Puri, R, Hinder, MR, Canty, AJ and Summers, JJ

Facilitatory non-invasive brain stimulation in older adults: the effect of stimulation type and duration on the induction of motor cortex plasticity.

Facilitatory non-invasive brain stimulation in older adults: the effect of stimulation type and duration on the induction of motor cortex plasticity.

Rohan Puri[1*], Mark R. Hinder[1], Alison J. Canty[2], and Jeffery J. Summers[1, 3].

1. Sensorimotor Neuroscience and Ageing Laboratory, School of Medicine, Faculty of Health, University of Tasmania, Hobart, Australia.
2. Wicking Dementia Research and Education Centre, Faculty of Health, University of Tasmania, Hobart, Australia.
3. Research Institute of Exercise and Sport Sciences, Liverpool John Moores University, Liverpool, United Kingdom.

* Correspondence:

Rohan Puri
Sensorimotor Control and Ageing Laboratory, Private Bag 30,
School of Medicine, Faculty of Health,
University of Tasmania,
Hobart, TAS 7001
Australia

E: rohan.puri@utas.edu.au

P: +61 3 6226 2558

Key words: transcranial magnetic stimulation, theta burst stimulation, transcranial direct current stimulation, older adults, non-invasive brain stimulation, plasticity.

Abstract

Despite holding significant promise for counteracting the deleterious effects of ageing on cognitive and motor function, little is known of the effects of facilitatory non-invasive brain stimulation (NBS) techniques on corticospinal excitability (CSE) in older adults.

Thirty-three older adults (≥ 60 years) participated in four NBS sessions on separate days receiving 10 and 20 min anodal transcranial direct current stimulation (atDCS), and 300 and 600 pulses of intermittent theta burst stimulation (iTBS) over the left M1. Motor evoked potentials measured in the contralateral hand served as a measure of CSE before, and for 30 min following each NBS intervention.

At the group level, generalized post-stimulation CSE increases were observed ($p < 0.001$) with no significant differences between the two durations of each stimulation type (atDCS: $p = 0.5$; iTBS: $p = 0.9$). For individuals exhibiting overall facilitatory change to atDCS ("responders", $n = 10$), 20 min atDCS resulted in longer lasting CSE facilitation than 10 min. No such difference was observed between the two iTBS protocols.

Considerable variability was observed *inter*-individually – where 52-58% of the cohort exhibited the expected facilitation after each of the NBS protocols – as well as *intra*-individually, where 45-48% of the cohort maintained consistent post-stimulation responses across the varying durations and types of stimulation.

In conclusion, as shown previously in young adults, older adults demonstrate substantial variability in response to different facilitatory NBS protocols. Studies to assess the intra-individual reliability of these protocols are critical to progress towards translation of appropriate protocols (i.e. those that elicit the greatest response for each individual) into clinical practice.

Acknowledgements

The research was supported by a National Health and Medical Research Council Project Grant (APP1050261; JJS, AJC, and MRH) and an Australian Research Council Discovery Project (DP130104317; JJS and MRH). The authors would like to thank Emily L. Goss for assistance with data collection and Michael I. Garry for helpful conversations regarding data analyses. Lastly, the authors would like to sincerely acknowledge all participants for volunteering their valuable time.

Introduction

Healthy ageing is associated with widespread declines in cognitive (Deary et al. 2009) and motor (Seidler et al. 2010) function, having a significant impact on an individual's daily activities and quality of life. Projections suggest that the number of persons aged 60 or over worldwide will double from 901 million in 2015 to about 2 billion by 2050 and will keep expanding at a significantly higher rate than the world population (United Nations 2015). In this respect, interventions that may slow, or even reverse, age-related declines have gained significant attention. Indeed, non-invasive brain stimulation (NBS) techniques - with their ability to modulate corticospinal excitability (CSE) beyond the duration of stimulation - hold considerable appeal in the modulation of behavioural function in older adults (Hsu et al. 2015; Summers et al. 2016).

Two widely used facilitatory NBS techniques, with respect to changes in corticospinal excitability they purportedly induce, are intermittent theta burst stimulation (iTBS) and anodal transcranial direct current stimulation (atDCS). iTBS is a patterned form of repetitive transcranial magnetic stimulation (rTMS) - involving 2s bursts of three 50 Hz pulses every 200ms for a total duration of 192s - demonstrated to have an excitatory effect on corticospinal excitability, inducing LTP-like plasticity effects (Huang et al. 2005). In contrast, atDCS involves the delivery of a weak current between a pair of electrodes - usually with the anode over a targeted cortical region and cathode over a reference location - resulting in membrane potential changes that lead to facilitatory effects on corticospinal excitability (Nitsche and Paulus 2000). Although not entirely overlapping in regards to their underlying mechanisms, pharmacological studies have implicated NMDA receptor-dependent glutamergic transmission in mediating the LTP-like after-effects of both iTBS (Huang et al. 2007) and atDCS (Nitsche et al. 2003).

Despite the aforementioned seminal studies that reported robust group level effects of facilitatory NBS protocols, a number of recent studies in young adults have begun to report a lack of group level efficacy and considerable individual variability in regards to the magnitude of post-stimulation facilitation (i.e. amplitude of motor evoked potentials). Typically, only approximately half of the tested sample exhibit the expected facilitatory response to both iTBS (Hamada et al. 2013; Lopez-Alonso et al. 2014; Vallence et al. 2013) and atDCS (Lopez-Alonso et al. 2014) with the remaining participants exhibiting either an opposite (inhibitory) effect, or exhibiting little to no modulation. On an *intra-individual* level too, a similar magnitude of variability has been reported in regards to test-retest paradigms (iTBS: Hinder et al. 2014; atDCS: Lopez-Alonso et al. 2015) as well as manipulations of stimulation parameters, such as intensity of atDCS (Chew et al. 2015).

Given the potential impact that facilitatory NBS protocols could have at reducing or slowing any deleterious effects of healthy ageing on motor function, it is perhaps surprising that little research has been conducted to investigate group level efficacy and individual variability in older adults. Characterizing this variability is important not only on an inter-individual level for different NBS techniques but also on an intra-individual level for different types of NBS techniques and for manipulations of technical parameters. Krause and Cohen Kadosh (2014) highlight this in a recent review on transcranial electrical stimulation (tES) stating that "…using tES may also lead to beneficial behavioural effects in the elderly but it is unclear how the type and dosage of the stimulation affects elderly individuals differently from

younger age groups.", concluding that the evidence on "… the effects of tES in elderly populations is currently extremely scarce."

Consequently, the aim of this *within-subject* study was to investigate - in a cohort of healthy, community dwelling, older adults - group level efficacy and individual variability in response to two facilitatory NBS protocols, atDCS and iTBS, and two variants (duration) of each stimulation. To this end, all older participants received, over the left primary motor cortex, in four separate sessions - 10 or 20 min atDCS and 300 or 600 pulses of iTBS. Moreover, to test for possible determinants of individual NBS responses, participants underwent an initial session in which various measures of trait motor function (dexterity, grip strength, standing balance, gait speed, and endurance) were recorded.

Methods

2.1 Participants

Thirty-three healthy older adults (mean age = 65.97 years, S.D. = 4.75 years; 21 females) aged between 60 and 76 years participated in five separate sessions. All except one (who was left-handed) self-declared right-hand dominance. Participants were screened for cognitive integrity using the Mini-Mental State Examination (Dick et al. 1984) with all participants scoring within a normal range (score $\geq$ 26). Furthermore, contra-indications to NBS techniques were assessed using a medical history questionnaire and all participants were free of neuromuscular or neurological dysfunction. The study was approved by the Tasmanian Human Research Ethics Committee Network and all participants provided written informed consent prior to participation in the study, conducted in accordance with the Declaration of Helsinki.

2.2 Experimental procedure

Participants attended five sessions of 2 hours duration each on separate days. The first session involved, amongst other neuropsychological tests not reported here, trait motor function assessment using the NIH Toolbox Motor Battery (Reuben et al. 2013). Following this, participants underwent four NBS sessions – atDCS of two durations (10 and 20 min) and iTBS with two train lengths (300 and 600 pulses), receiving only one stimulation per session. Within the manuscript the duration of atDCS/train length of iTBS is referred to as stimulation 'duration', and atDCS/iTBS as stimulation 'type'.

All atDCS sessions[1] were conducted prior to iTBS sessions, and the duration factor was counterbalanced within each stimulation type. For each participant, all NBS sessions were conducted at least 72 hours apart to prevent any carry over effects from the previous session and at a similar time of the day to minimize the effect that diurnal fluctuations of cortisol have on corticospinal excitability (Sale et al. 2008). Muscle activation in the forearm and hand muscles was minimized by resting the seated participant's right arm on a pillow. Following standard procedures, motor hotspot and motor thresholds were established (see Section 2.4 below). Baseline cortical excitability was then measured in two separate blocks of TMS conducted 5 mins apart. Participants were then administered NBS, after which corticospinal excitability was examined every 5 minutes for a 30 min period (Fig. 1).

[1] We have reported some aspects of the atDCS data that are not related to the current study elsewhere (Puri et al. 2015).

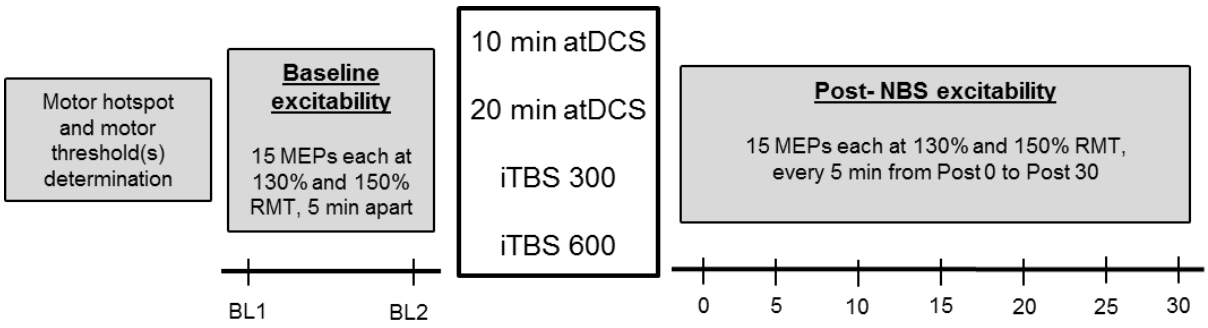


Fig. 1 For each participant, motor hotspot and motor threshold(s) were determined, following which baseline corticospinal excitability was measured (two blocks, 5 min apart). In four separate sessions, participants then received 10 min atDCS, 20 min atDCS, 300 pulses of iTBS, and 600 pulses of iTBS, followed by post-NBS excitability measurement (7 blocks – Post 0 to Post 30, 5 min apart)

2.3 Trait motor function assessment

The NIH Toolbox Motor Battery includes 5 instruments measuring key components of motor function; a) dexterity b) muscle strength c) standing balance d) locomotion and e) cardiorespiratory and muscle endurance, as outlined in detail by Reuben and colleagues (2013). Briefly, dexterity was measured by the time required to accurately place and remove plastic pegs in a 9-hole pegboard, muscle strength by squeezing a digital dynamometer as hard as possible, standing balance by recording postural sway using an accelerometer in various poses (eyes open/closed on a solid/foam surface), locomotion by measuring gait speed over a 4-meter course and lastly, muscle/cardiorespiratory endurance by measuring the total distance walked as fast as possible in 2 minutes. Participants were given the opportunity of adequate rest between tests.

2.4 Transcranial magnetic stimulation and electromyography

Surface electrodes (Ag/AgCl) were placed over the right first dorsal interosseous (FDI) in a belly-tendon montage to measure EMG activity using a 16-bit AD system (CED 1902, Cambridge, UK) with signals sampled at 4000 Hz, band- pass filtered (20-1000 Hz), and amplified with a gain of 1000. Using a standard figure of eight coil (internal diameter of 70mm), connected to a Magstim 200^2 stimulator (Magstim Company, Dyfed, UK), single pulse TMS was applied over the left motor cortex. To ensure current flow in the brain was in the optimal posterior-anterior direction, the TMS coil was held tangentially to the scalp with the handle pointing ~45 degrees backwards. Standard procedures were used to determine the motor 'hotspot' and marked using a felt-tip pen (Puri et al. 2015).

Resting motor threshold (RMT) - defined as the lowest stimulator intensity required to evoke motor evoked potentials (MEPs) of $\geq$ 50μV in three out of five consecutive trials (Carroll et al. 2001; Hinder et al. 2010) was determined for each participant's right FDI at the beginning of each session. Fifteen single TMS pulses with a fixed inter-stimulus interval of 5s were delivered randomly at each of two intensities, 130% and 150% RMT, to assess corticospinal excitability at all time-points (before and after the administration of NBS - see Fig. 1). Active motor threshold (AMT) - defined as the minimum intensity required to evoke MEPs of $\geq$ 200 μV in three out of five consecutive trials using a Magstim Super Rapid^2 stimulator and figure-

of-eight coil (Hinder et al. 2014) was determined during voluntary contraction of the right FDI at 10% of an individual's maximum voluntary contraction (MVC), maintained using visual feedback. MVC was determined by asking participants to isometrically abduct their right index finger as hard as possible against a force transducer 3 times (2s each time with ~ 10s rest between each contraction) and averaging the peak value of those 3 contractions. RMT and AMT were determined for both iTBS sessions, whereas only RMT was determined for atDCS sessions.

2.5 Intermittent theta burst stimulation

Using the Magstim Super Rapid^2 stimulator, iTBS was delivered over the motor hotspot at 80% of AMT for each participant. iTBS involves 2 s trains (3 pulses at 50 Hz repeated at 5 Hz) of stimulation occurring every 10 s, either for a total of 92 s (300 pulses) or 192 s (600 pulses) (Huang et al. 2005).

2.6 Anodal transcranial direct current stimulation

Direct current stimulation was delivered via anodal (5cm x 5cm) and cathodal (6cm x 8.5 cm) conductive rubber electrodes placed in saline soaked sponges using HDCStim™, a battery-operated constant direct current stimulator (Newronika s.r.l., Milan, Italy). Participants received either 10 or 20 mins of 1.5 mA atDCS with the anode placed over the FDI representation within the left M1 and the cathode placed over the right supraorbital region. Current was ramped up from 0 to 1.5 mA over 7s, where it was maintained for the duration of the stimulation. Participants were made aware that they might feel a mild itching sensation under the electrodes with impedance always monitored throughout the session and kept below 10 kΩ. Participants were instructed to look passively forwards and keep their hands stationary and relaxed for the duration of the stimulation.

2.7 Data processing, analysis and statistical procedures

Peak-to-peak MEP amplitude in the right FDI in a time window 10 - 100 ms following TMS was used as a measure of CSE within each stimulation trial. Trials that were contaminated with muscle activity - determined visually and using root mean square analysis (greater than 0.025 mV in a 50 ms time window immediately prior to the TMS pulse) - were excluded from further analysis due to the effect of background EMG activity on MEP amplitude. Following this, average peak-to-peak MEP amplitude (in mV) was determined across the 30 TMS pulses for each NBS protocol at every time point (two baseline and seven post-NBS blocks). Averaging across both baseline blocks, differences in baseline CSE between the four NBS protocols were investigated using a one-way repeated measures ANOVA with the factor of NBS (atDCS10, atDCS20, iTBS300, iTBS600). Considering no baseline differences in CSE were observed between the four NBS protocols (see Section 3.1.1), MEP amplitude at each of the seven post-stimulation time-points was normalized to the average MEP amplitude of both the baseline blocks combined for each protocol separately. Data were then subjected to various statistical analyses to investigate post-stimulation changes in CSE, both on a group and individual level, as outlined below.

2.7.1 Group level analyses

Normalized post-stimulation MEP values were natural log-transformed to address violations of normality as revealed by significant Kolmogorov-Smirnov tests.

Post-stimulation changes in CSE due to different stimulation durations were analysed separately for atDCS (atDCS10 vs. atDCS20; Section 3.1.2) and iTBS (iTBS300 vs. iTBS600; Section 3.1.3) for the whole sample as well as for 'responders' to both stimulation durations (see Section 2.7.2 for operational definition of 'responders'). To this end, two-way repeated measures ANOVAs were conducted with factors of DURATION (atDCS10 vs. atDCS 20 OR iTBS300 vs. iTBS600) and TIME (Post 0, 5, 10, 15, 20, 25, 30) with pairwise comparisons utilized for follow up analyses.

In addition, to compare post-stimulation CSE changes between all four NBS protocols, a two-way repeated measures ANOVA was conducted with factors of NBS (atDCS10, atDCS20, iTBS300, iTBS600) and TIME (Post 0, 5, 10, 15, 20, 25, 30) for the whole sample. This analysis could not be conducted for responders only due to the low number of participants who displayed an excitatory response to *all four* NBS protocols ($n = 4$; see Section 3.2.2).

Significant differences in grand mean values relative to 0 for all the aforementioned analyses were interpreted as significant changes in post-stimulation CSE compared to baseline CSE, averaged across all within-subjects factors, with back-transformed log-ratios providing geometric means of the normalized data.

2.7.2 Individual level analyses

Inter-individual variability was characterized using two standard approaches. Firstly, for every participant, a grand average (GA) post-stimulation response was calculated - based on the mean of all normalized post-stimulation time points - for each NBS protocol. Using a 10% cut-off as representing a possibly clinically relevant change in CSE (Hinder et al. 2014), participants were grouped as those who exhibited an 'excitatory response' ($GA > 1.1$; 'responders'), 'no response' ($0.9 < GA < 1.1$) or 'inhibitory response' ($GA < 0.9$). Chi-square goodness of fit tests were then conducted, for each NBS protocol separately, to determine if participant numbers in each grouping differed significantly from a random distribution (i.e. 11 participants in each category). Secondly, since GA analysis does not take into account the *temporal pattern* of post-stimulation response, SPSS TwoStep cluster analyses were used to determine the presence of any clusters for each NBS protocol.

Intra-individual variability in response to different durations of stimulation (atDCS10 vs. atDCS20 and iTBS300 vs. iTBS600) as well as to the two different types of stimulation (averaged atDCS vs. averaged iTBS) was investigated by conducting correlation analyses using GA values. Lastly, frequency analyses (i.e., the number of participants) were conducted to characterize the extent of variation in post-stimulation response across the four NBS protocols.

2.7.3 Predictors of NBS response

For all trait motor assessment tests, unadjusted scale scores (raw scores normalized to the entire normative representative sample of the NIH Toolbox with a mean of 100 and SD of 15) were utilized except for the muscle strength test where fully-adjusted scale scores were used as normalization takes into account expected gender differences. Higher scores indicate better performance.

Correlation analyses were then conducted for each NBS protocol separately, between an individual's GA response and trait motor function scores as well as between GA response and

resting motor threshold intensity (% of MSO) to investigate any possible predictors of NBS response.

IBM SPSS Statistics 21 (Armonk, NY, USA) was used for all statistical procedures and the *a-priori* level of two-tailed significance was set at 0.05. Huynh- Feldt adjusted values are reported if the assumption of sphericity was violated as indicated by a significant Mauchly's test of sphericity. Bonferroni multiple comparisons correction was utilized where applicable. Partial eta squared (η_p^2), Cohen's *d*, and Pearson's *r* are provided for ANOVAs, Student's t-tests, and correlations respectively to assist in the interpretation of inferential statistics. Cut-offs ≥ 0.01 small, ≥ 0.06 medium, ≥ 0.14 large were applied for η_p^2 and ≥ 0.2 small, ≥ 0.5 medium, ≥ 0.8 large were applied for Cohen's *d* where appropriate (Sink and Stroh 2006).

Results

All results are reported as means ± 95% confidence intervals (CI). Two participants' standing balance test data could not be collected due to technical difficulties.

3.1 Group level analyses

In this subsection, analysis was conducted to probe baseline differences in CSE, after which post-stimulation responses were analysed for each stimulation type separately as well as for all four NBS protocols together.

3.1.1 Baseline corticospinal excitability

One-way ANOVA revealed no statistically significant difference in baseline corticospinal excitability between the four NBS sessions as evidenced by a non-significant main effect of NBS, F (3, 96) = 0.348, p = 0.791, η_p^2 = 0.011. Accordingly, any differences in post-stimulation response to NBS cannot be explained by differences in baseline excitability.

3.1.2 atDCS10 vs. atDCS20

Across the whole participant cohort (N = 33), a significant general increase in CSE was observed (7.14% ± 5.50%), averaged across both durations of atDCS compared to baseline, as revealed by a statistically significant grand mean effect, F (1, 32) = 7.012, p = 0.012, η_p^2 = 0.180, which was associated with a large effect size. No significant differences were detected between atDCS10 and atDCS20 as the main effect of DURATION, F (1, 32) = 0.385, p = 0.539, η_p^2 = 0.012, and the interaction effect between DURATION and TIME, F (1, 32) = 0.085, p = 0.998, η_p^2 = 0.003, were not statistically significant (Fig. 2a; left panel).

However, when we consider only the responders (GA > 1.1 to both atDCS10 *and* atDCS20; n = 10), a main effect of DURATION, F (1, 9) = 5.241, p = 0.048, η_p^2 = 0.368, was observed such that atDCS20 (35.66% ± 9.64%) caused significantly greater increase in CSE compared to atDCS10 (20.08% ± 7.90%) (Fig. 2b; left panel). The interaction effect between DURATION and TIME approached statistical significance, F (6, 54) = 2.093, p = 0.069, η_p^2 = 0.189. As this interaction was associated with a large effect size, and due to its potential significance, we conducted follow-up analyses. These indicated that the difference between atDCS10 and atDCS20 was significant at late time points, i.e., Post 25 (p = 0.007, d = 0.97) and Post 30 (p = 0.011, d = 0.95). Indeed at these time points, CSE was still significantly above baseline for atDCS20, but not for atDCS10 (Fig. 2b, left panel).

3.1.3 iTBS300 vs. iTBS600

As was the case for atDCS, across the entire cohort and averaged over both iTBS durations, there was a statistically significant increase in CSE (9.64% ± 5.98%), as illustrated by a significant grand mean effect, F (1, 32) = 10.440, p = 0.003, η_p^2 = 0.246 (Fig. 2a; right panel). Again, this was associated with a large effect size. No significant differences were detected between iTBS300 and iTBS600 as the main effect of DURATION, F (1, 32) = 0.016, p = 0.899, η_p^2 = 0.001, and the interaction effect between DURATION and TIME, F (1, 32) = 0.461, p = 0.837, η_p^2 = 0.014, were both not statistically significant.

In relation to the analyses of the responders (GA > 1.1 to *both* iTBS300 and iTBS600; n = 12), no statistically significant main or interaction effects were observed (all p > 0.251, all η_p^2 < 0.118) (Fig. 2b; right panel).

3.1.4 All four NBS protocols

Lastly, when all four NBS protocols were considered together in one analysis, a statistically significant increase in post-stimulation CSE was observed (8.44% ± 3.46%) averaged across all four NBS protocols compared to baseline, as shown by the grand mean effect, F (1, 32) = 23.502, p < 0.001, η_p^2 = 0.423. All main or interaction effects involving NBS were not statistically significant (all p > 0.595, all η_p^2 < 0.026).

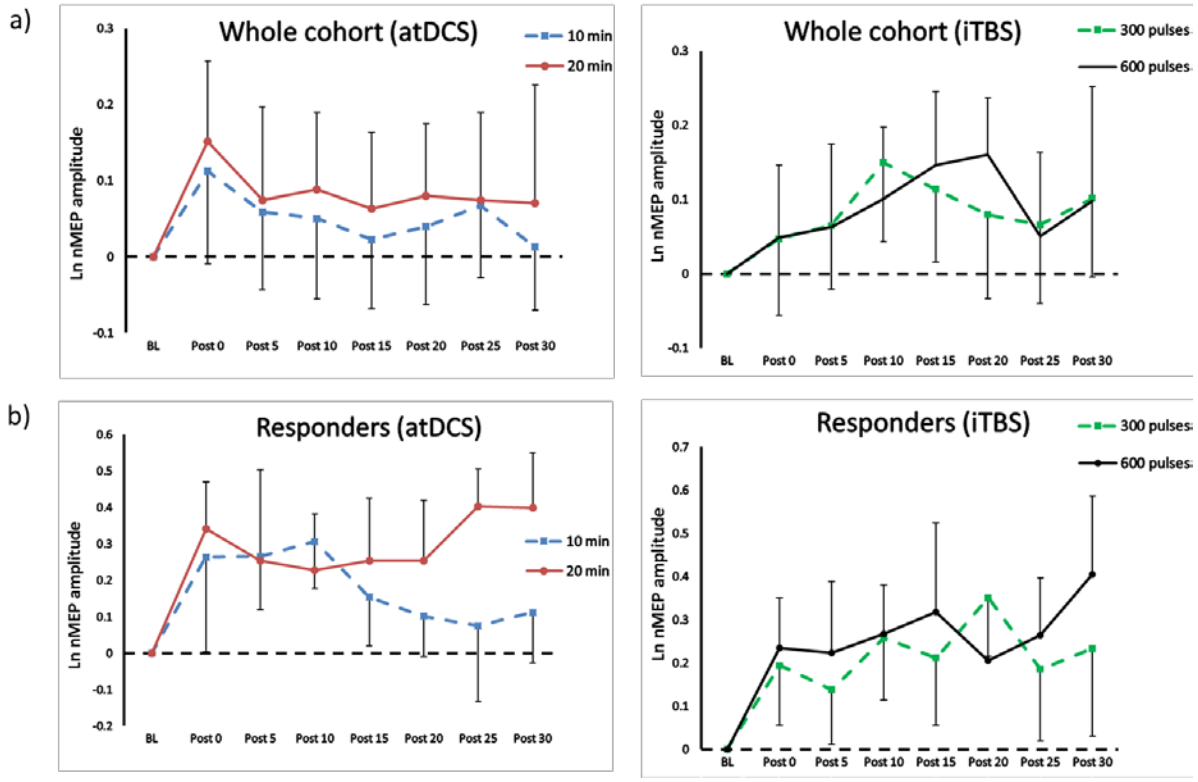


Fig. 2 Natural log transformed normalized MEP amplitude (ordinate) plotted at every post-stimulation time-point (abscissa) for the a) whole cohort (N = 33) and b) responders only (n = 10 for atDCS; n = 12 for iTBS) separately for atDCS (left panels; atDCS10 – dotted black line, atDCS20 – solid black line) and iTBS (right panels; iTBS300 – dotted grey line,

iTBS600 – solid grey line). Ordinate passing through 0 indicates baseline CSE, error bars denote 95 % CI around the mean in one direction, and asterisks (*) indicates significant differences between time-points at $p < 0.05$.

3.2 Individual level analyses

In this subsection, analyses were conducted to investigate individual variability in response to the four NBS protocols.

3.2.1 Inter-individual variability

Grand average analyses, based on the average of all post-stimulation time points, revealed a similar proportion of participants exhibiting an excitatory response (GA > 1.1) to each of the four NBS protocols [atDCS10: 55% (18 out of 33); atDCS20: 52% (17 out of 33); iTBS300: 58% (19 out of 33); iTBS600: 55% (18 out of 33)] (Table 2). For all four NBS protocols, chi-square goodness of fit tests revealed that the distribution of participants across the 3 categories differed significantly from a random distribution (all $\chi^2 > 6.55$, all $p < 0.04$). TwoStep cluster analyses, which takes into account the temporal pattern of post-stimulation MEPs for each individual, revealed a bimodal grouping of participants for iTBS600, where 52% (17 out of 33) of participants exhibited the expected facilitatory response (see Fig. 3); however, no participant clusters were identified for iTBS300, or either atDCS protocol.

Table 2 Frequency of the different type of responses to each of the four NBS protocols for all participants ($N = 33$).

	atDCS 10	atDCS 20	iTBS 300	iTBS 600
Excitatory Response	18 (55%)	17 (52%)	19 (58%)	18 (55%)
Inhibitory Response	5 (15%)	5 (15%)	4 (12%)	7 (21%)
No Response	10 (30%)	11 (33%)	10 (30%)	8 (24%)

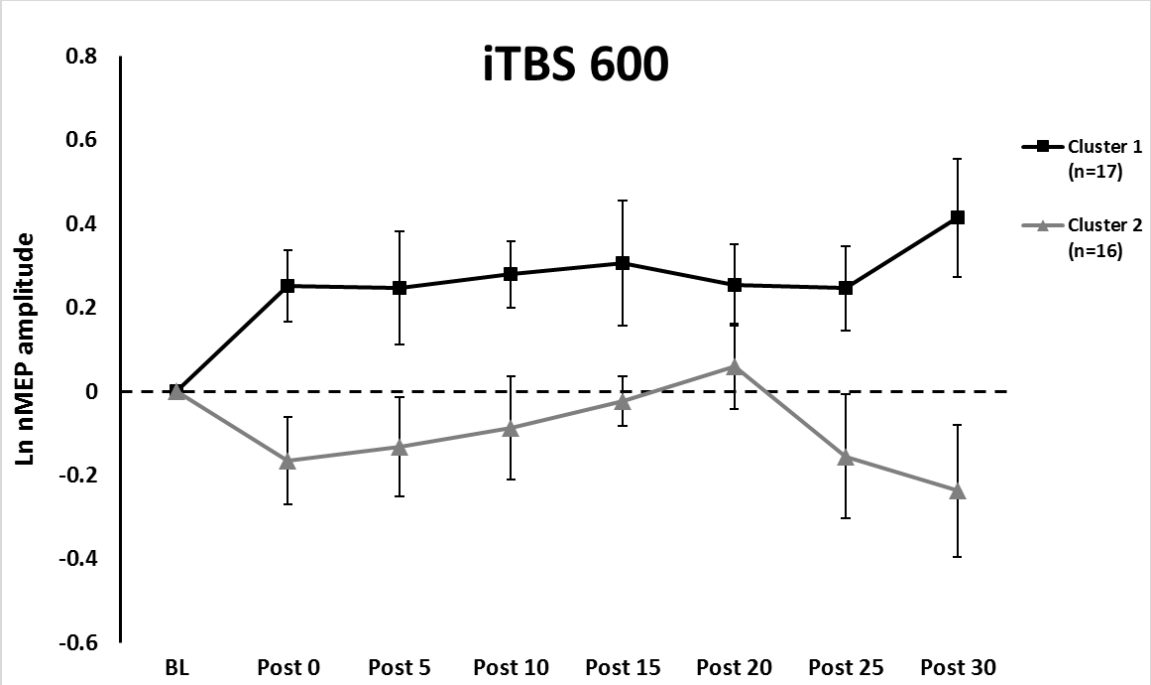
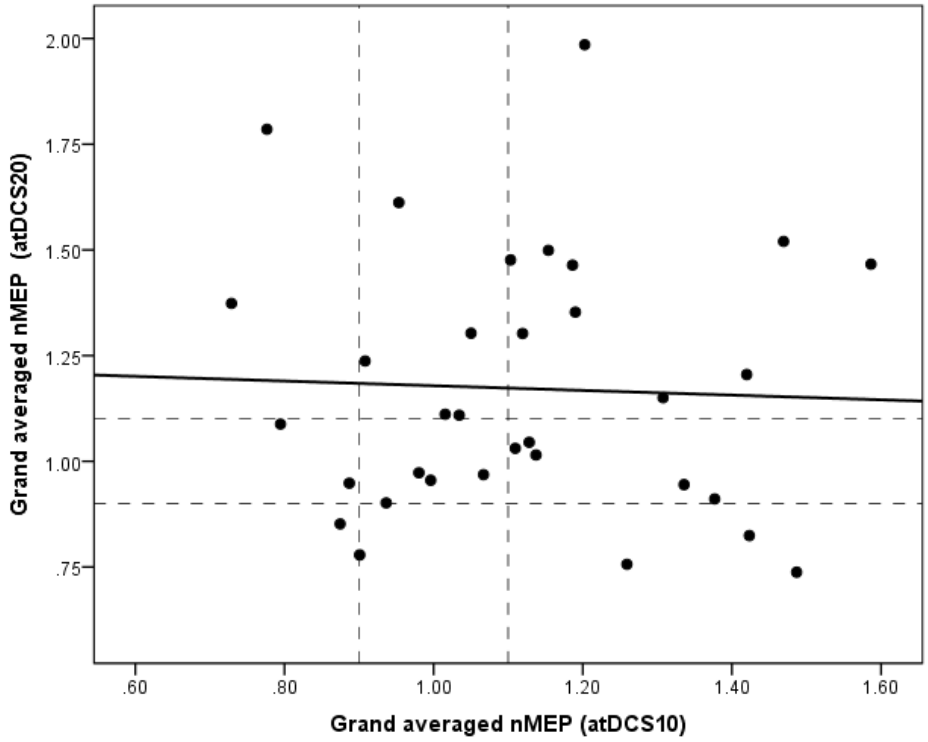


Fig. 3 Natural log transformed normalized MEP amplitude (ordinate) plotted at every post-stimulation time-point (abscissa) for cluster 1, exhibiting a facilitatory response (solid black line with square markers; $n = 17$), and cluster 2, exhibiting inhibitory or no response (solid grey line with triangle markers; $n = 16$). Ordinate passing through 0 indicates baseline CSE and error bars denote 95 % CI around the mean in one direction.

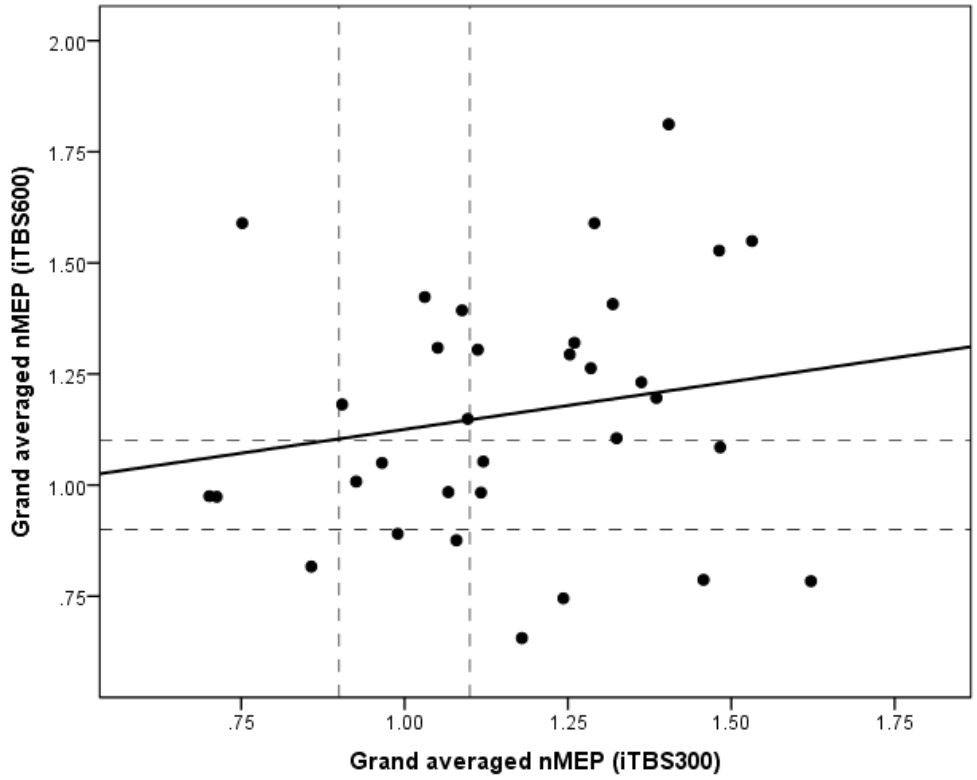
3.2.2 Intra-individual variability

Correlation analyses revealed no significant correlation between an individual's response to atDCS10 and their response to atDCS20 ($r = -0.040$, $p = 0.826$). 15 out of the 33 participants exhibited consistency in post-stimulation response (i.e. excitatory, inhibitory, or no response) after both durations of atDCS (Fig. 4a; unfilled triangles). Similarly, no significant correlation between the responses to iTBS300 and iTBS600 ($r = 0.182$, $p = 0.311$) was observed; 16 out of the 33 participants exhibited consistent responses after both durations of iTBS (Fig. 4b; unfilled triangles). Finally, no significant correlation was observed between an individual's average response to atDCS and their average response to iTBS ($r = -0.214$, $p = 0.233$); in this instance 16 out of the 33 participants exhibited a consistent response to both types of stimulation (Fig. 4c; unfilled triangles).

a)


Grand averaged nMEP (atDCS20)
2.00
1.75
1.50
1.25
1.00
.75
.60
.80
1.00
1.20
1.40
1.60
Grand averaged nMEP (atDCS10)

b)


Grand averaged nMEP (iTBS600)
2.00
1.75
1.50
1.25
1.00
.75
.75
1.00
1.25
1.50
1.75
Grand averaged nMEP (iTBS300)

c)

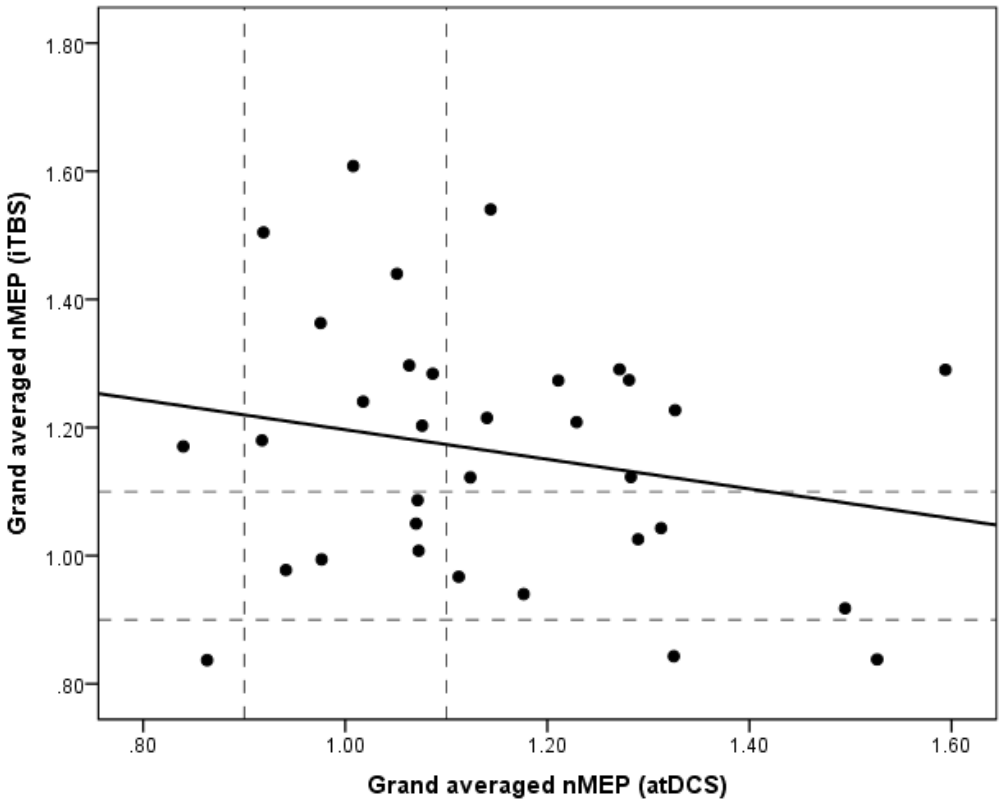


Fig. 4 Correlations of an individual's grand averaged normalized MEP amplitude between a) 10 min (abscissa) and 20 min (ordinate) atDCS; b) 300 pulses (abscissa) and 600 pulses (ordinate) iTBS and c) averaged atDCS (abscissa) and average iTBS (ordinate) NBS response. Dotted lines indicate 10% cut-offs used to define excitatory (GA > 1.1), inhibitory (GA < 0.9), and no response (0.9 < GA < 1.1) on both axes. Unfilled triangles in each panel represents those participants who maintained consistent NBS response (excitatory, inhibitory, or no response across both durations or both types of stimulation)

Finally, of those participants who exhibited an excitatory response to at least one NBS protocol (31 of 33 participants), four individuals exhibited the expected facilitation to all four protocols, nine participants exhibited facilitatory responses to three protocols while 11 and seven participants exhibited facilitatory responses to two or one NBS protocol, respectively (Fig. 5).

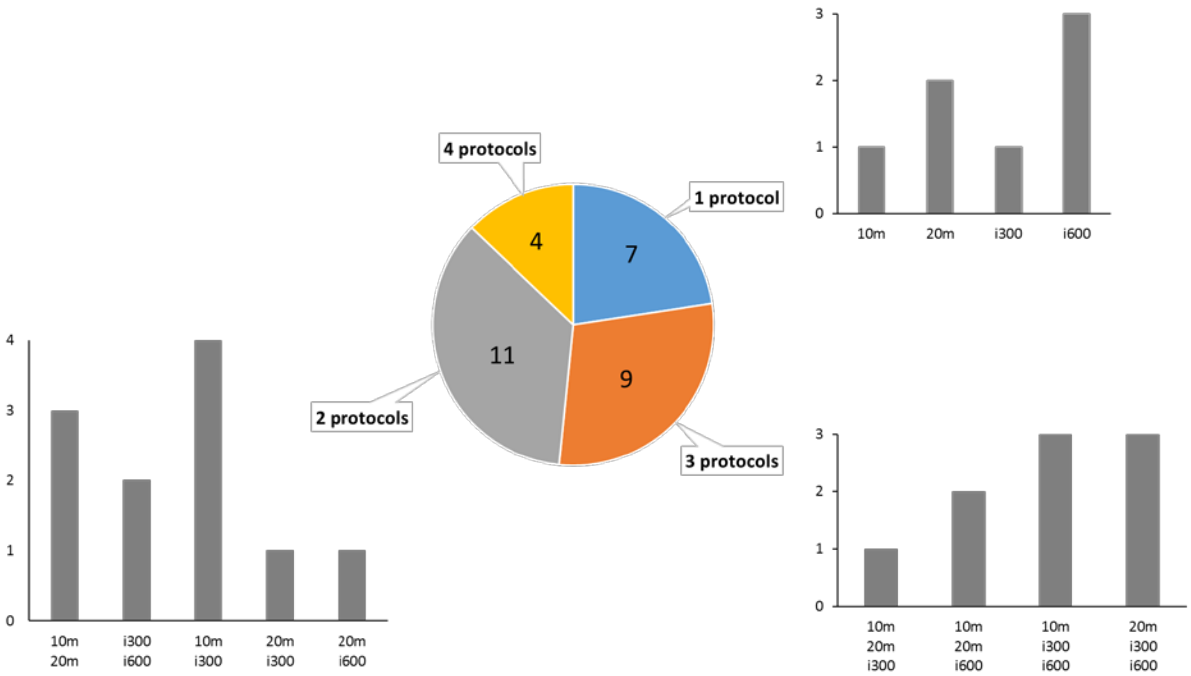


Fig. 5 For responders (GA > 1.1) to at least one NBS protocol (n = 31), the pie chart depicts the number of participants who exhibited the expected facilitation to one (n = 7; horizontal pattern), two (n = 11; dotted pattern), three (n = 9; vertical pattern), or all four (n = 4; no pattern) NBS protocols. In addition, corresponding bar graphs illustrate the breakdown of the number of participants (ordinate) for each protocol or combinations of protocols (abscissa; 10m – atDCS10, 20m – atDCS20, i300 – iTBS300, i600 –iTBS600).

3.3 Predictors of NBS response

Neither resting motor threshold intensity (all $p > 0.109$, all $r < 0.284$) nor any of the five tests of trait motor function (all $p > 0.166$, all $r < 0.255$) significantly predicted response to any of the four NBS protocols suggesting that the capacity for NBS-induced M1 plasticity was not dependent on these baseline measures.

Discussion

To date, this is the most comprehensive study conducted with older adults to investigate the efficacy of different types of NBS (atDCS and iTBS) for inducing corticospinal plastic changes and assessing the variability of those responses with a systematic manipulation of a key stimulation parameter (i.e., duration). Thirty-three participants received, in separate sessions, four different NBS protocols (10 and 20 min atDCS as well as 300 and 600 pulses of iTBS) along with an initial session assessing various trait motor functions. The current results indicate significant group level efficacy of both atDCS and iTBS in inducing post-stimulation facilitation of corticospinal excitability in older adults. Though these effects did not differ significantly as a function of either type or duration of stimulation, a subset of 'responders' to both durations of atDCS showed greater post-stimulation facilitation after atDCS20 than atDCS10, especially at late time-points (Fig. 2b, left panel). When considering responses to the NBS protocols at the level of individual participants, substantial inter-individual variability was observed with just over half of the total sample exhibiting (the

expected) facilitatory responses to each of the four separate NBS protocols (in the four separate sessions). Moreover, considerable *intra*-individual variability was also observed with individuals exhibiting different responses across the varying protocols (i.e. those individuals who responded in the anticipated manner to one stimulation protocol did not necessarily respond in the same manner to the other stimulation protocols).

4.1 Group level analyses

Group level findings are, first and foremost, discussed in regards to the increased post-stimulation CSE, followed by implications of the different stimulation types and durations.

4.1.2 Post-stimulation changes in corticospinal excitability

In our sample of 33 older adults, a statistically significant facilitation of corticospinal excitability was observed in response to the four NBS protocols. This finding is in line with a considerable body of research reporting significant post-stimulation facilitation for both iTBS (for review, see Wischnewski and Schutter 2015 and Chung et al. 2016) and atDCS (for review, see Bastani and Jaberzadeh 2012 and Horvath et al. 2015) in younger adults. At first glance, the group level efficacy observed here may seem surprising in view of research reporting reduced NBS-induced plasticity in older adults (Fathi et al. 2010; Freitas et al. 2011; Muller-Dahlhaus et al. 2008) and other studies reporting an absence of group level efficacy in response to facilitatory NBS protocols in younger adults (Hamada et al. 2013; Lopez-Alonso et al. 2014; Vallence et al. 2013). However, some important considerations must be taken into account to fully interpret the current findings.

Firstly, while age-related reductions in NBS-induced plasticity have been reported, these have been primarily in response to paired associative stimulation (PAS) (Fathi et al. 2010; Muller-Dahlhaus et al. 2008) and continuous TBS (Freitas et al. 2011) with no significant differences in the magnitude of stimulation-induced plasticity observed between older and younger adults following atDCS (Fujiyama et al. 2014) and iTBS (Dickins et al. 2015; Young-Bernier et al. 2014) - the two facilitatory protocols utilized in this study. Further studies comparing different NBS protocols in a cohort of younger and older adults may help reconcile these apparent differences.

Despite a number of recent reports indicating a lack of group level efficacy in younger adults (Hamada et al. 2013; Lopez-Alonso et al. 2014; Vallence et al. 2013), it should be noted that a number of other recent studies with largely comparable sample sizes and demographics *have* reported significant group level effects with respect to NBS-induced plasticity (Strube et al. 2015; Wiethoff et al. 2014). The varied proportions of responders and non-responders (utilizing the traditional binary categorization of grand average post-stimulation response greater or lesser than baseline excitability, respectively – see Hamada et al. 2013) that make up the cohorts of these different studies is likely to play a role in determining the group level results. Indeed, studies reporting approximately two-thirds or greater of the cohort as responders report significant group level efficacy (Hinder et al. 2014; Strube et al. 2015; Wiethoff et al. 2014, and current data) whereas those studies reporting around half or less of the cohort as responders fail to observe significant group level efficacy (Davidson et al. 2016; Hamada et al. 2013; Lopez-Alonso et al. 2014; Vallence et al. 2013). This clearly emphasizes the need to analyse post-stimulation responses at the individual level to understand more deeply the efficacy of these NBS protocols (see Section 4.2). Additionally, the use of

different a) stimulation parameters (montage, electrode size, intensity, and duration of stimulation), b) TMS parameters (number of trials, inter-trial interval, stimulus intensities, and duration of post-stimulation assessment) and c) statistical methodologies should also be noted as potential variables which may, at least to some extent, explain the disparate group-level findings.

Lastly, having not conducted a sham condition one must be slightly cautious in over interpreting the moderate, albeit statistically significant, group-level increase in post-stimulation CSE reported here (i.e., a 8.4% increase), especially in light of recent research reporting post sham tDCS facilitation to a similar extent as observed after anodal tDCS (Horvath et al. 2016).

4.1.2 Effect of stimulation type

No significant group-level differences were observed in the current study *between* the different facilitatory NBS protocols (atDCS vs. iTBS) in their ability to induce post-stimulation facilitation of corticospinal excitability. This finding in older adults is consistent with studies utilizing a repeated-measures design in younger adults: Strube et al. 2015 reported no significant differences in the magnitude of the facilitatory response to PAS or to atDCS, while Lopez-Alonso et al. 2014 report no significant differences in MEP facilitation following iTBS, atDCS, and PAS. Overall, these findings suggest at least some overlap in the underlying mechanisms by which these LTP-like after-effects are mediated, regardless of age. Indeed, pharmacological intervention studies have reported NMDA-receptor dependent effects for both iTBS (Huang et al. 2007) and atDCS (Nitsche et al. 2003).

4.1.3 Effect of stimulation duration

Few studies have investigated the effects of varied stimulation duration and at present there is no strong consensus regarding the dose-dependent effects of NBS. In the present study, we explored this issue by manipulating the duration of stimulation for atDCS (10 vs. 20 min) and iTBS (300 vs. 600 pulses). For iTBS, though a shortened 300 pulse burst of continuous TBS has been shown to induce LTD-like effects (Huang et al. 2005), to our knowledge, the current study is the first to evaluate, and observe, the effectiveness of a shortened 300 pulse train of the traditional 50 Hz iTBS protocol at inducing LTP-like effects in a cohort of adults. Our finding is consistent with a recent paper reporting significant M1 facilitation after iTBS300 (Pedapati et al. 2015); however the intra-burst frequency was reduced to 30 Hz in that study, which was conducted on adolescents. Dose-dependent research in young adults has mostly investigated *longer* durations, with iTBS1200 (Gamboa et al. 2010) resulting in a *reversal* of the initial facilitation expected from the standard 600 pulses and iTBS1800 (Nettekoven et al. 2014) a restoration of the initial facilitation. For atDCS, our findings partially substantiate the generic notion that longer durations of stimulation results in greater effects on CSE (Nitsche and Paulus 2000) as only responders exhibited greater post-stimulation CSE increases after atDCS20 than atDCS10. This was mostly evident at late time-points (Post 25 and 30), suggesting that longer stimulation durations may prolong the effect of atDCS in older adults. Though research in younger adults has suggested either no duration dependent effects (10 vs. 20 min of atDCS; Ho et al. 2016) or even *detrimental* effects of prolonged stimulation (13 vs. 26 min of atDCS; Monte-Silva et al., 2013), it remains unclear whether a subset of the tested cohort (responders to both durations of stimulation) do indeed benefit from a longer stimulation duration as demonstrated in the current study.

4.2 Individual level analyses

Despite the observed group-level efficacy, considerable variability was observed in responses across our cohort of older adults, similar to that recently reported in younger adults. Here, we discuss this on an inter-individual level (i.e. between-individual variability for each NBS protocol) and on an intra-individual level (i.e. within-individual variability in response to the four NBS protocols) along with possible predictors and mechanisms that may explain the variability.

4.2.1 Inter-individual comparisons

Grand average analyses revealed similar proportions of responders (GA > 1.1) to all four NBS protocols, with just over half of the sample (~ 52-58%) exhibiting the expected facilitation, suggesting comparable levels of inter-individual variability across both durations and types of stimulation. Consistent with research in *younger* adults for iTBS (Hamada et al. 2013; Lopez-Alonso et al. 2014; Vallence et al. 2013) and atDCS (Horvath et al. 2016; Lopez-Alonso et al. 2014; Strube et al. 2015; Wiethoff et al. 2014), our results demonstrate similar inter-individual variability in a cohort of older adults indicating maintained response to NBS in the ageing nervous system.

TwoStep cluster analyses revealed a bimodal participant grouping only for iTBS600; while a similar proportion of participants exhibited the expected excitatory response to this stimulation (55%) as seen for the other protocols (52-58%), the number of participants exhibiting an inhibitory response (GA <0.9) was higher for iTBS600 (21%) than the other protocols (12-15%). This fact, along with temporal consistency in post-stimulation response across the measured time-window, played a role in the formation of two distinct clusters of participants for iTBS600 but not the other protocols. This highlights the value of utilizing cluster analyses (to account for the temporal pattern of post-stimulation response) as well as reporting grand average analyses.

4.2.2 Intra-individual comparisons

Variability was also observed with respect to each individual's response to the different types and durations of stimulation. Analysis of grand average post-stimulation response (across both durations) for each stimulation type revealed no significant correlation between an individual's response to atDCS and their response to iTBS (Fig. 4c). Indeed, only 16 out of 33 participants exhibited consistency with respect to the direction (no response, facilitation, or depression) of responses across the two stimulation types. Although atDCS and iTBS share common mechanisms (NMDA receptor dependent), subtle differences in the underlying mechanisms mediating after-effects might play a role in the intra-individual variation in response between these two types of facilitatory NBS.

We also observed intra-individual variability in response to the different durations of each stimulation (atDCS10 vs. atDCS20, Fig. 4a; iTBS300 vs. iTBS600, Fig. 4b). Recently, Chew and collaborators (2015) utilized 4 different atDCS *intensities* (0.2, 0.5, 1, and 2 mA) in a within-subjects design and reported intra-individual variability where only 33% of young participants (7 out of 21) maintained consistency and displayed the expected facilitation (GA > 1.2) to more than one stimulation intensity condition. Our novel results build upon their findings by demonstrating similar intra-individual variability in response to different *durations* of atDCS and iTBS, suggesting an important role of both these stimulation

parameters on an individual level. Conceivably, differences between studies with respect to the extent of *inter*-individual variability (and thus, group level efficacy too – see above) are affected by the different stimulation parameters utilized.

4.2.3 Predictors of NBS response

Trait motor function was tested for participants across five subdomains (dexterity, grip strength, standing balance, gait speed, and endurance) relating to fundamental daily living activities that have significant clinical relevance for older adults (Reuben et al. 2013). Given their central role in motor functioning, they were interpreted as proxy measures of primary motor cortex integrity and subsequently tested to investigate any correlations with NBS induced M1 plasticity. However, in our sample of older adults, none of the measures of trait motor function correlated with post-stimulation response after any of the NBS protocols. It is conceivable that these motor functions rely on diffuse cortical networks, such that response to NBS applied to M1 is too specific for assessing the integrity and responsiveness of those networks. Another possibility is that the tests of motor function in our sample of community older adults were insufficiently sensitive to provide enough behavioural range to adequately correlate motor function with NBS response.

Differences in resting motor threshold intensity between individuals did not underlie the inter-individual variability for any of the NBS protocols. For our iTBS protocols, this finding is in line with studies showing no correlation between RMT and post-stimulation response (Hamada et al. 2013; Lopez-Alonso et al. 2014; Nettekoven et al. 2015). For atDCS, it has been suggested that sensitivity to TMS (defined as the TMS intensity required to produce 1 mV MEPs) may predict response to atDCS such that those who are more sensitive (i.e. lower TMS intensity) show greater post-atDCS response in an early epoch lasting 30 mins post-stimulation (Labruna et al. 2016). However, when TMS sensitivity wasn't treated as a categorical variable (using a median split), there was no significant correlation between TMS intensity and post-atDCS response. Additionally, a recent study has suggested a possible role of intracortical facilitation (Strube et al. 2015) in predicting post-atDCS response, warranting further research.

Though none of our baseline measures correlated with an individual's NBS response, other possible mechanisms may help explain the inter- and intra-individual variability. Indeed, there is a strong case that the functional organization of local circuits may play an important role in mediating responses to NBS. Studies have shown that the after-effects of atDCS are mediated by both D and I waves (Di Lazzaro et al. 2013; Lang et al. 2011) whereas those of iTBS are primarily mediated by late I waves (Di Lazzaro et al. 2008). Using a surrogate measure of I wave recruitment, recent research has suggested that individuals more likely to recruit *early* I waves show the expected facilitation after atDCS (Davidson et al. 2016; McCambridge et al. 2015; Wiethoff et al. 2014), whereas those who recruit *late* I waves show the expected facilitation after iTBS (Hamada et al. 2013). Although speculative, it is not only conceivable that the inter-individual variability we observed in our study is at least in part due to differences in I wave recruitment between individuals but also that the intra-subject variability in response to the different types of stimulation (atDCS vs. iTBS) can be explained to some extent by differences in the physiological underpinnings of their after-effects.

Additionally, as suggested by Krause and collaborators (2013; 2014), differences between individuals in baseline levels of glutamate and GABA, and hence the balance between

cortical excitation and inhibition (E/I), may play an important role in the extent of responsiveness to NBS. In this regard, the *same NBS protocol* would cause individuals to be on different points of the E/I spectrum. That is, the same NBS protocol may cause certain individuals to reach optimal levels of plasticity induction whereas this may not be achieved for other individuals. As a result, at least some of the inter-individual variability observed in our study may be due to differences in baseline glutamate and GABA. Similarly, it is also conceivable that for the *same individual*, the different durations of stimulation utilized here may cause the resultant E/I balance to differ such that for some individuals none or both durations lead to optimal levels of plasticity induction, whereas for other individuals only a certain duration leads to optimal plasticity induction. This speculative postulation is consistent with our finding that although almost all participants (31 of 33) responded to at least one of the NBS protocols, the protocol which produced the maximal response differed across individuals.

4.3 Limitations and conclusions

Certain limitations of the current study exist that should be taken into account in future studies, such as the lack of a sham condition, especially in light of recent research suggesting no significant group level facilitation after atDCS compared to sham in younger adults (Horvath et al. 2016). Furthermore, the inclusion of a group of younger adults would have allowed the direct assessment of age-related differences in response to varied types and durations of stimulation. Lastly, in light of research reporting session to session intra-individual variability after iTBS (Hinder et al. 2014) and atDCS (Chew et al. 2015; Horvath et al. 2016; Lopez-Alonso et al. 2015) in younger adults, it is possible that older adults show similar variability from session to session (in each of the four NBS protocols we utilised), which was not assessed or accounted for in the current study.

In conclusion, we report significant group level efficacy in older adults following four different facilitatory NBS protocols. Considerable inter- and intra-individual variability was observed with trait motor function not significantly predicting NBS response. However, most of the cohort responded to at least one variant of facilitatory NBS, suggesting that the ability for NBS to induce plasticity on an individual level to be dependent on determining factors that may predispose an individual to not only certain types of stimulation but also to certain parameters of stimulation. In this regard, our study has important clinical implications, especially in an elderly cohort in whom NBS holds great promise.

Reference List

Bastani A, Jaberzadeh S (2012) Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: A systematic review and meta-analysis Clin Neurophysiol 123:644-657 doi:10.1016/j.clinph.2011.08.029

Carroll TJ, Barry B, Riek S, Carson RG (2001) Resistance training enhances the stability of sensorimotor coordination P Roy Soc B-Biol Sci 268:221-227

Chew T, Ho KA, Loo CK (2015) Inter- and Intra-individual Variability in Response to Transcranial Direct Current Stimulation (tDCS) at Varying Current Intensities Brain Stimul 8:1130-1137 doi:10.1016/j.brs.2015.07.031

Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB (2016) Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis Neurosci Biobehav R 63:43-64 doi:10.1016/j.neubiorev.2016.01.008

Davidson TW, Bolic M, Tremblay F (2016) Predicting Modulation in Corticomotor Excitability and in Transcallosal Inhibition in Response to Anodal Transcranial Direct Current Stimulation Front Hum Neurosci 10 doi:10.3389/fnhum.2016.00049

Deary IJ et al. (2009) Age-associated cognitive decline Br Med Bull 92:135-152 doi:10.1093/bmb/ldp033

Di Lazzaro V et al. (2008) The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex J Physiol-London 586:3871-3879 doi:10.1113/jphysiol.2008.152736

Di Lazzaro V et al. (2013) Transcranial Direct Current Stimulation Effects on the Excitability of Corticospinal Axons of the Human Cerebral Cortex Brain Stimul 6:641-643 doi:10.1016/j.brs.2012.09.006

Dick JP, Guiloff RJ, Stewart A, Blackstock J, Bielawska C, Paul EA, Marsden CD (1984) Mini-mental state examination in neurological patients J Neurol Neurosurg Psychiatry 47:496-499

Dickins DSE, Sale MV, Kamke MR (2015) Plasticity Induced by Intermittent Theta Burst Stimulation in Bilateral Motor Cortices Is Not Altered in Older Adults Neural Plast doi:10.1155/2015/323409

Fathi D, Ueki Y, Mima T, Koganemaru S, Nagamine T, Tawfik A, Fukuyama H (2010) Effects of aging on the human motor cortical plasticity studied by paired associative stimulation Clin Neurophysiol 121:90-93 doi:10.1016/j.clinph.2009.07.048

Freitas C et al. (2011) Changes in cortical plasticity across the lifespan Front Aging Neurosci 3:5 doi:10.3389/fnagi.2011.00005

Fujiyama H, Hyde J, Hinder MR, Kim SJ, McCormack GH, Vickers JC, Summers JJ (2014) Delayed plastic responses to anodal tDCS in older adults Front Aging Neurosci 6:115 doi:10.3389/fnagi.2014.00115

Gamboa OL, Antal A, Moliadze V, Paulus W (2010) Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation Exp Brain Res 204:181-187 doi:10.1007/s00221-010-2293-4

Hamada M, Murase N, Hasan A, Balaratnam M, Rothwelll JC (2013) The Role of Interneuron Networks in Driving Human Motor Cortical Plasticity Cereb Cortex 23:1593-1605 doi:10.1093/cercor/bhs147

Hinder MR, Goss EL, Fujiyama H, Canty AJ, Garry MI, Rodger J, Summers JJ (2014) Inter- and Intra-individual Variability Following Intermittent Theta Burst Stimulation: Implications for Rehabilitation and Recovery Brain Stimul 7:365-371 doi:10.1016/j.brs.2014.01.004

Hinder MR, Schmidt MW, Garry MI, Summers JJ (2010) Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb Exp Brain Res 205:423-433 doi:10.1007/s00221-010-2379-z

Ho KA et al. (2016) The Effect of Transcranial Direct Current Stimulation (tDCS) Electrode Size and Current Intensity on Motor Cortical Excitability: Evidence From Single and Repeated Sessions Brain Stimul 9:1-7 doi:10.1016/j.brs.2015.08.003

Horvath JC, Forte JD, Carter O (2015) Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review Neuropsychologia 66:213-236 doi:10.1016/j.neuropsychologia.2014.11.021

706 Horvath JC, Vogrin SJ, Carter O, Cook MJ, Forte JD (2016) Effects of a common
707 transcranial direct current stimulation (tDCS) protocol on motor evoked potentials
708 found to be highly variable within individuals over 9 testing sessions Exp Brain
709 Res:1-14 doi:10.1007/s00221-016-4667-8
710 Hsu WY, Ku Y, Zanto TP, Gazzaley A (2015) Effects of noninvasive brain stimulation on
711 cognitive function in healthy aging and Alzheimer's disease: a systematic review and
712 meta-analysis Neurobiol Aging 36:2348-2359
713 doi:10.1016/j.neurobiolaging.2015.04.016
714 Huang YZ, Chen RS, Rothwell JC, Wen HY (2007) The after-effect of human theta burst
715 stimulation is NMDA receptor dependent Clin Neurophysiol 118:1028-1032
716 doi:10.1016/j.clinph.2007.01.021
717 Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of
718 the human motor cortex Neuron 45:201-206 doi:10.1016/j.neuron.2004.12.033
719 Krause B, Cohen Kadosh R (2014) Not all brains are created equal: The relevance of
720 individual differences in responsiveness to transcranial electrical stimulation Frontiers
721 in Systems Neuroscience 8 doi:10.3389/fnsys.2014.00025
722 Krause B, Marquez-Ruiz J, Cohen Kadosh R (2013) The effect of transcranial direct current
723 stimulation: a role for cortical excitation/inhibition balance? Front Hum Neurosci
724 7:602 doi:10.3389/fnhum.2013.00602
725 Labruna L et al. (2016) Efficacy of Anodal Transcranial Direct Current Stimulation is
726 Related to Sensitivity to Transcranial Magnetic Stimulation Brain Stimul 9:8-15
727 doi:10.1016/j.brs.2015.08.014
728 Lang N et al. (2011) Transcranial direct current stimulation effects on I-wave activity in
729 humans J Neurophysiol 105:2802-2810 doi:10.1152/jn.00617.2010
730 Lopez-Alonso V, Cheeran B, Rio-Rodriguez D, Fernandez-del-Olmo M (2014) Inter-
731 individual Variability in Response to Non-invasive Brain Stimulation Paradigms
732 Brain Stimul 7:372-380 doi:10.1016/j.brs.2014.02.004
733 Lopez-Alonso V, Fernandez-del-Olmo M, Costantini A, Gonzalez-Henriquez JJ, Cheeran B
734 (2015) Intra-individual variability in the response to anodal transcranial direct current
735 stimulation Clin Neurophysiol 126:2342-2347 doi:10.1016/j.clinph.2015.03.022
736 McCambridge AB, Stinear JW, Byblow WD (2015) 'I-wave' Recruitment Determines
737 Response to tDCS in the Upper Limb, but Only So Far Brain Stimul 8:1124-1129
738 doi:10.1016/j.brs.2015.07.027
739 Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, Nitsche MA
740 (2013) Induction of Late LTP-Like Plasticity in the Human Motor Cortex by
741 Repeated Non-Invasive Brain Stimulation Brain Stimul 6:424-432
742 doi:10.1016/j.brs.2012.04.011
743 Muller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U (2008) Interindividual variability and
744 age-dependency of motor cortical plasticity induced by paired associative stimulation
745 Exp Brain Res 187:467-475 doi:10.1007/s00221-008-1319-7
746 Nettekoven C et al. (2014) Dose-Dependent Effects of Theta Burst rTMS on Cortical
747 Excitability and Resting-State Connectivity of the Human Motor System J Neurosci
748 34:6849-6859 doi:10.1523/Jneurosci.4993-13.2014
749 Nettekoven C et al. (2015) Inter-individual variability in cortical excitability and motor
750 network connectivity following multiple blocks of rTMS Neuroimage 118:209-218
751 doi:10.1016/j.neuroimage.2015.06.004
752 Nitsche MA et al. (2003) Pharmacological modulation of cortical excitability shifts induced
753 by transcranial direct current stimulation in humans J Physiol-London 553:293-301
754 doi:10.1113/jphysiol.2003.049916

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation J Physiol 527 Pt 3:633-639
Pedapati EV, Gilbert DL, Horn PS, Huddleston DA, Laue CS, Shahana N, Wu SW (2015) Effect of 30 Hz theta burst transcranial magnetic stimulation on the primary motor cortex in children and adolescents Front Hum Neurosci 9 doi:10.3389/fnhum.2015.00091
Puri R, Hinder MR, Fujiyama H, Gomez R, Carson RG, Summers JJ (2015) Duration-dependent effects of the BDNF Val66Met polymorphism on anodal tDCS induced motor cortex plasticity in older adults: a group and individual perspective Front Aging Neurosci 7:107 doi:10.3389/fnagi.2015.00107
Reuben DB et al. (2013) Motor assessment using the NIH Toolbox Neurology 80:S65-S75 doi:10.1212/WNL.0b013e3182872e01
Sale MV, Ridding MC, Nordstrom MA (2008) Cortisol inhibits neuroplasticity induction in human motor cortex J Neurosci 28:8285-8293 doi:10.1523/Jneurosci.1963-08.2008
Seidler RD et al. (2010) Motor control and aging: links to age-related brain structural, functional, and biochemical effects Neurosci Biobehav Rev 34:721-733 doi:10.1016/j.neubiorev.2009.10.005
Sink C, Stroh H (2006) Practical Significance:The Use of Effect Sizes in School Counseling Research Professional School Counseling 9:401-411 doi:doi:10.5330/prsc.9.4.283746k664204023
Strube W, Bunse T, Malchow B, Hasan A (2015) Efficacy and Interindividual Variability in Motor-Cortex Plasticity following Anodal tDCS and Paired-Associative Stimulation Neural Plast doi:10.1155/2015/530423
Summers JJ, Kang N, Cauraugh JH (2016) Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis Ageing Res Rev 25:42-54 doi:10.1016/j.arr.2015.11.004
United Nations, Department of Economic and Social Affairs, Population Division (2015) World Population Ageing 2015 (ST/ESA/SER.A/390).
Vallence AM, Kurylowicz L, Ridding MC (2013) A comparison of neuroplastic responses to non-invasive brain stimulation protocols and motor learning in healthy adults Neurosci Lett 549:151-156 doi:10.1016/j.neulet.2013.05.064
Wiethoff S, Hamada M, Rothwell JC (2014) Variability in Response to Transcranial Direct Current Stimulation of the Motor Cortex Brain Stimul 7:468-475 doi:10.1016/j.brs.2014.02.003
Wischnewski M, Schutter DJ (2015) Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans Brain Stimul 8:685-692 doi:10.1016/j.brs.2015.03.004
Young-Bernier M, Tanguay AN, Davidson PSR, Tremblay F (2014) Short-latency afferent inhibition is a poor predictor of individual susceptibility to rTMS-induced plasticity in the motor cortex of young and older adults Front Aging Neurosci 6 doi:10.3389/fnagi.2014.00182