Modifying Motor Skill Learning via Neuromodulation of Frontoparietal Networks

by

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ABSTRACT

Motor skill learning is important to rehabilitation, sports, and many occupations. When attempting to learn or adapt a motor skill, some individuals learn slower or less compared to others despite the same amount of motor practice. This dissertation aims to understand the factors that contributed to such variability in motor learning, and thereby identify viable methods to enhance motor learning. Behavioral evidence from our lab showed that visuospatial ability is positively related to the extent of motor learning. Neuroimaging studies suggest that motor learning and visuospatial processes share common frontoparietal neural structures, and that this visuospatial-motor relationship may be more pronounced in the right hemisphere compared to the left. Thus, the overall objective of this dissertation is to determine if aspects of motor learning (such as the rate and extent of skill acquisition) may be modifiable through neuromodulation of the right frontoparietal network.

In Aim 1, anodal transcranial direct current stimulation (tDCS) was used to test whether modulating the right parietal area affects visuospatial ability and motor skill acquisition. A randomized, three-arm design was used, which added a no-tDCS control group to the double-blinded sham-control protocol to address placebo effects. No tDCS treatment effect was observed, likely due to low statistical power to detect any treatment effects as the study is still ongoing. However, the current results revealed a unique finding that the placebo effect of tDCS was stronger than its treatment effect on motor learning, with implications that tDCS and motor studies should measure and control for placebo effects.

In Aim 2, right frontoparietal connectivity during resting-state EEG was estimated via alpha band imaginary coherence to test whether it correlated with visuospatial performance and motor skill acquisition. As a preliminary step towards leveraging the frontoparietal network for EEG-neurofeedback applications, this work found that alpha imaginary coherence was positively correlated with visuospatial function, but not with motor skill acquisition during a limited dose of motor practice (only 5 trials). This work establishes a premise for developing frontoparietal alpha IC-based neurofeedback for cognitive training in rehabilitation, while warranting future studies to test the relationship between alpha IC and motor learning with a more extensive motor training regimen.

DEDICATION

To grandma.

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CHAPTER 1

INTRODUCTION

1.1 Background

Improving motor performance in rehabilitation and sports, controlling surgical tools, and controlling brain-computer interfaces all require repetitive practice of a particular skill. However, when attempting to learn or adapt a motor skill, some individuals learn slower (or not at all) compared to others despite practicing the same amount (Brooks, Hilperath, Brooks, Ross, & Freund, 1995) (i.e., a slow learner or 'non-learner'). This observation leads to the following questions: What factors contributed to variability in motor learning? Are there viable methods to enhance motor learning to benefit motor rehabilitation? This dissertation aims to identify factors and methods to enhance motor learning, which could in turn be used to optimize motor rehabilitation and/or sport performance.

Motor learning is a relatively permanent change in the ability to execute movements as a result of practice or experience (Schmidt, 2005). In this dissertation, motor learning is described via skill acquisition (which characterizes the within-session changes in performance of a skill during the actual process of motor practice), as well as via a retention test (which tests the amount of learning retained after a period of no practice/consolidation). Thus, motor learning can be regarded as the formation and retention of motor memories. In this fashion, motor skill acquisition is considered to measure memory encoding, whereas motor retention reflects consolidation and retrieval (Kantak & Winstein, 2012).

Recent evidence from our lab has shown that the extent of motor skill learning is related to visuospatial ability (Schaefer & Duff, 2017; Lingo VanGilder, Hengge, Duff, & Schaefer, 2018). Specifically, higher one-month motor retention of a functional reaching task is correlated with higher scores of the Visuospatial/Constructional Index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in cognitively intact older adults (Lingo VanGilder et al., 2018), providing initial evidence that visuospatial ability could explain differences in motor learning. This relationship is also supported by neuroimaging studies showing that motor learning and visuospatial processes share common frontoparietal neural structures (Brandes-Aitken et al., 2019; Regan et al., 2021; Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012). Furthermore, functional connectivity between frontal and parietal cortical regions has been shown to predict both visuospatial processes (Cooper et al., 2015) and the learning of a visuomotor task (Wu, Knapp, Cramer, & Srinivasan, 2018; Wu, Srinivasan, Kaur, & Cramer, 2014; Zhou et al., 2018). Thus, frontoparietal networks may be a crucial neural correlate for the interaction between cognitive processes and early-stage motor learning (Fitts & Posner, 1967). And this visuospatial-motor relationship may be more pronounced in the right hemisphere compared to the left, based on neuropsychological findings of right hemispheric (parietal) specialization for visuospatial processes (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Foxe, McCourt, & Javitt, 2003).

Collectively, these behavioral and neuroimaging studies suggest that the right frontoparietal networks may be crucial neural correlates for motor learning, due to the established interaction between motor learning and visuospatial processes. However, it remains unknown whether modulation of this network (i.e., neuromodulation) will mediate changes in motor learning processes. Thus, the overall objective of this dissertation is to determine if aspects of motor learning (such as the rate and extent of skill acquisition) are modifiable through neuromodulation of the right frontoparietal network. This work innovates in its targeting of frontoparietal networks to modulate motor learning, as most studies target motor cortices as their regions of interest. The longer-term goal of this work is to identify viable methods to enhance motor learning in the context of clinical motor rehabilitation.

1.2 Specific Aims of this dissertation

To this end, two neuromodulation techniques are explored in two aims: transcranial direct current stimulation (tDCS; Aim 1) and electroencephalography (EEG)-based neurofeedback (Aim 2), each with slightly different focus and ambitions.

<u>Aim 1: To test whether right parietal anodal tDCS modulates visuospatial ability and motor skill acquisition.</u> By adopting a more robust study design, this aim also quantified placebo effects induced by expectations of tDCS on motor skill acquisition. tDCS is a non-invasive brain stimulation technique, which delivers a direct current (DC) through scalp electrodes to modulate spontaneous neural activity (Fritsch et al., 2010). A number of previous studies have attempted to use tDCS enhance motor learning, but with mixed results (Buch et al., 2017). Here, I emphasize that the overwhelming majority of these studies targeted primary motor areas, while few have targeted right parietal regions or frontoparietal networks, which may help clarify the equivocal findings. In addition,

tDCS research faces reproducibility challenges due to its high response variability (Vannorsdall et al., 2016). However, studies of response variability of tDCS have largely ignored the effect of individual differences in expectation, which could induce placebo effects that can be comparable true treatment effects (Moseley et al., 2002). Considering expectations is an important merit for this aim, since expectations alone can manipulate motor performance and learning (Wulf & Lewthwaite, 2016). However, to the best of my knowledge, variance in expectations was rarely measured or controlled for in tDCS-motor studies, and no study has compared the magnitudes of a placebo (expectancy) effect and a true treatment effect of tDCS on motor learning. Thus, Aim 1 was expanded to examine the strengths of both the tDCS treatment effect on motor learning, as well as its placebo effect.

<u>Aim 2: To test whether connectivity between right frontal and parietal regions at rest (measured by resting-state EEG alpha coherence) is related to both visuospatial function and early skill acquisition.</u> This aim is a preliminary and necessary step towards determining if EEG-neurofeedback may be effective in modulating the frontoparietal network to enhance motor learning. EEG-neurofeedback is a type of biofeedback in which EEG signals are analyzed and presented to the participants in real-time to facilitate self-regulation/modulation of neural activities (Sitaram et al., 2017). In EEG-neurofeedback, most protocols use amplitude- and power-based feedback that do not directly leverage the dynamic connectivity of brain networks. To provide information about the frontoparietal network through EEG coherence, an option is to employ EEG-coherence as a target signal, which measures the degree of synchronization between

oscillations of different neuronal ensembles underlying any two scalp electrodes (Nunez, Nunez, & Srinivasan, 2016). Thus, it is necessary to first establish whether EEG frontoparietal coherence is the functional correlate of visuospatial function and motor learning. As such, Aim 2 is a crucial step to establish an important brain-behavior relationship, and will thereby provide necessary evidence for using frontoparietal coherence for EEG-neurofeedback training for motor skill acquisition in the future.

1.3 Organization of this dissertation

This dissertation has seven chapters. Chapter 1 (the current chapter) provides background, motivation, and overall aims for the work described in this dissertation.

Chapters 2 and 3 are two studies that incrementally replicated and expanded on the key relationship between visuospatial function and motor learning. They serve as foundational work to further the scientific premise for the major aims. Chapter 2 replicated previous findings relating visuospatial function to motor learning by with a shorter, simpler cognitive screen (the Montreal Cognitive Assessment), a different retention test interval (24-hours), and a participant sample across a wider age range (39-89 years old) than our previous study (Lingo VanGilder et al., 2018). Chapter 2 is adapted from my previously published manuscript in the *Journal of Motor Learning and Development* (Wang, Infurna, & Schaefer, 2019). Chapter 3 investigates how visuospatial function impacted motor skill acquisition during motor training in a cohort of healthy older adults. The work in Chapter 3 extends the findings from motor retention (in Chapter 2) to within-session skill acquisition. The method used in Chapter 3 – nonlinear mixed effects modeling – was also the major approach for following chapters. This chapter will be submitted to *Nature Aging* at the completion of this dissertation.

Chapters 4 and 5 focus on the effect of tDCS on motor learning (Aim 1). Chapter 4 is adapted from my previous publication in the journal *Brain Stimulation* (Wang, Hooyman, Schambra, Lohse, & Schaefer, 2021). This editorial described how the expectation of tDCS for improving motor performance is common and variable, thereby confirming the motivation and study design for Chapter 5. Chapter 5 discusses the treatment and placebo effects from right parietal tDCS on visuospatial performance and motor skill acquisition. The study for Chapter 5 has been pre-registered on Open Science Framework, and is still ongoing. Preliminary findings are presented here, and the work will be published upon its completion.

Chapter 6 describes the methodology for analyzing resting-state EEG alpha frontoparietal coherence, and its relationship with visuospatial function and motor performance (Aim 2). This chapter will be submitted as an abstract to the 2021 Society for Neuroscience annual conference and for publication in the journal *Neuroregulation*.

Lastly, Chapter 7 is a general discussion about the overall findings of this dissertation. I also provide my own reflections on research within the field of motor learning and neuromodulation.

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CHAPTER 2

PREDICTING MOTOR SKILL LEARNING IN OLDER ADULTS USING VISUOSPATIAL PERFORMANCE

Abstract

Between-group comparisons of older and younger adults suggest that motor learning decreases with advancing age. However, such comparisons do not necessarily account for group differences in cognitive function, despite the co-occurrence of aging and cognitive decline. As such, cognitive differences may explain the observed age effects on motor learning. Recent work has shown that the extent to which a motor task is learned is related to visuospatial function in adults over age 65. The current study tested whether this relationship is replicable across a wider age range and with a brief, widely available cognitive test. Thirty-three adults (aged 39-89 years old) completed the Montreal Cognitive Assessment (MoCA) prior to practicing a functional upper extremity motor task; performance on the motor task was assessed 24 hours later to quantify learning. Backward elimination stepwise linear regression identified which cognitive domains significantly predicted retention. Consistent with previous findings, only the Visuospatial/Executive subtest score predicted change in performance 24 hours later, even when accounting for participant age. Thus, the age-related declines in motor learning that have been reported previously may be explained in part by deficits in visuospatial function that can occur with advancing age.

Introduction

Much of what is known about aging and motor learning has come from between-group comparisons of older (typically 65 years and older) and younger adults (typically college-aged). The current consensus is that older adults tend to retain less motor skill after practice compared to younger adults, as evidenced by several types of motor learning paradigms, including sensorimotor adaptation (McNay & Willingham, 1998; Seidler, 2006), complex motor skill acquisition (Brown, Robertson, & Press, 2009; Pratt, Chasteen, & Abrams, 1994), and motor sequence learning (Ehsani, Abdollahi, Mohseni Bandpei, Zahiri, & Jaberzadeh, 2015; Harrington & Haaland, 1992). While this suggests that motor learning capacity, on average, decreases with advancing age, comparing learning between older and younger adults tends to overlook 1) the notable variations in motor learning within older age groups (Bock & Girgenrath, 2006; Ehsani et al., 2015) and 2) the age-related differences in cognition (Harada, Natelson Love, & Triebel, 2013; Hedden & Gabrieli, 2004) despite the reliance of motor learning on cognitive processes, especially in the early stages (Fitts & Posner, 1967). Thus, differences in cognitive status may explain why older adults tend to have poorer motor learning outcomes than younger adults.

Motor learning is a relatively permanent change in the ability to execute movements as a result of practice or experience (Schmidt & Lee, 2005). As such, the extent of learning can be approximated by the amount of improvement following a period of delayed retention (Kantak & Winstein, 2012). Recent findings have suggested that neither chronological age nor global cognitive status is predictive of retained improvements (Schaefer, Dibble, & Duff, 2015; Schaefer & Duff, 2015), while visuospatial function may be (Schaefer & Duff, 2017; VanGilder, Hengge, Duff, & Schaefer, 2018). However, these studies only used one neuropsychological assessment (the Repeatable Battery for the Neuropsychological Status, RBANS) (Randolph, 1998) and only tested adults age 65 years and older, making it unclear whether these previous findings truly reflect a relationship between visuospatial function and motor learning, or are simply an artifact of the cognitive test used. Thus, the purpose of this study was to test the robustness of the previous findings with the more commonly used Montreal Cognitive Assessment (MoCA) (Brenkel, Shulman, Hazan, Herrmann, & Owen, 2017; Tsoi, Chan, Hirai, Wong, & Kwok, 2015), and with a wider age range. We hypothesized that the Visuospatial/Executive subtest of the MoCA would be the most predictive of how much participants learned the motor task, compared to all other MoCA subtests.

Methods

Participants

Data from thirty-three adults (aged 39-89 years old) with no self-reported physician-diagnosed neurological disorders (e.g. no history of stroke, Parkinson's disease, or dementia) were retrospectively analyzed. Informed consent was obtained prior to study participation. The research procedures were approved by the University Institutional Review Board, in accordance with the Helsinki Declaration.

Cognitive, sensorimotor, and functional assessments

Cognitive status was measured using the Montreal Cognitive Assessment (MoCA), a brief and widely-available screening tool. It has seven subtests including Visuospatial/Executive, Naming, Attention, Language, Abstraction, Delayed Recall and Orientation (Nasreddine et al., 2005). The subtests are summed to provide a total score of 0-30 points ("normal" total score cut-off ≥ 26), with higher scores indicating better overall cognitive status. Although it is typically used as a cognitive screen, it can be used in cognitively-intact individuals for purposes such as quantifying overall function (e.g., Kenny et al., 2013), change over time (e.g., Krishnan et al., 2017) or acute cognitive performance (e.g., Kaliyaperumal, Elango, Alagesan, & Santhanakrishanan, 2017). Unlike other more expensive and more time-consuming cognitive assessments (e.g., Repeatable Battery for the Assessment of Neuropsychological Assessment or Wechsler Adult Intelligence Scale), the MoCA is not age-adjusted against normative data and therefore does not account for age-related differences in its scoring, although studies associate lower scores with older age (Malek-Ahmadi, O'Connor, Schofield, Coon, & Zamrini, 2018; Rossetti, Lacritz, Cullum, & Weiner, 2011), even in cognitively-intact adults (Krishnan et al., 2017; Oren et al., 2015).

Sensorimotor function of the tested hand was characterized using tactile sensation, grip strength and handedness. Tactile sensation was measured with Semmes Weinstein monofilaments (Touch-Test, North Coast Medical, Inc, Gilroy, CA) at the distal end of the index finger. Maximal grip strength of the tested hand was tested via hand dynamometer (Jamar, Sammons-Preston-Rolyan, Bolingbrook, IL) (Andrews, Thomas, & Bohannon, 1996) as the average of three consecutive measurements. Hand dominance was determined using a modified Edinburgh Handedness Questionnaire.

General disability was screened for with the Index of Independence in Activities of Daily Living (Katz, Downs, Cash, & Grotz, 1970), in order to assess functional ability in daily life and to rule out the presence of dementia. This index is a paper-and-pencil test in which participants report their level of assistance needed to complete each of the six ADL functions: feeding, continence, transferring, going to toilet, dressing, and bathing. Reports of "no assistance needed" were scored as 1; the maximum (worst) score was 18, which indicated "dependent in all six functions." Thus, a total score of 6 indicates no disability (best). All cognitive, sensorimotor, and functional assessments were administered only one time in this study.

Upper extremity motor task

The upper extremity motor task used in this study was a functional motor task involving reaching, grasping, and object manipulation (Fig. 1). In this task, participants were required to use their nondominant hand to spoon raw kidney beans from a "home cup", to one of three distal cups as fast as possible. Because this task is used to study changes in performance over time due to practice, the nondominant hand was used to minimize any ceiling effects (Schaefer, 2015). The cups (9.5 cm in diameter) were fixed to a thin board (60.5 cm × 40.0 cm). The home cup was oriented along the participant's midline and 15 cm in front of the seated participant. The three distal target cups were radially placed 16 cm away around the home cup at 45°, 90°, and 135°. One trial of the motor task consisted of 15 repetitions of spooning two and only two beans at once from the home cup to one of the target cups. Participants first moved beans to the ipsilateral cup, then to the middle cup, and lastly to the contralateral cup, with respect to their nondominant hand. This procedure was repeated for five times in one trial, resulting in 15 repetitions in total. Each trial began when the participants picked up the spoon (plastic, 5.21 g) and ended when participants finished 15 repetitions. If any beans were dropped during transport, participants were instructed not to re-scoop them, but to proceed on to the next repetition; this repetition was counted as an error. The error rate in this sample was <1% of total repetitions, and therefore not considered as a factor in learning. Trial time (to the nearest 100th of a second via stopwatch) was recorded.

Figure 1. Overhead view of motor task apparatus. The start and center locations were placed at participants' midlines.

Experimental Protocol

Participants were evaluated over two consecutive days. On Day 1, participants completed all cognitive, sensorimotor, and functional assessments, then completed two trials of the functional motor task for familiarization. Then participants completed 50 trials of the functional motor task (i.e., a total of 750 out-and-back movements). Baseline performance on the motor task was defined as the trial time of the first practice trial. On Day 2, participants completed a follow-up trial of the functional motor task 24 hours later. We note that only the motor task was re-evaluated on Day 2; the MoCA nor any of the other assessments were not.

Data and statistical analyses

The primary measure of motor learning was the change in trial time from baseline on Day 1 to follow-up on Day 2, normalized to baseline performance (Eq. 1):

$$24h\ performance\ change = \frac{Trial\ Time_{baseline} - Trial\ Time_{follow-up}}{Trial\ Time_{baseline}} \times 100 \quad (1)$$

A positive value indicates improved task performance 24 hours later, relative to baseline, with higher values indicated more learning. This measure quantified the extent to which individuals learned the task (Schaefer et al., 2015; VanGilder et al., 2018). Additional measures of interest were within-session performance change and retention. Within-session performance change was quantified as the change in trial time between baseline and the last practice trial on Day 1, normalized to baseline (Eq. 2):

$$within - session\ perf.change = \frac{Trial\ Time_{baseline} - Trial\ Time_{last\ trial}}{Trial\ Time_{baseline}} \times 100 \quad (2)$$

Again, a positive value indicates improved task performance at the end of practice, relative to baseline. This measure reflects more transient, immediate changes in response to repetitive practice, whereas Equation 1 reflects more persistent, longer-lasting effects that are conceptualized as learning (Kantak & Winstein, 2012). Lastly, retention was quantified as the change in trial time between the last trial of practice on Day 1 and follow-up on Day 2, normalized to baseline (Eq. 3):

$$retention = \frac{Trial\ Time_{last\ trial} - Trial\ Time_{follow-up}}{Trial\ Time_{baseline}} \times 100 \qquad (3)$$

This measure reflects the relative permanence of the level of performance achieved in acquisition (Kantak & Winstein, 2012) and is based on established measures of relative retention (Schmidt & Lee, 2005). To account for any initial differences in motor performance, due to factors such as age-related slowing (Birren & Fisher, 1991, 1995; Krampe, 2002; Myerson, Hale, Wagstaff, Poon, & Smith, 1990), all measures were normalized to baseline for each participant as recommended by Nuzzo, 2018.

To test whether individual subtest(s) of the MoCA significantly predicted 24-hour performance change (i.e., learning), within-session performance change (i.e., acquisition), and retention, all scores of the MoCA subtests (Visuospatial/Executive, Naming, Attention, Language, Abstraction, Delayed Recall and Orientation) were entered into three separate backward elimination stepwise linear regression models with an elimination criterion of $p > .05$. However, because the MoCA is not an age-adjusted assessment, participant age and any significant predictor(s) remaining from the stepwise regression were entered into a second regression model. Statistical analyses were done using R 3.4.1 (R Core Team, 2017). Any correlation coefficients (r) greater than 0.59 were considered to be strong, between 0.30 and 0.59 were moderate, and below 0.30 were weak effect sizes (Cohen, 1988).

Results

Summary statistics for participants are provided in Table 1, including age, education, ADL index, cognitive and sensorimotor variables. Most participants had intact tactile sensation in the tested hand (finest Semmes-Weinstein monofilament detectable, 2.83: n = 22; next finest detectable, 3.61: n = 9). Only two of the 33 participants had 'diminished protective sensation' in their index finger based on monofilament results. As shown in Table 1, the mean and standard deviation for the MoCA Total Score was 24.79 ± 2.65 (range = 18 - 30). Scores for each subtest of the MoCA are also provided in Table 1. Confirmatory analyses of linear regression indicated no significant relationship between baseline motor performance and the MoCA total score (p = .51), verifying that lower cognitive status did not interfere with participants' ability to understand the instructions and perform the motor task initially.

Table 1 Participant characteristics.

	Mean (*SD*)	Range
Age (years)	69.91 (11.41)	39 - 89
Education (years)	14.97 (2.51)	21-12 月
Grip strength (kg)	24.32 (8.38)	6.67 - 44.00
MoCA Total score	24.79 (2.65)	18 - 30
Visuospatial/Executive	3.56 (0.90)	5-2 月
Attention	5.27 (1.04)	6-2 月
Naming	2.91 (0.29)	3-2 月
Language	2.24 (0.87)	0 - 3
Abstraction	1.58 (0.71)	0 - 3
Delayed Recall	3.16 (1.51)	0 - 5
Orientation	5.97 (0.17)	6-5 月
Katz ADL Total score[a]	6.13(0.71)	10-6 月

n = 33; 8 males and 25 Females. 2 Left-handed, 31 Right-handed.

[a] All Katz ADL Total scores > 6 were due to continence issues, not upper extremity issues.

As expected, practice on the motor task improved participants' performance. Figure 2 shows how trial time decreased (i.e., improved) over the course of the 50 practice trials on Day 1 across participants. Also shown in Figure 2 is the mean (and standard error) trial time at the 24-hour follow-up. As described above, this trial was compared to participants' first trial on Day 1 to quantify the amount of learning (see Eq. 1). Overall, the amount of learning was significant with mean±SD = 13.38±13.68% (95% CI [8.71, 18.05]). However, the large standard deviation also indicated a wide range in this measure. As such, this study aimed to test whether variation in motor learning could be explained by cognitive factors associated with aging, described next.

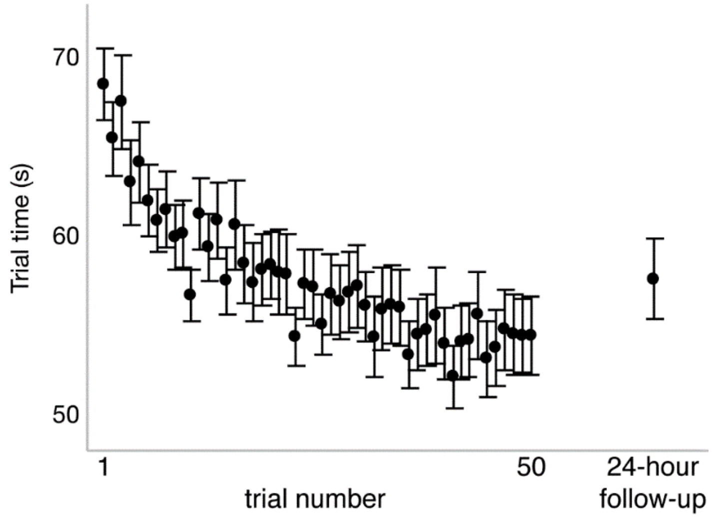

Figure 2. Task performance over time. Mean trial time for trials 1 through 50 on Day 1, and for the follow-up trial 24 hours later on Day 2. Error bars indicate standard error.

Relationship between learning and MoCA subtests

Bivariate linear regression revealed that none of the dependent variables were significantly correlated with the total MoCA score (all $p > .27$), indicating that learning, acquisition, and retention were not predicted by global cognitive status. Because the MoCA is comprised of seven subtests, however, individual subtest scores were entered into a backward elimination stepwise linear regression to identify whether specific cognitive domains could predict learning. The final model revealed that the only significant predictor of 24-hour performance change (see Eq. 1) was the Visuospatial/Executive score ($R^2 = 0.21$; adjusted $R^2 = .19$, $p = .007$), indicating a moderate effect size (Figure 3). Table 2 provides the iterative stepwise elimination of each predictor based on $p > .05$. Stepwise regressions for within-session performance change (Eq. 2) and retention (Eq. 3) measures eliminated all MoCA subtests as predictors, indicating no significant relationships (all $p > .05$).

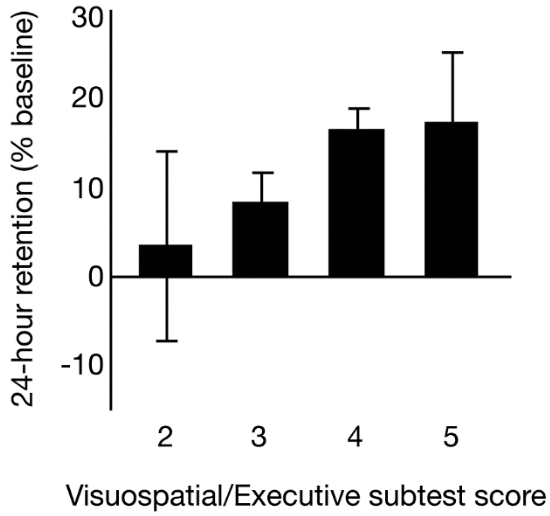

Figure 3. Retention and visuospatial function. Mean 24-hour performance change for each value of Visuospatial/Executive subtest score. (No participant had scores of 0 or 1). Error bars indicate standard error.

Table 2. Results from backwards elimination stepwise regression.

	Intercept	Visuospatial/ Executive	Naming	Language	Attention	Orientation	Delayed Recall	Abstraction	R^2	Adjusted R^2
B	21.36	11.96*	13.38	-2.52	-2.30	-12.36	0.61	-0.39		
SE B	80.93	2.84	7.14	3.14	2.04	13.91	1.43	3.27	0.48	0.33
β		0.75	0.29	-0.16	-0.18	-0.16	0.07	-0.02		
B	23.39	11.91*	13.44	-2.63	-2.30	-12.82	0.63			
SE B	77.57	2.76	6.98	2.95	2.00	13.11	1.39		0.48	0.36
β		0.76	0.29	-0.16	-0.18	-0.17	0.07			
B	-2.17	10.46*	13.28	-3.99	-1.62	-7.20				
SE B	82.10	2.82	7.27	3.09	2.10	13.87			0.37	0.26
β		0.69	0.28	-0.25	-0.12	-0.09				
B	-42.55*	10.40*	13.33	-4.61	-1.84					
SE B	26.07	2.78	7.18	2.82	2.03				0.37	0.28
β		0.69	0.28	-0.29	-0.14					
B	-52.68*	9.96*	13.94	-4.50						
SE B	23.47	2.73	7.12	2.81					0.35	0.28
β		0.66	0.30	-0.29						
B	-52.51*	7.61*	13.29						0.29	0.24

	Intercept	Visuospatial/ Executive	Naming	Language	Attention	Orientation	Delayed Recall	Abstraction	R^2	Adjusted R^2
SE B	24.08	2.36	7.29							
β		0.50	0.28							
B	-11.52	6.96*								
SE B	8.91	2.42							0.21	0.19
β		0.46								

Note. Dependent variable was 24-hour performance change. Independent variables were scores from subtests of the MoCA. The final model shows that only Visuospatial/Executive score of the MoCA predicted 24-hour performance change.
* p < .05.

Because the MoCA does not account for age (Nasreddine et al., 2005), age was added to the final regression model to account for any potential age-related differences in MoCA scores. As shown in Table 3, both Visuospatial/Executive score (p = .04) and age (p = .02) were significantly related to 24-hour performance change, indicating that participants' visuospatial function predicts learning above and beyond their age.

Table 3. Regression coefficients predicting 24-hour performance change.

	B	*SE B*	β	R^2	Adjusted R^2
Intercept	27.17	17.61		0.35	0.30
Age	-0.46*	0.19	-0.39		
Visuospatial/Executive	5.19*	2.35	0.34		

*p < .05.

Discussion

The purpose of this study was to test whether the Visuospatial/Executive subtest of the MoCA predicted learning of a functional motor task, as measured by a change in performance at a 24-hour follow-up. The relationship between visuospatial function and motor learning has been suggested by previous studies using a lengthier cognitive test in adults over age 65 with and without cognitive impairment (Schaefer and Duff 2017; VanGilder et al. 2018), but this study extends these findings by demonstrating the same trend with a briefer cognitive screen and in a wider age range.

Moreover, the Visuospatial/Executive score of the MoCA remained a significant predictor of learning even when accounting for participant age, suggesting that earlier studies showing age-related declines in motor learning (e.g., Harrington & Haaland, 1992) may in part be due to age-related visuospatial deficits (Techentin, Voyer, & Voyer, 2014). In other words, two older adults may have the same chronological age but one may have visuospatial deficits, while the other does not, resulting in differences in motor learning. This was the case in this study, for example, with two participants with similar ages (age 67 and 68), but one had a Visuospatial/Executive score of 2 and had a learning value of -19.4%. This is contrast to another who had a Visuospatial/Executive score of 5 and had a learning value of +28.5%. These findings, particularly in the context of previous work (Schaefer & Duff, 2017; VanGilder et al., 2018), suggest that visuospatial tests could be used in rehabilitation to predict how much an older patient can recover motor skill and/or probe the patient's capacity for skill learning.

Furthermore, this study adds to the longstanding findings of Fleishman and Rich (1963), which showed that the early stages of learning a new motor task rely on visuospatial abilities. By re-testing participants 24 hours after practice, the current study extends this classical paper to show the role of visuospatial ability not just early on (as shown by Fleishman & Rich, 1963) but also for inducing longer-lasting change. The lack of relationship between the Visuospatial/Executive subtest and the acquisition and retention measures further underscores the role that visuospatial abilities play in the process of learning, rather than in immediate and transient behavioral changes. This relationship thereby raises interesting questions about 1) the underlying mechanism and, in turn, 2) the practical application of this study. The extent to which older adults learn to compensate for visuomotor perturbations has been associated with spatial working memory processes linked to mental rotation (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2009; Fernandez-Ruiz, Wong, Armstrong, & Flanagan, 2011). Moreover, Jeunet and colleagues have shown that the ability to learn motor imagery brain-computer interfaces (i.e., BCI literacy) is also related to mental rotation (Jeunet, N'Kaoua, Subramanian, Hachet, & Lotte, 2015), so much so that they advocate for additional training for people who perform poorly on mental rotation tasks initially (Jeunet, Jahanpour, & Lotte, 2016). These studies implicate a shared mechanism between visuospatial ability (specifically mental rotation) and motor learning that leads to hypotheses about learning enhancement. There is evidence that visuospatial abilities, including mental rotation, can be improved through targeted interventions (Hohenfeld et al., 2017; Oldrati, Colombo, & Antonietti, 2018; Zhou et al., 2018), which, in the context of the current study, would suggest that if older adults with low visuospatial scores (e.g., ≤2 on the MoCA subtest) underwent some sort of visuospatial training prior to motor practice, the visuospatial training may generalize to improve their motor learning. Future proof-of-concept studies are needed, however, as well as to identify what sorts of visuospatial training might generalize to improve motor learning above and beyond the known benefits of motor practice itself.

Interestingly, within-session performance change (i.e., acquisition) was not predicted by any global or specific cognitive measure, including visuospatial. Although the group overall improved over the course of practice on Day 1 (refer to Fig. 2), some individual participants actually showed negative acquisition values, indicating worse performance at the end of practice compared to the beginning. It is argued that within-session performance change is not reflective of true learning (Kantak & Winstein, 2012), particularly for older adults or neurological populations (Park & Schweighofer, 2017) due to fatiguability or attentional factors. Future studies are needed to identify which cognitive tests can predict poor acquisition in older adults such that their practice scheduling can be optimized, much like Schweighofer et al. (2011).

Finally, there are several limitations to this study. First, while the MoCA is a quick and simple test for probing global cognitive function, the individual subtests of the MoCA may not necessarily yield sufficient information to draw conclusions about specific impairments that can be detected by lengthier and more thorough neuropsychological testing (Moafmashhadi & Koski, 2013). Thus, the MoCA and its individual subtests are not typically used to diagnose any specific cognitive impairments, be they visuospatial or otherwise. Nevertheless, individual subtests have been used experimentally to explore cognitive predictors of functional outcomes in clinical settings (Schweizer, Al-Khindi, & Macdonald, 2012; Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011). Second, most neuropsychological assessments used clinically (e.g., Wechsler Adult Intelligence Scale, WAIS, or RBANS) report scores as age-adjusted percentiles to account for normal variations in chronological age, whereas the MoCA does not. However, once the effect of age was accounted for statistically in this study, the effect of the Visuospatial/Executive subtest on learning was still significant. Third, the visuospatial tests used in this study all involve a motor response (i.e., drawing). Although participants in this study completed the MoCA with their dominant hand and the motor practice with their nondominant hand, their scores on the Visuospatial/Executive subtest could in part reflect participants’ overall motor function, which could then partially explain variations in learning of the skill among older adults (Park & Schweighofer, 2017). Thus, future research should incorporate both motoric and non-motoric visuospatial tests to better control for any potential confounds. A more comprehensive visuospatial battery will also determine which specific visuospatial function(s), such as visuospatial working memory, mental rotation, visuoconstruction, or visual perception, are most predictive of motor skill learning.

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CHAPTER 3

MODELING ASSOCIATIONS BETWEEN VISUOSPATIAL MEMORY AND FUNCTIONAL MOTOR SKILL LEARNING IN OLDER ADULTS

Abstract

Age-related declines in motor learning are well-established, such as less and slower performance improvements due to practice. Visuospatial memory has been proposed as a key factor explaining age-related declines in sensorimotor adaptation (a specific form of motor learning), although few studies have used standardized visuospatial memory tests nor controlled for age-related visuospatial memory declines. This study now explores this relationship in motor skill learning, a broader form of motor learning that is relevant to rehabilitation of activities of daily living, while controlling for age and utilizing a standardized visuospatial memory test. Motor practice data from 49 nondemented older adults were retrospectively modeled as with three-parameter exponential decay functions, with age and visuospatial memory as covariates for model parameters. Higher visuospatial memory scores, after controlling for age, were associated with faster rates of within-session performance improvement and more one-week performance improvement, but only for relatively low skill levels.

Introduction

Numerous studies have shown that motor learning declines with advancing age, evidenced primarily as slower and less improvement in motor performance (e.g., motor sequence response time, bimanual coordination accuracy) during a single session of task exposure among older adults compared to younger adults (Harrington & Haaland, 1992; Swinnen, 1998). Sensorimotor adaptation demonstrates similar age-related decline, such that older adults typically show less and slower adaptation within-session while reaching to visual or dynamic perturbations than younger adults (Buch, Young, & Contreras-Vidal, 2003; Seidler, 2006; Vandevoorde & Orban de Xivry, 2019).

Visuospatial memory has recently been proposed as a key correlate for age-related declines in sensorimotor adaptation (Christou, Miall, Mcnab, & Galea, 2016; Trewartha, Garcia, Wolpert, & Flanagan, 2014; Wolpe et al., 2020), as evidenced by correlations between measures of visuospatial memory and motor adaptation measures (e.g., direction error and adaptation rate). However, since visuospatial memory can decline early in later adulthood, it is important to control for chronological age when associating visuospatial memory (or any other cognitive ability) and motor learning in an older adult sample. Otherwise, it is plausible that observed relationships between visuospatial memory and learning could in fact be mutually driven by other common age-related declines, such as cortical thickness or frailty (Drag et al., 2016; Ferreira et al., 2015; Wiesman & Wilson, 2019), rather than the actual visuospatial memory-motor learning relationship. To the best of our knowledge, very few studies have controlled for participant age (e.g., Wolpe et al., 2020), making it difficult to explore effects of visuospatial memory on motor learning without age as a confound. In another study, Anguera et al (2011) reported correlation between visuomotor adaptation and spatial working memory performance only in younger adults, but not within an older adult cohort. It is possible that this lack of replication was due to a lack of controlling for participant age within the older adult cohort, since this group had a wider age range (ages 71.4 ± 4.2 years) than their younger counterparts (ages 21.1 ± 2.5 years). Additionally, many previous studies have used non-standardized, unvalidated methods to evaluate and quantify visuospatial memory, rather than using standard neuropsychological tests to do so.

To better dissociate the effects of age and visuospatial function on motor learning, we have begun using standardized neuropsychological assessments. Consistent with work in visuomotor adaptation, we have shown that long-term functional motor skill learning (i.e., one-week or one-month retention) is associated with visuospatial components of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Lingo VanGilder, Hengge, Duff, & Schaefer, 2018; Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021; Schaefer & Duff, 2017). Other work has supported this as well (i.e., the visuospatial/executive subtest of the Montreal Cognitive Assessment, controlling for age) (Wang, Infurna, & Schaefer, 2020). When comparing across standardized neuropsychological tests of visuospatial function, our most recent study showed that the Delayed Recall portion of the Rey-Osterrieth Complex Figure Test (ROCFT) was the strongest predictor of long-term (i.e., one-month) learning (Lingo VanGilder et al., 2021), suggesting the findings from visuomotor adaptation studies on the role of visuospatial memory in aging and motor learning also apply to the learning of less constrained, more functional movements (like those performed in clinical motor rehabilitation) (Toglia, Fitzgerald, O’Dell, Mastrogiovanni, & Lin, 2011). To understand how generalizable previous models of adaptation are, however, it is important to test whether the ROCFT

Delayed Recall test is also associated with the acquisition (i.e., within-session changes in performance) of a more functional motor skill, rather than simply looking at long-term retention.

Thus, the purpose of this study was to investigate whether the delayed recall portion of the ROCFT test (a standardized visuospatial memory test) is associated with performance changes on a functional motor task during a single session of practice (i.e., skill acquisition) in older adults, even after controlling for age. To this end, data from the initial motor practice session reported by Lingo VanGilder et al. (2020) was retrospectively analyzed. This dataset was chosen because it demonstrated the expected association between one-month motor retention and visuospatial memory, but did not investigate within-session change. In the analyses presented here, performance changes during motor practice were modeled with a three-parameter exponential decay function to capture rate and amplitude of change, with age and the ROCFT delayed recall scores as covariates. We therefore hypothesized that the rate of skill acquisition would be negatively associated with age and positively associated with delayed recall score.

METHODS

Participants

A subset of data included in this study has been published previously (VanGilder et al., 2020). The current study includes additional participants and different timepoints in the longitudinal design. Fifty-one nondemented, community-dwelling older adults provided informed consent prior to study participation. This study was approved by the

Arizona State University Institutional Review Board (Study 000004214). The current study evaluated 20 trials (15 reaches each, totaling 300 reaches) of motor task performance (to assess initial skill acquisition over the initial practice session) and two trials of motor task performance at the beginning of the second practice session (to assess one-week improvement), as well as demographic and visuospatial data collected prior to motor practice. Prior to any analysis, two participants were excluded from the current study for being ambidextrous or having neurological dysfunction, resulting in a sample size of 49 (69.69 ± 6.35 years; 17 males, 32 females). More information about the motor task, as well as visuospatial assessments, is provided below.

Experimental design and protocol

The motor practice session considered in this study consisted of 50 trials of a functional upper extremity task (Fig. 1). Construct validity (Schaefer & Hengge, 2016) and ecological validity (Schaefer et al., 2020) of the task have been established previously. The task was completed with the nondominant hand to minimize ceiling effects (Schaefer, 2015). For each trial, participants use their nondominant hand to acquire and transport two raw pinto beans at a time from a center 'home' cup to one of three target cups, arranged at a radius of 16 cm relative to the home cup. The home cup was placed at the participants' midline, with the target cups arranged at 0° and 40° to the left and right of the home cup (see Fig. 1). Participants were instructed to reach for the ipsilateral cup first, then the center cup, then the contralateral cup, then repeating this sequence four more times for a total of 15 reaches. Thus, one trial included 15 reaches, totaling 750 reaches in the practice session (50 trials x 15 reaches). The goal of the task was to complete each trial "as quickly yet as accurately as possible". Dropping beans or reaching to the wrong cup were counted as errors; we note, however, that the error rate for the dataset was 10.6%. The amount of time taken to complete all 15 reaches was recorded as *trial time*, with lower values indicating better task performance. In this study, *long-term motor learning* (sometimes referred to as 'longer-term learning' throughout) was quantified by comparing the average trial time from the first two trials of the practice session (i.e., baseline performance) with the average trial time of the first two trials at one-week follow-up testing (i.e., follow-up performance) One-week motor improvement, the measure of long-term learning, was calculated as the percent change from baseline to follow-up testing, normalized by baseline performance.

Figure 1. Motor task apparatus. This figure was adapted from "Dexterity and Reaching Motor Tasks" by MRL Laboratory licensed under CC BY 2.0.

Visuospatial assessment was done via the Rey-Osterrieth Complex Figure Test (ROCFT; Randolph, 1998), which includes a Copy trial (for visual construction), and immediate and delayed recall trials (for visuospatial memory). The delayed recall subtest from the ROCFT is the visuospatial variable of interest in this analysis. In brief, participants were presented with an image of a complex figure and asked to redraw it as accurately as possible; the image was then removed and a timer was set for 30 minutes, at which point participants were asked to redraw the image from memory.

Nonlinear mixed-effect modeling of motor skill acquisition

Based on previous literature (Lang & Bastian, 1999; Martin, Keating, Goodkin, Bastian, & Thach, 1996; Schaefer, Dibble, & Duff, 2015), motor performance data (trial time) for the first 20 practice trials were modeled with an exponential decay function for each participant, specified by:

$$Trial\ Time_{i,j} = A_j e^{-{}^{i}/_{\tau_j}} + C_j + \varepsilon_{i,j} \tag{1}$$

where *i* was trial number and *j* was participant number. Each of the three model parameters (A_j, τ_j and C_j) were estimated as the sum of a fixed term (representing the group mean) and a random term (representing individual variability). A_j, τ_j and C_j were assumed to be independent, log-normal random variables, and the error model was specified as exponential. Age, as well as ROCFT Delayed Recall score, was mean-centered and included as covariates for τ_j. Models were fitted using the MATLAB (Mathworks) *nlmefit* and *nolmefitsa* function. Model comparisons were based on BIC values and covariate effect was tested with the log-likelihood Ratio Test (Comets, Lavenu, & Lavielle, 2017). Quality of model fit was determined by root-mean-square error (RMSE).

Participant grouping criteria

Since it possible that some participants may not exhibit exponential learning during skill acquisition (Newell, Liu, & Mayer-Kress, 2001), we included an initial quality control step to examine whether this model was sufficient for our sample. To do so, we first fit the exponential decay model to all participants' data (initial model), and then examined the time constant parameter τ. As τ indicates the trial number at which performance is reduced to 0.37 (1/e) times the initial performance, a τ value of <1 is not functionally meaningful in terms of our design. Further, τ values <1 indicated considerable performance change from the first to second trial, with little improvement after the second trial, a pattern not amenable to being modeled with an exponential function. We therefore divided participants into two groups: a group whose modeled time constant τ (from the initial model) is greater than one, and another group whose τ is less than one and therefore removed from further modeling analyses. Further analyses of these parameter-based subgroups indicated that they differed based on initial skill level (see Results).

To verify the grouping criteria based on the value of τ, we created a family of 20 threshold values for τ between 0.1 and 2, at increments of 0.1. For each threshold value, participants with τ values below the threshold were removed, and we fit the exponential decay model again to the remaining participants' data. We then compared the RMSE of each of the 20 model fits and verified that the grouping criteria of τ equals one resulted in the best fit model.

Statistical Analyses

Independent two-sample t-tests were used to test whether the τ >1 and τ <1 groups were different in terms of age, visuospatial memory scores, and motor performance changes. Satterthwaite approximation was used to account for any unequal group variances. Multivariate linear regression was used to test for predictors of one-week motor improvement, including model parameters, age, and visuospatial memory scores. Robust linear regression was used to in some cases to reduce the effects of outliers, through the iteratively reweighted least squares algorithm implemented in MATLAB. This method is more robust than the standard least-squares regression, as it can identify and remove outliers and still estimates the model coefficients using ordinary least squares.

RESULTS

Model-based groups with distinct skill acquisition characteristics

Task performance data from one session (20 trials) of motor practice in 49 nondemented, community-dwelling older adults were analyzed here, along with follow-up performance data collected one-week after practice, ROCFT Delayed Recall scores and age.

To first quantify the rate and amplitude of skill acquisition for each participant, non-linear mixed-effect modelling was used to fit each participant's motor practice data with a decreasing exponential decay function (see Methods), which was characterized by three parameters: the amplitude, the time constant and the performance asymptote of the exponential decay. To determine whether this nonlinear mixed effects approach sufficiently quantified skill acquisition for all participants, model fit for each individual were plotted in Figure 2.

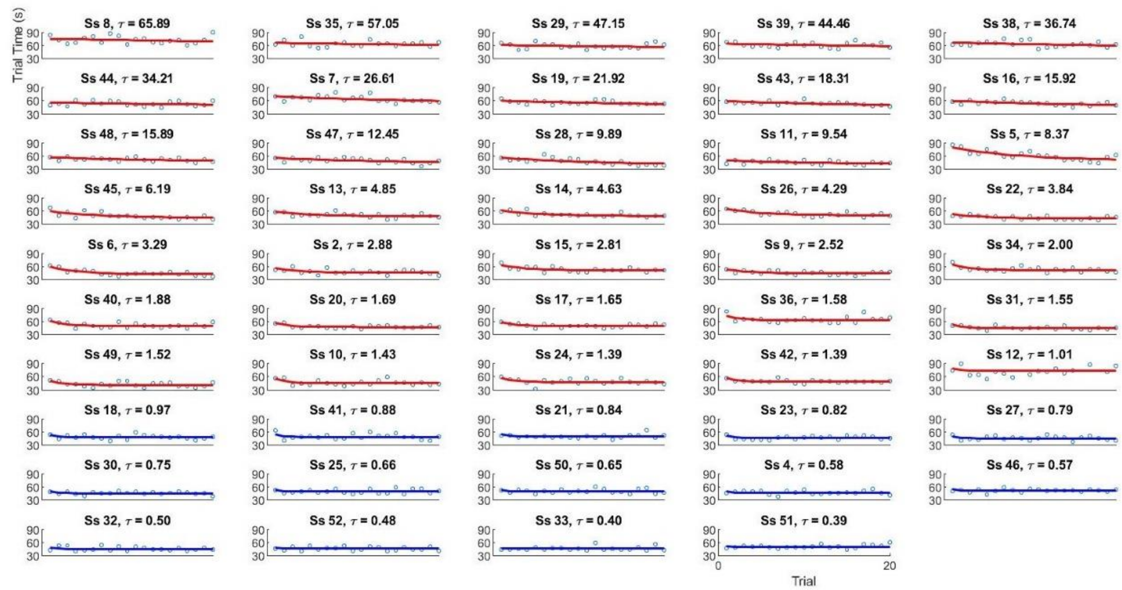

Figure 2. Individual model fits of within-session performance change. Participants were grouped based on their time constant (τ value). Red color indicates participants with τ >1; blue color indicates participants with *τ* <1.

As a group, participants demonstrated decrease in trial time characterized by the exponential decay function. However, a subset of participants had a time constant (*τ* value) <1, indicating that their task performance plateaued (according to the model) after the first trial; thus, their data from the practice session should not be modeled with an exponential decay fit (see blue curves in Fig 2, n = 14). Comparison of this subset to the remaining participants showed that they were had significantly better task performance initially (t-tests with Satterthwaite approximation for unequal variances: M = 49.74, SD = 5.50 vs. M = 60.84, SD = 9.95, $t(41.9)$ = - 4.97, $p < 0.000$), as well as average performance throughout the practice session (t-tests with Satterthwaite approximation: M

= 46.24, *SD* = 2.22 vs. *M* = 51.26, *SD* = 7.53, *t*(44.9) = - 3.57, $p < 0.001$) (Fig 3). Despite differences in initial and average performance, however, both groups demonstrated performance improvements (Fig. 4, panel C&D). Based on this, participants in this study were separated into two groups based on the τ parameter: a "high skill" group with $\tau < 1$ and a "low skill" group with $\tau > 1$. Group characteristics are summarized in Table 1. Note that these two groups had similar ROCFT Delayed Recall scores and age.

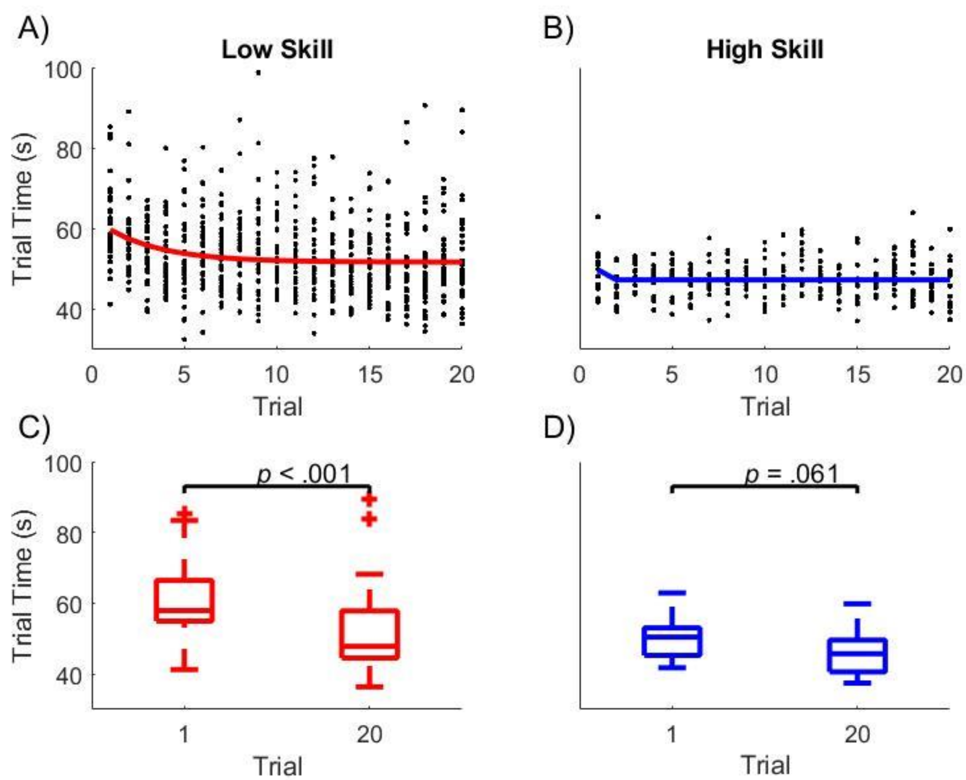

Figure 3. Within-session performance characteristics of the two groups. Red: low skill group; Blue: high skill group. A) Group level fit for the low skill group. B) Group level fit for the high skill group. Note how performance barely improved after the 2nd trial. C) Performance changes from trial 1 to 20 for low skill participants (1st trial versus 20th trial: 60.84 ± 9.95 vs. 51.95 ± 11.76, t(66.2) = 3.41, $p < 0.001$). D) Performance changes from trial 1 to 20 for high skill participants (1st trial versus 20th trial: 50.08 ± 5.56 vs. 46.60 ± 6.31, t(23.6) = 1.49, $p = 0.074$).

Table 1. Comparison of Low and High Skill Groups

	Low Skill (n = 35)		High Skill (n = 14)				
	M	*SD*	*M*	*SD*	*t*	*df*	*p*
Age, years	70.57	6.63	67.50	5.16	1.73	30.7	0.094
ROCF Delayed Recall	15.06	6.88	17.39	7.06	-1.05	23.5	0.303
Initial Performance, sec	60.84	9.95	49.74	5.50	-4.97	41.9	0.001
Average Performance, sec	51.26	7.53	46.24	2.22	-3.57	44.9	0.001
One-week improvement, %	9.34	11.96	5.01	7.85	1.48	36.6	0.148

Notes. *M*: mean, *SD*: standard deviation.

Effect of age and visuospatial memory on rate of skill acquisition

Since the "high skill" group did not follow an exponential decay pattern in terms of repeated task performance, only model parameters from the "low skill" group were compared to visuospatial memory and age. Specifically, ROCF Delayed Recall score and age were included as covariates to model parameters. For example, τ_j was modeled as:

$$\ln(\tau_j) = \beta_\tau + \beta_{age,\tau} \times age_j + \beta_{visuospatial,\tau} \times VS_j + b_\tau + \varepsilon_\tau \qquad (2)$$

where VS_j is the visuospatial score for subject j; β_τ is the fixed effect parameter; $\beta_{age,\tau}$ and $\beta_{visuospatial,\tau}$ are the fixed-effect coefficients for age and visuospatial memory scores, respectively; and b_τ is the random effect parameter. Model selection was based on Bayes information criterion (BIC), and significant covariate effects were identified via the log-likelihood ratio test. Results suggested that the best model was the one in which both age and ROCF Delayed Recall scores were included as covariates for the rate parameter. More detail on the consistency between model parameters and practice data is provided in Supplementary Material. Specifically, older age was associated with larger time constant, and thus a slower rate of skill acquisition (95% CI of $\beta_{age,\tau}$ [0.044, 0.189]). In contrast, higher (better) delayed recall scores were associated with smaller time constants (i.e., faster skill acquisition) (95% CI of $\beta_{Rey,\tau}$ [-0.147, -0.011]), thereby supporting the hypothesis. To illustrate this relationship, we performed median splits to separate participants based on their age and visuospatial memory scores (i.e., top and bottom 50th percentile), and visualized raw performances change data (Fig 4, A&B) as well as the predicted skill acquisition curve from the model (Fig. 4C). Figure 4C shows that better visuospatial memory scores correspond to faster skill acquisition, while controlling for age.

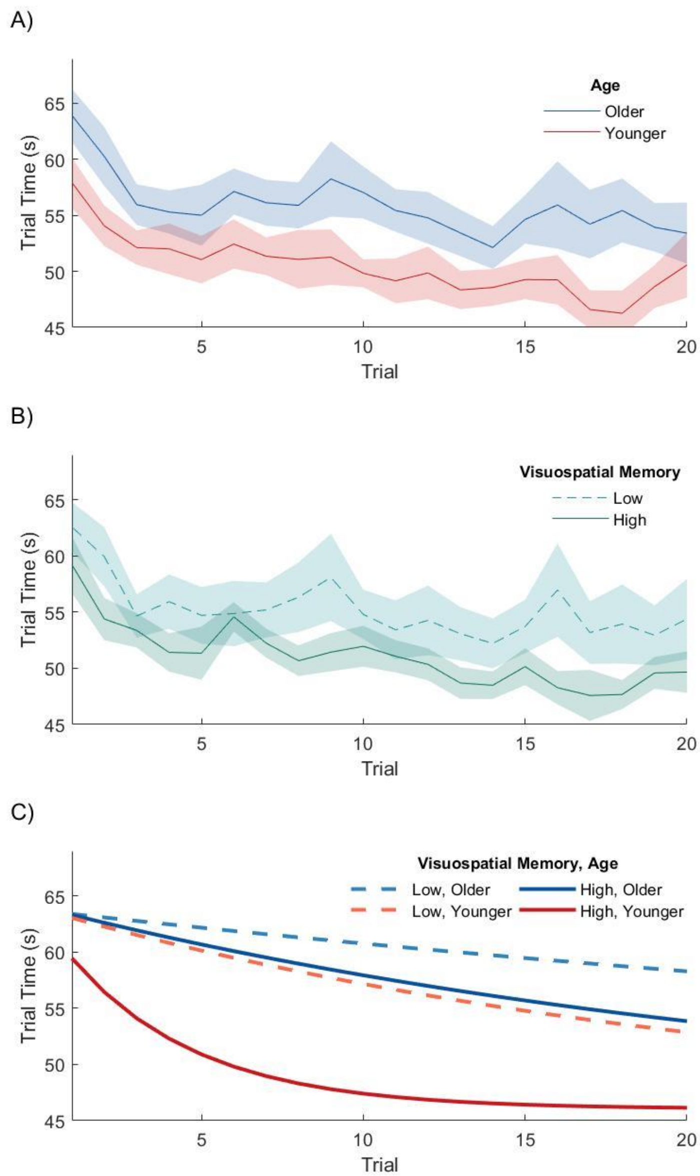

Figure 4. Effect of age and visuospatial memory on motor skill acquisition. For illustrative purposes, we performed median split on age and visuospatial memory scores. Participants were separately plotted based on younger (n = 17, blue) and older (n = 18, red) age, as well as low (n = 17, dashed line) and high (n = 18, solid line) visuospatial memory scores. A) Older age was associated with slower rate of skill acquisition. Line indicates group mean, whereas shaded patches indicate standard error. B) High visuospatial memory score was associated with faster rate of skill acquisition. C) Modeled skill acquisition curves by age and visuospatial memory scores. High visuospatial memory and younger age (n = 10, red, solid line) was associated with the fastest acquisition rate, whereas low visuospatial memory and older age (n = 9, blue, dashed line) was associated with the slowest rate. For the other two groups, n = 8.

Effect of visuospatial memory, but not age, on long-term motor improvement

Lastly, we tested the relationship between skill acquisition parameters (from the "low skill" group only) and one-week motor improvement (i.e., learning). Robust regression was used in place of regular linear regression to reduce the effect of outliers. Findings showed that the amplitude parameter *A* predicted one-week improvement (β = 1.85, $t = 4.75$, $R^2 = 0.42$, $p < 0.000$). The time-constant, τ, however, did not ($t = 0.32$, p = 0.753), indicating that the rate of skill acquisition was unrelated to how much skill was retained. However, it is plausible that the high vs. low skill groups could demonstrate differential effects of visuospatial memory and age on one-week motor improvement, which was not explored previously in this dataset since these subgroups had not been identified. In the low skill group, multiple linear regression revealed that ROCF Delayed Recall score predicted one-week improvement ($\beta = 0.72$, $t = 2.38$, $p < 0.024$; adjusted R^2 for overall model = 0.10), whereas age did not ($t = 0.10$, $p = 0.727$)[1]. In comparison, neither ROCFT Delayed Recall score nor age predict one-week improvement in the high skill group ($t = -1.03$, $p = 0.327$ and $t = -1.71$, $p = 0.116$, respectively). These results were consistent with the reports from previous skill acquisition studies that visuospatial function, rather than age, predict long-term performance improvements (Lingo VanGilder et al., 2018; Schaefer & Duff, 2017; Wang et al., 2020) and further clarified that ROCFT Delayed Recall score only predicted one-week improvement in the "low skill" group, but not the "high skill" group (Fig 5), despite the two groups being comparable in age, delayed recall scores and normalized skill improvement (refer to Table 1). Thus,

[1] Interaction was inspected and the resulting effect was not significant. Likelihood Ratio Test indicated no difference in model fit with the addition of the interaction term.

collectively these data suggest that age negatively impacted the rate of skill acquisition, but was not associated with the amount of long-term motor improvement in older adults, thereby supporting previous findings. After accounting for age, however, visuospatial memory (as measured by ROCFT Delayed Recall) was associated with faster skill acquisition and more long-term motor improvement (i.e., learning).

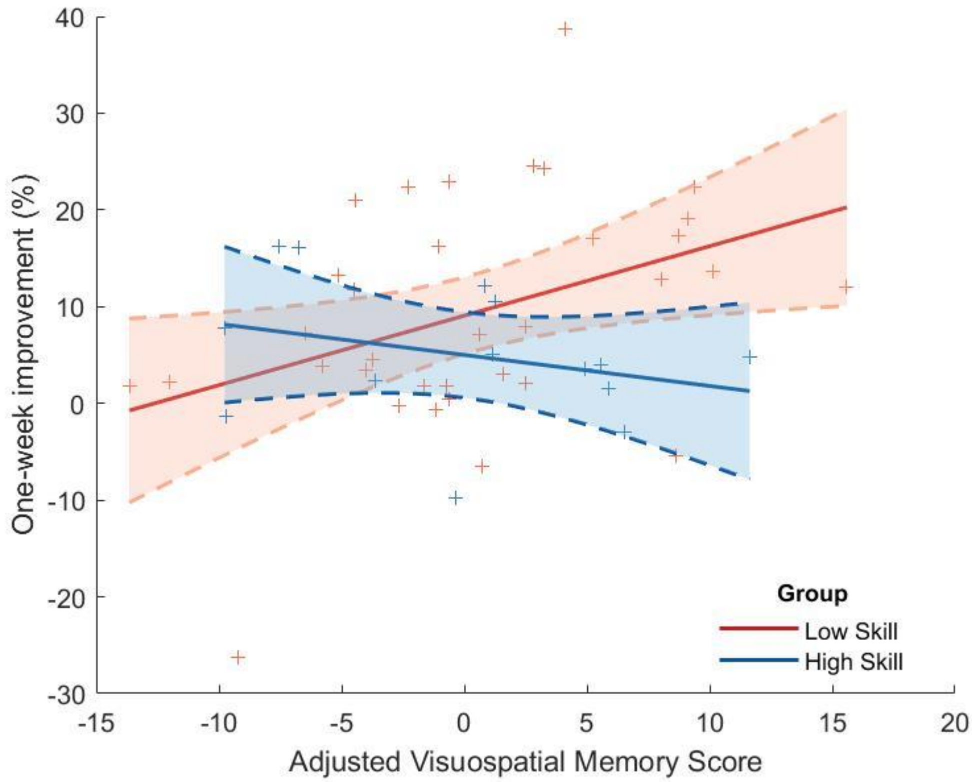

Figure 5. Correlations between visuospatial memory and one-week improvement. A positive correlation only existed for the low skill group. Scores were age-adjusted and mean-centered.

DISCUSSION

This study tested whether visuospatial memory, after controlling for age, was associated with motor skill acquisition. Modeling change in motor performance over the course of the first 20 practice trials with an exponential fit yielded two subgroups of participants: one group who demonstrated exponential learning and a relatively low level of skill on the task, and another group who did not demonstrate exponential learning but had relatively high level of skill on the task. The main finding of this analysis was that higher visuospatial memory scores were associated with faster rates of within-session skill acquisition and more longer-term (one-week) improvement in the low skill group, after controlling for age. This study expands on previous findings by clarifying that skill level (i.e., how good someone is at a task) may affect the relationship between motor learning and visuospatial memory, as the high skill group did not exhibit the significant associations observed in the low skill group. Age was negatively associated with rate of skill acquisition, but not with long-term performance improvements. Thus, visuospatial memory may offset the effect of chronological age on the rate of motor skill acquisition, and is more reflective of long-term skill learning than chronological age, especially when skill level is low.

Effect of visuospatial memory on motor skill learning

Results demonstrated that better visuospatial memory, as measured by higher ROCFT Delayed Recall scores, is associated with faster rates of skill acquisition, whereas older age is associated with slower rates of skill acquisition. Although this relationship has been shown previously in motor adaptation studies of point-to-point reaching

(Anguera et al., 2011; Christou et al., 2016; Trewartha et al., 2014; Wolpe et al., 2020), few studies have considered (and controlled for) the covariance between age and visuospatial (as well as other cognitive) functions, or testing whether this is the case for more functional, real-world actions. This study now extends the role of visuospatial memory to motor skill acquisition, and dissociates the effect of visuospatial memory on the rate of learning from that of age. This is important, as recent evidence suggests that age-related declines in motor adaptation were largely driven by declines in explicit learning (Vandevoorde & Orban de Xivry, 2019; Wolpe et al., 2020), which could be explained by declines in visuospatial memory (Christou et al., 2016; Wolpe et al., 2020). Moreover, studies have found no correlation between visuospatial memory and implicit learning (Christou et al., 2016). As such, Wolpe et al (2020) proposed that declines in explicit motor learning may be related to temporal brain regions, such as the hippocampus, which has been consistently shown as responsible for visuospatial memory and explicit memory (Longoni et al., 2015; Shavitt, Johnson, & Batistuzzo, 2020). Based on these recent studies, our results suggest that the early acquisition of skill on our motor task involved explicit learning strategies, particularly since the analyses focused on the first 20 trials of a 50-trial practice session, where explicit knowledge is more relied upon at the start of learning (Fitts & Posner, 1967).

We also observed that the effect of visuospatial memory on motor improvement (i.e., the extent of learning) differed between the two groups, such that visuospatial memory was positively correlated with motor improvement for the “low skill” group but not the “high skill’ group. This finding clarified the previous findings of Lingo Vangilder et al. (2020) by revealing that the observed correlation relationship between visuospatial memory and motor improvement could be, in part, driven by older adults who were at a lower skill level. One explanation for such group differences is that the low skill group learned more by explicit strategies that relied on visuospatial memory, whereas the high skill group learned more by implicit strategies. According to the stages of learning theory by Fitts and Posner (1967), as skill level advances, learning gradually transitions from depending more on cognitive, explicit knowledge to more on procedural, implicit knowledge. When skill level is low (which can and often be the case in older adults, compared to younger adults), participants need to rely on visuospatial ability to explore the spatial relationship between the hand, the tool (spoon) and the objects (beans) in order to construct explicit task strategies to improve performance. The high skill group, on the other hand, may have relied less on explicit knowledge (because they could) and more on automatic, procedural learning. This interpretation is in line with data from a similar tool-use skill learning study (Bosch, Hanna, Fercho, & Baugh, 2018), in which improved performance was associated with fewer confirmatory fixations (i.e., eye fixations on the interactions between the hand, tool, and objects) and shorter fixation duration, indicating that performance is less dependent on forming explicit strategies. Although our finding focused on longer-term motor improvement, it is again consistent with (but also expands) Christou et al. (2016) who found that visuospatial working memory capacity was correlated with visuomotor adaptation only when the task relies on explicit learning strategies, and not for implicit learning. Thus, future studies are needed to investigate if and which cognitive factors contribute to implicit learning.

Effect of age on motor skill learning

Unlike previous studies of skill acquisition, we found a dissociation in the effect of age on motor skill learning such that age is associated with slower rate of within-session acquisition but not with longer term motor improvement. This finding is not entirely surprising. Motor memory encoding during skill acquisition, memory consolidation at task intervals, and memory retrieval at follow-up testing are separate processes (Kantak & Winstein, 2012), so it is plausible that aging impacts the processes differently. For example, some studies have shown that compared to younger adults, older adults have slower acquisition but comparable learning capacity (Boyke, Driemeyer, Gaser, Büchel, & May, 2008; Carnahan, Vandervoort, & Swanson, 1996; Voelcker-Rehage & Willimczik, 2006). It is possible that the lack of an age effect on skill retention may be due to more implicit learning mechanisms. As noted above, motor adaptation studies suggest that implicit learning may be spared by aging (Vandevoorde & Orban de Xivry, 2019; Wolpe et al., 2020), such that the more implicit learning components of motor skill acquisition are not affected by advancing age), as evidenced by our findings in our high skill group. It is also possible that the low skill group in this study also demonstrated extensive implicit learning, since age-related differences in learning between younger and older adults diminished when learning was primarily non-declarative and implicit, even during early stages of learning (Chauvel et al., 2012). More research is needed, however, to explore the interactions between skill level and cognition and their effects on implicit and explicit learning in older adults.

One advantage of this study is that it involved a naturalistic motor task that has ecological validity among older adults (Schaefer, Hooyman, & Duff, 2020), which, compared to more constrained motor tasks (e.g., planar reaching), can allow for more functional and perhaps informative variability in motor behavior. Individual differences in skill level (i.e., task performance) are, unsurprisingly, more pronounced in older cohorts with increased sample heterogeneity due to sensorimotor declines with age (Sosnoff & Newell, 2011). The present study highlights the need for caution when identifying relationships between cognitive functions and motor learning, especially in the research context of aging. Specifically, we advocate for developing and employing methods to better quantify participants' baseline skill levels and acquisition to potentially identify and group participants accordingly (Brooks, Hilperath, Brooks, Ross, & Freund, 1995; Uehara, Mawase, Therrien, Cherry-Allen, & Celnik, 2019).

Limitations and future work.

Although we reasoned that the two groups of participants learned by differentially recruiting explicit and implicit learning components, no clear methods exist for dissociating explicit and implicit learning processes in functional, real-world movements. Such methods are needed to better isolate and therefore guide learning at different stages of acquisition, particularly when implicit learning is relied upon for cognitive rehabilitation in older adults (Kessels & Haan, 2003). Furthermore, this study did not identify any age or cognition effects on longer-term improvement in the high skill group, leaving this question largely unanswered. It is plausible, as described above, that these individuals relied primarily on more implicit/procedural learning, which may be robust to any declines in visuospatial memory. This highlights the importance of identifying factors that can promote/maintain implicit learning that can compensate for explicit learning deficits due to advancing age or pathology (Harrison, Son, Kim, & Whall, 2007; Machado et al., 2009; van Halteren-van Tilborg, Scherder, & Hulstijn, 2007).

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CHAPTER 4

EXPECTATIONS ABOUT THE EFFICACY OF TRANSCRANIAL DIRECT CURRENT STIMULATION FOR IMPROVING MOTOR PERFORMANCE

The effects of transcranial direct current stimulation (tDCS) on motor performance and learning remain unclear (Buch et al., 2017). Differences in stimulation parameters, study design, and individual anatomy have all been proposed as factors explaining equivocal results (Buch et al., 2017). Only recently have psychological factors, namely expectancy effects, been considered within tDCS research at large (Rabipour, Vidjen, Remaud, Davidson, & Tremblay, 2019; Schambra, Bikson, Wager, DosSantos, & DaSilva, 2014; Turi et al., 2018). Based on well-established placebo mechanisms (Wager & Atlas, 2015), it is plausible that one's *expectation* of tDCS to improve motor performance could produce a sizeable placebo effect comparable to the actual treatment effect of tDCS. Thus, equivocal findings of tDCS within the motor domain could, in part, be attributed to variations in participant expectation of tDCS within and/or between experimental groups (i.e., active tDCS and sham tDCS groups). In general, participants' prior experience or knowledge of a treatment can lead to expectancy effects (Wager & Atlas, 2015); however, there are virtually no data on expectancy effects of tDCS, nor on even what the general public's expectations about the efficacy of tDCS are. We therefore surveyed expectations about whether tDCS could enhance motor performance, and explored whether these expectations varied by prior tDCS experience/knowledge, sex, and age.

Participants (n=379) completed an online questionnaire (after providing consent) through the Amazon Mechanical Turk (MTurk) platform. All participants had an MTurk ≥98% approval rate, had completed ≥500 studies on MTurk, and reported living in the United States. Participants were directed from MTurk to the link of a survey presented with Google Forms (available, along with data and scripts, at https://osf.io/6gb7r/). The study was approved by the Arizona State University Institutional Review Board.

To ensure that the age distribution of our survey sample resembled that which is typical for tDCS studies in the motor domain, we first extracted the age distribution from 282 published studies indexed from the online tDCS Database (Grossman et al., 2018) using keywords: "tDCS" and "motor" that reported mean participant age >18 years old. This yielded a bimodal distribution centered around 25.8 and 56.7 years old, fit via Gaussian Mixture Model (GMM) using R package *mclust* (Scrucca, Fop, Murphy, & Raftery, 2016). Using iterative age constraints in MTurk, we collected 379 surveys across a comparable age distribution (bimodal centered around 30.2 and 49.6 years old) (Fig. 1A). The GMM clustering algorithm classified the sample into a younger age group (≤40; n = 276) and an older group (>40; n = 100).

The survey contained two quality-check questions to exclude responses from inattentive participants or automated bots. Age and biological sex were collected, along with prior knowledge of/experience with brain stimulation, based on self-report. Participants then read a brief prompt about tDCS, followed by two questions that assessed their expectancy towards tDCS as a way to improve motor performance: "Do you think brain stimulation would improve your motor performance?" and "Following brain stimulation, would you notice an improvement in your motor performance? (i.e., would you feel it?)". Responses were on a 5-point scale, with 0 = *"no, not at all"*, 2 = *"neutral"*, and 4 = *"yes, very much."* These were adapted from the Credibility and Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000). Scores from these two questions were averaged, yielding a composite expectancy score.

Survey data from 376 (99.2%) participants passed the quality check and were analyzed. Higher-than-neutral expectations of tDCS to improve motor performance were reported (mean composite score ± *SD* = 2.14 ± 1.06, $t(375) = 2.576$, $p = 0.005$); however, scores were widely distributed, with slight skew toward higher scores (Fig. 1B). Contributions to this variance were then explored using an estimation-based approach, focusing on confidence intervals rather than null-hypothesis tests. Average marginal effect size (AME) was calculated using R package *margins* (Leeper, 2018), which is the average of the partial derivatives of a regression equation with respect to a certain variable over the observed sample. One-hundred and sixteen participants had prior knowledge (having heard of brain stimulation), but only 19 had any prior experience; thus, only prior knowledge was further analyzed. Prior knowledge increased expectancy score by 0.344 (95% CI [0.115, 0.572]), whereas sex (male vs. female: *AME* = -0.096, 95% CI = [-0.308, 0.117]) and age group (older vs. younger: *AME* = -0.133, 95% CI [-0.372, 0.107]) minimally influenced expectancy, on average. Upon closer inspection (Fig. 1C), having prior knowledge had the largest influence on expectancy scores for females (*AME* = 0.603, 95% CI = [0.253, 0.954]) but much less so in males (*AME* = 0.147, 95% CI = [-0.154, 0.449]). Regarding age, prior knowledge had large effect on expectancy scores among younger adults (*AME* = 0.409, 95% CI = [0.141, 0.677]) but this difference was much smaller among older adults (*AME* = 0.164, 95% CI = [-0.273, 0.603]).

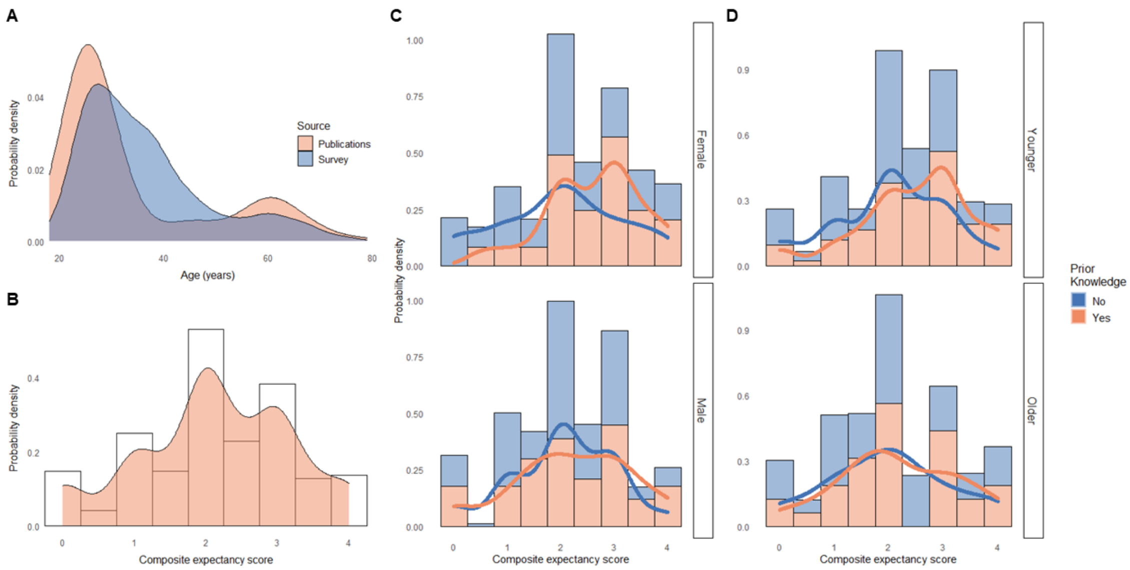

Figure 1. Probability distributions. **A)** The age distribution from the sampled survey data (blue) is comparable to that of mean age reported by relevant tDCS publications indexed in the tDCS Database (orange). **B)** Expectancy scores were right-skewed toward higher scores, though variable across the sample. **C)** Expectancy score varied with prior knowledge and sex. Prior knowledge (orange) increased scores for females (upper panel), but not for males (lower panel). **D)** Expectancy score varied with prior knowledge and age. Prior knowledge (orange) increased scores for the younger age group (upper panel), but not for the older age group (lower panel).

These findings suggest that expectations about tDCS for improving motor performance are higher than neutral, and depend on prior tDCS knowledge, sex, and age. In light of this, although no studies to date have investigated sex differences in the effect of tDCS on motor performance, four studies in the tDCS Database outside of the motor domain showed stronger (or only) tDCS effects in females than males (Grossman et al., 2018). A recent meta-analysis also revealed that tDCS effect sizes are higher when more females are included in a given study (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016); could this be due in part to expectations? Expectancy effects may also partly explain mixed findings of identifying age-related differences in tDCS effects.

Rabipour et al. (2019) provides supporting evidence of tDCS expectancy effects on motor performance, such that manipulating expectations prior to stimulation resulted in different motor outcomes, irrespective of whether the stimulation was active or sham. This suggests that the variability in outcome measures in placebo-controlled studies may be due not only to actual tDCS exposure, but also to variability in tDCS expectancy (Wager & Atlas, 2015). Thus, in the common *double-blind, sham-controlled* study design, failing to control for tDCS expectations could unknowingly mask (when expectations in sham group > treatment group) or inflate (when expectations in sham group < treatment group) treatment effects. The potential for group differences in expectations is more likely for small sample sizes common in motor-tDCS studies (from the studies indexed here, the average *N* across 112 sham-controlled ones was 22.34). We therefore recommend quantifying tDCS expectations to control for expectancy effects in sham-controlled study designs and analyses.

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CHAPTER 5

RIGHT PARIETAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON VISUOSPATIAL PERFORMANCE AND MOTOR SKILL ACQUISITION

ABSTRACT

Modify motor skill learning is desired in rehabilitation, sports and other professions. This current research tests whether anodal tDCS applied to the right parietal lobe will modulate motor skill acquisition. In consideration of previous mixed findings in tDCS research, this study also included a no-tDCS control group to quantify placebo effects induced by tDCS. Thus, the current study employed a randomized, three-arm design to test the effect of right parietal anodal tDCS on visuospatial ability and motor skill acquisition, and to quantify any placebo effect induced by tDCS and its expectations. A total of 47 young adults (aged 23.74 ± 4.37 years old) were included in the study. Participants completed a pre-test of the Mental Rotation Task, 20-minutes of training on the Corsi Block Tapping Task, post-test of Mental Rotation Task, 30 trials of motor training on a functional reaching task, and lastly an exit questionnaire to that measured expectations about tDCS. 20-min tDCS stimulation was paired with visuospatial training for the sham and anodal tDCS groups. The results did not observe any tDCS treatment effects, such that the sham group demonstrated more improvement in reaction times of the mental rotation task than the anodal group (p = .046). As for motor skill acquisition, nonlinear mixed-effect modeling suggested that the sham and anodal group did not differ in the amplitude and asymptote parameters of the modeled exponential learning curve during motor training (all ps > .160). However, placebo

effects were observed. The sham group demonstrated more improvement in reaction times of the mental rotation task than the no-tDCS control group (p = .037). The sham group also had larger amplitude during skill acquisition than the control group for both the object manipulation (p = .036) and object transfer phases of the task (p = .044). Moreover, the magnitude of placebo effects varied by expectations and suggestibility, such that better task performance at the end of training (smaller asymptote) were associated with higher expectation (p = .015) and suggestibility ($p < .001$). The unique finding of this study is that the placebo effect over-shadowed the treatment effect on motor skill acquisition, which has implications for the field of tDCS and motor research. Future studies are needed to explore placebo effects in other neuromodulation interventions, and should aim to control and measure such effects to better exploit them in rehabilitative or performance-enhancing contexts.

INTRODUCTION

Is motor skill learning modifiable? Previous studies have attempted to use transcranial direct current stimulation (tDCS) to enhance learning, but with mixed results (Buch et al., 2017). The overwhelming majority of these studies have targeted the motor cortex or the cerebellum. The current research described here, however, innovates in testing whether anodal tDCS applied to the right parietal lobe will modulate visuospatial ability and motor skill acquisition.

The decision to stimulate the right parietal lobe to modulate motor learning is based on our previous findings. Specifically, we have demonstrated that the extent of motor skill learning is related to visuospatial ability such that better visuospatial scores correlate with more retention (Lingo VanGilder, Hengge, Duff, & Schaefer, 2018; Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021; Wang, Infurna, & Schaefer, 2020). Neuroimaging findings also show that that frontoparietal pathways underlie both motor learning and visuospatial processes (Brandes-Aitken et al., 2019; Regan et al., 2021; Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012), suggesting an underlying neural mechanism for our behavioral findings. Thus, the right parietal lobe was selected as the stimulation site for this study because neuropsychological findings have shown that many visuospatial processes are specialized to the right parietal cortex (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Foxe, McCourt, & Javitt, 2003). Although these findings suggest an important relationship between motor learning and right frontoparietal networks, it remains unknown whether modulation of this network will mediate changes in motor learning processes.

The primary purpose of this study was to investigate whether right parietal tDCS stimulation affects motor learning (such as motor skill acquisition) using a double-blinded, sham-controlled design. The main hypothesis was that motor skill acquisition would be positively influenced by anodal tDCS applied to the right parietal lobe. Anodal stimulation has been chosen due to its proposed excitatory effects (Nitsche & Paulus, 2000; Rahman et al., 2013; Utz, Dimova, Oppenländer, & Kerkhoff, 2010). A secondary purpose of this study, however, was to quantify placebo effects induced by tDCS by comparing motor skill acquisition of the sham and the no-tDCS control group, as well as measuring the effect of expectations associated with parietal tDCS on motor skill acquisition.

Why should we study a placebo effect in tDCS? As with many other tDCS paradigms, parietal tDCS is also subject to null- or mixed-findings. Mixed-results in tDCS research have been attributed to high response variability to tDCS (Vannorsdall et al., 2016). Explanations of response variability of tDCS have focused on differences in stimulation protocols and individual brain anatomy, yet have largely ignored the possible effect of individual differences in the expectation of (and susceptibility to) participants' perceptions of tDCS treatment, which could induce placebo effects comparable to (or greater than) true treatment effects (Moseley et al., 2002). New evidence suggests that expectations can alter treatment outcomes of tDCS (Rabipour, Wu, Davidson, & Iacoboni, 2018; Ray et al., 2019), and that motor performance itself is susceptible to expectations and verbal suggestions alone (Fiorio, 2018). Moreover, expectations about tDCS are quite common; we have recently shown that the general public has higher-than-neutral expectations for tDCS to improve motor performance, and such expectations vary considerably in different age and sex groups (Wang, Hooyman, Schambra, Lohse, & Schaefer, 2021). Collectively, this evidence prompted the inclusion of a no-tDCS control group to assess for any confounding placebo effects (Colloca & Barsky, 2020), as well as the collection of self-reported measures for expectations and suggestibility to control for the individual variabilities in motor learning due to varying expectations, particularly in the case of null findings within the double-blinded, placebo-controlled portion.

Figure 1 illustrates how motor skill acquisition measured in a given tDCS study is the summed outcome from within-session practice effects due to motor training, and treatment and placebo effects due to tDCS. The practice effect occurs by practicing during motor training, which can be modeled as the exponentially-shaped skill acquisition curve (Figure 1, grey) with parameters such as amplitude, time constant and asymptote. The placebo and treatment effects due to tDCS treatment could theoretically induce changes to the skill acquisition curve, thereby changing the modeled skill acquisition parameters. For this particular study, a treatment effect would be measured as the difference between the sham and anodal tDCS group (Figure 1, red). Similarly, if a placebo effect is present, it would be measured as the difference between the control (no-tDCS) and sham tDCS group (Figure 1, blue). A placebo effect, irrespective of group, may also be presented such that skill acquisition parameters are related to expectation measures, such that more acquisition is associated with higher expectations about tDCS (Figure 1, blue). If the placebo effect has a larger effect size than the treatment effect, null results may occur where the treatment group's outcome variable (skill acquisition in this case) is not significantly different from that of the sham group due to individual variability in both effects (Buch et al., 2017; Colloca & Benedetti, 2006). This again motivated the inclusion of 1) a no-tDCS control group and 2) self-reported measures of participant expectations.

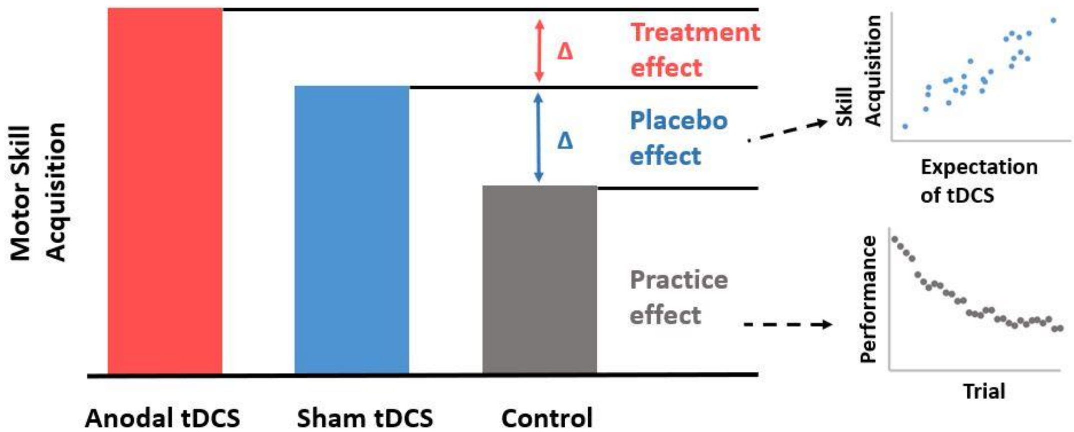

Figure 1. Overall experimental scheme.

METHODS

Participants

Forty-seven adults (aged 23.74 ± 4.37 years old, 24 females and 23 males) were recruited through campus flyers and university announcements. Participants must be at least 18 years old, right-handed, and without diagnosed neurological disorders. To be eligible to receive tDCS stimulation, participants would have passed the screening questionnaire for tDCS studies (Thair, Holloway, Newport, & Smith, 2017). Informed consent was obtained prior to study participation. The study was approved by the Arizona State University Institutional Review Board. We note that this study is still ongoing.

Experimental design

Overall, this experiment followed a randomized, three-arm, and mixed within- and between-subjects design. Participants were randomly assigned to one of three groups – an anodal tDCS group, a sham tDCS group and a no-tDCS control group – that underwent the same experimental protocol, except for the tDCS condition they received. This three-arm design was chosen as an expansion of the sham-controlled design to account for any confounding placebo effects (L. Colloca & Barsky, 2020), as shown in Figure 1. Experimenters were trained to ensure participant-experimenter interactions were similar for all participants. During consenting, the anodal and sham tDCS groups were informed that "The study aims to test whether tDCS can improve visuospatial ability and how well people learn a motor skill". For the control group, we added that "you were assigned to the control group." Figure 2 illustrates the order of the experimental procedures. Participants completed pre-test of the Mental Rotation Task, 20-minutes of training on the Corsi Block Tapping Task, post-test of Mental Rotation Task, 30 trials of motor training on a Functional Reaching Task, and lastly an exit questionnaire. tDCS stimulation, anodal or sham, was paired with visuospatial training to ensure cortical engagement during stimulation (Bikson et al., 2018). The experimental design has been preregistered at Open Science Framework (https://osf.io/scwr4/).

Figure 2. Experimental design

Mental Rotation Task

The Mental Rotation Task as distributed by the PEBL Battery (Mueller & Piper, 2014) was chosen as the primary visuospatial task. The PEBL Mental Rotation Task is an

2D version the classic Shepard and Metzler's mental rotation task (Shepard & Metzler, 1988), which has been studied previously in the context of motor learning. As such, it was chosen as the primary visuospatial task for this proposal. In each trial, participants were presented with a pair of 2D asymmetrical objects, either identical or mirroring each other, on a laptop screen (Fig. 2). Participants were instructed to respond, as quickly as possible (via key press), whether the two objects depicted were identical, or different (mirror images). The objects could take one of two shapes, either resembling the letter "L" or the letter "Z". The pairs of objects were presented at one of eight possible rotational angles with respect to each other (-135 to 180 degrees, at 45-degree increments, randomly sampled). For each trial, stimulus shape ("L" or "Z"), condition (identical or mirror), and angle was randomly combined. Each combination was presented two times, resulting in 64 trials in total. Each stimulus was presented for 3000 ms, and feedback of response accuracy (correct or incorrect) was presented for 500 ms after each response. A trial with no response within 3 seconds was registered as incorrect. Accuracy was calculated as the percentage of correct responses at each angle of rotation. Reaction time was analyzed for correct trials only and was collapsed across all angles of rotation. Accuracy and reaction time of the mental rotation task was the primary measures for visuospatial function.

Corsi block tapping task

The Corsi Block Tapping task, also distributed by the PEBL battery, was adapted for visuospatial training. The Corsi Block Tapping task (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000)(Kessels et al., 2000) is a visuospatial working memory task, where participants were instructed to memorize sequences of locations for squares on the screen. For any trial, nine blue squared blocks were presented on the screen at first, and then a number of the squares sequentially lighted up in yellow, one at a time. Participants were instructed to observe and memorize the sequence in which the blocks lighted up. After the sequence was finished, participants were asked to click on the blocks in the exact sequence they had observed. Difficulty of the task was manipulated through the number of blocks to be memorized, the maximum difficulty being nine blocks. Because the Corsi Block Tapping task was administered during tDCS stimulation, it was adapted such that the difficulty level was continuously adjusted based on performance to ensure challenge and cortical engagement (Bikson et al., 2018; Thibaut, Zafonte, Morse, & Fregni, 2017) and that the duration is set to be 20 minutes (the same as tDCS stimulation). Participants first completed three practice trials at a length of three. Following practice, the length of the sequence increased by one only when participants have done two correct trials in a row until maximum difficulty was reached, at which point task difficulty remained at a length of nine for the remainder of time.

tDCS stimulation protocol

For anodal and sham tDCS groups, 20-minute stimulation was administered concurrently with visuospatial training to ensure functional cortical engagement during stimulation (Bikson et al., 2018). The tDCS equipment was a classic 1x1 tDCS machine (Soterix Medical Inc.). The active electrode (anode) was be placed on the right posterior parietal lobe (P4 on the International 10-20 System), and the return electrode (cathode) on the contralateral supraorbital area. The anodal tDCS group received a 20 min, 2 mA anodal stimulation, including a 30 sec ramp-up and a 30 sec ramp-down at the beginning and end of the 20-min period. The sham tDCS group received a sham stimulation, where in the first 30 seconds current intensity increased to 2mA and was immediately followed with a 30-sec ramp-down to 0mA. The current density would remain at 0mA for 18 more minutes, followed by another 30-sec ramp-up to 2mA and 30-sec ramp-down to zero. These stimulation parameters have been effective in other motor-tDCS studies (Buch et al., 2017). Participants and the experimenters were all blinded to the stimulation, as the tDCS equipment was set up by another researcher who was not involved with the experiment.

Motor practice on a Functional Reaching Task

Motor skill learning was assessed with motor skill acquisition in a 30-trial practice session of a functional reaching task, as shown in Figure 2. Videos of the task can be viewed on Open Science Framework (https://osf.io/phs57/wiki/Functional_reaching_task/). This functional task has been validated against more traditional point-to-point reaching paradigms (Schaefer & Hengge, 2016), and the within-session change of the task can characterize longer-term learning (Schaefer & Duff, 2017). In the task, participants used their nondominant hand to manipulate a spoon to acquire and transport raw pinto beans (two at a time) from the center home cup to one of the three outer cups in order (left, middle then right) for a total of 15 reaches in one trial. The nondominant hand was used to minimize any ceiling effect and allow for measurable practice effects. Participants were instructed to complete trials as quickly as possible without any drops. If any drops occurred, participants were instructed to continue with the task without attending to the dropped beans. Participant completed 30 trials of the task as motor practice. The total number of beans dropped was noted for each trial. The primary measure of task performance is trial time, which was extracted from kinematic data and described in detail in the section of “Kinematic data acquisition and analysis”.

Exit questionnaire

To assess placebo effects associated with tDCS, as well as individual and contextual factors that could contribute to placebo effects, an exit questionnaire was administered to the anodal and sham tDCS groups only, not to the control group. The questionnaire included a Short Suggestibility Scale (Kotov, Bellman, & Watson, 2004), which is a 21-item, 5-point scale used to measure the tendency to accept suggestions. Expectancy was measured with an adapted question from the Credibility and Expectancy Questionnaire (Devilly & Borkovec, 2000). Expectation of tDCS to improve motor performance was measured via a question “Do you think brain stimulation would improve your motor performance?”, with a scale of 0-8 (0 being ‘no, not at all’, 8 being ‘yes, very much). For exploratory purposes, remaining questions of the exit questionnaire measured participants’ experience with tDCS. These include: participants perceived stimulation group (real, fake, not sure), and whether participants have heard of or participated in tDCS studies before (yes or no). The complete exit questionnaire can be accessed at Open Science Framework (https://osf.io/scwr4/).

Kinematic data acquisition and analysis

Three-dimensional (3D) positional data were acquired at 100 Hz via an electromagnetic sensor (Ascension Model 130) integrated with the MotionMonitor software (Innovative Sports Training Inc.). The sensor was attached to the bottom base of the handle of a plastic spoon. The center of the home cup was specified as the origin of the coordinate system. The x-axis was defined along the medial-lateral axis of the participant, with participants' right side as the positive direction. The y-axis was defined as the anterior-posterior axis, with participant facing the positive y-direction. The z-axis was defined as the inferior-superior axis, with upward movement as positive direction. Kinematic data was low-pass filtered at 8Hz with a 4th order Butterworth filter with the Motion Monitor Software and exported to MATLAB for data analysis.

Customized MATLAB codes were used to segment every single trial into 15 repetitions, and within each repetition two phases: 1) object manipulation in the home cup (acquiring two beans with the spoon) and 2) object transfer to a target cup (outward reach with beans in the spoon). The inward reaches back to the home cup were not analyzed here. As shown in Figure 3, four event markers were identified for each repetition: 1) start of "scoop", registered when the spoon was within the boundaries of the home cup and z-velocity changed direction from negative (downward movement) to positive (upward movement) for the first time; 2) start of reach, registered when the spoon was within the boundaries of the home cup and at the latest occurrence when resultant velocity exceeds 0.05 m/s); 3) peak velocity, registered when resultant velocity reached its maximum; and 4) end of transport, registered when the spoon reached its maximum y-position during the repetition. With the event markers, object manipulation was defined as the period between the start of "scoop" and the start of reach, and object transfer defined between the start of reach and the end of transport.

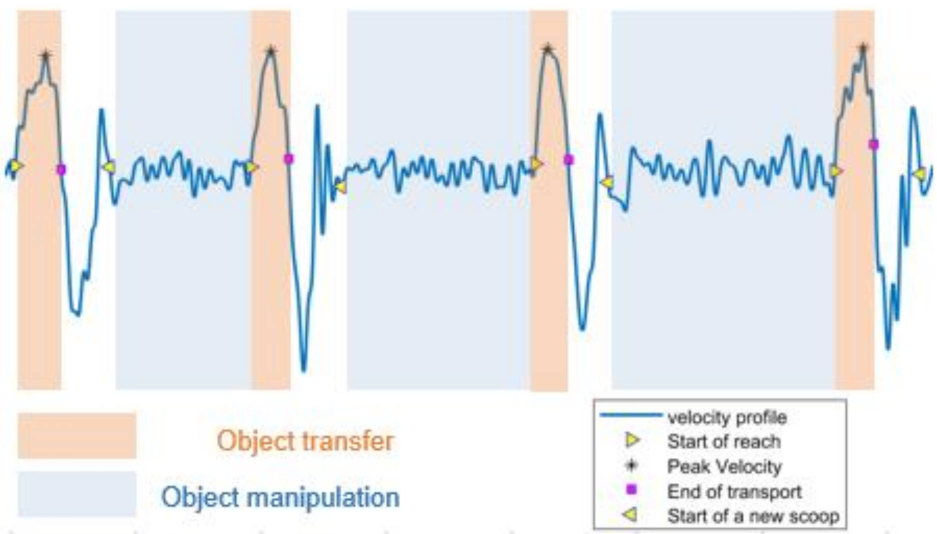

Figure 3. Movement phases during the functional reaching task.

The primary performance measure, trial time, is defined as time elapsed from the start of "scoop" of the first repetition to the end of reach of the last (15th) repetition. Secondary performance measures were obtained for the object manipulation and object transfer phases, which were averaged from all 15 repetitions to study in detail how each movement phase changed during skill acquisition. Dwell time was calculated as the average time spent during object manipulation (within the home cup) across all repetitions within each trial, and transport time the average time spent during object transfer across all repetitions. This breakdown of movement phases was previously shown to reveal different motor processes for this task (Hooyman, Wang, & Schaefer, 2021). The dwell time and transport time measure served another purpose in this analysis – to increase signal-to-noise ratio by averaging across repetitions for each trial. The primary performance measure, as well as the two secondary measures, were entered into three separate nonlinear mixed-effect models to quantify skill acquisition for each, as described in the following section.

Quantifying motor skill acquisition

General skill acquisition was quantified by modeling changes in performance (trial time), fine motor (dwell time) and gross motor (transport time) progression over all 30 trials. Specifically, for each performance measure (trial time, dwell time and transport time), motor skill acquisition was quantified as exponential changes in performance across 30 trials of practice with nonlinear mixed-effect modeling. For example, trial time was modeled as:

$$Trial\ Time_j = A_j e^{-\,{}^{t}/_{\tau_j}} + C_j + \varepsilon_j \tag{1}$$

where t was trial number and j was participant number. A_j is the amplitude of skill acquisition; τ_i is the time constant of the exponential decay (the inverse of learning rate); C_j is performance asymptote and ε_j the error term. Model parameters will be estimated via non-linear mixed effect modeling in MATLAB (via *nlmefit* and *nlmefitsa*) with subjects as random effect. A_j, τ_j and C_j were assumed to be log-normal random variables, and were estimated as the exponential transform of the sum of the fixed term (representing the group mean) and the random term (representing individual variability), which ensured positive values. Error model was specified as exponential.

Statistical analysis

Testing for group differences in motor skill acquisition

To perform statistical tests for group differences in skill acquisition, a binary grouping variable, G, was added to the exponential models for each group pair (sham vs. real, and control vs. sham). The model fitting and selection process was done via an exploratory approach. For any group comparisons, the model was fit 8 ways: one without any grouping variable, three with the variable G added to only one parameter (A_j, τ_j or C_j) at a time, three with G added to two of the three parameters at once, and one with G added to all parameters. Two sample model specifications using trial time as examples – a model where G was only added to the amplitude parameter to test for group differences (Eq. 2), and a model where G was added to all three parameters (Eq. 3) – are provided below:

$$Trial\ Time_j = (A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j \qquad (2)$$

$$Trial\ Time_j = (A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j \qquad (3)$$

where *t* was trial number and *j* participant number. G is a within-subject grouping binary variable valued 0 or 1. G is set to 1 for the group with the effect of interest (G = 0 for sham and G = 1 for anodal for tDCS treatment effect; G = 0 for control and G = 1 for sham for placebo effect). A_j, τ_j and C_j the mixed effect model parameters at the control condition (corresponding to G =0). The mixed-effect parameters associated with the grouping variable, a_j, b_j, and c_j, are representing the group difference in amplitude, time constants, and asymptote. In this fashion, statistical differences in skill acquisition were tested by the p-values associated with a_j, b_j and c_j. Motivation for this analysis is based on Oh and Schweighofer (2019).

The Log-likelihood Ratio Test (LRT; Comets, Lavenu, & Lavielle, 2017) was used to select the model with the largest log-likelihood as the best model fit. After the best fit model was chosen, z-scores were computed for the group difference parameters and p-values were tests.

Testing for covariates for motor skill acquisition

To test whether expectancy and suggestibility were related to motor skill acquisition, expectation and suggestibility measures were first mean-centered and then included to the exponential mixed-effect model (Eq. 1) as covariates to modeled skill acquisition parameters A_j, τ_j and C_j. Relationship between random effects of model parameters and expectation and suggestibility were visually inspected first. When visual inspection suggested a potential relationship, the covariates were added to the model iteratively. The covariate was added to a model parameter when LRT test suggested that a model with the covariate was better than the model without. Then another covariate may be added to the same or other model parameters and tested via LRT. The process was repeated until the best model with covariates was identified.

Because the skill acquisition parameters (A_j, τ_j and C_j) were log-transformed to model parameters to ensure non-negative values, the effect of added covariates on these parameters are exponentiated. As a result, effects of the covariates on the motor skill acquisition parameters are expressed as a multiplicative to the skill acquisition parameters, because the covariates have an additive effect on the model parameters. For example, expectation can be added as a covariate for asymptote. Then the log-transform of asymptote, C, is expressed as:

$$\log (C_j) = \exp (\beta_0 + \beta_1 \times expecation_j + b) \tag{4}$$

where j is participant number; β_0 is the fixed-effect model parameter and b is the random-effect model parameter; and β_1 is the fixed-effect coefficient for the expectation covariate. As a result, the relationship of expectation and asymptote parameter C is expressed as:

$$C_j = e^{\beta_0 + \beta_1 \times expecation_j + b} = \mathrm{e}^{\beta_0 + b}\mathrm{e}^{\beta_1 \times expecation_j} \tag{5}$$

In this example, the effect of expectation on C is, therefore, more intuitively understood as factor of multiplication. The 95% confidence interval of the effect of expectation on C_j was therefore calculated as the exponential transform of the 95% confidence interval of β_1. The significance of covariate was tested via the significance tests of β_1.

Testing for group differences in visuospatial performance

To test for a treatment effect and placebo effect of tDCS, reaction time data of the mental rotation task were subjected to a linear mixed effects model, with time (pre-tDCS vs. post-tDCS) and group (anodal, sham, and no-tDCS control), and time-by-group interaction as fixed-effects, and participant as random effects. The model was fit with two random effects: a random intercept and a random slope for time. The reference level for time was set to pre-tDCS, and the reference level for group was set to the sham group. Significant level was set to 0.05 for all statistical tests. The *mixedlm* function in Python Statsmodels package (Seabold & Perktold, 2010) was used.

RESULTS

Participant characteristics were summarized in Table 2. The three groups were not significantly different in terms of age, and the sham and the anodal groups were not significantly different in terms of expectation and suggestibility measures (all $p > .568$).

Table 2. Participant Characteristics

	Control	Sham tDCS	Anodal tDCS
N	11	17	19
n, females	9	7	8
Age	23.91 ± 4.85	23.82 ± 3.91	23.58 ± 4.69
Expectation	N/A	5.65 ± 1.97	5.21 ± 2.51
Suggestibility	N/A	53.76±14.38	55.68 ± 9.76

Motor skill acquisition of the sham- and anodal-tDCS groups (treatment effect)

To recap, motor skill acquisition was assessed by modeling change in motor performance with respect to trials with an exponential decay function. The main performance measure was trial time, and the secondary performance measures were dwell time (for the object manipulation phase) and transport time (for the object transfer phase, Fig. 3). Mixed-effect modeling characterized within-session learning on each performance measure with an amplitude, a time constant, and an asymptote.

In comparing the overall learning of the motor task (changes in trial time) between the sham and anodal groups, the best fit model tested whether the anodal group had different time constant and asymptote parameters than the sham group (see methods "*Testing for group differences in motor skill acquisition*"). The model shows that the anodal group had a significant larger time constant than the sham group (sham group time constant = 5.04, 95% C.I.: [3.53, 7.20] trials; anodal group time constant = 11.87, 95% C.I.: [10.36, 13.60] trials, p = 0.025 for difference, Fig. 4). However, the two groups did not differ in their asymptote (p = .160 for difference) nor amplitude of skill acquisition, which is already implicitly stated because the current model was selected as the best fit model over other models in which the grouping variable were added to the amplitude parameter.

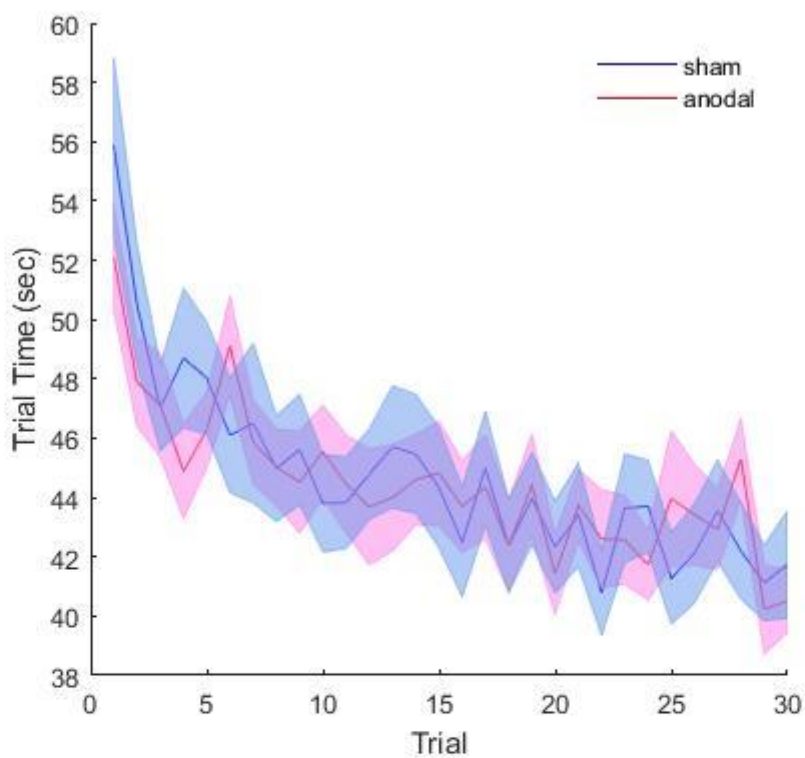

Figure 4. Trial time progression between the sham and anodal tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the anodal group had a larger time constant than the sham group (p = .025).

As for the object manipulation phase, group differences in amplitude and asymptote parameters for changes in dwell time over trials were tested. The model shows that the anodal group had a significant smaller amplitude than the sham group (sham group amplitude = 0.81, 95% C.I.: [0.62, 1.05] seconds; anodal group amplitude = 0.50, 95% C.I.: [0.47, 0.53] seconds, p = .031 for difference, Fig. 5). The two groups did not differ in their asymptote (p = .156 for difference) nor their time constant.

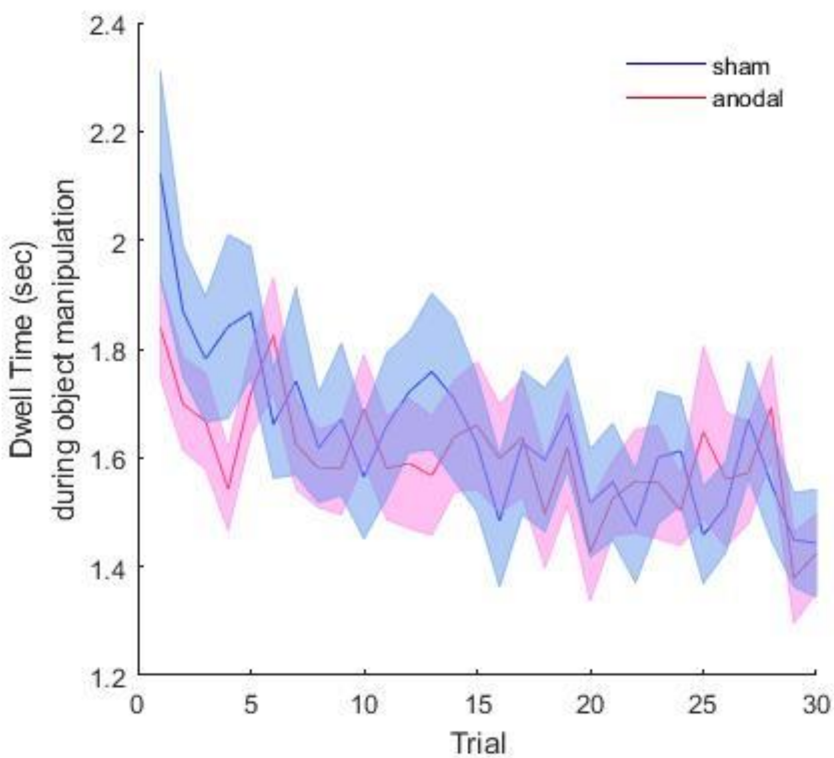

Figure 5. Dwell time progression between the sham and anodal tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the anodal group had a smaller amplitude of skill acquisition than the sham group (p = .031).

As for the object transfer phase, the best fit model tested group differences in all three parameters for change in transport time over trials. No group difference was found in either amplitude, time constant, or asymptote (all ps > .222 for difference, Fig 6). For all the analyses described above, the best fit models and the model selection processes are detailed in Appendix A.

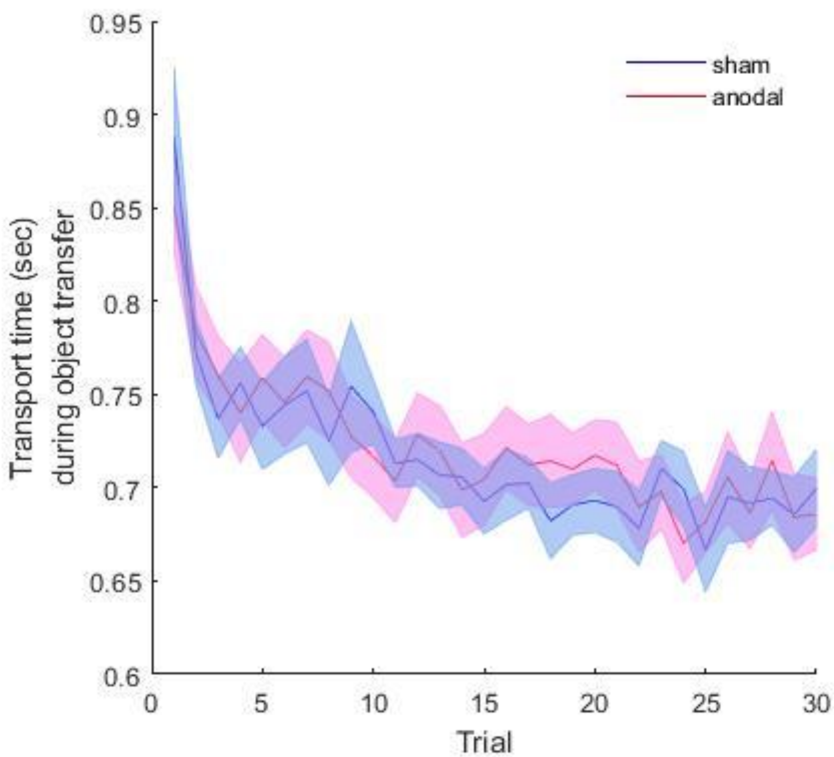

Figure 6. Transport time progression between the sham and anodal tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the two groups were not different.

Motor skill acquisition of the sham and control group (placebo effect)

The best fit models and the model selection processes for this section are detailed in Appendix B. To increase readability, p-values are reported for any parameters to which the group variable was added to in the mixed-effect model and the group difference for that parameter was tested. For parameters, it was implicitly stated that there was no group difference.

For trial time, the model shows that the sham group nearly had a larger amplitude than the control group in skill acquisition, although it did not reach significance (control group amplitude = 8.51, 95% CI: [5.75, 12.59] seconds; group amplitude = 12.82, 95% CI: [11.64, 14.12] seconds, p = .097 for difference, Fig. 7). The sham group did not differ from the control group in asymptote (p = .382 for difference) or in time constant.

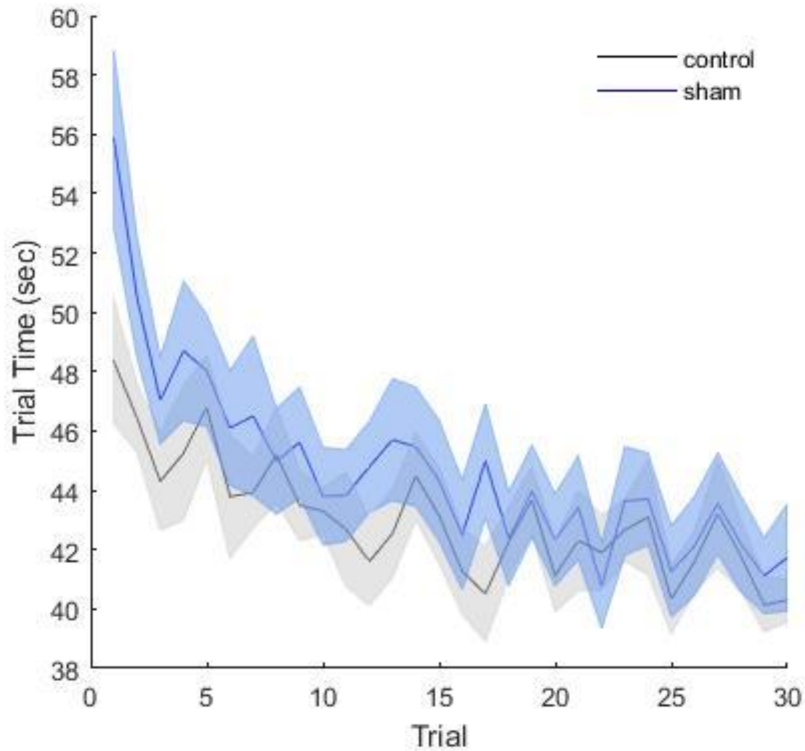

Figure 7. Trial time progression between the control and sham tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the average amplitude of the sham tDCS group was not larger than that of the control group, although it was reaching significance (p = .097).

For the object manipulation phase, group differences in change in dwell time over trials were tested. The model shows that the sham group had a significant larger amplitude than the control group (control group amplitude = 0.42, 95% CI: [0.28, 0.62] seconds; sham group amplitude = 0.72, 95% CI: [0.65, 0.79] seconds, p = .036 for difference, Fig. 8). The sham group did not differ from controls in either time constant or asymptote (ps > .378).

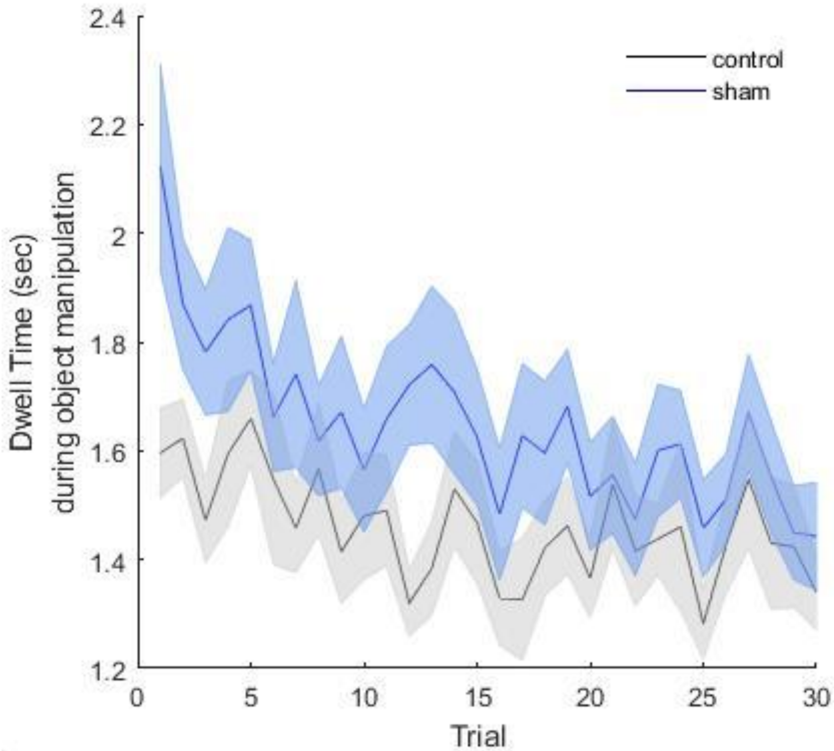

Figure 8. Dwell time progression between the control and sham tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the sham tDCS group had larger average amplitude than the control group (p = .036).

For the object transfer phase, group differences in change in transport time over trials were tested. The sham group had a larger amplitude than the control group (control group amplitude = 0.14, 95% CI: [0.10, 0.21] seconds; sham group amplitude = 0.26, 95% CI: [0.23, 0.29] seconds, p = .044 for difference, Fig. 9). No group difference was found in time constant or asymptote (p = .522).

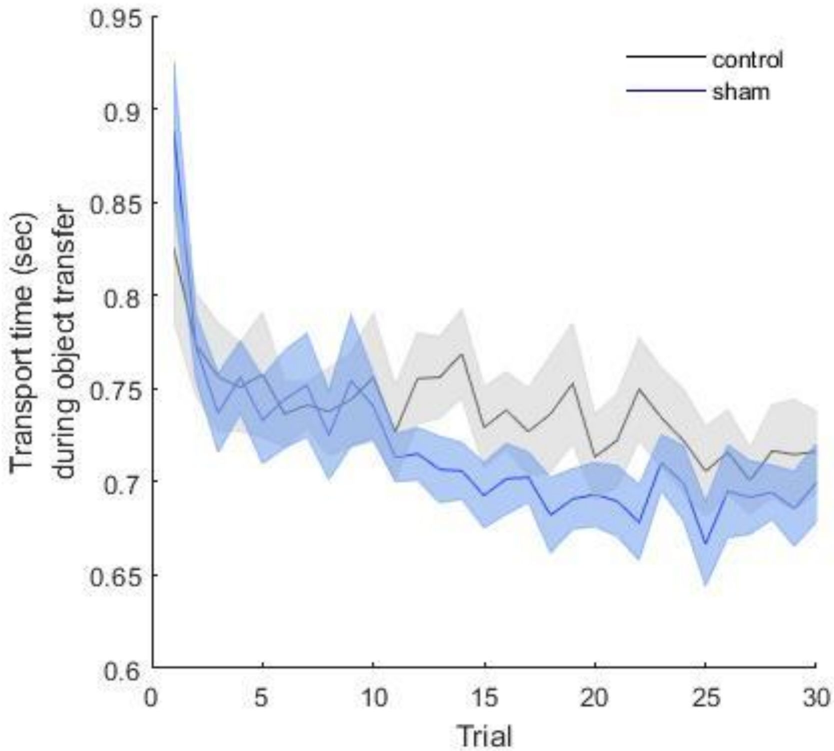

Figure 9. Transport time progression between the control and sham tDCS groups. Shaded areas indicate standard error. Exponential modeling suggests that the sham tDCS group had a larger amplitude than the control group (p = .044).

Expectation, suggestibility and motor skill acquisition

Expectation and suggestibility measures did not differ between the sham and the anodal groups (Table 2). To test whether expectations and suggestibility to tDCS were related to motor skill acquisition, expectation and suggestibility measures were included to the exponential mixed-effect model as covariates to model parameters (see methods *"Testing for covariates for motor skill acquisition"*). The models were fit to data from the sham and anodal groups.

For trial time, the best model fit was one in which expectation was added as covariates for the amplitude, time constant and asymptote parameters, with suggestibility added as a covariate for the asymptote parameter only. As shown in Figure 10, higher expectation and suggestibility were both associated with smaller asymptotes (faster performance). Specifically, a one-point increase in expectations decreased the performance asymptote to 0.980 times its original value (mean coef. = 0.980, 95% C.I. of factor: [0.964, 0.996], p = .015), and a 10-point increase in suggestibility decreased asymptote to 0.950 times its original value (mean coef. = 0.950, 95% C.I of factor: [0.927, 0.972], p < .001). We also observed that a one-point increase in expectation corresponded to a larger time constant by 1.39 times its previous value (mean coef. = 1.388, 95% C.I. of factor: [1.169, 1.648], p = < .001). For reference, the suggestibility measure is valued on a scale of 1-100, with higher values indicating higher suggestibility, and the expectation measure is valued on a scale of 0-8.

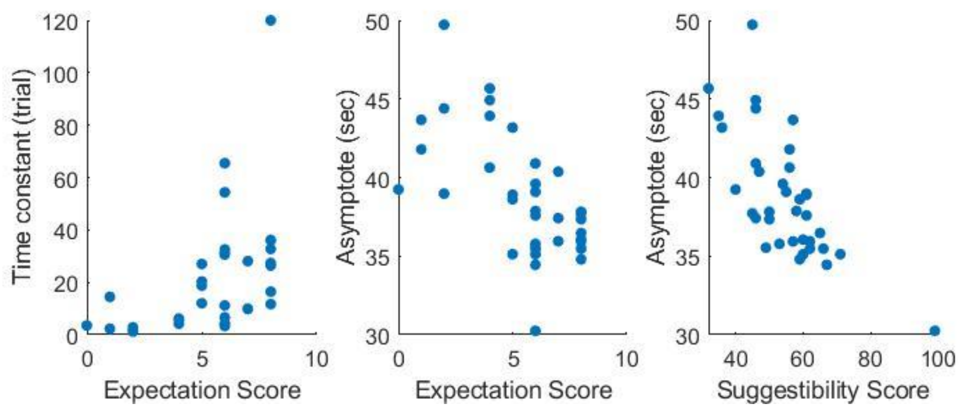

Figure 10. Expectation and suggestibility as covariates for motor skill acquisition, modeled with trial time. Higher expectation was associated with larger time constants (p < .001) and smaller asymptotes (p = .015). Higher suggestibility was associated with smaller asymptotes (p < .001).

In modeling change in the object manipulation phase, expectation was added as covariates to the amplitude and time constant parameter for dwell time, whereas suggestibility was added to the time constant and asymptote parameters. As shown in Figure 11, higher expectation was associated with larger time constants, such that a one-point increase in expectations increased time constant to 1.276 times its original value (mean coef. = 1.276, 95% C.I of factor: [1.076, 1.513], p = .005). Higher suggestibility is related to smaller asymptote, a 10-point increase in suggestibility leading to a decrease in asymptote to 0.941 times its original value (mean coef. = 0.941, 95% C.I of factor: [0.891, 0.993], p = .027). Higher suggestibility is also related to smaller time constants, such that a 10-point increase in suggestibility leading to a decrease in time constants to 0.752 times its original value (mean coef. = 0.752, 95% C.I of factor: [0.606, 0.932], p = .009).

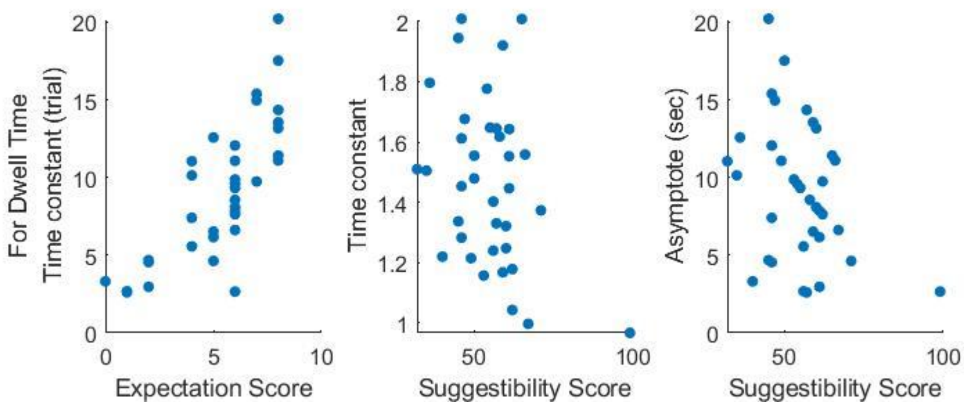

Figure 11. Expectation and suggestibility as covariates for motor skill acquisition, modeled with dwell time. Higher expectation was associated with larger time constants (p = .005). Higher suggestibility was associated with smaller asymptotes (p = .027) and smaller asymptotes (p = .009).

For the object transfer phase, no models with expectation and suggestibility as covariates fit the data better than the simple model without any covariates, as indicated by the LRT tests. Thus, expectation and suggestibility did not explain variances in motor skill acquisition of transport time specifically.

Visuospatial performance of all groups

As shown in Table 2, linear mixed effects modeling revealed a main effect of time for the sham group in decreasing reaction time (β = -286.49, 95% C.I. = [-375.74, -197.25]), p < .001), but not a main effect of group (ps > .313). However, there was a significant interaction between time and group, such that the anodal group demonstrated smaller reduction in reaction time from pre- to post-tDCS than the sham group (β = 125.29, 95% C.I. = [2.45 248.13], p = .046, Fig. 12), and that the control group also demonstrated smaller reduction in reaction time from pre- to post-tDCS than the sham group (β = 151.58, 95% C.I. = [9.19, 293.96], p = .037).

Table 2. Mixed effects modeling on reaction time of the Mental Rotation Task

	Coef.	**Std.Err.**	**z**	**P>|z|**	**[0.025**	**0.975]**
Intercept	1700.453	59.839	28.417	0.000	1583.170	1817.735
Time[Post]	-286.492	45.534	-6.292	0.000	-375.737	-197.247
Group[Control]	-96.368	95.470	-1.009	0.313	-283.486	90.749
Group[Anodal]	-46.696	82.368	-0.567	0.571	-208.134	114.743
Time[Post]:Group[Control]	151.575	72.647	2.086	0.037	9.190	293.961
Time[Post]:Group[Anodal]	125.291	62.677	1.999	0.046	2.446	248.135

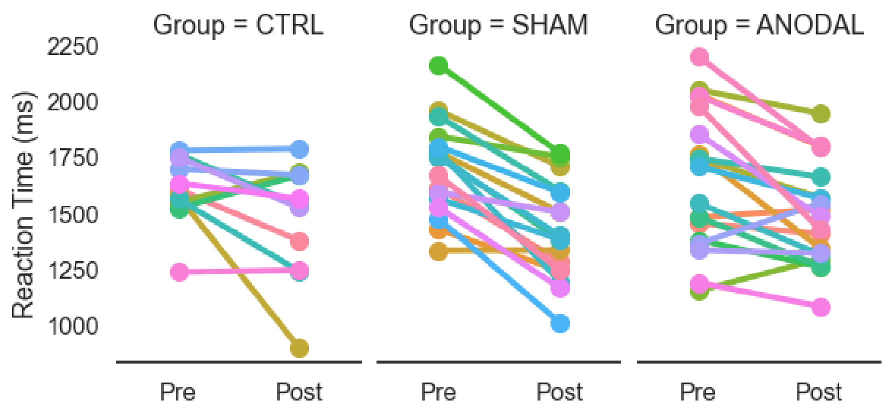

Figure 12. Reaction time of the mental rotation task in pre- and post-tDCS tests. Linear mixed effects modeling suggests that the sham group demonstrated more reduction in reaction time than both the anodal group (p = .046) and the control group (p = .037).

The relationship between visuospatial performance and motor skill acquisition

Finally, as a replication step, performance measures of the mental rotation task at pre-test were added as covariates to motor skill acquisition of trial time, for all three groups together. The best-fit model was one in which accuracy was added as covariate for the time constant parameter and reaction time was added as covariates for both the time constant and the asymptote parameter.

The chosen best fit model, however, unexpectedly revealed higher reaction time in the mental rotation task also was related to a smaller asymptote of skill acquisition. Further visual inspection on the data identified one high-leverage outlier participant whose asymptote parameter was smaller than the rest of participants and therefore was driving this effect. After this participant was removed from the analyses, and consequently reaction time were no longer a significant covariate for asymptote (p = 0.410). The current model, with the outlier removed, revealed that higher accuracy of the mental rotation was related to smaller time constant of motor skill acquisition, such that a

10% increase in accuracy corresponded with a time constant 79.8% its original value (per 10% change in accuracy: mean coef. = 0.798, 95% C.I. of factor: [0.644, 0.989], p = .040). Higher reaction time in the mental rotation task also was related to a larger time constant, such that a 100-ms increase in reaction time leading to an averaged increase in the time constant to 1.19 times its original value (per 100ms increase in reaction time, mean coef. = 1.198, 95% C.I. of factor: [1.054, 1.361], p = .006). These results are therefore consistent with our previous findings relating visuospatial function and motor skill acquisition (Chapter 3).

DISCUSSION

This current study employed a randomized, three-arm, and mixed design to test whether right parietal anodal tDCS could modulate visuospatial ability and motor skill acquisition, while also quantifying placebo effects induced by tDCS and its expectations. As illustrated with Figure 1 (red), to test the main hypothesis, treatment effects were assessed by comparing the outcome variables (reaction times from the mental rotation task and modeled motor skill acquisition parameters) between the sham and anodal tDCS groups. For the secondary purpose, placebo effects were quantified by comparing the outcome variables s between the no-tDCS control group and the sham group, as well as by quantifying the relationship between expectations and motor skill acquisition variables (Fig. 1, blue).

Firstly, the results demonstrated that baseline performances of the mental rotation task were associated with motor skill acquisition parameters. Specifically, higher accuracy of the mental rotation was related to smaller time constants, or faster learning rate, of motor skill acquisition, whereas higher reaction time was related to a larger time constant, or slower learning rate. These findings replicate the findings from Chapter 3, in which higher visuospatial function assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) was associated with faster online learning rates in older adults. These findings were in line with previous findings from the lab (Lingo VanGilder et al., 2018; Schaefer & Duff, 2017; Wang et al., 2020), demonstrating that visuospatial function and motor learning processes are closely related, therefore supporting the premise of the current study. Again, based on the positive relationship between visuospatial function and motor learning, the primary hypothesis of the study was that right parietal anodal tDCS would improve visuospatial performance, and thereby improve within-session learning of the motor task.

No tDCS treatment effects on visuospatial performance

Contrary to the primary hypothesis, the anodal tDCS group did not demonstrate improved performance in the mental rotation task or improved motor skill acquisition over the sham group. Instead, the sham group showed more improvement in reaction time from pre-test to post-test. Thus, the result did not support the hypothesis that right parietal tDCS improved performance of the mental rotation task. This finding is likely due to a lack of power in the current dataset to detect treatment effects. Based on pilot data, power analysis suggested that 31 participants per group was needed to achieve a statistical power of 0.80 with an alpha level of 0.05 in detecting differences in mental rotation performance. Since data collection is still ongoing and only 45% of targeted recruitment was achieved, current study lacks statistical power to detect an effect.

No tDCS treatment effects on motor skill acquisition

We also did not detect any treatment effects of tDCS on motor skill acquisition. In terms of changes in trial time, the anodal group and the sham group did not differ in the modeled amplitude or the asymptote parameters (Fig. 4), suggesting that anodal tDCS and sham tDCS resulted in similar after-effects for within-session performance improvement (indicated by amplitude) and final performance (indicated by asymptote) over 30 trials of motor training. The anodal group, however, demonstrated a larger time constant on average, than the sham group. The larger time constants in the anodal group could indicate that anodal tDCS induced continual improvement that may be longer-lasting than simple practice effects observed in sham tDCS. Therefore, it is possible that the effect of anodal tDCS could be more obvious when paired with higher training volumes/intensity, or over multiple training sessions. Also, a lack of power may explain this null result, as the current sample size is only 45% of targeted recruitment. According to a prior power analysis, a targeted sample size of 40 participant per group was needed to achieve power 0f 0.8 with an alpha level of 0.05 in detecting differences in motor learning.

Additional analyses of dwell time and transport time further described performance changes during the object manipulation phase and the object transfer phase over practice, respectively. Differences between the anodal and sham group were revealed for dwell time, but not for transport time (Fig. 5 and Fig. 6), consistent with Hooyman et al. (2021). The sham and anodal group did not differ in any skill acquisition variables in transport time, likely because the transport phase is ‘overlearned’ and subject to ceiling effects, even with the nondominant hand (see Schaefer & Hengge, 2016). For dwell time, however, the sham tDCS group had increased amplitude compared to the anodal tDCS group (Fig 5), suggesting that the sham group demonstrated more improvement in dwell time performance within the training session than the anodal tDCS group. However, this finding does not necessarily suggest that the sham group learned, or acquired, more skills during the object manipulation phase than the anodal group. Given that the sham and anodal groups had comparable performance asymptotes, the larger performance improvement of the sham group could be due to their slower initial performance. Such an inverse relationship has been observed for this motor task (Wang & Schaefer, 2020).

Combined, the results demonstrated that anodal tDCS had no distinguishable effect on motor skill acquisition from that of sham tDCS. In other words, this study did not observe tDCS treatment effects on motor skill acquisition for a single training session. It is not unexpected that we did not observe a treatment effect of tDCS on motor skill acquisition, when the treatment effect of tDCS on visuospatial function was also absent. This finding echoes the study by Convento et al. (2014) such that anodal tDCS on P4 doesn't have a strong effect on performance of the Jebsen–Taylor Hand Function Test. However, the sample size of this study was 12. Thus, the negative findings may be due to small sample sizes in both studies. This study faces insufficient power to detect tDCS treatment effects, due to a limited sample size at the time of this writing (45% of targeted 40 participants per group). However, we note that even with a modest sample size here, this study detected that the sham group over-performed the anodal group in both the mental rotation task (more improvement in reaction time) and motor task acquisition (faster learning rate and more improvement in dwell time performance), both with statistical significance.

Placebo effect of tDCS on motor skill acquisition of the sham and control group

As mentioned in the Introduction and illustrated in Figure 1, null findings in terms of a treatment effect of tDCS may be the result of an “unlucky” combination of large individual variabilities, placebo effect and sampling randomness. To better address this possibility, we explored whether there were placebo effects due to tDCS in this study and if so, was the placebo effect larger in magnitude than the treatment effect on motor skill acquisition? As a reminder, a placebo effect would be measured as a difference in motor skill acquisition between the sham and the control group (demonstrated in Figure 1). Although our findings showed no difference between the sham group and the control group in learning of the overall task (as assessed by modeling trial time (Fig. 7), the sham group did have a higher amplitude of improvement in both dwell time and transport time than the control group (Fig. 8 and Fig. 9), suggesting a placebo effect.

Combined, this meant that the placebo effect could induce improvements even in well-learned behaviors, for which tDCS was not as effective. The unique finding of this study is that this placebo effect over-shadowed the treatment effect on motor learning, which has implications for the field of tDCS and motor research. In theory and in practice, the distributions of tDCS expectations could vary from group to group within or across studies due to differences in random sampling. However, this study offers methods to control for placebo effects – i.e., measuring and co-varying for expectations in tDCS studies (Wang et al., 2021). Including a control group is also strongly recommended, as it can reveal the size of placebo effects (Colloca & Barsky, 2020). Lastly, open and transparent science can benefit tDCS studies. Pre-registered reports can increase the likelihood of null results studies being published, which arguably is just as (if not more) valuable for tDCS research as positive findings.

Expectation and suggestibility influenced motor skill acquisition

Because there was no treatment effect of tDCS, and because there were no significant differences in expectations between the anodal tDCS and sham tDCS groups, expectation data from these groups were pooled for nonlinear mixed effects modeling of skill acquisition with expectation and suggestibility as covariates. As hypothesized, expectation and suggestibility were both significant covariates for on online motor learning, positively affecting overall trial time as well as dwell time. We found that higher expectation was associated with smaller performance asymptote for trial time (Fig. 10). That is, participants who more strongly expected tDCS to improve their motor performance also demonstrated better (faster) final performance in the training session. These findings are consistent with other new pieces of evidence showing that priming participants' expectations could alter treatment outcomes of tDCS (Rabipour et al., 2018;

Ray et al., 2019). In fact, outside of tDCS research, this relationship between expectation on motor performance has been well documented and studied (Wulf & Lewthwaite, 2016). Higher suggestibility also was related to better (faster) performance asymptote, supporting the idea that participants who are more likely to be influenced by extrinsic information tended to perform better after they were subjected to tDCS, regardless of stimulation type (anodal or sham).

CONCLUSION

In conclusion, the current study employed a randomized, three-arm design to test the effect of right parietal anodal tDCS on visuospatial ability and motor skill acquisition, and to quantify any placebo effect induced by tDCS and its expectations. This study did not observe any tDCS treatment effect, but rather a significant placebo effect. Specifically, the anodal group did not demonstrate better improvement of mental rotation task performance or motor skill acquisition than the sham group. However, the sham group had more improvement in motor skill acquisition than the control group. Moreover, the magnitude of placebo effects varied by expectations and suggestibility, such that better task performance at the end of training (and more continual learning during training) were associated with higher expectation and suggestibility. Future studies are needed to explore placebo effects in other neuromodulation interventions, and should aim to control and measure such effects to better exploit them in rehabilitative or performance-enhancing contexts.

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CHAPTER 6

INVESTIGATING THE RELATIONSHIP BETWEEN RESTING-STATE EEG FRONTOPARIETAL COHERENCE AND VISUOSPATIAL AND MOTOR SKILL PERFORMANCE – A RETROSPECTIVE STUDY

ABSTRACT

Visuospatial ability may explain individual variabilities in the extent of motor skill learning. Recent research suggested that better visuospatial scores correlate with more retention. Neuroimaging evidence suggests that the frontoparietal structures underlie both visuospatial performance and visuomotor learning. Furthermore, neuropsychological findings suggest that right frontoparietal networks specifically may be critical for this relationship, as many visuospatial processes are specialized to the right parietal cortex. Thus, this proof-of-concept study aims to test whether frontoparietal functional connectivity at rest, measured by resting-state EEG coherence, is related to both visuospatial performance and early motor skill acquisition. A retrospective dataset of 21 participants was analyzed, with 2-min eyes-closed resting state EEG, Visuospatial/Constructional Index score from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and five trials of motor practice on a functional motor task. Right frontoparietal coherence in the alpha band (8-12Hz) was computed with imaginary coherence (IC) between electrodes F4 and P4. ICs from the left (F3-P3) and midline (Fz-Pz) electrodes were also included as negative controls. Results indicated that F4-P4 alpha IC was highly correlated with the RBANS Visuospatial Constructional

Index ($r = 0.55$, $p = .035$), while left and midline alpha ICs were not (all *p*s > .140). This study extends previous structural findings and indicated that frontoparietal functional connectivity, especially in the right hemisphere, may underlie visuospatial function. However, this study did not find a correlation between right frontoparietal alpha IC with motor skill acquisition ($p = .474$), measured as within-session rate of improvement. This null finding is likely due to the limited dose of motor practice (only 5 trials) in the retrospective dataset, which was not inherently designed to investigate motor skill acquisition per se. Further studies are needed to use a larger training dose to accurately evaluate motor skill acquisition and its relationship with right frontoparietal coherence. However, this study supports that right frontoparietal IC is positively related with visuospatial function. This finding has implications for developing right frontoparietal alpha IC-based neurofeedback applications for cognitive training in and of itself, or to benefit slow- or non-learners in motor rehabilitation.

INTRODUCTION

Improving motor performance in rehabilitation and sports, controlling surgical tools, and controlling brain-computer interfaces all require repetitive practice. Yet, some individuals learn slower than others with the same amount of practice, or not at all (Brooks, Hilperath, Brooks, Ross, & Freund, 1995). Recently, we have demonstrated that individual variabilities in the extent of motor skill learning can be explained by visuospatial ability such that better visuospatial scores correlate with more retention.

(Lingo VanGilder, Hengge, Duff, & Schaefer, 2018; Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021; Regan et al., 2021; Wang, Infurna, & Schaefer, 2020).

Evidence suggests that the right frontoparietal network may be crucial for the interaction between motor learning and visuospatial processes. Frontoparietal neural structures such as the superior longitudinal fasciculus, have been shown to underlie skilled motor performance (Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012), and both cognitive and visuomotor control (Brandes-Aitken et al., 2019). Further, neuropsychological findings suggest that many visuospatial processes are specialized to the right parietal cortex (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Foxe, McCourt, & Javitt, 2003).

Based on the structural findings, this study aims to test whether functional connectivity between right frontal and parietal regions at rest, measured by resting-state EEG coherence, is related to both visuospatial function and early skill acquisition. EEG coherence is a correlation measure based on the frequency spectrum, which measures the degree of synchronization between oscillations of different neuronal ensembles underlying any two scalp electrodes (Nunez & Srinivasan, 2009). Recent studies have suggested that resting-state EEG coherence is linked to visuomotor learning (Wu, Knapp, Cramer, & Srinivasan, 2018; Wu, Srinivasan, Kaur, & Cramer, 2014; Zhou et al., 2018). Coherence in the alpha band (8-12Hz) is of particular interest in this study, because higher alpha power has been linked with improved performance in a spatial rotation task (Zoefel, Huster, & Herrmann, 2011), and resting-state EEG coherence of the motor network in the mu (11-14Hz) frequency band also predicted within-session improvement of a visuomotor skill task (Wu et al., 2014).

However, it remains unknown whether right **frontoparietal** alpha coherence between is related to visuospatial function or motor acquisition. To this end, I retrospectively analyzed an existing dataset from 21 participants with eyes-closed resting state EEG data. This retrospective analysis was done during the COVID-19 pandemic when face-to-face data collection was prohibited. Participants in this dataset also completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998), which contains a Visuospatial Index score, and five trials of a functional motor task, used throughout this dissertation (Schaefer, Dibble, & Duff, 2015). Right frontoparietal alpha coherence was computed with imaginary coherence (IC; Nolte et al., 2004) between electrodes F4 and P4. ICs from the left (F3-P3) and midline (Fz-Pz) electrodes were also included as negative controls. Correlation analyses between coherence and the Visuospatial Index Score of the RBANS, and motor skill acquisition were conducted. I hypothesized that F4-P4 coherence, not F3-P3 or Fz-Pz coherence, would be positively correlated with motor skill acquisition, as well as the Visuospatial Index Score from the RBANS.

METHODS

Experimental Design

The dataset contained data from 21 healthy younger adults (aged 23.29 ± 3.47 years, 10 females). Eyes-closed resting-state EEG data was recorded for 2 minutes prior to completing the RBANS test battery and five trials of a functional motor task, as illustrated in Figure 1. Visuospatial Index of the RBANS was computed according to the scoring manual (Randolph et al., 1998). The functional motor task involves acquiring and transporting objects between locations with the nondominant hand as fast as possible (the same task as used in other chapters of this dissertation), and performance is quantified with trial time.

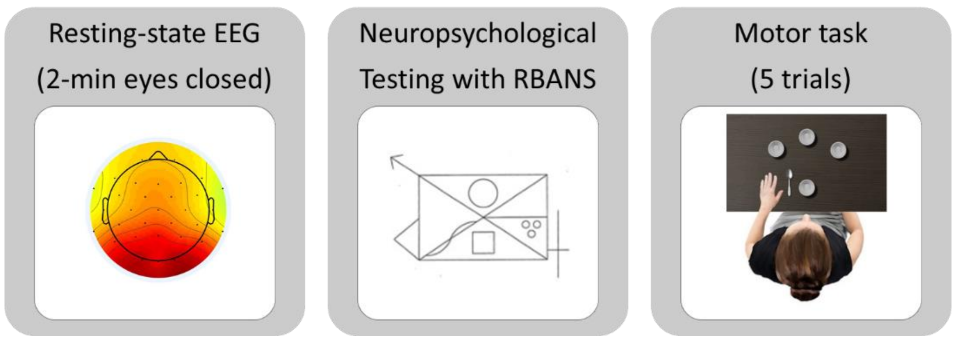

Figure 1. Experimental protocol

Modeling motor skill acquisition

To quantify motor skill acquisition, trial time data (in seconds) from each individual were fit with a linear model[2]:

$$Trial\ Time_i = A_i - B_i t \tag{1}$$

where t is trial number, A intercept term and B the slope term. Individual participant was specified as i. Initial performance was estimated with A, where smaller A

[2] A mixed-effect model was not used here because it failed to capture the individual variabilities for the slope term (B). That is, the random effect of slope is zero for all subjects when the data were fit with a mixed-effect linear model.

values indicates better initial performance. The rate of improvement was estimated with B, where larger B values indicates a faster rate of improvement.

EEG Acquisition and Preprocessing

Eyes closed resting state EEG data were collected for 2-minutes. Data were online referenced to the right earlobe, and that the ground electrode was the left earlobe. Sampling rate was 1000Hz. Preprocessing was done via the EEGLAB toolbox (Delorme & Makeig, 2004) and the Zapline package (de Cheveigné, 2020) in MATLAB. Continuous data were high-passed at 1Hz with a zero-phase non-causal window sinc FIR filter (EEGLAB function ‘pop_eegfiltnew’), which had a filter of 3300 and a cutoff of 0.5 Hz at 6dB.

As the current dataset contains heavy line noise, Zapline was used to remove line for its superiority in specifically cleaning 60Hz noise while preserving signals at other frequencies (de Cheveigné, 2020). Faulty channels and data segments with heavy muscle artifacts were manually rejected. Channels whose power spectrum did not demonstrate 1/f decline or with power less than other channels were removed. This resulted in 1.94 ± 1.24 removed channels for each participant, mostly temporal electrodes (T7, T8, TP9 & TP10, 83.9%) and some FT electrodes (9.7%). Then continuous data were visually inspected to reject segments with spatially wide-spread muscle artifact. This resulted in average data length of was 107.63 ± 8.61 seconds for the sample. Following data rejection, data were then submitted to an infomax ICA (Delorme, Sejnowski, & Makeig, 2007). ICLabel (Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019) was used to identify and remove independent component(s) with eye artifacts and muscle artifacts. Any IC components with eye and muscle artifacts over 90% probability as identified by ICLabel were removed. On average, 2.3 ± 1.5 independent components were removed from the sample. After ICA artifact correction, rejected channels were interpolated with spherical splines interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989). Data were then segmented into non-overlapping 1-second epochs.

Lastly, to appropriately perform electrode-level connectivity with EEG, the preprocessed data (scalp potentials) was submitted to a reference-free surface Laplacian algorithm to mitigate volume conduction (Kayser & Tenke, 2015). The surface Laplacian is a current source density measure that estimates the spatial second derivatives of scalp EEG potentials as an approximation for the amplitudes of underlying current generators (Tenke & Kayser, 2012). Due to the nature of taking derivatives, the EEG data now were reference free. A spline Surface Laplacian was used with default flexibility ($m = 4$) and regularization (λ = $10- 5$) parameters (Cohen, 2015; Perrin et al., 1989). The Surface Laplacian step were completed with X code (Cohen, 2014) in Matlab.

EEG coherence

Imaginary coherence (IC) was chosen as the primary coherence measure, because it avoids inflated and artifacted coherence values caused by volume conduction, and thus provides a robust estimate of EEG connectivity (Nolte et al., 2004). IC was estimated with the frequency spectrum, and reflects the amount of phase synchronization between two time series. However, IC only measures time-lagged synchronizations by taking only the imaginary part of the complex cross-power spectrum of the two EEG signals (see Eq 3). IC was computed using customized codes in MATLAB as described in the following paragraphs.

Laplacian-referenced, preprocessed 1-second data segments were submitted to Fourier transforms using the Matlab *fft* function and normalized by segment length to yield Fourier coefficients. No windowing function was used. Frequency resolution was 1Hz. The Fourier coefficients were then used to calculate auto- and cross- power spectra via Welch's method:

$$S_{xy}(f_n) = \frac{2}{K} \sum_{k=1}^{K} X_k(f_n) Y_k^*(f_n) \;\; n = 1, 2, \ldots, \frac{N}{2} - 1 \qquad (2)$$

where n stands for the index of frequencies after the Fourier transform, N is the total number of time points for each segment, k indicates the index of segments and K the total number of segments. $X_k(f_n)$ is the complex Fourier coefficients of time series $x(t)$ at frequency f_n, whereas $Y_k^*(f_n)$ is the conjugated complex Fourier coefficients of time series $y(t)$ at frequency f_n. The notation and definition for S_{xy} is consistent with that from Nunez (Nunez & Srinivasan, 2009), such that the formula contains a factor of two because only positive frequencies were included, and the DC signal (f = 0) and Nyquist frequency (f = N/2) were omitted.

Therefore, the cross-power spectrum Sxy between signals x and y is estimated from the average of individual power spectra of all segments. This estimation can increase signal to noise ratio, and therefore obtains robust estimates (Nunez & Srinivasan, 2009). When the two signals are the same, $x(t) = y(t)$, the complex-valued cross spectrum S_{xy} is reduced to a real-valued auto spectrum for that signal, noted as S_{xx}.

Imaginary coherence (IC) is calculated with the magnitude of the imaginary part of cross power spectrum normalized by the square root of both auto power spectra (Nolte et al., 2004):

$$IC_{xy} = \frac{Im\left(S_{xy}(f_n)\right)}{\sqrt{S_{xx}(f_n)S_{yy}(f_n)}} \; n = 1, 2, \ldots, \frac{N}{2} - 1 \tag{3}$$

where Im denotes taking the imaginary part of the complex cross spectrum. IC reflects the level of consistency of the phase difference between two channels of interest, and is valued from 0 to 1. A higher IC value indicates that the two channels are more connected. By definition, the IC between a channel and itself is zero, because there is no time-lagged coherence. Thus, IC avoids inflated and artifacted coherence values caused by volume conduction, and can provide a robust estimate of EEG connectivity.

Statistical Analysis

Brain behavior correlations between coherence and motor or visuospatial variables were tested with bivariate correlation. All bivariate correlation analyses were tested using Spearman Rank correlation. Significance level was set to 0.05. I did not correct for multiple comparisons for fear of rejecting true positives in this initial study with a relatively small sample size. Instead, statistics are reported comprehensively for all analyses, including those for null results.

RESULTS

Data from 21 participants were analyzed. One participant was excluded for missing motor performance data and four participants were excluded due to substantial artifacts in the EEG data (neither alpha peaks in power spectra nor not following typical 1/f shape). This resulted in a final sample of 15 participants (8 females; age 22.73 ± 2.69 years old).

On average, motor performance improved from the first trial to the fifth trial by a reduction of 9.15 ± 4.77 in trial time ($t(14) = 7.42$, $p < .001$, 95% CI [6.50, 11.79] seconds). The distribution of trial times is presented in Fig 2, showing that motor performance improved across participants with considerable individual variability. Individual model fits (Fig 3) demonstrated an average intercept of 52.05 ± 5.97 seconds for baseline performance, and an average slope of 1.80 ± 1.30 for rate of improvement over trials. Modeled baseline performance and slope were correlated (r = 0.78, $p < .001$).

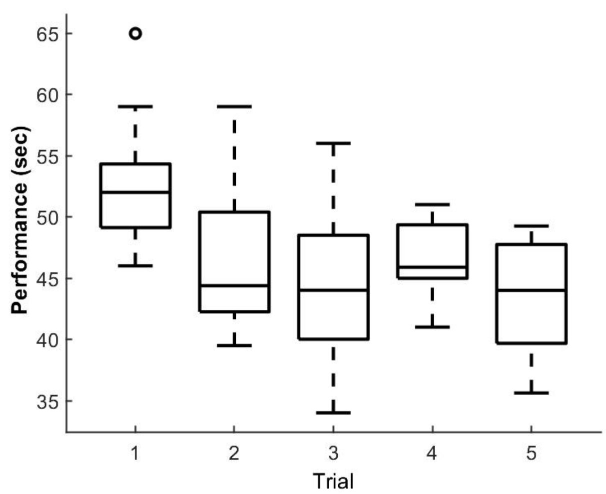

Figure 2. Progression of motor performance over five trials.

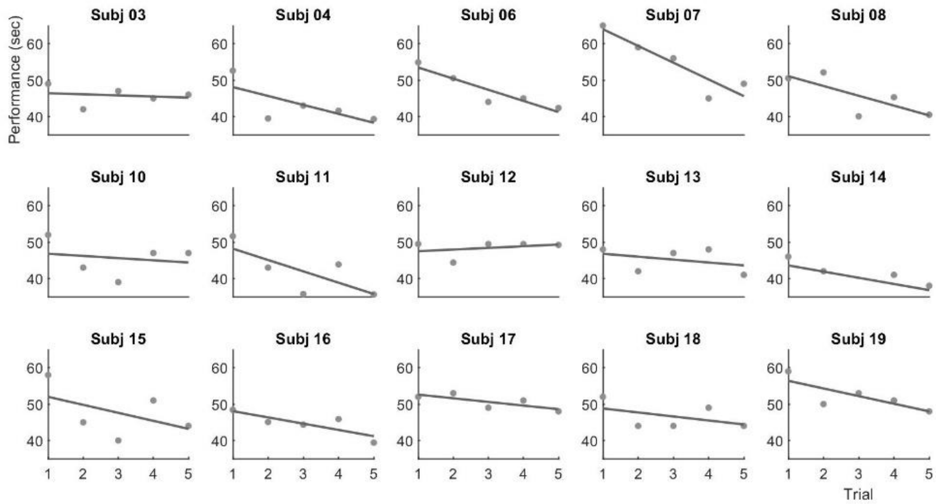

Figure 3. Individual model fits for motor performance over five trials.

Right frontoparietal imaginary coherence did not correlate with motor variables

Right frontoparietal (F4-P4) imaginary coherence, the primary coherence measure, did not correlate with the modeled initial performance (p = .271) or the rate of improvement (p = .474). On the contrary, initial performance was strongly correlated with both control imaginary coherence measures (Fig 4, left and middle). Left frontoparietal (F3-P3) imaginary coherence correlated with initial performance (r = -0.77, p = .001). Midline frontoparietal (Fz-Pz) imaginary coherence also correlated with initial performance (r = -0.64, p = .012). Although two control ICs also demonstrated correlations with rate of improvement (r = -0.51, p = .052 for left imaginary coherence; and r = -0.52, p = .051 for midline imaginary coherence), this relationship was driven the innate relationship between initial performance and rate of learning. When follow-up regression analyses used both IC and baseline performance to predict rate of improvement, IC was no longer correlated to the rate of improvement (p =.812 for left IC, p =.712 for midline IC) while baseline performance was (beta = 0.74, p = .019; and beta = 0.83, p = .005 for the two models separately).

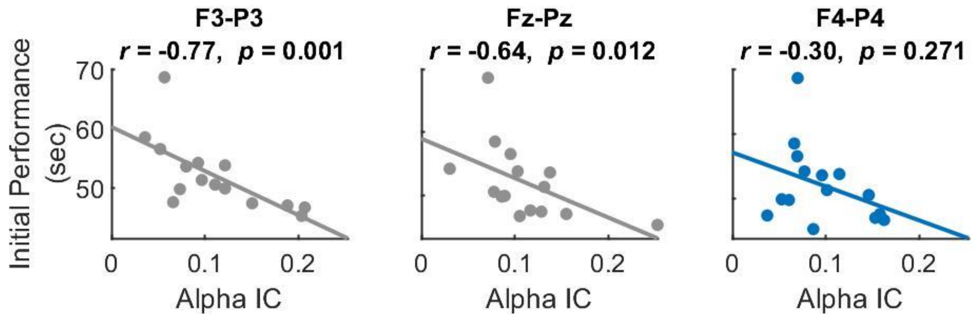

Fig 4. Relationship between frontoparietal alpha ICs and initial motor performance. Color blue suggests the analysis between the right frontoparietal coherence (primary IC measure) and motor performance. Color grey suggest control analyses with left and midline frontoparietal coherence.

Right frontoparietal imaginary coherence correlated with RBANS Visuospatial Index

Spearman Rank correlation revealed that right frontoparietal (F4-P4) alpha IC correlated with the RBANS Visuospatial Index (r = 0.55, p = .035; Fig. 5, right). Control analyses using left (F3-P3) and midline (Fz-Pz) alpha IC did not reveal any correlations between ICs and the RBANS Visuospatial Index (all *p*s > .140; Fig. 5, left and middle).

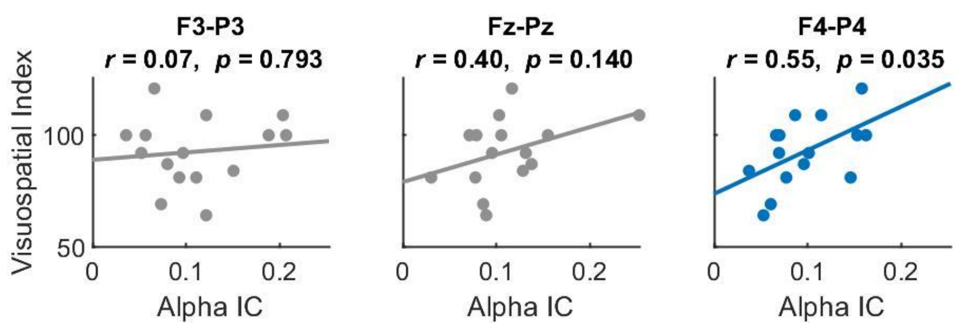

Fig 5. Relationship between frontoparietal alpha ICs and Visuospatial Index. Color blue suggests the analysis between the right frontoparietal coherence (primary IC measure) and visuospatial performance. Color grey suggest control analyses with left and midline frontoparietal coherence.

DISCUSSION

This study tested whether right frontoparietal EEG resting-state connectivity was associated with visuospatial function (measured as the RBANS Visuospatial Constructional Index) and motor skill acquisition. F4-P4 alpha IC, measured at rest with eyes-closed, was highly correlated with the RBANS Visuospatial Constructional Index, while left and midline alpha ICs were not. In terms of motor skill acquisition, F4-P4 IC did not correlate with motor skill acquisition (measured as within-session rate of improvement), nor with baseline motor performance. However, F3-P3 and Fz-Pz IC were highly correlated with baseline motor performance. No IC measure correlated with rate of improvement (i.e., how quickly motor performance improved).

Current results indicate that the right frontoparietal coherence, not left or midline coherence, is highly correlated with visuospatial function. This study extends previous structural neuropsychological findings (Brandes-Aitken et al., 2019; Corbetta et al., 2000; Foxe et al., 2003; Steele et al., 2012) by showing that functional connectivity at rest between right frontal and parietal cortical regions also predicts visuospatial function. This study further supports that the link between alpha coherence and visuospatial function could be causal. Rizk et al. (2013) showed that right parietal cortex stimulation reduced visuospatial attention and induced neglect-like behavior. After stimulation, alpha coherence between the parietal stimulation site and other cortical regions decreased. This suggests that right frontoparietal coherence may be a biomarker for visuospatial function, a critical finding that has important clinical applications. For example, F4-P4 alpha coherence could be a therapeutic target in neurofeedback training to improve visuospatial function via self-regulation of the coherence signal itself. One could potentially regulate the frontoparietal networks that underlie visuospatial processes. Neurofeedback approaches that provide feedback of dynamic brain networks (such as coherence signals) are considered to be more effective in achieving neural regulation than those providing signals from one single brain region (Sitaram et al., 2017). The feasibility and efficacy of alpha imaginary coherence neurofeedback has been demonstrated previously (Anaïs Mottaz et al., 2018; Anais Mottaz et al., 2015). Alpha coherence can be successfully modulated via neurofeedback (Anais Mottaz et al., 2015) and up-regulating alpha coherence between the motor cortex and the rest of the cortical regions can improve motor performance after stroke (Anaïs Mottaz et al., 2018). Given the prevalence of visuospatial deficits following stroke (Jokinen et al., 2015; Jongbloed, 1986) and in preclinical Alzheimer's disease (Caselli et al., 2020; Johnson, Storandt, Morris, & Galvin, 2009), there is a clinical need for effective visuospatial training paradigms. Results from the current study warrant follow-up studies that directly test the feasibility of a frontoparietal alpha neurofeedback intervention for improving visuospatial function.

Contrary to the hypothesis, this study did not find a correlation between right frontoparietal alpha IC with motor skill acquisition, or baseline motor performance. One potential reason for this could be the limited dose of motor practice (only 5 trials) in this retrospective dataset, which was not inherently designed to investigate motor skill acquisition per se. In previous studies using the same motor task, visuospatial function correlated with one-month motor retention after 50 or more trials of practice (VanGilder, Lohse, Duff, Wang, & Schaefer, 2020), as well as with 1-week retention after at least 10 trials of practice (Lingo VanGilder et al., 2018; Schaefer & Duff, 2017). In Chapter 3 where I demonstrated that the Delayed Recall score of the Rey-Osterrieth Complex Figure test was related to learning rate, participants also completed more than 30 motor training trials. The dose of practice in the current dataset may be too small to accurately evaluate motor skill acquisition and the learning process, but future studies are needed to test whether right frontoparietal coherence correlates with skill acquisition over a larger training dose, as suggested by the multi-session motor training paradigm reported in Zhou et al. (Zhou et al., 2018).

This study did, however, identified a relationship between left and midline frontoparietal coherence with baseline motor performance. This is particularly provocative since 14 out of 15 participants used their left (nondominant) hand on the motor task, for whom the dominant (left) cortex is the ipsilateral cortex. Other studies have demonstrated that the alpha coherence in the left, but not right, hemisphere was related to visuomotor learning (Manuel, Guggisberg, Theze, Turri, & Schnider, 2018) and motor skill acquisition (Wu et al., 2014) when using the right (dominant) hand. Moreover, alpha and beta coherence between left M1 and the rest of the cortical regions predicts motor skill acquisition (Wu et al., 2014; Zhou et al., 2018). Because this dataset used in the current study did not include any dominant hand motor data, we cannot directly test whether our data are consistent with these previous studies. However, our data do suggest a left parietal specialization for motor planning regardless of which effector is used, consistent with Kumar et al. (2020).

We acknowledge that the current study only focused on a single EEG frequency band (the alpha band). This was because this retrospective dataset included substantial artifacts that contaminated the beta band even after rigorous pre-processing (described in Methods), preventing the analyses of the beta frequency. Beta-band oscillations are strong sensorimotor rhythms (Hari & Salmelin, 1997; Jensen et al., 2005) that have been shown to predict performance both during task and at rest. Beta coherence at rest may also play a role in predicting motor learning. Wu et al. (2014) found that beta coherence from M1 to other parts of the brain predicted motor learning in high accuracy, while alpha coherence demonstrated a weaker correlation. It is worth pointing out that Wu et al. (2014) also showed that left premotor-parietal beta coherence was not related to motor learning. In further support of the beta frequency band, beta coherence can predict training-related behavioral gains in stroke patients (Zhou et al., 2018) and beta oscillations at rest were confined to sensorimotor cortex, inferior parietal lobes, as well as the dorsolateral prefrontal cortex (Hillebrand, Barnes, Bosboom, Berendse, & Stam, 2012). These findings suggest that frontoparietal beta coherence should be investigated as a biomarker for motor learning in future studies.

In conclusion, this retrospective analysis used imaginary coherence in the alpha frequency band to measure frontoparietal functional connectivity with EEG, and demonstrated that right frontoparietal connectivity is positively related with visuospatial function. This finding has implications for developing right frontoparietal alpha IC-based neurofeedback applications for cognitive training, which may benefit slow- or non-learners to motor rehabilitation and motor training. Future studies are needed to test the relationship between alpha IC and motor learning with more extensive motor training.

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CHAPTER 7

DUSCISSION

Summary and Future work

With the longer-term goal to optimize motor learning for rehabilitation, this dissertation aimed to identify factors and methods to enhance motor learning. Based on previous lab findings on the relationship between visuospatial function and motor retention, this work first replicated and extended such behavioral findings to within-session skill acquisition (Chapters 2 and 3), and consequently investigated the neural correlates underlying this relationship (Chapters 5 and 6).

The effect of right parietal anodal tDCS on motor skill acquisition was investigated with a randomized, three-arm design that added a no-tDCS control group to the double-blinded sham-control protocol (Chapter 5). This design was motivated by the prevalence of mixed-findings in tDCS and motor research (Buch et al., 2017) and aimed to control for the placebo effects, especially considering that the general public has a higher-than-neutral expectation for tDCS to improve motor performance (Chapter 4; Wang, Hooyman, Schambra, Lohse, & Schaefer, 2021). No tDCS treatment effect was observed on visuospatial performance or motor skill acquisition, as the active (anodal) tDCS group did not differ from the sham group in their mental rotation task performance or learning the motor task after receiving stimulation. This result is likely due to low statistical power to detect any treatment effects. Pilot data on reaction time of the mental rotation task suggested that 31 participants per group was needed to achieve a statistical power of 0.80 with an alpha level of 0.05. Pilot motor learning data suggested that 40 participants per group is required for the same power. Since the data collection was delayed due to COVID-19 and is still ongoing, we have only collected 45% of our targeted recruitment (n = 17 for sham, n = 19 for anodal group).

However, the unique finding of the current work is that the placebo effect of tDCS over-shadowed its treatment effect on motor learning. Not only did the sham stimulation resulted in more skill acquisition than no-tDCS at all, but for both the sham and tDCS groups, higher expectation and suggestibility were related to better motor performance at the end of training, as well as more continual improvement during training. These findings of Chapter 5 are consistent with other new pieces of evidence showing that priming participants' expectations could alter treatment outcomes of tDCS (Rabipour, Wu, Davidson, & Iacoboni, 2018; Ray et al., 2019), which represents a future direction we would like to pursue as well. Moreover, our findings also support how motor performance itself is susceptible to expectations and verbal suggestions alone (Fiorio, 2018). In this study, participants were exposed to no priming information other than being informed that the purpose of the research was "to test whether tDCS could improve motor performance" during consenting. This finding has implications for the field of tDCS and motor research. In theory and in practice, the distributions of tDCS expectations could vary not only between sham and active tDCS groups within a study but also across studies, leading to mixed findings and challenging study replications. It is recommended that future research studying the effect of an intervention on motor learning control for placebo effects, i.e., measuring and co-varying for expectations in tDCS studies (Wang et al., 2021), or including a control group in study design (L.

Colloca & Barsky, 2020). Future research may also focus on how to leverage the placebo effect to maximize behavioral gains in enhancing motor performance. It is noted that this project has been funded by a North American Society for the Psychology of Sport and Physical Activity Graduate Research Grant.

Chapter 6 reported a study that tested whether connectivity between right frontal and parietal regions is related to both visuospatial function and early skill acquisition. Note that an existing dataset was retrospectively analyzed, since new data collection was prohibited during COVID-19. This study is a preliminary and necessary step towards determining if the frontoparietal network can serve as target training signals for EEG-neurofeedback to enhance motor learning. Right frontoparietal connectivity at rest, estimated with imaginary coherence between electrodes F4 and P4 in the alpha frequency band, was shown to be positively related with visuospatial function. The study did not find a correlation between F4-P4 alpha coherence and motor skill acquisition, however, likely due to the limited dose of motor practice (only 5 trials) in this retrospective dataset. All other work replicating the positive relationship between visuospatial and motor learning contained at least 10 practice trials (Lingo VanGilder, Hengge, Duff, & Schaefer, 2018; Schaefer & Duff, 2017; VanGilder, Lohse, Duff, Wang, & Schaefer, 2020; Wang, Infurna, & Schaefer, 2020). Thus, future studies are needed to test the relationship between alpha IC and motor learning with more extensive motor training.

By demonstrating the relevance of alpha imaginary coherence and visuospatial performance, this work grants further research in the feasibility of using right frontoparietal alpha IC-based neurofeedback for cognitive training, which may still benefit slow- or non-learners to motor rehabilitation and motor training. In fact, the feasibility and efficacy of a similar alpha imaginary coherence neurofeedback has been demonstrated previously (Anaïs Mottaz et al., 2018; Anais Mottaz et al., 2015). Alpha coherence can be successfully modulated via neurofeedback (Anais Mottaz et al., 2015) and up-regulating alpha coherence between the motor cortex and the rest of the cortical regions (projected back to source space via beamforming) can improve motor performance after stroke (Anaïs Mottaz et al., 2018). Future studies should test whether alpha imaginary coherence between scalp electrodes, with proper spatial filtering, can be effectively modulated in neurofeedback. It is noted that this project has been funded by a Foundation for Neurofeedback and Neuromodulation Graduate Research Grant.

Reflections

I acknowledge that the work finished and presented in the dissertation may seem to have not fully fulfilled the aims of this dissertation, as summarized by the title. The Aims of the dissertation were defended in 2019 and experimental designs was finalized in early 2020. Since then, the progress was considerably hindered by the challenges presented by the COVID-19 pandemic, due to the restrictions to conduct in-person human subject research. With reduced capacity for data collection, I decided to focus data collection efforts on Aim 1 (Chapter 4 and 5), and utilize retrospective data for Aim 2 (Chapter 6). As a result, Chapter 6 is a retrospective study with a limited dosage for motor training, and therefore is not inherently suitable to study motor skill acquisition. This resulted in a partially fulfilled Aim 2. Besides, due to a combination of the admittedly high ambition of mine in the research proposal and the black-swan event of the pandemic, I was not able to run pilot studies on EEG-neurofeedback, which is what truly matches the "neuomodulation of frontoparietal network" description indicated by the title. Not reported in this dissertation is an early prototype of a real-time EEG processing and visualization pipeline I developed for neurofeedback presentation, which was realized through Lab Streaming Layer, BCILAB and Psychtoolbox. All in all, although my dissertation still leaves an important question to be answered – can frontoparietal coherence be used as a EEG-neurofeedback target for improving motor skill acquisition? – the research method to answer this question is developed.

Uncertainties and random setbacks are almost a guaranteed experience in research. As the pandemic amplified and synchronized this experience for all researchers, I just happened to be a graduate student completing a dissertation project. I have had tremendous help and understanding from my committee to adapt my research and keep going. I am even presented with this unique opportunity to write my dissertation title "post hoc", to make it more reflective of the work presented here. I would like to re-write the title as "Investigation of motor skill acquisition with a behavioral neuroscience approach: from visuospatial function to neuromodulation".

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APPENDIX A

MODEL SELECTION FOR TESTING TDCS TREATMENT EFFECT

Model selection process for trial time is described below. In the model specifications below, *t* was trial number and *j* participant number. G is a within-subject grouping binary variable valued 0 or 1. G is set to 1 for the group with the effect of interest (G = 0 for sham and G = 1 for anodal for tDCS treatment effect). A_j, τ_j and C_j the mixed effect model parameters at the control condition (corresponding to G =0). The mixed-effect parameters associated with the grouping variable, a_j, b_j, and c_j, are representing the group difference in amplitude, time constants, and asymptote. In this fashion, statistical differences in skill acquisition were tested by the p-values associated with a_j, b_j and c_j. The selected model was **bolded**.

Model for trial time	Log likelihood	BIC	RMSE
$(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j$	-3200.79	6433.84	0.095
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-3200.72	6433.70	0.095
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-3201.07	6434.40	0.095
$(A_j + a_j G)\, e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-3200.54	6440.49	0.095
$(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-3200.59	6440.61	0.095
$\boldsymbol{A_j e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j}$	**-3193.63**	**6426.67**	**0.095**
$(A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-3200.48	6447.55	0.095

Model selection process for dwell time is described below.

Model for dwell time	Log likelihood	BIC	RMSE
$(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j$	-330.49	693.22	0.191
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-330.88	694.01	0.191
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-331.87	695.99	0.191
$(A_j + a_j G)\, e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-330.38	700.19	0.191
$\boldsymbol{(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j}$	**-328.59**	**696.59**	**0.191**
$A_j e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-333.02	705.47	0.192

Model selection process for transport time is described below.

Model for transport time	Log likelihood	BIC	RMSE
$(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j$	1560.92	-3089.59	0.068
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	1565.43	-3098.61	0.068
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	1567.84	-3103.43	0.067
$(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	1565.42	-3091.42	0.068
$\boldsymbol{(A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j}$	**1570.01**	**-3093.44**	**0.067**

APPENDIX B

MODEL SELECTION FOR TESTING TDCS PLACEBO EFFECT

Model selection process for trial time is described below. For details about model parameters, see APPENDIX A. G is a within-subject grouping binary variable (G = 0 for control and G = 1 for sham for placebo effect). The selected model was **bolded**.

Model for trial time	Log likelihood	BIC	RMSE
$(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j$	-2420.50	4870.98	0.089
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-2422.59	4875.17	0.089
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-2420.22	4877.09	0.089
$(A_j + a_j G)\, e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-2418.38	4866.74	0.089
$\boldsymbol{(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j}$	**-2417.02**	**4870.70**	**0.089**
$A_j e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-2421.43	4879.50	0.091
$(A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-2434.17	4908.32	0.092

Model selection process for dwell time is described below.

Model for dwell time	Log likelihood	BIC	RMSE
$\boldsymbol{(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j}$	**-209.12**	**448.23**	**0.187**
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-213.39	456.77	0.186
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-208.60	447.20	0.186
$(A_j + a_j G)\, e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-209.22	455.10	0.187
$(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-209.07	454.80	0.187
$A_j e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-212.91	462.48	0.186
$(A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-210.09	463.49	0.187

Model selection process for transport time is described below.

Model for transport time	Log likelihood	BIC	RMSE
$(A_j + a_j G)e^{-t/\tau_j} + C_j + \varepsilon_j$	-209.12	448.23	0.187
$A_j e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-213.39	456.77	0.186
$A_j e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j$	-208.60	447.20	0.186
$(A_j + a_j G)\, e^{-t/(\tau_j + b_j G)} + C_j + \varepsilon_j$	-209.22	455.10	0.187
$\boldsymbol{(A_j + a_j G)\, e^{-t/\tau_j} + (C_j + c_j G) + \varepsilon_j}$	**-209.07**	**454.80**	**0.187**
$(A_j + a_j G)e^{-t/(\tau_j + b_j G)} + (C_j + c_j G) + \varepsilon_j$	-210.09	463.49	0.187

APPENDIX C

PERMISSIONS

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BIOGRAPHICAL SKETCH

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