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REVIEW

Driving working memory with frequency-tuned noninvasive brain stimulation

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Frequency-tuned noninvasive brain stimulation is a recent approach in cognitive neuroscience that involves matching the frequency of transcranially applied electromagnetic fields to that of specific oscillatory components of the underlying neurophysiology. The objective of this method is to modulate ongoing/intrinsic brain oscillations, which correspond to rhythmic fluctuations of neural excitability, to causally change behavior. We review the impact of frequency-tuned noninvasive brain stimulation on the research field of human working memory. We argue that this is a powerful method to probe and understand the mechanisms of memory functions, targeting specifically task-related oscillatory dynamics, neuronal representations, and brain networks. We report the main behavioral and neurophysiological outcomes published to date, in particular, how functionally relevant oscillatory signatures in signal power and interregional connectivity yield causal changes of working memory abilities. We also present recent developments of the technique that aim to modulate cross-frequency coupling in polyrhythmic neural activity. Overall, the method has led to significant advances in our understanding of the mechanisms of systems neuroscience, and the role of brain oscillations in cognition and behavior. We also emphasize the translational impact of noninvasive brain stimulation techniques in the development of therapeutic approaches.

Keywords: rhythmic TMS; tDCS; tACS; behavior; brain oscillations; neural networks

Brain oscillations as functional markers of cognition

Brain oscillations are remarkable components of brain activity. They are accessible at multiple scales, with depth recordings in animal preparations and patients and noninvasively with scalp electroencephalography or magnetoencephalography (EEG/MEG) source imaging. These signal elements provide the experimental material for mechanistic inferences about the dynamical structure of distributed brain activity.^{1,2} A prominent view is that oscillations are generated by network activity of synchronized cell assemblies.³ At rest and during task performance, the signal properties of brain oscillations (frequency, phase, and amplitude) vary considerably across brain regions, depending on the mental state and the task being performed.¹ It has been suggested that polyrhythmic oscillatory

brain signals reflect nested networks that oscillate at different frequencies and spatial scales.⁴ Recently, several oscillatory patterns (e.g., power, interregional coherence) have been interpreted as supporting brain function, not only by synchronizing at the same frequency but also through complex cross-frequency interactions.^{5–7}

Over the last decades, oscillatory components of neural signalling have been defined as signatures of distributed cognitive processes.⁸ Delta-band (2–4 Hz) and theta-band (4–8 Hz) oscillations are typically considered as markers of attention, arousal, or memory during demanding cognitive tasks.⁹ Oscillatory activity in the alpha band (8–15 Hz) is consistently reported to desynchronize (i.e., to show reduced amplitude) during such tasks and is recently described as reflecting cortical excitability.^{10,11} An emerging view of oscillations

in the beta (15–30 Hz) and gamma (>30 Hz) frequency ranges is that of complementary markers, with beta oscillations associated with top-down signaling (carrying prediction mechanisms via corticocortical long-distance communication¹²) and gamma rhythms marking bottom-up and local (intraregional) processes.^{4,13}

Overall, endogenous and stimulus-driven neural oscillations in the delta–gamma frequency ranges correlate with and/or can predict the participant's behavioral performance.⁴ Although these studies have suggested that brain oscillations are involved in various sensory and cognitive processes, their causal relationship with behavior needs to be clarified: do neuronal oscillations causally affect behavior and performance, or is it the other way around? The recent development of frequency-tuned noninvasive brain stimulation techniques^{14–16} allows us to investigate this causal relationship by directly modulating brain oscillations during task performance.

Frequency-tuned transcranial brain stimulation

Noninvasive brain stimulation techniques¹⁷ are potent tools to investigate the causal relationship between brain and behavior. Such techniques employ either magnetic or electric fields to stimulate cortical cell assemblies directly transcranially, which in turn may causally modulate behavioral responses. The most widely used techniques are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), oscillatory tDCS (otDCS), and transcranial alternating current stimulation (tACS). OtDCS/tDCS and tACS use electrical currents applied with at least two scalp electrodes. TMS is based on the principle of electromagnetic induction.

To date, these techniques have been successfully employed offline (i.e., not concurrently with task performance) in numerous cognitive and clinical studies.^{18,19} Functional neuroimaging performed during stimulation reveals the distributed effect of magnetic or electric stimulation, spreading from the target anatomical location (under the TMS coil or the stimulation electrode) to other brain regions via anatomical connections.^{19,20} Consequently, the behavioral outcome of these stimulation techniques needs to be interpreted in the context of network effects.²¹

Furthermore, the functional specificity of the stimulation effect depends both on the anatomical location of the targeted brain regions and on the temporal properties of the stimulation signal. This is suggested by recent studies that employed rhythmic transcranial stimulation protocols (such as otDCS, tACS, or rhythmic TMS) and identified the more functionally relevant frequencies of stimulation that aim to modulate cognitive functions^{22–25} (see Refs. 14–16 for reviews). Rhythmic TMS and otDCS/tACS are complementary tools for influencing oscillatory brain activity. Rhythmic TMS applies time-varying magnetic fields, which causes the phase resetting of intrinsic/ongoing oscillations via a depolarization of neural assemblies.²⁶

With otDCS/tACS, the electrical currents are oscillatory and can be tuned to the frequency of target brain oscillations. OtDCS consists of cycles of ramp-like increases and decreases in current amplitude,²⁷ while in tACS the current is sinusoidal, with the polarity at each stimulation electrode being reversed rhythmically (antiphase stimulation; see below) at the target frequency. In terms of mechanisms of actions, tACS is assumed to induce plastic changes in neural networks dynamics rather than local entrainment (phase resetting).²⁸

High-density (HD)-tACS uses montages with more than two electrodes to stimulate distant cortical regions with variable amplitude and phase parameters.²⁴ In-phase stimulation (0° phase difference between two electrodes) is assumed to increase functional coupling (phase synchronization) between distant areas. Conversely, antiphase stimulation (180° phase difference between two electrodes) aims to decrease interregional synchrony.^{24,29} It is relevant to note, however, that the results from HD-tACS (also called dual-site tACS) studies should be interpreted with caution because, in these studies, the spatiotemporal properties of the stimulation were not always appropriately controlled. Indeed, while the electrode montage used in most of these studies (see Refs. 24 and 30–32) aimed to modulate the phase of the electric fields delivered to the target brain areas, all other stimulation features, such as the spatial focus with respect to the targeted brain areas or peak field strengths, were not estimated or reported. In a recent modeling study, Saturnino *et al.*³³ produced forward models of the spatiotemporal properties of the stimulation for the montages

used in References 24 and 30–32. They revealed that several other regions were also stimulated in addition to the target areas. Furthermore, and more importantly, the spatial pattern of the stimulation differed between the in- and antiphase conditions. This study underlines that differences in the spatiotemporal properties of in-phase and antiphase HD-TACS protocols might spuriously contribute to the observed behavior and electrophysiological effects. More modeling efforts are thus needed to disambiguate the flow of the electric currents in HD-tACS protocols (see also Ref. 16 for a critical review of the coupling/decoupling literature).

Several studies have demonstrated an immediate behavioral effect, in addition to functional changes as revealed by concurrent MEG/EEG, caused by stimulation frequencies that match those of endogenously generated brain rhythms (see Refs. 15 and 16). Using otTCS/tACS, such effects have been reported in multiple cognitive domains such as memory/cognition (e.g., Refs. 29, 34, and 35), motor control (e.g., Refs. 36 and 37), multisensory processing (e.g., Ref. 38), and unimodal perception (e.g., Refs. 24, 25, 39, and 40). Similar results have been obtained with rhythmic TMS.^{41–48} Overall, these studies suggest that frequency-tuned noninvasive brain stimulation can modulate brain oscillations to clarify their role in brain functions. Here, we review the potential of such approaches in modulating working memory, a cognitive ability that is required in learning, communication, and most task realization.⁴⁹

Distributed networks and oscillatory dynamics underlying working memory

Working memory is a cognitive ability allowing the simultaneous maintenance and processing of information (monitoring and manipulation) for a short period of time.^{49–52} In cognitive psychology studies, working memory is composed of three distinct stages: (1) *encoding*, engaging processes to register the information (memory items); (2) *maintenance*, corresponding to the storage (and manipulation) of information over time; and (3) *retrieval*, which refers to accessing the information by recall or recognition.⁴⁹ We focus here on the maintenance mechanisms where sustained endogenous brain activity is generated in the absence of external stimuli.

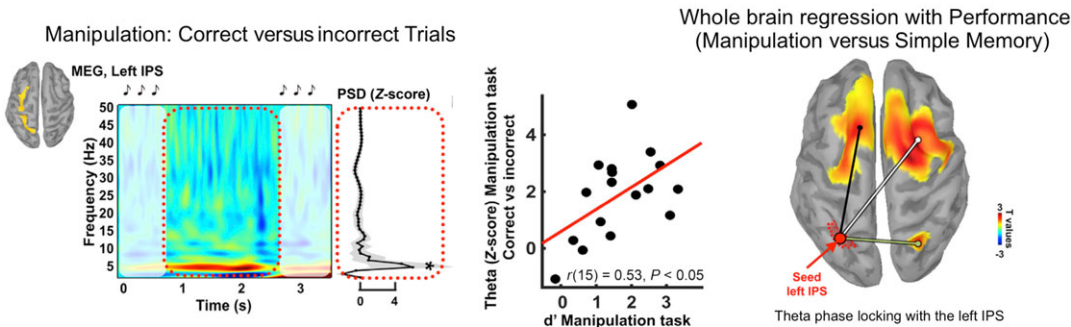
The brain networks and oscillatory dynamics associated with working memory have been studied extensively (see Refs. 53 and 54 for reviews). Note that although working memory networks involve both cortical and subcortical regions, we are focusing here only on the cortical systems. The transient maintenance of information (auditory, visual, tactile, multisensory) in memory involves the recruitment of distributed frontoparietal networks in addition to task-related sensory areas.⁵⁴

First, sensory areas and the ventral–lateral–prefrontal cortex (VLPFC) are assumed to trigger active low-level memory strategies (such as rehearsal). This hypothesis is supported by fMRI findings of persistent delay-period activity in these regions and of their functional interconnections during active rehearsal.^{50,55–57} These activations have been associated with low-frequency oscillations, mainly in the theta band.⁵⁸ Notably, theta oscillations are known to play a key role in ordering items that were presented sequentially in working memory (manipulation; see Ref. 53).

Second, a posterior parietal network has been identified that supports maintenance^{50,59–63} and retrieval⁶⁴ of information. This parietal network involves (1) the angular and supramarginal gyri, (2) the superior parietal lobe, (3) the perisylvian parietal cortex, and (4) the intraparietal sulcus (IPS).^{65,66} Notably, the IPS has been proposed to be fundamental to working memory.^{65,66} By investigating brain activity in the IPS and dorsolateral prefrontal cortex (DLPFC) during the realization of working memory tasks in which either monitoring or manipulating information was required, Champod and Petrides⁶⁶ highlighted the specific contribution of each region to working memory. Their results show that the IPS is involved in manipulation processes (see also Refs. 41, 67, and 68), whereas activation of the DLPFC is more related to the monitoring of the information manipulated. In terms of oscillatory signatures, memory manipulations generate theta activity, with effects in power, phase modulations, and coherent long-range communication and synchronization among frontoparietal regions^{29,41,69–72} (Fig. 1A).

Third, superior frontal regions, notably the DLPFC, mediate complex types of processing, as they are mainly recruited when active monitoring (and manipulation) of the remembered information is required.^{73,74} One possible role for the DLPFC

A Theta power and interregional phase locking support memory manipulation



B Gamma activity in the DLPFC supports memory maintenance

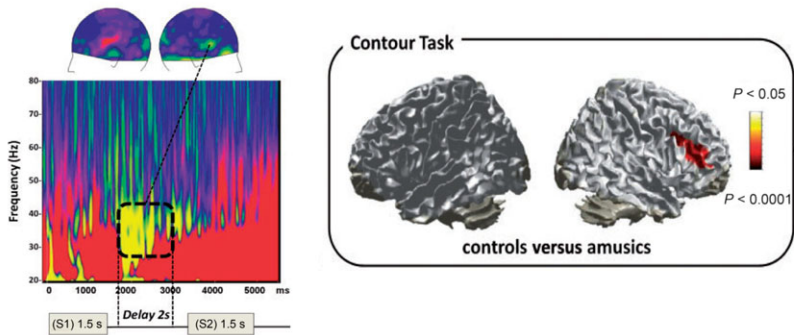


Figure 1. Theta and gamma oscillations support memory manipulation and maintenance, respectively. (A) Left panel: time–frequency plot (correct trials versus incorrect trials) for a trial time window (–100 to 3500 ms) of a delayed match-to-sample task (manipulation task; active mental reversal task). The ROI is located in the left intraparietal sulcus (IPS). Red dotted outlines indicate the time period of interest. The time–frequency map was Z-scored with baseline activity (–1000 to –100 ms before stimulus onset). Shaded error bars indicate SEM. Asterisk indicates significance. Central panel: scatter plots of participants’ performance in the manipulation task against theta power in the retention period for the manipulation task (correct versus incorrect contrast). Right panel: whole-brain regression between theta phase-locking value with left IPS, (manipulation task versus simple melody-comparison task) and behavioral performance in a manipulation task (compared with simple melody comparison). PSD, power spectrum density. Adapted from Ref. 41. (B) Left panel: time–frequency plot of a right temporal MEG sensor (MRT22, MEG right temporal) for a trial time window (–100 to 5500 ms) in a delayed match-to-sample task (simple melody-comparison task). The time–frequency power values are plotted after subtraction of the mean power values of the baseline for each frequency. Right panel: cortical mesh showing the statistics of two-sided *t*-tests for a group comparison between typical listeners (controls) and congenital amusics, a developmental disorder related to pitch-related memory deficits.^{76–79} Adapted from Ref. 75.

is that of a specialized region where stimuli or events that have been first interpreted and maintained in other association cortical areas can be monitored.⁵⁰ The DLPFC has been related to the central executive of Baddeley and Hitch,⁴⁹ as it is able to monitor multiple cognitive representations in working memory. In terms of oscillatory dynamics, it has been suggested that DLPFC functions during maintenance of working memory information are supported by high-frequency oscillations in the beta and gamma ranges^{53,75} (Fig. 1B). Notably, gamma oscillations

in the right DLPFC have been reported to support maintenance of pitch information in typical listeners. Interestingly, a decrease in gamma power during memory maintenance in these regions has been associated with memory developmental disorders (Fig. 1B; congenital amusia, a condition associated to pitch related memory deficits; see Refs. 76–81). Finally, the roles of other frequency bands in the working memory network (delta, alpha, beta) have also been investigated. Delta oscillations are commonly associated with attention processes.⁹ While

alpha oscillations are reduced in frontoparietal regions (indicating increased excitability) in working memory tasks, alpha synchronization (increase in signal power indicating reduced cortical excitability) is observed in brain regions unrelated to the task⁵⁸ (inhibition hypothesis; see Refs. 10 and 82). However, the hypothesis of decreased excitability in task-irrelevant brain regions is debated: augmented alpha activity has also been related to active task-relevant processing.⁸³ Beta oscillations are assumed to mark endogenous, top-down-controlled processing (for reviews, see Refs. 13 and 84) and to carry long-range communications in cortical networks.¹³ In the predictive coding framework,⁸⁵ there is growing evidence that beta oscillations are associated with communication of top-down predictive signals to sensory regions.^{12,86,87}

In summary, large corpuses of neurophysiological studies of working memory emphasize the relation between brain oscillations and the maintenance (and manipulation) of information in memory in a distributed network of frontal, parietal, and sensory areas. Below, we review how the modulation of these oscillatory signals influences behavior and contributes to establishing a causal link between the neurophysiology of brain activity and cognitive functions.

Impact of theta stimulation on working memory

Offline (i.e., nonconcurrent to task realization) non-invasive brain stimulation has been used extensively in studies of working memory (see Ref. 88 for review) but has yielded mixed outcomes. Here, we focus on more recent studies that used temporal stimulation parameters calibrated from the frequency of oscillatory activity associated with the performance of working memory tasks. Those studies aim either to (1) enhance memory performance by boosting task-related oscillatory markers (connectivity, power) or (2) transiently impair memory functions by applying stimulation at task-unrelated frequencies (or by inducing desynchronization between distant areas).

To date, most studies of memory maintenance and manipulation focused on theta oscillations and their role both in local processing (as measured by regional signal power) and interregional functional connectivity (via measures of, e.g., phase coupling or coherence) in the frontoparietal network.⁵³

Using theta-tACS, Jausovec *et al.*⁸⁹ alternatively stimulated at theta frequency the left frontal, left parietal, and right parietal cortices before testing participants' working memory abilities (offline). They reported that theta-tACS administered to either the right or left parietal cortex, but not frontal or sham stimulation, had a positive effect on subsequent working memory storage capacity during backward recall. Using a visual-array comparison task, the same group⁹⁰ reproduced this effect using theta-tACS over the left parietal cortex: participants showed increased memory span after stimulation (in comparison with frontal and sham stimulation). However, these studies tested the participants offline (after delivery of the tACS stimulation); hence, the possible interaction between task-related brain oscillations and behavior could not be evaluated. Indeed, although Jausovec and Jausovec⁹⁰ recorded EEG poststimulation during task performance and reported aftereffects on the P300 latency over left parietal brain areas, they did not investigate the oscillatory changes induced by the stimulation.

Several studies have overcome these limitations by applying stimulation during task performance. Merion and Lavidor⁹¹ applied theta-tACS over bilateral DLPFC during a verbal working memory task and reported a positive effect on accuracy compared with sham stimulation. Recently, Tseng *et al.*³² studied the effect of in-phase and antiphase theta (6 Hz) tACS over the left and right parietal cortices during visual working memory. They show that, while in-phase stimulation improved participants' performance, but only in low performers, antiphase stimulation decreased high performers' memory abilities. Polania *et al.*²⁹ investigated left-hemisphere frontoparietal long-range functional connectivity with theta-tACS applied continuously during a delayed letter-discrimination task. Using in-phase (synchronized) and antiphase (desynchronized) stimulation, they showed that tACS-induced phase synchronization of frontoparietal regions at theta resulted in decreased reaction times (faster processing) and that tACS-induced desynchronization produced the opposite effect. These results seemed to be frequency specific, as they were not observed for the control 35-Hz tACS (gamma frequency that is supposed to support local neural processes rather than long-range functional connectivity mechanisms).

More recent studies have used the same approach complemented with concurrent EEG/MEG

recordings during stimulation to clarify the links between neurophysiological signals and behavior. Notably Alekseichuk *et al.*⁹² showed increased reaction times in a 2-back visuospatial task during bihemispheric frontoparietal desynchronization (theta-tACS). The EEG data confirmed the decrease in phase connectivity (phase locking) between the prefrontal and parietal lobes induced by tACS-driven desynchronization. Similar results were reported in a MEG/tACS study⁹³ that targeted frontal midline theta activity via electrodes placed over the medial prefrontal and medial parietal areas (FPz and Pz). This stimulation reduced verbal working memory performance and induced frontoparietal desynchronization and decreased midline activity in the theta range. Neurophysiological effects of stimulation have also been explored with fMRI. Violante *et al.*⁹⁴ reported that in-phase frontoparietal theta-tACS during a verbal working memory task increased parietal fMRI activity, which correlated with behavioral performance (decreased reaction time for 2-back but not 1-back tasks).

Overall, these tACS studies suggest a causal role of theta oscillations in working memory performance and establish a correspondence between behavior and underlying cortical processes. However, as mentioned above, the results from HD-tACS (or dual-site tACS) studies need to be replicated with validated electrode montages to control the spatiotemporal properties of the stimulation (see Refs. 16 and 33). Notably, in a recent study, Kleinert *et al.*⁹⁵ controlled for stimulation intensities as well as for the direction of current flow during in-phase and antiphase right frontotemporal tACS. The authors did not report any behavioral effect of the stimulation in a visuospatial working memory task, which underlines the importance of using a proper electrode montage. However, they did not model the spatial focal concentration of the stimulation, which could differ between the in-phase and antiphase stimulation conditions. A second limitation of the study was the lack of online EEG recordings during tACS: EEG was measured only after tACS, revealing unspecific effects of the stimulation in other frequency bands.

Overall, while tACS studies suggest a causal role of theta oscillations in working memory, more research efforts are required to characterize the respective spatiotemporal properties of in-phase and antiphase stimulation protocols, by combining

the properties of the electrode montage, forward models of the stimulation's spatial focus, and concurrent EEG measurements to assess actual electrophysiological effects.^{16,33}

Another limitation of these tACS studies is the fact that the stimulation was applied continuously while the tasks were being performed. Consequently, the approach has limitations in identifying selective effects of the applied stimulation over distinct processing stages of the task (such as encoding versus maintenance, or retrieval). Rhythmic TMS, by nature, is an appropriate tool to target the functionally relevant time period of the task. Recently, Li *et al.*⁹⁶ stimulated the superior parietal lobe with theta-rhythmic TMS applied during the first half of the maintenance period of a delayed-recognition working memory task (memory for letters). By analyzing EEG directly after the stimulation (second half of the delay: 6-s delay, 3-s stimulation followed by 3 s of EEG analysis), they showed that rhythmic TMS increased the power of theta activity in occipitoparietal areas. They also reported that rhythmic TMS boosted theta phase synchronization between frontoparietal regions. Interestingly, the theta-band power changes observed positively correlated with TMS-induced behavioral changes (with faster reaction times). However, this study did not investigate the functional changes that occurred during the stimulation.

In order to address the various weaknesses identified above, we recently developed a novel protocol in which we defined participant-specific stimulation parameters to modulate theta signatures during the manipulation of information in auditory working memory. We identified in each volunteer when (functionally relevant time segment of the task), how (frequency of stimulation), and where (target network brain regions) the stimulation was applied.⁴¹ We used MEG imaging at baseline (before applying stimulation) to identify the anatomical origins of tonic oscillations that emerged during two working memory tasks: a simple melody-comparison task and an active mental-reversal task (manipulation task). Compared with simple memory, manipulation of melodies has been reported to recruit the dorsal pathway, including the IPS and superior and inferior frontal regions.^{67,68} The involvement of this network was confirmed by the MEG, as we showed that the participants' ability to manipulate auditory items in working

memory was related to the power of theta oscillations originating from the IPS and to the strength of theta interregional phase locking in a dorsal network encompassing the IPS and frontal areas (Fig. 1A).

In a subsequent session, we applied theta-rhythmic (and theta-arrhythmic as a control condition) TMS to the IPS theta-generating site in each individual during the first half of the silent memory-retention period. By combining EEG with TMS, we showed that the rhythmic stimulations delivered boosted the power and phase consistency of theta oscillations in the dorsal stream and resulted in significantly improved behavioral performances (accuracy) in mental manipulation (Fig. 2A). The degree of oscillatory entrainment scaled with behavioral enhancement, and both these behavioral and neurophysiological gains varied as a function of the participants' baseline memory-manipulation abilities. These effects were not observed for the simple memory task or when applying arrhythmic TMS. The observation of such task-specific effects suggests that rhythmic TMS interacted with ongoing, functionally relevant brain oscillations and resulted in enhanced cognitive performances (see Refs. 14–16). Moreover, the effects of rhythmic TMS on the phase and power of neural oscillations were expressed differentially: while power enhancement of induced oscillations was limited to the stimulation time period, the augmentation of their phase consistency extended further in time (for 1 s poststimulation (Fig. 2A)).

Overall, these studies indicate that theta activity (both in terms of regional power and interarea connectivity) can be manipulated with tACS and rhythmic TMS and is directly related to working memory performance. Below, we review several studies that have investigated, using transcranial stimulation, the function of other frequency bands (alpha, beta, gamma) in working memory.

The functional role of alpha, beta, and gamma oscillations in working memory

Most studies of alpha oscillations in working memory are in line with the inhibition hypothesis.¹⁰ For example, Kuhnke *et al.*⁹⁷ showed that rhythmic TMS applied at alpha frequency over the left VLPFC (posterior inferior frontal gyrus) selectively reduced manipulation abilities (sentence reordering) during sentence processing (relative to sham TMS). Similarly, Sauseng *et al.*⁵⁸ reported

that memory capacity can be increased when alpha-TMS is applied over cortical regions where irrelevant information is processed.

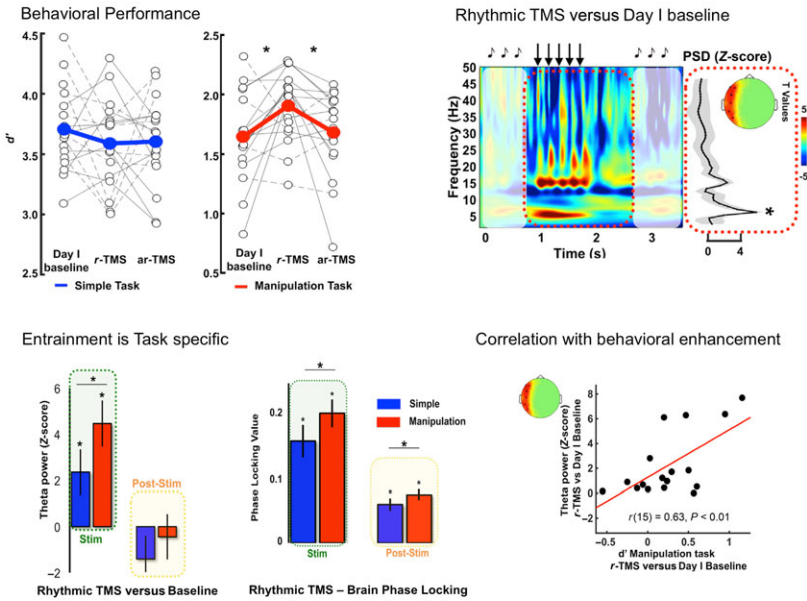
The contribution of beta oscillations to top-down control processes in cognitive functions, such as working memory maintenance, attention, and decision-making,⁹⁸ has also been investigated using the noninvasive stimulation techniques reviewed here. Feurra *et al.*⁹⁹ reported a frequency-specific effect of beta-tACS over the left parietal cortex that increased forward memory span for digits (but not backward memory span, which requires manipulation). Finally, both offline¹⁰⁰ and online^{101,102} modulations of gamma oscillations with tACS over frontal regions have been shown to boost working memory performance: right DLPFC gamma-tACS improved accuracy in a pitch-memory task of participants affected by congenital tonal memory deficit¹⁰¹ (Fig. 2B); left frontal gamma-tACS reduced reaction times in a 3-back task;¹⁰⁰ and left middle frontal gyrus gamma-tACS reduced reaction times on fluid intelligence.¹⁰² Effects on interregional communication supported by gamma oscillations were reported by Tseng *et al.*,¹⁰³ who showed that temporoparietal gamma desynchronization using tACS facilitated binding in a visual working memory task.

Overall, frequency-tuned stimulation studies have improved the understanding of the neural dynamics supporting working memory in humans. They revealed that oscillatory activity (power) and interregional functional connectivity at multiple frequency bands are causally linked to memory maintenance and manipulation. Recently, stimulation studies have begun to investigate the functional role of cross-frequency coupling between neural oscillations, whereby oscillatory signal components at different frequency bands are interdependent.^{1,7} Understanding cross-frequency coupling holds promise for future studies because of its important role recently highlighted in neuronal computation, communication, and associated cognitive functions, such as learning and memory.⁶

Perspectives: multiband stimulation, long-term effects, and translational impact on brain dysfunctions

Phase-amplitude coupling (PAC) is a widely observed form of cross-frequency coupling of the statistical dependence of the amplitude of

A Theta rhythmic TMS over the IPS specifically boosts memory manipulation



B Gamma tACS over the DLPFC boosts pitch memory maintenance

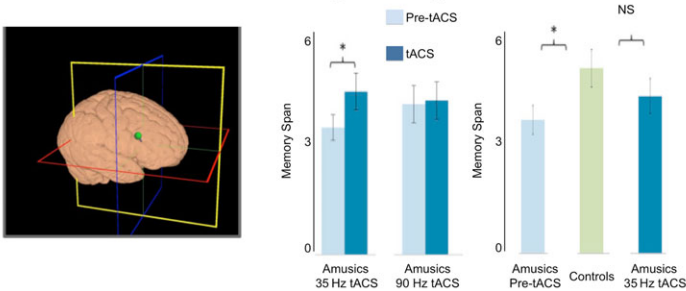


Figure 2. (A) Selective modulations of theta and gamma oscillations with frequency-tuned noninvasive stimulation causally boost memory manipulation and maintenance, respectively. Upper left panel: accuracy in terms of d' for three recording sessions (day 1 baseline (no stimulations), theta rhythmic TMS (r-TMS), and arrhythmic TMS (ar-TMS)) for a simple melody-comparison task (blue) and a manipulation task (red) (active metal reversal). White circles, individual performance; solid lines, participants showing increased performance for the rhythmic TMS condition as compared to day 1 baseline; dashed lines, participants showing decreased performance for the rhythmic TMS condition compared with day 1 baseline. Upper right panel: time–frequency plots of EEG activity for a trial time window for rhythmic TMS versus day 1 baseline. Time–frequency plots show the grand average of manipulation and simple tasks. Shading indicates SEM. Asterisks represent significant effects. Scalp topographies show significant clusters of electrodes. Lower left panel: bar plots representing average power in the ROI for the stimulation and poststimulation time windows. Blue, simple task correct trials; red, manipulation task correct trials. Error bars represent SEM. Lower central panel: rhythmic TMS. Brain phase locking was estimated by calculating the PLV between EEG signals and a perfect theta oscillation (simulating the TMS pulses). Scalp topography show significant clusters of electrodes for the manipulation task versus simple task contrast. Bar plots represent average PLV in this cluster for the two time windows of interest (stimulation and poststimulation). Lower right panel: scatter plots of participants' performance against theta power in the retention period (rhythmic TMS versus baseline). PSD, power spectrum density for the retention time period. Adapted from Ref. 41. (B) Left panel: tACS-targeted area in Schaal *et al.*'s study:¹⁰¹ the right DLPFC was defined by the MNI coordinates $x = 45$, $y = 31$, $z = 25$, based on Ref. 75. Right panel: gamma (35 Hz) tACS over the DLPFC led to a significant facilitation of pitch-memory performance in congenital amusia. Note that this effect was not significant at 90-Hz stimulation (control condition). While amusics showed a selective impairment in pitch memory compared with the controls' performance pre-tACS, this difference was no longer significant during gamma tACS. Error bars represent the SEM. Adapted from Ref. 101.

high-frequency oscillatory bursts with the phase of a low-frequency rhythm.⁶ In working memory, PAC between the phase of theta and the power of gamma has been hypothesized as a mechanism to implement working memory.^{53,104} This hypothesis of a theta–gamma neural code¹⁰⁴ proposes that items retained in working memory are registered via theta-nested gamma cycles in sensory regions. These gamma cycles are assumed to mark local neural computations, which are paced along the phase of a theta cycle. According to this principle, this coding scheme also participates in the coordination of functional communication between brain regions during sensory and memory processes.

Recently, Alekseichuk *et al.*¹⁰⁵ investigated the causal role of theta–gamma code (see also Ref. 35) using cross-frequency tACS tuned to continuous theta and repetitive gamma costimulation. They showed an enhancement of working memory performance during left frontal theta–gamma tACS in a visuospatial task. This behavioral gain was related to an increase in functional connectivity only when the delivery of high-gamma bursts coincided with the peaks of the underlying theta waves. This study opens interesting research avenues for frequency-tuned stimulation protocols by allowing the modulation of more elaborated cross-frequency mechanisms than narrow-band oscillatory activity.

Overall, our review reports on homogeneous effects of frequency-tuned noninvasive stimulation during working memory. We believe that this method is a promising tool for direct interventions into brain functions and cognitive processes. However, reports of possible positive long-lasting effects remain scarce. Veniero *et al.*¹⁰⁶ reviewed the aftereffects of frequency-tuned stimulation methods (applied during multiple cognitive processes) and did not find any consistent aftereffect patterns across studies. They identified several potential explanations for such lack of consistency in the literature, such as (1) the absence of matching between the stimulation frequency and individuals' own/self-generated neural oscillations; (2) the lack of investigation of the frequency space, in terms of applied stimulation frequency and the effect on other frequency ranges; (3) the variability in stimulation montages/sites across studies; and (4) inter- and intraindividual variability in the response to stimulation in general. They also suggest that disentangling stimulation outcomes according to

participants' ongoing state (during or few milliseconds before) would improve the consistency for reporting noninvasive brain stimulation studies.

Further work is needed to realize the full potential of optimized, functionally relevant, noninvasive brain stimulation on human cognitive abilities, such as perception, long-term memory, or learning. The translational impact of these approaches as personalized therapeutic tools for brain disorders also needs to be further investigated. Indeed, there is a growing trend toward investigating the pathophysiology of neurological and neuropsychiatric diseases via abnormal patterns of brain oscillations (for a review, see Ref. 107). Defining the means of obtaining aftereffects is thus a critical step to design frequency-tuned stimulation protocol to brain dysfunctions. Observing such long-term/effective modulation of brain oscillatory signals after stimulation would constitute a significant advancement in noninvasive brain stimulation therapies.

Competing interests

The authors declare no competing interests.

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