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Research Report

Oppositional transcranial direct current stimulation (tDCS) of parietal substrates of attention during encoding modulates episodic memory

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ABSTRACT

Effective learning requires that attentional resources be focused on target information and withheld from irrelevant events in the learner's surroundings. This requires engagement of the brain substrates of selective attention and the concurrent disengagement of brain substrates of orienting toward changes in the environment. In the present study, we attempted to modulate activation of cortical substrates of attention during learning by physiological intervention, using transcranial direct current stimulation (tDCS). To effect adversarial modulation, we applied anodal stimulation directed toward left intraparietal sulcus/superior parietal cortex (IPS/SPL; a substrate of selective attention) and cathodal stimulation directed toward right inferior parietal cortex (IPL; a substrate of orienting). Such stimulation during study of verbal materials led to superior subsequent recognition memory relative to the opposite polarity of stimulation. To our knowledge, this is the first application of direct current stimulation to parietal regions implicated in different forms of attention in an oppositional manner in order to modulate learning in a verbal recognition memory task. Additionally, these results may have practical implications for the development of interventions to benefit persons with various types of attentional deficits.

1. Introduction

Allocation of attention to specific aspects of our experience appears to be an important factor in determining whether resilient mnemonic representations of those aspects will be formed (Chun and Turk-Browne, 2007; Craik, 2001). Unattended percepts are far less likely to be remembered than attended information, and under certain circumstances may be totally absented from explicit memory (Bentin et al., 1995; Fisk and Schneider, 1984; Yi and Chun, 2005). Furthermore, dividing attention between two concurrent tasks during encoding impairs declarative memory for studied information (Anderson and Craik, 1974; Baddeley et al., 1984; Craik et al., 1996; Femandes and Moscovitch, 2000). In contrast, attending to specific features of a perceived object leads to better subsequent memory for that feature (Uncapher and Wagner, 2009). The neuronal basis of this effect seems to be that hippocampal encoding mechanisms are sensitive to attentional modulation of cortical activity (Uncapher and Rugg, 2009).

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Attention is not a single entity. In recent years, compelling evidence has accumulated for the existence of several attention systems, with separable brain substrates, functions, and even different key neurotransmitters (Fan and Posner, 2008; Raz, 2004; Tsal et al., 2005). The ventral attentional network that supports orienting, including the temporo-parietal junction (TPJ), inferior parietal lobe, and ventral prefrontal cortex, appears to be primarily concerned with detecting change in the environment (Behrmann et al., 2004; Corbetta and Shulman, 2002; Corbetta et al., 2008). Damage to this system, especially right hemisphere lesions, yields hemi-neglect and extinction deficits, reflecting loss of awareness of the appearance of perceptual objects. In contrast, the dorsal attentional network, including superior parietal cortex and the frontal eye fields, appears to support top-down focus of attention on selected spatial, object, or feature characteristics that are chosen for enhanced processing (Corbetta and Shulman, 2002; Corbetta et al., 2008).

Under ecological conditions, our ongoing sensory experience represents a dynamic interchange between the latter two attentional systems — the ventral network pulling in the direction of orienting toward change or salience of the overall environment, and the dorsal system directing our limited resources toward specific pre-selected goal-relevant information (Corbetta and Shulman, 2002). The effects of activation of the ventral and dorsal systems on encoding have been highlighted in a recent meta-analysis of functional neuroimaging studies of parietal cortex using the subsequent memory paradigm (Uncapher and Wagner, 2009). The authors show that the vast majority of positive subsequent memory effects are observed in dorsal parietal areas associated with selective attention, while all negative subsequent memory effects localize to ventral parietal areas associated with orienting, including TPJ and angular gyrus (Uncapher and Wagner, 2009). The competition between these two systems is mediated by the executive attention system. When executive function is impaired, as occurs in diverse situations including ADHD, schizophrenia, and frontal lobe damage, attentional allocation is sub-optimal, and ongoing cognitive performance is impaired (Alvarez and Emory, 2006; Barkley, 1997; Velligan and Bow-Thomas, 1999). Currently, pharmacological interventions such as methylphenidate (O'Driscoll et al., 2005) are the methods of choice for assisting people with executive deficits (as well as providing controversial enhancement of attentional focus of healthy individuals). Might other effective methods exist for the modulation of attention in favor of the selective processes that support learning and success in other cognitive tasks?

We hypothesized that one such possible method might be the electrical stimulation of cortical areas supporting the relevant attentional systems. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which utilizes persistent direct current injection into the brain. Current is passed between a positively charged anode and a negatively charged cathode. Because flow of current is directional, anodal and cathodal stimulation may have different effects on brain activity. In a pioneer study, Nitsche and Paulus (2000) found that anodal stimulation increases human motor cortex excitability, while cathodal stimulation decreases it, both during stimulation and for a few minutes thereafter. In the wake of that spearhead study, tDCS effects on cognitive functions have been broadly investigated. Most studies found the anodal facilitation effect reported by Nitsche and Paulus (2000): Flöel et al. (2008); Iyer et al. (2005); Kincses et al. (2004); Sparing et al. (2008); and Stone and Tesche (2009). Some of them also reported the cathodal inhibition effect (Berryhill et al., 2010; Knoch et al., 2008; Loui et al., 2010, but see Flöel et al., 2008; Iyer et al., 2005; Priori et al., 2008, who did not find inhibitory cathodal effect).

Application of anodal tDCS has been shown to be effective in improving a number of types of learning. Flöel et al. (2008) applied tDCS over the posterior part of the left peri-sylvian area and found an improvement in associative language learning, Kincses et al. (2004) applied tDCS over the prefrontal cortex and found an improvement in probabilistic classification learning, and Vries et al. (2010) applied tDCS over Broca's region and found an improvement in artificial grammar implicit learning. The effects of tDCS have also been reported for motor learning. For example, Antal et al. (2004) applied tDCS over visual areas and found an improvement in visuo-motor learning, and Nitsche et al. (2003) applied tDCS over primary motor cortex and found an improvement in implicit motor learning. Other cognitive functions can be improved by tDCS as well. Iyer et al. (2005) applied tDCS over left prefrontal cortex and found an improvement in verbal fluency, and Ross et al. (2010) applied tDCS over right anterior temporal lobe and found an improvement in person naming. Notably, it has recently been demonstrated that repeated application of tDCS in the context of cognitive processes may lead to long-lasting beneficial modulation (Cohen-Kadosh et al., 2010).

One particular aspect of tDCS is especially intriguing in view of its possible relation to the dynamic competition between orienting and selective attentional systems postulated above. As noted, it is sometimes found that while anodal stimulation improves cognitive function dependent on underlying cortex, cathodal stimulation may impair such processes (Nitsche and Paulus, 2000). Accordingly, in the current study we engaged in what might be termed 'adversarial modulation': we conducted simultaneous anodal stimulation of left intraparietal sulcus/superior parietal lobe (IPS/SPL; a substrate of selective attention) and cathodal stimulation of right inferior parietal lobe (IPL; a substrate of orienting). We thus attempted to modulate attention during learning in favor of selection processes, in the hope of benefitting subsequent episodic memory for that information. The choice of right IPL as the primary locus of attentional orienting was specific, supported by a host of lesion and functional imaging studies that attest to a much stronger role in orienting of right hemisphere than left hemisphere (Corbetta et al., 2008; Downar et al., 2000). However, IPS/SPL involvement in selective attention is more bi-laterally distributed (Corbetta et al., 2008). Because the effects of tDCS are not very spatially precise, we chose to stimulate left IPS/SPL in order to improve the separation between the two loci of stimulation.

Based on the above literature, we hypothesized that participants undergoing tDCS in the Cathodal R-IPL/Anodal L-IPS/SPL condition during encoding of verbal material would subsequently demonstrate better recognition than in the opposite condition of stimulation. Furthermore, we predicted that recognized stimuli would be more vividly remembered as a result of their better encoding, and accordingly would yield more recollection-related than familiarity-related responses (Yonelinas, 2002) than those in the Anodal R-IPL /Cathodal L-IPS/SPL. Because the effects of attentional modulation were hypothesized to be interactive rather than absolute, in this initial examination we employed opposite conditions of stimulation rather than stimulation vs. sham condition. We chose not to add a third session because a pilot study showed that in multiple sessions the effects of task habituation overshadow the experimental manipulation. To partially compensate for this clear limitation, we also compared memory performance in the two conditions with baseline performance data collected in a different control group of participants.

2. Results

A pair-wise comparison of *d'* scores for recognition accuracy (*Right Ventral Anodal*, $d'=1.34$, and for *Left Dorsal Anodal,* $d'=1.58$; Fig. 1A) yielded a significant effect of stimulation condition, $t\,(11)=2.73$, $p=0.01$ (one-tailed). The significant effect of higher accuracy in the *Left Dorsal Anodal* compared to the *Right Ventral Anodal* was found for 9 out of the 12 subjects. Cohen's *d*, calculated as mean accuracy in the *Left Dorsal Anodal* condition minus mean accuracy in the *Right Ventral Anodal* condition divided by pooled SDs, was 0.54, which is considered a moderate effect size. In addition, we analyzed the stimulation condition effect on the confidence level subject felt when correctly indicating whether the word was presented. As described in the methods, there were five response keys in the verbal recognition test; three of them ('*surely new*', '*surely old*', '*surely old+concrete memory*') represented high levels of confidence, and two of them ('*seemingly new*', '*seemingly old*') represented low level of confidence. There were numerically more correct high confidence responses in the *Left Dorsal Anodal* condition (mean=37) than in the *Right Ventral Anodal* condition (mean=33); however, the difference was not significant, $t\,(11)=1.39$, $p>0.1$.

Response times for each of the four responses (hit, miss, false alarm, correct rejection) in the two stimulation conditions were subjected to ANOVA in order to determine whether the superior performance in the *Left Dorsal Anodal* condition was due to a shifting in response times. There was no significant difference between conditions in the response times for each of the responses, $F\,(3,9)=.55$, $p=.66$; Fig. 1B).

Between-subject comparison of the memory performance of the stimulation conditions with baseline data without stimulation was based on data sampled from a different group of 12 comparable participants who performed two sessions of the task. Their mean score was $d'=1.16$. This was a marginally significant difference from the *d'* score of the *Left Dorsal Anodal* scores of the experimental group, $t(22)=2.06$, $p<0.05$ (one-tailed), but not different from their *Right Ventral Anodal* scores, $t(22)=1.11$, $p>0.1$. While such between-subject comparisons are limited in their analytic power, they are in consonance with the within-subject results.

3. Discussion

In the present study, we found differential effects in a verbal recognition memory task following the application during study of tDCS to parietal regions implicated in different attentional processes, specifically, anodal stimulation directed toward left intraparietal sulcus/superior parietal cortex and cathodal stimulation directed toward right inferior parietal cortex. This stimulation condition resulted in a significant improvement of the ability to discriminate studied from unstudied words compared to the opposite polarity of stimulation, as expressed by *d'* measure of recognition accuracy.

The current study is in consonance with a number of previous studies that modulated memory capabilities using tDCS.

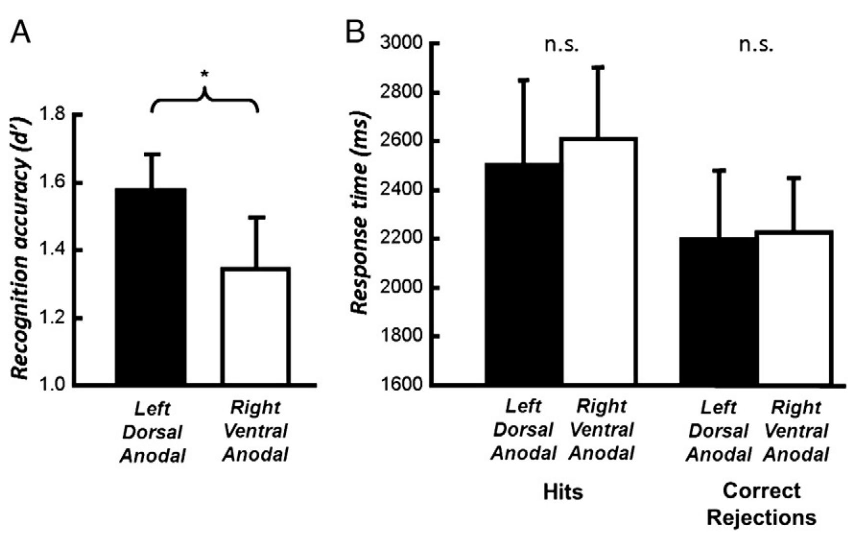

Fig. 1 – A: Mean recognition accuracy as expressed by *d'* for 12 participants. *Left Dorsal Anodal:* Anodal stimulation over left intraparietal sulcus (IPS) and superior parietal lobe (SPL) and cathodal stimulation of right inferior parietal lobe (IPL); *Right Ventral Anodal:* Anodal stimulation of right IPL and cathodal stimulation of left IPS and SPL. * indicates significance at $p=.01$. B: Response times for correct responses in the two stimulation conditions; n.s., not significant.

Some studies have found a beneficial effect of tDCS on memory functions. Cho et al. (2010) improved visual memory by bilateral stimulation over anterior temporal lobes. Working memory has been improved by anodal stimulation applied over left dorsolateral prefrontal cortex (DLPFC) for healthy individuals (Fregni et al., 2005), post-stroke patients (Jo et al., 2009) and patients with Parkinson's disease (Boggio et al., 2006). Marshall et al. (2004) applied anodal tDCS over lateral frontal locations during slow wave sleep, and found increased subsequent retention of word pairs. In contrast, other studies have found tDCS to impair memory functions. Berryhill et al. (2010) showed that cathodal stimulation over right inferior parietal cortex impaired object recognition working memory, while Ferrucci et al. (2008) showed that both anodal and cathodal stimulation over the cerebellum impair the practice-dependent increase in visual working memory task proficiency. Vines et al. (2006) showed impaired levels of performance in a short-term pitch memory task after cathodal stimulation over left supramarginal gyrus, and Marshall et al. (2005) impaired performance in a working memory task by applying bilateral stimulation over lateral frontal locations. A particularly germane study is that of Kirov et al. (2009), who applied transcranial slow oscillation stimulation to bilateral frontal location during an auditory verbal learning task, and found improvements in free recall during some stages of the task. However, in that study, stimulation was also applied during the retrieval phases of the task. Furthermore, in that study stimulation was not found to affect recognition. A synoptic appraisal of these studies does not yield a consistent pattern of results in the direction of effect of stimulation (improving or impairing learning), nor does it reveal consistency in the pattern of effects over retention period (working vs. long-term memory), or polarity effects. Our study differs from previously published research both in the use of attentionally-directed stimulation in order to affect learning, and in our use of "adversarial modulation" — applying opposite polarities of electrical stimulation to differentially modulate activity in cortical areas implicated in attention and shown to have opposite effects on encoding information into long-term memory (as documented by Uncapher and Wagner, 2009).

Several limitations of the current study must be acknowledged. Due to the channel limitations of the currently available tDCS apparatus, we were able to stimulate only some of the cortical regions identified as relevant to the target attentional systems. Furthermore, only some of the possible montages of parietal regions were tested. While we controlled for repetition effects by counterbalancing stimulation conditions across repeated sessions, the comparison is between interventions rather than relative to a sham condition. Therefore, these results do not demonstrate any absolute improvement of learning, but only modulation. On the other hand, it is noteworthy that even when learning takes place in the relatively optimal circumstances of quiet laboratory conditions without distractions, tDCS that might have resulted in attentional modulation lead to relative improvement in episodic memory. Finally, we did not directly test attentional capacities, only verbal learning, and therefore our contention that the effect reflects attentional modulation has not been directly proven, but rather is based on prior research regarding the attentional functions of the stimulated areas.

It is true that the spatial resolution of conventional transcranial direct current stimulation (tDCS) is considered to be relatively diffuse owing to skull dispersion (Datta et al., 2009). Indeed, tDCS is often not considered focal enough to map cortical functions within a centimeter range, in contrast with transcranial magnetic stimulation (Wassermann and Grafman, 2005). However, the tDCS effects largely come from the cortical area beneath the electrode (Zaghi et al., 2010). In fact, computer-based modeling studies indicate that the direct functional effects of tDCS are restricted to the area under the active electrode, since the strength of the electrical field is fairly homogeneous under the electrode (in the current study, a 5×5 cm sponge), but decreases very rapidly at a distance from it (Miranda et al., 2006; Wagner et al., 2007). We therefore believe that the "mid-range" resolution of tDCS enables us to reasonably propose that we have successfully stimulated the attentionally implicated areas that we targeted, but not other memory-related areas, such as prefrontal cortex or medial temporal lobes.

These findings have potential theoretical and practical implications. On the theoretical level, these results support the view that our attentional state is a function of dynamic interactions between separate attentional systems, which compete for resources in their interaction with the environment. The outcome of that competition affects other cognitive processes, such as learning. Additionally, these results seem to have practical implications for the development of interventions to benefit persons with various types of attentional deficits. In the young, academic participants of this study, the benefit of stimulation, while significant, was relatively modest. We predict that for older adults or people with attentional impairments caused by conditions such as ADHD or schizophrenia, greater benefits should be found.

In future studies, we hope to investigate tDCS attentional modulation effects on learning in a disrupting environment which challenges the attention-memory mechanisms, the long lasting effect of tDCS on memory which is important in the context of tDCS as therapeutic interventions, and the effects of tDCS in more memory- and attention-challenged populations.

4. Experimental procedures

4.1. *Participants*

Twelve healthy young adult participants (7 females, 5 males, mean age 26.7 years, SD 8.7 years, mean education 13.6 years, SD 2.3 years) volunteered to take part in the study in return for payment. Another 12 healthy young adult participants (7 females, 5 males, mean age 24.2 years, SD 0.9 years, mean education 14.0 years, SD 0.9 years) participated in an independent sample which provided baseline data. All subjects were without any known neurological or psychiatric disorders, had normal or corrected-to-normal vision, and were right handed. All were naive to the purpose of the experiment, and gave a written informed consent before taking part in the study, which was approved by the Bar Ilan University IRB committee.

4.2. Tasks

4.2.1. Stimuli

The memoranda were 160 common Hebrew words, divided into four lists of 40 words, balanced using reported ratings of familiarity (a proxy for word frequency; mean = 4.3/7), rated concreteness (mean = 4.8/7), number of letters (mean = 4.4), and number of syllables (mean = 2.3; all ratings taken from Henik et al., 2005). The lists were counterbalanced across participants in roles of either targets or foils in either the first or second sessions. Additional words were used for training trials.

4.2.2. Verbal encoding task

At study, participants serially viewed 40 Hebrew words, and were instructed to count the number of syllables of each of the words and to remember the words for a later memory test. The task started with five practice trials, by which the experimenter confirmed that participants understood the task, adding more practice trials as needed. Each trial began with a fixation cross, followed by a word, which was presented center screen in a black font on a white background. The distance between participants and the screen was about 65 cm, with 48 point stimulus font. The response keys were '1', '2', or '3', according to the number of syllables. The word remained on screen until the subject pressed one of the response keys.

4.2.3. Delay period task

During the 20 minute delay period, participants were asked to solve a selection of up to 52 non-verbal reasoning problems, in order to prevent rehearsal. The problems were selected from Raven's progressive matrices tests — RAPM (Raven, 1965) and RSPM (Raven, 1976), and from the Test of Nonverbal Intelligence (TONI-3). Participants were asked to work as rapidly and accurately as possible, and in almost all cases this task completely filled the delay period.

4.2.4. Recognition memory task

Following the delay period, participants serially viewed 80 words on computer screen, half of which had been previously studied and half of which were new foil words. Participants were instructed to make a memory judgment for each of the presented words. Five response keys were available: 'B' — "I'm sure the word was presented and I have a concrete memory about the presented word"; '4' — "I'm sure the word was presented"; '3' — "It seems to me that the word was presented"; '2' — "It seems to me that the word was not presented"; '1' — "I'm sure the word was not presented". Therefore, buttons 'B', '4', and '1' represent high levels of confidence, while buttons '2' and '3' represent low levels of confidence. This response structure reflects the "modified Remember-Know procedure", often used in studies of recognition memory (Yonelinas et al., 2005). The test started with four practice trials, by which the experimenter confirmed that participants understood the task, adding more practice trials when needed. On-screen presentation was as at encoding. The visual stimulus remained on screen until the subject pressed on one of the response keys. The entire experiment was presented on a portable computer with a 13 in. screen, using E-prime software (Psychology Software Tools, Pittsburgh, USA).

4.2.5. Control group

The control group who provided the baseline data performed the learning task in this fashion without stimulation. They executed two sessions, and we randomly sampled half of their data from the first session and half from the second session, to match the conditions of the experimental group.

4.3. tDCS

A direct current of 1 mA for 10 min was induced by two saline-soaked surface sponge electrodes (5 × 5 cm) and delivered by a battery-driven, constant-current stimulator (Rolf Schneider Electronics, Germany). Previous studies have shown this intensity of stimulation to be safe in healthy volunteers (Iyer et al., 2005).

Electrode placement was done with the assistance of an ElectroCap EEG 10–20 montage fitted to participants' head sizes, which enabled marking of the P3 and P6 loci. The P3 location was used for the L-IPS/SPL placement, and the P6 location was used for the R-IPL placement.

The difference between conditions was in the polarity of the tDCS electrodes: Anodal R-IPL + Cathodal L-IPS/SPL *(Right Ventral Anodal* condition*)* or Anodal L-IPS/SPL + Cathodal R-IPL *(Left Dorsal Anodal* condition*)*.

All participants completed the experiment, and reported no after-effects of stimulation. The studies were conducted under double-blind conditions, with neither the participants nor the experimenters aware of which condition was supposed to improve recognition memory performance.

4.4. Experimental design

The experiment was conducted as a within-subject design. Each participant completed two sessions, spaced approximately one week apart. The order of the conditions was counterbalanced across participants, who were blind to the stimulation condition. Each session began with 10 min of tDCS; during the last 3 min of stimulation, subjects studied the word list as described above. Study was immediately followed by the filled delay period of 20 min, during which participants solved one of two versions of the reasoning problems described above (counterbalanced across participants). This delay period played the dual role of ensuring that the recognition task was sufficiently challenging, and enabling some dissipation of the effects of tDCS stimulation before the retrieval session. The recognition memory test was administered immediately thereafter.

4.5. Analysis

The primary dependent measurement was recognition accuracy, which was calculated for each participant in terms of the *d'* statistic, reflecting Z(Hit) minus Z(False Alarm). In other words, we subtracted the Z-score associated with the amount that each participant's false alarm rate was below the default 0.5 chance probability for the yes/no judgment from the Z-score associated with the amount that each participant's hit rate was above the default 0.5 chance probability for the yes/no judgment (Macmillan and Creelman, 2005); zero values were replaced with a conservative 1/N value. Additionally, we compared the number of correct high confidence responses ('surely old+concrete memory' and 'surely old' for hits, 'surely new' for correct rejections) vs. correct low confidence ('seemingly old' for hits and 'seemingly new' for correct rejections) responses given in each condition, and response times for hits and correct rejections. We compared the performance in the two conditions with baseline performance data collected on a control group of 12 other participants.

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