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On the effectiveness of event-related beta tACS on episodic memory formation and motor cortex excitability

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ABSTRACT

Background: Transcranial alternating current stimulation (tACS) is widely used to entrain or modulate brain oscillations in order to investigate causal relationships between oscillations and cognition.
Objective: In a series of experiments we here addressed the question of whether event-related, transient tACS in the beta frequency range can be used to entrain beta oscillations in two different domains: episodic memory formation and motor cortex excitability.
Methods: In experiments 1 and 2, 72 healthy human participants engaged in an incidental encoding task of verbal and non-verbal material while receiving tACS to the left and right inferior frontal gyrus (IFG) at 6.8 Hz, 10.7 Hz, 18.5 Hz, 30 Hz, 48 Hz and sham stimulation for 2s during stimulus presentation.
In experiment 3, tACS was administered for 10s to M1 at the individual motor beta frequency of eight subjects. We investigated the relationship between the size of TMS induced MEPs and tACS phase.
Results: Beta tACS did not affect memory performance compared to sham stimulation in experiments 1 and 2. Likewise, in experiment 3, MEP size was not modulated by the tACS phase.
Conclusions: Our findings suggest that event-related, transient tACS in the beta frequency range cannot be used to modulate the formation of episodic memories or motor cortex excitability. These null-results question the effectiveness of event-related tACS to entrain beta oscillations and modulate cognition.

Introduction

Brain oscillations represent regular fluctuations in the local field potential and play a crucial role in establishing synchronous firing patterns [1]. Especially oscillations in the beta frequency range (~13–30 Hz) have been linked to a variety of cognitive and sensorimotor processes [2–6]. Beta power decreases, for example, have been shown to predict successful memory encoding [7,8]. Such desynchronized activity occurs in highly task relevant regions [9], and is negatively correlated with blood oxygenation level dependent (BOLD) activity [10]. It has further been demonstrated that power and phase of beta oscillations over the motor cortex influence the amplitude of transcranial magnetic stimulation (TMS) evoked potentials (MEPs) [11,12].

Despite the numerous associations between these processes and beta oscillations, the causal relationship between them remains unclear. Transcranial alternating current stimulation (tACS), an increasingly popular non-invasive human brain stimulation technique [13], has been suggested to provide this causal link between brain oscillatory activity and cognitive processes. Recent findings suggest that tACS entrains brain oscillations in a frequency specific way [14,15]. This modulation of underlying oscillatory activity can affect behaviour [16–19], interacts with underlying oscillatory activity [20–24], and elicits frequency specific neuronal spiking [25].

tACS could be a very beneficial and powerful method for cognitive research, if it was also able to modulate brain oscillations in a time-critical way [26,27]. During cognitive tasks brain oscillations show a very dynamic behaviour and are modulated in the range of seconds. However, most studies having demonstrated effects of tACS on behaviour applied tACS throughout cognitive tasks in a sustained way, resulting in stimulation durations of up to 20 minutes [15–18,20,21,28]. This makes it difficult to directly link oscillatory activity associated with specific cognitive dynamics with the results of these tACS studies. In order to demonstrate that tACS is indeed a useful tool for modulating dynamic cognitive processes, tACS should be administered within a short period of time at certain phases of a cognitive task in event-related, randomized designs.

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In the present study we sought to investigate the effectiveness of event-related beta tACS. In a series of experiments we explored whether tACS in the beta frequency range is effective in modulating two different processes: the formation of episodic memories and motor cortex excitability.

Beta power decreases and episodic memory formation

Successful memory formation for verbal material has been associated with power decreases in the beta frequency range [8]. This beta desynchronization can be localized to the left inferior frontal gyrus (IFG) [10], a region which has been linked to successful semantic memory encoding in numerous studies [29]. Using rhythmic transcranial magnetic stimulation (rTMS), Hanslmayr et al. [30] demonstrated a causal link between beta desynchronization in the left IFG and memory encoding. By artificially synchronizing the left IFG via rTMS in the beta frequency range, memory formation for words was impaired at beta but not at other frequencies. These findings provide a first causal link between beta power decreases and episodic memory. However, due to safety considerations [31] rTMS stimulation could not be applied at higher frequencies, and hence their effects could not be investigated. Therefore, experiments 1 and 2 aimed to replicate and extend these findings and further examine whether tACS may be a useful addition to TMS. In these two experiments, the differential and specific effects of beta tACS to the left IFG on the encoding of verbal material and the effects of beta tACS to the right IFG on the encoding of non-verbal material were investigated. Several studies report material-specific lateralization during episodic memory encoding with left frontal involvement during the encoding of verbal material and right frontal activation for non-verbal material [29,32,33]. Therefore beta (18.5 Hz) tACS should only affect memory performance for words when administered to the left IFG (as has been shown by Hanslmayr et al. [30]) while right IFG stimulation should result in decreased memory performance for non-verbal material only.

Beta phase and motor cortex excitability

Several simultaneous tACS-TMS studies investigated the causal relationship between beta power and corticospinal excitability [23,34], with recent studies investigating whether the phase of 20 Hz tACS can modulate MEP amplitude [35–37]. However, in these studies tACS was applied for prolonged periods of time. Raco et al. [35] for instance applied 20 Hz tACS for 200s and found a phase-dependent modulation for the last three MEPs only. In experiment 3 we aim to investigate whether 10s of tACS tuned to the individual motor beta frequency can lead to a modulation of the amplitude of TMS evoked MEPs by the phase of the ongoing tACS.

Aims of the studies

Being able to modify beta oscillations within a short period of time in an event-related, randomized manner is crucial for quantifying the effectiveness of beta tACS and ultimately its usefulness for modulating dynamic cognitive processes. Therefore, different stimulation parameters were used to reveal the ideal stimulation set-up for transient tACS. The effects of different electrode sizes on episodic memory formation were investigated in experiments 1 and 2. In order to keep the current density and possible skin sensations comparable, the stimulation intensity was reduced from 1 mA (experiment 1) to 0.8 mA (experiment 2). Additionally, the specific effects of beta tACS were investigated using four control frequencies as well as sham stimulation. As episodic memory performance is a rather indirect read out for the effectiveness of brain stimulation, we investigated the effect of beta tACS on MEP size in experiment 3. This more direct way of quantifying the effectiveness of brain stimulation [38–42], allowed us to explore whether traditional montages with one electrode being placed directly at the target area are more effective than montages with both stimulation electrodes surrounding the target area. Although the same electrode size used in experiment 2 was chosen for experiment 3, lower stimulation intensities were used in order to reduce possible side effects, e.g. phosphenes that have been reported repeatedly by participants of experiment 2. Finally, the stimulation duration in experiment 3 was increased to 10s compared to 2s in experiments 1 and 2, allowing us to investigate whether slightly longer but still relatively short stimulation has effects on motor cortex excitability. Furthermore, in experiment 3, we aimed to optimize tACS parameters by stimulating at the participants' individual beta frequency rather than using a standard frequency (e.g. 20 Hz).

Experiments 1 and 2

Material and methods

Participants

Participants were screened for contraindications against transcranial alternating current stimulation prior to the experiment [43]. 36 subjects participated in experiment 1 (24 female; mean age: 20.03 $\pm$ 2.38 years) and 36 in experiment 2 (24 female, mean age: 20.97 $\pm$ 2.22 years). All participants were right handed, had normal or corrected-to-normal vision and reported no history of neurological disease or brain injury. Informed consent was acquired from each subject prior to the experiment. All were naive to the hypotheses of the study and were fully debriefed at the end of the experiment. The study was approved by the ethics committee of the University of Birmingham.

Stimulus material

Word stimuli consisted of 270 nouns derived from the MRC Psycholinguistic Database, Version 2.00 [44] and were presented in black. These were divided into 18 lists of 15 words and were matched for word frequency, word length, number of letters, number of syllables, concreteness, and imaginability. Face stimuli consisted of 270 faces drawn from several face databases. The faces were emotionally neutral and were presented in black and white on a black background. These were divided into 18 lists of 15 stimuli and were matched for gender, hair colour, and approximate age. Stimuli were presented in a randomized order, and counterbalanced across subjects. 360 stimuli (180 words, 180 faces) were presented during encoding and retrieval, serving as old items in the retrieval period, 180 stimuli (90 words, 90 faces) were presented during retrieval only, serving as new items (Fig. 1).

Experimental setup and procedure

Participants were seated approximately 80 cm from a 19 inch LCD monitor (resolution: 1280 $\times$ 1024 pixels, 60 Hz frame rate). Stimuli were presented on a grey background on the centre of the screen using the Psychophysics Toolbox extension for Matlab [45]. Before the start of the main experiment participants were familiarized with tACS and desensitized to the stimulation intensity in order to avoid adverse reactions.

Encoding

During encoding, participants had to perform a pleasantness rating of a presented stimulus on a 4-point rating scale (very pleasant – very unpleasant). Answers were given manually by pressing one of four buttons on a computer keyboard using the middle and index finger of both hands; whether the left or right hand corresponded to the *pleasant* or *unpleasant* category was