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Somatosensory and transcranial direct current stimulation effects on manual dexterity and motor cortex function: A metaplasticity study

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ABSTRACT

Background: Non-invasive neuromodulation may provide treatment strategies for neurological deficits affecting movement, such as stroke. For example, weak electrical stimulation applied to the hand by wearing a "mesh glove" (MGS) can transiently increase primary motor cortex (M1) excitability. Conversely, transcranial direct current stimulation with the cathode over M1 (c-tDCS) can decrease corticomotor excitability.

Objective/Hypothesis: We applied M1 c-tDCS as a priming adjuvant to MGS and hypothesised metaplastic effects would be apparent in improved motor performance and modulation of M1 inhibitory and facilitatory circuits.

Methods: Sixteen right-handed neurologically healthy individuals participated in a repeated measures cross-over study; nine minutes of sham- or c-tDCS followed by 30 min of suprasensory threshold MGS. Dexterity of the non-dominant (left) hand was assessed using the grooved pegboard task, and measures of corticomotor excitability, intracortical facilitation, short-latency afferent inhibition (SAI), short-interval intracortical inhibition (SICI), and SAI in the presence of SICI (SAIxSICI), were obtained at baseline, post-tDCS, and 0, 30 and 60 min post-MGS.

Results: There was a greater improvement in grooved pegboard completion times with c-tDCS primed MGS than sham + MGS. There was also more pronounced disinhibition of SAI. However, disinhibition of SAI in the presence of SICI was less and rest motor threshold higher compared to sham + MGS.

Conclusions: The results indicate a metaplastic modulation of corticomotor excitability with c-tDCS primed MGS. Further studies are warranted to determine how various stimulation approaches can induce metaplastic effects on M1 neuronal circuits to boost functional gains obtained with motor practice.

Introduction

Non-invasive brain stimulation can modulate cortical excitability for a period of time outlasting the stimulation and may provide a useful priming approach to address cortical excitability abnormalities in certain neurological conditions such as stroke or Parkinson's disease [1]. For example, approaches which prime primary motor cortex (M1) before physical rehabilitation have been shown to improve motor function of stroke patients [2–5].

Plasticity-inducing protocols may induce long-term potentiation (LTP) or long-term depression (LTD) as observed in direct stimulation and recordings of CA1 neurons in rodent hippocampus, or by using non-invasive stimulation of human M1 [6]. Interestingly, both techniques induce effects that can be primed to either

Abbreviations: AMT, Active motor threshold; CS, Conditioning stimulus; CME, Corticomotor excitability; c-tDCS, Cathodal transcranial direct current stimulation; EMG, Electromyography; FDI, First dorsal interosseous; F/M, F-wave amplitude; GPT, Grooved pegboard test; GABA, Gamma-aminobutyric acid; ICF, Intracortical facilitation; LME, Linear mixed effects; LTD, Long-term depression; LTP, Long-term potentiation; M1, Primary motor cortex; MEP, Motor evoked potential; MGS, Mesh glove stimulation; MTAT 2.0, TMS Motor Threshold Assessment Tool V2.0; NC, Non-conditioned; RMT, Rest motor threshold; SAI, Short-latency afferent inhibition; SAIxSICI, SAI in the presence of SICI; SEM, Standard error of the mean; SICI, Short-interval intracortical inhibition; SPT, Sensory perceptual threshold; tDCS, Transcranial direct current stimulation; TMS, Transcranial magnetic stimulation; T0, Baseline; T1, Post-tDCS; T2, Post-MGS; T3, 30 min post-MGS; T4, 60 min post-MGS; TS, Test stimulus.

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enhance or diminish their effects by a preceding plasticity inducing protocol [6,7]. This "metaplasticity" may operate via homeostatic mechanisms. For example, the threshold for increasing neuronal excitability can be raised if the previous level of neuronal activity is high. Conversely, the threshold can be reduced if the previous level of neuronal activity is low [8]. In contrast non-homeostatic metaplasticity allows the threshold for neuronal excitability to be lowered when the neuronal activity is high [9]. Non-homeostatic metaplasticity principles also allow the threshold to be further increased when neuronal activity is low.

Cathodal transcranial direct current stimulation (c-tDCS) has been shown to induce LTD-like plasticity within human M1. The decreased corticomotor excitability (CME) [10] is associated with decreased intracortical facilitation (ICF) and increased gamma-aminobutyric acid $(GABA)_A$-ergic intracortical inhibition (SICI) [11,12]. These changes also occur alongside a decrease in short-latency afferent inhibition (SAI), which is a measure of $GABA_A$-ergic and cholinergic sensorimotor integration [13,14]. Hence, SICI and SAI must probe distinct $GABA_A$ receptor subtypes differentially modulated by c-tDCS [15].

Transcutaneous electrical stimulation of the hand can induce LTP-like facilitation in human M1. For example, CME increases after applying low-level mesh glove stimulation (MGS) [16,17]. Weak transcutaneous MGS is thought to activate slow and fast adapting cutaneous receptors of the hand, resulting in synchronous tonic input to M1 [16]. The increased CME is accompanied by an increased strength of corticospinal projections and ICF, as well as a decrease in SICI [17,18], and may have functional implications in a neurorehabilitation context e.g., in ameliorating deficits in hand function resulting from stroke [16]. However, whether or not MGS modulates sensorimotor integration, as measured with SAI, remains unclear.

The aim of the current study was to examine whether priming MGS with c-tDCS enhances the modulation of M1 CME and inhibition via metaplastic mechanisms. It was hypothesised that increases in CME and ICF as well decreases in SICI and SAI after MGS would be enhanced after c-tDCS primed MGS [8,19,20]. It was also hypothesised that an improvement in motor performance (grooved pegboard test; GPT) would be accompanied by increased CME and decreased inhibition after MGS [16,21]. Repetitive motor practice alone can modulate CME for up to 15 min, as was found after repetition of the Purdue pegboard test [22], whereas in a similar study, CME did not facilitate hand MEP amplitudes after GPT training [23]. However, improvements on GPT performance were enhanced by afferent stimulation prior to training [23]. Therefore, we expected improvements in GPT performance that may occur with training would be enhanced with c-tDCS primed MGS [9].

Methods

Participants

Sixteen healthy volunteers with no known neurological impairments (9 female, mean age 25 ± 4.91, range 19–36) participated in the study. All participants were right handed (laterality quotient mean $89.06 \pm 15.29\%$) as determined using the four item version of the Edinburgh Handedness Inventory [24]. The level of physical activity of all participants (2 inactive, 8 minimally active, 6 active) was determined using the short version of the International Physical Activity Questionnaire. All participants gave informed written consent and the study was approved by the University of Auckland Human Participants Ethics Committee (Ref. 018903).

Experimental design and protocol

Participants completed two experimental sessions, receiving sham- or c-tDCS in a pseudorandomised order (Fig. 1), separated by at least one week. Participants were seated with their hands in a neutral and relaxed position except when assessing active motor threshold (AMT) and F-waves. Neurophysiology and behavioural assessments were performed at baseline (T0), immediately after (T1) 9 min of tDCS (sham- or c-), immediately (T2), 30 min (T3), and 60 min (T4) after 30 min of supra-sensory threshold MGS.

Assessments completed at each time point (T0-T4) were; GPT, rest motor threshold (RMT), motor evoked potential (MEP) amplitude, ICF, SAI, SICI, SAIxSICI, F-wave amplitude (F/M) and persistence, the procedures for which are explained below.

Grooved pegboard test

The time taken to complete the 25-hole GPT (Lafayette Instruments, Lafayette, IN) with the left hand was recorded at each time point. Participants were instructed to keep their right hand flat on the table next to the pegboard. They were then instructed to move the pegs one at a time into the holes, row by row, from the right to left side of the pegboard. Participants performed one trial at each time point and were verbally encouraged to go as quickly as possible while maintaining accuracy.

Electromyography

Surface electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscle of the non-dominant (left) hand using 10-mm-diameter Ag-AgCl surface electrodes in a belly-tendon montage (Ambu Blue Sensor Paediatric NS, Ballerup, Denmark), with a 20 mm diameter ground electrode (Red Dot: 3 M Health Care, London, Canada) positioned on the dorsum of the hand. EMG signals were amplified and bandpass-filtered (10–1000 Hz) using a CED1902 amplifier (Cambridge Electronic Design, Cambridge, UK), and sampled at 2 kHz with a CED A-D interface (MICRO1401mkII, Cambridge Electronic Design, Cambridge, UK). Data were also recorded onto a computer to allow offline analysis using Signal 5.07 (Cambridge Electronic Design, Cambridge, UK). The EMG electrode locations were marked prior to MGS using a permanent marker. Electrodes were removed before MGS. After MGS, the skin was re-prepped and new electrodes were applied in the same location.

Transcranial magnetic stimulation

Single- and paired-pulse transcranial magnetic stimulation (TMS) over the right M1 of the participant was delivered using two MagStim® 200^2 magnetic stimulators connected to a BiStim^2 unit (Magstim® Company Ltd., Whitland, UK). A figure-of-eight coil (70 mm diameter) was positioned 45° to the midline and held tangentially to the scalp to induce a monophasic posterior-to-anterior current over M1. The optimal location for eliciting MEPs in the left FDI was marked directly onto the scalp.

Motor thresholds (RMT, AMT)

Motor thresholds were determined using the TMS Motor Threshold Assessment Tool V2.0 (MTAT 2.0) software [25]. RMT was determined as the minimum stimulator intensity that produced a MEP amplitude in the left FDI of at least 50 μV. This was repeated at each time point as a measure of CME. AMT was determined as the minimum stimulator intensity that produced a MEP amplitude of at least 200 μV during a weak voluntary muscle contraction (~10% maximum voluntary contraction). AMT was only measured at

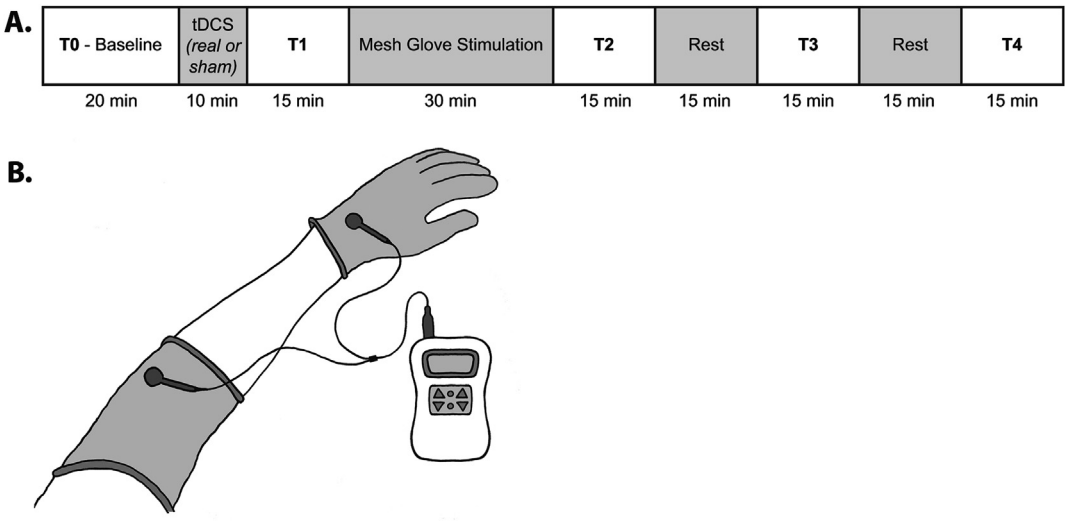

Fig. 1. A. Timeline of experimental sessions. Measures obtained at T0-T4: Grooved pegboard test, rest motor threshold, motor evoked potential amplitude, intracortical facilitation, short-latency afferent inhibition (SAI), short-interval intracortical inhibition (SICI), SAIxSICI, and F-waves. The total time to complete each session was 180 min **B. Experimental mesh glove stimulation setup.** A dual channel stimulator delivers electrical stimulation (50 Hz, pulse width 300 μs) at suprasensory threshold intensity (ranging from 6 to 8 mA) for 30 min. The mesh glove acts as the anode and the mesh sleeve as the cathode.

baseline and used to set the conditioning stimulus (CS) intensity for the ICF protocol.

Non-conditioned MEP

MTAT 2.0 was also used to determine the minimum stimulator intensity that produced a non-conditioned (NC) MEP amplitude in the left FDI of 1 mV. This intensity was used as the test stimulus (TS) for the ICF, SAI and SICI protocols, as well as a measure of CME. Twenty MEPs were collected.

ICF and SICI

Paired-pulse TMS was used for the ICF and SICI protocols, with interstimulus intervals of 15 and 2 ms, respectively [26,27]. For ICF the CS intensity was set to 80% AMT [28]. For SICI the CS intensity was set at the intensity that produced 50% inhibition of the NC MEP amplitude [29,30] to avoid 'floor effects' [31]. For both protocols the TS intensity was set at NC_{1mV}. Twelve MEPs in the ICF and SICI conditions were collected.

SAI

Single-pulse TMS conditioned by transcutaneous electrical digital stimulation of the left index finger (D2) was used for the SAI protocol. A pair of ring electrodes were placed on the proximal section of the index finger with the anode 2 cm distal to the cathode. Electrical stimulation was applied at the intensity three times sensory perceptual threshold (SPT) using a Digitimer Constant Current DS7A Stimulator (0.1 ms duration, 400 V) (Digitimer Limited, UK) [32]. SPT (range, 2.3–6.8 mA) was defined as the lowest stimulator intensity that was detectable by the participant. Electrical stimulation was delivered 25 ms prior to the TMS pulse at a TS intensity of NC_{1mV}. Twelve MEPs in the SAI condition were collected.

SAI x SICI

Paired-pulse TMS combined with transcutaneous electrical digital stimulation of the left index finger was used to examine the influence of SAI on SICI [15]. The CS intensities and interstimulus intervals were consistent with those used in the respective SICI and SAI protocols. To remove a potential floor effect the TS intensity was adjusted to produce a MEP amplitude of approximately 1 mV in the presence of SICI ($SICI_{adj}$) [15]. Twelve MEPs with the TS of $SICI_{adj}$ and CS of 50% inhibition were recorded. Also, twelve MEPs with the SAIxSICI combined protocol were recorded.

Blocks of 80 MEPs were recorded with 5 s intervals between sweeps (20% variation). The 6 measures were randomised throughout each block. Example EMG traces with MEPs showing all six measures are shown in Fig. 2.

F-wave measurements

F-waves were measured with the participant sitting relaxed with their arm in a supine position to allow optimal access to the ulnar nerve. Supramaximal stimulation of the left ulnar nerve was delivered through a Digitimer Constant Current DS7 stimulator (0.1 ms duration, 400 V, 0.3 Hz; Digitimer Limited, UK) via two surface electrodes (Red Dot: 3 M Health Care, London, Canada) separated by 2 cm, with the cathode on the most distal wrist location. Stimulator intensity was set at 110% (range, 28.05–59.40 mA) of that required to elicit a maximal M-wave. The maximal M-wave was determined by increasing the stimulation intensity until the amplitude plateaued with three consecutive increasing pulses. Twenty trials were recorded. An example EMG trace showing M- and F-waves is shown in Fig. 2.

Transcranial direct current stimulation

A neuroConn DC-stimulator PLUS (Ilmenau, Germany) was used to administer tDCS through two rubber electrodes inserted into saline soaked sponges. The cathode electrode (25 cm^2) was placed over the left M1 FDI hotspot. The anode electrode (35 cm^2) was placed over the right supraorbital ridge. For c-tDCS, current was ramped up to 1 mA (current density over M1 = 0.04 mA/cm^2) over 30 s, maintained for 9 min, and then ramped back down to 0 mA over 30 s [33]. For sham-tDCS, current was once again ramped up to 1 mA over 30 s, but then immediately ramped back down to 0 mA over 30 s [34]. Participants were instructed to sit quietly for the duration of the stimulation. TMS and tDCS were performed by different operators, with the TMS operator blinded to the tDCS session. Session order was randomised and counterbalanced (http://www.rando.la) with participant characteristics matched for age, gender, and handedness.

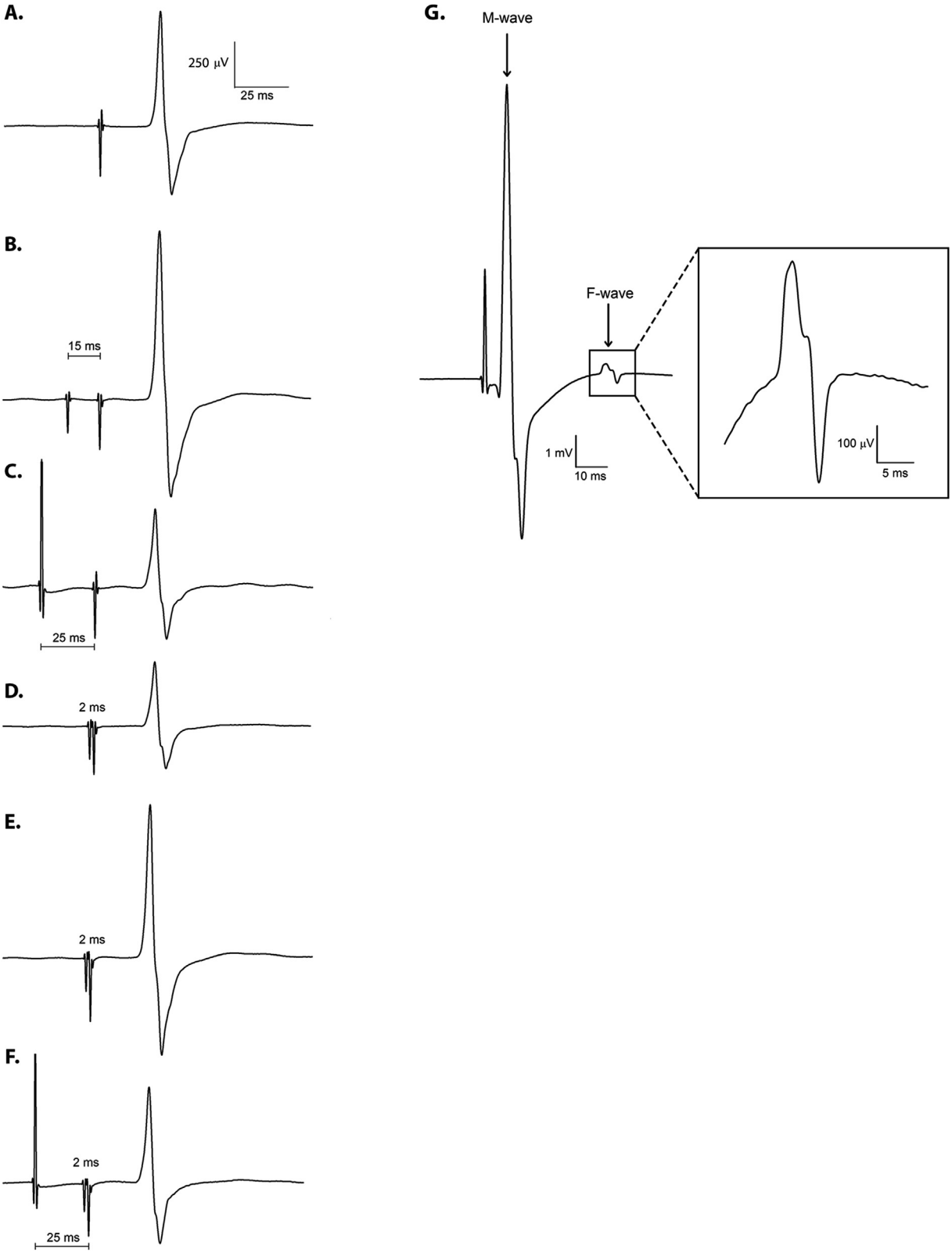

Fig. 2. Representative EMG from *first dorsal interosseous* of a typical participant showing MEPs or F-waves. A. *Non-conditioned (NC),* motor evoked potential (MEP) elicited in response to test stimulus (TS) alone, ~1 mV in amplitude. B. *Intracortical facilitation,* MEP elicited in response to TS and conditioning stimulus (CS) (*80%AMT*) at a 15 ms interstimulus interval (ISI). C. *Short-latency afferent inhibition (SAI),* MEP elicited in response to TS and transcutaneous electrical digit stimulation (3 × sensory perceptual threshold) at an ISI of 25 ms. D. *Short-interval intracortical inhibition (SICI)*, MEP elicited in response to TS and CS (*50% inhibition*) at 2 ms ISI. E. $SICI_{adj}$, MEP elicited in response to TS ($SICI_{adj}$) and CS (*50% inhibition*) at 2 ms ISI. F. *SAIxSICI,* MEP elicited in response to TS ($SICI_{adj}$), CS (*50% inhibition*) at 2 ms ISI and transcutaneous electrical digit stimulation (3 × SPT) at an ISI of 25 ms. MEP traces represent individual means. (*A,* n = 16; *B,C,D,E,F,* n = 10) G. *M- and F-wave*s in response to supramaximal ulnar nerve stimulation. Traces represent one individual mean. (n = 20).

Mesh glove stimulation

The mesh glove and sleeve (Saebo Inc, Charlotte, NC) were connected to a dual channel stimulator (Neuro Trac Rehab, Verity Medical LTD, UK). The mesh glove was connected as the anode and the mesh sleeve worn over the elbow connected as the cathode (Fig. 1). Prior to fitting, conductive cream (Thera-Cream, Saebo Inc, Charlotte, NC) was applied generously to the skin underlying the glove and sleeve areas. Stimulation was administered for 30 min at a frequency of 50 Hz and pulse width of 300 μs [17]. The stimulation intensity (range 6–8 mA) was set to 150–200% SPT, resulting in a strong tingling sensation of the hand with no muscle contractions. SPT was defined by increasing the stimulus intensity until a light tingling was felt in the hand by the participant. Participants were informed that they would receive suprasensory threshold intensity stimulation but would most likely habituate to the stimulus after several minutes.

Data analysis and statistics

EMG analysis

Peak-to-peak MEP amplitude for all TMS measures (MEP amplitude, ICF, SAI, SICI, $SICI_{adj}$ and SAIxSICI) was calculated 10–45 ms after the TS from the EMG recordings. MEPs were excluded from analysis if the root mean squared EMG was greater than 10 μV in the 50 ms preceding the stimulus. Subsequent MEPs for all measures at each time point were then trimmed removing the top and bottom 10% of trials [35]. The remaining trials were then subject to a box and whisker plot to identify and remove any potential outliers. Data points were classified as outliers using the following formula:

$$If\ data\ point < Q1 - 1.5 \times IQR,\ or > Q3 + 1.5 \times IQR$$

where Q1 is Quartile 1, Q3 is quartile 3 and IQR is the interquartile range (Q3-Q1). An additional 1% of trials were discarded due to either high level of pre-trigger root mean squared EMG or outlier detection.

The remaining trials were then averaged for each condition at each time point. For ICF, SAI and SICI a ratio of facilitation or inhibition was calculated from the conditioned/NC MEP amplitudes, where 1 indicates no change, >1 indicates facilitation and <1 indicates inhibition compared to the NC response. Note: smaller ratios indicate more inhibition.

For the SAIxSICI condition, a ratio of MEP amplitudes from SAIxSICI/$SICI_{adj}$ was calculated, where a ratio of 1 indicates no change, >1 indicates facilitation and <1 indicates inhibition compared to the NC response.

For F-wave analysis, peak-to-peak M-wave and F-wave amplitude was calculated 5–35 ms and 25–55 ms after the TS from the EMG recordings. If the F-wave peak-to-peak amplitude was ≥25 μV then it was classified as present [36]. F-wave amplitude for each trial was then analysed as a percentage of M-wave amplitude using the following formula:

$$F/M\ (\%) = (\text{F-wave amplitude} / \text{M-wave amplitude}) \times 100$$

At each time point, F-wave persistence was calculated as a percentage using the following formula:

$$\text{F-wave persistence}\ (\%) = (\text{Number of trials F-wave is present} / \text{total number of trials}) \times 100$$

Statistical analyses

To assess the validity of the facilitation and inhibition measures, one sample t-tests were performed at baseline for ICF, SAI, SICI and SAIxSICI in both the sham- and c-tDCS conditions. Paired t-tests were used to assess whether RMT, GPT time, F/M and F-wave persistence differed between sham- and c-tDCS conditions. To ensure SAI was interacting with SICI, a paired *t*-test was used to assess whether SAIxSICI differed from SAI at baseline.

A linear mixed effects (LME) model was performed on each dependent measure (MEP, ICF, SAI, SICI, SAIxSICI, RMT, GPT time, F/M, F-wave persistence) to assess the individual and combined effects of tDCS and MGS. A Shapiro-Wilk's test indicated data were not normally distributed. A square root transformation of the data provided the best outcome to better satisfy the assumption of normality required for LME models. For the overall LME the three fixed effects for each model were **Stimulation** (sham- or c-tDCS), **Time** (T1/T0, T2/T0, T3/T0, T4/T0) and the **Stimulation × Time** interaction. For the tDCS alone LME, the three fixed effects for each model were **Stimulation**, **Time** (T1/T0, T2/T0) and the **Stimulation × Time** interaction. MGS alone was assessed using the sham-tDCS condition with one fixed effect of **Time** (T1, T2, T3, T4). The Akaike information criterion was used to determine which random effects should be included in the analysis. The criterion value was lower when the analysis included the random effects *age, gender, handedness* and *physical activity level*. Thus, all tests were performed with these random effects included in the LME analyses. For all tests a significance level of $\alpha = 0.05$ was used. Multiple comparisons were corrected using a step-up procedure based on Rom's exact critical values [37]. Rom's Method only includes comparisons where $p \leq 0.05$ from the omnibus analysis, since those are the only comparisons that warrant further inspection. For example, if two of six comparisons have $p \leq 0.05$ from the omnibus analysis, then the adjusted p-value is 0.025 (i.e. $\alpha = 0.05/2$). Data are reported as mean ± standard deviation unless stated otherwise.

Linear regression

Linear regression was performed to investigate the relationship between motor performance and neurophysiology measures. A Pearson's correlation analysis was used on all measures deemed significant in the overall LME.

Results

Baseline measurements

Average baseline neurophysiological and behavioural measurements are shown in Table 1. GPT, MEP amplitude, RMT, F/M, and F-wave persistence did not differ between sham- and c-tDCS experimental sessions. In both experimental sessions normalised ICF was larger than 1 and normalised SAI, SICI and SAIxSICI were smaller than 1, indicative of facilitation and inhibition respectively. Average baseline SAIxSICI (0.74 ± 0.25) was larger than SAI (0.56 ± 0.23; $t_{36} = -3.15$, $p = 0.004$) (Fig. 3). F-waves were detected and measured from 11 of 16 participants.

Neurophysiology and behavioural data after tDCS

For SAIxSICI there was a main effect of **Stimulation** ($F_{1, 41} = 4.10$, $p = 0.049$) with less inhibition for c-tDCS (0.89 ± 0.15) than sham-tDCS (0.81 ± 0.17). All other main effects and interactions were not statistically significant (Table 2).

Neurophysiology and behavioural data after MGS

For GPT there was a main effect of **Time** ($F_{3, 28} = 4.21$, $p = 0.014$) with paired t-tests showing that performance improved from T1 (0.99 ± 0.01) to T4 (0.96 ± 0.01, $p < 0.001$). All other comparisons for

Table 1
Baseline (T0) neurophysiological and behavioural assessments.

	Sham-tDCS (x ± SD)	One sample *t*-test p-value (n = 16)	c-tDCS (x ± SD)	One sample *t*-test p-value (n = 16)	Paired *t*-test, p- value (n = 16[a], 11[b])
MEP amplitude (mV)	0.99 (±0.60)	–	0.99 (±0.26)	–	0.661
ICF	1.27 (±0.40)	**3.28E-2**	1.29 (±0.28)	**7.93E-4**	–
SAI	0.61 (±0.33)	**5.82E-4**	0.51 (±0.21)	**8.34E-7**	–
SICI	0.53 (±0.27)	**1.80E-5**	0.54 (±0.24)	**1.80E-5**	–
SAIxSICI	0.67 (±0.23)	**1.49E-4**	0.81 (±0.26)	**7.81E-3**	–
GPT (s)	61.35 (±7.63)	–	63.42 (±8.93)	–	0.270
RMT (%MSO)	50.44 (±9.34)	–	50.00 (±8.76)	–	0.724
F/M (%)	1.00 (±0.06)	–	0.81 (±0.05)	–	0.257
F Persistence (%)	88.81 (±6.49)	–	87.01 (±11.72)	–	0.482

Bold indicates a significant modified p-value ($\alpha < 0.05$). [a] RMT and GPT. [b] F/M and F persistence. F/M, F-wave amplitude normalised to M-wave amplitude; F persistence, F-wave persistence; GPT, grooved pegboard test; ICF, intracortical facilitation; MEP, motor evoked potential; RMT, rest motor threshold; SAI, short afferent inhibition; SAIxSICI, short afferent inhibition with short interval intracortical inhibition; SICI, short interval intracortical inhibition; tDCS, transcranial direct current stimulation.

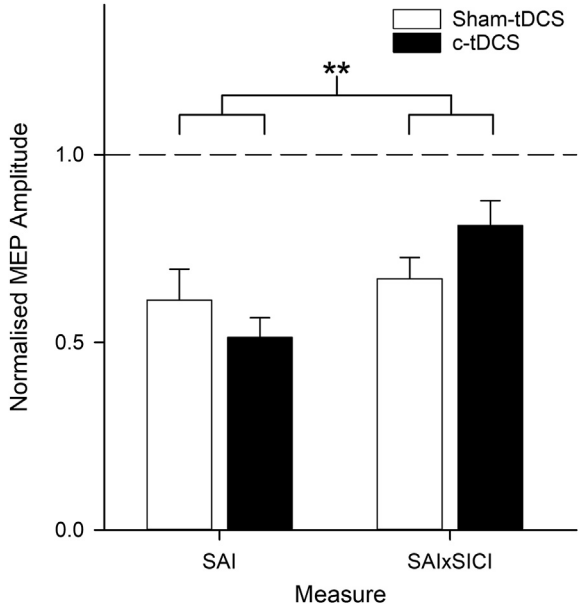

Fig. 3. Baseline short-latency afferent inhibition (SAI) and SAI with short-interval intracortical inhibition (SAIxSICI). SAI data from each session are normalised to the non-conditioned motor evoked potential (MEP) amplitude that produced 1 mV. SAIxSICI data from each session are normalised to the MEP amplitude of the adjusted test stimulus that produced a MEP 1 mV in the presence of SICI. MEP amplitude was suppressed to a greater extent with SAI than SAIxSICI. Bars represent group means + SEM (n = 16). **P < 0.01.

GPT were not significant ($p > 0.1$). There were no main effects for any other dependent measures after MGS alone (Table 3).

Effects of primed mesh glove stimulation

For GPT time there was a main effect of **Stimulation** ($F_{1, 99} = 6.15$, $p = 0.015$) with performance improvement greater for c-tDCS (0.96 ± 0.05) compared to sham-tDCS (0.98 ± 0.04) (Table 4, Fig. 4a). For GPT there was also a main effect of **Time** ($F_{3, 54} = 7.93$, $p < 0.001$) with performance improving from T1 (0.98 ± 0.04) to T2 (0.98 ± 0.05), T3 (0.96 ± 0.04), and T4 (0.95 ± 0.04) (Table 4). For RMT there was a main effect of **Stimulation** ($F_{1, 99} = 12.16$, $p = 0.001$) with c-tDCS (1.00 ± 0.04) having a higher threshold than sham-tDCS (0.99 ± 0.03) (Table 4, Fig. 4b). For MEP amplitude, ICF, SICI, F/M (average ratio for each time point: sham-tDCS ranged between 0.008 and 0.011, c-tDCS ranged between 0.008 and 0.010) and F-wave persistence (average persistence for each time point: sham-tDCS ranged between 87% and 90%, c-tDCS ranged between 84% and 88%) there were no overall main effects or interactions found (Table 4, Fig. 4c and d). For SAI there was a main effect of **Stimulation** ($F_{1, 103} = 7.53$, $p = 0.007$) with greater disinhibition after c-tDCS (1.16 ± 0.28) than sham-tDCS (1.04 ± 0.27) (Table 4, Fig. 4e). For SAIxSICI there was a main effect of **Stimulation** ($F_{1, 96} = 6.96$, $p = 0.010$) with less disinhibition after c-tDCS (1.00 ± 0.19) than sham-tDCS (1.10 ± 0.27) (Table 4, Fig. 4f). There were no correlations between significant measures at any time points (all $p > 0.1$).

Table 2
Statistical Results from Linear Mixed Effects Model for tDCS Effect between Baseline (T0) and Post-tDCS (T1 only).

	Model Term	df (num, den)	F	P- value
GPT	Stimulation	1, 43	0.63	0.433
	Time	1, 43	3.01	0.090
	Stimulation x Time	1, 43	0.58	0.451
RMT	Stimulation	1, 39	0.00	0.989
	Time	1, 39	0.01	0.922
	Stimulation x Time	1, 39	0.22	0.640
MEP	Stimulation	1, 36	0.02	0.889
	Time	1, 36	0.11	0.741
	Stimulation x Time	1, 36	0.65	0.425
ICF	Stimulation	1, 49	0.45	0.506
	Time	1, 49	0.01	0.944
	Stimulation x Time	1, 49	0.02	0.888
SAI	Stimulation	1, 40	0.25	0.623
	Time	1, 40	1.20	0.281
	Stimulation x Time	1, 40	0.70	0.407
SICI	Stimulation	1, 62	0.36	0.552
	Time	1, 62	0.20	0.653
	Stimulation x Time	1, 62	0.52	0.476
SAIxSICI	Stimulation	1, 41	4.10	**0.049**
	Time	1, 41	0.10	0.752
	Stimulation x Time	1, 41	0.06	0.816
F/M	Stimulation	1, 26	0.38	0.544
	Time	1, 26	0.00	0.980
	Stimulation x Time	1, 26	0.71	0.407
F persistence	Stimulation	1, 23	1.13	0.298
	Time	1, 23	0.84	0.370
	Stimulation x Time	1, 23	0.00	0.969

Bold indicates a significant p-value ($\alpha < 0.05$). Den; denominator; df, degrees of freedom; F/M, F-wave amplitude normalised to M-wave amplitude; F persistence, F-wave persistence; GPT, grooved pegboard test; ICF, intracortical facilitation; MEP, motor evoked potential; num, numerator; RMT, rest motor threshold; SAI, short latency afferent inhibition; SAIxSICI, short latency afferent inhibition with short interval intracortical inhibition; SICI, short interval intracortical inhibition.

Table 3
Statistical Results from Linear Mixed Effects Model for Mesh-Glove Effect between T1 and T4 Normalised to Baseline (T0) for Sham-tDCS only.

	Model Term	df (num, den)	F	P- value
GPT	Time	3, 28	4.21	**0.014**
RMT	Time	3, 17	0.80	0.509
MEP	Time	3, 24	1.07	0.379
ICF	Time	3, 26	1.70	0.191
SAI	Time	3, 20	1.08	0.379
SICI	Time	3, 23	0.09	0.963
SAIxSICI	Time	3, 27	0.53	0.668
F/M	Time	3, 16	1.38	0.285
F persistence	Time	3, 14	2.90	0.072

Bold indicates a significant p-value ($\alpha < 0.05$). Den; denominator; df, degrees of freedom; F/M, F-wave amplitude normalised to M-wave amplitude; F persistence, F-wave persistence; GPT, grooved pegboard test; ICF, intracortical facilitation; MEP, motor evoked potential; num, numerator; RMT, rest motor threshold; SAI, short afferent inhibition; SAIxSICI, short afferent inhibition with short interval intracortical inhibition; SICI, short interval intracortical inhibition.

Table 4
Omnibus linear mixed effects model for Post-tDCS and MGS (T1-T4) data normalised to baseline (T0).

	Model Term	df (num, den)	F	P- value
GPT	Stimulation	1, 99	6.15	**0.015**
	Time	3, 54	7.93	**1.78E-4**
	Stimulation x Time	3, 54	0.08	0.972
RMT	Stimulation	1, 99	12.16	**0.001**
	Time	3, 46	0.07	0.975
	Stimulation x Time	3, 46	0.91	0.445
MEP	Stimulation	1, 103	3.58	0.061
	Time	3, 48	1.19	0.324
	Stimulation x Time	3, 48	0.14	0.938
ICF	Stimulation	1, 98	0.24	0.627
	Time	3, 44	0.21	0.892
	Stimulation x Time	3, 44	2.27	0.094
SAI	Stimulation	1, 103	7.53	**0.007**
	Time	3, 48	1.25	0.301
	Stimulation x Time	3, 48	0.54	0.659
SICI	Stimulation	1, 70	0.00	0.981
	Time	3, 39	0.16	0.924
	Stimulation x Time	3, 39	0.31	0.821
SAIxSICI	Stimulation	1, 96	6.96	**0.010**
	Time	3, 55	0.08	0.970
	Stimulation x Time	3, 55	1.08	0.366
F/M	Stimulation	1, 51	2.39	0.128
	Time	3, 34	1.44	0.249
	Stimulation x Time	3, 34	0.28	0.839
F persistence	Stimulation	1, 51	0.01	0.931
	Time	3, 34	2.82	0.054
	Stimulation x Time	3, 34	0.10	0.962

Bold indicates a significant p-value ($\alpha < 0.05$). Den; denominator; df, degrees of freedom; F/M, F-wave amplitude normalised to M-wave amplitude; F persistence, F-wave persistence; GPT, grooved pegboard test; ICF, intracortical facilitation; MEP, motor evoked potential; num, numerator; RMT, rest motor threshold; SAI, short latency afferent inhibition; SAIxSICI, short latency afferent inhibition with short interval intracortical inhibition; SICI, short interval intracortical inhibition.

Discussion

There were several novel and confirmatory findings. In support of the hypothesis, visuomotor hand dexterity, as measured on GPT task, improved after MGS and was even greater when primed with c-tDCS. Further evidence of the hypothesis was observed with a greater decrease in SAI with c-tDCS primed MGS compared to sham, indicative of a priming effect. Priming MGS with c-tDCS decreased the effects of SICI on SAI, leading to less SAI compared to sham. Similarly, RMT increased following c-tDCS primed MGS compared to sham. The pattern of neurophysiological effects and motor performance after c-tDCS primed MGS are characteristic of metaplasticity.

Neurophysiological effects of c-tDCS

Single- and paired-pulse TMS, spinal excitability and motor performance were not modulated by c-tDCS. For example, RMT was not affected by c-tDCS corroborating previous studies [12,38]. RMT is thought to reflect neuronal membrane excitability [39]. The mode of tDCS may be confined to intracortical neurons, and may explain the lack of RMT modulation [33,40]. For SAI in the presence of SICI, a main effect of stimulation, but no interaction with time, was noted between real and sham sessions perhaps owing to lower baseline values for the sham session (see Supplementary Table 1). There were no other effects of c-tDCS [11–13]. The lack of other CME modulation after c-tDCS, may be due to high inter-individual variability, perhaps owing to differences in tDCS parameters such as electrode size, montage, duration and intensity, and participant characteristics such as age and genetic polymorphisms of neurotrophins implicated in M1 plasticity induction [41–44].

Neurophysiological and behavioural effects of MGS

Motor performance on GPT improved after MGS, similar to previous findings on GPT after associative neuromuscular electrical stimulation [23]. However, there was no control group that received both sham-tDCS and sham-MGS in the present study. While improvements in GPT performance after MGS cannot be dissociated from simply repeating the task five times, MGS applied during GPT training has previously been shown to improve motor performance compared to bare hand training [21].

In contrast to previous studies, MGS alone (i.e., after sham-tDCS) did not reduce motor threshold or inhibition, or increase motor cortex excitability [17,18]. Differences in experimental procedures may have contributed to these discrepancies. Previous studies administered MGS using a common anode and two separate 4×3 cm electrodes placed over the foreman flexors and extensors as cathodes [17,18]. Perhaps, the more proximal location of the cathode with the sleeve over the elbow used in the current study produced stimulation over a larger area resulting in a dispersal of stimulation. Similarly, conditioning and test stimulus intensities were not adjusted post stimulation to correct for changes in motor threshold over time as previously done [17,18]. However, as there was no change in MEP amplitude over time or through sessions, we can be confident the test stimulus remained constant throughout.

Effects due to homeostatic vs. non-homeostatic metaplasticity

The present study showed a greater improvement in GPT after c-tDCS primed MGS compared with sham + MGS [45,46]. This finding corroborates the homeostatic principle where motor performance is enhanced when the threshold for inducing synaptic plasticity is decreased by previously lowering neuronal activity [9]. MEP amplitude after c-tDCS was not decreased in the present study. However, it is possible for c-tDCS to not overtly decrease CME but have the capacity to prime [47,48]. There was also no concomitant increase in MEP amplitude after MGS [49]. It is plausible that the two interventions may not be optimal for a strong metaplastic interaction due to activation of distinct neuronal circuits. For example, tDCS administered over M1 modulates excitability at a global level [50], whereas MGS likely activates sensory afferents and modulates excitability at a synapse-specific level [51]. As

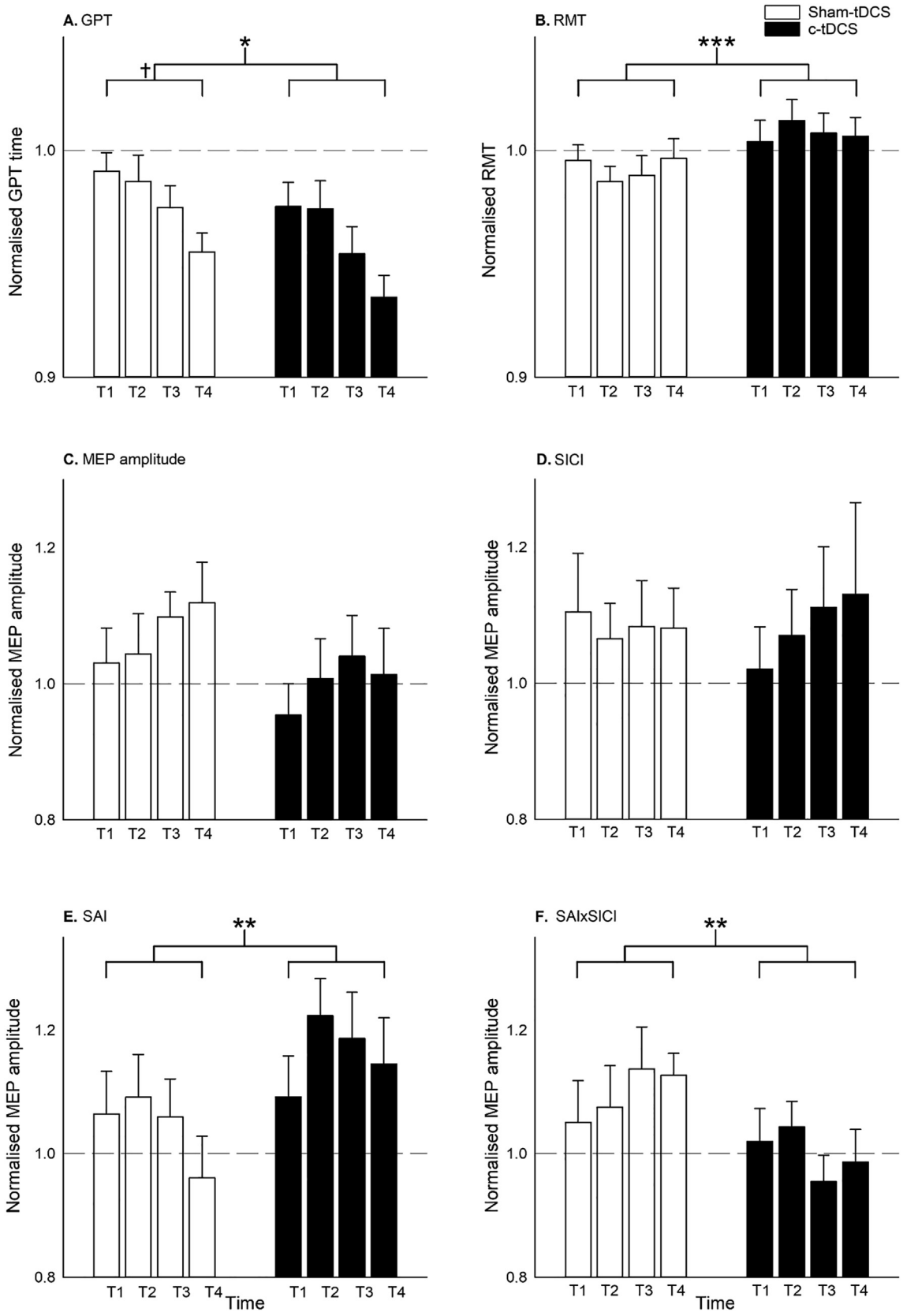

Fig. 4. Overall effects of sham-(open bars) and cathodal-(filled bars) transcranial direct current stimulation (tDCS) and mesh glove stimulation (MGS) on neurophysiological and behavioural measures. Data from all time points are normalised to the baseline (T0) of each session. T1: immediately post tDCS, T2: immediately post MGS, T3: 30 min post MGS, T4: 60 min post MGS. A value of 1 (dashed line) indicates no change from baseline. A, Grooved pegboard test (GPT), showing a main effect of STIMULATION and TIME. B, Rest motor threshold (RMT), showing a main effect of STIMULATION. C, Motor evoked potential (MEP) amplitude. D, Short-interval intracortical inhibition (SICI). E, Short-latency afferent inhibition (SAI) showing a main effect of STIMULATION. F, SAI with SICI, showing a main effect of STIMULATION. Bars represent group means + SEM (n = 16). Overall LME:*P < 0.05, **P < 0.01, ***P < 0.001, MGS alone LME:†P < 0.05.

expected, spinal motoneuron excitability assessed using F-wave amplitude and persistence was not affected by c-tDCS [52] and MGS [17]. This finding lends support to the idea that c-tDCS and MGS produce neuromodulatory effects at a supraspinal level. Therefore, c-tDCS priming may have modulated behaviour in the absence of direct effects on CME (MEP amplitude) between T0 and T1.

Enhanced GPT performance after c-tDCS primed MGS was accompanied by reduced SAI. After c-tDCS primed MGS there was reduced SAI (disinhibition), indicative of modulation along cholinergic and GABA-ergic sensorimotor pathways [14]. Disinhibition of SAI was greater than disinhibition of SICI. It may be that SAI mediated interneurons are more likely to cause a greater disinhibition of the common SAIxSICI corticospinal neuron than SICI interneurons. The reduced inhibition from SICI acting on SAI observed immediately after tDCS was followed by a gradual increase (return of) inhibition thirty-sixty minutes post c-tDCS primed MGS, although SAI remained in a disinhibited state overall. In a previous study, SICI in the presence of SAI did not influence plasticity induction in human M1 [53]. The mechanisms responsible for these effects remain unclear and warrant further investigation.

A non-homeostatic mechanism may account for the greater motor improvement after c-tDCS primed MGS and cannot be excluded. One possible mechanism is “gating”, whereby the existing state of postsynaptic excitability (high or low) facilitates (or “gates”) excitability change (increase or decrease) in the same direction [9]. However, gating occurs through the weakening of intracortical inhibitory circuits concurrently with motor practice or plasticity inducing protocols [9]. Therefore, exploring the potential role of gating in the current paradigm will require the application of concurrent tDCS and MGS.

There are potential clinical implications from the present study. In chronic stroke, MGS to the paretic limb has been shown to improve limb function and sensation [16], perhaps due to an increase in CME observed in the contralateral M1 [17,18]. In general, c-tDCS primed MGS does not modify excitability induced with MGS alone, perhaps due to non-homeostatic metaplasticity mechanisms. Future research could examine whether an LTP-like protocol such as anodal-tDCS could up-regulate CME increases obtained after MGS.

The present study has a number of limitations. First, a sham-MGS condition was not included so we are unable to purely assess the effects of MGS alone. Successful sham-MGS has been achieved in studies using subsensory threshold stimulation where both the real and sham stimulation are below perceivable threshold [16]. However, when using suprasensory threshold stimulation, it is less conceivable to deliver a realistic sham stimulation. Second, performing the GPT prior to MEP measures may have diminished the effects of tDCS priming or MGS [54]. Despite this limitation, metaplastic effects on SAI were still observed. Third, due to time constraints, the current study only measured CME and motor function for up to 60 min post stimulation, compared to previous reports which had longer follow-ups [21,55–57]. Finally, priming MGS with a protocol that relies on input specificity, such as paired associative stimulation [58], may provide a better understanding of potential homosynaptic interactions.

In conclusion, c-tDCS primed MGS produced metaplastic effects within M1, paralleled by an improvement in motor performance. Hence, c-tDCS may be an effective priming modality to induce metaplasticity via homeostatic or non-homeostatic mechanisms.

Conflicts of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Author contributions

Conceived and designed the experiments: AT JC WB. Performed the experiments: AT. Analysed the data: AT JC WB. Wrote and edited the manuscript: AT JC WB.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.02.010.

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