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Research article

Combined motor point associative stimulation (MPAS) and transcranial direct current stimulation (tDCS) improves plateaued manual dexterity performance

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HIGHLIGHTS

- We asked if combining central and peripheral stimulation could improve hand dexterity without motor practice.
- Subjects were healthy young adults and had already reached plateau on a manual dexterity task.
- Combining anodal tDCS with MPAS significantly improved manual dexterity beyond the ceiling of performance.
- Central tDCS to complement peripheral MPAS may be a promising avenue of treatment for patients with impaired hand dexterity.

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ABSTRACT

Motor point associative stimulation (MPAS) in hand muscles is known to modify motor cortex excitability and improve learning rate, but not plateau of performance, in manual dexterity tasks. Central stimulation of motor cortex, such as transcranial direct current stimulation (tDCS), can have similar effects if accompanied by motor practice, which can be difficult and tiring for patients. Here we asked whether adding tDCS to MPAS could improve manual dexterity in healthy individuals who are already performing at their plateau, with no motor practice during stimulation. We hypothesized that MPAS could provide enough coordinated muscle activity to make motor practice unnecessary, and that this combination of stimulation techniques could yield improvements even in subjects at or near their peak. If so, this approach could have a substantial effect on patients with impaired dexterity, who are far from their peak. MPAS was applied for 30 min to two right hand muscles important for manual dexterity. tDCS was simultaneously applied over left sensorimotor cortex. The motor cortex input/output (I/O) curve was assessed with transcranial magnetic stimulation (TMS), and manual dexterity was assessed with the Purdue Pegboard Test. Compared to sham or cathodal tDCS combined with MPAS, anodal tDCS combined with MPAS significantly increased the plateau of manual dexterity. This result suggests that MPAS has the potential to substitute for motor practice in mediating a beneficial effect of tDCS on manual dexterity.

1. Introduction

Increasing the excitability of corticospinal projections has been found to improve recovery in stroke patients [1]. Efforts to increase corticospinal excitability have ranged from simple ballistic movement [2] and task-specific performance [3] to peripheral [4] and central [5,6] electrical stimulation. For example, paired associative stimulation (PAS), which consists of peripheral nerve stimulation (PNS) in association with motor cortex stimulation, is based on the Hebbian principle of spike timing-dependent plasticity [7]: if neurons are repeatedly depolarized in synchrony, the strength of synaptic connections among them increases.

A related technique involves synchronous peripheral stimulation of two muscles that cooperate for fine hand movement: Abductor Policis Brevis (APB) and First Dorsal Interosseous (FDI).

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Motor point associative stimulation (MPAS) increases the excitability of corticospinal projections to the stimulated muscles, similar to what has been observed in motor learning [8], and has been shown to increase the learning rate, though not the plateau, in a manual dexterity task in healthy subjects [9]. However, MPAS facilitation in upper limb dexterity is only obtained when used in combination with motor practice, e.g. training in a grooved pegboard test in healthy subjects [9] or physical therapy in stroke patients [4]. Because substantial upper limb motor training can be tiring and difficult for patients [10,11], and MPAS is a simple and low-cost technique that can be used in the clinic, an MPAS-based rehabilitation technique that did not require active movement would have considerable advantages.

Non-invasive central electrical stimulation, such as transcranial direct current stimulation (tDCS), results in tonic changes in cortical excitation and corticospinal connections when applied over sensorimotor cortex. tDCS involves two sponge electrodes, a cathode and an anode, which are placed on the head. When a small electric current is passed through the electrodes, the current flow modulates cortical excitability in the target area in a polarity-specific way. The anode causes an increase in excitability under the electrode while the cathode does the opposite [12]. The majority of work on tDCS has focused on primary motor cortex. Anodal tDCS over this region improves performance of a serial reaction time task in healthy subjects [13]. This technique also improves skilled motor function in chronic stroke patients [5]. In general, tDCS has demonstrated an effect on manual dexterity mostly when it is combined with a motor task practiced during stimulation [5,13,14]. Without motor practice, the cumulative effects of repeated sessions of tDCS can improve motor function in stroke patients [6], but multiple sessions of tDCS over days or weeks are required. tDCS is a simple and affordable technique that could be adapted for clinical use, but an approach that did not require physical practice would be the most useful.

There is some evidence that combining peripheral and central stimulation may yield stronger effects than either alone. Combining tDCS with PNS has been shown to cause lasting increases in motor cortex (M1) excitability [15,16] in healthy subjects. Furthermore, in stroke patients, in the presence of manual practice, PNS in combination with tDCS facilitated the beneficial effect of each intervention [17]. The effect of combining tDCS with MPAS has not been explored in healthy or clinical populations, but could have substantial advantages, as the synchronous muscle activations of MPAS may serve the function normally played by motor practice in tDCS interventions.

Here we ask whether adding tDCS over sensorimotor cortex enhances the effect of MPAS on manual dexterity in healthy adults. In this preliminary study we tested healthy subjects who were performing at or near their plateau of manual dexterity, reasoning that if combining tDCS and MPAS can further improve performance in this population, even by a small amount, then in clinical populations performing far from their peak, the effects of this technique could be substantial. We target sensorimotor cortex because MPAS affects both motor and somatosensory pathways. We therefore expected this tDCS positioning to maximally enhance relevant cortical plasticity. To identify any changes in motor cortex physiology related to these functional changes, we used transcranial magnetic stimulation (TMS) to assess the relationship between stimulus intensity and response amplitude (input/output or I/O curve). We addressed these questions in two experiments, first comparing the effects of adding sham, anodal, or cathodal tDCS to MPAS, and then examining the effects of tDCS alone.

2. Materials and methods

2.1. Subjects

Thirteen right-handed subjects (10 females) aged 18–40 years participated in Experiment 1. Twelve right-handed subjects (9 females) aged 18–40 years participated in Experiment 2. Ten subjects participated in both experiments. All subjects were naïve to the purpose of the study and gave written informed consent approved by Indiana University Institutional Review Board. Participants reported that they had no history of neurological or neuromuscular injury or disorder in the brain or upper limbs.

2.2. Experimental design

Each session consisted of behavioral and neurophysiological (TMS) measurements taken pre-and post-intervention (Fig. 1). Subjects were seated comfortably throughout the intervention, which entailed 30 min of sham or real MPAS in combination with 25 min

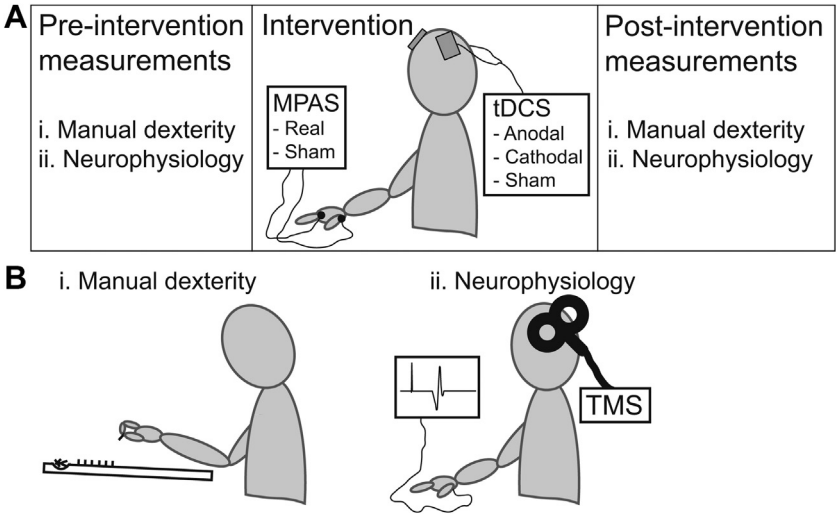

Fig. 1. A. Study design and interventions. Each session consisted of behavioral and neurophysiological measures before and after an intervention consisting of real MPAS (Experiment 1) or sham MPAS (Experiment 2) combined with cathodal (Experiment 1 only), anodal, or sham tDCS. B. Outcome measurements. i. Manual dexterity was measured with the Purdue Pegboard Test, with the time to transfer 20 pegs to the holes in the board representing manual dexterity. A thumb and index finger grip was used. ii. Neurophysiology measurement using TMS. The APB representation in motor cortex was stimulated with various TMS intensities. MEP amplitude at each intensity was recorded with EMG and used to construct an I/O curve, the slope of which represents cortical excitability.

Table 1
Summary of experimental sessions and interventions. Session order within each experiment was randomized.

Experiment	Session	MPAS	tDCS
1	1	Real	Sham
	2	Real	Anodal
	3	Real	Cathodal
2	1	Sham	Sham
	2	Sham	Anodal

of sham, anodal, or cathodal tDCS (Table 1). All measurements and interventions targeted the right hand. The order in which measurements were conducted (TMS first or behavioral assessment first) was randomized across subjects. The duration of each session was 2.5–3 h. Experimental sessions were conducted at least one week apart. All subjects completed a familiarization session before any of the experimental session, to become accustomed to the stimulation techniques and to learn and practice the manual dexterity task to plateau.

2.3. Interventions

2.3.1. MPAS

2.3.1.1. Real MPAS intervention. The MPAS protocol followed the paradigm described by Ridding & Uy [8]. A Grass Instruments S88 electrical stimulator (Astro-Med; RI, USA) with in-series stimulus isolation unit (SIU-5) and constant-current unit (CCU-1) was used to generate a 1.0-ms duration square-wave pulse to the FDI and APB motor points simultaneously. The timing between successive pairs of stimuli was randomized from 0.15 to 2.85 s (in the range of 0.35–6.7 Hz). The total number of delivered pulses in the 30 min stimulation period was 6345 on average. The intensity of stimulation was set at a level just sufficient to evoke a minimal visible motor response for each muscle (range 10–30 mA) [8]. After determination of stimulation intensity, subjects were asked if the stimulation was painful. All subjects reported in each session that the stimulation was not painful.

2.3.1.2. Sham MPAS intervention. Both sessions in Experiment 2 were done with sham MPAS, to isolate the effect of tDCS alone in this paradigm. To control for non-specific effects of MPAS, we followed the principle of non-associative MPAS [8]. We applied the electrical stimuli on APB and FDI motor points with a 300 ms interstimulus delay. Other properties of the stimulation were retained.

2.3.2. tDCS

2.3.2.1. Real tDCS intervention. Two sponge electrodes (TransQE from IOMED®, surface area: 25 cm^2) soaked in saline solution were applied to the subject's head and held in place with an ACE-style bandage. For the anodal tDCS session, the anodal sponge was placed over the sensorimotor cortex, 1 cm caudal to the motor hotspot for APB (left hemisphere) and the cathode was placed over the contralateral forehead. For cathodal tDCS, the positions were reversed [18,19]. A weak DC current (2 mA, with calculated current density of 0.08 mA/cm^2) was delivered through the sponge electrodes using a Chattanooga Ionto™ dual channel iontophoresis system (Chattanooga Group, Hixson, TN) for 25 min, after which the subject had a 10 min rest. We started the MPAS intervention 5 min before tDCS in order to achieve 30 min of MPAS and 25 min of tDCS. tDCS is normally applied for no more than 20–25 min [20], while MPAS has mainly been studied with an application period of one hour [9]. We wanted to match the timing of tDCS and MPAS as closely as possible, given these constraints. Based on the PAS literature [21,22], we predicted that 30 min of MPAS was the shortest period of stimulation likely to cause measurable effects for the time it would take us to perform the TMS and behavioral measures. We chose to start the tDCS 5 min after starting MPAS to give subjects the opportunity to become accustomed to one stimulation before adding the second. Both modes of stimulation concluded at the same time.

2.3.2.2. Sham tDCS intervention. The tDCS machine was turned on as in the regular tDCS sessions, but the current was switched off after 30 s without the subject's knowledge. With this procedure, participants are usually unable to differentiate between real tDCS and sham stimulation [23].

2.4. Outcome measures

2.4.1. Manual dexterity: purdue pegboard test (PPT)

PPT is an assessment for manual dexterity [24]. The PPT has been widely used in hand functional assessment for stroke recovery [25]; assessment of digit dexterity in a study of motor cortex excitability and handedness [26]; and measurement of fine motor learning [3]. In the task, subjects used a precision grip (pinch) to grab a metal peg from a pit and transfer it to vertical holes. The time [25,27] taken to transfer 20 pegs was recorded as one trial. Subjects completed one block of 3 trials before and after the intervention. To compare pre- and post-intervention performance in the experimental sessions, each set of three trials was averaged. The pegboard trials were timed by research assistants who were blind to the stimulation condition.

To plateau performance in the familiarization session, subjects performed the task in blocks of 3 trials. Performance was considered plateaued when the average time for the 3 trials in one block did not change from the previous block by more than 0.5 s. Subjects had 2 min of rest between blocks. Depending on prior hand dexterity it took subjects 5–8 blocks (15–24 trials) to reach plateau.

2.4.2. Neurophysiology: TMS

2.4.2.1. TMS and neuronavigation. Single transcranial magnetic stimuli were delivered using a standard Magstim 200^2 stimulator (Magstim Company LTD, UK) with a 70 mm figure-eight shaped coil. The coil handle was pointing posteriorly and the coil was situated tangential to the skull. The position of the coil was maintained at 45° to the inter-hemispheric line to evoke anterior-directed current in the cortex. Both of the subject's arms were relaxed on a pillow on their lap. Head and coil positions were tracked with a Brainsight neuronavigation system (Rogue Research, Montreal, Canada). The motor cortex hot spot for APB was located and stored in Brainsight, after which we determined the TMS stimulus intensity needed to evoke a 1 mV MEP in APB (the SI1 mV).

2.4.2.2. I/O curve. We recorded 10 MEPs at each of following intensities: 60, 80, 90, 100, 110, 120, and 130% of SI1 mV [28,29]. The order of intensities was randomized. While there is considerable variety in the approaches taken to construct and evaluate an I/O curve, taking the slope of the middle, most linear part of the sigmoidal curve is common [30]. This range of stimulation intensities corresponds to 120–140% of resting motor threshold [30]. As percentages of SI1 mV, this works out to roughly 80–120% of SI1 mV in our subjects, a range consistent with the literature [28,29]. I/O curves were therefore evaluated as the slope of the best fit line from 80 to 120% of SI1 mV [28].

2.4.2.3. EMG. EMG activity was recorded from APB of the right hand. A single common ground electrode was placed over the ulnar styloid process of the right arm. EMG recordings were amplified (AMT-8; Bortec Biomedical, Calgary, Alberta), band-pass filtered (10–1000 Hz), sampled at 5000 Hz, and recorded on a hard drive for subsequent analysis using Signal software (Cambridge Electronic Design Ltd, UK) and MATLAB (Mathworks Inc., MA, USA).

EMG was monitored online to confirm that subjects were keeping their hand relaxed during stimulation. If background EMG revealed any >50 μV contraction before or during the MEP, the trial was thrown out. Subjects were given verbal feedback to keep their muscles relaxed. If 20% of trials were thrown out in any session, we excluded the subject's EMG data from analysis. One subject in Experiment 1 had to be removed from I/O curve analysis for this reason.

2.5. Statistical analysis

Within each experiment, two-way repeated measures ANOVAs (ANOVA-RMs) were performed on pegboard time, I/O curve slope, and MEP amplitude at 120% of SI1 mV as outcome variables. The predictors for each of those models were time (pre or post) x stimulation condition (anodal, cathodal, or sham for Experiment 1; anodal or sham for Experiment 2). For significant interactions of time x condition, post-hoc ANOVA-RMs were performed. We also performed one-way ANOVA-RMs (Experiment 1) or paired sample *t*-tests (Experiment 2) on the "pre" data, to determine whether baseline values were equivalent across stimulation conditions.

Although the study was primarily designed for within-experiment comparisons, we used several linear multilevel regressions to contrast Experiment 1 to Experiment 2. This contrast was done with respect to percent change in pegboard time, I/O curve slope, and MEP amplitude at 120% of SI1 mV. However, because Experiment 2 did not have a cathodal session, we could only include sham and anodal data in these models. We chose the multilevel approach because it could deal with unbalanced designs, as the one emerging when contrasting the two experiments, as some subjects participated in both and others only one. We fitted all models using the lme4 package (Version 1.1.12) [31] of the R programming language [32]. The predictors for each model were MPAS (real or sham), time (pre or post), and the interaction between MPAS and tDCS. We could not include a 3-way interaction between MPAS, tDCS, and time due to the lack of enough data points for model estimation. Nonetheless, the interaction between time and stimulation condition was further studied within each experiment via repeated measures ANOVAs.

3. Results

3.1. Manual dexterity: purdue pegboard test

3.1.1. Experiment 1

MPAS combined with anodal tDCS, but not sham or cathodal tDCS, improved plateaued pegboard performance time by nearly 3% (Fig. 2A,B). ANOVA-RM showed a significant interaction between time point (pre vs. post) and stimulation condition ($F_{2,24} = 4.15$, $p = 0.028$), indicating that pegboard performance changed differently from pre- to post-intervention for the different stimulation conditions. There was also a main effect for tDCS condition ($F_{2,24} = 5.81$, $p = 0.0088$), but not for time point ($p = 0.46$). *Post hoc* analysis revealed a significant time point x tDCS condition interaction between sham and anodal conditions ($F_{1,12} = 11.40$, $p = 0.0055$), and a tendency for an interaction of time point x stimulation condition between anodal and cathodal conditions ($F_{1,12} = 3.48$, $p = 0.087$). Consistent with this, a paired sample *t*-test suggests that pegboard performance improved significantly from pre- to post-intervention ($t_{12} = 4.18$, $p = 0.0013$). Pegboard performance pre-intervention did not differ across stimulation conditions ($p = 0.58$).

3.1.2. Experiment 2

Sham MPAS combined with anodal or sham tDCS did not affect pegboard performance time (Fig. 2C,D). There was no interaction between time point and stimulation condition, and no main effect (all $p > 0.82$). This suggests that anodal tDCS alone does not improve the plateau of subjects' pegboard performance time.

Consistent with these results, multilevel regression comparing Experiments 1 and 2 suggested a significant interaction between MPAS real and tDCS anodal ($\beta = -1.09$, SE = 0.48, $t(81.26) = -2.27$, $p = 0.026$). No other predictor showed a statistically significant association with this outcome variable (Table 2).

3.2. I/O curve and MEP amplitude

3.2.1. Experiment 1

While I/O slope increased 37% with anodal and decreased 14% with cathodal tDCS in the presence of MPAS (Fig. 3), ANOVA-RM indicated no interaction between time point and stimulation condition ($p = 0.21$). Because the greatest changes in MEP amplitude appear to be at the higher stimulation intensities, we also examined MEP amplitude at 120% of SI1 mV. ANOVA-RM yielded a tendency toward interaction of time point and stimulation condition for 120% ($F_{22,2} = 2.57$, $p = 0.099$). However, pre-intervention values were not equivalent across stimulation conditions for I/O curve slope ($F_{22,2} = 3.46$, $p = 0.049$), nor for MEP amplitude at 120% SI1 mV ($F_{22,2} = 6.17$, $p = 0.0075$).

3.2.2. Experiment 2

For subjects who experienced sham and anodal tDCS with sham MPAS, ANOVA-RM showed no interactions of time point and stimulation condition and no main effects for I/O curve slope or MEP amplitude at 120% of SI1 mV (Fig. 3B; all $p > 0.21$). Pre-intervention values were equivalent across conditions in both measures (paired sample *t*-test $p > 0.19$).

Multilevel models did not suggest statistically significant associations of any predictors with either changes in I/O curve slope or MEP amplitude at 120% SI1 mV (Table 2).

4. Discussion

When peripheral associative stimulation (MPAS) was combined with excitatory central stimulation (anodal tDCS), manual dexterity improved significantly beyond the ceiling of performance. Importantly, these functional changes were specific to the MPAS with anodal tDCS session; neither MPAS nor tDCS alone generated these effects. Our results suggest that neuroplastic changes caused by the cumulative effect of anodal tDCS and MPAS led to an increase in manual dexterity plateau in healthy individuals. While the functional improvement was small in healthy adults performing at their plateau, the fact that any improvement was possible in this population suggests that in clinical populations, where there is much room for improvement, the effects could be substantial.

4.1. Peripheral vs. central stimulation

Due to similarities with PAS, the effect of MPAS has been suggested to result from LTP-like neuroplasticity [9,33]. LTP is a persistent increase in the synaptic strength that is long lasting [34]. McDonnell & Ridding [9] found that MPAS increased the rate of learning a manual dexterity task, but did not improve performance beyond plateau. Consistent with this, in the current study, MPAS alone (with sham tDCS) did not improve manual dexterity. Because our interventions were aimed at increasing the ceiling of performance rather than at increasing the rate of learning, subjects had already reached their plateau in the task prior to their first experimental session.

There is evidence that tDCS affects the excitability of intracortical neurons and not the corticospinal tract [35]. The

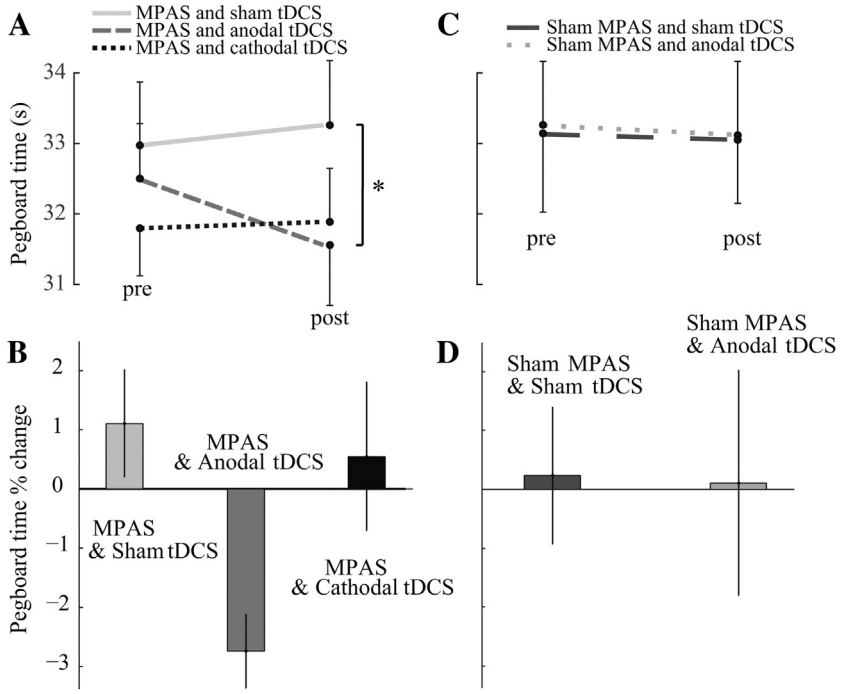

Fig. 2. Manual Dexterity results. Experiment 1: A. Changes from pre- to post- intervention in plateaued pegboard performance when MPAS is combined with anodal, cathodal, or sham tDCS. While the time required to place 20 pegs remains fairly constant after sham or cathodal tDCS, anodal tDCS made subjects about 1 s faster on average. *significant tDCS x time (pre ore post) interaction indicating that performance changed differently during the anodal session compared to sham. B. Percent change in plateaued pegboard performance when tDCS is combined with MPAS. Positive y-axis indicates slower performance (increased time to place 20 pegs) whereas negative y-axis indicates faster performance (decreased time to place 20 pegs). Experiment 2: **C.** Changes from pre- to post-intervention in plateaued pegboard performance when sham MPAS is combined with anodal or sham tDCS. **D.** Percent change in plateaued pegboard performance when sham or anodal tDCS is combined with sham MPAS. There is no significant difference between the two sessions. Error bars represent standard error.

polarity-dependent effect of tDCS on cortex corresponds to depolarization (anodal effect) or hyperpolarization (cathodal effect). However, depolarization does not reach the threshold to cause action potentials [35,36]. The modulatory effect of tDCS has been shown in glutaminergic, GABAergic, dopaminergic, serotonergic and cholinergic synapses [36]. The effect of tDCS on manual dexterity has shown different results based on the type of task that has been used for assessment. For example, in healthy subjects, tDCS over M1 improves dynamic force regulation in thumb and index finger in the dominant hand [37]. However, while tDCS also improves performance on the Jebsen-Taylor hand function test for fine motor control, these benefits are restricted to the non-dominant hand [38], possibly due to a ceiling effect [37]. In our study, using the Purdue pegboard task to assess fine manual dexterity, we did not find any improvement in the dominant hand as a result of tDCS application (with sham MPAS). This may also be a result of ceiling effect in the dominant hand.

4.2. Behavioral changes: manual dexterity

Combining MPAS and anodal tDCS improved manual dexterity beyond the ceiling of performance. This effect was specific to anodal tDCS; no improvement was observed when sham or cathodal tDCS was added to MPAS. This suggests that MPAS alone is insufficient to improve plateaued performance, consistent with earlier literature [9].

The finding of small but robust improvements in manual dexterity after anodal tDCS combined with MPAS in healthy young adults who are already at a performance plateau suggests a potential for strong effects in populations performing far from their peak, such as stroke. In stroke survivors, excitability of the affected motor cortex is lower than the intact side [1]. Anodal tDCS reduces this imbalance [39] and can yield small improvements in manual dexterity [5]. However, combining tDCS with motor training is still considered a more robust approach. For example, Celnik et al. [17] combined PAS and tDCS with manual practice as a strategy for improving manual dexterity in stroke patients and found a beneficial effect of

Table 2
Linear multilevel regression coefficients for percent change in pegboard time, I/O curve slope, and MEP amplitude at 120% of SI1 mV.

	Pegboard time			I/O curve slope			MEP amplitude at 120% of SI1 mV		
	β	CI for β	p	β	CI for β	p	β	CI for β	p
Fixed Parts									
(Intercept)	33.03	31.47–34.59	**<0.001**	0.11	0.08–0.15	**<0.001**	4.41	3.25–5.56	**<0.001**
MPAS Real	0.43	−0.58–1.45	0.405	0	−0.03–0.03	0.883	0.12	−0.93–1.17	0.829
Time	−0.22	−0.90–0.46	0.53	0	−0.02–0.02	0.766	0.13	−0.57–0.83	0.711
MPAS Sham: tDCS Anodal	0.1	−0.88–1.08	0.847	0.01	−0.02–0.03	0.531	0.32	−0.67–1.31	0.533
MPAS Real: tDCS Anodal	−1.09	−2.04–−0.15	**0.026**	−0.01	−0.04–0.02	0.494	−0.41	−1.40–0.58	0.416
Random Parts									
N_{ID}		15			15			15	
Observations		100			96			96	

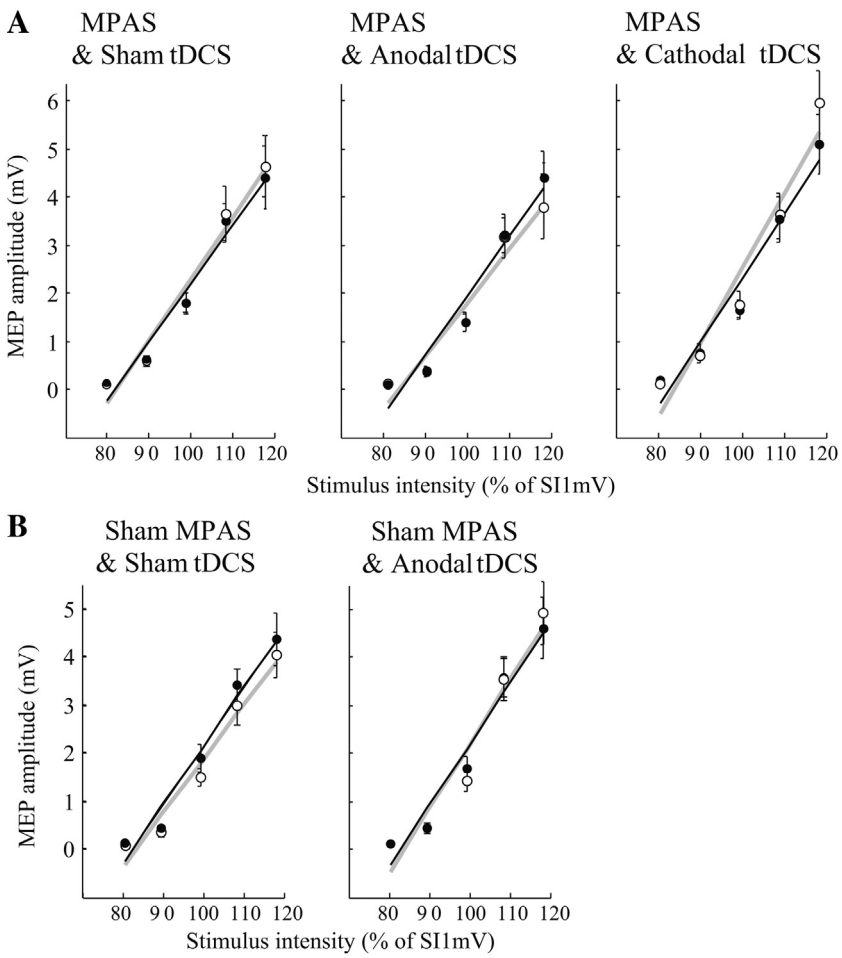

Fig. 3. Input-Output (I/O) curve slope and MEP amplitudes at each TMS intensity. A. Experiment 1. The effect of adding tDCS to MPAS on I/O curve slope. Pre I/O slope in light grey and post I/O slope in dark gray. B. Experiment 2. The effect of Anodal tDCS on I/O curve slope. Error bars represent standard error.

each intervention with manual practice, beyond the effect of manual practice alone. Substituting MPAS for motor training may be a viable alternative, providing organized muscle activations without the movements, which are tiring and difficult for stroke patients.

4.3. *Neurophysiological changes: I/O curve*

Previous studies of MPAS have shown a significant increase in excitability of the corticospinal projection to the stimulated muscles, similar to what has been observed in motor learning [8,9]. Similarly, anodal tDCS is known to increase the I/O curve slope, reflecting larger response to the same stimulus (increased excitability) while cathodal tDCS has the opposite effect [40]. In the present study, I/O curve slope did not change significantly after any of the interventions. While MEP amplitudes at higher TMS intensities did exhibit a tendency to show changes related to stimulation condition in Experiment 1, differences in pre-intervention values across conditions severely limit the conclusions that can be drawn. The trend in MEP amplitudes at high intensities could be caused by the pre-intervention differences, rather than by the differences in tDCS condition. For example, MEP amplitude may have increased after the anodal tDCS session only because it started out abnormally low (i.e., a regression to the mean effect).

A different method of I/O curve measurement, such as determining maximum MEP amplitude and fitting a Boltzman sigmoidal function [36], is unlikely to have yielded different results in this case, given the differences in pre-intervention measures, but may be useful in a future study with more subjects. It should also be noted that a variety of effects of tDCS on neurophysiology have been documented. E.g., 2 mA cathodal tDCS decreased I/O curve slope in one study [25], but had no effect in a different study, and in fact increased MEP amplitude at SI1 mV [37]. In contrast, 1 mA cathodal tDCS did decrease MEP amplitude at SI1 mV and tended to decrease I/O curve slope [37]. However, neurophysiological effects often do not correspond to behavioral effects in a straightforward manner. We chose 2 mA for both anodal and cathodal stimulation because of the opposite effects these parameters have shown in behavior, but it is possible that the neurophysiological differences would have been more robust with 2 mA anodal and 1 mA cathodal stimulation. Further study is needed to determine whether motor cortex neurophysiology plays a role in the effect on manual dexterity of combining MPAS and anodal tDCS.

Contrary to Nitsche et al. [40], anodal tDCS with sham MPAS did not affect I/O curve slope. This may because while we chose to focus on the APB muscle because of its role in fine hand movements, Nitsche et al. [40] used abductor digiti minimi (ADM), which does not play a central role in fine motor skill. Although to our knowledge there is no evidence to show that tDCS affects less-trained muscles more effectively, there is evidence that tDCS most strongly affects the non-dominant hand, which is less trained for dexterity [38]. Thus, it may be possible that, compared to APB which is a very important muscle in hand dexterity, hand muscles that are less involved in fine hand movement (i.e. ADM or muscles in the non-dominant hand), because they have more room for improvement, receive more benefits from tDCS. Our anodal tDCS with sham MPAS result is, however, consistent with the Batsikadze et al. (2013)

finding that tDCS does not affect I/O curve slope for the FDI muscle, which, like APB, is critical for fine motor skill.

5. Conclusions

MPAS combined with anodal tDCS improved plateaued manual dexterity. Importantly, no motor training was needed during stimulation to achieve these effects. The functional result of this combined stimulation has implications for patients who may not have the ability to perform motor training along with electrical stimulation. Further studies of combined stimulation techniques are needed to address the functional effects on neurologic patient populations, i.e. stroke survivors.

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