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Combining Transcranial Electrical Stimulation With Electroencephalography: A Multimodal Approach

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Abstract

Although numerous studies have been performed using transcranial electrical stimulation (tES), our understanding of tES-induced effects on neural activity remains limited, especially regarding the effects on neural networks. The use of an approach, such as electroencephalography (EEG) in combination with tES, could allow for a more detailed understanding of the neural mechanisms involved in these observed changes. Co-registration of tES and EEG might provide high temporal resolution information regarding tES-induced modifications/modulations to cortical activity that corresponds to different stages of processing. This article aims at presenting new knowledge about this recent and innovative approach that can possibly provide information about the dynamics of human brain functions beyond what is possible by the use of either method alone.

Keywords

noninvasive brain stimulation, electroencephalography (EEG), tDCS, tACS, TMS-evoked potential (TEP), co-registration, multimodal imaging, functional imaging

Why Combine tES and EEG?

The recent emergence of new, noninvasive brain stimulation (NIBS) techniques for inducing reversible changes in brain activity has allowed the temporary modulation of a wide range of functions.[1] The development of NIBS techniques for the study of mechanisms underlying perceptual, motor, and cognitive functions, as well as the ability to modulate these functions in the human brain, has constituted a significant advance in basic neuroscience. The combination of NIBS with neuroimaging techniques has gained popularity in recent years, due to its potential to investigate the state of targeted brain areas and the roles of these areas in specific functions.

The NIBS techniques used to modulate cortical activity include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). The tES technique[2,3] involves the application of weak electrical currents directly to the head for several minutes. These currents generate an electrical field that modulates neuronal activity according to the duration, intensity, and modality of the application, which can be direct (transcranial direct current stimulation [tDCS]), alternating (transcranial alternating current stimulation [tACS]), or random noise (transcranial random noise stimulation [tRNS]).[4]

The mechanisms underlying the neuromodulatory effects induced by tDCS are well established. Several studies using animal models[5,6] have suggested that neurons respond to membrane polarization changes induced by tDCS,[7] thereby leading to a reduction in spontaneous neuronal firing rates after cathodal tDCS and an opposite effect after anodal stimulation. Firing increases when the positive pole (anode) is located near the cell body or dendrites and decreases when the field is reversed. Accordingly, the first studies performed on the motor cortex showed that cathodal polarization induced robust inhibition of motor cortex excitability, whereas anodal polarization increased motor cortex excitability.[8]

Similar results have been observed using tRNS,[9,10] although the mechanisms for tRNS-induced alterations have been assumed to be the result of repeated subthreshold stimulations. Therefore, in the same manner as tDCS, tRNS can change the cortical excitability by means of mechanisms of membrane polarization. In addition, the advantage of using tRNS over tDCS is that tRNS is not constrained by the sensitivity of the current flow direction. Instead, random frequencies are typically presented, and all coefficients have a similar size (i.e., white noise).

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To date, few studies have evaluated the modulation effects induced by tRNS, which have been shown to induce substantial behavioral modifications.[9,10] The use of an approach, such as EEG, could allow for a more detailed understanding of the neural mechanisms involved in these observed changes.

The few studies published to date on cortical measures have indicated that the alternating stimulation used as tACS is a powerful tool for investigating human brain oscillations. Using tACS, it is possible to deliver an oscillatory current to the cortex in a frequency-specific manner to induce a particular oscillatory entrainment.[11] In this respect, tACS may serve as an instrument to interact with ongoing cortical oscillations[12] and induce entrainment,[13] thereby contributing to a better understanding of cortical binding through frequencies during different functions.

Although numerous studies have been performed using tES, our understanding of tES-induced effects on neural activity remains limited, especially regarding the function of neural networks. Thus, the effects induced by these different types of tES can provide evidence that the stimulated regions are critical to the function being investigated. Nevertheless, such observations do not clearly demonstrate how the stimulated area or the involved circuit has been modified. Whether the effect of tES is induced by the modification of the stimulated area or whether tES remotely affects neural processing in distal brain regions remains to be elucidated.

In the same manner as TMS, tES can be combined with other neuroimaging techniques, such as functional magnetic resonance (fMRI), positron emission tomography[14] and EEG, to provide several advantages (see Siebner et al[15] regarding TMS and neuroimaging) including the opportunity to collect objective and direct measurements of brain activity.

A significant advantage of functional neuroimaging is the ability to acquire simultaneous measurements of activity in the entire brain, thereby providing a broader picture of the cortical responses to any given condition (e.g., a specific task or resting state). Inferences regarding neuronal activity that are based solely on functional neuroimaging data, however, are limited by our understanding of the coupling between the observed behavior and the neuronal activity within the region of the signal change.

In this respect, the incorporation of neuroimaging with tES techniques is emerging as a new field with multimodal potential. By combining these two methods, significant progress can be achieved toward overcoming the correlational problems associated with neuroimaging and the interpretational problems related to tES; that is, information provided by correlational analyses (e.g.,EEG) can be supplemented using a technique that can establish a causal link between brain function and behavior (e.g.,tES), thereby overcoming the limitations of each single technique. The combination of these methods can allow for the evaluation of causal effects over the entire brain. This methodology can be defined as a "multimodal imaging approach" because it provides an assessment of how tES (as well as TMS) can locally affect neural processing by means of objective measures of cortical activity, reactivity, and connectivity.

The objective of this review is to present the potential of this recently developed approach, termed "co-registering brain activity during and after the tES stimulation with EEG," or "tES-EEG," and highlighting the challenges and the power of this novel approach.

The clear utility of tES-EEG lies in the fact that the observed signals are directly coupled to neuronal electrical activity. That is, the EEG recordings reflect the electric potential resulting from synaptic transmembrane currents in neurons that are (or are not) modified by tES. Moreover, this approach offers the potential to identify responses to tES within an area or across circuits, thereby helping to determine in vivo the brain areas that are directly or indirectly affected by tES.

The tES-EEG Integration Approach

Applications that use tES-EEG integration can be divided into two methodological approaches: the offline method, which evaluates the short- and long-term aftereffects induced by brain stimulation, and the online method, which evaluates the immediate changes that occur during the stimulation. We extend the classification of offline and online study designs to include all tES techniques (i.e., not only tDCS[16] but also tACS and tRNS) and propose EEG measurements as surrogate outcomes of excitability changes induced during and after tES.

The combined tES-EEG approach can be utilized in interactive and rhythmic manners, as recently proposed by Miniussi and Thut[17] for TMS-EEG co-registration.

In the interactive approach, EEG is used to probe the state of the cortical area affected by tES, which could be the target area of the stimulation or an interconnected region, and to evaluate the changes in excitability and connectivity within a functional network. Different EEG measures can be used to this end, such as TMS-evoked potentials (TEPs), event-related potentials (ERPs), and the spectral power of oscillatory activity.

The polarization induced using tES techniques (e.g., tDCS) is not sufficiently fast nor intense to elicit a recordable neural response (i.e., depolarization), whereas during TMS-EEG, the magnetic pulse induces a current that can elicit action potentials in neurons, and therefore, a rapid change can be recorded as TEPs and measured from the scalp using EEG.[18–20] By introducing the use of TMS-EEG while stimulating the brain with tES, it is possible to study how the reactivity of the target area (usually tested using single-pulse TMS) is modulated by electrical stimulation. In addition, this combination allows the study of the TEP amplitude, which is dependent on the state of the cortex and thus reflects the overall reactivity of the tES-stimulated cortex.[21,22] The TEPs could also provide a method for investigating brain connectivity during tES.[23,24] When a cortical region is stimulated, the spreading of the induced activation can be traced by means of the distribution of EEG signals over the scalp or via cortical source reconstruction of the signals.

To the same extent as TEPs, ERPs are EEG deflections time locked to specific external or internal signals.[25] When the ERPs are generated in response to somatosensory, visual, or auditory targets, they reflect the cortical activation of the early sensory areas responsible for the processing of the stimuli. Thus, the amplitude and latency of the ERPs may provide information regarding the modulation of activity induced by tES in specific cortical regions.

In addition, changes in oscillatory activity of the brain play an important role in physiological and psychological processes, thereby reflecting the level of synchronous activity in different brain regions. Distinct frequency bands, each of which is closely associated with a specific function, can be identified in the oscillatory activity. The investigation of tES effects on EEG oscillatory activity can help elucidate the influence of tES on communications between different cortical areas.

The rhythmic approach,[13,17] which combines EEG with certain tES techniques (e.g., tACS), can be used to evaluate specific changes in the frequency of brain oscillations in a precise area or in the entire brain. The application of tACS is expected to induce changes in patterns of oscillations that are specifically associated with different perceptual, motor, and cognitive processes[26] in the directly stimulated cortical area and in distant areas belonging to the same neural network. In this respect, the rhythmic approach refers to the possibility of investigating how tACS interacts with oscillatory brain activity.[13]

Therefore, the tES approach can be used to interact with a specific brain region that is thought to be involved in a given function. When using a combined approach, the correlation between EEG measurements of the tES-induced modifications and participant's performance in task experiments can be evaluated.[17]

Offline Recording

Several studies have used the offline recording approach to evaluate the effects of tES on the neurophysiological responses related to cortical processing. Cortical electrophysiological measurements, such as evoked potentials and frequency bands, have been recorded before and after tES to index the neuromodulatory effects in different cortices.

The Interactive Approach

Consistent with the interactive approach, Antal and colleagues[27] evaluated the ability of tDCS to affect the visual-evoked potentials (VEPs) in a polarity-specific manner as probes of occipital activation in response to visual inputs. The authors performed an offline study in which VEPs were recorded before, immediately after, and 10, 20, and 30 minutes after the delivery of 5, 10, or 15 minutes of anodal or cathodal tDCS (1 mA, 35 cm^2 electrode) over the primary visual cortex. The authors also evaluated the differential effects of 3 distinct stimulating montages (Cz-Oz, O1-O2, and Oz-Mastoid) and found that anodal and cathodal tDCS, respectively, increased and decreased the amplitude of an early occipital component (N70). Differences in the buildup and duration of the effect were also observed with a stronger and faster effect for cathodal stimulation relative to anodal tDCS and longer stimulation periods found to be more effective in modulating VEPs. Moreover, a trend toward an increased P100 amplitude was found only after cathodal stimulation. These differences were significant only for the Cz-Oz-stimulating electrode montage, suggesting that the current direction is an important component for inducing neuromodulation. In this study, the measurement of tDCS effects in the VEPs and the study of current polarity effects on a direct electrophysiological index allowed the authors to infer the magnitude of the visual cortical excitability changes induced by brain polarization.

A similar approach was adopted by Accornero and colleagues[28] using an extracephalic reference (i.e., anterior or posterior neck). They found that after the delivery of 3 or 10 minutes of cathodal stimulation (1 mA, 40 cm^2 electrode) over the primary visual cortex, an increase in the P100 amplitude had occurred, whereas a decrease in same component was observed when using anodal tDCS (also see the online approach). This finding differs somewhat from the results of Antal et al[27] who found only a mild facilitatory effect on the P100 due to cathodal polarization, with anodal polarization being ineffective. This discrepancy likely has several causes, including differences in the experimental tasks (e.g., the intensity and duration) or differences in the stimulation parameters, such as the electrode size and reference electrode placement (and therefore the location and direction of the flux of current). Nevertheless the authors suggested that the reasons are probably related to the fact that anodal tDCS was applied during visual activation and not during rest. These results suggest that tDCS directly modulates the activity of visual cortical neurons in a polarity-dependent manner, and several technical parameters are important in determining the effectiveness of the stimulation.[4]

Several studies have adopted an interactive approach to evaluating the polarity-specific changes induced by tDCS on somatosensory-evoked potentials (SEPs).[29-33] These studies attempted to use electrical stimulation as a tool to induce plasticity in cortical sensory processing and use the evoked potential changes as markers of the effects on neuroplasticity.

Matsunaga et al[33] studied the short- and long-term offline effects of tDCS on the sensorimotor cortex in terms of the amplitudes of SEPs following anodal tDCS (1 mA, 35 cm^2 electrode, 10 minutes). These authors found an increased amplitude of parietal (P25/N33, N33/P40) and frontal (P22/N30) SEP components that lasted for 60 minutes after the end of the stimulation. The observed changes in these SEP components represented an assessment of a clear and focused effect of tDCS at the cortical structures.

With a similar goal, Dieckhofer et al[31] used low-frequency SEPs (N20 and N30) and high-frequency SEP oscillations (HFOs) as electrophysiological measures to evaluate the effect of tDCS on locally and functionally distinct somatosensory generators. These authors applied tDCS (1 mA, 16 electrodes for a total area of 24 cm^2, 9 minutes) over the somatosensory cortex and found a significant reduction in the N20 amplitude that lasted several minutes after cathodal stimulation. No effects were observed after anodal stimulation. As previously observed by Matsunaga et al,[33] differences in the type of the modulated component were found specifically at the site of tDCS application (i.e., motor cortex or somatosensory cortex).

Using laser-evoked potentials (LEPs), somatosensory cortical markers have been investigated to evaluate the aftereffects of tDCS on acute pain perception. The assessment of LEP amplitude changes before and after tDCS as measures of the modulated activation of distributed and interconnected neural populations allows for the investigation of the underlying mechanisms of pain. For example, Antal et al[29] found that the application of cathodal tDCS (1 mA, 35 cm^2 electrode, 15 minutes) over the somatosensory cortex significantly diminished the perception of pain. Moreover, a reduction in pain perception was correlated with the N2 component amplitude. The relationship between this decrease in pain perception and its electrophysiological correlate following cathodal stimulation highlights how tDCS combined with ERPs can be used to yield a clear contribution to the understanding of the functional role of specific LEP components and identifies a cortical marker of modulated sensory-discriminatory processes.

Csifcsak et al[30] evaluated laser-induced pain responses at the cortical level relative to anodal, cathodal, and sham tDCS (1 mA, 35 cm electrode, 10 minutes) applied over the primary motor cortex. Cathodal tDCS significantly reduced the amplitude of N2 and P2 components compared with anodal or sham stimulation. Nevertheless, these component modulations did not correlate with laser energy values that were necessary to induce pain. These studies encourage further exploration of the possible therapeutic effects of tDCS on pain modulation and on the evaluation of cortical components, such as physiological markers.

Kirimoto et al[32] applied tDCS (1 mA, small 9 or large 17 cm^2 electrode, 15 minutes) over the left premotor cortex (PM) and supplementary motor area (SMA). The evoked somatosensory potentials were recorded before and after stimulation. Anodal tDCS, applied with the large electrode, induced an increase in SEP components (N20 and P25), whereas the opposite effects were observed after cathodal tDCS. The small electrode did not influence SEPs. Interestingly, the authors also recorded motor-evoked potentials (MEPs), thereby indicating that anodal and cathodal tDCS, respectively, induced a decrease and increase in MEPs. Therefore, this manipulation induced opposite effects on primary motor (MI) and somatosensory (SI) areas. This finding suggests that MI was inhibited and SI was excited by the activation of the PM and SMA after anodal tDCS. An opposite effect was observed after cathodal tDCS. In this study, the recording of neurophysiological measures as MEPs and SEPs allowed the discrimination of the neural mechanisms of MI and SI (inhibitory or excitatory inputs) that are affected by two polarity current stimulations. Moreover, the evaluation of a specific difference in MI and SI excitability using a tES-EEG interactive approach allows for the elucidation of how PM-MI-SI are linked via corticocortical connectivity.

Finally, electrophysiological markers for tDCS-induced excitability modulation over the auditory cortex have been recently demonstrated by Zaehle et al.[34] These authors applied tDCS (1.25 mA, 35 cm^2 electrode, 11 minutes) over the temporal (T7) and temporoparietal (TP5) cortices and evaluated the auditory-evoked potentials (AEPs). Anodal stimulation over the temporal cortex increased the P50 amplitude, whereas cathodal stimulation over the temporoparietal cortex induced an increase in NI amplitudes. Consistent with previous findings, this work suggests a polarity-specific effect on cortical activity. Zaehle et al[34] suggested that the opposite effects of tDCS on P50 and N1 AEPs might be due to the distinct effects of tDCS on different types of neurons present in these cortices, therefore raising the possibility that the consequences of polarization effects are probably due to the morphological aspects.

Several studies have investigated modulations in the oscillatory activity induced by tDCS applied over the motor, visual, or prefrontal cortices. Ardolino et al[35] presented the first study to analyze power spectral density in response to tES applied over the motor cortex. Cathodal and sham tDCS (1.5 mA, 35 cm^2 electrode, 10 minutes) were delivered over MI while the participants were in a resting state. The comparison of oscillatory frequency power recorded before and after stimulation revealed an increase in low frequencies (i.e., delta [2-4 Hz] and theta [4-7 Hz]) after cathodal stimulation but not after sham stimulation. No modulation in the alpha (8-13 Hz) and beta/gamma (>14 Hz) frequencies was reported. These results are consistent with EEG findings that showed increased slow EEG activity (3-8 Hz) after cathodal polarization of the cerebral cortex of cats[6]

Opposing effects on the mu rhythm (8-13 Hz, i.e., alpha over the sensorimotor area) due to the orientation of the stimulation were reported by Matsumoto et al.[36] This study evaluated how tDCS applied over the left primary motor area (1 mA, 35 cm^2 electrode, 10 minutes) influenced event-related desynchronization of the mu rhythm recorded during the imaging of right-hand grasping. An increase and decrease in mu desynchronization after anodal and cathodal stimulation, respectively, were observed, thereby reflecting the facilitatory and inhibitory effects on the cortical excitability of tDCS. These results were also significantly correlated with motor thresholds. Overall, these data are in partial disagreement with the aforementioned report by Ardolino et al.[35] Nevertheless, this apparent discrepancy might be explained by the different state of the tested participants (i.e., resting state vs active task). Because brain oscillatory activity reflects the cortical state, it is likely that tES-induced cortical effects are also influenced by the state of activation of the participant.

The studies presented above evaluated how anodal or cathodal tDCS modulates the power of a given frequency. In addition, Polania et al[37] used functional connectivity and graph theoretical analysis to investigate the functional changes in the motor cortical network that were induced by tES. The EEG activity was acquired before and after anodal and sham tDCS applied over MI (1 mA, 16 cm^2 electrode, 10 minutes) in a resting state and during voluntary hand movements. The tDCS induced significant changes in intra- and interhemispheric connectivity within all of the sensory motor areas of the stimulated hemisphere in multiple frequency bands. A specific functional connectivity pattern in the 60 to 90 Hz frequency range was observed, although this effect was seen only during the motor task. This approach is useful for the direct evaluation of changes in the functional organization of networks induced by tES and task interaction. Moreover, these data provide evidence that the excitability increase induced by anodal stimulation might be related to the functional connectivity increase between cortical areas involved in the performance of a motor task.

To the best of our knowledge, only 1 study has investigated the changes in oscillatory activity induced by tDCS in the visual system. Antal and coworkers[38] applied anodal and cathodal tDCS (1 mA, 35 cm^2 electrode, 10 minutes) over Oz with the reference electrode located over Cz. Prior to stimulation and at 0, 10, 20, and 30 minutes after the end of the stimulation, the oscillatory activity in the beta (15-31 Hz) and gamma (31-65 Hz) frequency ranges was recorded during the presentation of visual stimuli as a measure of early sensory activation. The authors found a decrease in the power both in the beta and gamma frequencies after cathodal stimulation, whereas no changes were observed after anodal stimulation. The modulation by cathodal tDCS was present immediately after and at 10 to 20 minutes after the end of stimulation. These results are consistent with the previously published data by the same group[27] and with the concept that the power of high frequencies is correlated with behavioral performance in visual tasks.

Two studies have investigated the effects of tDCS applied over the prefrontal cortex on the performance of a working memory (WM) task and on the related spectral activity.[39,40] Zaehle et al[40] examined the impact of anodal and cathodal tDCS (1 mA, 35 cm^2 electrode, 15 minutes) with the active electrode placed over F3 according to the international 10-20 system for EEG and with the reference electrode placed over the ipsilateral mastoid. Also, tDCS was applied while the participants were in a resting state, and EEG activity was acquired during the execution of a WM task after the stimulation session. The authors reported a stronger improvement in WM performance after anodal than after cathodal tDCS compared to the sham stimulation. They also showed a concurrent increase in theta and alpha power after anodal tDCS, whereas cathodal tDCS induced a decrease in the same frequencies.

Keeser and colleagues[39] applied only anodal and sham tDCS (2 mA, 35 cm^2 electrode, 20 minutes) with the active electrode over F3 and the reference electrode above the right supraorbital region. The application of tDCS was followed by EEG acquisition, both of which were performed during resting state and a WM task (the n-back task). Anodal tDCS induced a reduction in the mean current densities (sLORETA) for the delta band over the left frontal cortex, which was accompanied by a decrease in reaction times and increased P200 and P300 ERPs during the execution of the n-back task.

The effects of tDCS on sleep were investigated offline by Roizenblatt et al.[41] The authors recorded sleep after anodal or sham tDCS treatment (2 mA, 35 cm^2 electrode, 20 minutes for 5 consecutive days) applied over the dorsolateral prefrontal cortex (DLPFC) or MI in fibromyalgia patients. Anodal tDCS had an effect on sleep and pain that was specific to the site of stimulation. Specifically, MI and DLPFC treatments induced opposite effects on sleep and pain, whereas sham stimulation induced no significant changes in sleep or pain. In addition, MI treatment increased sleep efficiency and decreased arousal, whereas DLPFC stimulation was associated with a decrease in sleep efficiency and an increase in rapid eye movement (REM) and sleep latency. In addition, a decrease in REM latency and an increase in sleep efficiency were associated with an improvement in fibromyalgia. The findings suggest that one possible mechanism to explain the therapeutic effects of tDCS in fibromyalgia is via sleep modulation that is specific for primary MI activity.

Finally, Iyer et al[42] applied anodal, cathodal, or sham tDCS (1 mA, 25 cm^2 electrode, 20 minutes) over the prefrontal cortex. The authors reported no discernible changes by a simple visual inspection in the EEG recordings. Similar results were observed by Tadini et al[43] using the addition of tACS.

The Rhythmic Approach

The goal of EEG acquisition using the rhythmic approach is to verify that tACS actually induces an entrainment of specific cortical oscillations. One hypothesis regarding tACS function postulates that tACS resets the ongoing rhythmic activity of local pacemaker networks and consequently synchronizes brain oscillations according to the applied tACS frequency. The rhythmic approach permits the investigation of the effective role of brain oscillatory activity.

Antal and colleagues[44] were the first to apply tACS (0.4 mA, 16 cm^2 electrode, 5 minutes) over the primary motor area with the objective of specifically influencing brain oscillations. Stimulation was applied at different frequencies (1-45 Hz) during the performance of an implicit motor learning task. The authors found a significant effect on the performance of the motor task only after 7 minutes of a 10-Hz stimulation, although no significant effect was seen in the EEG. A likely explanation for this result might be the very weak intensity of stimulation that was used.

Pogosyan et al[12] applied tACS (0.58 ± 0.004 mA, 14.4 cm^2 electrode, 10 seconds) over the primary motor cortex; although in this case, they specifically attempted to entrain the cortical activity at the beta frequency (20 Hz). Beta activity has been often considered to be a motor rhythm because it is observed during the preparation and the execution of a movement. Pogosyan et al[12] applied tACS at 20 Hz or 5 Hz (a control condition) during a concurrent visuomotor task, thereby inducing a retardation of voluntary movement only during the 20-Hz stimulation. The EEG data showed that stimulation induced a strong increase in the beta coherence in the contralateral motor cortex. These results can be considered as evidence of the causality between oscillatory brain activity and concurrent motor behavior. The importance of this work lies in the fact that combining tACS with EEG provided the opportunity to establish the degree and the extent to which rhythmic activity drives functions and, eventually, how rhythmic stimulation induces neural reorganization in maladaptive patterns of brain oscillations.[13]

Using a similar approach, Zaehle et al[45] delivered stimulation and sham tACS (1.120 $\pm$ 0.489 mA, 35 cm^2 electrode, 10 minutes) to the visual system with 2 electrodes placed bilaterally at the parietooccipital cortex (PO9 and PO10). For the stimulation, the frequency was set at the alpha frequency of $\sim$8 to 12 Hz. The objective of this study was to determine whether tACS induces an entrainment of the applied oscillatory activity. The results showed that tACS induced an increase in alpha power compared to the sham controls, thereby providing important evidence that it is possible to interact with ongoing cortical oscillatory activity by means of tACS and elevate the alpha power in the EEG.

Online Recording

The aforementioned studies demonstrate the benefits of combining tES and EEG offline; nevertheless, the online approach represents the most promising future application of this combination. Online approaches can yield information regarding the effects that are directly induced by tES. Clearly, several technical problems can be encountered during tES-EEG co-registration; and to date, only a small number of studies have successfully applied this approach.

The first work that combined tES and EEG was performed by Schroeder and Barr[46] in 2001 (please note that Schroeder and Barr refer to tES as "cranial electrotherapy stimulation"). In this study, EEG was recorded for 30 minutes (5 minutes before, 20 minutes during, and 5 minutes after stimulation) in a group of normal participants in an eye-closed condition. The authors used a basic noise-canceling method to minimize the presence of tES in the EEG. The actual tES signal recorded directly from the tES device was subtracted online from the EEG signal using 3 amplifiers. It should be noted that this operation did not take into account the specific interactions between the tES signal and the scalp elements or the brain response. Nevertheless, the authors were able to record and analyze EEG data collected using Ag/AgCl electrodes, one of which was located above the inion (Oz) while the reference electrode was placed over the vertex (Cz), and the left mastoid was used as ground. The EEG analysis was performed in both the time and frequency (1-30 Hz) domains. Each participant was submitted to 3 randomized sessions on different days. These 3 sessions included a sham control (no tES) or tES given at 0.5 or 100 Hz. The current delivered at 0.5 and 100 Hz was in the form of a biphasic, square pulse. The current level was adapted for each participant based on the absence of sensation at the electrode site, and the mean intensity was 0.048 mA (range, 0.01-0.1 mA). The tES electrodes were applied to the earlobes.

The results showed a decreasing trend in the mean alpha band frequency and power in both stimulation frequencies used. In addition, the tES at 100 Hz caused a decrease in the alpha band median frequency and beta band power fraction. These changes in alpha activity were associated with a previously observed beneficial effect of this stimulation on the general mental state of the patients. The authors concluded that tES at 100 Hz might have a stronger beneficial effect, due to a greater modulatory role in alpha and beta activity. Although the stimulation intensity was notably low and the interpretation of these results was not entirely clear, this was the first successful attempt to record EEG during tES.

A similar "rhythmic" online approach was used by Marshall et al[47] to evaluate the role of cortical oscillatory activity in sleep and memory. Anodal tES was applied intermittently (i.e.,15 seconds on, 15 seconds off; 0.75 Hz; current density of 0.26 mA/cm^2) over a period of 30 minutes during non-REM sleep. Active electrodes were located above the prefrontal cortex (F3 and F4), and the return electrodes were located above the mastoids. The EEG was recorded continuously using a DC/AC amplifier (band pass of 1-35 Hz) over 14 sites that were equally distributed over the scalp. The initial and final 2 seconds of the EEG signal at the start and end of tES were discarded from analyses. Power spectra and corresponding bands were calculated.

Marshall et al[47,48] showed that tES applied at this low frequency improved declarative memory retention and enhanced EEG slow-wave oscillatory activity (0.4-1.2 Hz) during sleep. In addition, Kirov et al[49] showed the same effects during wakefulness, thereby demonstrating an additional increase in EEG theta (4-8 Hz) activity. These applications showed an enhancement in the consolidation of hippocampus-dependent memories during sleep, whereas they facilitated the encoding of hippocampus-dependent memories when applied during learning in awake participants. These results are consistent with the idea that low-frequency oscillations play an important role in memory tasks.[50] The application of tES induces a modulation of both behavioral performance and brain oscillations, thus suggesting a causal relationship between these functions. Nevertheless it should be noted that according to Groppa and coworkers,[51] the findings in the Marshall et al[48] are due to the direct stimulation component of the current.

Finally, Accornero et al[28] evaluated VEPs during tDCS over the primary visual cortex (see the offline section above for the details of stimulation). Two experiments were performed using different polarization times (3 and 10 minutes). The EEG was recorded with the reference electrode (Ag/AgCl) over the vertex and 1 recording electrode above the inion (Oz; band-pass filter between 2 and 100 Hz). The polarizing scalp electrode was placed on the occipital region on top of the VEP recording electrode (1 cm in diameter) and was isolated from the VEP electrode with a 1-mm thick plastic disk measuring 3 cm in diameter. The return electrode was placed over the neck, and the recording period for each condition was approximately 45 seconds. The results observed during the online recording were more consistent than during the offline recordings: cathodal tDCS induced an increase in the P100 amplitude component, whereas anodal tDCS induced a decrease.[28] These results provide a direct demonstration of the tDCS-induced modulation of excitability over the stimulated cortex.

In general, EEG recording during tES may be technically challenging because tES induces an electrical field that can saturate recording amplifiers. This phenomenon mainly occurs due to the initiation of the current that induces charges in the electrodes, amplifiers, and skin, which induce a saturation that might last up to several seconds before EEG signal recovery. The application of tACS can even induce an oscillation that hinders the signal recording. Advances in amplifier technology, however, have led to the development of tES-compatible EEG equipment with wide dynamic ranges that can be used in constant stimulation fields without long periods of saturation. In addition, algorithms that can clean the signal from tACS-induced artifacts are currently under study. It has also been shown that it is possible to record EEG activity during tES without substantial problems by employing compatible pellet electrodes (such as those used for MRI or TMS) and by maintaining low electrode impedance values.

Given the interest in this approach, several groups are working on further developing tES-EEG applications, and it is likely that additional studies will be published in the near future.

Concluding Remarks

The combined tES-EEG approach can provide information about the dynamics of human brain functions beyond what is possible by the use of either method alone. Co-registration of tES and EEG might provide high temporal resolution information regarding tES-induced modifications/modulations to cortical activity that corresponds to different stages of processing. Moreover, tES-EEG will provide an assessment of how tES can remotely affect neural processing in distal brain regions. Most critically, the modifications caused by electrical stimulation spread to connected areas, and simultaneous EEG recordings will permit the tracking of these activations/modifications over the entire brain. When applied to an experimental context, in which the psychological and physiological states of the brain are modulated, this approach allows direct observation of the mechanism by which tES modulates the areas that are functionally activated during a task, or of the effects of a given state in shaping cortical connectivity.

Overall, ongoing technical advances are making it easier to perform experiments that were prohibitively difficult several years ago. For many different research interests, the combination of tES and EEG is indeed a promising approach, because it allows direct investigation of the effects of tES on cortical connectivity and reactivity.

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