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Anodal transcranial direct current stimulation applied over the supplementary motor area delays spontaneous antiphase-to-in-phase transitions

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Carter MJ, Maslovat D, Carlsen AN. Anodal transcranial direct current stimulation applied over the supplementary motor area delays spontaneous antiphase-to-in-phase transitions. *J Neurophysiol* 113: 780–785, 2015. First published November 5, 2014; doi:10.1152/jn.00662.2014.—Coordinated bimanual oscillatory movements often involve one of two intrinsically stable phasing relationships characterized as in-phase (symmetrical) or antiphase (asymmetrical). The in-phase mode is typically more stable than antiphase, and if movement frequency is increasing during antiphase movements, a spontaneous transition to the in-phase pattern occurs. There is converging neurophysiological evidence that the supplementary motor area (SMA) plays a critical role in the successful performance of these patterns, especially during antiphase movements. We investigated whether modulating the excitability of the SMA via offline transcranial direct current stimulation (tDCS) would delay the onset of anti-to-in-phase transitions. Participants completed two sessions (separated by ~48 h), each consisting of a pre- and post-tDCS block in which they performed metronome-paced trials of rhythmic in- and antiphase bimanual supination-pronation movements as target oscillation frequency was systematically increased. Anodal or cathodal tDCS was applied over the SMA between the pre- and post-tDCS blocks in each session. Following anodal tDCS, participants performed the antiphase pattern with increased accuracy and stability and were able to maintain the coordination pattern at a higher oscillation frequency. Antiphase performance was unchanged following cathodal tDCS, and neither tDCS polarity affected the in-phase mode. Our findings suggest increased SMA excitability induced by anodal tDCS can improve antiphase performance and adds to the accumulating evidence of the pivotal role of the SMA in interlimb coordination.

bimanual coordination; neurostimulation; phase transition; motor control

IT IS WELL-ESTABLISHED the human neuromuscular system displays two relatively stable modes of interlimb coordination: in-phase and antiphase (Swinnen 2002; Swinnen and Wenderoth 2004). In-phase movements (0° relative phase) are mirror-symmetrical and typically require the synchronized activation of homologous muscle groups, whereas antiphase (180° relative phase) movements are synchronized movements of the limbs in the same direction and typically involve the simultaneous activation of nonhomologous muscle groups (cf. Mechsner et al. 2001). Kelso and colleagues (Kelso 1984, 1995; Kelso et al. 1986) described the time-dependent changes of the human motor system during rhythmic bimanual movements as a function of oscillation frequency. At low frequencies, in- and antiphase patterns could be performed stably and accurately. When oscillation frequency was gradually increased, antiphase movements became more variable and less accurate with respect to the goal pattern, and at a critical frequency an abrupt switch to the in-phase pattern occurred. However, the reverse transition does not occur spontaneously. This pattern switching phenomenon was modeled as the motor system undergoing a phase transition that exhibits hysteresis from a bistable to a monostable (in-phase only) attractor landscape once a critical frequency was reached (e.g., Haken et al. 1985). This finding has been replicated multiple times using a variety of bimanual tasks and effector pairings (e.g., Aramaki et al. 2006; Carson et al. 1995; Smethurst and Carson 2003).

One area of the brain thought to be critically involved in the production of bimanually coordinated movements is the supplementary motor area (SMA; Aramaki et al. 2006; Debaere et al. 2001; Nachev et al. 2008; Swinnen 2002). For example, Aramaki et al. (2006) used functional magnetic resonance imaging (fMRI) and showed that the SMA was activated during both in- and antiphase movements but was also a key neural correlate of the spontaneous transition to in-phase from an initially prepared antiphase movement once a critical threshold was reached. Another study using fMRI showed that the magnitude of SMA activation was greater during antiphase coordination relative to in-phase coordination (Debaere et al. 2001). In fact, the role of the SMA in organizing bimanual movements is hypothesized to involve the simultaneous coding of actions for each limb as well as their temporal sequencing (Swinnen and Wenderoth 2004), suggesting a functional link between the SMA and pattern stability exists during bimanual tasks. Support for this hypothesis has come from transcranial magnetic stimulation (TMS) studies showing bimanual performance is disrupted when TMS is applied over the SMA (e.g., Meyer-Lindenberg et al. 2002; Obhi et al. 2002; Serrien et al. 2002; Steyvers et al. 2003). For example, Serrien et al. (2002) found that immediately following repetitive TMS (rTMS) of the SMA (5 Hz, 10 s, 90% motor threshold), antiphase finger tapping accuracy significantly deteriorated. Decreased bimanual coupling during antiphase finger movements was also found by Steyvers et al. (2003) using much shorter trains of rTMS applied over the SMA (20 Hz, 0.5 s, 120% motor threshold). Finally, it has been demonstrated that a double-pulse TMS (50-ms interval) over the SMA triggered early phase transitions from antiphase to the more stable in-phase pattern, which in turn was not affected by TMS (Meyer-Lindenberg et al. 2002). Overall, the observations from neuroimaging and neurostimulation studies have indicated the

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SMA plays a key role in the temporal regulation of bimanual actions, particularly in the less stable antiphase pattern.

In the present study, we investigated the behavioral consequences of modulating SMA excitability via transcranial direct current stimulation (tDCS) to examine further its functional influence on phase transitions and pattern stability during bimanual coordination. tDCS is a noninvasive, polarity-dependent brain stimulation technique that has been shown to increase (anodal stimulation) or decrease (cathodal stimulation) the excitability of cortical areas by passing a small electrical current between scalp-mounted electrodes (Nitsche and Paulus 2011; Stagg and Nitsche 2011). Pattern stability and accuracy were expected to depend on coordination mode and tDCS polarity. Based on past SMA stimulation studies, we expected antiphase movements to be affected by tDCS application but not in-phase movements. Specifically, we hypothesized that increasing SMA excitability with anodal tDCS would decrease the vulnerability of antiphase movements to spontaneous phase transitions, thereby improving the ability to maintain a more accurate and stable relative phase relationship between effectors as oscillation frequency increased. Our predictions were less certain for cathodal tDCS due to the disparity of previous results. Although some studies have shown opposing effects for anodal and cathodal tDCS, others have found either similar results between the two stimulation methods or no effect of cathodal tDCS stimulation [see Nitsche et al. (2008) and Stagg and Nitsche (2011) for recent reviews]. Thus it was unclear whether cathodal tDCS would improve, hinder, or have no effect on antiphase performance.

MATERIALS AND METHODS

Participants. Ten volunteers (6 men, 4 women; mean age = 25.2 ± 6.46 yr; all right-handed by self-report) with no sensory or motor dysfunctions participated in the experiment after providing written, informed consent. The experiment was approved by and conducted in accordance with the ethical guidelines set by the Health Sciences and Science Research Ethics Board at the University of Ottawa and conformed to the latest revision of the Declaration of Helsinki.

Participant setup. Participants sat facing a 24-in. computer monitor with their arms in a neutral position, elbows bent at 90°, and forearms resting semiprone in armrests such that thumbs pointed upward. Each hand gripped a separate handle (12-cm length × 2.5-cm diameter) that could be rotated around a central axis in the coronal plane by supinating and pronating the forearm. A linear potentiometer powered by a 5-V direct current power supply attached to the central axis of each handle was used to provide position data. Position of each handle was sampled at 1 kHz for the duration of each trial using analog-to-digital hardware (PCI-6030E; National Instruments). The same hardware was used to generate the auditory signals used to pace the movements during each trial. The auditory signals (82-dB, 1-kHz, 40-ms-duration square waves) were amplified and presented via loudspeaker (MG Electronics M58H) positioned behind the participant.

Task and instructions. Participants were tested individually and performed metronome-paced trials of rhythmic supination-pronation bimanual movements in the in- and antiphase modes. The task required a displacement of ±5° from the starting position (handle positioned vertically representing 0°). Real-time visual feedback was provided on the computer monitor during trials and consisted of the participants' movements represented as separate horizontally moving cursors relative to marked target displacement limits. Testing involved 2 sessions (i.e., anodal and cathodal tDCS), separated by a minimum of 48 h to ensure a complete washout of any residual tDCS effects, with 2 blocks per session (i.e., pre- and post-tDCS). At the beginning of each session, participants performed 2 familiarization trials (1 of each pattern) before the 14 experimental trials (7 of each pattern, randomly presented). Each trial lasted 56 s, and metronome frequency was systematically increased from 1.75 to 3.25 Hz in 0.25-Hz increments every 8 s. This range of oscillation frequencies and the scaling increment were selected based on past research eliciting anti-to-in-phase transitions with these parameters (e.g., Kelso 1984; Smethurst and Carson 2003). To control for fatigue, each participant determined the duration of the intertrial interval on an individual basis with participants typically requiring 10–20 s between each trial.

Participants were informed they would be performing the bimanual task in one of the two coordination modes in a randomized schedule. Participants were instructed to perform each cycle in synchronization with the auditory metronome such that the right hand would be at the inward target (i.e., toward the body midline) on each metronome pulse. They were also instructed to adhere to the target displacement limits provided by the online visual feedback. Participants were further instructed the speed of the metronome would gradually increase and if their performance of the initially prepared coordination mode became unstable that they were not to fight it and give in and establish the most comfortable pattern compatible with the prevailing frequency (Kelso 1984). For all testing blocks, participants were reminded of these instructions before *trials 1* and *8*.

tDCS protocol. Direct current stimulation was delivered via two scalp electrodes. The active electrode (sponge electrode, 1.5 ml, 7.8 cm^2; Ionto+) was saturated with sterile saline (0.9% NaCl) and was positioned 1.8 cm anterior to Cz (measured based on the International 10-20 system for EEG), which was determined by mapping the centroid of the SMA based on Talairach space onto standardized head coordinates (Jasper 1958; Talairach and Tournoux 1988). This site has been previously used for SMA stimulation using TMS (Muri et al. 1994) and tDCS (Hayduk-Costa et al. 2013). The reference electrode (carbon foam, 39 cm^2; Ionto+) was placed above the eyebrows in the center of the forehead. This reference electrode allowed the current density to be sufficiently low such that it would have a negligible effect on underlying cortical areas (Nitsche et al. 2008). Both electrodes were self-adhesive, but additional foam underwrap was used to hold the electrodes in place, thereby ensuring optimal contact throughout stimulation. A double-blind stimulation design was used to ensure the participant and the researcher conducting the experimental trials were unaware of stimulation polarity. Anodal or cathodal tDCS was applied over the SMA between the pre- and post-tDCS blocks in each session. A direct current of 1 mA was applied for 10 min using a Dupel iontophoresis constant current delivery device (Empi); thus current density at the active electrode was 0.128 mA/cm^2. Stimulation polarity was determined based on which lead was connected to the active electrode, with polarity order counterbalanced across participants. Past research using similar stimulation parameters has shown that tDCS effects are greatest 10–25 min poststimulation (Kuo et al. 2013); therefore, an 8-min waiting interval following stimulation was incorporated so the post-tDCS block would be performed within this time frame.

Data reduction and statistical analyses. Continuous relative phase (Φ) between the effectors was calculated for the final 7 s of each frequency level to eliminate transient fluctuations during the first second of frequency transitions. Relative phase of the left in relation to the right effector was calculated for each sample after the velocity and position of the limbs were rescaled to the interval [−1, 1] using the formula $\Phi = \theta_R - \theta_L$, where θ (phase) for each limb = $\tan^{-1}$ $[(dx/dt)/(dx)]$ (Scholz and Kelso 1989). To avoid any misrepresentation due to the circular nature of relative phase (whereby 0° is equal to 360°), calculations were constrained in a different manner for in-phase compared with antiphase trials. For in-phase trials (where transitions were not expected), relative phase was constrained to a value between −180 and 180°. For antiphase trials (in which a transition to in-phase was expected to occur), relative phase before

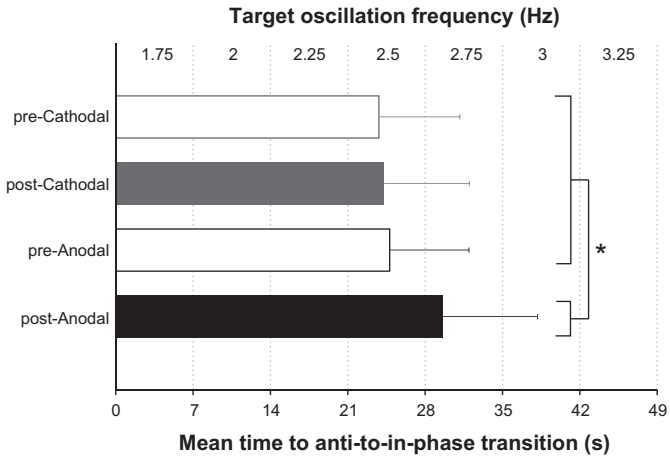

Fig. 1. Mean (SD) time to transition from antiphase to in-phase, including oscillation frequency, for testing blocks pre- and postcathodal and -anodal transcranial direct current stimulation (tDCS). Note the significantly (*) longer time to transition following anodal tDCS stimulation.

the transition was constrained to a value between 0 and 360°. After a transition, it was constrained to a value between −180 and 180°. In this manner, relative phase was always converted to a value ranging between the expected pattern ±180°.

Performance accuracy and variability were assessed using mean relative phase and root-mean-square error [RMSE; see Franks et al. (1982) for calculation details], respectively. Although RMSE includes both accuracy and consistency, it was chosen as the variability measure as standard deviation of relative phase would be confounded by the expected phase transition on antiphase trials. That is, increased stability of the antiphase pattern was expected to be reflected by a longer time period spent around the target pattern (albeit with increased variability), whereas a transition to in-phase would result in the performance of the in-phase pattern with low variability. Thus it was critical that our variability measure also include an accuracy component to differentiate between which pattern was being performed. These dependent measures were calculated for each participant at each frequency level. Phase transitions were examined using a partially interactive procedure that allowed an experimenter (blind to condition) to view a graphical representation of the entire relative phase time series for each trial offline [as described by Smethurst and Carson (2003)]. For trials where a phase transition occurred, an experimenter positioned two cursors to demarcate the beginning (i.e., final point of successful antiphase coordination) and the end (i.e., sustained in-phase coordination for 1 s) transition time points. Based on past research, relative phase of 0 ± 60° was defined as in-phase and 180 ± 60° as antiphase (Carson 1995; Mechsner et al. 2001). Our analyses were restricted to trials in which a phase transition occurred that resulted in the removal of 23 trials (~4% of all trials).

Time to transition, mean relative phase, and RMSE were analyzed using repeated-measures ANOVA (RM ANOVA) as described below. An alpha of <0.05 was considered significant, and partial eta squared (η_p^2) is reported as an estimate of effect size. Tukey honestly significant difference post hoc tests were administered to determine the locus of any differences. In cases where sphericity was violated, Greenhouse-Geisser adjusted P values are reported.

RESULTS

Summary. Overall, the results indicate that stability of the antiphase pattern was improved following anodal tDCS, whereas cathodal tDCS had no effect. Neither anodal nor cathodal tDCS had an effect on performance of the in-phase pattern.

Time to phase transition. As abrupt in-to-antiphase transitions do not occur (Swinnen 2002; Swinnen and Wenderoth 2004), data from the in-phase trials were excluded from this analysis. Time to transition in antiphase trials was analyzed using a 2 (Polarity: anodal, cathodal) × 2 (Block: pre-tDCS, post-tDCS) RM ANOVA. A main effect of Block, $F(1,9) = 9.795$, $P = 0.012$, $\eta_p^2 = 0.521$, was superseded by a significant Polarity × Block interaction, $F(1,9) = 8.257$, $P = 0.018$, $\eta_p^2 = 0.478$. Post hoc testing showed the mean time to anti-to-in-phase transition was significantly delayed following anodal stimulation (mean = 29.6, SE = 2.7) compared with the preanodal (mean = 24.8, SE = 2.3), precathodal (mean = 23.8, SE = 2.3), and postcathodal (mean = 24.3, SE = 2.4) testing blocks (Fig. 1). No other significant comparisons were found (all P values >0.05).

Mean relative phase. Mean relative phase data (Fig. 2) were analyzed using a 2 (Pattern: in-phase, antiphase) × 2 (Polarity: anodal, cathodal) × 2 (Block: pre-tDCS, post-tDCS) × 7 (Frequency) RM ANOVA. The analysis revealed significant main effects for Pattern, $F(1,9) = 134.610$, $P < 0.001$, $\eta_p^2 = 0.937$, Block, $F(1,9) = 8.943$, $P = 0.015$, $\eta_p^2 = 0.498$, and Frequency, $F(6,54) = 66.554$, $P < 0.001$, $\eta_p^2 = 0.879$. These main effects were superseded by significant interactions in Pattern × Frequency, $F(6,54) = 63.493$, $P < 0.001$, $\eta_p^2 = 0.876$, Block × Frequency, $F(6,54) = 2.551$, $P = 0.030$, $\eta_p^2 = 0.221$, and Pattern × Polarity × Block, $F(1,9) = 8.048$, $P = 0.020$, $\eta_p^2 = 0.472$. As expected, post hoc testing of the Pattern × Frequency interaction revealed that as oscillation frequency increased, relative phase of the antiphase pattern changed, whereas no differences were found for the in-phase pattern. Post hoc comparisons for the Block × Frequency interaction indicated a significant pre-tDCS to post-tDCS difference existed at 2.5 Hz. All other pre- to post-tDCS comparisons collapsed across Pattern and Polarity were not significant. Most relevant to the current study was a significant three-way Pattern × Polarity × Block interaction. Post hoc testing indicated no significant differences in mean relative phase existed between pre- and post-tDCS blocks for the in-phase pattern (precathodal: mean = −2.2, SE = 2.5; postcathodal: mean = 0.7, SE = 2.5; preanodal: mean = −2.0, SE = 3.5; postanodal: mean = −0.2, SE = 2.5). However, antiphase

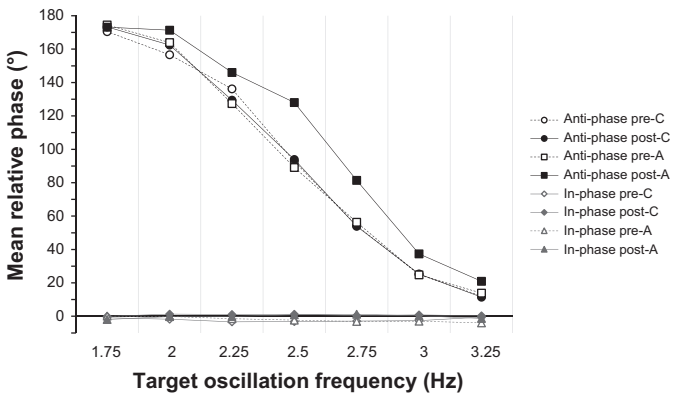

Fig. 2. Mean relative phase as a function of oscillation frequency for testing blocks pre- and postcathodal (C) and -anodal (A) tDCS. Participants were able to maintain the in-phase (0°) pattern as oscillation increased (gray lines), but during antiphase (180°) trials eventually transitioned to in-phase. Note that on average, participants performed the antiphase pattern closer to 180° as frequency increased following anodal tDCS stimulation (■).

coordination significantly increased in relative phase following anodal tDCS (mean = 108.3, SE = 9.9) compared with the preanodal (mean = 92.9, SE = 9.1), the precathodal (mean = 92.5, SE = 9.3), and the postcathodal (mean = 92.8, SE = 10.1) blocks, which did not differ significantly from each other. All other comparisons failed to reach significance (P values $>$ 0.05).

RMSE of relative phase. RMSE was analyzed using the same statistical procedures as the relative phase data and produced similar patterns of results (Fig. 3). Analysis using a 2 (Pattern) $\times$ 2 (Polarity) $\times$ 2 (Block) $\times$ 7 (Frequency) RM ANOVA confirmed significant main effects for Pattern, $F(1,9) = 151.691$, $P < 0.001$, $\eta_p^2 = 0.944$, Block, $F(1,9) = 16.829$, $P = 0.003$, $\eta_p^2 = 0.652$, and Frequency, $F(6,54) = 75.298$, $P < 0.001$, $\eta_p^2 = 0.893$. These main effects were superseded by significant Pattern $\times$ Frequency, $F(6,54) = 65.211$, $P < 0.001$, $\eta_p^2 = 0.879$, Block $\times$ Frequency, $F(6,54) = 2.946$, $P = 0.015$, $\eta_p^2 = 0.247$, and Pattern $\times$ Polarity $\times$ Block, $F(1,9) = 5.941$, $P = 0.038$, $\eta_p^2 = 0.398$, interactions. Post hoc analysis of the Pattern $\times$ Frequency interaction revealed antiphase coordination became more variable as oscillation frequency increased, whereas no differences were noted across frequencies for in-phase coordination. In-phase coordination was also significantly more consistent compared with antiphase coordination at oscillation frequencies of 2.25–3.25 Hz. Post hoc tests for the Block $\times$ Frequency interaction indicated significant pre-tDCS to post-tDCS differences only at 2.5–3.25 Hz. Consistent with the relative phase data, the three-way Pattern $\times$ Polarity $\times$ Block interaction revealed no significant variability differences between pre- and post-tDCS blocks for the in-phase pattern (precathodal: mean = 28.4, SE = 2.4; postcathodal: mean = 24.0, SE = 1.8; preanodal: mean = 26.6, SE = 2.6; postanodal: mean = 24.1, SE = 1.8). In contrast, the postanodal block (mean = 93.9, SE = 9.1) had a lower RMSE compared with the preanodal (mean = 109.5, SE = 8.5), the precathodal (mean = 110.2, SE = 8.3), and the postcathodal (mean = 106.8, SE = 8.9) blocks, which did not differ significantly from each other. All other comparisons failed to reach significance ($P > 0.05$).

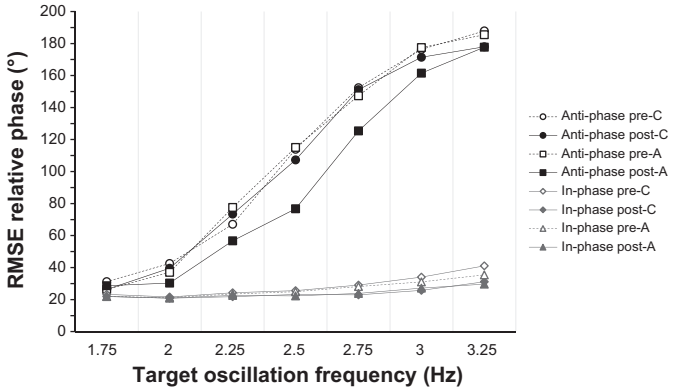

Fig. 3. Average root-mean-square error (RMSE) of relative phase as a function of oscillation frequency for testing blocks pre- and postcathodal and anodal tDCS. Participants maintained low RMSE during in-phase (0°) trials as oscillation increased (gray lines), but transitions during antiphase (180°) trials resulted in large RMSE values. However, note that participants performed the antiphase pattern with lower RMSE as frequency increased following anodal tDCS stimulation (■).

DISCUSSION

Although in-phase and antiphase configurations represent intrinsically stable interlimb coordination patterns, behavioral and clinical studies have revealed in-phase to be the most stable pattern of the human motor system, especially at high movement frequencies [see Swinnen (2002) and Swinnen and Wenderoth (2004) for reviews]. Neuroimaging research has shown that differences in SMA activation are associated with each coordination mode and hence the stability of the respective movement patterns with greater involvement in the antiphase pattern (Aramaki et al. 2006; Debaere et al. 2001). The SMA has been recognized as playing a crucial role in a distributed network that governs coordinated behavior as it operates bilaterally with interhemispheric connections. Thus one of the purported roles of the SMA involves the temporal organization of multiple effector actions (Swinnen 2002; Swinnen and Wenderoth 2004) by adjusting the activity of both primary motor cortices (Serrien et al. 2002; Steyvers et al. 2003). As a result, a functional link between the SMA and pattern stability exists during bimanual activities. Here, we investigated this role of the SMA by examining how the relative phasing between the upper limbs during rhythmic bimanual movements was affected following tDCS applied over SMA, a novel technique that has been reported to modulate the excitability of the underlying cortical tissue. Consistent with predictions, results revealed that anodal tDCS resulted in significantly delayed anti-to-in-phase transitions (Fig. 1) and improved antiphase coordination (Figs. 2 and 3). Conversely, cathodal tDCS had no effect on antiphase coordination, and neither tDCS polarity affected performance of the more stable in-phase pattern.

The results of the present study show a gradual decrement in antiphase bimanual coordination as movement speed was systematically increased throughout the experimental trials. However, this degradation in performance occurred at a slower rate following anodal tDCS applied over the SMA. That is, following anodal tDCS, participants were able to perform the antiphase pattern more accurately (Fig. 2) and consistently (Fig. 3) across the target oscillation frequencies as well as delay their transition to in-phase (Fig. 1). Anodal tDCS has been shown to result in increased excitability of motor cortical areas (Nitsche et al. 2008; Stagg and Nitsche 2011), and assuming a similar effect on SMA, the current data suggest that increased SMA excitability can transiently improve temporal interlimb regulation of the less stable antiphase pattern. Although SMA excitability was not directly assessed in the present experiment and a control site was not used, these results are in line with predictions of the effects associated with increased SMA excitability and showed polarity-specific effects. Moreover, this novel result adds to the accumulating evidence that the SMA has a pivotal role in bimanual coordination (Immisch et al. 2001; Serrien et al. 2002; Steyvers et al. 2003; Swinnen 2002; Swinnen and Wenderoth 2004) and is consistent with functional imaging experiments that have shown greater SMA activation during antiphase coordination (Debaere et al. 2001; Immisch et al. 2001; Jäncke et al. 2000; Toyokura et al. 1999; Ullen et al. 2003). Unsurprisingly, anodal tDCS had no effect on in-phase pattern performance, as this pattern is inherently more stable and thus unlikely to be affected by changes in SMA activation.

Although the results of anodal tDCS presented here were consistent with predictions, it was less clear how cathodal tDCS would affect bimanual coordination performance. Although many studies have found opposite effects of cathodal and anodal tDCS, others have found similar excitability effects with both types of stimulation (e.g., Batsikadze et al. 2013), whereas still others have found no effect of cathodal tDCS (e.g., Hayduk-Costa et al. 2013; Matsunaga et al. 2004). The current data indicate that cathodal tDCS had no effect on any of the dependent measures for both in-phase and antiphase patterns. Although is it possible that cathodal tDCS did have a negative effect on antiphase performance that was counteracted by a between-block practice effect, this explanation is unlikely as these contrasting effects would need to be of similar magnitude for all dependent measures to explain the observed results. In addition, a post hoc examination of any possible practice effects was performed by examining time-to-transition performance in the pretest block on a trial-by-trial basis using a 2 (Polarity) $\times$ 7 (Trial) RM ANOVA. This analysis confirmed there was no change in transition time performance as a result of practice in the pretest block [$F(6,36) = 0.247$, $P = 0.958$, $\eta_p^2 = 0.039$] as well as no effect of polarity [$F(1,6) = 0.110$, $P = 0.751$, $\eta_p^2 = 0.018$] or interaction effect [$F(6,36) = 0.684$, $P = 0.664$, $\eta_p^2 = 0.102$]. As any practice effects would be expected to be most apparent early in practice, this result provides additional confirmation that the observed effects are more likely due to the tDCS stimulation rather than practice. That is, anodal tDCS increased performance accuracy and stability, whereas cathodal tDCS had no effect on performance and effectively functioned as a sham condition, similar to that previously observed with cathodal tDCS applied over the SMA during a stop-signal reaction-time task (Hayduk-Costa et al. 2013), confirming that modification of SMA activation does affect performance of the antiphase bimanual coordination pattern.

The use of tDCS represents a previously unused neuromodulation method to examine SMA contributions to stability of coordination patterns as previous research has typically utilized TMS-induced disruption protocols. For example, both Serrien et al. (2002) and Steyvers et al. (2003) demonstrated that perturbing the motor system via high-frequency rTMS presented over the SMA could significantly increase the mean relative phase error between the moving effectors during antiphase but not in-phase coordination. Similarly, Meyer-Lindenberg et al. (2002) found that when double-pulse TMS (50-ms interstimulus interval) was applied over the SMA during bimanual movements, it triggered early transitions from the antiphase mode to the in-phase mode, whereas the in-phase pattern could not be affected. Although the current data support these studies, highlighting the importance of SMA in the production of a bimanual antiphase pattern, the results indicate increased SMA activation can lead to an improvement in maintaining antiphase coordination and a delay in transitioning to the more stable in-phase pattern. At first glance, our findings seemingly contradict those of Serrien et al. (2002) and Steyvers et al. (2003) as anodal tDCS (present experiment) and high-frequency rTMS ($\geq$5 Hz; their experiments) are both thought to increase cortical excitability of the stimulated area and thus would be expected to have similar effects on motor behavior. This discrepancy may result from differences in the mechanisms of action for rTMS and tDCS as well as differences in the experimental protocols. Unlike the pulsed stimulation of rTMS, which uses a rapidly changing magnetic field to stimulate nerve cells in a brain region directly, tDCS affects the resting membrane threshold in part by influencing the electrical balance of ions inside and outside of the neural membrane (Bolognini et al. 2009). Moreover, the concept of a simple rTMS frequency threshold that results in a directional change of neuromodulatory effects from inhibitory to facilitatory is likely an oversimplification of the complex interactions between other parameters such as train length, number of pulses, and intertrain interval [e.g., Modugno et al. 2001; Pascual-Leone and Hallett 1994; and see Pell et al. (2011) for an in-depth discussion]. Finally, tDCS was applied offline in the present experiment, whereas an online rTMS protocol was used in the work by Serrien et al. (2002) and Steyvers et al. (2003). High-frequency rTMS applied for short trains online can create a "virtual lesion" whereby ongoing neuronal activity is transiently disrupted to interfere with motor performance (Gerloff et al. 1997; Walsh and Rushworth 1999). Thus the timing of stimulation (online vs. offline) can produce opposite effects on motor behavior, independent of cortical excitability effects, and may explain the discrepancy between the current results and previous findings.

Finally, it must be acknowledged that as SMA excitability was not directly measured, it is possible that the tDCS may have affected adjacent structures comprising the distributed network involved in bimanual coordination such as the primary motor areas and the lateral premotor cortices (Immisch et al. 2001; Swinnen 2002; Swinnen and Wenderoth 2004). Although we cannot rule out this possibility, the experimental methods selectively targeted the SMA using standardized head coordinates (Jasper 1958; Talairach and Tournoux 1988) used successfully in previous experiments (e.g., Hayduk-Costa et al. 2013; Muri et al. 1994). Furthermore, given the aforementioned role of the SMA in the performance of antiphase coordination and the improvement in performance following anodal tDCS over the area of the SMA, we argue that the most likely explanation is that increased SMA excitability contributed to increased stability, accuracy, and time to transition for the antiphase pattern. Although the exact circuitry involved in the production of cyclical bimanual coordination patterns is not known, it is hypothesized to involve a network of regions including the SMA, cerebellum, premotor cortex, and corpus callosum (Swinnen and Wenderoth 2004). As the tDCS protocol used in the present experiment involved electrodes centered along the midline of the scalp, the current would be expected to stimulate both left and right SMA equally, resulting in changes that are not lateralized. Speculatively, the observed improvements in coordination may have also been partially due to improved SMA-specific interhemispheric communication as information regarding the spatial codes of each limb is thought to be exchanged between the hemispheres (Eliassen et al. 2000; Franz et al. 1996), which would be most relevant when the limbs are moving in an asymmetrical manner. This hypothesis could be tested in future studies through the use of a more focal, unilateral stimulation of either left or right SMA to determine differences in performance when the excitability of only one hemisphere is altered. Furthermore, tDCS applied over cerebellum or premotor cortex during antiphase performance may assist in better understanding of the relative con-

tributions of these regions to the stability of bimanual coordination patterns.

In summary, the current data provide compelling evidence that further recognizes the important integrative role the SMA has in the coordination of bimanual movements, especially during the performance of a demanding antiphase pattern at high oscillation frequencies. In particular, anodal tDCS applied over the SMA increased antiphase pattern stability and consistency and delayed transitions to the more stable in-phase pattern.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

M.J.C. and A.N.C. conception and design of research; M.J.C. and A.N.C. performed experiments; M.J.C. analyzed data; M.J.C., D.M., and A.N.C. interpreted results of experiments; M.J.C. prepared figures; M.J.C. and D.M. drafted manuscript; M.J.C., D.M., and A.N.C. edited and revised manuscript; M.J.C., D.M., and A.N.C. approved final version of manuscript.

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