HHS Public Access

Author manuscript

Nat Neurosci. Author manuscript; available in PMC 2023 April 03.

Published in final edited form as:

Nat Neurosci. 2022 September ; 25(9): 1237–1246. doi:10.1038/s41593-022-01132-3.

Long-lasting, dissociable improvements in working memory and long-term memory in older adults with repetitive neuromodulation

Shrey Grover[1], **Wen Wen**[1], **Vighnesh Viswanathan**[1], **Christopher T. Gill**[1], **Robert M. G. Reinhart**[1,2,3,4,5,✉]

[1]Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA.

[2]Department of Biomedical Engineering, Boston University, Boston, MA, USA.

[3]Center for Systems Neuroscience, Boston University, Boston, MA, USA.

[4]Cognitive Neuroimaging Center, Boston University, Boston, MA, USA.

[5]Center for Research in Sensory Communication and Emerging Neural Technology, Boston University, Boston, MA, USA.

Abstract

The development of technologies to protect or enhance memory in older people is an enduring goal of translational medicine. Here we describe repetitive (4-day) transcranial alternating current stimulation (tACS) protocols for the selective, sustainable enhancement of auditory-verbal working memory and long-term memory in 65–88-year-old people. Modulation of synchronous low-frequency, but not high-frequency, activity in parietal cortex preferentially improved working memory on day 3 and day 4 and 1 month after intervention, whereas modulation of synchronous high-frequency, but not low-frequency, activity in prefrontal cortex preferentially improved long-term memory on days 2–4 and 1 month after intervention. The rate of memory improvements over 4 days predicted the size of memory benefits 1 month later. Individuals with lower baseline cognitive function experienced larger, more enduring memory improvements. Our findings demonstrate that the plasticity of the aging brain can be selectively and sustainably exploited

✉**Correspondence and requests for materials** should be addressed to Robert M. G. Reinhart., rmgr@bu.edu.

Author contributions

Conceptualization: R.M.G.R. and S.G.; data acquisition: R.M.G.R. and V.V.; data analysis and interpretation: R.M.G.R., S.G., W.W., V.V. and C.T.G.; writing—original draft: S.G. and W.W.; writing—review and editing: R.M.G.R., S.G., W.W., V.V. and C.T.G.; funding acquisition: R.M.G.R.; supervision: R.M.G.R.

Competing interests

The authors declare no competing interests.

Code availability

No custom codes were used for the experiment or the primary analyses.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41593-022-01132-3.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41593-022-01132-3.

using repetitive and highly focalized neuromodulation grounded in spatiospectral parameters of memory-specific cortical circuitry.

The world is facing many challenges due to a rapidly aging global population. The shift in age demographics is associated with considerable personal, social, healthcare and economic costs[1]. A critical factor contributing to aging-induced costs is the impairment in basic memory systems essential for activities of daily living, such as making financial decisions or comprehending language[2]. Emerging reports suggest an increased likelihood of such impairments due to the ongoing Coronavirus Disease 2019 (COVID-19) pandemic[3]. Moreover, there exists considerable variability in memory decline across individuals during aging[4], with accelerated decline potentially predicting subsequent Alzheimer's disease and other dementias[5]. Substantial progress in neuroscience has identified the brain circuits and networks that underpin memory capacities, and studies have suggested that the rhythmic activity of cognitive circuitry may be important for the coordination of information processing[6]. What is needed now are technologies to non-invasively isolate and augment the rhythmic activity of neural circuits, inspired by models of healthy aging, to determine whether it is possible to protect or even enhance memory function for older adults in a rapid and sustainable fashion[6,7].

A challenge in improving memory function in older adults is that memory function may not be instantiated by a single cognitive mechanism. Previous research has characterized a capacity-limited working memory (WM) store for brief maintenance of information and an unlimited long-term memory (LTM) store for sustained maintenance of information[8]. Within this dual-store framework, previous research has identified both concurrent deficits[9] and selective deficits[10] in WM and LTM function with aging, using the classic immediate free recall paradigm, associating these stores with the canonical recency and primacy effects, respectively[11]. Neuropsychological research has long alluded to distinct anatomical and functional substrates of primacy and recency effects and the corresponding WM and LTM stores[11–13]. Differential contributions of the dorsolateral prefrontal cortex (DLPFC) and the inferior parietal lobule (IPL) have been suggested[14]. However, it is not known whether distinct rhythmic mechanisms in these regions subserve distinct memory processes during free recall. If unique rhythmic mechanisms in spatially distinct brain regions can be identified, then these brain rhythms can be independently and non-invasively manipulated using techniques such as high-definition transcranial alternating current stimulation (HD-tACS) for selectively improving memory function in older adults.

Rhythmic activity in the theta and gamma frequency ranges are thought to contribute to both WM[15] and LTM[16] function, particularly during free recall[17]. However, previous attempts at modulating these rhythms to improve memory have yielded inconsistent findings. Although there are some suggestions of improvements in WM with modulation of parietal theta rhythms[18], changing theta rhythms in the frontal regions[7,19] and gamma rhythms in the parietal[20] and frontal[21] regions have yielded contradictory results. Similarly, although frontal gamma tACS has previously suggested improvements in LTM[22,23], other spatiospectral combinations, such as frontal theta[24,25] and parietal theta[26] modulation, have shown variable effects. In addition, although modulation of gamma rhythms in the medial parietal cortex

has shown some benefits to LTM[27], causal evidence for involvement of these rhythms in lateral parietal cortices is scarce. Moreover, much of this evidence comes from studies in young adults, using paradigms targeting visuospatial memory and using conventional tACS, which has poorer spatial resolution and target engagement than techniques such as HD-tACS guided by current flow models[28]. Thus, which specific combinations of location and frequency of neuromodulation are effective for selectively improving WM and LTM function, particularly in older adults, are unknown.

Based on the balance of evidence, we tested the hypotheses that modulation of theta rhythms in the IPL would improve auditory–verbal WM function (recency effect), whereas modulation of gamma rhythms in the DLPFC would improve auditory–verbal LTM function (primacy effect) in older adults (Experiment 1). To modulate these rhythms, we applied tACS with optimal source-sink configurations of nine 12-mm ring electrodes (8 × 1 tACS) guided by current flow models to improve the focality of current flow[28]. Moreover, we sought to induce long-lasting effects by performing repetitive neuromodulation over multiple days and tested memory performance up to 1 month after intervention. Furthermore, we examined the effect of interindividual differences[4] and tested whether older individuals with lower general cognitive performance would benefit more from neuromodulation. To confirm the location specificity and frequency specificity of our hypotheses and address the conflicting findings in the field, we performed a second experiment (Experiment 2) in which we switched the entrainment frequencies in the two regions to examine the effect of gamma entrainment in the IPL and theta entrainment in the DLPFC on memory function. To explicitly test the replicability of the principal findings, we performed a third experiment (Experiment 3), similar to Experiment 1, examining the effect of gamma modulation in the DLPFC and theta modulation in the IPL in an independent sample of participants. Across these three experiments, we sought evidence for a double dissociation in the two memory stores according to the distinct spatiospectral characteristics of their underlying anatomical and functional substrates and, consequently, for selective and long-lasting improvements in memory function in older adults.

Results

We conducted a randomized, double-blind study consisting of two sham-controlled experiments to target memory function in older adults and an additional experiment to test the replicability of the principal findings. In Experiment 1, 60 participants (Table 1) were randomized into three groups (sham, DLPFC gamma and IPL theta; Fig. 1). We used a repetitive neuromodulation protocol in which each participant received 8 × 1 tACS according to their assigned group for 20 minutes each day on four consecutive days. Gamma frequency 8 × 1 tACS was administered at 60 Hz, whereas theta frequency 8 × 1 tACS was administered at 4 Hz, following previous studies suggesting stronger benefits at these frequencies[18,22]. On each day, participants performed five runs of the free recall task. In each run, they encoded a list of 20 words and were asked to immediately recall the words at the end of the presentation of the list. Neuromodulation was performed through the entire duration of encoding and recall of all five lists to increase functional specificity[29], and this procedure took approximately 20 minutes (Methods). We examined memory performance across the five runs as a function of the serial position of the presented words. This

allowed us to isolate changes in LTM and WM, separately, indexed by the primacy and recency serial position curve effects according to dual-store models[11]. In addition to these online assessments, we evaluated memory performance offline, at baseline and at 1 month after intervention. We also determined general cognitive function, quantified using the Montreal Cognitive Assessment (MoCA)[30], and depression symptoms, assessed using the Geriatric Depression Scale (GDS)[31], at baseline. Experiment 2 served as a control to test the frequency specificity of the effects in Experiment 1. Here, we switched the neuromodulation frequency between the two regions of interest. Sixty older participants (Table 1) were randomized into three groups (sham, DLPFC theta and IPL gamma; Fig. 1) and proceeded similarly to Experiment 1. Experiment 3 served as a test for replication of the primary findings from Experiment 1. Here, a new sample of 30 participants was randomized into the two critical conditions of interest from Experiment 1 (DLPFC gamma and IPL theta) and received neuromodulation for only three consecutive days; as in Experiment 1, we examined memory performance at baseline and during each neuromodulation session.

DLPFC gamma modulation selectively improves LTM.

In Experiment 1, free recall performance across the five word lists administered during neuromodulation was averaged and entered into a mixed ANOVA with day (baseline, day 1, day 2, day 3, day 4 and 1 month after intervention) and serial position (primacy, middle 1, middle 2, middle 3 and recency) as within-subjects factors and group (sham, DLPFC gamma and IPL theta) as a between-subjects factor. We observed a significant day × serial position × group interaction ($F_{21.4,611.5} = 3.875$, $P < 0.001$, $\eta_p^2 = 0.120$). A follow-up mixed ANOVA examining performance between the sham and DLPFC gamma groups showed a similar day × serial position × group interaction effect ($F_{10.1,384.0} = 3.064$, $P < 0.001$, $\eta_p^2 = 0.087$). Additional follow-up analyses testing the effect of day on the serial position × group interaction showed that the differences in the sham and DLPFC gamma groups were present on day 2 ($F_{3.3,126.8} = 7.228$, $P < 0.001$, $\eta_p^2 = 0.160$), day 3 ($F_{2.9,110.3} = 15.331$, $P < 0.001$, $\eta_p^2 = 0.287$), day 4 ($F_{2.8,107.0} = 10.698$, $P < 0.001$, $\eta_p^2 = 0.220$) and 1 month after intervention ($F_{2.6,100.5} = 3.435$, $P = 0.024$, $\eta_p^2 = 0.083$). Examining the effect of serial position on the day × group interaction, we observed significant improvements in memory performance for the primacy cluster in the DLPFC gamma group with respect to sham ($F_{3.6,140.4} = 7.470$, $P < 0.001$, $\eta_p^2 = 0.164$) and no differences in any other serial position cluster ($Fs < 2.262$, $ps > 0.085$). Parsing the improvements in the primacy cluster, independent-sample *t*-tests revealed significantly higher primacy performance in the DLPFC gamma group relative to the sham group on day 2, day 3, day 4 and 1 month after intervention (Fig. 2a, top, middle). The pattern of results remained unchanged when accounting for additional factors such as age, sex, years of education, MoCA and GDS scores as covariates (Supplementary Tables 1–3). Exploratory analyses suggested potentially greater improvements in males than females, but these effects did not survive correction for multiple comparisons (Extended Data Fig. 1). The results suggest that rhythmic neuromodulation in the gamma band targeting left DLPFC preferentially improved LTM in older adults. The improvements were rapidly induced by the second day of neuromodulation, persisted on all following neuromodulation days and lasted for at least 1 month after intervention.

IPL theta modulation selectively improves WM.

We also examined a day × serial position × group interaction effect between sham and IPL theta groups in Experiment 1, using a mixed ANOVA. This interaction effect was significant ($F_{9.0,342.9} = 3.111$, $P = 0.001$, $\eta_p^2 = 0.076$). Follow-up mixed ANOVAs demonstrated the specific days at which the serial position × group interaction was significant. Improvements in memory performance were observed on day 3 ($F_{3.6,137.3} = 5.713$, $P < 0.001$, $\eta_p^2 = 0.131$), day 4 ($F_{3.1,120.6} = 18.93$, $P < 0.001$, $\eta_p^2 = 0.333$) and 1 month after intervention ($F_{2.8,109.3} = 3.852$, $P = 0.013$, $\eta_p^2 = 0.092$). Additional ANOVAs revealed that the day × group interaction was significant only for the recency serial position cluster ($F_{2.6,100.7} = 5.116$, $P = 0.004$, $\eta_p^2 = 0.119$) but not other position clusters ($Fs < 1.005$, $ps > 0.407$). Independent-sample *t*-tests revealed significant improvements in the recency effect in the IPL theta group relative to sham group on day 3 and day 4 of neuromodulation, and these improvements were sustained at the 1-month post-intervention timepoint (Fig. 2a, top and bottom). The pattern of effects was not affected by inclusion of additional covariates (Supplementary Tables 1–3). The results suggest that theta-rate neuromodulation aimed at left IPL selectively enhanced WM in older individuals without behavioral costs to other memory systems. These selective memory improvements were evident by day 3 of the intervention and lasted for at least 1 month, relative to memory performance of participants in the sham group.

Specific location and frequency combinations are necessary.

Experiment 1 demonstrated improved WM function with repetitive modulation of IPL theta rhythms. However, both theta and gamma frequency rhythms contribute to WM function[32]. As a result, it is important to confirm whether WM improvements occur specifically due to theta modulation in the IPL or whether they are also possible with gamma modulation in the IPL. Likewise, it is important to confirm whether LTM improvements with DLPFC modulation are specifically due to gamma entrainment or whether theta entrainment can produce similar effects. To test these possibilities, we performed Experiment 2 following the same design as Experiment 1, except that the three experimental groups received sham, IPL gamma or DLPFC theta modulation. A mixed ANOVA with day (baseline, day 1, day 2, day 3, day 4 and 1 month) and serial position (primacy, middle 1, middle 2, middle 3 and recency) as within-subjects factors and group (sham, DLPFC theta and IPL gamma) as between-subjects factor failed to find any significant differences in the recall performance (day × serial position × group: $F_{25.3,721.9} = 0.535$, $P = 0.971$, $\eta_p^2 = 0.018$; Fig. 2b). This was not influenced by inclusion of covariates ($F_{24.3,633.2} = 0.630$, $P = 0.916$, $\eta_p^2 = 0.024$). This indicates that the improvements we observed in Experiment 1 are both location specific and frequency specific: modulation of theta rhythms in the IPL, and not gamma rhythms, improved WM without affecting LTM; and modulation of gamma rhythms in the DLPFC, and not theta rhythms, improved LTM without affecting WM. Moreover, the two different frequency conditions for a given brain region across the two experiments serve as active controls for each other. Consequently, these findings confirm that the effects observed in Experiment 1 are not due to any non-specific effect of tACS such as transretinal or transcutaneous modulation[33] but due to frequency-specific entrainment of relevant brain circuits.

Validation of sham and pre-intervention baseline controls.

To test the validity of the control procedures and, thus, the strength of the principal findings, we examined the recall performance at the pre-intervention baseline timepoint across groups (Experiment 1: sham, DLPFC gamma and IPL theta; Experiment 2: sham, DLPFC theta and IPL gamma; Fig. 2a,b, 'Baseline' timepoint) and serial positions. A mixed ANOVA comparing these groups did not find a significant interaction effect of serial position (primacy, middle 1, middle 2, middle 3 and recency) or group (Experiment 1: sham, DLPFC gamma and IPL theta; Experiment 2: sham, DLPFC theta and IPL gamma) on performance at the pre-intervention baseline timepoint with or without covariates in either experiment ($Fs < 0.925$, $ps > 0.488$). These results suggest that the three groups in each experiment did not differ in their baseline memory performance for any serial position cluster. Thus, the selective effects of neuromodulation on serial positions were not driven by any inherent differences within the three groups in either experiment. Furthermore, we tested how stable and reliable the recall performance was for serial position clusters within the sham group across timepoints in each experiment (baseline, day 1, day 2, day 3, day 4 and 1 month; Fig. 2a,b, top). A repeated-measures ANOVA examining the day × serial position interaction effect within the sham group did not show any significant differences with or without covariates in either experiment ($Fs < 1.603$, $ps > 0.135$). Together, these results demonstrate the stability and reliability of memory performance during the pre-intervention baseline across different groups of participants and within the same group of participants over different timepoints of assessment lasting more than 1 month, which together strengthen confidence in the validity of the control procedures and the resulting tACS improvements.

Four-day improvement rate predicts benefits 1 month later.

Having established the location specificity and frequency specificity of the memory improvements, we next explored factors that predict sustainable effects. We evaluated the rates of improvement in LTM (primacy) and WM (recency) over the 4-day intervention in Experiment 1. Of the 20 participants in the DLPFC gamma group, 17 (85%) showed a positive rate of primacy improvements over the 4 days. Similarly, of the 20 participants receiving IPL theta modulation, 18 (90%) showed a positive rate of recency improvements over the 4 days. By modeling these data using linear regression, we observed a significantly higher mean rate of improvement for primacy over 4 days of DLPFC modulation relative to sham and for recency during IPL modulation relative to sham (Fig. 3), but the reverse was not true. Neither recency in the DLPFC gamma group nor primacy in the IPL theta group were significantly different relative to sham after Bonferroni correction (Fig. 3). Strikingly, the rate of improvement over the course of the intervention was highly predictive of post-intervention memory benefits: participants with greater primacy improvement rates during DLPFC modulation showed the largest primacy benefits at 1 month ($r_{18} = 0.817$, $P_{corr} < 0.001$), and participants with greater recency improvement rates during IPL modulation showed the largest recency benefits at 1 month ($r_{18} = 0.655$, $P_{corr} = 0.002$) (Fig. 4a,b). Again, the opposite was not true (DLPFC recency: $r_{18} = 0.243$, $P_{corr} = 0.303$; IPL primacy: $r_{18} = 0.385$, $P_{corr} = 0.094$; Pearson test, two-sided, Bonferroni correction, $P_{corr} < 0.0125$). The results indicate that not only did the overwhelming majority of older individuals experience memory improvements—selectively for WM or LTM depending on the nature of neuromodulation—the size and, thus, the sustainability of the memory improvements 1

month later were highly predicted by the speed of memory improvements during the 4-day intervention.

General cognitive function moderates memory improvements.

Previous studies demonstrated that the effects of tACS can be modulated by baseline behavioral[34] and neural[35] states. We, therefore, examined whether memory improvements due to neuromodulation in Experiment 1 were moderated by levels of baseline cognitive function. We performed participant-wise regression of MoCA scores, memory performance at the 1-month post-intervention timepoint and the rate of change in memory performance during days 1–4 for the primacy and recency serial position clusters (Fig. 5). Participants with lower baseline cognitive performance in the DLPFC gamma group showed higher rates of primacy improvement over the 4-day intervention ($r_{18} = -0.822$, $P < 0.001$; Fig. 5a) and showed larger primacy gains at 1 month after intervention ($r_{18} = -0.795$, $P < 0.001$; Fig. 5b). No such relationships held for recency in the DLPFC gamma group ($rs_{18} > -0.25$, $ps > 0.288$; Fig. 5c,d). Moreover, participants with lower baseline cognitive performance in the IPL theta group showed higher recency improvement rates over the 4-day period ($r_{18} = -0.824$, $P < 0.001$; Fig. 5g) and greater recency improvements after 1 month ($r_{18} = -0.499$, $P = 0.025$; Fig. 5h). Consistent with previous analyses, the level of cognitive performance did not predict changes in primacy during or after IPL modulation ($rs_{18} > -0.274$, $ps > 0.242$; Fig. 5e,f). Thus, older participants with relatively low baseline cognition more strongly revealed the preferential nature of the gamma-rate DLPFC and theta-rate IPL modulation effects on primacy and recency, respectively. This conclusion, which suggests distinctive functions of prefrontal gamma rhythms for LTM and parietal theta rhythms for WM, was reinforced by the absence of participant-wise correlations in the sham group between baseline cognitive behavior and primacy or recency measured during or after sham ($rs_{18} > 0.064$, $ps > 0.79$). These results suggest that the large-scale population dynamics that support memory function in older people can be differentially modulated depending on the individual level of general cognitive performance.

Replication of primary findings in an independent sample.

We performed an additional experiment to test whether the primary observations from Experiment 1 replicate in an independent sample. Experiment 3 consisted of 30 older participants randomized to receive either DLPFC gamma or IPL theta neuromodulation during performance of the free recall task. The neuromodulation protocol followed was largely similar to Experiment 1, except that the neuromodulation was performed for three rather than four consecutive days and did not include a long-term follow-up. Memory performance was examined at baseline and during each neuromodulation session. A mixed ANOVA with day (baseline, day 1, day 2 and day 3) and serial position (primacy, middle 1, middle 2, middle 3 and recency) as within-subjects factors and group (DLPFC gamma and IPL theta) as between-subjects factor revealed significant differences in memory performance (day × serial position × group: $F_{7.9,220.8} = 6.315$, $P < 0.001$, $\eta_p^2 = 0.184$; Fig. 6a), and this effect remained significant even after accounting for covariates ($F_{7.7,176.1} = 5.887$, $P < 0.001$, $\eta_p^2 = 0.204$). Follow-up ANOVAs revealed a significant interaction between serial position and group on days 2 and 3 of neuromodulation and a significant interaction between day and group for the primacy and recency clusters (Supplementary

Table 4). Two-sided independent-sample *t*-tests showed that memory performance in the primacy cluster was significantly improved in the DLPFC gamma group relative to the IPL theta group on day 2 and day 3 of neuromodulation (Fig. 6a, top). Performance in the recency cluster was significantly higher in the IPL theta group relative to the DLPFC gamma group on day 3 of the intervention (Fig. 6a, bottom). These results parallel observations from Experiment 1 (Fig. 2a, left). Baseline performance did not differ between the two groups (Supplementary Table 4), thus ruling out non-specific between-group differences. Examining the relationship between baseline cognitive function and memory performance, we found that individuals with lower MoCA scores in the DLPFC gamma group showed better memory performance at day 3 only in the primacy cluster ($r_{13} = -0.672$, $P = 0.006$; Fig. 6b,c), whereas those with lower MoCA scores in the IPL theta group showed better memory performance on day 3 only in the recency cluster ($r_{13} = -0.618$, $P = 0.014$; Fig. 6d,e), similar to the findings in Experiment 1 (Fig. 5). Together, these observations in an independent sample of participants replicate the primary findings of Experiment 1, further strengthening confidence in the inferences drawn from them.

Discussion

We present evidence for selective improvements in WM and LTM in older adults through dissociable spatiospectral entrainment of brain rhythms, and the improvements are sustained for at least 1 month after intervention. Experiment 1 showed that selective changes to WM and LTM function are possible through entrainment of theta rhythms in the IPL and gamma rhythms in the DLPFC, respectively. Experiment 2 showed that switching the modulation frequencies between the two regions did not produce any benefits. Consequently, it is the combination of anatomical location and rhythmic frequency that determines the appropriate substrate for memory improvement. Moreover, it confirmed that the improvements observed during Experiment 1 were due to entrainment of functionally specific brain circuits and not due to non-specific effects such as transretinal or transcutaneous stimulation[33]. In addition, we observed greater improvements in individuals with poorer cognitive function. These findings were further replicated in an independent sample in Experiment 3. We further found that the speed with which the memory function improves during the intervention predicts memory strength 1 month after the intervention, thus yielding an important metric to measure treatment responsiveness in future studies. Together, these findings suggest that memory function can be selectively and sustainably improved in older adults through modulation of functionally specific brain rhythms.

The specificity with which distinct rhythmic neuromodulation protocols affected different memory functions may seem surprising given the literature documenting general involvement of both frontal and parietal regions and both theta and gamma rhythms to WM and LTM function[36,37]. This is particularly the case because neuromodulation was performed during both encoding and recall of all words presented during a list. Our findings strongly suggest that our interventions manipulated two distinct cognitive operations. Following the dual-store framework, we hypothesize that IPL theta modulation improved WM operations. However, unlike in previous neuromodulation studies with visuospatial memoranda[18], we do not think that IPL theta modulation improved WM capacity per se. If that were the case, then improvements in memory performance would have also been

observed in some middle position clusters in addition to the recency cluster. We also do not expect increases in general attention function with IPL theta modulation. Although parietal theta rhythms are hypothesized to facilitate attentional sampling[38], there is little evidence to suggest changes in attention with parietal theta entrainment[39]. Instead, we propose that IPL theta modulation may have facilitated the temporal segregation between successive memory representations, minimizing interference among them[15]. Moreover, theta rhythms are also known to facilitate temporal context-mediated recall[40], potentially reflecting a common neurophysiological mechanism underlying preserved maintenance and context-based retrieval of WM representations. Intrinsic limitations on the WM capacity, unaffected by neuromodulation, may constrain these improvements to only the later words in the list, thereby only improving the recency cluster. If so, then these findings may reflect an additional approach for non-invasively improving WM function within the influential theta–gamma cross-frequency coupling theory[15], besides changing memory capacity[18]. The possibility that, although IPL theta modulation may have facilitated maintenance and recall of later list items, it may not have improved the transfer of previously presented information to LTM, may have further contributed to the selectivity of effects. This could be due to the presence of distinct encoding mechanisms for the two memory stores, a possibility supported by a recent transcranial magnetic stimulation (TMS) study[14]. Alternatively, transfer of representations between the two memory systems may involve separate executive control processes[41] that were unaffected by the current neuromodulation design. Consequently, IPL theta modulation may not have affected memory representations in the primacy cluster. Instead, improvements in the primacy effect emerged selectively with DLPFC gamma modulation. This protocol may have selectively improved the ability to retrieve the representations separately encoded or transferred to LTM, by potentially affecting hippocampus and other temporal lobe structures[42], which also simultaneously exhibit gamma activity during delayed recall[36]. A previous neuromodulation study, although examining memory function in young adults with single-session conventional tACS, aligns with this proposal[22]. Thus, although both theta and gamma rhythms, and both DLPFC and IPL regions, are known to generally contribute to WM and LTM performance, they may index distinct cognitive processes that selectively underlie the dissociable improvements observed in the current study.

The findings of the present study also contribute to the debate surrounding theoretical models of free recall. Segregated neural bases of primacy and recency effects have been a hotly debated topic in neuropsychology with conflicting evidence[14,43]. The selective modulation of primacy and recency effects observed in the current study support distinct underlying mechanisms, in agreement with the dual-store models[11] and neuropsychological observations[12,13]. However, our findings, at present, are not incompatible with alternative models of free recall. For instance, one theory attributes primacy effects to ‘long-term working memory’ in which long-term storage and retrieval operations support WM function contingent upon expertise-dependent retrieval structures[44,45]. This view is not inconsistent with the aforementioned hypothesis that DLPFC gamma neuromodulation may have affected retrieval from LTM, albeit— in this view—in service of WM. A way to disambiguate between these two perspectives is to use the method of personalization to modulate expertise[45], in which case this theory would predict a stronger effect of

DLPFC gamma neuromodulation in the presence of stronger expertise-dependent retrieval structures. Furthermore, although the contextual retrieval theories are not designed to explain primacy effects, deficits in primacy effects in older adults have been attributed to attentional processes[46], which, in turn, are associated with DLPFC gamma activity[47]. It is possible that DLPFC gamma neuromodulation may have further enhanced the intrinsic gradient in the efficiency of encoding mechanisms with benefits to early events in a series[46]. Notably, increased gamma activity in the temporal lobe is associated with this effect[17]. As discussed above, DLPFC gamma neuromodulation may have led to downstream effects on gamma activity in the temporal lobe structures[42], enhancing the primacy effect. Whether DLPFC gamma neuromodulation specifically affects LTM retrieval processes or attentional mechanisms can be potentially addressed through a granular analysis of memory performance within the primacy cluster. For instance, the LTM retrieval account predicts an additive shift to memory performance with increasing serial position in the primacy cluster due to similar benefits to retrieval processes at all serial positions, whereas the attentional account predicts a reduction in the slope of memory performance as a function of the serial position, thereby reflecting a stabilization in sustained attention[46]. The success of the neuromodulation protocol in selectively manipulating the primacy effect will be a powerful tool to test these competing predictions. Future studies that are sufficiently powered to systematically test these hypotheses can disambiguate between these competing predictions to refine and reconcile the various theories of free recall.

This work contributes to the growing literature that suggests potential clinical benefits for memory function in older adults with non-invasive techniques[7]. The protocols used in the current study demonstrate that memory function can be selectively improved for at least 1 month after a 4-day intervention. These long-lasting effects may arise due to neuroplastic changes[48] after phase-locking of intrinsic brain rhythms with tACS[49]. In addition, these findings suggest that functional differentiation, which typically reduces with aging[50], can be promoted through functionally specific neuromodulation. Findings from the present study may motivate several lines of investigation to further examine their clinical potential. For instance, future studies should examine the generalizability of these findings to different cognitive paradigms spanning memory function across various sensory domains and replicate them in larger study samples. Moreover, how to promote sustainable effects that go beyond the 1-month duration observed in the current study needs to be determined. Personalization of the neuromodulation protocol according to individual anatomical and functional characteristics is one possible approach[6]. In addition, the specific frequency within the theta and gamma ranges, the number and duration of modulation sessions, the optimal gap between successive sessions and the interaction of baseline cognitive and neural function with these metrics can be systematically varied to determine the most optimal modulation designs. Furthermore, in addition to MoCA, future studies should use more comprehensive neuropsychological assessments to quantify baseline cognitive function and its association with tACS-induced improvements. Finally, beyond potential benefits to healthy older adults, the translational implications for people with neuropsychiatric and neurodegenerative disorders, particularly those with selective memory deficits[10] and at risk for dementia[5], should be examined. Findings from the present study serve as a stepping stone toward investigating these questions of clinical interest.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41593-022-01132-3.

Methods

Participants.

Participants were recruited from the greater Boston metropolitan area via advertisements on local and electronic bulletin boards. In total, 156 older participants provided informed written consent to procedures approved by the Boston University Institutional Review Board. Four participants (three from Experminent 2 and one from Experiment 3) were lost to attrition, and two participants (from Experiment 1) voluntarily withdrew before completing the study. Data on the remaining 150 participants (Experiment 1, $n = 60$; Experiment 2, $n = 60$; Experiment 3, $n = 30$) at all timepoints were analyzed. Inclusion criteria included participants aged 65 years or older, native or fluent in English and normal or corrected-to-normal vision and hearing. Exclusion criteria were any metal implants in the head; implanted electronic devices; history of seizure, stroke, neurological problems or head injury; current psychiatric or neurological disorders; substance abuse; skin sensitivity; claustrophobia; smoking; psychotropic medication; left-handedness; and severe tinnitus. At baseline, participants' depressive symptoms were assessed using the GDS[31], and general cognitive performance was assessed using the MoCA[30]. Participants' demographics and neuropsychological data are summarized in Table 1. Across the three experiments, the racial and ethnic distributions of the participants were as follows: 11% African American, 55% Caucasian, 33% Asian and 0.7% Native American/Pacific Islander; 3% of the participants identified as Hispanic. All participants were compensated $15 per hour.

The necessary sample size was estimated from a pilot experiment using a sample of 24 participants (DLPFC gamma $n = 8$; IPL theta $n = 8$; sham $n = 8$). By conservatively pooling mean difference and s.d. values in behavioral responses between active and sham conditions for day 3, day 4, and 1-month timepoints, we estimated Cohen's d effect size based on independent-sample two-tailed t-tests (recency IPL theta versus sham, $ds > 0.94$; primacy DLPFC gamma versus sham, $ds > 0.92$). We found that a sample size of 20 participants was sufficient to detect an effect of the same magnitude with 80% power at the $P = 0.05$ significance level.

Stimuli and procedures.

Overview.—We conducted two randomized, double-blind, sham-controlled behavioral experiments (Experiments 1 and 2) involving four consecutive days of HD-tACS in an 8 × 1 source-sink configuration, and an additional randomized, double-blind replication experiment involving three consecutive days of HD-tACS in the same configuration (Experiment 3). Participants were randomly assigned to one of three (Experiments 1 and 2) or two (Experiment 3) neuromodulation groups (Experiment 1: sham, DLPFC gamma

and IPL theta; Experiment 2: sham, DLPFC theta and IPL gamma; Experiment 3: DLPFC gamma and IPL theta) using block randomization stratified by age and baseline general cognitive performance. WM and LTM functions were evaluated at baseline before the intervention, during each 8 × 1 tACS session (that is, on day 1, day 2, day 3 and day 4 in Experiments 1 and 2; day 1, day 2 and day 3 in Experiment 3) and 1 month after the last day of the intervention (Experiments 1 and 2).

Experimental task.—On each test day, participants performed a classic immediate free recall task consisting of five lists of 20 unrelated English high-frequency words, ranging from four to 12 letters in length. The words were drawn from the Penn Electrophysiology of Encoding and Retrieval Study word pool consisting of 1,638 words with clear meaning that could be reliably judged in size and animacy encoding tasks[51]. Words with extreme values along frequency, concreteness and emotional valence dimensions were removed to create a relatively homogenous word pool. For each participant, 30 lists of words were randomly assigned to one of six test days (five lists/100 words per day). During each experiment, words were read aloud to the participant one at a time at a rate of 1.5–2 seconds per word with an inter-word interval of approximately 2 seconds. Immediately after the presentation of each list, participants freely recalled as many words as they could within a 2-minute period. Two experimenters independently noted the remembered words and their serial position. Task duration was approximately 18 minutes. Data were collected electronically in Excel (version 16.16.27) by two experimenters, independently.

HD-tACS.—The alternating current was non-invasively delivered using an M×N nine-channel high-definition transcranial electrical current stimulator (Soterix Medical). A BrainCap (Brain Vision) embedded with high-definition plastic holders consisted of nine 12-mm-diameter Ag/AgCl ring electrodes, filled with conductive gel. The choice of DLPFC and IPL targets for modulating LTM and WM, respectively, was based on previous research[14]. Electric field modeling using HD-Targets (version 3.0.1, Soterix Medical) guided electrode number, location and intensity for each montage (see Fig. 1 for neuromodulation parameters). The left DLPFC target (Brodmann's area 9) corresponded to the following coordinates determined from neuroimaging research: $x = -31$, $y = 44$ and $z = 25$[52]. The left IPL coordinates, $x = -42$, $y = -54$ and $z = 42$ (Brodmann area 40), corresponded to the left supramarginal gyrus[53]. A bipolar sinusoidal alternating current was applied at 60 Hz for DLPFC targeting and at 4 Hz for IPL targeting in Experiments 1 and 3 and at 60 Hz for IPL targeting and 4 Hz for DLPFC targeting in Experiment 2. The modulation intensity was chosen to induce a minimum voltage gradient of 0.2 volts per meter (V/m) in the targeted regions while staying within established safety guidelines. The choice of modulation intensity was also constrained by meta-analysis research showing that tACS studies using intensities above 1 mA have a greater probability of enhancing performance[54]. With these considerations, electric field modeling with specified cortical targets and the 8 × 1 source-sink electrode design determined 1.58 mA, peak-to-peak, as maximal net intensity at the scalp. All participants tolerated the intervention well, and no adverse events were reported.

We took several steps to ensure that information about the experiments would not bias the results according to previously established methods[7,29,34,41,55–57]. First, Experiments 1 and 2 were sham-controlled. The passive sham protocol followed the same procedure as active neuromodulation but, critically, lasted only 30 seconds, ramping up and down at the beginning and end of the 20-minute period, reproducing the warming and poking sensations participants commonly endorse and then habituate to during active neuromodulation[29]. Such sham procedures are considered the gold standard in non-invasive neuromodulation research. Second, in addition to passive sham, Experiment 1 benefited from active control procedures implemented throughout the study[7]. Both DLPFC gamma and IPL theta protocols in Experiment 1 delivered the same modulation intensity. Moreover, the DLPFC theta and IPL gamma protocols in Experiment 2 targeted the same cortical targets in Experiment 1 at the same modulation intensity but at opposite frequencies. These active control procedures built within and across the two experiments effectively eliminated potential confounds associated with shunting or peripheral co-stimulation, such as transretinal or transcutaneous stimulation[33], and ensured robust inferences about the location specificity and frequency specificity of any observed effects. Third, we performed Experiment 3 to replicate the principal findings from the conditions of interest in Experiment 1 (DLPFC gamma and IPL theta) in a new sample of participants. Converging findings from both experiments would engender confidence in the robustness of the inferences. Fourth, the present experiments also benefited from a pre-intervention baseline control condition. We were able to examine the stability and reliability of recall performance at each position cluster within the sham group across timepoints in Experiments 1 and 2. Moreover, we were able to examine the pre-intervention baseline recall performance across modulation groups to eliminate potential confounds related to between-group differences. Fifth, we used a double-blind method in which the participant and both experimenters performing data collection were blinded to the experimental manipulation. An additional experimenter set the mode (for example, active or sham) on the neuromodulation machine but, otherwise, did not interact with the participant or the experimenters who performed data collection. Sixth, all testing was conducted in a sound-attenuated, electrically shielded chamber. Seventh, the experimental designs were between-participants to avoid potential carryover effects from different neuromodulation protocols, which is important in multi-day applications. Eighth, we confirmed that participants were blinded to the presence of the neuromodulation. After each test day, we administered a safety questionnaire[58] and visual analog scale[59], which included questions regarding attention, concentration, mood, vision, headache, fatigue and skin sensations under the modulating electrodes. Scores on these ratings did not significantly differ between groups (Experiment 1: $Fs_{2,57} < 0.362$, $ps > 0.698$, $n = 60$; Experiment 2: $Fs_{2,57} < 2.106$, $ps > 0.131$, $n = 60$; Experiment 3: $Fs_{1,28} < 1.135$, $ps > 0.296$, $n = 30$; one-way ANOVA). In addition, all participants were asked at the end of each experiment whether they could guess whether they were participating in an active or sham procedure and were at chance levels (Experiments 1 and 2: 33%; Experiment 3: 50%).

Data analysis.

Consistent with prior research[14], serial position effects were examined by collapsing the 20-word lists into four-word clusters of primacy (serial positions 1–4), three middles (5–8, 9–12 and 13–16) and recency (17–20). Mean recall probability was computed across lists

for each cluster, participant and modulation group. Given the five serial position clusters, six measurement timepoints (baseline, days 1–4, 1 month after intervention) and three groups (Experiment 1: sham, DLPFC gamma and IPL theta; Experiment 2: sham, DLPFC theta and IPL gamma), 90 distributions of mean recall probability across participants, were examined in Experiments 1 and 2. Similarly, given the five serial position clusters, four measurement timepoints (baseline and days 1–3) and two groups (DLPFC gamma and IPL theta), 40 distributions of mean recall probability across participants, were examined in Experiment 3. We first examined whether the data were normally distributed to determine their appropriateness for parametric statistical tests. Although the Shapiro–Wilk test for normality was significant in a minority of distributions (25/90 in Experiment 1; 21/90 in Experiment 2; 2/40 in Experiment 3), the skewness statistic overwhelmingly lay between −1.96 and 1.96 (89/90 distributions in both Experiments 1 and 2, 40/40 in Experiment 3), which does not indicate a significant departure from normality[60–62]. Accordingly, we proceeded with parametric mixed and repeated-measures ANOVAs to test our hypotheses about selective effects of the modulation group on memory recall probability according to the serial position and measurement day. An omnibus mixed ANOVA was used to test the presence of a significant interaction effect of the within-subjects factors serial position (primacy, middle 1, middle 2, middle 3 and recency) and day (Experiment 1 and 2: baseline, day 1, day 2, day 3, day 4 and after 1 month; Experiment 3: baseline, day 1, day 2 and day 3) and between-subjects factor of group (Experiment 1: sham, DLPFC gamma and IPL theta; Experiment 2: sham, DLPFC theta and IPL gamma; Experiment 3: DLPFC gamma and IPL theta). If a significant interaction effect was observed, then follow-up mixed ANOVAs were performed to compare the group × serial position × day interaction between pairs of groups. Follow-up mixed and repeated-measures ANOVAs and two-tailed independent-sample *t*-tests were conducted to parse the specific serial position and days at which significant differences were observable between the two given groups. For verification of control procedures, a repeated-measures ANOVA was performed within the sham group in Experiments 1 and 2 testing the serial position × day interaction to ensure the reliability and stability of repeated recall measurements. Moreover, a mixed ANOVA testing the main and interaction effects of serial position and group at the baseline timepoint was performed to ensure that the groups did not differ in memory performance at baseline in any experiment. Additional control analyses included covariates including age, sex, years of education, MoCA and GDS scores to ensure that the observed effects were not influenced by these demographic and clinical characteristics. In an exploratory analysis, we included biological sex as an additional factor in a mixed ANOVA to examine sex differences in the group × serial position × group interaction. In another exploratory analysis, we used mean rate of change in primacy or recency recall probability over the 4-day intervention as a dependent variable and tested for differences between groups in Experiment 1 (DLPFC gamma versus sham and IPL theta versus sham) using independent-sample *t*-tests (two-sided), Bonferroni-corrected for multiple comparisons ($P_{corr} < 0.0125$). We also examined whether an individual's mean rate of change induced by DLPFC or IPL modulation later predicted their primacy or recency recall performance at 1 month after intervention using regression analyses in Experiment 1 ($n = 20$, Pearson test, two-sided, Bonferroni correction, $P_{corr} < 0.0125$). Before these analyses, we confirmed the appropriateness of these parametric procedures by examining the skewness of the rate of change distributions across participants

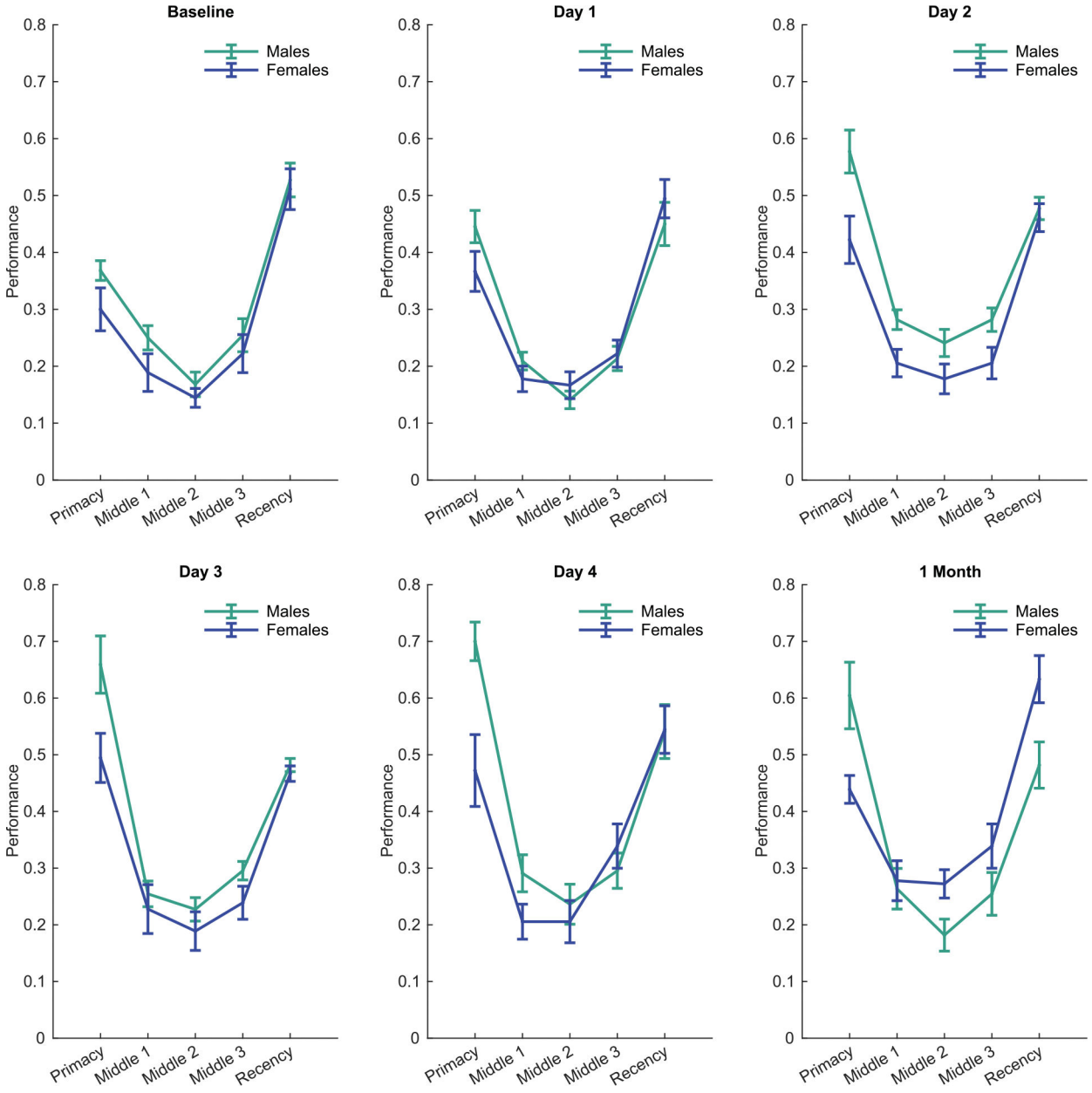
and 1-month post-intervention memory scores across participants, for both primacy and recency clusters. Finally, for each modulation group in Experiment 1 (DLPFC gamma, IPL theta and sham), regression analyses were used to examine relationships between individual cognitive performance measured by mean MoCA scores and the rate of primacy and recency change over the 4-day intervention as well as recall performance at 1 month after intervention. To test whether these relationships between memory performance and baseline individual cognitive function replicate, we performed regression analyses between MoCA scores and the recall performance of the primacy and recency clusters on the last day of assessment (day 3 of the intervention) in Experiment 3. Data were analyzed using SPSS version 27 software.

Partial eta squared (η_p^2) values and Cohen's d effect sizes are reported for the ANOVA and independent-sample t-test analyses, respectively, to facilitate comparison between studies and promote replication.

Reporting summary.

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Extended Data



Extended Data Fig. 1 |. Differences in memory performance according to biological sex in the DLPFC gamma group in experiment 1.

Exploratory analyses examining the impact of biological sex showed a significant interaction effect of serial position × group × biological sex ($F_{6.1,164.7} = 6.139$, $p = 7 \times 10^{-6}$, $\eta_p^2 = 0.185$) in Experiment 1 (N = 20 in the DLPFC gamma group, N = 20 in the IPL theta group, and N = 20 in the sham group). Follow-up analyses showed that the serial position × biological sex interaction was significant in the DLPFC gamma group ($F_{2.4,43.2} = 19.160$, $p = 2.86 \times 10^{-7}$, $\eta p^2 = 0.516$) but not in the IPL theta and sham groups ($Fs < 1.754$, $ps > 0.173$). Independent samples t-tests were performed to compare the memory performance for a given serial position on a given day between males and females in the DLPFC gamma

group. Better primacy performance was observed among males in the DLPFC gamma group than females on day 2 (t_{18} = 2.619, p = 0.017, d = 1.177), day 3 (t_{18} = 2.288, p = 0.034, d = 1.028), day 4 (t_{18} = 3.151, p = 0.006, d = 1.416), and 1 month ($t_{13.4}$ = 2.477, p = 0.027, d = 1.029) timepoints. Other trends observed were improved performance in males on day 2 of neuromodulation, evident in the middle 1 (t_{18} = 2.490, p = 0.023, d = 1.119) and the middle 3 (t_{18} = 2.136, p = 0.047, d = 0.960) clusters, and better performance among females at the offline timepoint 1 month after intervention in the middle 2 (t_{18} = −2.226, p = 0.039, d = −1.001) and recency (t_{18} = −2.448, p = 0.025, d = −1.1) clusters. However, none of these effects survived correction for multiple comparisons (Bonferroni correction; p_{cutoff} = 0.0017). Data are represented as mean values +/− S.E.M. across participants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by grants from the National Institutes of Health (R01-AG063775 and R01-MH114877) and a generous gift from an individual philanthropist awarded to R.M.G.R. We thank C. Willing and B. Lahner for assistance with data collection and X. (P.) Cheng and the anonymous reviewers for their thoughtful feedback on the manuscript.

Data availability

The data used for analysis in this study are freely and permanently available on Open Science Framework (https://osf.io/g4wcq/).

References

1. Centers for Disease Control and Prevention. Trends in aging—United States and worldwide. MMWR Morb. Mortal. Wkly. Rep 52, 101–104 (2003). 106. [PubMed: 12645839]
2. Samanez-Larkin GR & Knutson B Decision making in the ageing brain: changes in affective and motivational circuits. Nat. Rev. Neurosci. 16, 278–289 (2015). [PubMed: 25873038]
3. Søraas A et al. Self-reported memory problems 8 months after COVID-19 Infection. JAMA Netw. Open 4, e2118717 (2021). [PubMed: 34323987]
4. Rapp PR & Amaral DG Individual differences in the cognitive and neurobiological consequences of normal aging. Trends Neurosci. 15, 340–345 (1992). [PubMed: 1382333]
5. Gauthier S et al. Mild cognitive impairment. Lancet 367, 1262–1270 (2006). [PubMed: 16631882]
6. Grover S, Nguyen JA & Reinhart RMG Synchronizing brain rhythms to improve cognition. Annu. Rev. Med. 72, 29–43 (2021). [PubMed: 33035432]
7. Reinhart RMG & Nguyen JA Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat. Neurosci. 22, 820–827 (2019). [PubMed: 30962628]
8. Cowan N What are the differences between long-term, short-term, and working memory? Prog. Brain Res. 169, 323–338 (2008). [PubMed: 18394484]
9. Parkinson SR, Lindholm JM & Inman VW An analysis of age differences in immediate recall. J. Gerontol. 37, 425–431 (1982). [PubMed: 7086078]
10. Sullivan EV & Sagar HJ Double dissociation of short-term and long-term memory for nonverbal material in Parkinson's disease and global amnesia. A further analysis. Brain 114, 893–906 (1991). [PubMed: 2043956]

11. Atkinson RC & Shiffrin RM Human memory: a proposed system and its control processes. in The Psychology of Learning and Motivation: Advances in Research and Theory Volume 2 (ed. Spence KW) 89–195 (Academic Press, 1968).
12. Baddeley AD & Warrington EK Memory coding and amnesia. Neuropsychologia 11, 159–165 (1973). [PubMed: 4713392]
13. Shallice T & Warrington EK Independent functioning of verbal memory stores: a neuropsychological study. Q. J. Exp. Psychol. 22, 261–273 (1970). [PubMed: 5431401]
14. Innocenti I et al. TMS interference with primacy and recency mechanisms reveals bimodal episodic encoding in the human brain. J. Cogn. Neurosci. 25, 109–116 (2013). [PubMed: 23198892]
15. Lisman JE & Jensen O The theta–gamma neural code. Neuron 77, 1002–1016 (2013). [PubMed: 23522038]
16. Heusser AC, Poeppel D, Ezzyat Y & Davachi L Episodic sequence memory is supported by a theta–gamma phase code. Nat. Neurosci. 19, 1374–1380 (2016). [PubMed: 27571010]
17. Serruya MD, Sederberg PB & Kahana MJ Power shifts track serial position and modulate encoding in human episodic memory. Cereb. Cortex 24, 403–413 (2014). [PubMed: 23081881]
18. Wolinski N, Cooper NR, Sauseng P & Romei V The speed of parietal theta frequency drives visuospatial working memory capacity. PLoS Biol. 16, e2005348 (2018). [PubMed: 29538384]
19. Alekseichuk I, Turi Z, Amador de Lara G, Antal A & Paulus W Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr. Biol. 26, 1513–1521 (2016). [PubMed: 27238283]
20. Feurra M, Galli G, Pavone EF, Rossi A & Rossi S Frequency-specific insight into short-term memory capacity. J. Neurophysiol. 116, 153–158 (2016). [PubMed: 27121583]
21. Hoy KE, Whitty D, Bailey N & Fitzgerald PB Preliminary investigation of the effects of γ-tACS on working memory in schizophrenia. J. Neural Transm. 123, 1205–1212 (2016). [PubMed: 27116682]
22. Javadi A-H, Glen JC, Halkiopoulos S, Schulz M & Spiers HJ Oscillatory reinstatement enhances declarative memory. J. Neurosci. 37, 9939–9944 (2017). [PubMed: 28912159]
23. Nomura T, Asao A & Kumasaka A Transcranial alternating current stimulation over the prefrontal cortex enhances episodic memory recognition. Exp. Brain Res. 237, 1709–1715 (2019). [PubMed: 31011766]
24. Klink K, Peter J, Wyss P & Klöppel S Transcranial electric current stimulation during associative memory encoding: comparing tACS and tDCS effects in healthy aging. Front. Aging Neurosci. 12, 66 (2020). [PubMed: 32256337]
25. Köhler S, Paus T, Buckner RL & Milner B Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI—rTMS study. J. Cogn. Neurosci 16, 178–188 (2004). [PubMed: 15068590]
26. Wynn SC, Kessels RPC & Schutter DJLG Effects of parietal exogenous oscillatory field potentials on subjectively perceived memory confidence. Neurobiol. Learn. Mem. 168, 107140 (2020). [PubMed: 31843652]
27. Benussi A et al. Exposure to gamma tACS in Alzheimer's disease: a randomized, double-blind, sham-controlled, crossover, pilot study. Brain Stimul. 14, 531–540 (2021). [PubMed: 33762220]
28. Edwards D et al. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. Neuroimage 74, 266–275 (2013). [PubMed: 23370061]
29. Reinhart RMG, Cosman JD, Fukuda K & Woodman GF Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. Atten. Percept. Psychophys. 79, 3–23 (2017). [PubMed: 27804033]
30. Nasreddine ZS et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc 53, 695–699 (2005). [PubMed: 15817019]
31. Herrmann N et al. A validation study of the Geriatric Depression Scale short form. Int. J. Geriatr. Psychiatry 11, 457–460 (1996).
32. Axmacher N et al. Cross-frequency coupling supports multi-item working memory in the human hippocampus. Proc. Natl Acad. Sci. USA 107, 3228–3233 (2010). [PubMed: 20133762]

33. Karabanov AN, Saturnino GB, Thielscher A & Siebner HR Can transcranial electrical stimulation localize brain function? Front. Psychol 10, 213 (2019). [PubMed: 30837911]
34. Grover S, Nguyen JA, Viswanathan V & Reinhart RMG High-frequency neuromodulation improves obsessive-compulsive behavior. Nat. Med. 27, 232–238 (2021). [PubMed: 33462447]
35. Nguyen J, Deng Y & Reinhart RMG Brain-state determines learning improvements after transcranial alternating-current stimulation to frontal cortex. Brain Stimul. 11, 723–726 (2018). [PubMed: 29482970]
36. Sederberg PB et al. Gamma oscillations distinguish true from false memories. Psychol. Sci. 18, 927–932 (2007). [PubMed: 17958703]
37. Burke JF et al. Theta and high-frequency activity mark spontaneous recall of episodic memories. J. Neurosci. 34, 11355–11365 (2014). [PubMed: 25143616]
38. Fiebelkorn IC & Kastner S A rhythmic theory of attention. Trends Cogn. Sci. 23, 87–101 (2019). [PubMed: 30591373]
39. Deng Y, Reinhart RM, Choi I & Shinn-Cunningham BG Causal links between parietal alpha activity and spatial auditory attention. eLife 8, e51184 (2019). [PubMed: 31782732]
40. Herweg NA, Solomon EA & Kahana MJ Theta oscillations in human memory. Trends Cogn. Sci. 24, 208–227 (2020). [PubMed: 32029359]
41. Reinhart RMG & Woodman GF Enhancing long-term memory with stimulation tunes visual attention in one trial. Proc. Natl Acad. Sci. USA 112, 625–630 (2015). [PubMed: 25548192]
42. Simons JS & Spiers HJ Prefrontal and medial temporal lobe interactions in long-term memory. Nat. Rev. Neurosci. 4, 637–648 (2003). [PubMed: 12894239]
43. Ranganath C & Blumenfeld RS Doubts about double dissociations between short- and long-term memory. Trends Cogn. Sci. 9, 374–380 (2005). [PubMed: 16002324]
44. Ericsson KA & Kintsch W Long-term working memory. Psychol. Rev. 102, 211–245 (1995). [PubMed: 7740089]
45. Guida A et al. The effect of long-term working memory through personalization applied to free recall: uncurbing the primacy-effect enthusiasm. Mem. Cogn. 41, 571–587 (2013).
46. Healey MK & Kahana MJ A four-component model of age-related memory change. Psychol. Rev 123, 23–69 (2016). [PubMed: 26501233]
47. Benchenane K, Tiesinga PH & Battaglia FP Oscillations in the prefrontal cortex: a gateway to memory and attention. Curr. Opin. Neurobiol. 21, 475–485 (2011). [PubMed: 21429736]
48. Schwab BC, König P & Engel AK Spike-timing-dependent plasticity can account for connectivity aftereffects of dual-site transcranial alternating current stimulation. Neuroimage 237, 118179 (2021). [PubMed: 34015486]
49. Krause MR, Vieira PG, Csorba BA, Pilly PK & Pack CC Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc. Natl Acad. Sci. USA 116, 5747–5755 (2019). [PubMed: 30833389]
50. Koen JD & Rugg MD Neural dedifferentiation in the aging brain. Trends Cogn. Sci. 23, 547–559 (2019). [PubMed: 31174975]
51. Long NM, Danoff MS & Kahana MJ Recall dynamics reveal the retrieval of emotional context. Psychon. Bull. Rev. 22, 1328–1333 (2015). [PubMed: 25604771]
52. Wagner AD, Maril A, Bjork RA & Schacter DL Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. Neuroimage 14, 1337–1347 (2001). [PubMed: 11707089]
53. O'Connor AR, Han S & Dobbins IG The inferior parietal lobule and recognition memory: expectancy violation or successful retrieval? J. Neurosci. 30, 2924–2934 (2010). [PubMed: 20181590]
54. Schutter DJLG & Wischnewski M A meta-analytic study of exogenous oscillatory electric potentials in neuroenhancement. Neuropsychologia 86, 110–118 (2016). [PubMed: 27085766]
55. Reinhart RMG Disruption and rescue of interareal theta phase coupling and adaptive behavior. Proc. Natl Acad. Sci. USA 114, 11542–11547 (2017). [PubMed: 29073084]
56. Reinhart RMG, Xiao W, McClenahan L & Woodman GF Electrical stimulation of visual cortex can immediately improve spatial vision. Curr. Biol. 25, 1867–1872 (2016).

57. Reinhart RMG, Zhu J, Park S & Woodman GF Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain. Proc. Natl Acad. Sci. USA 112, 9448–9453 (2015). [PubMed: 26124116]

58. Poreisz C, Boros K, Antal A & Paulus W Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. 72, 208–214 (2007). [PubMed: 17452283]

59. Gandiga PC, Hummel FC & Cohen LG Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin. Neurophysiol. 117, 845–850 (2006). [PubMed: 16427357]

60. Kim H-Y Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. Restor. Dent. Endod. 38, 52–54 (2013). [PubMed: 23495371]

61. Field A Discovering Statistics Using IBM SPSS Statistics (Sage Publications, 2013).

62. West SG, Finch JF & Curran PJ Structural equation models with nonnormal variables: problems and remedies. in Structural Equation Modeling: Concepts, Issues, and Applications (ed. Hoyle RH) 56–75 (Sage Publications, 1995).

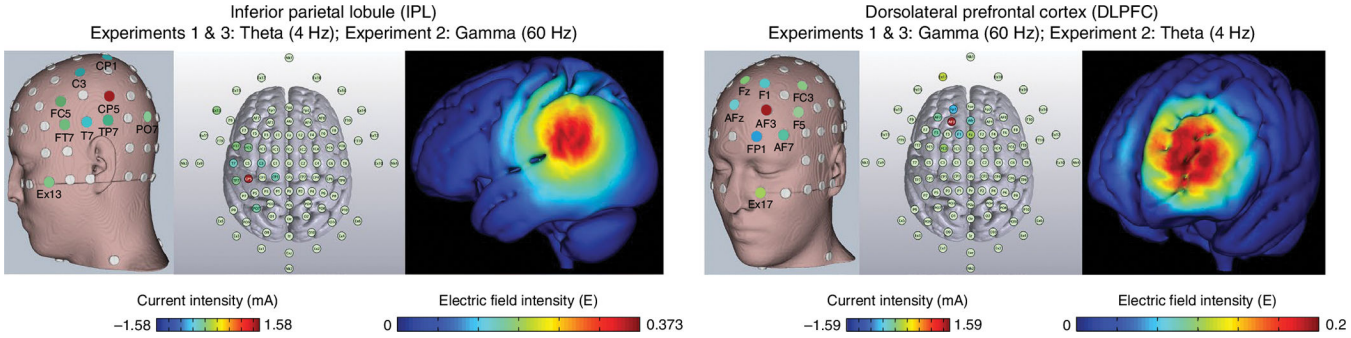


Fig. 1 |. Model-guided, high-definition neuromodulation.

The theta-rate IPL and gamma-rate DLPFC HD-tACS protocols and corresponding electric field models shown on three-dimensional reconstructions of the cortical surface. The left DLPFC and left IPL were targeted, each protocol using nine electrodes configured in a center-surround, source-sink pattern to achieve maximum focality. The location and current intensity value of each modulating electrode are shown. The DLPFC protocol included (in mA): FP1 (−0.6662), Fz (0.0739), F1 (−0.4438), AF3 (1.5892), FC3 (−0.0048), F5 (−0.2312), AF7 (−0.194), AFz (−0.3744) and EX17 (0.2513). The IPL protocol included (in mA): C3 (−0.2997), T7 (−0.3386), CP1 (−0.2975), FC5 (−0.1284), CP5 (1.5818), FT7 (−0.0852), TP7 (−0.1413), PO7 (−0.2366) and EX13 (−0.0545).

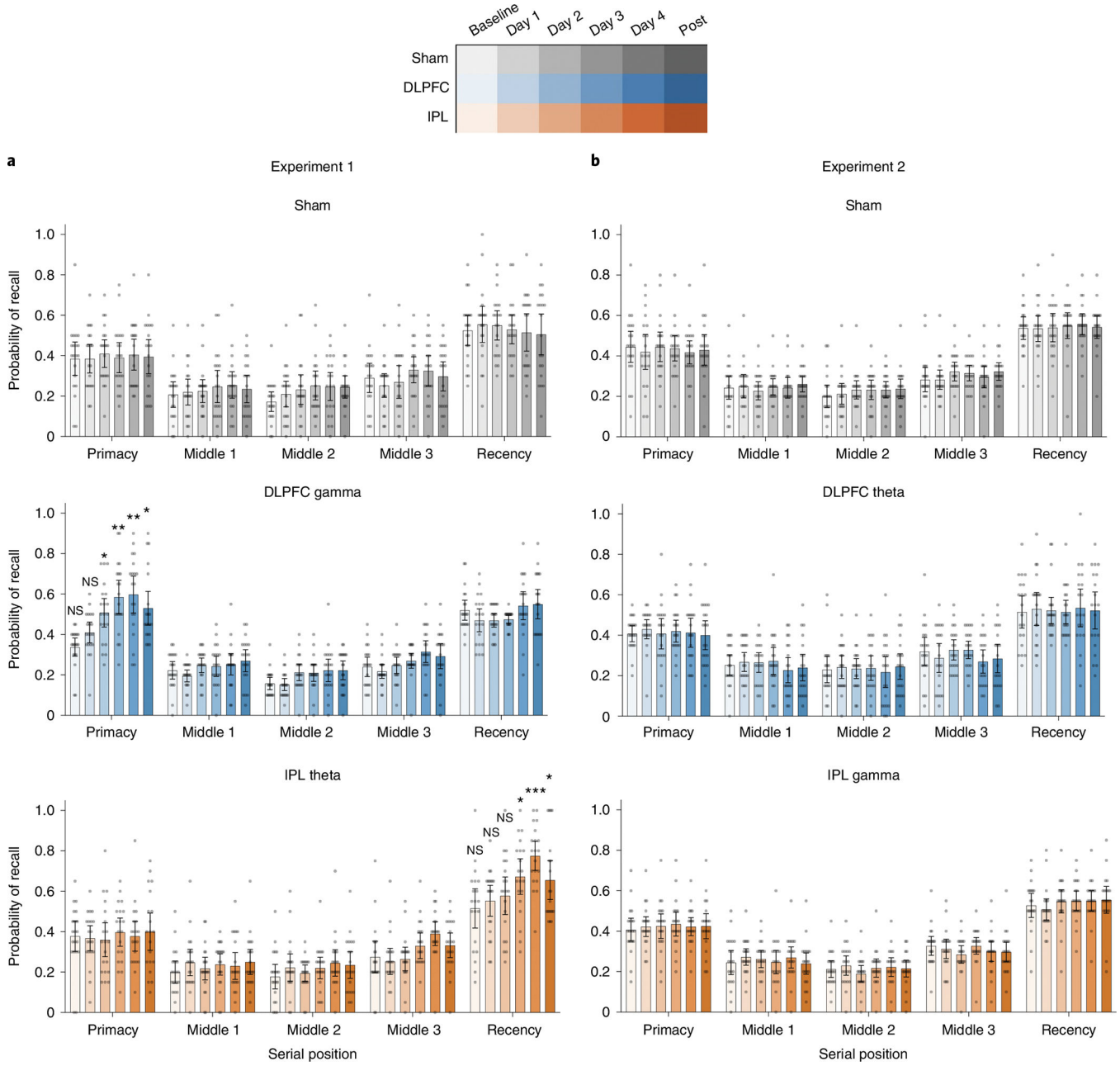


Fig. 2 |. Selective, sustainable memory improvements via spatiospectral-dissociable neuromodulation.

A mixed ANOVA was performed to examine differences in recall probabilities in each experiment with the following factors: day (baseline, days 1–4 and 1 month), serial position (primacy, middles 1–3 and recency) and groups (E1: sham, DLPFC gamma and IPL theta; E2: sham, DLPFC theta and IPL gamma). Interaction effects were parsed with follow-up ANOVAs and two-sided independent-sample *t*-tests. **a**, Mean recall probabilities plotted across serial position clusters (primacy, three middles and recency) at pre-intervention baseline, day 1, day 2, day 3, day 4 and 1 month after intervention for Experiment 1 groups: sham (top, grays, $n = 20$), DLPFC gamma (middle, blues, $n = 20$) and IPL theta (bottom,

oranges, $n = 20$) neuromodulation groups. Gray dots show individual participant data. Mean of center shows the average recall probability, and the error bars show 95% CI across participants. Asterisks identify days on which significant differences were observed among the modulation groups and serial positions during the follow-up two-sided independent-sample *t*-tests. These indicate significantly higher recall probability within the primacy cluster in the DLPFC group, relative to the sham group, in Experiment 1, on day 2 ($t_{38} = 2.075$, $P = 0.045$, $d = 0.66$), day 3 ($t_{38} = 3.660$, $P = 0.001$, $d = 1.16$), day 4 ($t_{38} = 3.381$, $P = 0.002$, $d = 1.07$) and 1 month ($t_{38} = 2.381$, $P = 0.022$, $d = 0.75$) timepoints and significantly higher recall probability within the recency cluster in the IPL theta group, relative to the sham group, in Experiment 1, on day 3 ($t_{38} = 2.631$, $P = 0.012$, $d = 0.83$), day 4 ($t_{38} = 4.650$, $P = 3.9 \times 10^{-5}$, $d = 1.47$) and 1 month ($t_{38} = 2.253$, $P = 0.030$, $d = 0.98$) timepoints. **b**, Mean recall probabilities as in **a** for Experiment 2 groups: sham (top, grays, $n = 20$), DLPFC theta (middle, blues, $n = 20$) and IPL gamma (bottom, oranges, $n = 20$). No significant differences in mean recall probabilities were observed in Experiment 2. Comparisons within the primacy and recency cluster were hypothesis driven and were not subjected to any corrections for multiple comparisons. Comparisons within the middle position clusters were exploratory and subjected to Bonferroni correction. $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$. CI, confidence interval; NS, not significant.

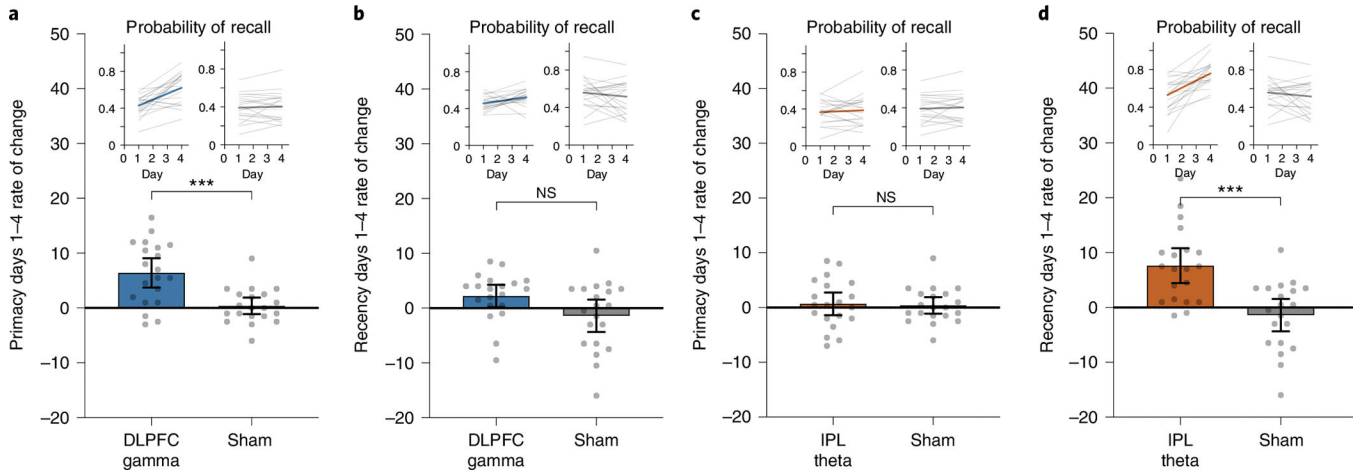


Fig. 3 |. Neuromodulation selectively determines speed of memory improvement over days in experiment 1.

Mean rates of change in primacy (**a**) and recency (**b**) over the 4-day intervention shown for the DLPFC gamma group (blue, $n = 20$) compared to sham (gray, $n = 20$). Gray dots show individual participant data. Center of the error bars shows the mean rate of change in primacy or recency recall probabilities across the 4 days of the intervention, and the error bars show 95% CI across participants. Insets show the strength (or slope) of each participant's linear relationship between primacy or recency recall probabilities and time over the 4-day intervention, in gray, and the average slope for the specific group and the serial position cluster is highlighted in color. Two-sided independent-sample *t*-tests showed differences in mean rates of change between DLPFC gamma and sham groups in the primacy cluster ($t_{29.97} = 4.090$, $P_{corr} = 2.98 \times 10^{-4}$, $d = 1.29$) but not the recency cluster ($t_{38} = 2.110$, $P_{corr} = 0.042$, $d = 0.67$). **c**, Similar plot as in **a** showing the rate of change in the primacy cluster in the IPL theta group (orange, $n = 20$) compared to sham. No significant differences were observed ($t_{38} = 0.225$, $P_{corr} = 0.824$, $d = 0.07$). **d**, Similar plot as in **b** showing the rate of change in the recency cluster in the IPL theta group (orange, $n = 20$) compared to sham. Two-sided independent-sample *t*-tests showed significantly higher rates of change in the IPL theta group relative to sham for the recency cluster ($t_{38} = 4.361$, $P_{corr} = 9.5 \times 10^{-5}$, $d = 1.38$). These analyses were exploratory and were subjected to Bonferroni correction for multiple comparisons ($P_{corr} < 0.0125$). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. CI, confidence interval; NS, not significant.

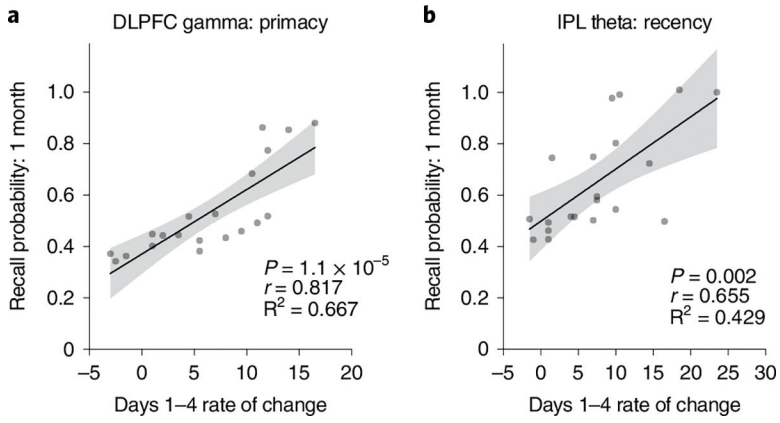


Fig. 4 |. Speed of memory improvement during neuromodulation predicts size of memory benefits at 1 month in experiment 1.

Regression analyses were performed to test for the presence of a linear relationship across participants between the rate of change in recall performance during neuromodulation and the recall performance 1 month after the intervention. **a**, Scatter plot shows the speed (rate of change) of each participant's improvement in primacy over 4 days of DLPFC gamma neuromodulation against the same individual's primacy score 1 month after intervention in Experiment 1. Gray dots show individual participant data ($n = 20$). The solid line indicates a regression fit, and the error bands show 95% CI. This exploratory analysis identified significant, positive linear relationships between the rate of primacy improvements and 1-month primacy performance in the DLPFC gamma group ($r_{18} = 0.817$, $P = 1.1 \times 10^{-5}$). **b**, Scatter plot as in **a** for recency in the IPL theta group ($n = 20$) in Experiment 1. Significant, positive, linear relationship was observed between the rate of recency improvements and 1-month recency performance in the IPL theta group ($r_{18} = 0.655$, $P = 0.002$). These analyses were subjected to Bonferroni correction for multiple comparisons ($P_{corr} < 0.0125$). CI, confidence interval.

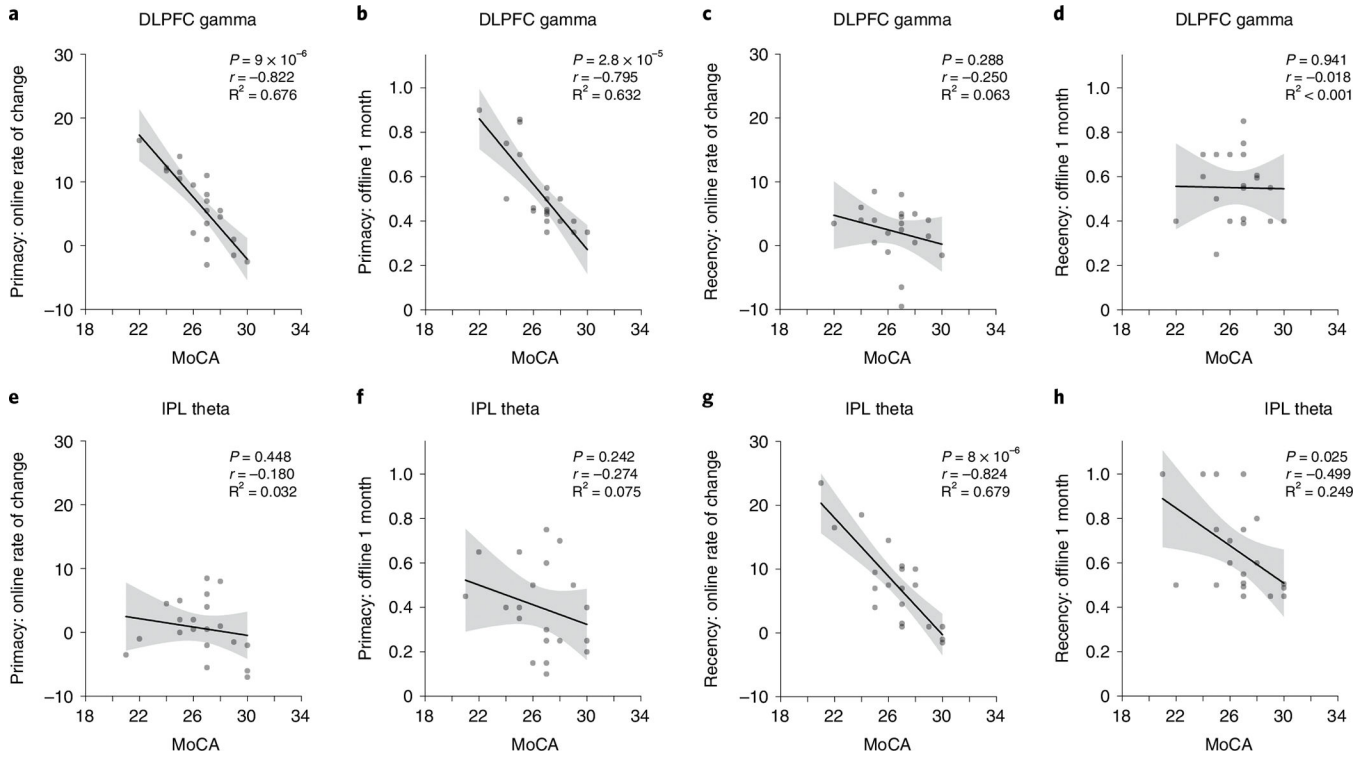


Fig. 5 |. Individual differences in general cognitive function moderate selectivity and sustainability of neuromodulation effects on memory performance in experiment 1.

Participant-wise correlations between general cognitive function, quantified by MoCA scores and memory performance measures in the DLPFC gamma ($n = 20$) and IPL theta ($n = 20$) groups. Memory performance measures include 'online' measures quantified by the rate of change in memory performance across days 1–4 of neuromodulation and 'offline' measures quantified by the memory performance at the 1-month post-intervention timepoint, separately computed for the primacy and recency clusters. **a**, Correlation between MoCA scores and online measure for the primacy cluster in the DLPFC gamma group ($r_{18} = -0.822$, $P = 9 \times 10^{-6}$). **b**, Correlation between MoCA scores and offline measure for the primacy cluster in the DLPFC gamma group ($r_{18} = -0.795$, $P = 2.8 \times 10^{-5}$). **c**, Correlation between MoCA scores and online measure for the recency cluster in the DLPFC gamma group ($r_{18} = -0.250$, $P = 0.288$). **d**, Correlation between MoCA scores and offline measure for the recency cluster in the DLPFC gamma group ($r_{18} = -0.018$, $P = 0.941$). **e**, Correlation between MoCA scores and online measure for the primacy cluster in the IPL theta group ($r_{18} = -0.180$, $P = 0.448$). **f**, Correlation between MoCA scores and offline measure for the primacy cluster in the IPL theta group ($r_{18} = -0.274$, $P = 0.242$). **g**, Correlation between MoCA scores and online measure for the recency cluster in the IPL theta group ($r_{18} = -0.824$, $P = 8 \times 10^{-6}$). **h**, Correlation between MoCA scores and offline measure for the recency cluster in the IPL theta group ($r_{18} = -0.499$, $P = 0.025$). Solid lines indicate the regression fit across participants between the MoCA scores and the neuromodulation effects (rate of change during modulation/recall probability after 1 month) in the primacy or recency clusters. Error bands show 95% CI. These hypothesis-driven analyses were not subjected to multiple comparisons correction. CI, confidence interval.

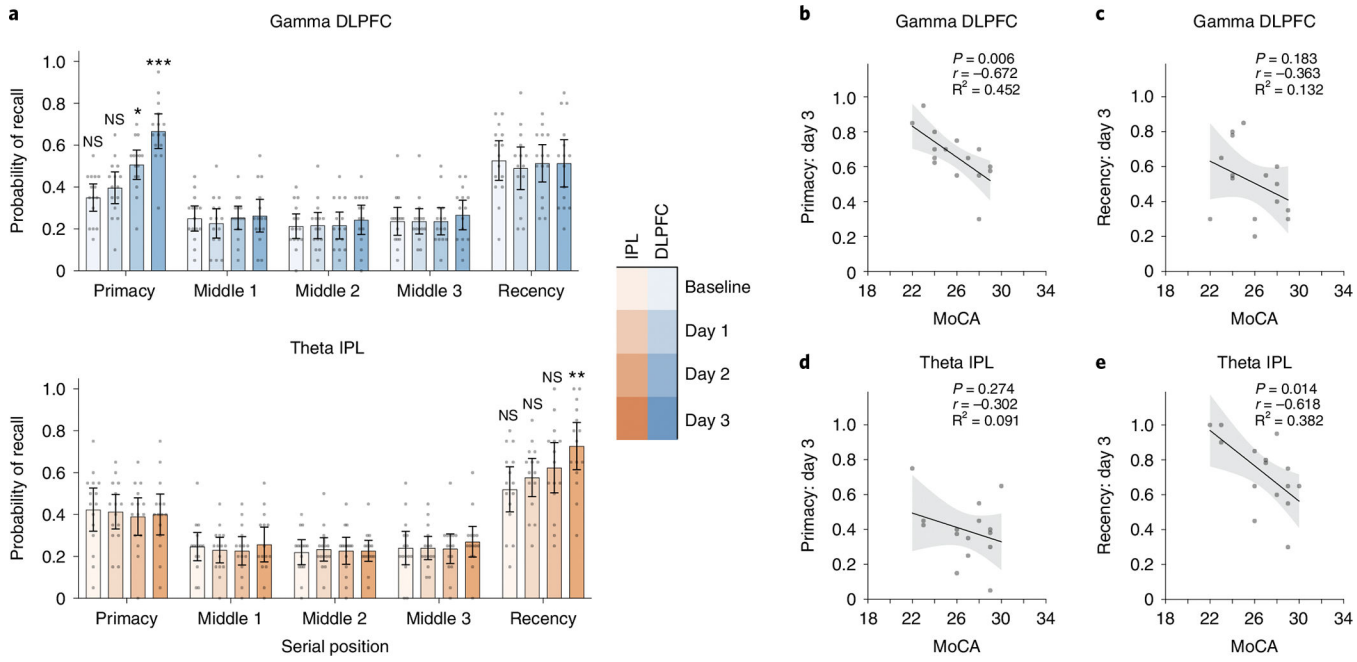


Fig. 6 |. Replication of selective improvements in memory, associated with individual differences in general cognitive function, in experiment 3.

a, Mean recall probabilities plotted across serial position clusters on all measurement days for Experiment 3 groups: DLPFC gamma (top, blues, $n = 15$) and IPL theta (bottom, oranges, $n = 15$). Gray dots show individual participant data. Mean of center shows the average recall probability, and the error bars show 95% CI across participants. Following mixed ANOVAs (see text), two-sided independent-sample t-tests identified significant differences in recall probability across days, groups and serial positions (see asterisks). Participants in the DLPFC gamma group showed higher recall probability within the primacy cluster on day 2 ($t_{28} = 2.2$, $P = 0.037$, $d = 0.80$) and day 3 ($t_{28} = 4.467$, $P = 1.25 \times 10^{-4}$, $d = 1.63$). Participants in the IPL theta group showed higher recall probability within the recency cluster on day 3 ($t_{28} = -2.868$, $P = 0.008$, $d = 1.05$). Comparisons within the primacy and recency cluster were hypothesis driven and were not subjected to any corrections for multiple comparisons. Comparisons within the middle position clusters were exploratory and subjected to Bonferroni correction. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$. NS, not significant. **b**, Participant-wise correlations between MoCA scores and memory performance in the primacy cluster on day 3 of neuromodulation in the DLPFC gamma group ($r_{13} = -0.672$, $P = 0.006$). Similar correlations are shown for the recency cluster performance on day 3 in the DLPFC gamma group ($r_{13} = -0.363$, $P = 0.183$) in **c**, for the primacy cluster performance in the IPL theta group ($r_{13} = -0.302$, $P = 0.274$) in **d** and for the recency cluster performance in the IPL theta group ($r_{13} = -0.618$, $P = 0.014$) in **e**. Gray dots indicate individual participant data. Solid line indicates a regression fit, and the error bands show 95% CI across participants. These hypothesis-driven regression analyses were not subjected to multiple comparisons correction. CI, confidence interval.

Table 1 |

Demographic characteristics by neuromodulation group

	DLPFC gamma, *n* = 20	**IPL tdeta, *n* = 20**	**Sham, *n* = 20**	
	Mean (s.d.)/count	**Mean s.d.)/count**	**Mean (s.d.)/count**	***P* value**
Experiment 1				
Age (years)	74.25 (5.58)	75.9 (6.45)	73.85 (6.55)	0.545[a]
Sex (male/female)	11/9	12/8	11/9	0.934[b]
Education (years)	16.23 (3.05)	15.57 (3.14)	16.1 (2.17)	0.743[a]
MoCA	26.5 (1.93)	26.55 (2.44)	27.4 (2.35)	0.371[a]
GDS	1.6 (1.53)	1.85 (1.5)	1.4 (1.1)	0.594[a]
Experiment 2				
	DLPFC theta *n* = 20	**IPL gamma *n* = 20**	**Sham *n* = 20**	
	Mean (s.d.)/count	**Mean (s.d.)/count**	**Mean (s.d.)/count**	***P*value**
Age (years)	76.85 (7.18)	76.7 (5.64)	76.55 (6.87)	0.990[a]
Sex (male/female)	11/9	10/10	9/11	0.819[b]
Education (years)	14.75 (2.27)	15.45 (2.09)	14.65 (2.56)	0.496[a]
MoCA	25.9 (2.95)	26.2 (2.71)	25.45 (2.6)	0.689[a]
GDS	1.55 (1.15)	1.75 (1.12)	1.8 (1.47)	0.802[a]
Experiment 3				
	DLPFC gamma *n* = 15	**IPL theta *n* = 15**		
	Mean (s.d.)/count	**Mean (s.d.)/count**		***P*value**
Age (years)	71.80 (5.92)	72.33 (5.25)		0.796[a]
Sex (male/female)	8/7	6/9		0.464[b]
Education (years)	13.93 (2.05)	14.2 (2.70)		0.763[a]
MoCA	25.8 (2.27)	26.8 (2.48)		0.260[a]

GDS	1.40 (0.83)	1.47 (1.30)	0.802[a]

[a]One-way ANOVA.

[b]Two-sided chi-squared test.