

Individual Differences and Long-term Consequences of tDCS-augmented Cognitive Training

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Abstract

■ A great deal of interest surrounds the use of transcranial direct current stimulation (tDCS) to augment cognitive training. However, effects are inconsistent across studies, and meta-analytic evidence is mixed, especially for healthy, young adults. One major source of this inconsistency is individual differences among the participants, but these differences are rarely examined in the context of combined training/stimulation studies. In addition, it is unclear how long the effects of stimulation last, even in successful interventions. Some studies make use of follow-up assessments, but very few have measured performance more than a few months after an intervention. Here, we utilized data from a previous study of tDCS and cognitive training [Au, J., Katz, B., Buschkuehl, M., Bunarjo, K., Senger,

T., Zabel, C., et al. Enhancing working memory training with transcranial direct current stimulation. *Journal of Cognitive Neuroscience*, 28, 1419–1432, 2016] in which participants trained on a working memory task over 7 days while receiving active or sham tDCS. A new, longer-term follow-up to assess later performance was conducted, and additional participants were added so that the sham condition was better powered. We assessed baseline cognitive ability, gender, training site, and motivation level and found significant interactions between both baseline ability and motivation with condition (active or sham) in models predicting training gain. In addition, the improvements in the active condition versus sham condition appear to be stable even as long as a year after the original intervention. ■

INTRODUCTION

Given the importance of working memory (WM) for success in a wide variety of real-life contexts, including school (Alloway & Alloway, 2010) and work (Higgins, Peterson, Pihl, & Lee, 2007), it is unsurprising that a variety of WM interventions have been proposed in recent years. Transcranial direct current stimulation (tDCS) and cognitive training are two cognitive enhancement techniques that have recently been used together to improve WM, with promising, but by no means conclusive, results. A recent meta-analysis from Mancuso, Ilieva, Hamilton, and Farah (2016) suggests that dorsolateral pFC (DLPFC) stimulation during training results in a small but significant enhancement effect, which survives corrections for publication bias. Recent research from our own laboratory (Au et al., 2016) provides further evidence that DLPFC stimulation (both right and left) enhances performance on a widely used *n*-back training task over the course of seven sessions, relative to a sham stimulation condition. Although these initial findings do provide some preliminary support for the use of tDCS to enhance learning of WM-intensive tasks, we note considerable heterogeneity in

the literature. For example, a similarly designed *n*-back/tDCS training study failed to find an effect of tDCS after correcting for baseline differences (Martin et al., 2013), and the 10 tDCS/WM training studies covered in the Mancuso et al. (2016) meta-analysis differ substantially in the magnitude of their effects, with Hedges' *g* values ranging from 0.074 to 0.565. A variety of factors, including differences in stimulation intensity, density, location, and other parameters, as well as the design and implementation of the cognitive training paradigm, may explain the disparities in the strength of these effects (see Au et al., 2016, for a brief discussion). However, one additional possibility is that individual differences among participants—including motivation, sex, and baseline ability, among many factors—may play important roles. These factors may influence the outcome of the combined intervention in their own right, but they may also be associated with other individual difference characteristics that influence performance (e.g., different geographic training locations may be confounded with educational background). Although extant research does suggest that individual differences play a significant role in both tDCS interventions (Krause & Cohen Kadosh, 2014) and cognitive training interventions (Katz, Jones, Shah, Buschkuehl, & Jaeggi, 2016; Jaeggi, Buschkuehl, Shah, & Jonides, 2014), by themselves, these factors have rarely been investigated directly in studies that combine both interventions.

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Baseline Performance and Other Individual Difference Factors in tDCS

Studies by Wiethoff, Hamada, and Rothwell (2014) and López-Alonso, Cheeran, Río-Rodríguez, and Fernández-del-Olmo (2014) have found that, even in tDCS experiments that successfully demonstrate an effect on cognition overall, less than half of the participants demonstrate improved performance. This suggests that a considerable proportion of participants in each study may not be responding to the treatment. In addition, recent work has raised controversy about the previously dominant neural explanation for tDCS-related cognitive enhancement (Underwood, 2016). Although the consensus thus far has been that anodal stimulation causes depolarization of the resting membrane potential, facilitating the production of action potentials, Underwood's work with cadavers questions the amount of current that actually reaches the cortex. Thus, it is possible that certain individual physical characteristics could have a larger effect than expected previously. For example, even something as seemingly minor as hair thickness may impact electrode contact and further reduce the amount of current passing through the scalp and skull. However, several individual difference factors have been studied in conjunction with tDCS before Underwood's provocative findings. Krause and Cohen Kadosh (2014) suggested that age, sex, and neuronal factors, namely, regional cortical excitability, may influence the effectiveness of transcranial electrical stimulation. For example, it has been proposed that an optimal balance of excitation/inhibition in different cortical regions promotes optimal cognitive functioning. Therefore, tDCS may exert different and sometimes contradictory effects in populations that vary with respect to this balance, such as those with attention deficit hyperactivity disorder or depression (Krause, Marquez-Ruiz, & Cohen Kadosh, 2013). Furthermore, genetic factors (Brunoni et al., 2013; Plewnia et al., 2013) and anatomical differences that impact the electric field generated by tDCS (Kim et al., 2014) may also influence the response to stimulation.

In addition to these physiological characteristics, it is also possible that psychological characteristics, such as baseline cognitive ability, may influence the outcome of stimulation. Several studies have demonstrated selective tDCS benefits among individuals with low, but not high, baseline WM abilities (Gozenman & Berryhill, 2016; Heinen et al., 2016; Tseng et al., 2012), and meta-analyses tend to report stronger effect sizes in clinical or older adult populations compared with the higher-performing young adult population (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Hill, Fitzgerald, & Hoy, 2016; Hsu, Ku, Zanto, & Gazzaley, 2015; Summers, Kang, & Cauraugh, 2015). Moreover, the evidence extends beyond the WM domain. Individuals with poorer motor coordination (Uehara, Coxon, & Byblow, 2015; McCambridge, Bradnam, Stinear, & Byblow, 2011), postural control (Zhou et al., 2015),

visual acuity (Reinhart, Xiao, McClenahan, & Woodman, 2016), and attention (Sikstrom et al., 2016; London & Slagter, 2015) all showed improvement in the relevant domains, whereas their higher-performing peers did not. However, it should be noted that these low baseline effects are not found universally. One group of researchers has repeatedly found an advantage for high-baseline individuals on WM performance during parietal stimulation (Jones, Gozenman, & Berryhill, 2015; Berryhill & Jones, 2012; Jones & Berryhill, 2012), which has been replicated by others (Learmonth, Thut, Benwell, & Harvey, 2015). Another group examining lateralized attention bias found both high- and low-baseline advantages in two separate experiments, but the direction of this advantage depended critically on stimulation intensity (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015). Therefore, there is no consensus on the influence of baseline performance at present. In addition, there are likely even more nuanced issues to consider, such as the brain-region-stimulated and task-specific optimum levels of neural activity. Thus, there is considerable value in studying tDCS effects in the context of baseline ability as well as other individual difference factors.

Baseline Performance and Other Individual Difference Factors in WM Training

Some research has also been done to examine the effects of individual difference factors in the outcome of WM training by itself, unaided by tDCS. For example, baseline performance has also been studied in this context, and, much like in the tDCS literature, there is also evidence that baseline WM abilities could impact training performance in two possible directions. Some have suggested that individuals with a lower baseline score should have more room to improve at the trained task during the intervention; for example, Zinke and colleagues have demonstrated this through two studies with older adults (Zinke et al., 2014; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2012). Others have posited that individuals with higher baseline WM performance are better prepared to take advantage of the intervention and thus improve more throughout the training (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). There is no consensus yet regarding the impact of baseline performance for the outcome of cognitive training; it also remains possible that ceiling effects and differences in the design of the training intervention itself may also influence the relationship between starting WM ability and level of improvement in any individual study.

A variety of other individual difference factors have also been discussed in the context of cognitive training. For example, motivation to complete a task may influence how receptive one is to a training intervention (Jaeggi et al., 2014; Jaeggi, Buschkuhl, Jonides, & Shah, 2011). Many interventions include game-like elements that may

influence a participant's motivation as well as their performance on the task (Katz, Jaeggi, Buschkuhl, Stegman, & Shah, 2014; Prins, Doyis, Ponsioen, ten Brink, & van der Oord, 2010). In addition, many training studies provide considerable monetary remuneration for participation, and it is possible that this payment may undermine motivation and thus impact overall performance (Au et al., 2015). As mentioned earlier, the study location (e.g., university vs. small college but also different countries; cf. Au et al., 2015) may influence the outcome of training, although it is difficult to identify which element of geographic location, including cultural factors, actually may play a role in performance. Age has also been studied extensively as a factor that may determine performance on cognitive training tasks. In general, older individuals seem to improve less on untrained tasks administered at pretest and posttest as well as on the training task itself (Borella et al., 2014; Zinke et al., 2014; Brehmer, Westerberg, & Bäckman, 2012; Schmiedek, Lovden, & Lindenberger, 2010). Although one meta-analysis found no differences in transfer improvements as a function of age (Karbach & Verhaeghen, 2014), another meta-analysis with a larger range of ages found that younger adults improved more on untrained tasks than older adults (Wass, Scerif, & Johnson, 2012). These age-related disparities make some sense given well-established differences in age-related WM performance (Park et al., 2002) and theoretical perspective on cognitive plasticity and aging (Lövdén et al., 2010). However, it remains unknown whether age-related differences in cognitive training performance are due to differences in baseline performance or other factors related to aging. Traits such as conscientiousness and neuroticism (Studer-Luethi, Bauer, & Perrig, 2015; Studer-Luethi, Jaeggi, Buschkuhl, & Perrig, 2012) may also impact the outcome of training. Finally, other factors, such as gender, have been found to influence the outcome of training in some studies (Söderqvist, Bergman Nutley, Ottersen, Grill, & Klingberg, 2012) but not others (Klingberg et al., 2005). It remains possible that a number of other factors that have been largely unexplored (e.g., socioeconomic status, although see Segretin et al., 2014) may play a role, at least in some interventions.

Given the relevance of individual difference factors to the outcome of cognitive training and tDCS independently, a salient question is how these individual difference factors influence combined interventions featuring both tDCS and WM training together. It is possible, and perhaps even likely, that there are interactions between these two interventions such that some individual difference factors matter more than others, particularly in the outcome of a combined intervention. For example, in light of the evidence that baseline cognitive ability impacts both the amount one is able to improve during a training intervention and the participant's response to tDCS, it is possible that it will play a much larger role in a combined intervention. The relative paucity of tDCS-

augmented cognitive training studies means that it is unsurprising that these factors have not yet been explored in combined interventions. However, given the possibility that they may play a substantial role in the outcomes of such interventions, there is considerable impetus for studying them. Thus, this article uses a recently published data set of tDCS and WM training data to evaluate the influence of individual differences including baseline performance, motivation, gender, and geographic training location on WM training performance.

As illustrated above, individual differences are one topic of relevance in improving our understanding of why stimulation-augmented cognitive training may be effective for any individual participant. Another point of significant practical importance is how durable training improvements may be over the weeks and months after the intervention. It would likely not make sense to utilize tDCS/WM interventions in real-world applications if the improvements generated by the stimulation dissipated shortly after the intervention. Although research from our own laboratory suggests that there is durability even several months after the intervention (Au et al., 2016), little extant tDCS work examines the stability of improvements over time, and results from WM training research suggest that washout may be a common occurrence within a short time after a training intervention (Melby-Lervåg & Hulme, 2013). By contrast, some studies suggest that improvements after tDCS interventions may remain weeks or even months after the stimulation. Jeon and Han (2012); Park, Seo, Kim, and Ko (2014); and Jones, Stephens, Alam, Bikson, and Berryhill (2015) all found continued improvements to WM performance from a week to 2 months after stimulation. Persistent, long-term changes have also been detected as a function of learning or training in other domains as well, such as motor skill training (Reis et al., 2009), math training (Looi et al., 2016), and episodic memory retrieval (Manenti, Sandrini, Brambilla, & Cotelli, 2016). However, to our knowledge, no other study of combined tDCS and cognitive training has examined whether these follow-up effects are maintained for periods in excess of 2–3 months after the intervention. In this article, we added to the follow-up findings from Au et al. (2016), including new data not previously reported in which participants returned an average of 12 months after the intervention to complete one more session of the WM training (without stimulation).

METHODS

Participants

Our data set was composed of largely the same participants as that of Au et al. (2016), which recruited healthy, right-handed individuals between the ages of 18 and 35 years as part of a collaborative effort from the campuses of the University of California, Irvine (UCI), and the University of Michigan, Ann Arbor (UM).

Six additional individuals completed study procedures subsequent to the previous report, one of whom was excluded as an outlier (see Results), for a total sample size of 67 in the current data set. As before, participants were excluded if they had had any history of psychological or neurological disorders (including seizures or strokes), previous cognitive training or neurostimulation, or past or present drug/alcohol abuse or if they were taking any medications that would affect attention or memory. All research procedures were approved by the institutional review boards at both universities, and each participant was provided informed consent.

General Procedure

The experiment, an extension of our previous report (Au et al., 2016), consisted of a between-participant pretest–posttest intervention design in which participants were randomized into one of two groups. Forty received active tDCS (active group) over the right or left DLPFC, and 27 received sham stimulation (sham group) to the same regions in which the current was turned off after the first 30 sec without the participants' knowledge. Our previous report analyzed the right and left DLPFC groups separately in the active condition, but because we found no differences in the training effect, they are collapsed together in the present report. Both groups completed 7 days of visuospatial n -back training concurrently with either active or sham stimulation.

After the initial training period, all participants were invited back for two follow-up sessions to examine the stability of training effects. Forty-one participants returned for the first follow-up (27 active and 14 sham), as reported previously (Au et al., 2016), and 26 participants returned for the second follow-up in this study (18 active and 8 sham). Because of the long delay, the follow-up visits were marred by substantial attrition rates, but 25 of the 26 participants in the second follow-up also participated in the first follow-up, thereby allowing us to evaluate the longitudinal trajectory of a stable cohort of individuals. The mean delay after the initial training period was 221 days (range = 97–393 days, SD = 82 days) for the first follow-up and 355 days (range = 251–471 days, SD = 73 days) for the second follow-up. Maintenance of transfer effects was not evaluated at this second follow-up because of the lack of sustained transfer during the first follow-up.

WM Training

The training task was a computerized adaptive visuospatial n -back task in which a series of blue squares was displayed one at a time, each in one of eight possible spatial locations. Participants were asked to indicate whether the current square was in the same position as the square presented n trials ago by responding with the letter “A” to targets and “L” to nontargets, using a

standard computer keyboard. The difficulty of the task adapted continuously based on the trainee's performance. The average n -back level at which a participant trained was calculated each day, and the primary dependent variable for analysis was the logarithmic slope of the seven-session training curve. Further details regarding the design of the training task can be found in Au et al. (2016).

Transcranial Direct Current Stimulation

Stimulation was administered via a Soterix Medical 1 × 1 low-intensity tDCS device (model 1300A; New York, NY) using 5 × 7 cm sponge electrodes placed horizontally on the head. The anode was placed over either the right or left DLPFC (sites F4 and F3 in the international 10–20 EEG system), and the cathode was placed over the contralateral supraorbital area (sites Fp1 or Fp2). Stimulation lasted 25 min, with a current intensity of 2 mA, which ramped up and down for the first and last 30 sec of stimulation. Sham tDCS was set up in the same way, except that the current was shut off between the 30-sec ramping periods at the beginning and end of each session.

Individual Difference Variables

Baseline

A baseline score for each participant was determined by their visual n -back score at pretest, measured as P_r , the proportion of hits minus the proportion of false alarms (Snodgrass & Corwin, 1988). The visual n -back task, which required participants to identify whether a series of colored balls matched the color of the items presented n before, is similar but not identical to the trained visuospatial n -back, which involved sequential presentation of a square in different spatial locations. In the absence of a true unstimulated baseline of the actual training task, the visual n -back was chosen as the closest reasonable proxy. Although our pretest battery consisted of four WM tasks—visual n -back, auditory n -back, digit span, and Corsi blocks—the latter two are span tests, which correlate only weakly with n -back performance (Redick & Lindsey, 2013), whereas the former two are structurally similar to the trained visuospatial n -back. Although our previous report (Au et al., 2016) made the a priori decision to combine these two n -back tests into a composite measure to test for group differences in baseline, we ended up finding strong transfer effects only in the visual, but not auditory, n -back test. This suggests a close link between visual n -back and our visuospatial training task (correlation between pretest visual n -back score and first visuospatial n -back training session: r = .65). Therefore, it is chosen as the most appropriate index of baseline WM ability in the current study. The average baseline performance on the visual n -back task in the active group was 0.66 (SD = 0.16), and the average score in the sham group was 0.62

($SD = 0.19$); the difference between groups was not significant ($p = .36$).

Motivation

Motivation was assessed before each training session by self-report. Participants were asked to rate their own motivational state on a scale from 1 to 10, with 10 being the most highly motivated. An average motivation score over all seven sessions was calculated for each participant and used as the dependent variable in the analyses. Average motivation scores were 6.1 ($SD = 1.24$) in the active group and 6.1 ($SD = 1.01$) in the sham group. We note that, although motivation was evaluated in our previous report (Au et al., 2016), our analysis focused on confirming the stability of motivation across groups and time, and we did not previously evaluate motivation as an individual difference factor to predict training outcome as we do in the current report.

Sex

Sex information was collected as part of a standard demographic questionnaire during the consent process. The active group was composed of 60% women, and the sham group was composed of 67% women.

Training Site

Fifty percent of the active participants were recruited on each campus (UCI and UM), and 59% of the sham participants were recruited at UM.

Analytic Approach

Statistical analyses were conducted using IBM SPSS Statistics Version 22 (IBM, Armonk, NY) and STATA Version 13 (StataCorp, 2013). To identify the effects of individual difference variables on training performance, separate regression models were calculated for each variable of interest using parameters of a logarithmic model run on the training data, yielding a seven-session training slope as the outcome variable, with condition, the variable of interest, and their interaction as predictor terms. Note that Au et al. (2016) used a seven-level repeated-measures ANOVA to analyze training performance. However, for our current analyses, we required an index of training performance as an outcome variable for the regression models. We opted for individual slopes to take into account the entire trajectory of training performance. Individual difference variables included sex, school site, motivation, and baseline n -back performance. All continuous variables were standardized and thus also mean-centered, whereas categorical variables remain unstandardized to preserve the inherent structure of the dummy coding and to maintain interpretability.

To identify the effects of the long-term follow-up, a similar method was used as in Au et al. (2016) in which gain on the training task was calculated by subtracting performance in the follow-up session from that of the initial training session. This gain was then used as the dependent variable in an ANCOVA with Condition as a between-participant factor. Because of the post hoc nature of this follow-up, the time lag between the final session of the initial intervention and the follow-up varied between participants and thus was included as a covariate.

RESULTS

Outlier Analysis

Outliers in the data were evaluated by examining the average training performance across all seven sessions for each participant, as done previously (Au et al., 2016). Outliers were only examined in the sham group because no new active participants were enrolled since our previous report. Using a criterion of 2 SD s, we identified one high-performing outlier who trained at an average n -back level of 7.9, almost twice the group average of the remaining sham participants (mean = 4.19, $SD = 1.27$). However, we also note that the primary findings presented below are not impacted by the presence or absence of this outlier.

Training Performance by Condition (Active vs. Sham)

Because five participants were added to the sample beyond the participants included in Au et al. (2016) and because here we use the parameters of a logarithmic model (slope of training curve) as a measure of training progress (instead of the mixed ANOVAs with training performance for each session as used before), an initial model was calculated to reestablish the difference between the sham and active conditions. A standard linear regression was performed between training slope as the outcome variable and condition (active and sham) as the predictor variable. The Condition factor was found to explain a significant amount of variance in the slope, $F(1, 65) = 11.65, p < .001, R^2 = .15, R^2 \text{ adjusted} = .14$. Condition significantly predicted slope ($\beta = 0.79, t(66) = 3.41, p = .001$) in that active participants, on average, performed 0.79 SD above sham participants.

Individual Difference Factors

For each individual difference factor, standard multiple regressions were performed between training slope as the outcome variable and condition, the individual difference, and the interaction between condition and the difference as predictor variables. Regression results are presented in Table 1.

Table 1. Regression Results for Individual Difference Measures

Model	Variable	<i>n</i>	<i>B</i>	<i>SE B</i>	β	<i>p</i>	<i>Adj. R</i> ²
Baseline	Condition	67	1.41	0.34	0.76	.002	.17
	Baseline WM		0.98	0.49	0.30	.07	
	Condition × Baseline		-1.07	0.53	-0.47	.04	
Motivation	Condition	67	-1.63	0.68	0.81	<.001	.25
	Motivation		-0.31	0.09	-0.64	.001	
	Condition × Motivation		0.35	0.11	0.73	.002	
Sex	Condition	67	0.45	0.16	0.78	.004	.15
	Sex		0.25	0.21	0.44	.25	
	Condition × Sex		-0.04	0.27	-0.06	.90	
Site	Condition	67	0.59	0.20	1.04	.004	.13
	Training site		0.08	0.21	0.15	.69	
	Condition × Site		-0.27	0.27	-0.48	.31	

Dummy coding of the categorical variables condition, gender, and training site employed the following references, respectively: sham, female, UCI. Unstandardized coefficients (*B*) are not mean-centered, whereas standardized coefficients inherently are and should be interpreted accordingly. For example, in the motivation model, *B* suggests a sham advantage of 1.63 in the training slope when motivation is zero, whereas β suggests a tDCS advantage of 0.81 *SD* when motivation is average.

Baseline Performance

The model containing Condition, Baseline *n*-back performance, and the interaction term between Condition and Baseline performance explained a significant amount of variance in the training slope, $F(3, 63) = 5.53, p = .002, R^2 = .21, R^2$ adjusted = .17. The partial effect of Condition was significant ($\beta = 0.76, t(66) = 3.30, p = .002$) with larger slopes in the active condition compared with sham, holding baseline constant at the sample mean (i.e., baseline is mean-centered to zero). The partial effect of Baseline, referenced to the sham condition, suggests at the trend level that greater baseline performance is associated with larger slopes in the absence of tDCS ($\beta = 0.30, t(66) =$

1.83, $p = .07$). Importantly, the interaction term between Condition and Visual *n*-back performance at baseline was significant ($\beta = -0.47, t(66) = -2.06, p = .04$), indicating that each standard deviation increase in baseline performance reduces the effect of condition by 0.47 *SD*. This suggests that tDCS is most effective among low-baseline individuals (Figure 1).

Motivation

The model containing Condition, Motivation, and the interaction term between Condition and Motivation also explained a significant amount of the variance in the training slope, $F(3, 63) = 8.45, p < .001$, with $R^2 = .29$

Figure 1. Plot of baseline regression results. Active participants with low baseline scores outperform sham participants with low baseline scores, but the tDCS advantage gradually disappears with increasing baseline ability. Individuals with high baseline ability all improve similarly on the training task, regardless of condition.

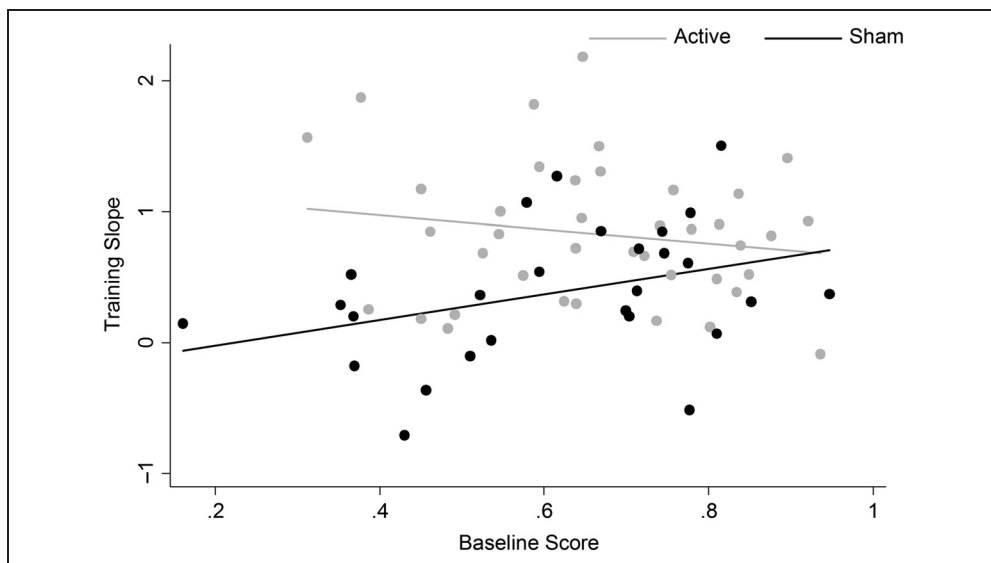
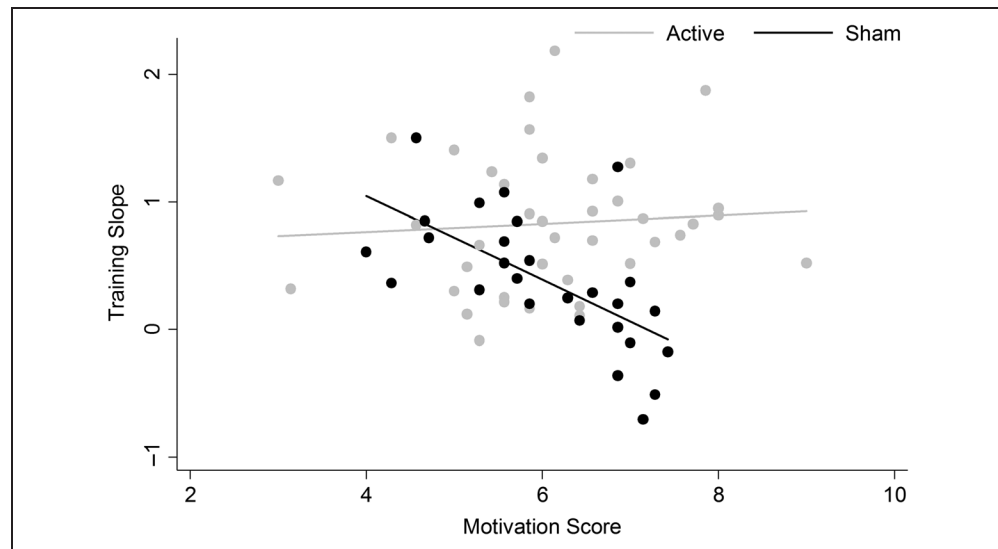


Figure 2. Plot of motivation regression results. Active participants all improve similarly irrespective of motivation, but sham participants show a paradoxical decrease in performance with increasing motivation.



and R^2 adjusted = .25. The partial effect of Condition, holding Motivation constant at the mean, was significant ($\beta = 0.81$, $t(66) = 3.78$, $p < .001$), reiterating the superior performance of the active condition. However, the partial effect of Motivation referenced to the sham condition was also significant ($\beta = -0.64$, $t(66) = -3.41$, $p = .001$), as was the interaction term between Condition and Motivation ($\beta = 0.73$, $t(66) = 3.15$, $p = .002$), suggesting somewhat paradoxically that, within the sham group, participants with self-reported higher motivation perform worse than participants with lower motivation (Figure 2).

Sex

The model containing Condition, Sex, and the interaction term between Condition and Sex explained a significant amount of the variance in the training slope, $F(3, 63) = 4.93$, $p = .004$, with $R^2 = .19$ and R^2 adjusted = .15. Whereas the partial effect of Condition holding Sex constant among women was significant ($\beta = 0.78$, $t(66) = 2.73$, $p < .01$), neither Sex ($\beta = 0.44$, $t(66) = 1.17$, $p = .25$) nor the interaction term between Condition and Sex ($\beta = -0.06$, $t(66) = -0.13$, $p = .90$) was significant.

Study Site

The model containing Condition, Site of training (i.e., UM or UCI), and the interaction term between Condition and Site also explained a significant amount of the variance in the slope, $F(3, 63) = 4.33$, $p = .008$, with $R^2 = .17$ and R^2 adjusted = .13. Again, whereas Condition was a significant predictor ($\beta = 1.04$, $t(66) = 2.98$, $p = .004$), neither Training site ($\beta = 0.15$, $t(66) = 0.40$, $p = .69$) nor the interaction term between Condition and Training site ($\beta = 0.48$, $t(66) = 1.02$, $p = .31$) was significant.

Long-term Follow-up

An ANCOVA was conducted with Condition as a factor, Time between the intervention and the follow-up as a covariate, and Gain on the training task from the first training session to the second follow-up as the dependent variable to evaluate whether an effect of Condition remained at the second follow-up that took place, on average, 355 days after the conclusion of the intervention. Condition remained a significant factor for the second follow-up, $F(1, 23) = 12.43$, $p = .002$, with active participants continuing to outperform sham participants (Figure 3), whereas, as in the first follow-up reported in Au et al. (2016), Time between the intervention and follow-up was not a significant predictor, $F(1, 23) = 1.18$, $p = .29$.

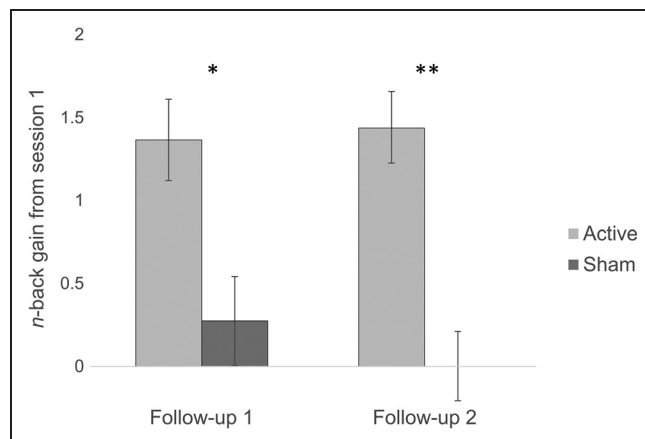


Figure 3. Follow-up performance. Follow-up 1 represents in n -back levels gain from the first session to the first follow-up for active and sham participants reported in Au et al. (2016); Follow-up 2 represents gain from the first session to the new second follow-up approximately 12 months after the intervention.

DISCUSSION

Here, we present evidence that certain individual difference factors do have a significant impact on the outcome of combined WM training and tDCS. The effect of baseline was particularly striking. We found a trend suggesting that sham participants who started with higher baseline ability tended to improve more over the course of training. Although this finding did not reach traditional levels of statistical significance ($p = .07$), it is nevertheless consistent with previous literature suggesting that cognitive training may be more helpful to those who already have strong cognitive abilities (Looi et al., 2016; Lövdén, Brehmer, Li, & Lindenberger, 2012). More importantly, however, the interaction between baseline ability and condition (active/sham) was significant (see Figure 1), suggesting that the effects of baseline ability affected active and sham participants differently. Specifically, the advantage of tDCS seemed to increase proportionately with decreasing baseline ability, such that a participant who started off 1 *SD* below the mean in terms of visual WM ability before training ended up outperforming a comparable sham participant by 0.46 *SD* over the course of training. However, this tDCS advantage declines with increasing baseline ability and confers little additional advantage to a participant who already performs high at baseline relative to a comparably high-performing peer in the sham group. Although it is unclear what may mediate this interaction between stimulation and low baseline performance, it may have to do with differences in brain state and baseline cortical excitability between high and low groups (cf. Krause & Cohen Kadosh, 2014). For example, it is known that the effects of TMS are influenced by the baseline excitability of the targeted cortex (Pasley, Allen, & Freeman, 2009; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008) and that lower or more suppressed levels of neural excitability can increase the facilitatory effect of TMS.

We note that this finding of selective tDCS enhancement among low-baseline individuals is not unique in the literature. For example, a number of studies also suggest a selective tDCS benefit among low-baseline populations, both within the WM domain (Gozenman & Berryhill, 2016; Heinen et al., 2016; Minichino et al., 2015; Tseng et al., 2012) as well as in other cognitive domains, such as attention and dual tasking (Reinhart et al., 2016; London & Slagter, 2015; Zhou et al., 2015). However, one critical difference between these studies and ours is that ours is a training study involving multiple sessions of stimulation in conjunction with task performance, rather than only a single session (but see also Looi et al., 2016). Consequently, our results demonstrate enhancements not only to overall WM performance but also, more specifically, to the rate of learning (as measured by the slope of improvement) across sessions. This raises the possibility that the selective effects of stimulation on low-baseline participants may impact not only online performance but

also offline consolidation, an important distinction for the enhancement of long-term learning (Au, Karsten, Buschkuhl, & Jaeggi, 2017). Although these offline effects were supported in our previous work by demonstrating special tDCS benefits when training sessions were spaced apart by a weekend (Au et al., 2016), a possible interaction of baseline performance and weekend consolidation in the present work is difficult to demonstrate due to power issues. For the same reason, the influence of baseline ability on follow-up performance is similarly difficult to evaluate.

Although self-reported motivation also had a significant impact on the outcome of training, the finding of a significant interaction between motivation and condition was somewhat puzzling. The nature of the interaction is such that motivation is inversely related to slope in the sham group only. It is unclear why lower-motivated individuals outperformed higher-motivated individuals in the sham condition, but one possibility is that lower motivation was also associated with other influential factors, such as higher baseline performance (it is possible that, for individuals who performed very well already, the intervention was not as interesting, whereas those who were aware of preexisting limitations were more eager to improve their cognitive abilities). In fact, there is a moderately strong inverse correlation between baseline and motivation within the sham group ($r = -.42$), suggesting that some of the observed motivation effect simply recapitulates the baseline effect. Nevertheless, we also note that both high- and low-motivated individuals within the active group experienced similar improvement during the intervention, suggesting that, for those individuals receiving stimulation, motivation was not a major factor that impacted performance. We also note that our motivation measure—a single question asked each day before training—may be less ideal than a more in-depth survey measure (and such a measure might be better equipped to explain the curious motivation results discussed here). Finally, neither gender, nor site of training, nor the interaction between those variables and condition predicted the slope of training. Thus, these analyses provide evidence that some individual difference factors, such as baseline WM performance, play a major role in the outcome of combined tDCS and cognitive training, whereas others do not.

Within the context of the larger corpus of tDCS research, these findings have significant implications for both existing and future studies that combine cognitive training with stimulation. Given the extent to which these factors, including baseline performance in particular, influence the outcome of training, it is possible that these differences may explain why so many participants in any individual study do not benefit from stimulation. Furthermore, it may also explain some of the null findings and even some of the varied outcomes observed among successful studies. At the very least, these findings provide an impetus for examining baseline differences as a

covariate of interest in training and stimulation studies. This also means that future studies must be adequately powered to account for these differences and allow for them to be examined.

We also note the continued difference between the active and sham conditions approximately a year (on average) after the intervention, extending the medium-term follow-up findings established in Au et al. (2016). This suggests that applying tDCS with cognitive training may result in not only more robust and rapid improvements on the training task but also that the improved performance on the training task relative to the sham group may remain stable, even up to a year after the intervention. Importantly, we note that this follow-up examined only training effects, rather than any improvements in transfer tasks. Future work will be needed to establish the extent that transfer gain may also persist at long-term follow-up.

We note that these results must be tempered by certain limitations in our data set. The baseline measure included here is perhaps less ideal than having the participant complete a session of the training task before stimulation, which would give a “true baseline” that might be a better predictor of subsequent performance. In addition, there was considerable attrition between the initial study and the second follow-up. Finally, although this study was fairly well powered for a tDCS and training intervention, even more participants would be needed to have better confidence about the individual difference findings presented here. Furthermore, we acknowledge that this study is not powered well enough to examine more than one individual difference factor at a time, and the follow-up sample is too small to examine in the context of the individual difference factors covered here. Thus, it is important to note the preliminary nature of the present analyses.

Despite these limitations, the practical implications of the baseline finding are of particular interest, both for cognitive training studies as well as tDCS-augmented learning more generally. Within cognitive training research, some studies have suggested that it is necessary for participants to demonstrate improvement on the training task to achieve transfer gains (e.g., Jaeggi et al., 2011). tDCS may enable participants with lower starting performance to reach gains similar to their higher-performing peers, thus overriding individual differences in baseline ability and allowing more to benefit from the intervention. In the context of learning more generally, tDCS may offer a means of helping individuals who might be struggling on a particularly WM-demanding task, such as math, improve more quickly. Preliminary research, albeit with only two sessions, suggests that this may indeed be possible (Looi et al., 2016). In addition, subsequent work should combine this line of investigation with fMRI or EEG; the combination of physiological or neuroimaging data may allow researchers to better understand how physical characteristics and anatomical differences may impact the flow of current generated

by the stimulation device. Most importantly, these results reinforce the importance of considering individual differences during the administration of tDCS and training as well as collecting samples well powered enough to actually examine them.

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REFERENCES

- Alloway, T. P., & Alloway, R. G. (2010). Investigating the predictive roles of working memory and IQ in academic attainment. *Journal of Experimental Child Psychology, 106*, 20–29.
- Au, J., Karsten, C., Buschkuehl, M., & Jaeggi, S. M. (2017). Optimizing transcranial direct current stimulation protocols to promote long-term learning. *Journal of Cognitive Enhancement, 1*, 65.
- Au, J., Katz, B., Buschkuehl, M., Bunarjo, K., Senger, T., Zabel, C., et al. (2016). Enhancing working memory training with transcranial direct current stimulation. *Journal of Cognitive Neuroscience, 28*, 1419–1432.
- Au, J., Sheehan, E., Tsai, N., Duncan, G. J., Buschkuehl, M., & Jaeggi, S. M. (2015). Improving fluid intelligence with training on working memory: A meta-analysis. *Psychonomic Bulletin & Review, 22*, 366–377.
- Benwell, C. S., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex, 69*, 152–165.
- Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters, 521*, 148–151.
- Borella, E., Carretti, B., Cantarella, A., Riboldi, F., Zavagnin, M., & De Beni, R. (2014). Benefits of training visuospatial working memory in young-old and old-old. *Developmental Psychology, 50*, 714–727.
- Brehmer, Y., Westerberg, H., & Bäckman, L. (2012). Working-memory training in younger and older adults: Training gains, transfer, and maintenance. *Frontiers in Human Neuroscience, 6*, 63.
- Brunoni, A. R., Kemp, A. H., Shiozawa, P., Cordeiro, Q., Valiengo, L. C. L., Goulart, A. C., et al. (2013). Impact of 5-HTTLPR and BDNF polymorphisms on response to sertraline versus transcranial direct current stimulation: Implications for the serotonergic system. *European Neuropsychopharmacology, 23*, 1530–1540.
- Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: Influence of stimulation parameters. *Brain Stimulation, 9*, 501–517.

- Gozenman, F., & Berryhill, M. E. (2016). Working memory capacity differentially influences responses to tDCS and HD-tDCS in a retro-cue task. *Neuroscience Letters*, *629*, 105–109.
- Heinen, K., Sagliano, L., Candini, M., Husain, M., Cappelletti, M., & Zokaei, N. (2016). Cathodal transcranial direct current stimulation over posterior parietal cortex enhances distinct aspects of visual working memory. *Neuropsychologia*, *87*, 35–42.
- Higgins, D. M., Peterson, J. B., Pihl, R. O., & Lee, A. G. (2007). Prefrontal cognitive ability, intelligence, Big Five personality, and the prediction of advanced academic and workplace performance. *Journal of Personality and Social Psychology*, *93*, 298–319.
- Hill, A. T., Fitzgerald, P. B., & Hoy, K. E. (2016). Effects of anodal transcranial direct current stimulation on working memory: A systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. *Brain Stimulation*, *9*, 197–208.
- Hsu, W. Y., Ku, Y., Zanto, T. P., & Gazzaley, A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: A systematic review and meta-analysis. *Neurobiology of Aging*, *36*, 2348–2359.
- Jaeggi, S. M., Buschkuhl, M., Jonides, J., & Shah, P. (2011). Short- and long-term benefits of cognitive training. *Proceedings of the National Academy of Sciences, U.S.A.*, *108*, 10081–10086.
- Jaeggi, S. M., Buschkuhl, M., Shah, P., & Jonides, J. (2014). The role of individual differences in cognitive training and transfer. *Memory & Cognition*, *42*, 464–480.
- Jeon, S. Y., & Han, S. J. (2012). Improvement of the working memory and naming by transcranial direct current stimulation. *Annals of Rehabilitation Medicine*, *36*, 585–595.
- Jones, K. T., & Berryhill, M. E. (2012). Parietal contributions to visual working memory depend on task difficulty. *Frontiers in Psychiatry*, *3*, 81.
- Jones, K. T., Gozenman, F., & Berryhill, M. E. (2015). The strategy and motivational influences on the beneficial effect of neurostimulation: A tDCS and fNIRS study. *Neuroimage*, *105*, 238–247.
- Jones, K. T., Stephens, J. A., Alam, M., Bikson, M., & Berryhill, M. E. (2015). Longitudinal neurostimulation in older adults improves working memory. *Plos One*, *10*, e0121904.
- Karbach, J., & Verhaeghen, P. (2014). Making working memory work: A meta-analysis of executive-control and working memory training in older adults. *Psychological Science*, *25*, 2027–2037.
- Katz, B., Jaeggi, S., Buschkuhl, M., Stegman, A., & Shah, P. (2014). Differential effect of motivational features on training improvements in school-based cognitive training. *Frontiers in Human Neuroscience*, *8*, 242.
- Katz, B., Jones, M. R., Shah, P., Buschkuhl, M., & Jaeggi, S. M. (2016). Individual differences and motivational effects. In T. Strobach & J. Karbach (Eds.), *Cognitive training: An overview of features and applications* (pp. 157–166). Berlin: Springer.
- Kim, J. H., Kim, D. W., Chang, W. H., Kim, Y. H., Kim, K., & Im, C. H. (2014). Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: Electric field simulation using individual MRI data. *Neuroscience Letters*, *564*, 6–10.
- Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., et al. (2005). Computerized training of working memory in children with ADHD—A randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*, 177–186.
- Krause, B., & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*, *8*, 25.
- Krause, B., Marquez-Ruiz, J., & Cohen Kadosh, R. (2013). The effect of transcranial direct current stimulation: A role for cortical excitation/inhibition balance? *Frontiers in Human Neuroscience*, *7*, 602.
- Learmonth, G., Thut, G., Benwell, C. S., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. *Neuropsychologia*, *74*, 108–119.
- London, R. E., & Slagter, H. A. (2015). Effects of transcranial direct current stimulation over left dorsolateral pFC on the attentional blink depend on individual baseline performance. *Journal of Cognitive Neuroscience*, *27*, 2382–2393.
- Looi, C. Y., Duta, M., Brem, A. K., Huber, S., Nuerk, H. C., & Kadosh, R. C. (2016). Combining brain stimulation and video game to promote long-term transfer of learning and cognitive enhancement. *Scientific Reports*, *6*, 22003.
- López-Alonso, V., Cheeran, B., Río-Rodríguez, D., & Fernández-del-Olmo, M. (2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimulation*, *7*, 372–380.
- Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin*, *136*, 659–676.
- Lövdén, M., Brehmer, Y., Li, S.-C., & Lindenberger, U. (2012). Training-induced compensation versus magnification of individual differences in memory performance. *Frontiers in Human Neuroscience*, *6*, 141.
- Mancuso, L. E., Ilieva, I. P., Hamilton, R. H., & Farah, M. J. (2016). Does transcranial direct current stimulation improve healthy working memory?: A meta-analytic review. *Journal of Cognitive Neuroscience*, *28*, 1063–1089.
- Manenti, R., Sandrini, M., Brambilla, M., & Cotelli, M. (2016). The optimal timing of stimulation to induce long-lasting positive effects on episodic memory in physiological aging. *Behavioural Brain Research*, *311*, 81–86.
- Martin, D. M., Liu, R., Alonzo, A., Green, M., Player, M. J., Sachdev, P., et al. (2013). Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *International Journal of Neuropsychopharmacology*, *16*, 1927–1936.
- McCambridge, A. B., Bradnam, L. V., Stinear, C. M., & Byblow, W. D. (2011). Cathodal transcranial direct current stimulation of the primary motor cortex improves selective muscle activation in the ipsilateral arm. *Journal of Neurophysiology*, *105*, 2937–2942.
- Melby-Lervåg, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology*, *49*, 270–291.
- Minichino, A., Bersani, F. S., Bernabei, L., Spagnoli, F., Vergnani, L., Corrado, A., et al. (2015). Prefronto-cerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder. *Neuropsychiatric Disease and Treatment*, *11*, 2265–2270.
- Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*, *17*, 299–320.
- Park, S. H., Seo, J. H., Kim, Y. H., & Ko, M. H. (2014). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *NeuroReport*, *25*, 122–126.
- Pasley, B. N., Allen, E. A., & Freeman, R. D. (2009). State-dependent variability of neuronal responses to transcranial

- magnetic stimulation of the visual cortex. *Neuron*, *62*, 291–303.
- Plewnia, C., Zwissler, B., Langst, I., Maurer, B., Giel, K., & Kruger, R. (2013). Effects of transcranial direct current stimulation (tDCS) on executive functions: Influence of COMT Val/Met polymorphism. *Cortex*, *49*, 1801–1807.
- Prins, P. J. M., DAVIS, S., Ponsioen, A., ten Brink, E., & van der Oord, S. (2010). Does computerized working memory training with game elements enhance motivation and training efficacy in children with ADHD? *Cyberpsychology, Behavior and Social Networking*, *14*, 115–122.
- Redick, T. S., & Lindsey, D. R. (2013). Complex span and *n*-back measures of working memory: A meta-analysis. *Psychonomic Bulletin & Review*, *20*, 1102–1113.
- Reinhart, R. M., Xiao, W., McClenahan, L. J., & Woodman, G. F. (2016). Electrical stimulation of visual cortex can immediately improve spatial vision. *Current Biology*, *26*, 1867–1872.
- Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., et al. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences, U.S.A.*, *106*, 1590–1595.
- Schmiedek, F., Lovden, M., & Lindenberger, U. (2010). Hundred days of cognitive training enhance broad cognitive abilities in adulthood: Findings from the COGITO study. *Frontiers in Aging Neuroscience*, *2*.
- Segretin, M. S., Lipina, S. J., Hermida, M. J., Sheffield, T. D., Nelson, J. M., Espy, K. A., et al. (2014). Predictors of cognitive enhancement after training in preschoolers from diverse socioeconomic backgrounds. *Frontiers in Psychology*, *5*, 205.
- Sikstrom, S., Jurgensen, A. M., Haghghi, M., Mansson, D., Smidelik, D., & Habekost, T. (2016). Self-rated attentiveness interacts with transcranial direct current stimulation and noise stimulation in reaction time in a go/no-go task. *Neural Plasticity*, *2016*, 5302538.
- Silvanto, J., Cattaneo, Z., Battelli, L., & Pascual-Leone, A. (2008). Baseline cortical excitability determines whether TMS disrupts or facilitates behavior. *Journal of Neurophysiology*, *99*, 2725–2730.
- Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: Applications to dementia and amnesia. *Journal of Experimental Psychology: General*, *117*, 34–50.
- Söderqvist, S., Bergman Nutley, S., Ottersen, J., Grill, K. M., & Klingberg, T. (2012). Computerized training of non-verbal reasoning and working memory in children with intellectual disability. *Frontiers in Human Neuroscience*, *6*, 271.
- StataCorp. (2013). *Stata statistical software: Release 13*. College Station, TX: StataCorp LP.
- Studer-Luethi, B., Bauer, C., & Perrig, W. J. (2015). Working memory training in children: Effectiveness depends on temperament. *Memory & Cognition*, *44*, 171–186.
- Studer-Luethi, B., Jaeggi, S. M., Buschkuhl, M., & Perrig, W. J. (2012). Influence of neuroticism and conscientiousness on working memory training outcome. *Personality and Individual Differences*, *53*, 44–49.
- Summers, J. J., Kang, N., & Cauraugh, J. H. (2015). Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis. *Ageing Research Reviews*, *25*, 42–54.
- Tseng, P., Hsu, T.-Y., Chang, C.-F., Tzeng, O. J. L., Hung, D. L., Muggleton, N. G., et al. (2012). Unleashing potential: Transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *Journal of Neuroscience*, *32*, 10554–10561.
- Uehara, K., Coxon, J. P., & Byblow, W. D. (2015). Transcranial direct current stimulation improves ipsilateral selective muscle activation in a frequency dependent manner. *PLoS One*, *10*, e0122434.
- Underwood, E. (2016). Cadaver study challenges brain stimulation methods. *Science*, *352*, 397.
- Wass, S. V., Scerif, G., & Johnson, M. H. (2012). Training attentional control and working memory—Is younger, better? *Developmental Review*, *32*, 360–387.
- Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimulation*, *7*, 468–475.
- Zhou, D., Zhou, J., Chen, H., Manor, B., Lin, J., & Zhang, J. (2015). Effects of transcranial direct current stimulation (tDCS) on multiscale complexity of dual-task postural control in older adults. *Experimental Brain Research*, *233*, 2401–2409.
- Zinke, K., Zeintl, M., Eschen, A., Herzog, C., & Kliegel, M. (2012). Potentials and limits of plasticity induced by working memory training in old-old age. *Gerontology*, *58*, 79–87.
- Zinke, K., Zeintl, M., Rose, N. S., Putzmann, J., Pydde, A., & Kliegel, M. (2014). Working memory training and transfer in older adults: Effects of age, baseline performance, and training gains. *Developmental Psychology*, *50*, 304–315.