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Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation (tACS)

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Abstract

Cognitive impairment represents one of the most debilitating and most difficult symptom to treat of many psychiatric illnesses. Human neurophysiology studies have suggested specific pathologies of cortical network activity correlate with cognitive impairment. However, we lack (1) demonstration of causal relationships between specific network activity patterns and cognitive capabilities and (2) treatment modalities that directly target impaired network dynamics of cognition. Transcranial alternating current stimulation (tACS), a novel non-invasive brain stimulation approach, may provide a crucial tool to tackle these challenges. We here propose that tACS can be used to elucidate the causal role of cortical synchronization in cognition and, eventually, to enhance pathologically weakened synchrony that may underlie cognitive deficits. To accelerate such development of tACS as a treatment for cognitive deficits, we discuss studies on tACS and cognition (all performed in healthy participants) according to the Research Domain Criteria (RDoC) of the National Institute of Mental Health.

Keywords

transcranial alternating current stimulation; tACS; RDoC; Research Domain Criteria project; psychiatric illness; cognitive symptoms; oscillations; non-invasive brain stimulation; non-pharmacological treatments; cortex

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Behavior arises from the dynamic interplay of sensory input and internal states such as motivation and expectation. Neural activity patterns in large-scale, distributed networks

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provide the substrate that mediates behavior. Over the last few years, there have been a rapidly rising number of reports that non-invasive brain stimulation with weak electric fields (transcranial current stimulation) can alter brain network dynamics and behavior. Most studies have employed transcranial direct current stimulation (tDCS), which modulates neuronal activity level and excitability in a polarity-specific way [1]. However, tDCS cannot be tailored to directly modulate specific activity patterns of brain networks. In contrast, transcranial alternating current stimulation (tACS) employs a sine-wave electric field that appears to preferentially enhance network oscillations at frequencies close to the stimulation frequency. The effect of tACS results from electric polarization of neurons which are aligned with the applied field [2]; in the case of tACS, the periodic nature of the sine-wave results in a temporally structured change in membrane voltages across the network thus influencing overall network activity [3,4]. See [5] for a review on the physiological mechanisms of tACS. Thus, at least theoretically, tACS can be used to probe for the causal role of specific cortical activity patterns in cognition and to then remediate deficits in activity patterns in patient populations with cognitive impairment. For example, tACS at 40 Hz could be used to demonstrate the causal role of gamma oscillations (>30 Hz) in a specific cognitive capability and then such stimulation could be used in patients with impaired gamma oscillations that cause the corresponding cognitive impairment. Clearly, this is an oversimplification that rests on several untested assumptions, yet the underlying conceptual framework at least provides guidance for a discovery process aimed at (1) elucidating the neural basis of cognition and (2) rational design of brain stimulation treatments for cognitive impairment.

Despite tACS being far from ready to implement in such applications of cognitive enhancement, we here discuss existing studies that utilize tACS. Specifically, this review follows the framework developed by the National Institute of Mental Health (NIMH) in the Research Domain Criteria project (RDoC) to provide a comprehensive update on the status of tACS research as related to the cognitive systems domain. The RDoC initiative was developed to aid psychiatry research by using a classification scheme based on neurobiological measures and observable behavior. The studies reviewed here were primarily conducted in healthy adult populations, and provide crucial insight into the effects of brain stimulation on cognitive processes. In turn, this work can inform future studies which more directly develop tACS as a treatment for neuropsychiatric disorders. The cognitive and behavior abnormalities observed in these patients may be related to the altered oscillatory activity in cortex [6,7]. Thus, future tACS paradigms may one day serve as an effective treatment modality towards alleviating cognitive and behavioral abnormalities associated with neuropsychiatric diseases.

To date, tDCS has been much more extensively studied that tACS [8,9]. Both basic science and clinical studies with tDCS have been extensively discussed and reviewed elsewhere [10–13]. Studies have demonstrated that tDCS can induce (1) modulation of neurophysiological measures (e.g. motor-evoked potentials, MEPs) [1], (2) changes in motor performance, (e.g. [14]), (3) alteration in brain activity as measured by EEG [15], and (4) state-dependent stimulation effects [16]. The use of tDCS for the treatment of tinnitus [17], major depression [18], Parkinson’s disease [19,20] and especially in stroke rehabilitation

[21] appear to be particularly effective, likely through correction of pathological hypo- or hyperexcitability.

However, a wide range of cognitive capabilities are mediated by the dynamic modulation of rhythmic oscillatory activity within and between different brain regions, rather than solely broad increases or decreases in excitability. For example, beta and gamma oscillations mediate interactions between sensory cortices and prefrontal cortex to direct attention [22], synchrony between frontal and parietal cortices in the delta frequency band appears to underlie decision making [23], and slow oscillatory activity aids the consolidation of declarative memories [24]. Similarly, cognitive deficits in neuropsychiatric disorders are associated with alterations in the structure of rhythmic oscillatory activity, rather than strict hypo- or hyper-excitability. A reduction in gamma band oscillations has consistently been demonstrated in patients with schizophrenia during working memory, executive control, and perceptual processing [25]. Interestingly, patients with schizophrenia also exhibit elevated baseline gamma power [26,27]. Individuals with autism spectrum disorder exhibit fronto-posterior networks with atypical modulation of gamma activity [28] and decreased frontoparietal theta coherence, which correlated with clinical disease severity [29].

In light of the physiological and pathological relevance of rhythmic brain activity, the brain stimulation community has recently witnessed a surge of interest in the non-invasive application of weak electric current using sine-wave waveforms (tACS) in order to target brain oscillations at specific frequencies (Figure 1, A: *In vitro* studies have demonstrated that sine-waves applied with different periods (T) entrain action potential firing. B: Illustration of sine-wave current used in tACS studies). In terms of changes to neurophysiological activity, tACS can induce modulation of MEPs in a frequency-specific manner [30–32], increase oscillatory power matched to the frequency of stimulation [33–35], and exhibit state-dependent effects [36,37]. Stimulation is typically delivered at frequencies within the range of the classic EEG frequency bands, which span the range of most commonly observed physiological oscillation frequencies of cortical network activity: delta (0.5–4Hz), theta (4–8Hz), alpha (8–12Hz), beta (12–30Hz), and gamma (30–80Hz) [38]. Importantly, the effects of tACS are dependent on the frequency of the applied alternating current stimulation [39,40].

Coinciding with the emergence of tACS and other neurostimulation techniques for investigating brain dynamics, new initiatives to encourage more mechanism-driven scientific investigations into neuropsychiatric pathology have gained traction. In 2009, the NIMH launched the Research Domain Criteria project (RDoC) to classify psychopathology “based on dimensions of observable behavior and neurobiological measures” [41]. In alignment with the fundamental premises of non-invasive brain stimulation, the framework postulates: “psychiatric conditions are disorders of brain circuits, tools of clinical neuroscience can characterize or identify brain circuit dysfunction, and biomarkers or biosignatures identified via neuroscience investigation can inform clinical management” [42]. Although RDoC stresses “circuits” as a primary or central unit of analysis within cognitive domains and other domains of behavioral function, the framework also includes subjective reports and other units of analysis associated with psychological investigation. Environmental and developmental factors are suggested as orthogonal dimensions that span

many levels of analysis [43]. Importantly, the authors of RDoC recognize the reliability of DSM diagnoses, which are largely based on clusters of clinical symptoms, but aim to provide a novel conceptual framework to guide and accelerate the study of fundamental brain pathologies (e.g. changes in the circuitry that mediates cognition) that often span many DSM diagnoses. They assert that the neurobiological mechanisms of psychiatric symptoms and syndromes do not map well onto DSM categories; in some cases there appears to be considerable heterogeneity of mechanisms within categories while in other instances there exists considerable mechanistic overlap between supposedly discrete categories or diagnoses.

We here make the argument that brain stimulation research should be driven by rational design such that stimulation paradigms are developed to target specific brain networks to alter and enhance brain function. Thus, we propose that the RDoC framework offers a unique opportunity to provide important structure and guidance to the rapidly growing tACS field and to accelerate targeted development of novel treatments based on tACS [44]. Therefore, in this review, tACS studies will be discussed though the lens of the RDoC domain of cognitive systems. We first review tACS studies which target or modulate the circuits and networks associated with the major cognitive domain constructs of RDoC: attention, perception, working memory, declarative memory, language, and cognitive control (Figure 2). The purpose, stimulation parameters, and findings of each study discussed here are summarized in Table 1. Each construct is introduced according to its RDoC definition and implicated neurobiological systems or circuits. Reflecting the purpose of RDoC, these constructs cut across multiple established diagnostic categories. The construct of perception, for instance, involves numerous brain systems and circuits related to each of the sensory modalities as well as higher order processing. Deficits in these circuits could become the subject of investigation of perceptual disturbances in any of the various DSM clinical categories of pathology, including schizophrenia, dementia, bipolar disorder, alcoholic hallucinosis, numerous substance withdrawal or intoxication syndromes, and delirium. Most of the other constructs in the cognitive domain span a comparable spectrum of existing clinical diagnostic categories.

We conclude this article with a five year perspective on extending the field of tACS from basic science research conducted in healthy human participants to the testing and development of treatments for clinical populations suffering from neuropsychiatric illnesses. In using this approach, we seek to illustrate how the RDoC approach can facilitate translation of tACS research into the development of clinically meaningful interventions.

Attention

According to RDoC, attention refers to “a range of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action. The concepts of capacity limitation and competition are inherent to the concepts of selective and divided attention” [45]. Attention is conceptualized as including attention control and attention implementation. With regard to attention control functions, the workshop proceedings cite dorsal and ventral networks distributed through frontal and parietal cortices and subcortical structures. Regarding implementation of attention, local circuit interactions

and feed-forward transmission of information through sensory systems are cited, and overlaps with the cognitive control construct are recognized [45]. Attention capacity is notably reduced in disorders such as attention-deficit-hyperactivity-disorder (ADHD) but also many other DSM-based diagnoses. Interestingly, EEG recordings conducted during the resting state in healthy control subjects and individuals with diagnosed ADHD have demonstrated that this clinical population exhibits increased oscillatory power in the low frequency bands and reduced power in higher frequencies (alpha and beta) [46]. Therefore, distinct patterns of oscillatory activity during rest [46] and during attention-demanding tasks [47] may be evident in psychiatric illnesses with deficits in attention.

To date, Laczo et al [48] is the only study which has directly tested the effect of tACS on attention. The authors assessed spatial visual attention, a process which enables selective and covert (i.e. without gaze shifts) direction of limited processing capacity to specific locations in the visual field. Changes in contrast sensitivity were used to study the effect of attention on visual information processing. Based on previous work demonstrating the importance of gamma frequency oscillations in spatial visual attention, the authors hypothesized that gamma frequency tACS applied to the primary visual cortex would alter neural synchronization and change the effect of attention on contrast perception. Utilizing the longest duration of stimulation published to date (45 minutes ± 10 minutes), the authors demonstrated that 60Hz tACS improved contrast detection in healthy adults. However, the authors did not find a change in spatial attention. The reported lack of stimulation effect when applied over V1 may ensue from non-optimal placement of stimulation electrodes to target attentional circuits, since attention modulates primary visual cortex and sensory perception but frontal and parietal areas have been implicated as the circuitry controlling attentional processing [49,50].

While much of the early work in tACS was conducted in the motor system, these studies mostly looked at alterations in excitability rather than capacity-limited allocation to the motor system. A notable exception, the study by Joundi and colleagues [51] used tACS to directly probe the role of oscillatory activity in determining motor behavior. The authors administered tACS over motor cortex at both beta and gamma frequencies to healthy adults during a go/no-go paradigm which cued either motor action or motor inhibition. In contrast to altering the excitability of motor cortex, this task required attention for the regulation of motor action (or inaction). The authors' findings support the general framework that beta oscillatory activity in motor cortex is antikinetic, while gamma oscillations in motor cortex are prokinetic. While the purpose of this study was not to directly assess the effect of tACS on the circuitry involved in attentional processing or modulation on performance, the involvement of attention in the behavioral task is important to note. Because the effect of tACS on attentional processing is unknown, it is difficult to disentangle the effects of stimulation on motor performance from potential modulation of attention which influenced performance on the motor task.

Understanding the effect of tACS on attention is still in its infancy. Future work should directly modulate frontal and parietal cortices, the putative control centers of attentional processing, and assess performance changes on attentional tasks. This work will need to assess if increased neuronal synchrony between cortical areas, enhancement of specific

rhythmic activity within a given area, or yet another mechanism is required for improvement in attention. Subsequently or concurrently, individuals with deficits in attention can be tested for stimulation-induced improvements in attentional performance.

Perception

The perception construct is defined as "process(es) that perform computations on sensory data to construct and transform representations of the external environment, acquire information from, and make predictions about, the external world, and guide action" [45]. Sub-constructs include (1) visual, (2) auditory, and (3) olfactory, somatosensory, and multimodal perception. Changes in gamma and alpha frequency oscillations are frequently observed with cognitive and perceptual tasks [52–54]. Substantial evidence suggests that individuals diagnosed with schizophrenia exhibit abnormal gamma band oscillations [55]. Saliently, schizophrenia is associated with impairments in perception, commonly manifested as auditory hallucinations [56]. During an auditory oddball task, individuals with schizophrenia exhibited abnormal gamma activation patterns compared to age- and gender-matched controls [57]. Together, this body of work suggests that altered oscillatory activity in the gamma frequency band may underlie changes in perception seen in schizophrenia. It remains to be studied if similar network pathologies may drive perceptual impairment in other psychiatricillnesses.

tACS studies on the visual modality of perception have built on the observation that switches in conscious perception of an ambiguous stimulus are correlated with alterations in synchronized activity in the gamma band [58]. Struber et al [59] sought to test a causal role of gamma activity in conscious perception by administering bilateral 40Hz tACS over occipito-parietal areas while subjects were presented bistable apparent motion stimuli; stimulation was administered with a 180° phase difference between hemispheres. Switches between horizontal and vertical apparent motion are believed to indicate changes in interhemispheric functional coupling. The authors report that interhemispheric gamma band coherence increased while the proportion of perceived horizontal motion decreased. There were no changes in interhemispheric coherence or perceived motion induced by control 6Hz tACS administered with 0° or 180° phase difference. The authors suggest that these counterintuitive results (one might expect increased interhemispheric gamma coherence to correlate with increased horizontal perception) may result from the phase offset of stimulation between the two hemispheres, which may have led to functional decoupling and thereby impaired perceived horizontal motion. The authors tested 0° phase difference 40Hz tACS, but did not find a significant effect on coherence or motion perception. Another study applied tACS over primary visual cortex at different gamma frequencies while subjects performed a four-alternative forced-choice detection task [48]. 60Hz tACS decreased contrast-discrimination thresholds, indicating an improvement in visual contrast perception. However, 40Hz and 80Hz tACS did not induce similar improvement on perception. Future studies may choose to look at the frequency of endogenous gamma oscillatory activity and incorporate theories of resonance when selecting a stimulation frequency for optimal modulation of activity.

While gamma oscillations have been implicated in switches in conscious perception, posterior alpha power is believed to regulate perception. Posterior alpha rhythms are influenced by visual spatial attention, and likely provide functional inhibition of non-relevant stimuli and locations. Specifically, studies have demonstrated that alpha activity in the posterior cortex decreases the quality of visual perception in the contralateral hemi-field [60,61], while alpha power increases have been measured in the occipital cortex hemisphere receiving visual information from the non-attended hemi-field [62,63]. Brignani et al [64] tested the role of alpha frequency activity on perception by delivering tACS at 10Hz over the left or right occipito-posterior area while healthy adults performed a visual detection and discrimination task. Individuals receiving alpha stimulation showed decreased visual perception compared to individuals who received sham tACS; however, individuals who received 6Hz tACS also exhibited poorer performance on the perception task. The authors were cautious about claiming tACS-induced modulation of visual perception because of only partially-confirmed frequency specificity and lack of retinotopic specificity. Lack of neurophysiological measurements in this study precludes conclusive statements about how the applied frequencies of tACS modulated posterior alpha rhythms. To address this question, Helfrich et al [65] developed a novel artifact rejection technique which permitted analysis of EEG data acquired during the application of tACS. The authors found that 10Hz alpha frequency tACS applied over the parieto-occipital cortex increased alpha activity in this area and induced synchronization of oscillatory activity with the phase of the applied stimulation. In further support of the role of alpha rhythms in gating perception, the authors found that alpha frequency tACS enhanced target detection performance in a phase-dependent manner through augmented cortical alpha synchronization.

In other studies of visual perception, tACS administered over occipital cortex was sufficient to induce visual phosphenes; beta frequency stimulation was most effective at inducing the perception of phosphenes in an illuminated room, whereas alpha frequency stimulation was more effective at inducing this visual experience in a dark room [66]. Furthermore, 20Hz tACS over the occipital region has been found to decrease the threshold for inducing visual phosphenes elicited by transcranial magnetic stimulation (TMS) pulses [67]. However, there is debate as to whether tACS-induced phosphenes originate in the visual cortex or because of retinal stimulation [68,69].

In the auditory sensory modality, alpha frequency tACS with a direct current offset modulated the detection of auditory stimuli embedded in continuous band-limited white noise [70]. Importantly, the authors found that detection threshold was dependent on the phase of the oscillation that was entrained by application of tACS. Such phase-dependent modulation of excitability has been previously shown in observational studies that employed EEG and MEG [71–74]. Effects of tACS on perception in the somatosensory system have also been tested. tACS was applied to right somatosensory cortex (exact stimulation location was localized with transcranial magnetic stimulation), corresponding to sensation in the contralateral hand [75]. Stimulation was applied systematically from 2–70Hz, in steps of 2Hz, and individuals were asked to subjectively rate the perception of tactile sensations in their hand. The authors found that alpha, beta, and high gamma frequency tACS produced tactile sensation in the contralateral hand in absence of physical stimulation. This report demonstrates frequency-specific effects of tACS on somatosensory perception.

Perception through the use of visual, auditory, olfactory, somatosensory, and multimodal modalities allows for internal representations of the external world. Oscillatory power and coherence between different brain areas and across the hemispheres mediates this processing. Continued work using tACS to selectively modulate these activity patterns can help to further elucidate the network activity patterns responsible for perception.

Working memory

The construct of working memory (WM) is defined in RDoC as: “the active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference. These representations: may involve flexible binding of representations; may be characterized by the absence of external support for the internally maintained representation; and are frequently temporary, though this may be due to ongoing interference” [76]. Sub-constructs include (1) active maintenance, (2) flexible updating, (3) limited capacity, and (4) interference control. The RDoC workshop (2010) cites representative examples of circuits as including “extensive loops from the PFC through the basal ganglia that may be important for driving the flexible updating of PFC representations, and in learning new tasks. There are connections between the PFC and medial temporal lobe that may support encoding of the contents of WM into long term memory and retrieval of stored memories that can be reactivated in WM” [76]. WM is critical in everyday life for communication, learning, and successful task completion.

Models of WM suggest that frontal areas are responsible for the executive function and processing aspects of WM, while posterior parietal cortex is linked to the limited capacity storage component of WM [77–79]. In electrophysiological investigations, activation of the frontoparietal network has been associated with WM tasks [80]. Theta frequency power and phase synchronization between frontal and parietal regions have been implicated in integrating WM associations into coherent representations [81,82]. However, evidence that PFC can maintain the memory of a sample trace in the presence of distractors, unlike posterior parietal cortex, suggests that dorsolateral prefrontal cortex (DLPFC) supports both the storage and processing functions of WM [83]. For example, patients diagnosed with Alzheimer’s disease exhibit deficits in WM. This clinical population often exhibits decreased evoked coherence in the left frontoparietal region in the theta frequency band and lower evoked coherence in the right frontoparietal region in the delta frequency band [84], indicating that altered frontoparietal connections may underlie WM deficits seen in Alzheimer’s disease.

Polania and colleagues [85] directly tested the effect of exogenously synchronizing (in-phase) and desynchronizing (anti-phase) left dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) on WM performance. The authors first conducted EEG while subjects performed a delayed recall task. Increase in theta phase synchronization between DLPFC and PPC during WM retrieval was correlated with improved reaction times on the working memory task. Based on these findings, the authors hypothesized that exogenously increasing frontoparietal theta coupling (by applying stimulation with 0° phase difference) would improve WM reaction times, whereas exogenously reducing theta coupling (by applying stimulation with 180° phase difference) would deteriorate task performance.

Indeed, they found that 0° relative phase tACS in the theta frequency administered between frontal and parietal areas decreased reaction time, while 180° relative phase tACS increased reaction time in healthy subjects; there was no significant effect for control stimulation at 35Hz applied with either 0° phase difference or 180° phase difference. This study provides early causal evidence that theta phase-coupling of frontal and parietal areas improves cognitive performance as measured in a WM task. Meiron & Lavidor [86] tested the effect of bilateral theta frequency tACS applied over DLPFC on a verbal working memory task. In healthy adults, tACS was effective at improving accuracy in a WM task compared to sham stimulation. Retrospective judgments were also assessed in this study, and the authors found that confidence scores improved in conditions of verum stimulation (the condition in which WM also improved).

Jausovec et al [87] administered theta tACS over left frontal cortex, left parietal cortex, or right parietal cortex in heathy adults who subsequently conducted tasks to assess spatial and verbal WM capacity. The authors found that tACS administered to either the right of left parietal cortex, but not frontal or sham stimulation, had a positive effect on subsequent WM storage capacity. The authors additionally found that left parietal tACS had a more pronounced effect on both spatial and verbal WM capacity in backward recall rather than forward recall. The findings of this study are consistent with the theory that the left parietal area is more important for WM storage capacity than DLPFC. In support of the aforementioned study, Jausovec & Jausovec [88] also applied theta tACS over either left parietal or left frontal cortex in healthy adults and assessed changes in WM storage capacity related to these two brain areas. They found that theta tACS over parietal areas, but not frontal or sham stimulation, improved performance on a visual-array comparison task. Furthermore, the authors report that exclusively parietal tACS induced a decrease in P300 latency in left parietal brain areas. The latency of this ERP component is an index of classification speed, thus the authors posit that theta tACS may have increased participant's capability to allocate resources to solve the working memory task more rapidly. Together, these studies do not fully elucidate the roles of frontal and parietal areas in working memory, but they provide appealing evidence that specific oscillatory activity in these areas contributes to cognitive performance.

Declarative memory

Declarative memory is defined as "the acquisition or encoding, storage and consolidation, and retrieval of representation of facts and events. Declarative memory provides the critical substrate for relational representations – i.e. for spatial, temporal, and other contextual relations among items, contributing to representations of events (episodic memory) and the integration and organization of factual knowledge (semantic memory). These representations facilitate the inferential and flexible extraction of new information from these relationships" [45]. The consolidation of declarative memories is believed to depend on slow oscillations (<1Hz) prominent during non-rapid-eye-movement (non-REM) sleep [24,89,90]. These slow oscillations originate in the neocortex and then organize activity in the neocortex, thalamus, and hippocampus [24].

Patients with schizophrenia often exhibit poor declarative memory, which has been linked to reduced hippocampal activation during conscious recollection but robust activation of the DLPFC during the effort to retrieve poorly encoded material [91]. Of particular interest, patients with schizophrenia also exhibit abnormal non-REM sleep, with a significant reduction in slow-wave sleep and sleep spindle activity [92]. It has been suggested that this altered neural activity during sleep may mediate deficits in declarative memory consolidation observed in patients with schizophrenia [93].

Marshall et al [94] tested changes in memory consolidation induced by brain stimulation applied during sleep. The stimulation parameters used in this study differ from traditional tACS; specifically, 0.75Hz oscillating current was applied with a DC offset (with current amplitude between 0 and 260 μA). Subjects performed a paired-associate learning task, and memory retention was assessed before and after sleep. The authors demonstrated that stimulation applied at 0.75Hz with DC offset (the authors call their stimulation paradigm slow-oscillating transcranial direct current stimulation, so-tDCS) during non-REM sleep enhanced the retention of hippocampus-dependent declarative memories in healthy humans. so-tDCS administered bilaterally in frontolateral locations increased slow oscillatory activity and slow spindle activity in frontal cortex, and improved memory recall to a greater degree than sham stimulation. These effects were specific to stimulation frequency and declarative memory; so-tDCS at 5Hz decreased slow oscillations and did not change declarative memory consolidation, and there were no effects of stimulation on procedural memory. In a follow-up study, the same group found that application of theta frequency so-tDCS with current amplitude between 0 and 260μA during non-REM sleep impaired declarative memory consolidation [95]. These studies were conducted in healthy young adults; a similar study conducted in elderly subjects found no enhancement of memory consolidation following so-tDCS with 0.75Hz with current amplitude between 0 and 260μA [96], indicating potential changes in offline memory consolidation with aging.

In the first application of TCS incorporating a periodic structure to a patient population, so-TDCS was applied during non-REM sleep to children with attention-deficit/hyperactivity disorder (ADHD) [97]. So-tDCS with 0.75Hz and current amplitude between 0 and 250μA, applied bilaterally to frontolateral locations, increased slow oscillatory power during sleep and improved declarative memory performance in children with ADHD to a level comparable to that of the unstimulated healthy control group. This study represents an important first milestone towards the study of tACS paradigms in patient populations.

The above work by Marshall and colleagues focused on changes in declarative memory consolidation. Additional studies have used so-tDCS to assess the role of slow-oscillatory activity during non-REM sleep and wakefulness on the encoding, rather than consolidation, of declarative memories. Application of bilateral frontolateral 0.75Hz so-tDCS (with current amplitude between 0 and 250 μA) during non-REM sleep periods during an afternoon nap was shown to improve subsequent encoding of declarative memory, with no effect on procedural learning [98]. Even when applied during wakefulness, bilateral 0.75Hz so-tDCS (with current amplitude between 0 and 260 μA) at frontolateral locations appeared to improve the encoding of hippocampus-dependent memories when applied during learning [99]. Together, this body of work demonstrates that slow oscillations play a causal role in

consolidation of hippocampal-dependent memories during sleep and enable subsequent encoding of declarative memories. However, it remains an open question if the DC-offset of the applied current is responsible for inducing improvements in consolidation and encoding of declarative memory. Work conducted in the motor cortex has demonstrated that so-tDCS can induce bidirectional shifts in motor excitability similar to constant tDCS [100]. Demonstration that tACS with no offset is capable of inducing these behavioral modifications will be required. Also, modeling the path and intensity of current flow will be beneficial for understanding how cortical areas contribute to hippocampus-dependent memory. Future work will be required to demonstrate if low frequency tACS or so-tDCS applied during sleep to patients with schizophrenia can increase slow-wave sleep and improve declarative memory consolidation.

Language

Language is defined as “a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication” [45]. There are no sub-constructs in RDoC. While it is clear that language is of critical importance for normal functioning, to date there have been no studies using tACS to enhance, modify, or probe language. However, previous research has established the importance of oscillatory activity in language processing and function. Neural synchronization achieved by the modulation of gamma frequency oscillations through cross-frequency coupling with theta oscillations is important for integration of activity across brain regions supporting language production and transmission [101]. Horton et al. [102] demonstrated that both attended and unattended speech streams exhibit phase-locking to EEG activity in the posterior temporal cortices; these results support a model in which syllables in the attended stream arrive during periods of high neuronal excitability, while syllables in the competing speech stream arrive during periods of low neuronal excitability. Of particular interest is the function of theta oscillatory activity in the context of language. The phase of theta oscillations recorded from human auditory cortex reliably tracks and discriminates spoken sentences, potentially providing a mechanism for cortical speech analysis [103]. Other work has shown that theta oscillatory amplitude is decreased in associative cortex during language production, and could reflect an inhibitory function similar to alpha rhythms in visual cortex and beta rhythms in motor cortex [104].

Non-invasive brain stimulation modalities such as tDCS have been shown to influence language performance in healthy individuals and serve as a treatment for post-stroke aphasia [11,105]. The parameters and findings in these studies may serve to inform the design of future tACS studies assessing language function. In healthy adults, anodal tDCS applied over the left PFC has been shown to improve performance on a letter cue-word generation task, improve naming performance, and decrease verbal reaction times, whereas cathodal tDCS decreased verbal fluency or had no effect [106,107]. Anodal tDCS of the left posterior perisylvian area (which includes Wernicke’s area) improved speed in a visual picture naming task without decrement in performance [108]. The first study which assessed the effect of tDCS on patients with aphasia found that cathodal stimulation over the left frontotemporal area improved naming abilities by 33.6% [109]. Additional studies with

patients with aphasia which administered tDCS over frontal or temporal areas alone or in combination with speech therapy also found improvements in language [11].

While brain stimulation therapies have demonstrated promise for the treatment of aphasia and other language disorders, it remains to be demonstrated if the improvement in language is ecologically relevant for patients and if language improvement continues over time or if 'maintenance' stimulation is required to sustain function.

Cognitive control

Cognitive control is "a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context. Additionally, control processes are engaged in the case of novel contexts, where appropriate responses need to be selected from among competing alternatives" [45]. Sub-constructs include (1) goal selection, (2) updating, (3) response election, inhibition or suppression, and (4) performance monitoring. As stated by the definition, the construct of cognitive control effectively organizes the other cognitive domain constructs. Conceptually, cognitive control is utilized in novel situations in order to perform a goal-directed behavior, whereas the construct of attention applies to directing limited-capacity systems. Of interest, a number of psychiatric illnesses exhibit both deficits in cognitive control and abnormal oscillatory activity. For example, individuals with bipolar disorder show cognitive deficits and disorganized behavior, which are thought to reflect a disturbance in neural synchronization [56]. Indeed, measures of neural synchronization evoked by auditory stimuli were reduced in patients with bipolar disorder compared to control subjects during both manic and mixed phases of the illness [110]. Another study demonstrated that the cortical brain activity of patients with bipolar disorder could be characterized by deficits in bilateral gamma band oscillatory power and exhibited synchronization to the stimulus across hemispheres during auditory click stimulation, both during periods of mild depression and euthymia [111]. Children and adolescents with autism spectrum disorder (ASD) exhibited deficits in cognitive control compared to age-, IQ-, and gender-matched controls [112], as well as decreased levels of functional connectivity between frontal, parietal, and occipital regions [113]. Current theories concerning ASD suggest that dysfunctional integrative mechanisms may result from reduced neural synchronization [114].

A small number of studies have directly assessed the effect of tACS in cognitive control. Santarnecchi and colleagues [115] assessed the effect of tACS on fluid intelligence. Fluid intelligence refers to the ability to efficiently encode and manipulate new information, in essence a recapitulation of the RDoC construct of cognitive control. tACS was applied over left medial frontal gyrus in healthy adults. This cortical area has been implicated in abstract reasoning in a modality-independent manner, particularly in tasks involving logical conditional arguments rather than simple perceptual relations. The authors found a 15% improvement in the time required to solve a neuropsychological instrument indexing fluid reasoning, with a clear frequency-specific effect. 40Hz tACS improved the speed of task performance without loss of accuracy, while 5Hz, 10Hz, and 20Hz stimulation did not improve performance. Gamma frequency stimulation was effective only for trials in which

conditional reasoning was required, indicating a specific effect on tasks requiring higher order cognitive control. Important for assessment of cognitive control, the authors included control experiments to assess waning attention and fatigue over the course of the session. The authors found no evidence of these confounding factors. No measures of neurophysiology were conducted in this study, so future work will be needed to demonstrate whether the improvement in fluid intelligence stems from positive modulation of mechanisms aiding performance, or negative modulation of processes detrimental to performance. Pahor & Jausovec [116] conducted an extension on this work by administering theta frequency tACS over either left frontal or parietal cortex in healthy adults, and then measuring EEG and assessing performance tests of fluid intelligence. The authors found that tACS improved performance on a modified version of Raven's progressive matrices and the Paper Folding and Cutting subtest of the Stanford-Binet IQ test; these improvements were more pronounced in cases of parietal stimulation. Parietal tACS decreased alpha power near the site of stimulation and increased theta power during rest, and frontal stimulation induced a task-dependent decrease in theta power in frontal areas.

Another aspect of cognitive control is the process of evaluating risks and benefits. Lateral prefrontal cortex has been implicated in adjusting decision making strategies according to dynamic contexts and demands [117,118]. The DLPFC is believed to play a critical role in decision making under situations of risk. In particular, theta oscillations are believed to coordinate lateral PFC and sensory-motor networks in order to facilitate adaptive changes in performance. The relative balance of theta oscillations between the right and left hemispheres appears to be particularly important for decision making involving risk. In order to directly test the hypothesis that there is a causal link between lateralized oscillatory activity and risky decision making behavior, Sela et al [119] applied tACS to DLPFC in the right or left hemisphere of healthy adults. They found that theta frequency tACS over left DLPFC induced riskier decision making, while subjects receiving tACS over right DLPFC exhibited decision making no different than during sham stimulation. This study supports the framework that lateralization of theta activity in DLPFC is critical for adaptive decision-making in situations involving risk. Together, these studies provide evidence that tACS can improve multiple facets of cognitive control through targeted application in prefrontal regions.

Expert Commentary

Brain stimulation represents a promising approach for treating aberrant neuronal activity that mediates the symptoms of central nervous system disorders. Indeed, invasive brain stimulation in the form of deep brain stimulation for the treatment of Parkinson's disease has turned into a clinical success over the last two decades [120,121]. Here, we propose that non-invasive brain stimulation can be employed to treat cognitive symptoms by targeting the underlying, more subtle and distributed aberrations in brain network activity. In particular, we argue that the shift in psychiatry towards neurobiological mechanisms (manifested most prominently in the RDoC effort) provides a helpful conceptual framework for the targeted development and validation of tACS, a novel form of non-invasive brain stimulation that targets cortical oscillations, as a future treatment modality. We have highlighted recent studies that evaluated the effects of tACS on cognition. Interestingly and (maybe)

surprisingly given their non-invasive nature and weak perturbation strength in comparison to TMS, most of these studies succeeded in providing some level of evidence for the causal (functional) role of cortical oscillations in mediating cognitive abilities. Since the field of tACS research is still in its infancy, it remains unclear to what extent these results from early pilot studies will withstand more rigorous large-scale, double-blinded studies. Nevertheless, we found that these early applications span most of the constructs in the cognitive systems domain (according to the RDoC framework) and therefore provide an attractive starting point for the development and evaluation of tACS-based treatment approaches for (psychiatric) illnesses that cause impairment of cognitive systems.

Indeed, the opportunity to potentially induce frequency–specific modulation of cortical network activity emphasizes the importance of identifying and validating network-level biomarkers of pathological functional activity in CNS disorders. Likely, this pathological activity (ideally detected with EEG) will be subtle and identification will require more sophisticated signal processing than the typical EEG markers currently used in routine neurological care. Yet, identification of such pathological EEG signatures that correspond to the individual constructs of the cognitive systems domain will not only provide novel biomarkers but also precipitate targeted, frequency-specific tACS paradigms. Therefore, tACS is well positioned to induce a shift from observational work to targeted, neurobiology-driven interventions. In essence, we here advocate for the rational design of tACS treatment approaches by bringing together the neurophysiology and the psychiatry scientific communities.

Five-Year View

Below we outline a non-exhaustive list of promising approaches to achieve the goal of rational design of tACS for neuropsychiatric diseases within the next five years.

State-dependent effects of stimulation

Individualized targeting of tACS can be achieved by a multitude of different approaches. tACS interacts with endogenous network dynamics that are quite complex. Therefore the response to stimulation may be hard to predict and mechanistically explain. Despite the emerging overall picture that resonance-like phenomena enable enhancement of endogenous oscillations [122–124], many fundamental aspects such as the possible context-dependence of stimulation effects remain mostly unclear [122]. A major premise of tACS is that the applied or exogenous oscillation is targeting an endogenous oscillation. However, the necessary and sufficient conditions for such synergistic interaction between endogenous and exogenous rhythmic signals remain to be elucidated.

Feedback stimulation

Motivated by the state-dependence of responses to brain stimulation and the often transient nature of impaired brain function in CNS disorders, targeted stimulation that is administered based on specific patterns of neuronal activity could be a promising avenue of research. Indeed, the most advanced “adaptive” or “feedback” brain stimulation systems that only apply stimulation when triggering network level activity patterns are detected have been

developed for epileptic seizures, both in animal models [125,126] and in humans [127]. Ideally, stimulation waveforms are adapted in real-time based on measurements of ongoing brain activity. One challenge for this approach is the requirement to record over several cycles of oscillations in order to capture the essential properties of the oscillatory activity. Additionally, the development of such closed-loop tACS systems is hampered by the technical challenge of simultaneously recording EEG signals and applying tACS. Recent work has suggested several workarounds, such as using other signals as surrogates for rhythmic brain activity (e.g. tremor signal measured with accelerometer in Brittain et al [128]) or leveraging intrinsic coupling of different cortical oscillation frequencies that allows for separation of recorded brain activity and stimulation artifacts by filtering [129].

Spatial targeting

Recent progress in methods of focusing the applied electric field by using small electrodes and more than two stimulation electrodes has enabled a significantly improved level of spatial specificity in tACS. Conventional stimulation paradigms utilize two 5×7cm electrodes. By using one smaller active electrode (typically a circle electrode with outer radius = 12mm and inner radium = 6mm) and four return electrodes each placed equidistant at 3.5cm from the stimulation electrode, electrode montages such as high-definition tDCS (HD-tDCS) [130,131] can focus current distribution onto a targeted cortical area. Finite element modeling is the standard approach to model the electric field applied to the brain by TCS. The electric field induced by conventional stimulation montages extends into cortical areas outside those directly under the stimulation electrodes; in contrast, electric fields applied to the brain using HD-tDCS montages were more restricted to the area under the region demarked by the return electrodes [132]. A realistic head model found that conventional stimulation with the anode over motor cortex and the cathode on the forehead induced modulation over the entire cortical surface, whereas HD-tDCS applied over the same location only induced electric fields in motor cortex, with no cortical modulation in frontal regions, the contralateral motor region, or the occipital lobe [133]. With more localized application of current, the likelihood for off-target effects is decreased. Likely, such increased spatial specificity can be employed not only for tDCS but also for tACS. However, the key strength of tACS may be the enhancement of coherence between brain areas, in which broad spatial targeting could indeed be crucial for frequency-specific synchronization of several cortical areas.

Limitations and Barriers to Successful Clinical Applications of tACS

Despite the promise of tACS to modulate oscillatory activity in cortex, there are a number of important unresolved questions that remain. Further work will be required to elaborate on these topics prior to the successful development of tACS as a neurotherapeutic. First, it remains an open question to what extent tACS can induce oscillatory activity at a chosen frequency. *In vitro* application of sine-wave electric field has demonstrated that weak electric fields are capable of enhancing endogenous oscillations when matched in frequency, but failed to induce a frequency shift if the stimulation frequency did not match the endogenous oscillatory frequency [134]. Application of 25Hz and 40Hz tACS during lucid dreaming, a period of elevated low-gamma power, further increases gamma oscillatory activity while other frequencies of tACS had no effect on oscillatory structure [35]. Thus,

future work will be required to ascertain the extent to which tACS is capable of inducing oscillatory structure in addition to increasing the strength of endogenous oscillations.

Second, the magnitude and duration of sustained aftereffects of tACS remain an open question. One study found enhanced oscillatory power matched to the stimulation frequency for 30 minutes following stimulation, but only when tACS was administered under conditions of low oscillatory power in the matched frequency [36]. Alpha frequency tACS administered to parieto-occipital cortex has been shown to induce enhanced alpha-band oscillations outlasting the duration of the stimulation [65]. Computer simulation of tACS have demonstrated that in the case of multistable states, stimulation can induce outlasting changes in the form of switching to another network activity state [135]. Outlasting effects of tDCS on the excitability of motor cortex have been reported to last multiple hours after stimulation [136]. It is unclear if the same mechanisms mediate outlast effects in tDCS and tACS. Finally, the effects of tACS must be studied in patient populations. Abnormal neuronal architecture, found in some neuropsychiatric diseases, may alter the way in which tACS modulates oscillatory activity.

Conclusion

The future application of tACS in the clinic for the treatment of cognitive impairment critically depends on interdisciplinary work that fuses basic science and clinical approaches to characterize the pathological changes in brain circuits that mediate cognitive symptoms and the ability of tACS to remediate these deficits. Creating a systematic way of approaching pathology in neuropsychiatric conditions, as done with RDoC, will assist in translating discoveries of basic neurophysiology to characterizing biomarkers or circuits that can be targeted with neuromodulation techniques such as tACS.

We recognize and stress that to our knowledge no published tACS study has targeted impairment of the cognitive domain in patients with psychiatric illness. Although it appears reasonable to assume that tACS interventions that enhance cognition in the healthy research participant will also enhance and therefore restore cognitive abilities in patients with cognitive impairment, no direct evidence for such extrapolation exists to date. However, tDCS has recently been used to improve deficits in cognitive control in patients with major depressive disorder [137]. Since cortical oscillations represent the fundamental mediator of cognition [138], we here make the argument that tACS, which directly targets these network activity patterns, may bring more specific and more effective treatment of cognitive dysfunction. Nevertheless, bridging the gap between the well-known, yet hard to treat, cognitive deficits in psychiatric illnesses and the exciting yet early studies on the effectiveness of tACS on modulating cognition represents the most fundamental challenge for tACS to become a candidate neurotherapeutic for the treatment of psychiatric disorders.

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Key Issues

- Rhythmic oscillatory activity in cortex is perturbed in neuropsychiatric disorders, particularly in those with cognitive dysfunction.
- tACS is a promising neurotherapeutic for modulating endogenous oscillatory activity in neocortex.
- Studies conducted in healthy subjects have demonstrated that tACS modulates endogenous oscillations and behavior in a frequency-dependent manner.
- The Research Domain Criteria project (RDoC) of the National Institute of Mental Health (NIMH) is beneficial for conceptualizing and characterizing psychopathology and helps organize and conceptualize today's tACS studies for targeted modulation of brain network dynamics.
- Next steps in the development of tACS as a clinical tool will likely include targeting previously characterized deficits in cortical network dynamics in patients with psychiatric disorders.
- tACS as a neurotherapeutic will depend on rational design for tailoring stimulation protocols to dynamic neurophysiological states of individual patients.

Box 1

Translational Applications of tACS

Many of the tACS studies summarized in this review characterize the causal effects of sine-wave oscillations on behavior and, in some cases, endogenous neural oscillatory dynamics. Comparing these findings to reports on the electrophysiology of neuropsychiatric conditions, new directions and hypotheses for translational studies emerge. The following are examples of how such studies could further explore the proposed tACS effects and electrophysiological mechanisms in patients with potentially shared neurobiological pathology extending across clinical categories as envisioned by RDoC:

Attention

Based on studies using tACS to modulate attention [48,51], translational tACS studies in clinical populations might explore the effects of gamma frequency stimulation versus theta (or lower) frequency stimulation on motor inhibition tasks or spatial visual attention. These populations might include patients with ADHD (a diagnosis which is associated with greater power in low frequency bands and reduced power in high frequency bands), as well as subjects with primary psychotic diagnoses known to experience prominent cognitive symptoms. Ideally, concurrent EEG or TMS based cortical excitability markers could verify electrophysiological mechanisms.

Perception

Investigations on the effects of tACS on perceptual modalities suggest a variety of routes for translational studies in psychiatric populations. The observation that subjects with schizophrenia demonstrate altered patterns of gamma oscillations [55] could inform future studies that explore effects of tACS protocols designed to suppress gamma or enhance slower frequencies such as alpha. Based on the findings by Neuling et al. [70], the effect of alpha frequency oscillations could be tested on patients with a variety of auditory perceptual distortions, including schizophrenia, bipolar disorder, and tinnitus.

Working Memory

Polania et al. [85] are among the researchers finding that frontoparietal theta synchronization has important implications for functional task performance. Given hypotheses that developmental disorders such as autism and schizophrenia exhibit features of a “disconnection syndrome”, modulation of frontoparietal theta could become a target of tACS in the clinic [139,140]. Future psychopathology studies might first leverage the above findings on theta synchrony by testing the effects of frontoparietal theta tACS in Alzheimer’s patients (as reported by Guntekin et al. [84]), in addition to patients with schizophrenia or autism.

Box 2

Lessons from Transcranial Magnetic Stimulation (TMS)

TMS, in which electric coils generate magnetic fields that induce relatively focal pulses of electric currents in the brain, represents a rapidly developing stimulation modality producing new insights applicable to more nascent areas of noninvasive brain stimulation such as tACS. These insights arise from three types of TMS studies: research on the network effects of TMS, studies targeting neural oscillations in clinical populations with cognitive deficits, and more general clinical studies in psychiatric disorders, where efficacy has been established for treatment-resistant depression and for auditory verbal hallucinations in schizophrenia. While a survey of the clinical efficacy of TMS is beyond the scope of this review, some important examples from the first two categories merit discussion in this context.

Perhaps most directly relevant to the current state of tACS research, considerable progress has been made in characterizing the effects of TMS on oscillatory activity in healthy individuals and in cases of neuropsychiatric disorders. Rosanova et al. [141], found that single pulses of TMS to Broadman's area across individual healthy subjects produced a characteristic "natural frequency" on EEG. Three areas within association cortices were targeted and dominant oscillation bands were consistently recorded at each area (gamma in the frontal cortex, beta in the parietal cortex, and alpha in the occipital cortex) regardless of which area was directly stimulated. These findings suggest that the observed oscillatory activity was mediated by local physiological mechanisms rather than being transmitted across long range thalamocortical networks unchanged.

Whereas Rosanova examined the effects of single pulses of TMS, Fuggetta et al. [142] demonstrated how brief trains of commonly used frequencies of rTMS applied to the motor cortex of healthy individuals produced very different effects on low frequency neural oscillations. 10Hz pulses enhanced synchrony between delta and theta oscillations, resembling "thalamocortical dysrhythmia" reported for a number of neurological psychiatric disorders [142]. 5Hz and 1Hz rTMS in contrast desynchronized delta and theta oscillations. The authors cite the difficulty of extrapolating these findings to clinical populations, where a given frequency of rTMS could affect oscillatory structure in a manner opposite of that observed in a healthy population stimulated at the same frequency of rTMS. Indeed, Barr et al. [143] demonstrated differing effects of rTMS between healthy individuals and a patient population. In a double blind study, 24 patients with schizophrenia and 22 healthy subjects completed an n-back working memory task during EEG. As expected, patients exhibited excessive gamma oscillations during this working memory task. Participants received either sham or 20Hz rTMS over bilateral DLPFC; 20Hz rTMS in healthy participants potentiated frontal gamma power, while stimulation reduced frontal gamma oscillations in patients with schizophrenia. The authors proposed that the difference in evoked gamma represents "homeostatic plasticity" in which a useful physiological range of oscillatory activity is maintained.

With respect to targeting cognitive symptoms in depressed subjects, Schutter et al. [144] found that low frequency rTMS increased depressed subjects' sensitivity for recognizing

emotional faces. In the double blind study, 28 patients scoring at least within the upper range of mild depression were randomized to receive 2Hz or sham rTMS over the right parietal cortex for two weeks. A significant increase in sensitivity to angry faces was observed among the active stimulation group. The authors did not use MRI navigation for rTMS target identification or measure EEG in this study, but they were able to cite previous findings of beta frequency asymmetry correlated with sensitivity to angry faces in healthy subjects [145].

The above studies provide examples of how non-invasive brain stimulation can target cognitive symptoms of neuropsychiatric disorders, with some evidence for achieving therapeutic effect via modulation of oscillatory activity. Despite the relative maturity of TMS compared to tACS, there are a number of reasons why we believe tACS may prove to be preferable for clinical applications. First, tACS is accompanied by fewer and less-severe side effects. TMS often induces substantial discomfort at the site of application, headache, facial twitching, and sometimes temporary hearing loss (because of the noise produced by the stimulation), while the side-effects of tACS are likely limited to mild skin sensation. Although healthy individuals are good candidates for either treatment, patients – especially those suffering from psychiatric illnesses – may not tolerate TMS. Secondly, tACS affords a more diverse set of potential stimulation paradigm. Critical for many cognitive processes, tACS can be used to enhance or interfere with synchronization between cortical areas or across hemispheres. Specifically, multiple stimulators can be used in concert to deliver phase-synchronized stimulation to selected brain regions. Lastly, the system requirements for administering tACS are much more portable and cost-effective than TMS equipment. The stimulators used for tACS easily fit into a briefcase, whereas most TMS systems include an integrated chair, stimulation coil, and computer system, and also need high electric currents that cannot be provided by portable batteries. Therefore the nature of the technology required for delivering tACS may be particularly attractive for practitioners who work in multiple clinics, or for patients who are not able to travel to a centralized treatment facility.

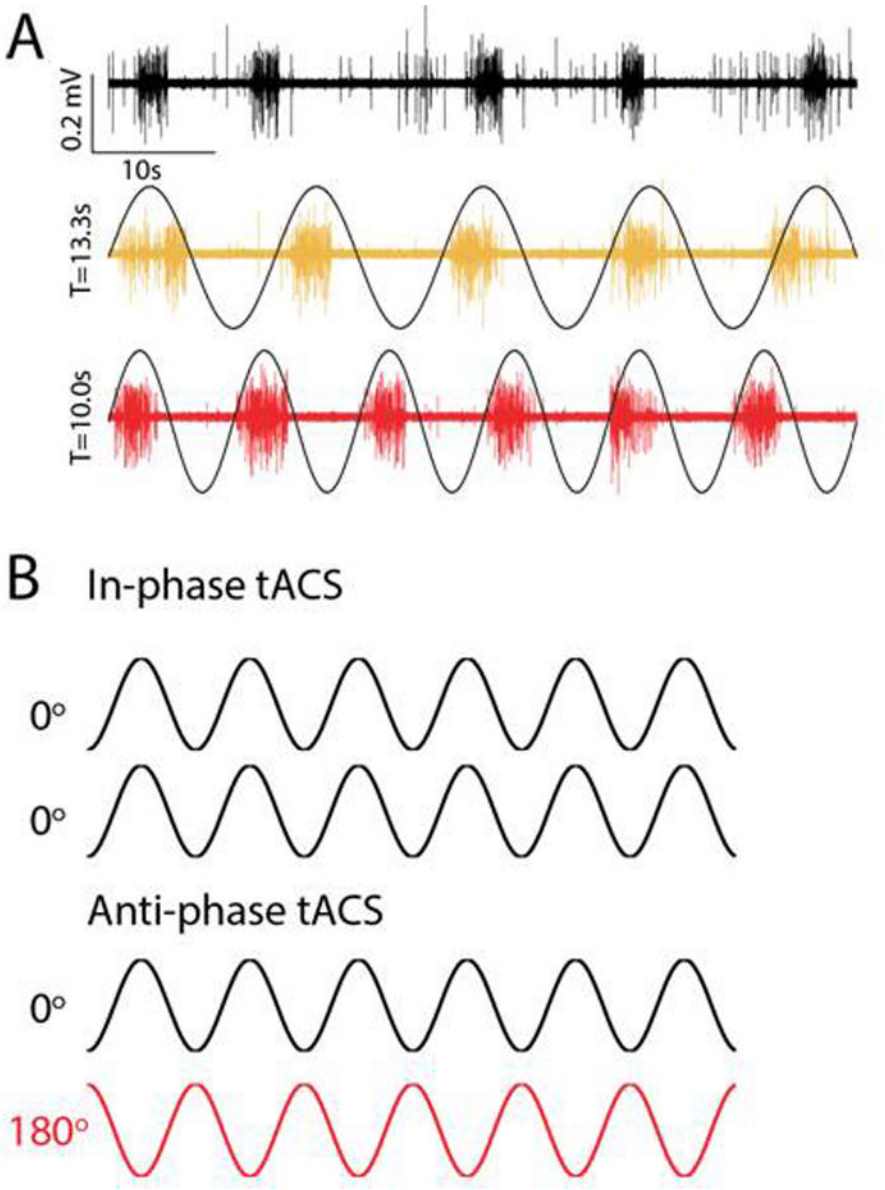

Figure 1.

Transcranial alternating current stimulation (tACS) applies a weak sine-wave electric field to the scalp.

(A) As demonstrated *in vitro*, weak sine-waves with different periods (T) entrain action potential firing. Top: no EF applied, middle: T = 13.3 seconds, bottom: T = 10.0 seconds. Adapted from [3], reprinted with permission.

(B) TACS delivers sine-wave electrical current of differing frequencies and phase-alignment (phase denoted on the far left).

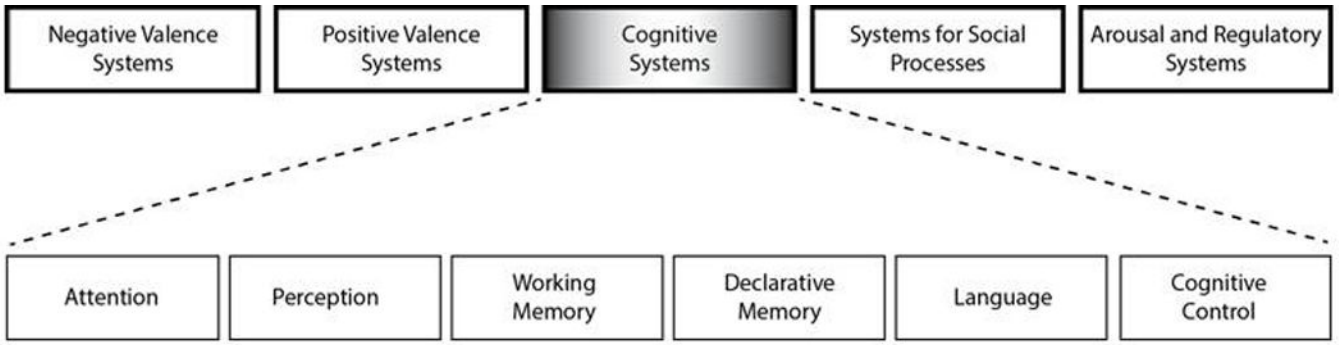

Figure 2.

The Research Domain Criteria project (RDoC) is an initiative by the NIMH to classify psychopathology based on dimensions of observable behavior and neurobiological measures. The project includes five domains (shown in bolded black boxes), each of which contains constructs. In this review, we focus on the six constructs of the Cognitive Systems domain [41].

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Table 1

Summary of the purpose, stimulation parameters, and findings of each tACS study discussed in this review.

ATTENTION							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
Joundi et al (2012)	Current Biology	Sought to demonstrate that oscillatory cortical activity can modify motor behavior. Subjects performed a task assessing motor performance in a go/no-go paradigm.	5×7cm electrodes over the hand area of left motor cortex and the ipsilateral shoulder.	Trials of 5 seconds of 20 or 70Hz sine-wave current. Amplitude selected per individual to be 50μA below phosphene/scalp sensation threshold.	None (stimulation delivered for half of the behavior trials)	18 healthy adults	In a task requiring attention for the regulation of motor (in)action, gamma frequency tACS was prokinetic and beta frequency tACS was antikinetic.
Laczo et al (2012)	Brain Stimulation	Sought to investigate if cortical oscillations in the gamma frequency range are the neuronal mechanism underlying the enhancement of information processing during spatial visual attention.	4×4cm electrode placed over Oz and 4×7cm reference electrode placed over Cz.	45±10 minutes of 40, 60, or 80Hz sine-wave current delivered at 1.5mA. Follow-up experiment, designed to avoid possible after effects of tACS, used 15±5 minutes of stimulation.	20 seconds of tACS	20 healthy male and female adults	60Hz tACS over primary visual cortex improved contrast detection during stimulation.
PERCEPTION							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
Helfrich et al (2014)	Current Biology	Studied neuronal entrainment by measuring EEG during tACS and implementing	5×7cm electrodes over Cz and Oz	20 minutes of 10Hz sine-wave current applied at 1mA	10Hz tACS ramped up for 10 seconds, and then discontinued	14 healthy right-handed male and female adults	EEG recordings conducted simultaneously with tACS revealed that 10Hz tACS over parieto-occipital

ATTENTION							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
		advanced artifact	rejection. Participants pe	rformed a visual oddball paradigm; t	he visual stimulus was presented at	four difference phase angles	cortex increased alpha activity and modulated target detection performance in a stimulation phase-dependent manner. of tACS.
Struber et al (2014)	Brain Topography	Tested a causal role for gamma activity in conscious perception, as assessed by perceived horizontal or vertical movement in bistable apparent motion stimuli presented during tACS.	5×7cm electrodes over P7-PO7 and P8-PO8 for anti-phase stimulation. 5×7cm electrodes over C3, C4, O1, and O2 for in-phase stimulation	15 minutes of 6 or 40Hz sine-wave current applied either in-phase or anti-phase between hemispheres; intensity determined by individual phosphene threshold (<1.5mA)	Stimulation turned off after detection of sensory threshold	45 healthy male and female adults	40Hz tACS, but not 6Hz tACS, increased interhemispheric gamma band coherence and decreased the proportion of perceived horizontal motion. This was only effective when stimulation was applied with 180° phase difference.
Brignani et al (2013)	PLoS One	Sought to determine if tACS could affect cortical activity; tested participants with a Gabor patch detection and discrimination task.	16cm^2 electrode over PO7 or PO8, 35cm^2 reference electrode positioned over Cz	3 blocks of 5 minutes of 6, 10, or 25Hz sine-wave current applied at 1mA	10Hz tACS for 10 seconds	96 healthy, right-handed male and female adults	Participants receiving 6Hz and 10Hz tACS showed poorer performance in detecting targets in comparison to participants who received no stimulation. However, these results were not retinotopically specific.
Laczo et al (2012)	Brain Stimulation	Sought to externally modulate gamma	4×4cm electrode over Oz and 7×4cm reference electrode over Cz	15 minutes each of 40, 60, and 80Hz sine-wave stimulation applied at 1.5mA (± 10 minutes total stimulation time). A second	20 seconds of tACS	20 healthy male and female adults	Contrast-discrimination thresholds decreased

ATTENTION							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
		oscillations, the hypothesized neuronal mechanism of spatial visual attention. The authors assessed modulation of gamma oscillations by probing contrast sensitivity and contrast		sets of experiments applied 15 ± 5 minutes of 40, 60, or 80Hz sine-wave stimulation at 1.5mA with at least 2 days separating conditions			significantly during 60Hz tACS, with no effect at 40Hz or 80Hz tACS
Neuling et al (2012)	NeuroImage	Sought to address the long-standing question of whether perception is continuous or periodic (mediated by spontaneous oscillatory activity) by applying an external oscillation to entrain brain oscillations and demonstrate behavioral consequences. Participants performed an auditory detection task.	5×7cm electrodes positioned at T7 and T8	21 minutes of 1mA direct current (anode on right hemisphere) modulated by 10Hz sinusoidal current of 425 ± 81μA (sinusoidal current amplitude was individually adjusted based on participants' feedback for comfort)	None	16 healthy right-handed male and female adults	DC-offset tACS enhanced alpha power relative to the pre-stimulation period, and auditory detection thresholds were dependent on the phase of the oscillation entrained by the stimulation. Detection thresholds were higher when the stimuli were presented during the stimulation positive half-wave compared to thresholds for stimuli presented during the negative half-wave.
Feurra (2011)	Frontiers in Psychology	Sought to probe the role of oscillatory neural activity by assessing if tACS applied over somatosensory cortex could elicit tactile	3×4cm electrode over right somatosensory cortex and 5×7cm reference electrode over P3	5 seconds per trial of sine-wave stimulation ranging from 2 to 70Hz, step-size 2Hz, (order randomized), applied at 1.5mA	None	14 healthy adults	Alpha and high gamma tACS applied over somatosensory cortex were effective at producing tactile sensation in the contralateral hand. Beta stimulation

ATTENTION							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
		sensation in a frequency-dependent manner. sensation in a frequency-dependent manner. sensation in a frequency-dependent manner.					produced weaker tactile sensation in the contralateral hand.
Kanai et al (2010)	Clinical Neuro-physiology	Investigated whether tACS can modulate the excitability of visual cortex in a frequency-dependent manner, without involving potential retinal stimulation. Authors assessed if tACS modulated the intensity threshold for transcranial magnetic stimulation (TMS) pulses to induce visual phosphenes when delivered to visual cortex.	3×3cm electrode over Oz and 5×7cm reference electrode over Cz; Control condition: 3×3cm electrode over Fz and 5×7cm reference electrode over Cz	5–8 minutes of 5, 10, 20, or 40Hz sine-wave stimulation delivered at 750μA	None	16 healthy male and female adults	20Hz tACS decreased TMS-phosphene threshold (increased the excitability of visual cortex); tACS at other frequencies did not affect visual cortex excitability.
Kanai et al (2008)	Current Biology	Tested if tACS can interact with ongoing rhythmic activity in visual cortex. Administered tACS with room lights on and off and assessed participant's perception of phosphenes.	3×4cm electrode 4cm above the inion (near the midpoint between O1 and O2), 6×9cm reference electrode placed over Cz	10 second trials of sine-wave stimulation delivered with room light on and then room lights off (4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 30, and 40Hz, order randomized) delivered at 1mA. Current intensity was then iteratively reduced (750, 500, 250, 125μA) to determine phosphene threshold at each frequency.	None	16 healthy male and female adults	tACS in the beta frequency range induced phosphenes most effectively when administered in an illuminated room, while alpha frequency stimulation most effectively induced phosphenes in a dark room. Theta and gamma frequency stimulation did not

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							produce visual phosphenes. produce visual phosphenes.
WORKING MEMORY							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
Meiron & Lavidor (2014)	Clinical Neuro-physiology	Sought to determine how theta tACS modulated associations between working memory accuracy and later retrospective self-evaluation scores. Participants completed a verbal working memory task.	4×4cm electrodes placed over F3-AF3, F4-AF4	20 minutes of 4.5Hz sine-wave stimulation delivered at 1mA	20 seconds of 4.5Hz sine-wave stimulation delivered at 1mA	24 healthy right-handed female adults	Online working memory accuracy improved with bilateral tACS over DLPFC, compared to sham stimulation; improvement in working memory was accompanied by higher subjective retrospective success-confidence scores.
Jausovec, Jausovec & Pahor (2014)	Acta Psychologica	Sought to explore the relationship between working memory functions and brain activity in frontal and parietal areas by analyzing the influence of theta tACS on performance in tasks of working memory storage capacity and executive process.	5×7cm electrode over either F3, P3, or P4; 5×7cm return electrode over right eyebrow	15 minutes of theta stimulation (individual alpha frequency - 5Hz) delivered at 250μA below individual thresholds for skin sensation (range = 1000μA to 2250μA).	30 seconds tACS	36 healthy right-handed male and female adults	tACS over right or left parietal areas improved working memory storage capacity, whereas there was no difference measured for frontal or sham stimulation.

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Jausovec & Jausovec (2014)	Biological Psychology	Sought to investigate the influence of tACS on left parietal and frontal brain activity on working memory storage capacity.	5×7cm electrode over either F3 or P3; 5×7cm return electrode over right eyebrow	15 minutes of theta stimulation (individual alpha frequency - 5Hz) delivered at 250μA below individual thresholds for skin sensation (range = 1000μA to 2000μA).	30 seconds tACS	24 healthy right-handed male and female adults	Left parietal tACS increased working memory storage capacity, whereas no difference was measured for either left frontal stimulation or sham stimulation. Increased working memory storage capacity was accompanied by ERP 300 latency decrease.
Polania et al (2012)	Current Biology	Sought to demonstrate a causal link between frontoparietal theta coupling and cognitive performance. Participants completed a delayed letter discrimination task.	5×5cm electrode placed over F3, P3, and return electrode over Cz	14 ±1.5 minutes of 6Hz sine-wave stimulation applied in-phase (0° phase difference) or anti-phase (180° phase difference) at 1mA. Control experiment: Same as above, with 35Hz tACS.	30 seconds of 6Hz sine-wave stimulation applied in-phase (0° phase difference), then 20 second linear ramp-down	46 healthy right-handed male and female adults	6Hz tACS with 0° phase difference (‘synchronizing’ condition) improved visual memory-matching reaction times relative to sham stimulation. 6Hz tACS with 180° phase difference (‘desynchronizing’ condition) impaired performance relative to sham stimulation. 35Hz tACS did not induce changes in performance.
DECLARATIVE MEMORY							
Author(s)	**Journal**	**Reason for study and behavioral task used**	**Stimulation location**	**Verum stimulation parameters**	**Sham stimulation parameters**	**Participant population**	**Main Finding(s)**
Prehn-Kristensen et al (2014)	Brain Stimulation		10mm in diameter electrodes were positioned at F3 and F4 (anodes), and the reference electrodes (cathodes) were	Five 5 minute epochs (each separated by 1 minute of no stimulation) of 0.75Hz sine-wave current was applied oscillating between 0 and 250μA.	Non-active sham.	12 children with ADHD and 12 healthy children; all males between the ages 9–14 years.	Stimulation enhanced slow oscillation power during sleep in children with ADHD and

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			placed at both mastoids. placed at both mastoids.				improved declarative memory performance to a level equal to that of healthy children who did not receive stimulation. Children with ADHD who received sham stimulation showed no improvement.
Antonenko et al (2013)	European Journal of Neuro-science	Sought to demonstrate a causal role for slow wave activity during sleep in enhancing the capacity for encoding of information during subsequent wakefulness. Participants completed a word pair learning task, the Verbal Learning and Memory Test, and a finger sequence tapping task.	10mm in diameter electrodes were positioned at F3 and F4, and the reference electrodes were placed at both mastoids.	Six to eight 4 minute stimulation epochs during non-REM sleep. 0.75Hz sine-wave current was applied oscillating between 0 and 250μA.	Non-active sham.	15 healthy, right-handed male and female adults	Stimulation enhanced slow wave activity during sleep and significantly improved subsequent encoding on declarative tasks (picture recognition, cured recall of word pairs, and free recall of word lists); stimulation had no effect on procedural finger sequence tapping skill.
Eggert et al (2013)	Brain Stimulation	Investigated whether sleep-dependent memory consolidation could be improved by application of brain stimulation in a population of	10mm in diameter electrodes were positioned at F3 and F4 (anodes), and the reference electrodes (cathodes) were placed at both mastoids.	Five epochs of 316 seconds of 0.75Hz sine-wave current was applied oscillating between 0 and 260μA.	Non-active sham	26 healthy, male and female adults between the ages of 60–90 years	Stimulation applied in this population of healthy older adults failed to demonstrate a beneficial effect on either declarative or procedural

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		older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s older adult participants (as has previously been shown for healthy young volunteers). Participants performed declarative (common word-pair association task) and procedural (s					memory consolidation.
Marshall et al (2011)	PLoS One	Sought to investigate the role of theta oscillations during REM and non-REM sleep for memory formation. Participants completed declarative (word paired-associates task) and procedural (finger sequence tapping, mirror-tracing tasks) memory tasks.	8mm in diameter electrodes were positioned at F3 and F4 (anodes), and the reference electrodes were placed at both mastoids (cathodes).	Five 5 minute epochs (each separated by 1 minute of no stimulation) of 5Hz sine-wave current was applied oscillating between 0 and 260µA.	Non-active sham	41 healthy male and female adults	5Hz DC-offset tACS during non-REM sleep reduced frontal slow oscillatory activity, reduced frontal slow spindle power, and induced a decrement in consolidation of declarative memory. Stimulation during REM sleep increased global gamma activity.
Kirov et al (2009)	PNAS	Sought to determine whether increases in slow oscillatory activity by DC-offset tACS improved memory consolidation specific to slow	8mm in diameter electrodes were positioned at F3 and F4 (anodes), and the reference electrodes were placed at both mastoids (cathodes).	Five 5 minute epochs (each separated by 1 minute of no stimulation) of 0.75Hz sine-wave current was applied oscillating between 0 and 260µA.	Non-active sham	28 healthy male and female adults	0.75Hz DC-offset tACS applied during wakefulness increased EEG slow oscillatory activity locally and theta activity globally. Stimulation improved

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		wave sleep, or whether this induced slow oscillatory activity could improve memory during wakefulness. Participants completed declarative (verbal and non-verbal paired-associate learning) and procedural (finger tapping and mirror tracing tasks) memory tasks.					
Marshall et al (2006)	Nature	Sought to investigate if brain potentials have a physiological meaning in memory function. Participants completed declarative (paired-associate learning) and procedural (finger sequence tapping and mirror tracing tasks) memory tasks.	8mm in diameter electrodes were positioned at F3 and F4 (anodes), and the reference electrodes were placed at both mastoids (cathodes).	Five 5 minute epochs (each separated by 1 minute of no stimulation) of 0.75Hz sine-wave current was applied oscillating between 0 and 260μA. Control stimulation: same as above, 5Hz sine-wave.	Non-active sham	13 healthy right-handed male and female adults	0.75Hz DC-offset tACS enhanced slow cortical oscillations and slow spindle activity during early non-REM sleep. Retention of hippocampus-dependent declarative memories was enhanced, while there was no effect on procedural memory; 5Hz stimulation decreased slow oscillations and did not change declarative memory.
COGNITIVE CONTROL							
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Pahor & Jausovec (2014)	International Journal of Psychophysiology	Sought to examine whether theta tACS can affect subsequent performance on tasks of fluid intelligence, and if theta tACS changed power in theta and alpha frequency bands.	5×7cm electrode over either F3 or P3, 7×10cm return electrode over Fp2	15 minutes of theta stimulation (individual alpha frequency - 5Hz) delivered at 250μA below individual thresholds for skin sensation (range = 1000μA to 2250μA).	1 minute of tACS	28 healthy right-handed male and female adults	Theta tACS improved subsequent performance on tests of fluid intelligence; this effect was more pronounced in individuals who received left parietal stimulation rather than left frontal stimulation. Theta tACS decreased alpha power in areas near the stimulation site.
Santarnecchi et al (2013)	Current Biology	Sought to demonstrate a causal role for gamma synchronization in fluid intelligence. Participants completed visuospatial abstract reasoning tasks (Raven's matrices).	5×7cm electrodes placed over left middle frontal gyrus and Cz	5H, 10, 20, or 40Hz sine-wave current delivered at 750μA. Stimulation delivered for duration of task performance.	20 seconds of stimulation applied at the frequency from the previous block	20 healthy right-handed male and female adults	Gamma frequency tACS improved completion time by 15% on a visuospatial abstract reasoning task for complex trials involving conditional/logical reasoning.
Sela et al (2012)	Frontiers in Neuro-science	Sought to investigate the hypothesis that the balance of theta frequency oscillatory activity between right and left frontal regions, with a dominant role for the right hemisphere, is crucial for regulatory control during	Left hemisphere: 5×5cm electrodes placed over F3 and CP5; right hemisphere: 5×5cm electrodes placed over F4 and CP6	15 minutes of 6.5Hz sine-wave current delivered at 1mA.	30 seconds of tACS	27 healthy right-handed male and female adults	Participants receiving theta frequency tACS in the left hemisphere exhibited riskier decision-making style compared to participants receiving right hemisphere or sham stimulation.

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		risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task. risky decision-making. Participants completed the Balloon Analog Risk Task.					