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ORIGINAL ARTICLE

Temporal gamma tACS and auditory stimulation affect verbal memory in healthy adults

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Abstract

Research suggests a potential of gamma oscillation entrainment for enhancing memory in Alzheimer's disease and healthy subjects. Gamma entrainment can be accomplished with oscillatory electrical, but also sensory stimulation. However, comparative studies between sensory stimulation and transcranial alternating current stimulation (tACS) effects on memory processes are lacking. This study examined the effects of rhythmic gamma auditory stimulation (rAS) and temporal gamma-tACS on verbal long-term memory (LTM) and working memory (WM) in 74 healthy individuals. Participants were assigned to two groups according to the stimulation techniques (rAS or tACS). Memory was assessed in three experimental blocks, in which each participant was administered with control, 40, and 60 Hz stimulation in counterbalanced order. All interventions were well-tolerated, and participants reported mostly comparable side effects between real stimulation (40 and 60 Hz) and the control condition. LTM immediate and delayed recall remained unaffected by stimulations, while immediate recall intrusions decreased during 60 Hz stimulation. Notably, 40 Hz interventions improved WM compared to control stimulations. These results highlight the potential of 60 and 40 Hz temporal cortex stimulation for reducing immediate LTM recall intrusions and improving WM performance, respectively, probably due to the entrainment of specific gamma oscillations in the auditory cortex. The results also shed light on the comparative effects of these neuromodulation tools on memory functions, and their potential applications for cognitive enhancement and in clinical trials.

KEYWORDS
cognition, gamma oscillations, GENUS, non-invasive brain stimulation, verbal memory

1 | INTRODUCTION

Brain oscillations are rhythmic fluctuations of electrical brain activity arising from the coordinated firing of large populations of neurons (Uhlhaas & Singer, 2012). These oscillations can be observed and measured using electroencephalography (EEG) and classified based on their frequency as delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (>30 Hz) oscillations. Gamma oscillations (γ) have emerged as a correlate of high-level cognitive processes, including cognitive control, information encoding, storage, and retrieval (e.g., Herman et al., 2004). Particularly, early studies have suggested that γ activity plays an important role in attention, working memory, and long-term memory (Jensen et al., 2007). Working Memory (WM) describes a system capable of manipulating the temporary storage of stimulus representations, while long-term memory (LTM) refers to the long-term storage process starting with stimuli processing (i.e., encoding) followed by consolidation and retrieval (James, 1890). Several brain regions contribute to dissociable memory processes. The temporal lobe, comprising the auditory cortex and the medial temporal lobe (MTL; a network of interconnected structures) plays a pivotal role in learning and memory processes involving verbal materials (Dimakopoulos et al., 2022; Squire et al., 2015).

Animal models showed a contribution of the γ frequency band to long-term potentiation (LTP), a crucial neurobiological marker of learning and memory formation (Muller et al., 2002). Cross-regional γ synchronization may communicate sensory information to the hippocampus during memory formation, and hippocampal representations to the cortex during retrieval (Griffiths & Jensen, 2023). More recent studies suggest that γ may coordinate pre- and post-synaptic neuronal firing to enhance plasticity (long-term potentiation) within the hippocampus (Igarashi, 2015). Moreover, phase coupling of theta oscillations (θ) with γ also seems to play an important role in hippocampus-based memory processes (Lisman & Jensen, 2013). This hypothesis is confirmed by studies in Alzheimer's Disease (AD), where early cognitive symptoms involve memory impairments due to neurodegenerative processes affecting mainly the MTL and the prefrontal cortex. In AD patients, γ alterations within the temporal-prefrontal pathway correlate with learning and memory impairments (Goodman et al., 2018; Güntekin et al., 2023).

These preliminary findings have led researchers to investigate the mechanisms by which gamma oscillations modulate memory processes in patients with neurodegenerative diseases. In this field, there is a growing interest in investigating the effect of γ entrainment on memory performance. Entrainment is defined as "synchronization to a rhythmic stream (or train) of external events" (Thut et al., 2011, page 1). Hence, the entrainment of γ and the investigation of its behavioral effects allow to infer causal associations between γ and memory processes (Bergmann & Hartwigsen, 2021; Gonzalez-Perez et al., 2019; Polanía et al., 2018). To date, two approaches have been demonstrated to be effective in modulating endogenous oscillations and related behavior in a safe and non-invasive manner: rhythmic (multi)sensory stimulation and transcranial alternating current stimulation (tACS). tACS involves delivering a weak sinusoidal electrical current to the cortex using two or more electrodes placed on the scalp (Antal & Herrmann, 2016), while rhythmic sensory stimulation entails exposing individuals to specific frequencies or rhythms of visual (i.e., flickering light), auditory (i.e., tones), tactile (i.e., vibrations), or combined multisensory stimuli (Chan et al., 2022). These neuromodulation techniques can be administered either *online* (during cognitive assessment) or *offline* (between cognitive assessments), and it is possible to test the effect of a single session or the cumulative effect of several stimulation sessions.

Within this framework, a growing interest has been raised regarding the effectiveness of γ frequency stimulation, including γ-tACS, and γ-sensory stimulation for improving memory processes (Etter et al., 2019; Nissim et al., 2023). The pioneering study by Iaccarino et al. (2016), showed that 40 Hz optogenetic stimulation of PV interneurons in mice models of AD reduced amyloid (Aβ) peptide and tau protein levels (e.g., the main markers of AD neuropathology) in the brains of multiple mouse AD models, likely by decreasing their production and increasing removal by microglia cells. Such findings have been successfully replicated by several researchers and translated to human patients using light flickering and/or auditory tones at 40 Hz (also known as gamma entrainment using sensory stimuli, GENUS) or using 40 Hz-tACS. While exploration of the impact of the GENUS protocol is still in its preliminary stages (Manippa et al., 2022), more consistent findings are available regarding 40 Hz-tACS (Manippa et al., 2023). On the other hand, the number of studies demonstrating the impact of gamma stimulation on memory processes of healthy individuals is scarce; one study (Manippa et al., 2024) showed that 60 Hz (but not 40 Hz) rhythmic auditory stimulation (rAS) resulted in a significant decrease in intrusive errors during word list learning compared to the control condition (no auditory stimulation), whereas two studies demonstrated an effect of dorsolateral prefrontal cortex (DLPFC) 60 Hz-tACS on declarative LTM (Javadi et al., 2017; Nomura et al., 2019). Javadi et al. (2017) suggested that LTM enhancement, rather than being determined by a specific frequency of stimulation, occurs when the frequency of stimulation used during both encoding and retrieval phases matches

(e.g., 60–60 or 90–90 Hz, as opposed to 60–90 or 90–60 Hz in the respective study).

To sum up, while research highlights the potential of 40 Hz stimulation for memory improvement in AD, uncertainties persist regarding its mechanisms and general effectiveness. Furthermore, there needs to be more definitive information if gamma sensory stimulation benefits cognitive processes in healthy individuals. Understanding the impact of specific intervention parameters—such as the type and intensity of sensory stimulation—and the targeted brain regions for techniques like tACS is essential. Comparative studies between sensory stimulation and tACS regarding their cognitive and behavioral effects are still largely missing. This study aims to address some of these gaps by exploring the effects of temporal cortex stimulation via a single session online γ-rAS and γ-tACS on memory processes of healthy individuals. Specifically, we aimed to explore two stimulation frequencies: 40 Hz, commonly used in clinical samples, and 60 Hz, frequently utilized in studies involving healthy participants.

2 | MATERIALS AND METHODS

2.1 | Participants

We recruited 80 healthy volunteers with normal or corrected-to-normal vision, devoid of any history of psychiatric or neurological disorders. The participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), the Beck Depression Inventory (BDI) (Beck et al., 1996), and the State-Trait Anxiety Inventory (STAI) forms Y1 and Y2 (Skapinakis, 2014). Six subjects were excluded due to self-reported relevant depressive (BDI > 30) or anxiety (STAI > 60) symptoms.

The final sample consisted of 74 participants (55 females; 6 left-handed, $M_{age} = 22.75$, $SD_{age} = 3.56$). Thirty-eight participants were pseudo-randomly assigned to the rAS group, and the remaining 36 to the tACS group. Groups were matched for sex, handedness, BDI, and STAI scores (see Table 1). The study adhered to the ethical standards of the World Medical Association Declaration of Helsinki, and the study protocol received approval from the Ethics Committee of the University of Bari Aldo Moro (protocol number: ET-19-01). All participants provided written informed consent.

2.2 | Memory assessment

LTM was assessed through the Ray Auditory-Verbal Learning Test (RAVLT), which involves presenting a list of 15 nouns over five successive trials. The participant hears the list and is immediately prompted to recall as many words as possible. This process is repeated for five consecutive trials (i.e., immediate recall trials). Following the conduction of another task or a fixed delay, the participant is then asked to recall the words from the list (delayed recall trial). For each trial, we calculated the following scores: (i) Immediate Recall score (IR1 to IR5), the number of correctly recalled words provided at each immediate recall trial; (ii) Delayed Recall score (DR), the number of correctly recalled words provided at the delayed recall trial; (iii) Immediate Intrusions, the sum of wrongly recalled words provided at the immediate recall trials; and (iv) Delayed Intrusions, the sum of wrongly recalled words provided at the delayed recall trial.

Verbal WM was assessed through the Digit Span Backward test (DS-B), in which a series of digits is presented, one at a time, with the participant required to recall and repeat the sequence in reversed order. In this version of the DS-B, the span length gradually increases from 3 digits up to 7 digits. Each span length includes three sequences, resulting in a total of 15 sequences, and the score of participants corresponds to the number of spans correctly recalled. Both the RAVLT and DS-B were

TABLE 1 Sociodemographic and psychological features of participants assigned to the rAS and tACS groups.

	rAS ($n = 38$), mean ± SD	tACS ($n = 36$), mean ± SD	p-Value
Age	23.31 ± 3.80	22.14 ± 3.38	.164
Sex (Female, Male)	25/13	30/6	.084
EHI	49.23 ± 42.27	54.86 ± 31.71	.521
BDI	9.63 ± 6.85	7.92 ± 5.74	.248
STAI-Y1	38.60 ± 9.25	37.05 ± 7.59	.316
STAI-Y2	43.97 ± 8.40	42.08 ± 7.64	.435

Note: The independent sample student t-tests and the chi-squared test (performed on sex distribution) revealed no significant differences between the groups.

Abbreviations: BDI, Beck Depression Inventory; EHI, Edinburgh Handedness Inventory (positive scores indicate right-handedness); STAI, State–Trait Anxiety Inventory (Y1 = State; Y2 = Trait).

administered via a computer, using headphones set at 70 dB, while responses were recorded by a trained psychologist using paper-and-pencil correction grids.

2.3 | γ stimulation protocols

This study aimed to modulate γ oscillations within the temporal cortex using two different techniques, to compare their effects on verbal LTM and WM. Both the auditory cortex (primary and secondary; see Figure 1a,b) and the MTL network (hippocampus, perirhinal, entorhinal, and parahippocampal cortices; see Figure 1b) are situated in the temporal lobe and involved in verbal stimuli processing and γ synchronization (Dimakopoulos et al., 2022; Squire et al., 2015). Although these areas are connected (Zhang et al., 2022), auditory cortex activity is crucial mainly for verbal/auditory short-term and WM (Scott et al., 2014; Yu et al., 2021), while the MTL network is critical for the formation of LTM (Jeneson & Squire, 2012). Hence, to confine stimulation of the temporal area, we opted for auditory stimulation (i.e., rAS) instead of stimulating both visual and auditory areas (which would induce a more extended neural entrainment; Chan et al., 2022), and temporal tACS.

Participants assigned to the rAS group were administered three versions of rAS, one for each experimental block. rAS consisted of the presentation of a sinusoidal auditory tone for 11 min delivered by Sony over-ear headphones with the output set at 40 dB. Participants received either 40 Hz (40 Hz-rAS), 60 Hz (60 Hz-rAS), or no/silent auditory stimulation (control-rAS).

Participants assigned to the tACS group were administered three versions of tACS, one for each experimental block. tACS was delivered by a battery-driven current stimulator (BrainSTIM stimulator; E.M.S. s.r.l.) via a pair of 4 × 4 cm electrodes placed over the bilateral temporal lobe (T8 and T7 based on the 10–20 EEG system). Participants received 11 min (including ramp up and down for 20 s each) of 2 mA peak-to-peak sinusoidal alternating current (current density: 0.125 mA/cm^2) with 40 Hz (40 Hz-tACS), 60 Hz (60 Hz-tACS), and a control stimulation (sham-tACS). In the control-tACS condition, the stimulation was activated only for 60 s to induce a brief skin sensation. It was linearly ramped up over 20 s, maintained at the peak of 2 mA for an additional 20 s, and then ramped down over 20 s. In Figure 1c,d, we show the current distribution estimated by the software SimNIBS, version 3.2 (Thielscher et al., 2015), according to our tACS montage and parameters.

Each stimulation was administered for 11 min (starting 2 min before the memory assessment and persisting for 9 min during the assessment) and the order of administration of each kind of stimulation (40, 60 Hz, and sham) was counterbalanced between participants. None of the participants reported major side effects or intolerable discomfort during or after either tACS or rAS. One participant assigned to the tACS group was excluded due to a technical issue during protocol administration.

2.4 | Experimental design

Each group underwent three experimental blocks lasting 11 min, separated by two rest blocks of 11 min. In each block, participants received either placebo stimulation, 40 or 60 Hz stimulation (rAS or tACS, depending on the group) during LTM and WM task performance. Particularly, within each experimental block, stimulation was started 2 min before memory assessment and persisted until the end of the session. After 2 min of stimulation, the RAVLT list was automatically read by a computer-generated voice within 25 s, followed by a 25 s recall period during which the participant had to repeat the list in a free recall condition (Immediate Recall). Afterward, the list was automatically repeated. After the last Immediate Recall trial, WM performance was assessed via the DS-B: in this case, response time was controlled by the experimenter (no time limit was set for sequence recall), after each span recall, irrespective of its correctness, the experimenter proceeded to the next span, the DS-B included 15 trials. Following the last DS-B trial, participants were asked to recall as many words as possible from the RAVLT list (Delayed Recall) within 50 s. A detailed description of the test administration is provided below. At the end of each experimental block, participants removed the headphones and completed an 8-item side effects questionnaire. In this questionnaire, which was composed based on available ones employed in neuromodulation studies before (e.g., Brunoni et al., 2011; Lee et al., 2021; Matsumoto & Ugawa, 2017), the participants answered on a 5-point Likert scale ranging from 0 to 4 (0 = "absent"; 1 = "mild"; 2 = "moderate"; 3 = "pronounced"; 4 = "strong") eight questions related to the discomfort experienced during the intervention (i.e., skin sensation, phosphenes, fatigue, pain, headache, dizziness, mental fog, auditory discomfort). Following an 11-min rest period with open eyes, the second experimental block was administered. To avoid the learning effect, a different list of the tests (RAVLT and DS-B) was administered during each experimental block (see Supplementary Tables, S1). The entire procedure lasted for approximately 60 min. A representative flow chart of the study procedure is shown in Figure 2.

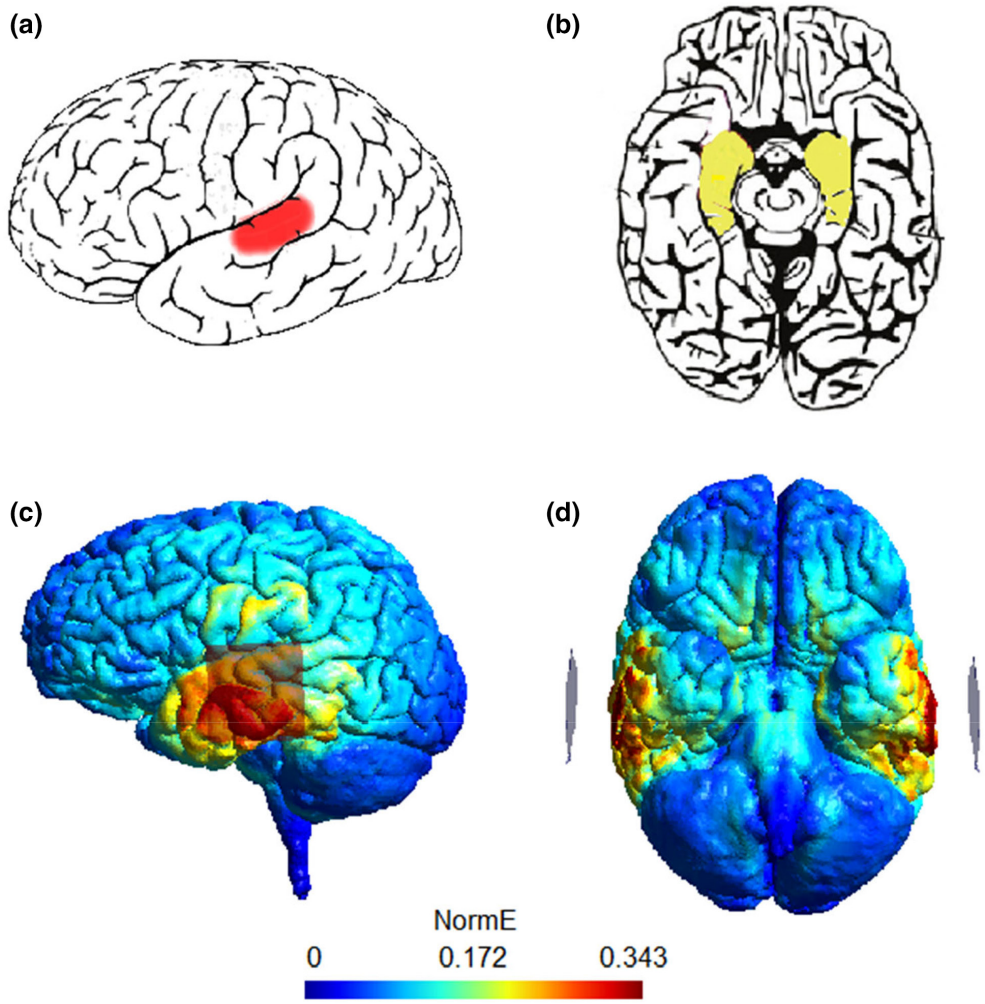

FIGURE 1 Location of (a) the primary and secondary auditory cortex in red (lateral view), and (b) the medial temporal lobe (MTL) structures (ventral view) in yellow within the temporal cortex. The lower panel shows the tACS-induced norm electric field (NormE) strength over a sample brain calculated via SimNIBS, according to our montage (two 4×4 cm electrodes placed over T7 and T8) and stimulation parameters (2 mA peak-to-peak); (c) left-side lateral and (d) ventral views of the current distribution. The dark opaque shapes represent the electrodes.

2.5 | Data analysis

The main outcomes were the number of correctly recalled words during the immediate and the delayed RAVLT trials, the immediate and delayed intrusions, and the DS-B scores (number of correct recalled spans). A secondary outcome was the average score for each SE measure (i.e., skin sensation, phosphenes, fatigue, pain, headache, dizziness, mental fog, auditory discomfort) on a scale of 0 to 5, indicating the intensity of experienced effects. The normal distribution of the data was assessed with the Kolmogorov–Smirnov normality test. RAVLT recalled words and DS-B scores showed normal distribution, while Immediate and Delayed Intrusions and Side Effect measurements did not (Kolmogorov–Smirnov test $p < .01$). Accordingly, we conducted an analysis of variances (ANOVAs) for normally distributed variables and a set of Wilcoxon matched-pairs (signed-rank) tests for not-normally distributed variables.

The first 2×3×6 mixed-factorial analysis of variance (ANOVA) for RAVLT recall was conducted with group (2 levels: rAS, tACS) as between-subject factor and stimulation condition (3 levels: control, 40, 60 Hz) and trials (6 levels: IR1, IR2, IR3, IR4, IR5, DR) as within factors. Then, we conducted a series of Wilcoxon matched-pair tests for RAVLT immediate and delayed intrusions, comparing the stimulation condition in the full sample and within rAS and tACS group. We conducted a 2×3 ANOVA on DS-B scores with group as between-subject factor and the stimulation condition as within-subject factor. In case of significant main effects or interactions, the Tukey post-hoc tests were used for multiple comparisons. SE measures (i.e., skin sensation, phosphenes, fatigue, pain, headache, dizziness, mental fog, and auditory discomfort) were assessed, separately for each group (Control, 40 and 60 Hz), through a series of Wilcoxon matched-pair tests. Finally, the potential influence of stimulation order and participant's sex on the main outcomes was

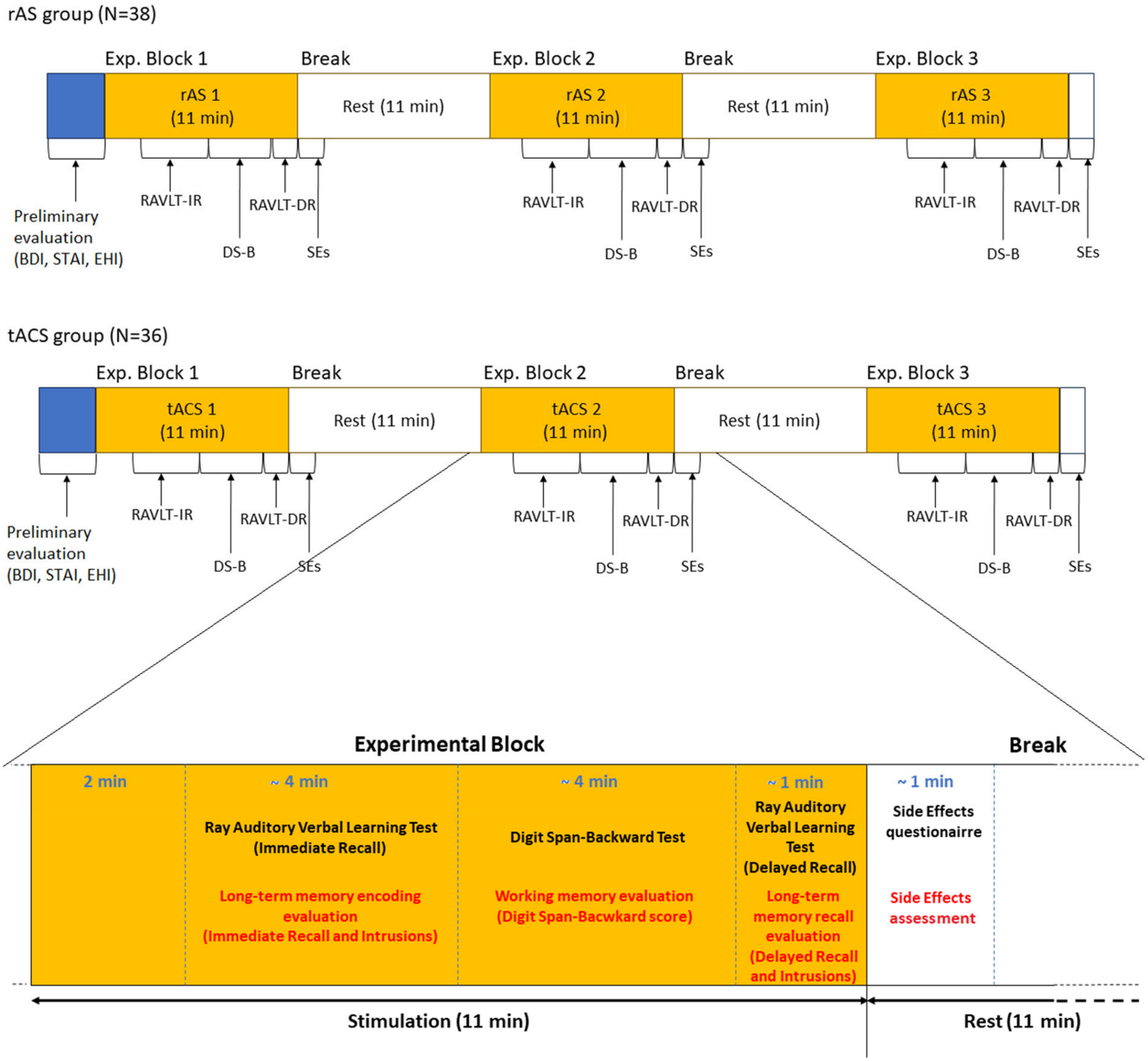

FIGURE 2 Experimental protocol (above) and example of an experimental block (below). First, participants were allocated to either the rAS or tACS group. The study comprised three sequential experimental blocks, each separated by equivalent breaks. During each experimental block, participants wore headphones, which were removed during the breaks. Every participant underwent three distinct stimulation conditions (control, 40, and 60 Hz), one condition per experimental block. The sequence of stimulation administration was counterbalanced across participants. Long-term memory (LTM) and working memory (WM) assessments were conducted during experimental blocks.

explored through 2 Analyses of Covariance (ANCOVA) on RAVLT recalled words and the DS-B score, respectively.

3 | RESULTS

The ANOVA ran for the RAVTL on the number of words recalled (see Table 2) showed a significant main effect of the trial ($F_{5,360} = 318.67$, $p < .001$, $\eta_p^2 = .816$; see Figure 3a), but no other significant main effects or interaction (see Figure 3b). Tukey's post hoc analyses revealed that the mean of correctly recalled words during IR1 was significantly lower compared to all other trials (all $p < .001$). The mean of correctly recalled words during IR2 was higher compared with IR1, but lower compared to all other trials (all $p < .001$). The mean of correctly recalled words during IR3 was higher compared to both IR1 and IR2, but lower compared to both IR4 and IR5 (all $ps < .001$) and did not differ significantly from DR ($p = .330$). Finally, the mean of correctly recalled words during IR4 and IR5 was higher

TABLE 2 Results of the 2×3×6 mixed-factorial ANOVA ran on the Rey Auditory Verbal Learning Test (RAVLT) with recalled words as dependent variable.

RAVLT recalled words 2×3×6 ANOVA	df	*F*	*p*-Value	η^2_p
Group	1,72	0.463	.498	0.006
Stimulation condition	2,144	0.778	.461	0.011
RAVLT Trial	5,360	318.672	<.001	0.816
Stimulation condition × Group	2,144	0.259	.772	0.004
RAVLT Trial × Group	5,360	0.679	.639	0.009
Stimulation condition × RAVLT Trial	10,720	0.370	.959	0.005
Stimulation condition × RAVLT Trial × Group	10,720	1.092	.366	0.015

Abbreviations: df, degrees of freedom; *F*, *F*-statistic; η^2_p, partial-eta squared.

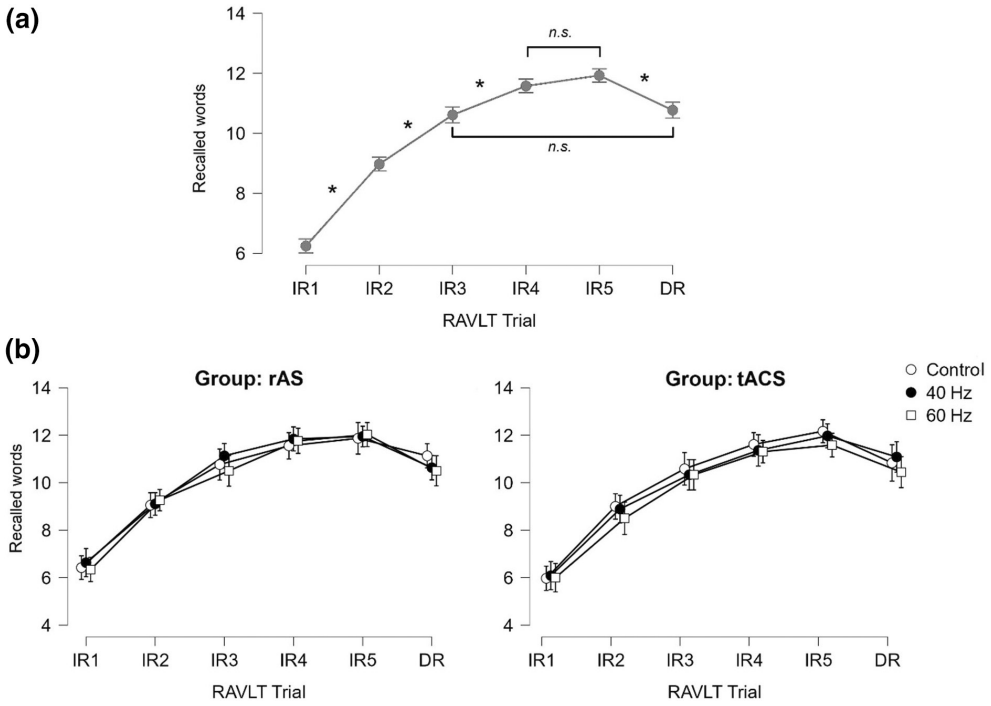

FIGURE 3 These graphs show the mean number of recalled words (with error bars indicating a 95% CI) from the Rey Auditory Verbal Learning Test (RAVLT). (a) A significant main effect was found for recalled words across trials. Asterisks indicate significant differences, while *n.s.* indicates nonsignificant comparisons (for a complete description of significances, refer to the main manuscript); (b) Neither the group nor the stimulation condition had a significant differential impact on the number of recalled words.

compared with all other trials (all $p < .001$) but did not differ from each other ($p = .070$).

The Wilcoxon tests ran on the full sample immediate intrusions (see Table 3) showed lower intrusions during 60 Hz compared with the control stimulation ($p = .048$) (see Figure 4a). This effect was driven mainly by the rAS group (see Figure 4b) with significantly lower intrusion during 60 Hz-rAS compared with Control-rAS ($p = .030$), but not during 60 Hz-tACS compared with Control-tACS ($p = .603$). The Wilcoxon tests ran on delayed intrusions showed no significant effects (see Table 4).

The ANOVA ran for the DS-B score (see Table 5 for the complete ANOVA results) showed a significant main effect of stimulation condition ($F_{2,144} = 4.338$, $p = .015$, $\eta_p^2 = .057$; see Figure 5a), but no other significant main effect or interaction. Tukey's post-hoc analyses showed significantly better performance during the 40 Hz stimulation compared with the control condition ($p = .009$).

Although both separate groups showed similar trends, no significance emerged in Tukey's post hoc comparisons conducted between the 40 Hz and control condition (control-rAS < 40 Hz-rAS $p = .275$; control-tACS < 40 Hz-tACS $p = .344$) within the single groups (see Figure 5b).

Finally, the Wilcoxon tests ran on each SE measure within the rAS group showed a more prominent reported auditory discomfort during both 40 Hz-rAS and 60 Hz-rAS stimulation compared to control-rAS (both $p = .004$) and a more pronounced headache during 40 Hz-rAS compared

with control-rAS ($p = .023$). On the other hand, the tACS group reported more prominent phosphenes during both the 40 Hz ($p = .006$) and 60 Hz-tACS ($p = .010$) compared with the Control-tACS condition, more pronounced pain during the 40 Hz-tACS compared with the Control-tACS ($p = .033$) and more pronounced fatigue during the 40 Hz-tACS compared with the 60 Hz-tACS ($p = .042$). Table 6 shows descriptive outcome data while Wilcoxon test results are reported in Supplementary Tables (S6, S7).

The supplementary ANCOVAs ran on the RAVLT recalled word and DS-B scores using the order of administration of the stimulation and the participant's sex as covariate, showed no main effect of the covariate and only minor difference with our main models (see Supplementary Tables: S2, S3, S4, S5). Furthermore, the full descriptive data for each variable are reported in Supplementary Tables (S8, S9, S10).

4 | DISCUSSION

γ-rAS and γ-tACS are supposed to improve cognitive processes by enhancing γ frequency activity in the temporo-prefrontal network, but so far, no study has directly compared the impact of γ-rAS and γ-tACS on verbal memory in healthy participants. In this study, we found that temporal γ-rAS and γ-tACS similarly affect memory processes. Specifically, for LTM, neither immediate recall nor delayed recall was influenced by any stimulation, while immediate intrusions were lower during

TABLE 3 Results of the Wilcoxon matched-pair tests on immediate intrusions.

Immediate intrusions	*W*	*z*-Score	*p*-Value
Control vs. 40 Hz	339	1.618	.106
Control vs. 60 Hz	377	1.979	.048
40 Hz vs. 60 Hz	324.5	0.667	.505
Control-rAS vs. 40 Hz-rAS	152	0.889	.374
Control-rAS vs. 60 Hz-rAS	82	2.166	.030
40 Hz-rAS vs. 60 Hz-rAS	41.5	1.916	.055
Control-tACS vs. 40 Hz-tACS	40	1.448	.148
Control-tACS vs. 60 Hz-tACS	110.5	0.519	.603
40 Hz-tACS vs. 60 Hz-tACS	83.5	−0.803	.422

Note: The first three comparisons include both groups.

TABLE 4 Results of the Wilcoxon matched-pair tests on delayed intrusions.

Delayed intrusions	*W*	*z*-Score	*p*-Value
Control vs. 40 Hz	120	0.857	.391
Control vs. 60 Hz	141.5	−0.565	.573
40 Hz vs. 60 Hz	149.9	−1.479	.141
Control-rAS vs. 40 Hz-rAS	57	−0.170	.864
Control-rAS vs. 60 Hz-rAS	51	−0.094	.924
40 Hz-rAS vs. 60 Hz-rAS	70	−0.307	.758
Control-tACS vs. 40 Hz-tACS	12	1.244	.213
Control-tACS vs. 60 Hz-tACS	23.5	−0.844	.398
40 Hz-tACS vs. 60 Hz-tACS	15	−1.882	.060

Note: The first three comparisons include both groups.

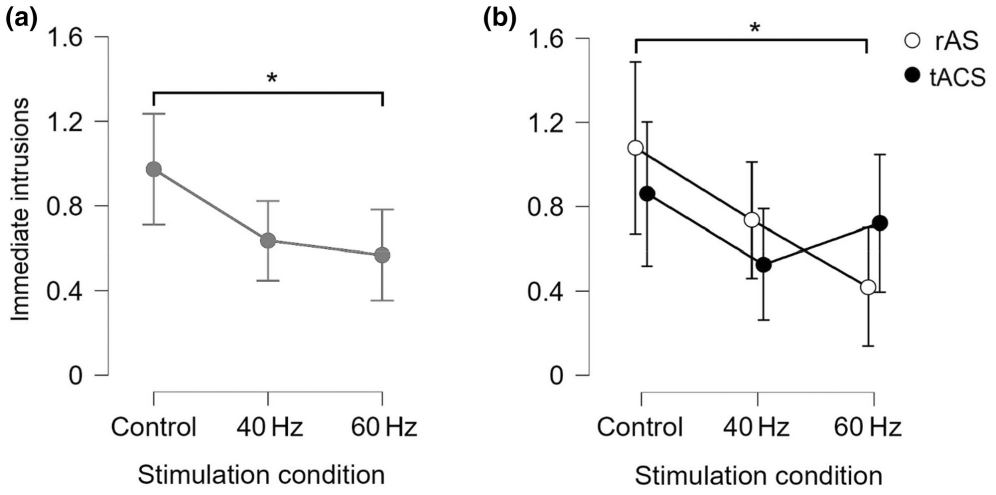

FIGURE 4 These graphs show the mean number of intrusions during all immediate recall trials with error bars indicating a 95% confidence interval from the Rey Auditory Verbal Learning Test (RAVLT). (a) A significant main effect of the stimulation condition was found with significantly lower immediate intrusions reported during 60 Hz compared with the control condition. (b) The only significant difference in stimulation conditions within groups was identified between the Control-rAS and 60 Hz-rAS conditions.

60 Hz stimulation compared with control. On the other hand, 40 Hz stimulation improved WM performance compared with the respective control stimulation conditions. Furthermore, the interventions were well tolerated; participants reported mild SEs during stimulations with few significant intervention-specific differences (out of 8 SE measurements) in each group: higher auditory discomfort at 40 Hz- and 60 Hz-rAS compared with control-rAS and more pronounced headache during 40 Hz- compared with control-rAS. Regarding the tACS group, participants reported increased phosphenes during 60 Hz- and 40 Hz-tACS compared with control-tACS. Moreover, in the tACS group, participant reported more pronounced pain during 40 Hz-tACS compared with control-tACS and fatigue during 40 Hz-tACS compared with 60 Hz-tACS, most likely being an unspecific effect of the experiments. Overall, the average score of all SE measures was low (mostly ranging from absent to mild), indicating good tolerance of the interventions.

The current study is the first endeavor to compare the effects of an online single session of γ-rAS and γ-tACS (administered at both 40 and 60 Hz) on memory processes. The selection of 40 Hz and 60 Hz stimulation frequencies

TABLE 5 Results of the 2 × 3 mixed-factorial ANOVA ran on Digit Span-Backward scores (DS-B).

Digit span-B 2 × 3 ANOVA	*F*	df	*p*-Value	η^2_p
Group	0.674	1,72	.414	0.009
Stimulation condition	4.338	1,72	.015	0.057
Stimulation condition × Group	0.012	2144	.988	<0.001

Abbreviations: df, degrees of freedom; *F*, *F*-statistic; η^2_p, partial-eta squared.

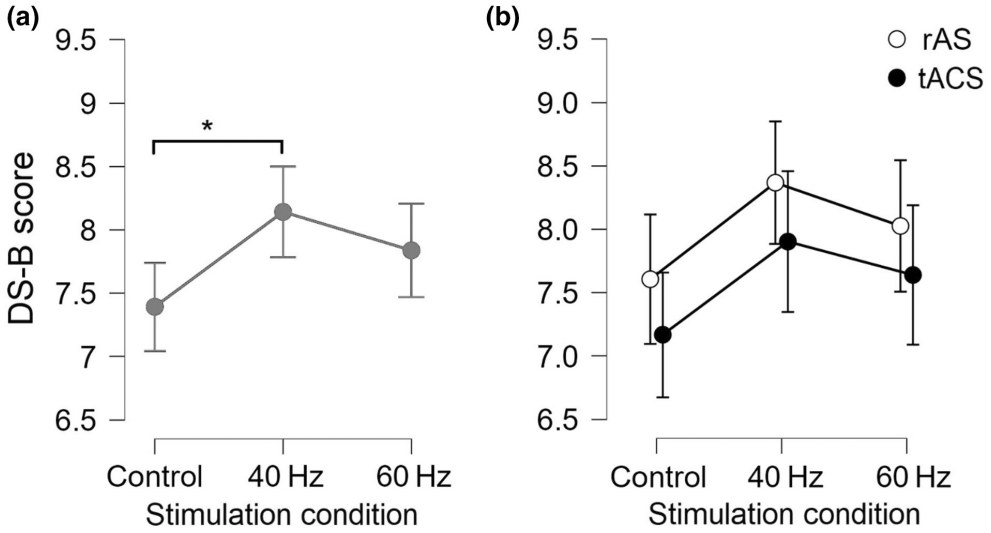

FIGURE 5 These graphs show the mean number of correctly recalled digit spans (with error bars indicating the 95% confidence interval) in the Digit Span-Backward (DS-B) task: (a) a significant effect was found for stimulation conditions for merged group data, with the asterisk indicating a significantly higher score in the 40 Hz compared with the control condition; (b) the effect appears similar in both intervention groups, but respective subgroup analyses resulted only in trend-wise effects.

TABLE 6 Descriptive statistics (Mean, *M* and Standard Deviation, *SD*) of side effect measures (in rows) reported by participants receiving rAS (first three columns on the left) and tACS stimulation (last three columns on the right).

SE measures	Control-rAS *M* (*SD*)	40 Hz-rAS *M* (*SD*)	60 Hz-rAS *M* (*SD*)	Control-tACS *M* (*SD*)	40 Hz-tACS *M* (*SD*)	60 Hz-tACS *M* (*SD*)
Skin sensation	0.03 (0.16)	0.18 (0.56)	0.08 (0.49)	1.14 (1.05)	1.06 (0.90)	0.97 (0.84)
Phosphenes	0.26 (0.55)	0.23 (0.49)	0.19 (0.42)	0.28 (0.66)	0.61 (0.90)	0.72 (1.00)
Fatigue	0.76 (1.00)	0.68 (0.74)	0.79 (0.90)	0.64 (0.93)	0.92 (1.05)	0.67 (0.83)
Pain	0.03 (0.16)	0.03 (0.16)	0.05 (0.04)	0.28 (0.70)	0.52 (0.81)	0.50 (0.94)
Headache	0.26 (0.55)	0.45 (0.64)	0.42 (0.76)	0.67 (1.04)	0.97 (1.03)	0.83 (1.00)
Dizziness	0.55 (0.98)	0.73 (0.95)	0.68 (0.90)	0.36 (0.87)	0.47 (0.94)	0.36 (0.87)
Mental Fog	1.21 (0.96)	1.26 (1.08)	1.24 (0.94)	0.83 (1.00)	0.97 (1.18)	0. 83 (0.97)
Auditory discomfort	0.12 (0.34)	0.66 (1.05)	0.63 (1.05)	0.11 (0.40)	0.22 (0.59)	0. 19 (0.62)

was based on previous studies that showed the specific relevance of these frequencies for modulating cognitive processes, particularly memory, in clinical populations and healthy controls, respectively. Although our previous study suggested that 60 Hz-rAS, but not 40 Hz improves intrusions (Manippa et al., 2024), both 40 and 60 Hz oscillations have been associated with various cognitive functions, including memory encoding, retrieval, and consolidation, sensory integration, and attention regulation, which are essential components of both LTM and WM.

Our data indicate that a single session of γ-rAS and γ-tACS targeting the temporal cortex did not influence the number of words recalled but affected verbal intrusions during a declarative LTM test. Although no significant differences emerged between the rAS and tACS groups, this effect was likely driven by the rAS. This result confirms our previous findings where a single session of 60 Hz-rAS (compared with no auditory stimulation and 40 Hz-rAS) deceased RAVLT immediate intrusions without influencing the number of correctly recalled words (Manippa et al., 2024). High (fast)-gamma oscillations (>55 Hz) are associated with refined processes involved in LTM management and organization (e.g., Javadi et al., 2017; Uhlhaas et al., 2011). It might be thus hypothesized that temporal 60 Hz stimulation improves some cognitive/auditory processes underlying the recall of intrusive words during IR trials (Assem et al., 2023). However, this online effect during the intervention, probably due to an optimization of neural network coordination, did not significantly affect memory formation (i.e., immediate, and delayed recall performance) or organization (i.e., intrusion during the delayed recall trial) (di Chanaz et al., 2023; McClelland et al., 1995). This might mean that γ-tACS has a timing- and process-dependent effect on LTM formation restricted to a reduction of noisy information processing during stimulation, which would selectively affect intrusions. Alternatively, the null findings on the number of correctly recalled words could be attributed to the choice of the RAVLT for assessing LTM recall, which might not be optimal for probing memory consolidation due to its brief administration time. Studies demonstrating gamma stimulation effects on LTM typically employ longer intervals between encoding and recall or utilize multi-session protocols, which might be better suited to probe the potential role of plasticity in these effects (Grover et al., 2022; Javadi et al., 2017; Nomura et al., 2019). Accordingly, the promising evidence for the beneficial effects of both multi-session temporal 40 Hz-tACS and GENUS in alleviating neuropathological manifestations and LTM impairment in AD patients (e.g., Chen et al., 2022; Sprugnoli et al., 2021; Zhou et al., 2021) may originate from neuroprotective (e.g., Hu et al., 2023) or neuroplastic long-term effects (e.g., Chen et al., 2022) induced by the sustained intervention protocols administered (Manippa et al., 2022, 2023). Therefore, we propose that the consolidation of declarative LTM involves synaptic changes and system-level reorganization operating on different timescales than those tackled here. Furthermore, most of the studies show declarative LTM improvement in healthy participants due to gamma stimulation modulated prefrontal cortex activity (Booth et al., 2021), a brain area involved in a wide range of cognitive and memory functions, including LTM management and organization (Crone et al., 2006; Javadi & Walsh, 2012). Due to its cortical position and the wide range of connections with the entire brain (Barbas, 2015), the activity of this region can be easily modulated with both electric and sensory stimulation (e.g., Hen et al., 2023). Conversely, noninvasive modulation of MTL activity with sensory or electric stimuli (involved in neuroplasticity-dependent declarative memory consolidation) might be more challenging due to its anatomical location near the skull base and the specific brain areas affected by auditory stimuli, which makes it likely that both interventions used in the present study affected the MTL only indirectly at best via connections with more superficial areas, or not relevantly (Bjekić et al., 2019; Huerta & Volpe, 2009). In accordance, two studies showed that γ-rAS, without coupling with flickering light, cannot entrain gamma in the hippocampus, but in prefrontal and auditory cortices (Chen et al., 2022; Han et al., 2023).

Moreover, our findings suggest that both rAS and tACS at 40 Hz enhanced WM performance, as shown by increased DS-B scores compared to the control stimulation. While Booth et al. (2021) highlighted the efficacy of parietal theta-tACS for improving WM and a recent study showed that prefrontal 40 Hz-tACS did not influence visual WM (Kvašňák et al., 2022), our study is the first which investigated the effect of gamma neuromodulation over the temporal cortex on verbal WM performance. By our results, Mainy et al. (2006) demonstrated increased γ activity in various brain regions associated with language processing, such as the Broca area and auditory cortex, the prefrontal cortex, and the hippocampus during a verbal WM task using intracranial EEG recordings in 9 epileptic patients. Particularly, multiple studies have acknowledged a role of the auditory cortex in verbal WM performance (Bidelman et al., 2021; Dimakopoulos et al., 2022). Our data might thus suggest that 40 Hz stimulation impacts auditory cortex γ activity, affecting verbal WM performance and immediate recall intrusions, without influencing MTL activity and memory consolidation. Particularly, a brief temporal 40 Hz intervention might improve real-time processing and coordination of information necessary for verbal WM (Crone et al., 2006; Howard et al., 2003; Sederberg et al., 2007). Although in our previous study γ-rAS did not

affect WM (Manippa et al., 2024), the lack of effects and the absence of difference between the single intervention groups (tACS vs. rAS), combined with significant effects in the whole group condition suggests that the stimulation modality may not be as influential as the stimulation frequency. It is noteworthy that in the current study, we recruited a sample twice as large as in the previous one. Therefore, the absence of an effect in the former experiment might have been due to a relatively small sample size and/or a high degree of effect variability.

Taken together, we observed that temporal/auditory 40 Hz stimulation improved verbal WM performance, while 60 Hz stimulation reduced immediate intrusions during declarative LTM task. These data provide evidence for the frequency-specific effects of gamma stimulation on different aspects of memory. Moreover, the lack of significant differences between the rAS and tACS groups suggests that the stimulation modality may not be as influential as the stimulation frequency itself. These results add information to our understanding of how gamma oscillations contribute to memory processes and highlight the importance of selecting appropriate stimulation parameters based on the specific cognitive functions targeted. Furthermore, they underscore the potential utility of gamma stimulation as a noninvasive neuromodulation technique for enhancing cognitive functions in healthy individuals. Further research exploring the underlying mechanisms of frequency-specific effects and the long-term impact of gamma stimulation on memory consolidation will be valuable for advancing our knowledge in this field and developing effective interventions for memory enhancement.

4.1 | Limitations, future research, and conclusions

Our study represents the first comparative exploration of cognitive effects generated by noninvasive stimulation of the temporal cortex in the γ frequency range with two gamma frequencies (40 and 60 Hz), and two widely used noninvasive stimulation tools (rAS and tACS) for brain oscillation entrainment. While gamma stimulation did not affect the number of correctly recalled words in an LTM task, 60 Hz reduced immediate intrusions in that task, and 40 Hz stimulation enhanced WM performance, compared to control stimulation. Nevertheless, some limitations of the present study should be acknowledged.

First, it is important to note that the sex distribution in our sample was not balanced, the samples included more females than males, although this distribution did not significantly differ between intervention groups, and respective ANCOVAs did not show a significant effect or interactions including the covariate sex on the results. Future studies might be valuable, which explore systematically the impact of sex, age, education, and other demographic parameters on the effects of intervention. Furthermore, we assigned different participant groups to rAS and tACS, exposing each group to three types of stimulation in a counterbalanced order, interspersed with breaks, within one day. Despite the absence of notable group differences in our results, this approach does not completely exclude a priori intergroup differences with an impact on intervention effects, or interference between the stimulations, although the latter is improbable because of non-significant order effects in the respective ANCOVAs. Future studies should improve methodology by using the same participants for both intervention types in a complete crossover design and extending the interval between the sessions. Additionally, while tACS induced oscillations in an anti-phasic pattern between the stimulation electrodes, rAS administered the sound synchronously over both ears. The lack of significant between-group differences suggests, however, that this difference did not critically affect intervention outcomes: accordingly, we hypothesize that the observed effects, particularly involving verbal stimuli, predominantly originate from left auditory cortex γ entrainment rather than from right-hemispheric stimulation. Because we used auditory stimulation and tACS over the auditory cortex, a transfer to other stimuli modalities, such as visuo-spatial stimuli, cannot be taken for granted and should be explored in future studies. Exploring effects beyond auditory stimuli by using visuo-spatial memory tests such as the Corsi block task, the Rey complex figure test, or the Luck-Vogel Task would broaden understanding of the applicability of these interventions. Furthermore, γ oscillations in the temporal cortex might also influence attention and executive functions, which might have impacted intrusions rate. Comprehensive cognitive assessments also incorporating attention and executive function tests could enhance mechanistic understanding of the foundation of the observed performance improvements.

Another limitation of the present study is the missing evaluation of γ entrainment via EEG recording, which could have confirmed that temporal gamma entrainment indeed underlies the observed cognitive effects. Other studies showed that a single session of gamma stimulation can also affect other frequency bands (e.g., Benussi et al., 2022; Naro et al., 2016) and alter functional connectivity (e.g., Zarei et al., 2022) beyond the targeted brain area (e.g., Han et al., 2023; Pahor & Jaušovec, 2017). Future studies should aim to include EEG recordings to improve mechanistic understanding of the impact of the respective stimulation protocols on cognitive performance. Additionally, optimizing stimulation parameters

such as session number, stimulation intensity, frequency, and duration for both rAS and tACS protocols might offer valuable insights relevant to clinical application (e.g., Lee et al., 2021; Sprugnoli et al., 2021). Finally, future neurostimulation studies should explore personalized approaches, considering individual variations in anatomy and neural responses by leveraging individual magnetic resonance imaging (MRI) or EEG data (Bjekić et al., 2019; Soleimani et al., 2023). These approaches aim to optimize the distribution of electrical currents and applied frequencies for each individual, potentially enhancing their efficacy. By tailoring stimulation parameters based on these factors, it might be possible to enhance the efficacy of neuromodulatory clinical protocols (Guerra et al., 2020; Koch & Hummel, 2017; Padberg et al., 2021).

Taken together, although none of our interventions affected immediate and delayed recall in the RAVLT task indicative for LTM, single session online 60 Hz stimulation reduced immediate intrusions in this task, while 40 Hz stimulation improved verbal working memory. We suggest that these frequency-specific effects may rely on the intervention-induced alterations of auditory cortex activity. A single session of online temporal rhythmic stimulation, whether auditory or transcranial, may improve real-time processing and coordination underlying WM and immediate recall intrusions, without significantly impacting LTM consolidation. The latter might involve system-level reorganization, operating on different timescales compared to immediate cognitive demands associated with intrusion reduction or WM enhancement. Further research is warranted to delve deeper into the underlying mechanisms and potential applications of these frequency-specific cognitive-enhancement effects.

AUTHOR CONTRIBUTIONS

Valerio Manippa: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing – original draft. **Michael A. Nitsche:** Supervision; writing – review and editing. **Marco Filardi:** Writing – review and editing. **Davide Vilella:** Writing – review and editing. **Gaetano Scianatico:** Investigation; resources; writing – review and editing. **Giancarlo Logroscino:** Funding acquisition; project administration; supervision; writing – review and editing. **Davide Rivolta:** Funding acquisition; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

MAN is in the Scientific Advisory Board of Neuroelectrics. All other authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1.

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