Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus

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Neuroimaging studies have implicated the left supramarginal gyrus in short-term auditory memory processing, including memory for pitch. The present study investigated the causal role of the left supramarginal gyrus in short-term pitch memory by comparing the effects of cathodal transcranial direct current stimulation when applied over the left or right supramarginal gyrus with sham transcranial direct current stimulation. Only cathodal transcranial direct current stimulation over the left supramarginal gyrus had a detrimental effect on short-term pitch-memory performance in 11 adult participants. These results provide support for the important role of the left supramarginal gyrus in short-term memory for pitch information, and they further demonstrate the potential of transcranial direct current stimulation to modulate the functional contribution of a brain area to a particular cognitive process. *NeuroReport* 17:1047–1050 © 2006 Lippincott Williams & Wilkins.

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Introduction

Imaging evidence supports a critical role for the left supramarginal gyrus in short-term memory processing for auditory information. In an functional magnetic resonance imaging (fMRI) study, Gaab and colleagues [1] found a significant, positive correlation between better performance on a pitch-memory task and increased fMRI signal changes in the supramarginal gyrus; the left supramarginal gyrus showed much greater activation than the right supramarginal gyrus. They hypothesized that the supramarginal gyrus might serve as a short-term auditory storage center, which might also influence the allocation of processing in earlier auditory regions as part of a top-down system. A further fMRI study [2] found that, compared with weak learners of a pitch-memory task, strong learners showed a significant increase in the fMRI signal change in the left supramarginal gyrus owing to practicing the task, providing additional evidence for the importance of the left supramarginal gyrus in pitch memory. Previous neuroimaging studies have implicated the left supramarginal gyrus in short-term memory for linguistic phonology as well [3,4], which suggests that this region might be involved more generally in auditory working memory, whether musical or linguistic. As the studies mentioned above used functional imaging, they do not substantiate a causal role for the supramarginal gyrus in short-term memory processing. To determine the functional role of the supramarginal gyrus in pitch memory, it would be necessary to measure the effects of interfering with the intrinsic supramarginal gyrus activity in a controlled study.

The noninvasive brain stimulation technique, transcranial direct current stimulation (tDCS), has been shown to alter excitability in a brain region, thus influencing the spontaneous firing rate for neurons in that region [5,6]. With this technique, an anodal electrode with positive charge is placed at one location on the scalp, and a cathodal electrode with negative charge is placed at another location on the scalp. The current runs from the anodal electrode to the cathodal electrode through the brain and other tissues of the head to complete a circuit. The electrode located over the targeted site for stimulation is termed the 'active electrode' while the other electrode is the 'reference electrode'. The reference electrode does not influence the effects under investigation in the experimental design. Researchers found that cathodal tDCS reduced neural excitability in the stimulated area [7,8], and that a decrease in neural excitability, owing to tDCS, can induce a decrement in performance on tasks involving the targeted brain area

[9–11]. Additionally, Vines *et al.* [12] found that cathodal tDCS over primary motor cortex led to a significant decrement in contralateral performance on a unimanual finger sequence task, compared with anodal tDCS. Therefore, we may posit that cathodal tDCS can be used to disrupt the contribution of a particular brain region to a process that directly involves that brain region; such a disruption would be analogous to a 'virtual lesion,' as induced by low-frequency repetitive transcranial magnetic stimulation [13].

In the present study, we sought to test whether the left supramarginal gyrus plays a functionally significant role in short-term pitch memory by examining the effects of disrupting left-supramarginal gyrus activity with cathodal tDCS. We used sham tDCS over left supramarginal gyrus and cathodal tDCS over right supramarginal gyrus as control conditions. The task and stimuli were drawn from previous neuroimaging studies mentioned above [1,2].

Methods

Participants

Twelve right-handed healthy participants (six men) gave their informed, written consent to participate in the study, which was approved by the local ethics committee. One male participant was removed from the analyses because he performed at ceiling on the pitch-memory task. Participants were unselected for musical training; most of our participants had some musical training, but none were actively practicing their instruments and none of them were professional musicians. None of our participants reported any history of hearing problems. Only participants who stated that they heard the testing stimuli equally loud in both ears were included in the experiment.

Task

Stimuli were 39 sequences of sine-wave tones. The tones were all of equal amplitude and duration, and were separated by a constant interstimulus interval of 300 ms. The target tones were semitones of the Western musical scale ranging from 330 Hz (E4) to 622 Hz (D#5). Microtones within that range were used as distracter tones between the two target tones. One-half of the sequences contained sixtones, and the other half contained seven tones (see Gaab and colleagues [1,2] for further detail on the stimuli). The task instructions for a single trial were to register as quickly as possible whether the first and last tones in a sequence were the same or different. One mouse button corresponded to the answer 'same' and the other to 'different.' The 39 pitch sequences were presented in a randomized order for each run, in which a run lasted for 5.2 min. Noise-reduction headphones minimized the influence of environmental sounds. Participants were instructed not to sing or to hum during task performance, but were allowed to close their eyes.

Procedure

One day before testing, participants practiced the pitch-memory task until reaching a stable performance level by completing at least three practice runs, and changing ≤ 2 points (in absolute numbers) in score between the last two runs. On the day of testing, participants performed one 'warm-up' run, and then underwent two tDCS sessions, one for cathodal stimulation and one for sham (with counter-balanced ordering across participants). For each session, participants completed one prestimulation baseline run and one poststimulation run immediately following 20 min of stimulation. The two sessions were separated by a washout period of at least 30 min to avoid carryover effects of the stimulation. During the washout period, participants were allowed to surf the internet. They were not allowed to listen to music. Although significant tDCS-induced effects on excitability have been measured over 1 h after stimulation [6,14], effects on behavioral performance have not been reported to last longer than 30 min beyond stimulation [11,15–17]. The active electrode (area=15 cm^2) was placed over TP3 of the international 10–20 system for electroencephalogram electrode placement, which corresponds to left Brodmann's area 40/39 – the area of the supramarginal gyrus [18]. A number of tDCS and Transcranial Magnetic Stimulation (TMS) studies have successfully employed the international 10–20 system to identify the location of brain areas [9–12,15–17,19,20]. The reference electrode (area=30 cm^2) was secured over the contralateral supraorbital area, and was functionally ineffective within this experimental design [21]. Ten out of the 11 participants (one participant did not consent to additional testing) also underwent cathodal stimulation of the right supramarginal gyrus, at least 1 week after the left-hemisphere sessions, by placing the active electrode over TP4, which corresponds to the right Brodmann's area 40/39 and the reference electrode over the left supraorbital area. A constant current stimulator (Phoresor II PM850; Iomed Inc., Salt Lake City, Utah, USA) delivered a 1.2-mA current during the 20 min of cathodal tDCS. For sham stimulation, the current was allowed to ramp up over the first 30 s before the experimenter reduced the current to 0 over the next 30 s, and it remained at 0 for the remaining time period. Participants reported a tingly/itchy sensation at the start of the stimulation, which typically faded away after approximately 1 min. This sensation was the same for real as well as sham stimulation (for more details on the usefulness of sham stimulation see Gandiga *et al.* [22]). Participants listened to a musical track from a CD during the first 2 min of each 20-min stimulation period; this music masked any clicking noises caused by the experimenter while manipulating the current, thus eliminating cues that might have made it possible to distinguish between real and sham stimulation. Participants heard the same music track at the beginning of each stimulation period.

Data analyses

We applied a two-by-two repeated-measures analysis of variance (ANOVA), with factors 'tDCS condition' (sham left supramarginal gyrus, cathodal left supramarginal gyrus) and 'time' (prestimulation, poststimulation) to the resulting data for the left hemisphere. Post-hoc analyses (paired *t*-tests) with a Bonferroni correction compared presham stimulation to postsham stimulation, precathodal stimulation to postcathodal stimulation, and presham stimulation to precathodal stimulation. In addition, we applied a two-by-two repeated-measures ANOVA with factors 'tDCS condition' (sham left supramarginal gyrus, cathodal right supramarginal gyrus) and 'time' (pre versus poststimulation) to compare the two different control conditions with each other.

Furthermore, we calculated the percentage of change in the number of correct answers from prestimulation to poststimulation for each session in order to compare the effects of sham and of cathodal tDCS directly. One paired two-sample *t*-test compared the percentage of change for sham with that for cathodal tDCS over left supramarginal gyrus. A second paired two-sample *t*-test compared the percentage of change for sham with that for cathodal tDCS over right supramarginal gyrus. We used the percentage of change, instead of a simple difference (post−pre), in order to control for variation in skill level across the participants.

Results

The repeated-measures ANOVA revealed no significant main effects for 'tDCS condition' [F(1,10)=0.309, P=0.590] or for 'time' [F(1,10)=3.2, P=0.104]. A significant interaction, however, exists between the two factors [F(1,10)=10.06, P=0.010]. Thus, the relationship between prestimulation and poststimulation scores was different for the two tDCS conditions. Post-hoc analyses, with a Bonferroni correction for multiple comparisons, revealed a significant difference between precathodal performance scores (mean=30.82; SD=3.92) and postcathodal performance scores (mean=28.09; SD=4.25), with P=0.005. Presham and post-sham performance scores were not significantly different (P=1.00). The difference between precathodal stimulation scores and presham stimulation scores was also nonsignificant (P=0.274). A separate repeated-measures ANOVA comparing the control conditions with each other revealed no significant main effect for 'tDCS condition' [F(1,9)=0.082, P=0.782] or for 'time' [F(1,9)=2.77, P=0.130], and there was no significant interaction between the two factors [F(1,9)=0.160, P=0.698].

The *t*-test directly comparing the percentage of change for cathodal stimulation over left supramarginal gyrus, to that for sham stimulation revealed a significant difference, $t(10)=-2.91$, P=0.016, with cathodal<sham. See Table 1 for raw performance scores prestimulation and poststimulation of left and right supramarginal gyrus. An additional *t*-test comparing the percentage of change for cathodal tDCS over right supramarginal gyrus, to that for sham stimulation revealed no significant difference, $t(9)=0.10$, P=0.92 (Fig. 1).

We found that cathodal stimulation over the left supramarginal gyrus had a significant detrimental effect on performance, while sham stimulation and cathodal stimulation over the right supramarginal gyrus had no effect. The nonsignificant result for the comparison between presham and precathodal scores provides evidence that the difference between cathodal tDCS over left supramarginal gyrus and sham effects was not due to a difference in the baseline for the two conditions. We also compared the effects of cathodal and sham stimulation directly, after normalizing participants' poststimulation scores to their baseline levels; this controlled for variation in pitch-memory skill across participants. The average percentage of change elicited by cathodal stimulation over left supramarginal gyrus was negative, and was significantly lower than the average percentage of change elicited by sham stimulation. In contrast, the average percentage of change elicited by cathodal stimulation over right supramarginal gyrus was positive, and was not significantly different than sham. Thus, applying cathodal tDCS to the left supramarginal gyrus led to a significant decrement in pitch-memory performance.

Table 1 Averaged performance scores and standard deviations

Region	Condition	Pre [Mean (SD)]	Post [Mean (SD)]
Left SMG	Sham tDCS	29.36 (4.68)	30.27 (3.63)
Left SMG	Cathodal tDCS	30.82 (3.92)	28.09 (4.25)
Right SMG	Cathodal tDCS	29.50 (4.95)	30.80 (5.75)

SMG, supramarginal gyrus.
Maximum score=39. N=11 for the left SMG, N=10 for the right SMG.

Discussion

The results of this study point to a causal role for the left supramarginal gyrus in short-term pitch memory, and provide further support for the potential of tDCS to interfere with the normal function of a particular brain area. We posit that the cathodal tDCS reduced excitability in the left supramarginal gyrus, which disrupted its contribution to pitch-memory processing. Gaab and colleagues [1] hypothesized that the supramarginal gyrus might serve as a short-term auditory storage center and, furthermore, that it might also be involved in the top-down allocation of processing in primary and early secondary auditory regions; this could be achieved by directing the flow of processing to the left temporal regions, which have been found to be important for fine pitch discrimination [23], without the additional pitch-memory component of the present study. Thus, reducing excitability in the left supramarginal gyrus might have two effects: (1) interfering directly with short-term auditory storage and (2) impeding top-down processing brain centers that are involved in pitch discrimination.

Results from the additional control condition in the present study – cathodal tDCS over the right supramarginal gyrus – provide evidence that the contribution of the supramarginal gyrus to pitch-memory processing is largely lateralized to the left hemisphere; only modulation of the left supramarginal gyrus led to a significant effect on performance. The additional control region (i.e. right supramarginal gyrus) also eliminates the possibility that cathodal tDCS over any part of the brain would lead to a detrimental effect. Thus, this study points to a causal role for the left supramarginal gyrus in pitch memory.

The results of the present study support the hypothesis that the left supramarginal gyrus is a general nodal point for short-term auditory working memory that is involved in both music and linguistic processing. As mentioned above, neuroimaging studies have implicated the left supramarginal gyrus in short-term memory for linguistic phonology [3,4]. It might be that phonological processing makes use of a brain center that is involved in general auditory short-term memory, or that pitch processing utilizes a language-devoted neural module that has some pure-auditory processing potential.

The present research complements previous studies that have applied tDCS to modulate specifically performance on working memory tasks. Fregni and colleagues [15] found that applying anodal tDCS to the left dorsolateral prefrontal cortex (centered on F3) improved performance on a working memory task involving letters of the alphabet. Marshal and colleagues [19] found that applying either cathodal or anodal tDCS simultaneously to both left and right lateral prefrontal cortices (centered on F3 and F4) slowed response selection in a linguistic working-memory task. The present study revealed a detrimental effect on working-memory

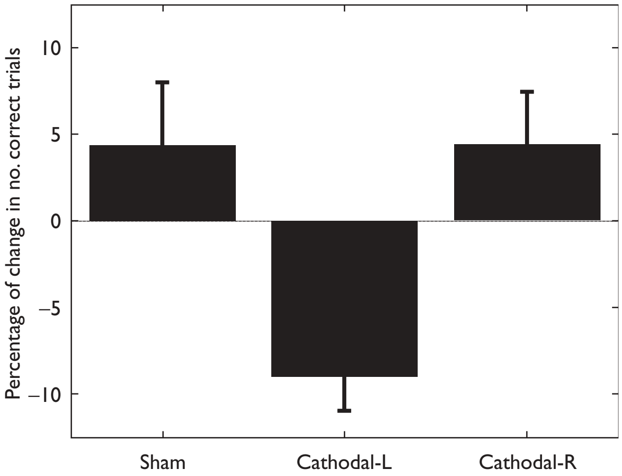

Fig. 1 The mean (standard error mean) percentage of change in the number of correct trials on a pitch-memory task, for sham (N=11), for cathodal transcranial direct current stimulation (tDCS) over left supramarginal gyrus (N=11), and for cathodal tDCS over right supramarginal gyrus (N=10).

performance owing to cathodal tDCS, using a nonverbal task and a stimulation site outside of prefrontal cortex – the left supramarginal gyrus. D'Esposito and colleagues [24] performed a meta-analysis on neuroimaging studies investigating working memory, and found that both the lateral prefrontal cortex and the parietal lobe (in the area of the supramarginal gyrus) were consistently activated across studies. These investigations [15,19,24] and the present study point to causal roles for both the supramarginal gyrus and the lateral prefrontal cortex in working memory. This raises the possibility of using tDCS to dissociate the contribution of different neural centers to a single cognitive process, such as working memory.

Conclusion

The results of this study point to a causal role for the left SMG in short-term pitch memory, and provide further support for the potential of tDCS to interfere with the normal functioning of a particular brain area. We propose that cathodal tDCS induced a reduction in excitability in the left SMG, which either interfered directly with auditory storage or interfered indirectly with top-down processes related to short-term pitch memory.

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