers the possibility to specifically target the α frequency range, potentially correcting the abnormal EEG profile seen in DLB.

The safety and efficacy of tACS in modulating brain oscillations and improving cognitive functions have already been demonstrated in various neurological conditions, such as AD.[13-15] However, its application in DLB is relatively unexplored. Given the distinct EEG alterations in DLB, and the significance of α oscillations in cognitive abilities, exploring the effects of α frequency tACS in the context of DLB presents a compelling avenue, potentially offering insights into novel therapeutic strategies for this condition.

To test this hypothesis, we conducted a pilot clinical trial using a double-blind, randomized, sham-controlled, cross-over design in patients with DLB.

Methods

Participants

Participants fulfilling current criteria for DLB[8] were recruited and at enrolment each patient underwent a standardized neuropsychological assessment, a routine blood analyses, magnetic resonance imaging (MRI) and [123I]FP-CIT SPECT (DAT-SPECT) or [^{18}F]Fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging, as previously reported.[2] Specifically, DAT-SPECT imaging was performed in participants where parkinsonism was unclear (n = 8), who resulted all positive. For patients with clear parkinsonism (n = 6), FDG-PET imaging was preferred, and in all cases, the results were suggestive of DLB. To assess disease severity, at baseline, the following measures were recorded: disease duration, the Unified Parkinson's Disease Rating Scale part-III (UPDRS-III) and the Hoehn and Yahr scale.

We applied the following exclusion criteria: (1) other causes of cognitive deficits other than DLB; (2) past history of head injury, abuse of alcoholic substances, transient ischemic attack or stroke, epilepsy, or medical disorders causing cognitive decline; and (3) having any cardiac device or past surgery to the brain.

All drugs taken by the patients, including cholinesterase inhibitors, were reported at baseline. Participants who were already on a stable pharmacologic regimen for at least 6 weeks before the intervention were allowed to continue it; however, the initiation of new medications after the start of the observation period was not permitted.

Full written informed consent was obtained from all participants according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Brescia Hospital, NP4758). The trial was registered at ClinicalTrials.gov (NCT05188105).

Study Design

Participants were randomized into two groups in a 1:1 ratio and each group received a single session of α-tACS targeting the occipital cortex or a single session of sham stimulation first and, after 1 week, stimulation was inverted (crossover phase) (Fig. 1). During the 60-minute tACS or sham sessions, patients were in a quiet room, awake, with an experimenter present to ensure that they did not fall asleep during the entire stimulation.

In each session, a set of tasks assessing visuospatial abilities, executive functions, and verbal episodic memory was administered twice, at baseline (pre-stimulation) and after tACS (post-stimulation). Moreover, a visual search task was carried out during the last 10 minutes of tACS stimulation (see section "Cognitive Assessment" below). In each session, transcranial magnetic stimulation (TMS) protocols assessing several neurotransmitter circuits ($GABA_A$, glutamate, acetylcholine) were tested at baseline and after every tACS session in all subjects (see section "Transcranial Magnetic Stimulation Assessment" below). High density EEG was recorded twice in each session, at baseline (pre-stimulation) and immediately after tACS (post-stimulation), before TMS assessment (see section "EEG Recordings" below).

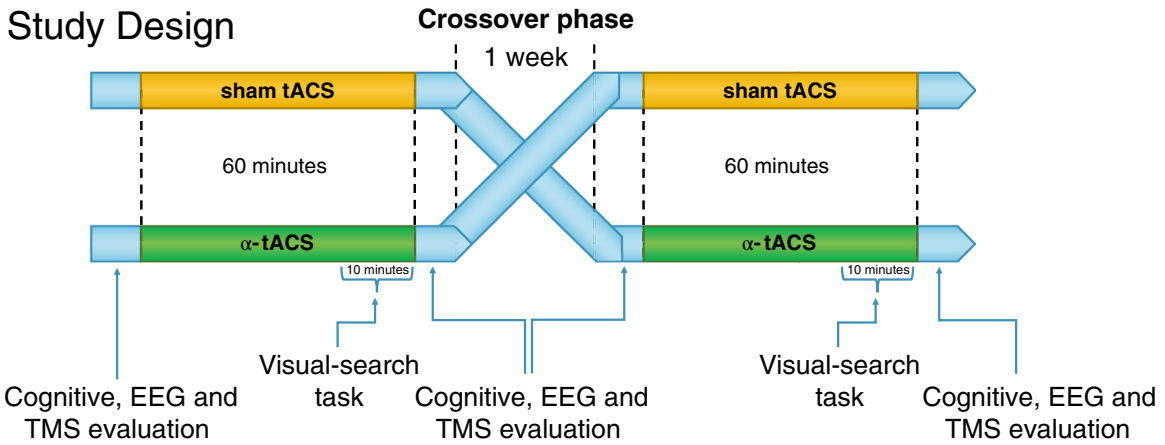

FIG. 1. Study design. tACS, transcranial alternating current stimulation; EEG, electroencephalography; TMS, transcranial magnetic stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

B.B. was responsible for random allocation sequences, enrolment of participants, and assignment of participants to specific interventions (programming tACS to real or sham stimulation). The participants and the examiners performing clinical ratings, EEG, and TMS protocols were blinded to the type of stimulation throughout the entire study period until the study concluded. The outcome assessor was also blinded to the type of intervention.

According to literature data, the effects of a single session of tACS are expected to last for 30 to 70 minutes.[16] Hence, participants were expected to return to their initial clinical status between the two stimulation sessions, which were separated by at least 1 week.

Cognitive Assessment

To assess visuospatial abilities, we used the Freedman version of the clock drawing test,[17] the qualitative scoring of the mini-mental state examination (MMSE) pentagon test,[18] and a computerized visual search task to assess both unique-feature and conjunction search, based on the principles outlined by Treisman and Gelade.[19] The task involved two types of visual searches: a unique-feature search with 64 trials requiring participants to find either the letter "S" or any letter in blue, and a conjunction search with 64 trials where the goal was to identify a green letter "T." The order of these blocks was randomized to control for order effects. Participants were instructed to respond to the presence or absence of these specific targets. The response protocol involved pressing the left mouse button as quickly as possible for target presence and the right mouse button for target absence, emphasizing rapid responses while maintaining accuracy. If participants did not respond quickly enough, the answer was considered missed, and they proceeded to the next trail. This task was performed during tACS/sham to assess the immediate effects of the stimulation on cognitive performance in real-time. This approach allowed us to capture dynamic changes induced by the stimulation that might not be evident in pre- and post-assessment setups.

Moreover, the trail making test part A (TMT-A) and B (TMT-B) were used to assess attention and executive functions,[20] whereas verbal episodic memory was assessed with the immediate and delayed recall scores at the Rey auditory verbal learning (RAVL) test[21] (see Supporting Data for further details).

Transcranial Magnetic Stimulation Assessment

A TMS figure-of-eight coil was used to assess short interval intracortical inhibition (SICI) (an indirect marker of $GABA_A$ergic transmission), intracortical facilitation (ICF) (an indirect marker of glutamatergic transmission), and short latency afferent inhibition (SAI) (an indirect marker partially dependent on cholinergic transmission), using a paired-pulse technique, using a conditioning-test design[22] (see Supporting Data for further details).

EEG Recordings and Analysis

EEG data were recorded using an actiCAP slim 64-channel active electrode system connected to an actiCHamp Plus 64 System amplifier (Brain Products, Gilching, Germany). Data were pre-processed in MATLAB (R2024a; The MathWorks, Natick, MA) using the EEGLAB toolbox[23] and custom scripts. Spectral power analyses were performed on the pre-processed EEG data across four frequency bands: Δ (1–4 Hz), θ (4–8 Hz), α (8–12 Hz), and β (12–30 Hz) (see Supporting Data for further details).

α-tACS

A single session of tACS was delivered by a battery-driven current stimulator (BrainStim, EMS, Italy) through a pair of saline-soaked (0.9% NaCl) surface

sponge electrodes (5.5 × 6 cm). One electrode was placed on the scalp over the occipital cortex (with the center over Oz position according to the 10–20 international EEG coordinates) and the other over the right deltoid muscle area. The electrodes were secured using elastic gauzes, and the electroconductive gel was applied to electrodes to reduce contact impedance (<5 kΩ for all sessions). During single session α-tACS stimulation, an alternating sinusoidal current of 1.5 mA peak-to-baseline (3.0 mA peak-to-peak, current density: 0.09 mA/cm^2) at a frequency of 12 Hz was applied for 60 minutes. For the sham condition, the electrode placement was the same, but the electric current was ramped down 60 seconds after the beginning of the stimulation to make this condition indistinguishable from the experimental stimulation. To detect differences in the perception of the stimulation, participants were asked whether they thought they received α-tACS or sham stimulation at the end of each session, and if they perceived tingling cutaneous sensations or phosphenes/light flickering. Sensations were rated on a scale from 0 to 4, with 0 = no sensations reported, 1 = mild, 2 = moderate, 3 = strong, and 4 = very strong sensations reported.

Outcome Measures

The primary endpoints were a priori defined as the difference in visual search task test scores between α-tACS and sham stimulation. Visual search tasks were chosen as the primary outcome measure because of their sensitivity in assessing visuospatial and attentional processes, which are prominently affected in DLB, and their ability to provide objective, numerical values. Additionally, given the single-session design, a sensitive measure was required to capture the immediate effects of the intervention.

The secondary endpoints were defined as: (1) changes from baseline in the RAVL test scores; (2) changes from baseline in the TMT-A and TMT-B test scores; (3) changes from baseline in the Freedman version of the clock drawing test and qualitative scoring of the MMSE pentagon test; (4) changes from baseline in the relative α power in occipital EEG electrodes; and (5) changes from baseline in SICI (an indirect maker of $GABA_A$ergic transmission), ICF (an indirect maker of glutamatergic transmission) and SAI (an indirect maker of cholinergic transmission), evaluated with TMS. Although SAI is often considered an indirect marker of cholinergic transmission, it is important to note that this relationship is not unequivocal and is subject to ongoing research and debate.[24]

Statistical Analyses

A power analysis was conducted to determine the required sample size, drawing from prior research on tACS in various neurodegenerative disorders.[13,14,25-28] Considering the involvement of distinct populations and the exploratory nature of the study, we extrapolated an estimated a partial η^2 of 0.16, corresponding to an effect size (f) of 0.436, from the referenced studies. Using a one-way repeated measures analysis of covariance (ANCOVA), at an α level of 0.05 and power (1-β) of 0.8 for the primary endpoint, we determined a total sample size of 14.

Cohen's κ was used to assess agreement between perceived sensations and the types of stimulation received. Additionally, the Wilcoxon signed-rank test was used to compare perceptions of cutaneous sensations during α-tACS versus sham stimulation.

To evaluate the impact of α-tACS treatment exposure on clinical scores and neurophysiological measures over time, either a one-way or two-way repeated measures ANCOVA was used. This included TIME (baseline and post-treatment) and TREATMENT (α-tACS vs. sham stimulation) as within-subject factors, with the order of tACS administration (α-tACS–sham or sham–α-tACS) as a covariate. Post hoc tests were conducted following a false discovery rate (FDR) correction for multiple comparisons.

For EEG analyses, paired *t*-tests were conducted to compare pre- and post-intervention conditions in both α-tACS and sham scenarios. *T*-statistics and *P*-values, post-FDR correction, were computed for each frequency band to identify statistically significant changes. Topographic maps were generated to illustrate *t*-statistics for each band, with significant differences indicated.

As exploratory analysis, Spearman rank-order correlations were used to assess associations between the change in cognitive scores, SAI and the modulation of EEG frequencies, pre-α-tACS and post-α-tACS.

A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 29 (SPSS, Chicago, IL).

Results

Participants

Fifteen participants were initially screened, with one participant not meeting the inclusion criteria. Fourteen participants were enrolled and randomized to receive α-tACS or sham stimulation first in a 1:1 ratio (see Table 1 for demographic and clinical characteristics of enrolled participants). Briefly, participants had an average disease duration of 4.3 ± 2.3 years from symptom onset, with moderate disease severity (Hoehn and Yahr scale: 2.4 ± 0.9, range: 1–4; UPDRS-III: 32.6 ± 13.6, range: 14–56). Six participants were on cholinesterase inhibitors.

All participants completed the study and were included in the final analysis. No tACS-related side

TABLE 1 *Demographic and clinical characteristics of included participants*

Variable	DLB (n = 14)
Age, y	73.1 ± 5.9
Gender, female	50%
Duration of symptoms, y	4.3 ± 2.3
Education, y	9.1 ± 4.0
Unified Parkinson's Disease Rating Scale part-III (range)	32.6 ± 13.6 (14–56)
Hoehn and Yahr scale (range)	2.4 ± 0.9 (1–4)
Acetylcholinesterase inhibitor yes/no	6/8
Mini-mental state examination	23.6 ± 3.3
Basic Activities of Daily Living, lost	1.2 ± 1.5
Instrumental Activities of Daily Living, lost	3.2 ± 2.0
Neuropsychiatric inventory	15.8 ± 8.7

Note: Results are express as mean ± standard deviation, unless otherwise specified.

effects were observed, and tACS was well tolerated by all participants. Regarding the differences in the participants' perception of the stimulation, there was no statistically significant association between the type of stimulation, as assessed by Cohen's κ (κ = 0.071, $P = 0.699$). Moreover, tingling cutaneous sensations were equally perceived in both α-tACS and sham conditions ($z = -1.144$, $P = 0.253$, according to the Wilcoxon signed-rank test), and none of the participants reported phosphenes or light flickering, suggesting that exposure to α-tACS could not be distinguished from sham stimulation.

Individual data for each participant, for each outcome measure and for each condition are reported in the Supplementary Figures in Data S1.

Effects on Visuospatial Abilities

Results for the computerized visual search task for unique-feature and conjunction search tasks are reported in Table 2. We observed a significant difference in the correct number of responses for the unique-feature search task between α-tACS and sham stimulation, $F^{1,12} = 18.74$, $P < 0.001$, partial $\eta^2 = 0.59$, with a mean difference of 3.2 (95% CI: 1.6–4.8) (Fig. 2A), and for the conjunction feature search task, $F^{1,12} = 36.37$, $P < 0.001$, partial $\eta^2 = 0.74$, with a mean difference of 8.9 (95% CI: 5.7–12.1) (Fig. 2B), indicating higher scores during α-tACS stimulation.

In the Freedman version of the clock drawing test, we observed a statistically significant TIME × TREATMENT interaction, $F^{1,12} = 16.24$, $P = 0.001$, partial $\eta^2 = 0.56$, with a significant mean difference of 1.8 points (95% CI: 0.7–3.1) between α-tACS and sham stimulation, post-stimulation ($P = 0.004$) (see Table 2 and Fig. 2C).

In the qualitative scoring of the MMSE pentagon test, a statistically significant TIME × TREATMENT interaction was observed, $F^{1,12} = 16.89$, $P = 0.001$, partial $\eta^2 = 0.57$, with a significant mean difference of 1.7

TABLE 2 *Difference in cognitive assessment scores and TMS measures pre- and post-stimulation and between α-tACS and sham stimulation*

Variable	Pre-sham vs. post-sham stimulation	Pre–α-tACS vs. post–α-tACS	Post–α-tACS vs. post-sham stimulation
Visual search task★			
Unique-feature search	–	–	3.2 (1.6 to 4.8)†
Conjunction search	–	–	8.9 (5.7 to 12.1)†
Freedman clock drawing	0.6 (−0.1 to 1.3)	2.5 (1.4 to 3.7)†	1.8 (0.7 to 3.1)†
MMSE pentagon test	0.5 (−0.1 to 1.0)	2.3 (1.2 to 3.3)†	1.7 (0.8 to 2.6)†
TMT-A	−13.3 (−33.2 to 6.6)	−10.9 (−35.6 to 13.7)	2.4 (−22.7 to 27.4)
TMT-B	−1.9 (−4.8 to 0.9)	−41.0 (−70.5 to −11.5)†	−39.1 (−68.5 to −9.6)†
RAVL immediate	1.9 (0.2 to 3.5)†	4.5 (1.6 to 7.3)†	2.6 (−0.8 to 6.1)
RAVL delayed	−0.1 (−0.2 to 0.1)	0.1 (−1.2 to 1.5)	0.1 (−1.2 to 1.5)
Mean SICI (1, 2, 3 ms)	−0.05 (−0.03 to 0.13)	−0.01 (−0.09 to 0.09)	−0.05 (−0.15 to 0.04)
Mean ICF (7, 10, 15 ms)	0.07 (−0.04 to 0.17)	0.05 (−0.06 to 0.15)	−0.02 (−0.13 to 0.09)
Mean SAI (0, 4 ms)	−0.05 (−0.15 to 0.06)	−0.41 (−0.51 to −0.31)†	−0.37 (−0.51 to −0.22)†

Note: Data are reported as difference (95% CI).
Abbreviations: TMS: transcranial magnetic stimulation; tACS, transcranial alternating current stimulation; MMSE, mini-mental state examination; TMT-A, trail making test part A; TMT-B, trail making test part B; RAVL, Rey auditory verbal learning test; SICI, short interval intracortical inhibition; ICF, intracortical facilitation; SAI, short latency afferent inhibition.
★For the visual search task, results are reported during stimulation, so pre and post α-tACS and sham stimulation differences are not reported.
†Significant difference at post-hoc FDR corrected tests.

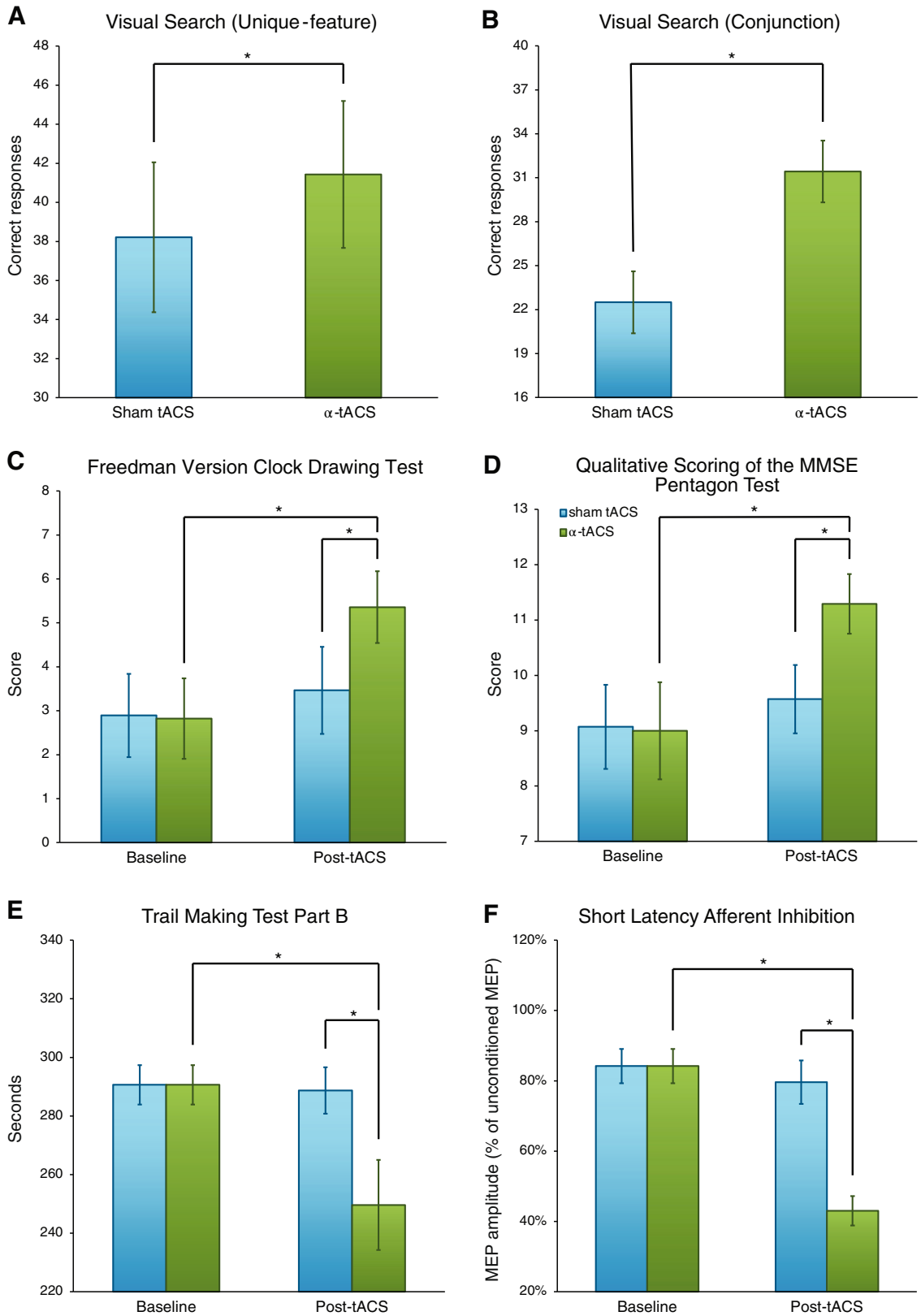

FIG. 2. Neuropsychological scores and neurophysiological measures pre-α-tACS and post−α-tACS or sham stimulation. (**A**) Visual unique-feature search task; (**B**) visual conjunction search task; (**C**) Freedman version of the clock drawing test; (**D**) qualitative scoring of the MMSE pentagon test; (**E**) Trail making test part B; (**F**) Short latency afferent inhibition. tACS, transcranial alternating current stimulation; MMSE, mini-mental state examination; for short latency afferent inhibition, % represents the MEP amplitude compared to the unconditioned MEP. *Significant difference after false discovery rate correction for multiple comparisons. [Color figure can be viewed at wileyonlinelibrary.com]

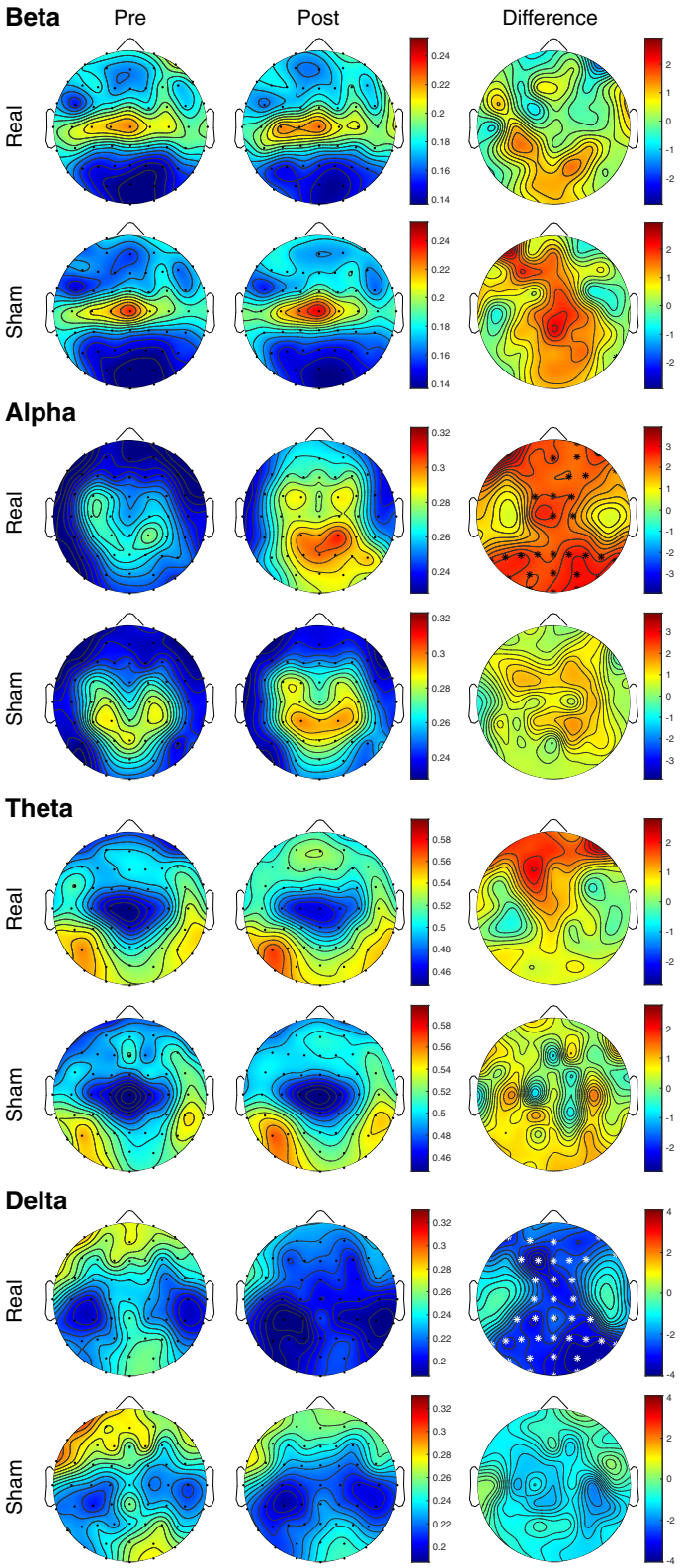

FIG. 3. Electroencephalography frequency analysis pre–α-transcranial alternating current stimulation (tACS) and post−α-tACS or sham stimulation. Frequency bands: θ (3–6 Hz), α (6–12 Hz), β (12–20 Hz), and γ (20–40 Hz). Relative power maps pre−α-tACS and post−α-tACS and sham stimulation, with t-maps showing differences between pre- and post-stimulation, for the following frequency bands: β (12–30 Hz), α (8–12 Hz), θ (4–8 Hz), and Δ (1–4 Hz). Blue areas indicate a power decrease, red areas a power increase. *Significant difference after false discovery rate correction for multiple comparisons. [Color figure can be viewed at wileyonlinelibrary.com]

points (95% CI: 0.8–2.6) between α-tACS and sham stimulation, post-stimulation ($P = 0.001$) (see Table 2 and Fig. 2D).

Effects on Executive Functions and Verbal Episodic Memory

For the TMT-A, we did not observe any significant TIME × TREATMENT interaction, $F^{1,12} = 0.04$, $P = 0.842$, partial $\eta^2 = 0.01$. However, in the TMT-B, we observed a significant TIME × TREATMENT interaction, $F^{1,12} = 8.22$, $P = 0.013$, partial $\eta^2 = 0.39$, with a significant mean difference of −39.1 seconds (95% CI: −68.5 to −9.6) between α-tACS and sham stimulation, post-stimulation ($P = 0.013$).

For verbal episodic memory tasks, we did not observe significant TIME × TREATMENT interactions for the RAVL immediate recall ($F^{1,12} = 24.45$, $P = 0.124$, partial $\eta^2 = 0.17$) and delayed recall scores ($F^{1,12} = 0.05$, $P = 0.824$, partial $\eta^2 = 0.01$) (see Table 2 and Fig. 2).

Effect on Neurotransmitter Deficits

Thirteen participants underwent an indirect assessment of several intracortical circuits, including SICI (an indirect maker of $GABA_A$ergic transmission), ICF (an indirect maker of glutamatergic transmission) and SAI (an indirect maker of cholinergic transmission). We observed a significant TIME × TREATMENT interaction for SAI, $F^{1,11} = 28.96$, $P < 0.001$, partial $\eta^2 = 0.71$, with a significant mean difference of −0.18 (95% CI: −0.26 to −0.11) between α-tACS and sham stimulation, post-stimulation ($P < 0.001$) (see Table 2 and Fig. 2).

In contrast, we did not observe significant TIME × TREATMENT interactions for mean SICI ($F^{1,11} = 1.69$, $P = 0.218$, partial $\eta^2 = 0.12$) or ICF ($F^{1,11} = 0.15$, $P = 0.707$, partial $\eta^2 = 0.01$).

Furthermore, restoration of SAI (ie, the difference between post−α-tACS and pre−α-tACS) directly correlated with improvement in the visual search task after α-tACS (ie, the difference between the score during α-tACS and during sham stimulation) for the conjunction search ($r = 0.65$, $P = 0.017$), but not for the unique-feature search task ($r = -0.35$, $P = 0.237$).

EEG Analysis

Compared with pre-stimulation, immediately after α-tACS we observed a significant increase in relative α power (8–12 Hz) and a significant decrease in Δ power (1–4 Hz) in the frontal, parietal, and occipital electrodes (all $P < 0.05$) (see Fig. 3 and Supplementary Table in Data S1). We did not observe significant modulation in any frequency ranges when comparing pre- to post-sham stimulation. To determine if the effects of tACS reduced over time, the 10-minute EEG recording was divided into two 5-minute blocks and analyzed separately. The analysis showed no significant differences between the two blocks, indicating that the effects of tACS were stable throughout the recording period.

We observed a significant positive correlation between the increase in global β and a decrease in global Δ frequencies from pre−α-tACS to post-α-tACS and the difference in the visual conjunction search task performance between α-tACS and sham stimulation (β $r_s = 0.740$, $P = 0.006$; Δ $r_s = {}^{-}0.828$, $P < 0.001$), but not for other frequencies or the unique-feature search task. Furthermore, the increase in SAI from pre−α-tACS to post-α-tACS, correlated with an increase in global β power ($r_s = 0.657$, $P = 0.020$) and with a decrease in global Δ power ($r_s = -0.734$, $P = 0.007$).

Discussion

In DLB, characteristic EEG alterations include a reduction in α frequencies (8–12 Hz) and an increase in slower Δ (1–3 Hz) and θ (4–7 Hz) frequencies, particularly over the posterior regions, including occipital and parietal lobes. These changes are significant as α rhythms are associated with cognitive alertness and are notably diminished in DLB, reflecting attention deficits and cognitive dysfunction.[6,29,30] Elevated Δ and θ rhythms indicate disorganized and slower cortical activity, correlating with the severity of cognitive impairment and a decline in mental processing.[7,31]

These observations defined the objective of the present pilot study, aimed at entraining brain oscillations at α frequencies over the occipital cortex in patients with DLB. tACS is a novel non-invasive brain stimulation technique that applies a low-intensity sinusoidal electrical current at specific frequencies to the brain through electrodes on the scalp,[12,32] able to influence neuronal firing patterns and interacts with ongoing neuronal activity, leading to the entrainment or synchronization of brain network oscillations.[33] In DLB, tACS can be tuned to specifically target and enhance α band activity, potentially restoring physiological brain rhythms, improving cognitive abilities, and reducing symptoms of cognitive decline.

In this randomized, double-blind, placebo-controlled, crossover study, we observed that α-tACS over the occipital cortex enhances visuospatial abilities in DLB patients. These improvements are supported by neurobiological effects on indirect markers of cholinergic transmission and EEG frequency modulation, specifically an increase in α and a reduction in Δ frequencies post α-tACS, particularly marked in occipital and parietal lobes, which are the areas most affected in DLB. This study highlights the potential of directly modifying the disrupted EEG profiles in DLB by enhancing α

oscillatory activity, which is traditionally diminished in these patients.

The observed enhancements in visuospatial function, particularly noted in the performance of the conjunction visual search task compared with the unique-feature visual search task following α-tACS administration, suggest a distinctive influence of induced brain oscillatory patterns on complex cognitive processing.[34,35] Although both tasks involve visual search, the conjunction task requires integrating multiple visual features (eg, color and shape), placing a higher cognitive demand compared to the unique-feature task, which involves searching for a single distinctive feature.[36] The cholinergic system plays a crucial role in attentional processes essential for complex tasks. Interestingly, improvements in conjunction tasks were more pronounced and correlated with indirect markers of cholinergic transmission (SAI). In contrast, unique-feature tasks are less demanding and may not require the same level of cholinergic modulation. This differential impact underscores the role of cholinergic transmission in complex cognitive processes.[37,38]

The interplay between cholinergic activity and EEG rhythms observed in this study may suggest a bidirectional influence where not only does the cholinergic system modulate EEG rhythms, influencing cognitive functions, but also the modulation of brain rhythms might enhance cholinergic activity. In DLB, the deterioration of the cholinergic system is well-documented, leading to altered EEG patterns that reflect the brain's compromised information processing capabilities.[39,40] Although enhancing cholinergic transmission through acetylcholinesterase inhibitors has been shown to improve EEG rhythm normalization and cognitive function,[41,42] our findings with α-tACS suggest a reciprocal relationship. By specifically targeting and entraining brain oscillations, particularly through the normalization of α and β frequencies and the reduction of Δ frequencies, α-tACS might indirectly stimulate cholinergic pathways. This hypothesis is supported by findings from our study, which show an association between increased β and decreased Δ frequencies, and increased SAI activity, which is indirectly and partially dependent on cholinergic circuits.

Despite the notable improvements in visuospatial abilities and executive functions, our study observed null effects of α-tACS on verbal episodic memory and no significant changes in measures of ICF and SICI. This specificity in the effects of α-tACS suggests that the stimulation parameters used, primarily targeting the occipital cortex, are more effective in modulating brain networks involved in visuospatial processing and attention rather than those engaged in memory or the balance of cortical excitability.[43]

In our study, no participants reported experiencing phosphenes or light flickering during occipital α-tACS stimulation. Although these phenomena are usually retinal in origin,[44,45] our electrode montage with an extracephalic electrode, along with specific parameters of the α-tACS protocol, likely minimized these occurrences.

We acknowledge that our study entails some limitations. Our study was powered for our primary endpoint, and the sample size was determined to be appropriate for a pilot study; however, a larger sample size might allow us to account for individual differences that could influence the efficacy of the treatment and will be essential to evaluate the real-life impact of this intervention, particularly on more relevant clinical rating scales. Moreover, the lack of control conditions applying tACS over different cortical areas should also be addressed in future studies.

Although these preliminary findings are promising, several questions remain unanswered. The mechanisms underlying the observed changes in EEG and neurotransmitter function, the duration of the cognitive improvements post-stimulation, and the potential cumulative effects of repeated α-tACS sessions, perhaps in home-based settings,[46] are areas that require further exploration. Although our study was primarily designed to assess target engagement rather than clinical relevance, the observed improvements in visuospatial abilities, executive functions, and cholinergic transmission are promising. Many of these measures correlate with daily living functioning, suggesting that even modest improvements could have meaningful impacts on patients' quality of life.

In summary, our study suggests that α-tACS is a promising approach for enhancing cognitive function and modulating neurophysiological deficits in DLB. These findings contribute to the growing body of literature supporting the use of non-invasive brain stimulation techniques in neurodegenerative diseases and pave the way for further studies that could ultimately lead to the development of more effective, targeted, and non-pharmacological interventions for managing DLB. ■

Acknowledgments: A.B. was partially supported by Fondazione Cariplo (grant no. 2021–1516), and by the Fondation pour la Recherche sur Alzheimer. M.C. has been supported by the Italian Ministry of Health (Ricerca Corrente). We thank all patients for their participation in this research. Open access publishing facilitated by Universita degli Studi di Brescia, as part of the Wiley - CRUI-CARE agreement.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.