



Review Paper

EEG oscillations: From correlation to causality

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ABSTRACT

Already in his first report on the discovery of the human EEG in 1929, Berger showed great interest in further elucidating the functional roles of the alpha and beta waves for normal mental activities. Meanwhile, most cognitive processes have been linked to at least one of the traditional frequency bands in the delta, theta, alpha, beta, and gamma range. Although the existing wealth of high-quality correlative EEG data led many researchers to the conviction that brain oscillations subserve various sensory and cognitive processes, a causal role can only be demonstrated by directly modulating such oscillatory signals. In this review, we highlight several methods to selectively modulate neuronal oscillations, including EEG-neurofeedback, rhythmic sensory stimulation, repetitive transcranial magnetic stimulation (rTMS), and transcranial alternating current stimulation (tACS). In particular, we discuss tACS as the most recent technique to directly modulate oscillatory brain activity. Such studies demonstrating the effectiveness of tACS comprise reports on purely behavioral or purely electrophysiological effects, on combination of behavioral effects with offline EEG measurements or on simultaneous (online) tACS-EEG recordings. Whereas most tACS studies are designed to modulate ongoing rhythmic brain activity at a specific frequency, recent evidence suggests that tACS may also modulate cross-frequency interactions. Taken together, the modulation of neuronal oscillations allows to demonstrate causal links between brain oscillations and cognitive processes and to obtain important insights into human brain function.

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1. Introduction

1.1. Discovery of EEG oscillations

In his first publication on the human electroencephalogram (EEG) in 1929, the German psychiatrist Hans Berger reported that he was able to record continuous and regular potential changes whenever he connected a sensitive string galvanometer via appropriate electrodes to the head of a subject in relaxed supine position (Berger, 1929). Having compared the results obtained with different types of electrodes and electrode positions, and after having conducted various control experiments in relation to possible vascular, muscular, or cardiac artifacts, Berger finally concluded: "Indeed, I believe that I have discovered the electroencephalogram of man and that I have published it here for the first time" (Berger, 1929, p. 567, translated by the authors).

He then went on in describing the EEG as a continuing curve of constant fluctuations, from which two types of waves can be discerned. Larger waves of the first order with an average duration of 90 ms

(Fig. 1), and smaller waves of the second order with an average duration of 35 ms with the larger waves having deflections of 0,00015–0,0002 V at most (Berger, 1929). Although, in his second report, Berger (1930) named the larger waves "alpha-waves" and the smaller waves "beta-waves", he originally used the terms "waves of the first/second order" in referring to the work of Práwdicz-Neminski (1925), who had described similar rhythms as first order waves with 11–15 Hz and second order waves with 20–32 Hz as the "Elektrocerebrogramm" of mammals. However, Berger (1929) did not adopt the term "Elektrocerebrogramm", because, for linguistic reasons, he considered the mixture of Greek and Latin components as barbarism and, therefore, proposed the term "Elektrenkephalogramm" (electroencephalogram) to denote the signals that he had described in humans for the first time.

Berger (1929) devoted the final pages of his first report to the question of where in the brain the EEG originates and what kind of processes might be reflected by the two different waveforms. From these pages, it becomes clear that Berger's primary interest in the EEG was not only its clinical application, but also the question of whether it would be possible to demonstrate an influence of intellectual activity on the EEG, i.e. the search for physiological correlates of cognitive processes. In this context, Berger mentions some preliminary experiments on his son Klaus that led him to the idea that intense mental effort and focused attention induce a predominance of the smaller and shorter waves,

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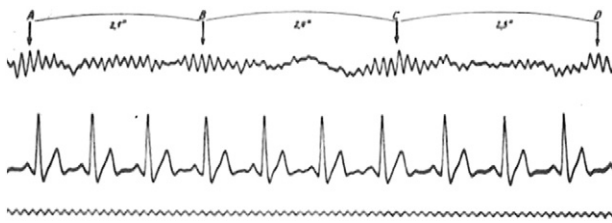


Fig. 1. EEG recorded by Berger. The alpha rhythm (top trace) is depicted together with the Electrocardiogram (middle trace) and a 10 Hz sine wave (bottom trace) used as time reference. Note the waxing and waning of the alpha rhythm with maxima at location of arrows A, B, C, and D. Berger measured that the amplitude maxima of the alpha activity are separated by about 1 to 3 s (2.1, 2.4, and 2.5 s in this figure as indicated by the numbers between arrows). This slow-frequency modulation (approx. 0.3 to 1 Hz) of a fast-frequency oscillation (10 Hz) represents a phenomenon that is nowadays referred to as cross-frequency coupling and will be discussed below (figure reprinted with permission from Berger, 1938).

which is now referred to as alpha blocking. However, he stresses the necessity of considerably more experimentation before one arrive at a final conclusion about this issue, and he hoped to be able to report on this particular question in the future. Following his initial report of 1929, Berger published another 13 reports “Über das Elektroencephalogramm des Menschen” (On the Electroencephalogram of Man) in numerical order until 1938, and returned repeatedly to the question of how attention and mental activity impacts on the EEG.

It was only in 1934—five years after Berger’s discovery of the human EEG—that his work received the deserved recognition from the scientific community, but only as the result of a replication of his main findings by the renowned British neurophysiologist E. D. Adrian. As pointed out by Adrian and Matthews (1934), their motivation to repeat Berger’s work stemmed from the difficulty to reconcile the regularity of the human alpha rhythm with previous results, including their own, from the exposed cortex of animals that revealed less regular potential changes mostly lacking a persistent 10 Hz rhythm. Despite their skepticism, Adrian and Matthews (1934) had to state: “The result has been to satisfy us, after an initial period of hesitation, that potential waves which he (Berger) describes do arise in the cortex, and to show that they can be explained in a way which does not conflict with the results from animals” (p. 356).

However, a dissent remained about the source and function of the alpha waves. Whereas Berger (1935) was convinced that the EEG arises from everywhere in the cortex and represents a fundamental brain function related to psychophysical processes with attention as the most important one, Adrian and Matthews (1934) favored the view of an occipital origin related to vision. To express this discrepancy, Adrian and Matthews even changed Berger’s original terminology: “Since the effect is so characteristic we shall refer to it in future as the Berger rhythm. Berger calls it the electroencephalogram, but the shorter title avoids the suggestion that the rhythm is produced by the entire cortex” (p. 356). At the end of his 10th report, Berger disagreed with that statement and strongly suggests maintaining the original name EEG, as it was given by him as the discoverer of these potential oscillations, instead of switching to the label that was chosen so honestly for him by Adrian and Matthews (Berger, 1935, p. 454).

Interestingly, to further support the vision-related occipital origin of the “Berger rhythm”, Adrian and Matthews (1934) discovered “... that regular potential waves at frequencies other than 10 a second can be induced by flicker” (p. 377). The authors recorded the EEG from the occipital lobe while subjects were exposed to flickering light with frequencies up to 25 Hz, thereby recording steady-state visual evoked potentials for the first time. When the flicker frequency was adjusted to the individual alpha frequency “... the waves may become extremely regular and may continue for many minutes without the usual waxing and waning in size” (p. 380). This response resembles a “resonance” frequency as has been later described by Walter et al. (1946) for subjects with a “well-marked” response to flickering light.

Soon after the successful confirmation of Berger’s work by Adrian and Matthews, electroencephalography became one of the most popular laboratory subjects with many EEG centers appearing in Europe and the United States (reviewed by Stone and Hughes, 2013). Although most of the early EEG research was devoted to further characterizing the alpha rhythm in various normal and abnormal conditions and populations (reviewed by Walter, 1938), some researchers were also interested in the functional roles of faster oscillations in the range of 20–30 Hz. Berger had described these beta waves as superimposed on the alpha rhythm, but they were regarded by many as artifacts arising from muscle activity. However, Jaspers and Andrews (1938) demonstrated a cortical origin of the beta rhythm that was independent from the sources of the alpha waves, in that it was found predominantly over sensory-motor brain areas. They also described faster waves around 50 Hz, for which they introduced the term “gamma rhythms” for the first time, albeit without discussing their possible relevance. EEG frequency components in the frequency range between 10 Hz and 50 Hz had already been reported by Dietsch (1932), who applied a Fourier analysis to EEG recordings at the urging of Berger. Even higher frequencies up to 1000 Hz were described by Rohracher (1935) and related to different kinds of mental activity like arithmetic or spelling. Slow waves below the alpha rhythm in the theta (4–7.5 Hz) and delta (0–3.5 Hz) range have been first reported by Walter (1936), who suggested the name “delta waves” for abnormal rhythms in the context of cerebral tumor location.

However, in contrast to the initial enthusiasm about the EEG in revealing physiological correlates of normal mental activities, the main application turned out to be restricted to clinical diagnostics. During the 1950s to 1970s the cortical origin of the alpha rhythm was questioned by several researchers due to the continuing difficulty in unraveling the basic neuronal mechanisms underlying the generation of brain waves (Shaw, 2003). In the 1960s, EEG research became dominated by the analysis of event-related potentials (ERPs), considering the background EEG as “noise” from which the brain response to a sensory or cognitive event had to be filtered out. Although in the 1970s only few electrophysiologists considered EEG oscillations as an important brain signal, some notable exceptions are the pioneering studies related to the gamma band by Freeman (1975) on the olfactory bulb of the rabbit and by Başar and coworkers on the auditory “40 Hz response” in the cat (Başar, 1972) and human brain (Başar et al., 1976). In the late 1980s, a dramatic reorientation towards oscillatory brain activity occurred inspired by the seminal work of Gray and Singer (1987) and Eckhorn et al. (1988) on synchronized gamma oscillations at the cellular level and their putative role for visual feature integration.

However, in the 1990s a corresponding interest in oscillations at other frequencies reappeared with the renaissance of alpha rhythms as a prominent example, as indicated by a conference on “Alpha Processes in the Brain” in 1994 and a related special issue on the functional correlates of alpha activity (Başar et al., 1997). The concept of a “diffuse and distributed alpha system” with various generators and diverse functions has been extended to other natural frequencies of the brain such as delta, theta, and gamma oscillations as reviewed by Başar et al. (2001). According to Başar (1998, 1999), the EEG should not be considered as background noise or cortical idling but as an important signal of the brain with the different oscillatory systems acting in concert to control the integrative brain functions at all sensory and cognitive levels.

1.2. The association of EEG oscillations with cognitive processes

Over the course of time, almost every cognitive process has been associated with an event-related EEG oscillation. However, there are many more different cognitive processes than the five different well-established frequency bands (delta, theta, alpha, beta, and gamma). Therefore, it is obvious that one cannot establish a 1:1

mapping between cognitive processes on the one side and EEG oscillations on the other side. It is more likely that EEG oscillations contribute to different cognitive functions depending on where in the brain and with what parameters (amplitude, frequency, phase, coherence) they occur. Four important assumptions support this notion:

1. Different brain regions may perform different but specific functions – a concept going back to the idea that different neuronal architecture implies different functionality (Brodmann, 1909).
2. EEG oscillations of slow frequency may represent the cooperative activity of large-scale neuronal networks in the brain whereas high-frequency oscillations may predominantly reflect the activity of local neuronal populations – a phenomenon that gives rise to the observed 1/f amplitude characteristics in EEG frequency spectra (Singer, 1993).
3. Coherent EEG oscillations in two distant brain regions may reflect the functional cooperation of these two regions (Siegel et al., 2012).
4. Combining assumptions 2 and 3, it has been suggested that cooperation between nearby cortical regions may be reflected by coherent high-frequency oscillations, whereas cooperation by distant brain regions may require coherent low-frequency oscillations (von Stein and Sarnthein, 2000).

In the sequel, we will give a brief overview of review articles that address the association between event-related EEG oscillations and cognitive processes. We will address the frequency bands in ascending order and focus on key concepts that have been replicated frequently and that are widely accepted.

1.2.1. Delta oscillations

The most prominent cognitive correlate of event-related delta activity is detecting a target or go-stimulus in a series of distractors or no-go stimuli. When subjects process such a stimulus that requires attentional resources, the ERP reveals a so-called P3 which is composed mainly of delta and theta oscillations (Başar-Eroglu et al., 1992). Sources of delta oscillations are often found in frontal and cingulate cortex, and in line with their low frequency these oscillations span a rather wide region of neural networks – possibly in an inhibitory manner (Harmony, 2013). This assumption is in line with a role in cognitive processes such as attention, since attending to one stimulus or location can be achieved by inhibiting other stimuli or locations.

1.2.2. Theta oscillations

Human EEG theta oscillations are most commonly associated with memory processes (Klimesch, 1999). It has been assumed that the cortical theta oscillations reflect the communication with hippocampus – a region that is known to serve memory functions and to exhibit oscillations in the theta range (Mitchell et al., 2008). In addition, human EEG theta activity is observed during functional inhibition subserving executive functions (Huster et al., 2013). In the latter case, theta oscillations are observed mainly in frontal cortex and typically regulate other brain structures via inhibition. A recent review on the mechanisms and functions of theta rhythms is given by Colgin (2013).

1.2.3. Alpha oscillations

EEG alpha oscillations are modulated during sensory stimulation (Schürmann and Başar, 2001). In addition, they reflect memory (Klimesch, 1997) and attentional processes (Hanslmayr et al., 2011). Alpha oscillations exhibit an inverse correlation with cognitive performance, thus suggesting an inhibition of task-irrelevant cortical structures (Jensen and Mazaheri, 2010). Since oscillations are ideally suited to serve as pacemakers, a recent hypothesis suggests how the two functions of inhibition and timing may be elementary building blocks of cognitive functions that require both suppression and selection (Klimesch, 2012). Recently, a critical review of the hypothesized

functional roles and physiological bases of alpha activity has been published by Başar (2012).

1.2.4. Beta oscillations

Modulation of human EEG beta oscillations has mainly been observed when subjects perform motor tasks (Neuper and Pfurtscheller, 2001). Interestingly, beta oscillations are also modulated during cognitive tasks requiring sensorimotor interaction (Kilavik et al., 2013). A recent hypothesis integrating aspects of motor and cognitive processes suggested that beta activity reflects whether the current sensorimotor state is expected to remain stable or to change in due course (Engel and Fries, 2010).

1.2.5. Gamma oscillations

While many of the low-frequency oscillations have been associated with functional inhibition, faster gamma-band oscillations are believed to reflect cortical activation (Merker, 2013). Depending on the exact cortical region, gamma oscillations are closely related to attentive processing of information (Fries et al., 2001; Womelsdorf and Fries, 2006), active maintenance of memory contents (Herrmann et al., 2004) and conscious perception (Singer, 2001).

1.3. Modulation of brain oscillations

In the past, researchers have mostly investigated oscillatory brain activity while the participants were engaged in certain cognitive processes. Thus, the experimental manipulation concerned the cognitive processes (independent variables) and physiological measures such as EEG oscillations (dependent variables). The approach of modulating brain oscillations inverts this procedure by manipulating the brain oscillation (independent variable) and searching for variations in cognitive processes (dependent variable). This offers the advantage to demonstrate that EEG oscillations are causal for cognitive processes. In principle, at least five methods are available in neuroscience to modulate EEG oscillations: 1) Neuromodulation via pharmacology, 2) Rhythmic sensory stimulation/steady-state-evoked potentials, 3) EEG-neurofeedback, 4) Repetitive transcranial magnetic stimulation (rTMS), and 5) transcranial alternating current stimulation (tACS). Here, we will not consider pharmacological interventions, since they represent a broad field on their own. Instead, we will particularly focus on tACS, since it is the most recent development and represents an inexpensive non-invasive technology, which is to be expected to raise considerable interest in the future. However, we will first briefly introduce the more established methods.

2. Established methods for modulating EEG oscillations

2.1. Rhythmic sensory stimulation/steady-state evoked potentials

Whenever a sensory stimulus is presented repetitively (see Fig. 2 for a visual example), this elicits a so-called steady-state evoked potential (SSEP) in the human EEG (Regan, 1982). This works across a wide range of frequencies, i.e. 1–100 Hz (Herrmann, 2001). Interestingly, the SSEP reveals resonance frequencies that resemble those frequencies of the EEG that are associated with cognitive processing, i.e. the frequencies that dominate ERPs. If the brain were a linear system, the response to a single stimulus (impulse response) would reveal the identical frequency peaks as driving the system with multiple frequencies in case of a steady-state paradigm – the so-called frequency response (Zaehle et al., 2010a). Although the brain is not a linear system (Stam, 2006) this simplification has been used successfully to predict SSVEPs from ERPs (Capilla et al., 2011). The close relation of resonance peaks in SSEPs and in ERPs suggests that driving the EEG with sensory stimuli at a specific resonance frequency might enhance the oscillation's amplitude at that frequency and might in turn enhance that frequency in the ERP as well as those cognitive processes that are associated

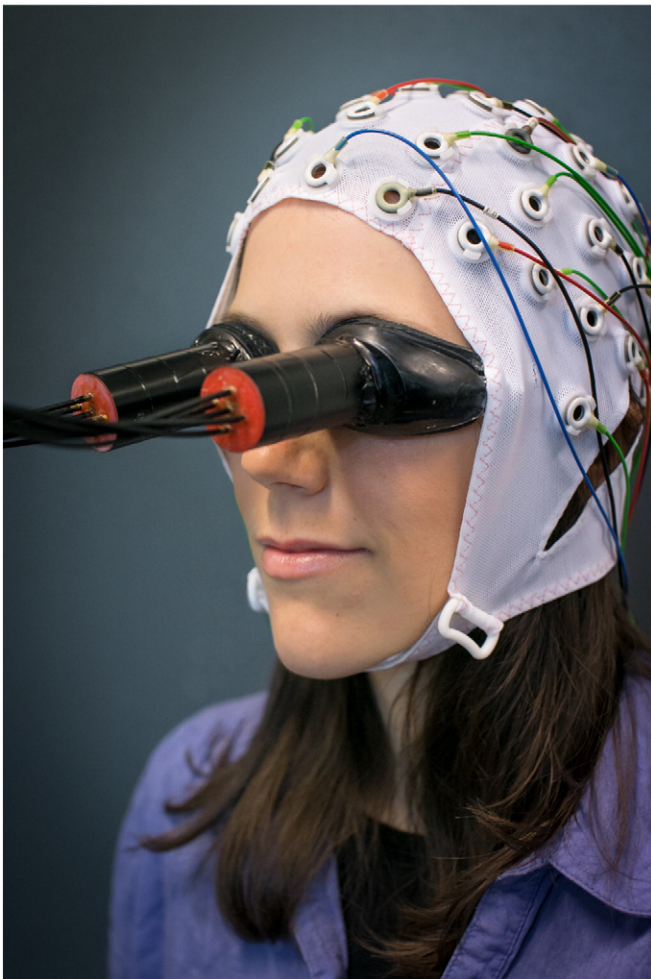


Fig. 2. Repetitive sensory stimulation during SSEP studies. Here, a visual stimulation via fiber-optic cables is shown. At the same time, EEG is typically recorded with 32 or 64 electrodes.

with that frequency. In the following, we will review studies that have demonstrated such a relationship.

For example, Kanizsa figures have been used to investigate the possibility of interfering with perception via sensory driving. Kanizsa figures are composed of multiple inducer elements and result in the perception of e.g. a square when the individual inducer elements are bound together – a phenomenon that was used to test the hypothesis that gamma oscillations are important for feature binding processes (Murray and Herrmann, 2013). Elliott and colleagues presented parts of a figure separately in time such that the visual percept of participants was that of a flickering figure (Elliott et al., 2000). The flicker frequency was 40 Hz due to a presentation time of 25 ms for each individual inducer. In some trials, the flickering figure contained a Kanizsa-like square (prime). Subsequent to the flickering stimulus, a stable stimulus (target) was presented and participants had to indicate whether or not this target contained a Kanizsa-like square. The evoked 40 Hz oscillations correlated significantly with the speeded reaction times in case primes were present in the flickering stimulus. This was taken to indicate that sensory driving at a specific frequency could not only enhance oscillatory EEG activity but also enhance cognitive processing.

Another study tried to exploit the finding that alpha oscillations correlate with memory processes. Williams and colleagues flickered the visual material for a recognition memory experiment on a computer screen at three different frequencies (Williams, 2001). At a flicker frequency of 10 Hz, participants of the study showed better memory performance than at 8.7 and 11.7 Hz. In a subsequent study, the authors

extended the paradigm to elderly people and placed light emitting diodes (LEDs) on top of a computer screen and let them flicker at different frequencies while subjects performed a visual memory task on the computer screen (Williams et al., 2006). When the flicker frequencies were around 10 Hz, the performance of the elderly subjects was almost as good as that of a younger control group. At higher or lower frequencies, the performance was worse. This was taken to indicate that indeed sensory stimulation at a frequency associated with memory processes could enhance these processes.

A very prominent example of how repetitive stimulation results not only in frequency-specific SSEPs but also in frequency-specific perceptual phenomena is the so-called flicker flutter illusion (Shiple, 1964). If a sound and a flash are both repetitively presented but at different repetition rates, the observer tends to perceive the sequence of flashes at the repetition rate of the sounds. For short sequences of sounds, even illusory flash perceptions in the absence of visual stimulation can be achieved (Shams et al., 2002).

In addition, repetitive sensory stimulation is believed to result in entrainment of neural oscillations and thus results in the entrained oscillation to continue for a few cycles after the end of stimulation (Halbleib et al., 2012). This entrained oscillation then affects cognitive processes even after the end of stimulation (Spaak et al., 2014).

An advantage of rhythmic sensory stimulation is its low cost and the possibility to drive sensory cortex sinusoidally resulting in a brain response of only one frequency. However, a disadvantage lies in its limitation to sensory cortices.

2.2. EEG-neurofeedback

A very interesting approach is to visualize EEG oscillations in order to make them accessible. When participants receive information on parameters of their brain activity, they are able to up- or down-regulate them – a phenomenon referred to as neurofeedback (Fig. 3). Modulation of brain activity via neurofeedback has been shown to influence a variety of cognitive processes (Vernon, 2005). However, it has been criticized that many authors demonstrated only enhanced cognitive functions without showing effects upon EEG oscillations (Egner et al., 2004). Therefore, subsequent studies reported both the modulation of EEG activity as well as the enhanced cognitive functions (for reviews, see Enriquez-Geppert et al., 2013; Gruzelić, 2014).

The advantage of neurofeedback is that subjects learn to modulate their brain activity and can subsequently use that skill also outside the lab or clinic. However, neurofeedback represents an endogenous technique that has to be learned by participants – an approach which is not viable in all subjects. Therefore, most studies investigating neurofeedback report non-responders. It seems plausible to assume that the other mechanisms described here, which employ exogenous stimulation techniques, may be suited to modulate the EEG oscillations of those non-responders.

2.3. Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS, Fig. 4) has been demonstrated to have differential effects upon cognitive functions depending on the frequency of the stimulation. Slow repetition rates of 1 Hz or lower lead to a decrease of cortical excitability, whereas faster rates of 20 Hz or above increase cortical excitation (Kobayashi and Pascual-Leone, 2003). The physiological mechanism of these phenomena was not clearly understood at the time and the use of EEG has subsequently shed new light on the underlying mechanisms (Johnson et al., 2010). Recent findings indicate that rhythmic magnetic impulses entrain brain activity much like sensory stimuli would (Thut et al., 2011b). Interestingly, the rTMS-evoked EEG oscillation outlasts stimulation offset, which suggests that indeed an oscillation has been entrained (Hanslmayr et al., 2014). Based on this assumption, rTMS in the alpha frequency range has been used to demonstrate the causal



Fig. 3. EEG-neurofeedback. In order to have subjects learn how to control a parameter of their EEG, this parameter has to be visualized and fed back to the subject. Usually, only a subset of the 32 or 64 electrodes is used for this purpose. Here, the amplitude of the frontal midline theta from a few frontal midline electrodes is fed back via a computer screen. Red or blue squares indicate an increase or decrease of theta amplitude as compared to a baseline, respectively.

role of EEG alpha oscillations for visual perception (Romei et al., 2010). In a similar vein, their role for memory processes was confirmed (Sauseng et al., 2009). The topic is nicely summarized in two recent reviews (Thut et al., 2012; Thut and Miniussi, 2009).

The advantages of rTMS are that it can be applied in an excitatory or inhibitory manner and that it represents an above-threshold stimulation technique, i.e. neural spikes and correlating muscle twitches or visual phosphenes can directly be elicited. Disadvantages of TMS are high equipment costs, high loudness levels associated with its operation, and the fact that the repetitive trains of impulses are not sinusoidal and therefore result in a brain response spanning many frequencies.

3. Recent method for modulating EEG oscillations: Transcranial alternating current stimulation

Whereas rTMS relies on magnetic impulses that directly stimulate neurons, there is another group of non-invasive brain stimulation techniques that is characterized by electric stimulation (Fig. 5) and includes transcranial random noise stimulation (tRNS), transcranial direct current stimulation (tDCS), oscillatory tDCS (otDCS), and transcranial alternating current stimulation (tACS). The application of sinusoidal currents via otDCS or tACS aims to directly modulate the ongoing rhythmic brain activity at the frequency of the applied current.



Fig. 4. Transcranial magnetic stimulation (TMS). TMS delivers one or multiple magnetic impulses to the human head via a coil that often has a figure-eight shape. The magnetic field passes the skull and induces an electric current that interacts with neural activity. Here, the subject is performing a task on the screen while being stimulated.



Fig. 5. Transcranial electric stimulation (TES). TES delivers an electric current directly to the human scalp, some of which passes through the skull and interacts with neural activity. At least two electrodes are used that received their names from tDCS: an anode (red electrode at top of head) and a cathode (blue electrode over back of head). For tACS, this terminology is misleading and recent paradigms employ multiple smaller electrodes for increased spatial resolution.

However, network simulations suggest that stimulation effects are also to be expected at harmonics and sub-harmonics of the stimulation frequency (Ali et al., 2013; see also Helfrich & Schneider, 2013). In addition, since tACS is believed to operate via entraining brain oscillations, an oscillation must be present at the frequency at which tACS is applied – otherwise it may have no effect (for a set of criteria see Thut et al., 2011a).

The effectiveness of tACS has been demonstrated in different approaches, ranging from purely electrophysiological or purely behavioral effects over combined electrophysiological and behavioral effects with offline EEG recordings to simultaneous (online) tACS-EEG recordings. Whereas purely physiological studies (Section 3.1) are useful in investigating the electrophysiological mechanisms that underlie the proposed tACS effects, i.e., the entrainment of spontaneous brain oscillations via external sinusoidal currents, they do not provide direct evidence for a functional relevance of the entrained brain oscillations. Pure behavioral studies (Section 3.2), on the other hand, demonstrate tACS effects on motor, sensory or cognitive processes but lack evidence for concurrent EEG effects. The rationale of those studies in choosing a particular stimulation frequency is usually based on well-established behavior-oscillation relationships obtained by previous correlative EEG experiments, e.g., the link between motor processes and beta-oscillations. Given that frequency specificity is demonstrated, i.e., a null effect for frequencies unrelated to the behavior under study, this approach allows inferring a causal role of the applied frequency for that specific behavior, although evidence regarding the underlying electrophysiological processes remains indirect. Therefore, study designs utilizing combined tACS/EEG measurements (Section 3.3) are desirable, because they allow, in principle, to directly link the observed tACS-induced behavioral effects to concurrent changes in EEG oscillatory activity. However, due to the strong artifacts induced by tACS, EEG had to be recorded offline to stimulation in most studies, whereas online recordings would be necessary in order to unequivocally establish neural entrainment (Thut et al., 2011a). Thus, even in current combined tACS/EEG recordings, electrophysiological evidence for entrainment is limited to comparing data before vs. after stimulation. Only recently, the first successful attempts were made to correct for tACS artifacts in online EEG recordings (Section 3.4).

3.1. Electrophysiological effects of tACS

An important progress in understanding the physiological basis of tACS was made by Fröhlich and McCormick (2010) in an animal study with simultaneous recording of local field potentials (LFPs) and multiunit activity (MUA) during intracranial stimulation of the cortex. These authors demonstrated a synchronization of MUAs and LFPs to the tACS waveform *in vivo*. Subsequent *in vitro* stimulation of cortical slices with weak alternating current resulted in a comparable synchronization, with the inter-burst frequency of the spontaneous activity following the stimulation frequency. The latter finding strongly indicates neuronal entrainment. A recent review on the mechanisms of tACS as revealed by *in vitro* and *in vivo* animal studies is given by Reato et al. (2013).

The first electrophysiological evidence for entrainment effects of tACS in humans was reported by Zaehle and colleagues, who stimulated participants at individual alpha frequencies and were able to demonstrate that alpha band power in the offline EEG was enhanced after tACS, but not after sham stimulation (Zaehle et al., 2010b). These findings have been replicated recently and it was shown that the after-effect outlasted the end of stimulation by at least 30 min (Neuling et al., 2013).

3.2. Behavioral effects of tACS

The effectiveness of tACS has been demonstrated by revealing frequency-dependent consequences on visual and tactile sensations. By application of tACS over the occipital cortex, Kanai et al. (2008) were able to induce visual sensations (phosphenes) in a frequency dependent manner. However, there is an ongoing debate whether tACS-induced phosphene induction is of cortical or retinal origin (see Herrmann et al. 2013 for a review). Feurra et al. (2011) delivered tACS at different frequencies over the primary somatosensory cortex and found that stimulation in the alpha, beta, and high gamma frequency range elicited tactile sensations, whereas other frequencies did not produce a perceptual effect. Laczó et al. (2012) applied tACS at 40, 60, and 80 Hz over the visual cortex and found an increase of contrast

perception only for 60 Hz stimulation. Whereas these studies were all able to demonstrate frequency-specific perceptual consequences of tACS, this pattern of results is not without exception (Brignani et al., 2013).

TACS effects on motor behavior have also been described. Using a go/no-go task, Joundi et al. (2012) reported a slowing down of voluntary movement during 20 Hz tACS, whereas gamma tACS at 70 Hz increased the performance in go trials. In a finger tapping task, Wach et al. (2013a) also found movement slowing with 20 Hz tACS, but increased movement variability after 10 Hz stimulation.

In addition to tACS effects on perceptual and motor functions, there are several reports of stimulation effects on higher-order cognitive processes. Frequency-specific performance modulations were reported in relation to fluid intelligence, demonstrating shorter solution times for a visuospatial abstract reasoning task during gamma (40 Hz) tACS as compared to stimulation at theta, alpha, and beta frequencies (Santarnecchi et al., 2013). A decrease in reaction times during a working memory task has been described for 6 Hz tACS (but not 35 Hz) during in-phase stimulation over left frontal and parietal regions (Polanía et al., 2012). Jaušovec et al. (2014) also explored the role of theta tACS over frontal and parietal brain areas in working memory and found an enhancement of storage capacity when stimulating the left and right parietal but not left frontal sites. Thus, this study demonstrates topographical specificity, but leaves frequency-specificity unaddressed. Similarly, Sela et al. (2012) restricted their analyses to topographical effects of theta tACS in showing that stimulation of the left dorsolateral prefrontal cortex led to riskier decision-making than stimulation of the right dorsolateral prefrontal cortex.

3.3. Combined behavioral and electrophysiological effects (offline EEG recordings)

Combined behavioral and electrophysiological effects of tACS have been investigated for various motor, perceptual, and cognitive functions. In a first exploratory study on tACS-induced modulations of motor functions, Antal et al. (2008) applied tACS at various frequencies (1, 10, 15, 30, and 45 Hz) and recorded EEG before and after tACS. Results showed improved implicit motor learning for 10 Hz only, and no EEG effects after any of the applied stimulation frequencies. In a combined tACS/MEG study, Wach et al. (2013b) analyzed the effects of 10 Hz and 20 Hz tACS on corticomuscular coherence and motor cortex oscillatory activity in several frequency bands during isometric forearm contraction. MEG was recorded before and after tACS was applied to the left primary motor cortex. Results showed a decrease in gamma corticomuscular coherence (30–45 Hz) as a consequence of 10 Hz tACS (Wach et al., 2013b).

tACS has also been applied in the gamma frequency band in order to modulate perception of bistable motion (Strüber et al., 2014). It had previously been shown that this type of motion perception depends on changes of the interhemispheric coherence in this frequency band. Applying tACS at 40 Hz elevated the interhemispheric coherence in the gamma-frequency band and resulted in a bias of the bistable percept. Also auditory perception has been shown to be modulated by tACS (Neuling et al., 2012). When a 10 Hz sinusoidal current is applied to the auditory cortex, it modulates near-threshold perception in a sinusoidal manner, suggesting that not only amplitude and frequency of stimulation are important but also phase. This study at the same time replicated the enhancement of EEG alpha amplitude, indicating that tACS at 10 Hz was physiologically effective.

The role of sleep-related oscillations for memory consolidation has been investigated using otDCS at a delta frequency (Marshall et al., 2006). The authors were able to show that their stimulation protocol enhanced EEG delta activity during sleep and resulted in improved performance during recall of memory items at the next morning. For a review of a series of similar studies, see Marshall and Binder (2013).

Recently, Jaušovec and Jaušovec (2014) assessed the role of theta oscillations for working memory by applying tACS at the individual theta frequency at left parietal or left frontal sites. After stimulation, EEG was recorded while subjects solved a working memory task. Results showed an increase of working memory capacity as well as a shortening of P300 latency in response to left parietal but not left frontal tACS.

3.4. Combined behavioral and electrophysiological effects (online EEG recordings)

The studies mentioned so far have investigated only offline effects of tACS on human EEG, since electric stimulation elicits a severe artifact in the EEG electrodes due to the electrically conducting connection of stimulation electrodes and EEG electrodes via the scalp. One way to circumvent this problem is to record another physiological signal that is not contaminated by the stimulation. This approach was used by Pogosyan et al. (2009). They computed the coherence between electromyographic (EMG) activity from a finger muscle that was not contaminated by tACS and scalp-recorded activity that did contain the artifact of a simultaneously applied 20 Hz tACS signal. This resulted in a peak of coherence at 20 Hz briefly before movement onset and led to a slowing of movements. These findings indicate that EEG oscillations in the beta frequency range are causally relevant for the execution of movements.

Another approach is to record EEG simultaneously to tACS and to disentangle EEG and the tACS-artifact. This has been demonstrated recently by Helfrich et al. (2014) who estimated a template of the tACS artifact from multiple adjacent seconds, scaled it to each data segment, and subtracted it from the contaminated EEG signal – a method that had previously been developed to eliminate the so-called gradient artifact when EEG is recorded during functional magnetic resonance imaging. A residual artifact remained in the EEG after this initial step that was subsequently removed with an independent component analysis. This method allowed analyzing EEG during tACS (cf. Fig. 6). This study again replicated the finding that 10 Hz tACS enhances EEG amplitudes in the alpha band. In addition, it showed that the EEG spectrum was already enhanced during stimulation. Interestingly, the spectral peak in the alpha band became more narrow in frequency, suggesting that the individual alpha frequency of subjects below and above 10 Hz were shifted towards 10 Hz as would be expected for entrainment of an oscillation.

4. Conclusion

Already from the very start of EEG research, oscillatory brain activity was in the focus of researchers' attention. Early work investigated the physiological basis of these oscillations. Later work revealed the important correlations of EEG oscillations with cognitive functions. The experimental modulation of brain oscillations made it possible to demonstrate that the relation of oscillations to cognitive processes is causal in nature. However, we are not at the end of a historical development but rather in an ongoing process. A 1:1 mapping of brain oscillations to cognitive functions is not possible. Instead, the function of oscillatory brain activity depends on the brain structures that participate in the oscillation. Recently, the interplay of multiple oscillations of different frequencies has received renewed attention. It has been hypothesized, for example, that the limit of items that can successfully be stored in working memory (roughly seven) results from the ratio of the involved brain oscillations in the theta and gamma frequency (roughly 1:7); i.e. the number of items is determined by the number of gamma cycles that fit into one theta cycle (Lisman and Idiart, 1995). Multiple electrophysiological studies were able to demonstrate a cross-frequency coupling of theta and gamma oscillations in humans (Mormann et al., 2005; Canolty et al., 2006; Demiralp et al., 2007). Good reviews on cross-frequency coupling are given by Canolty and

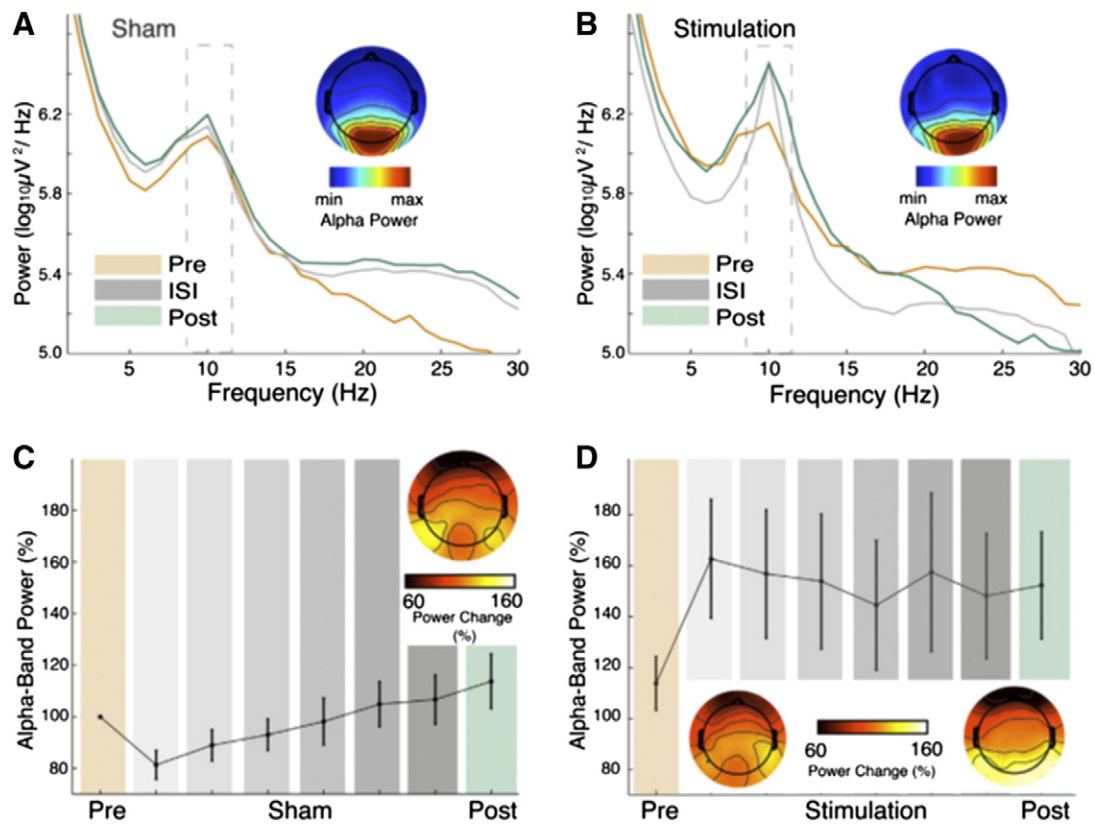


Fig. 6. Change of alpha power during 10 Hz tACS. A: During sham stimulation, alpha amplitude in the EEG spectrum does not differ significantly between conditions. B: When 10 Hz tACS is applied, the alpha amplitudes are enhanced already during stimulation (gray spectrum, ISI) as compared to before stimulation onset (orange spectrum, pre). This enhancement extends until after the end of stimulation (green spectrum, post). Note that the gray spectrum is not only elevated in amplitude but that also the alpha peak is sharper in frequency. C: During sham stimulation, alpha activity is at first reduced due to the presentation of visual stimuli. Over the course of the experiment, alpha activity increases, probably reflecting a decrease in vigilance. D: With the onset of 10 Hz tACS, alpha activity increases and remains elevated after the end of stimulation (figure reprinted with permission from Helfrich et al., 2014).

Knight (2010) and Jensen and Colgin (2007). As already noted by Berger in 1938, the human alpha rhythm is modulated by a slower oscillation. More recently, it could be demonstrated that the alpha rhythm in turn modulates the still faster gamma rhythm (Osipova et al. 2008). Importantly, the alpha-gamma interaction is modulated during cognitive tasks (Palva et al., 2005). Hitherto, the directionality of such cross-frequency interactions was uncertain. If, for example, gamma oscillations reflect states of high excitability, they serve as a “master process” in determining what is being processed – if, however, the amplitude of gamma oscillations is dictated by the phase of theta oscillations, the gamma oscillation is slave to theta (Schroeder and Lakatos, 2009). The abovementioned stimulation techniques offer a new tool to investigate this and similar questions. One could modulate one brain oscillation and analyze the effect upon another oscillation and vice versa, possibly revealing a directional influence. First evidence demonstrates that tACS in the gamma frequency range down-modulates amplitudes in the alpha frequency range (Boyle and Fröhlich, 2013) and vice versa (Wach et al., 2013b). While these two studies do not solve the question of directionality, they show that cross-frequency studies are feasible with tACS. Therefore, we believe that the investigation of brain oscillations – begun by Hans Berger in the 1920s – will continue to reveal important insights into human brain function.

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