Transcranial Random Noise Stimulation Does Not Enhance the Effects of Working Memory Training

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Abstract

■ Transcranial random noise stimulation (tRNS), a noninvasive brain stimulation technique, enhances the generalization and sustainability of gains following mathematical training. Here it is combined for the first time with working memory training in a double-blind randomized controlled trial. Adults completed 10 sessions of Cogmed Working Memory Training with either active tRNS or sham stimulation applied bilaterally to dorsolateral pFC. Training was associated with gains on both the training tasks and on untrained tests of working memory that shared overlapping processes with the training tasks, but not with improvements on working memory tasks with distinct processing demands or tests of other cognitive abilities (e.g., IQ, maths). There was no evidence that tRNS increased the magnitude or transfer of these gains. Thus, combining tRNS with Cogmed Working Memory Training provides no additional therapeutic value. ■

INTRODUCTION

Intensive training of working memory, the ability to retain information for short periods of time for ongoing mental activities, generates robust gains on untrained tests of working memory (von Bastian & Oberauer, 2013; Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008). In other cognitive domains, the efficacy and generalization of training benefits has been enhanced by transcranial electrical stimulation (Cappelletti et al., 2013; Snowball et al., 2013; Ditye, Jacobson, Walsh, & Lavidor, 2012). In this study, we combined the two approaches to investigate whether stimulation could increase the rate and magnitude of training gains and extend the benefits of training beyond highly similar untrained tests of working memory. To provide a rigorous test of the potential added value of stimulation we used a double-blind randomized controlled design, with sham stimulation as the control, and tested performance on multiple outcome measures. To maximize opportunities for modulating behavior, a multisession training program that consistently produces large gains in working memory was used (Schwaighofer, Fischer, & Bühner, 2015) in conjunction with stimulation parameters that have been shown to enhance the effects of maths training (Snowball et al., 2013).

Working memory training involves practice on working memory tasks that continually adapt to an individual's ability. The benefits of training are greatest for untrained tests of working memory that draw on the same underlying cognitive and neural processes as the training activities (Sprenger et al., 2013; von Bastian & Oberauer, 2013;

Dahlin et al., 2008). This has been termed process-specific transfer, and it is associated with changes in the neural structures and networks linked with working memory (Astle, Barnes, Baker, Colclough, & Woolrich, 2015; Kundu, Sutterer, Emrich, & Postle, 2013; Takeuchi et al., 2010; Dahlin et al., 2008; Olesen, Westerberg, & Klingberg, 2004). Evidence for the transfer of training gains to tests of working memory with distinct processing demands to the training tasks is less clear. Some studies report positive transfer across different categories of working memory tasks. For example, training on complex span tasks, which involve rapidly switching between the storage of memory items and an interpolated unrelated processing activity, generates gains on running span tasks that require the continuous monitoring and updating of a sequence of items (Harrison et al., 2013). However, other studies report selective benefits only for transfer tests of working memory that are the same as the training activities, with no transfer across working memory paradigms (e.g., Redick et al., 2013; Thompson et al., 2013; von Bastian & Oberauer, 2013). When the most rigorous randomized controlled study designs are used, there is little to no evidence for the generalization of training-related effects to complex everyday activities that depend on working memory, such as academic attainment and focussed attention (e.g., Cortese et al., 2015; Dunning, Holmes, & Gathercole, 2013; Rapport, Orban, Kofler, & Friedman, 2013).

Transcranial electrical stimulation is a noninvasive neuromodulatory tool in which a weak electric current is delivered to the brain through a pair of electrodes attached to the scalp. Transcranial electrical stimulation is associated with changes in cortical excitability (Nitsche &

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Paulus, 2000) and has been proposed to enhance learning by inducing long-term potentiation (Stagg & Nitsche, 2011). The potential of noninvasive brain stimulation to modulate and enhance human cognition means that, when combined with a learning task, it has the potential not only to increase the efficacy of cognitive training but also to enhance the generalization of training gains.

Previous studies combining stimulation with working memory training have used transcranial direct current stimulation (tDCS; Richmond, Wolk, Chein, & Olson, 2014; Martin et al., 2013), a polarity-dependent technique that generates opposing excitatory and inhibitory activity under the two electrodes: Anodal stimulation pulls neurons toward depolarization and is associated with an increase in cortical excitability, whereas cathodal hyperpolarizes neurons and is associated with decreased excitability, or inhibition (Nitsche & Paulus, 2000). In one study, tDCS shifted the learning curve of the training tasks upward relative to sham stimulation, but it did not enhance the rate of learning on these activities (Richmond et al., 2014). In the other, stimulation did not increase on-task training gains (Martin et al., 2013). Active stimulation combined with working memory training was associated with greater gains on untrained tests than either no intervention (no stimulation and no training; Richmond et al., 2014) or stimulation alone (no training; Martin et al., 2013). Both studies concluded that active tDCS enhanced the transfer of training outcomes. There is a problem with this conclusion, as critically there were no significant differences between groups who received training with active stimulation and groups who received training with sham (placebo) stimulation on the transfer tests. As such, these gains can be attributed to training alone. In both studies, tDCS anodal stimulation was applied to left dorsolateral pFC (DLPFC), meaning right DLPFC was either not stimulated (Martin et al., 2013) or was under cathodal stimulation (Richmond et al., 2014). Working memory task performance is associated with bilateral activation of DLPFC (Rottschy et al., 2012). Failure to stimulate DLPFC bilaterally may therefore explain why crucial differences between the active and sham stimulation groups were not significant.

In other cognitive domains, transcranial random noise stimulation (tRNS), an alternative method of brain stimulation, has shown more promise. Snowball et al. (2013) found tRNS applied bilaterally to the DLPFC to be effective in enhancing the efficacy and generalizability of gains following arithmetic training. Changes in neural activity and improvements on untrained mathematical problems persisted 6 months after training for the tRNS group relative to the sham group (Snowball et al., 2013). Similarly, Cappelletti et al. (2013) reported significantly steeper learning curves and long-lasting improvements in magnitude judgments following numerosity training combined with tRNS applied bilaterally to parietal regions compared with sham stimulation, training combined with tRNS over motor cortex, or tRNS alone.

In the current study, we investigated, for the first time, whether tRNS could modulate on-task training gains and enhance transfer to both untrained working memory tasks and other cognitive abilities related to working memory when combined with working memory training. tRNS offers potential advantages over tDCS, the stimulation technique combined with working memory training in previous studies (Richmond et al., 2014; Martin et al., 2013). Most importantly, it is polarity-independent allowing for bilateral stimulation of DLPFC, a region of the brain associated with working memory function (Owen, McMillan, Laird, & Bullmore, 2005) and influenced by working memory training (Takeuchi et al., 2010). It also has a higher cutaneous perception threshold, making it particularly suitable for blinding groups to stimulation condition (Ambrus, Paulus, & Antal, 2010).

Following Snowball et al. (2013), high-frequency (101–640 Hz) tRNS at a current strength of 1 mA was applied bilaterally over DLPFC. Cogmed Working Memory Training (Cogmed, 2005), a program that has been extensively researched and yields larger effect sizes for process-specific changes than other training packages (Schwaighofer et al., 2015; Sprenger et al., 2013), was used. Unlike many studies that have investigated the impact of training on working memory in a single session (e.g., Fregni et al., 2005), this package provided multisession training, allowing us to investigate the effects of stimulation on learning. A double-blind randomized controlled trial design was employed. Multiple outcome measures varied the degrees of overlap with the trained activities, allowing us to map out the extent to which gains generalized beyond the trained tasks. The primary outcome measures were working memory tests with processing components that overlapped with the training tasks. Any enhancement to training via stimulation should be evident in these measures as well as the trained tasks. To determine whether any benefits of combining training with stimulation extend beyond specific trained processes, participants also completed untrained working memory tasks with different processing demands to those in the training tasks. Secondary measures of cognitive processes linked with working memory, including tests of inhibition (Kane & Engle, 2003) and measures of selective attention (de Fockert, Rees, Frith, & Lavie, 2001), were included alongside tests of information processing and standardized tests of general cognitive abilities (e.g., language and nonverbal reasoning) to test whether stimulation enhanced transfer beyond working memory paradigms. An emotional recognition task with no memory component was included as a nonmemory control task. Previous studies claiming that cognitive training or brain stimulation are effective have relied on null hypothesis significance testing (NHST) to imply that the alternative hypothesis is true; they have rarely quantified the degree to which the evidence supports the null or alternative hypotheses (Sprenger et al., 2013). For this reason, Bayesian methods were employed to evaluate the strength of the evidence for and against the null hypothesis in addition to traditional NHST.

METHODS

Participants

Thirty native English-speaking adults aged between 18 and 35 years (11 men) provided written informed consent to participate in this study, which was approved by the University of Cambridge's psychology research ethics committee. All participants were recruited through the MRC Cognition and Brain Sciences Unit's research participation system. All participants were stimulation compatible (i.e., no metal implants or pacemakers, no previous history of epilepsy, head injury or neurological disorders, not currently taking medication affecting the CNS), had normal or corrected-to-normal hearing and vision, and were right-handed.

Materials

Process-specific Memory Tasks

Eight tests with processing components that overlapped with the training tasks were administered. These included four standardized tests from the Automated Working Memory Assessment (Alloway, 2007): a test of verbal STM (digit recall), visuospatial (VS) STM (dot matrix), verbal working memory (WM) (backward digit recall) and VS WM (Mr X). Standard scores ($M = 100$, $SD = 15$) were calculated for each task. Participants also completed four computerized experimental tests of verbal and VS storage (STM) and of verbal and VS storage with intrinsic processing (working memory). The storage tasks required participants to recall either a list of digits (verbal) or spatial locations (VS) in serial order. The working memory tasks were identical to the storage tasks, except participants were required to recall the digits (verbal) or spatial locations (VS) in reverse order. Trials were presented in blocks of four trials. Sequences in the first block started at a span of two items and increased in length by one item in each subsequent block if participants scored three or more trials correct. The tasks discontinued if two or more errors were made in any block. The maximum span length reached at this point was scored.

Memory Tasks with Distinct Processes

Participants completed four working memory tasks involving distinct processes to the training activities, two n-back tasks and two complex span tasks. For both n-back tasks, participants were presented with a sequence of stimuli one at a time (auditory digits for verbal n-back and abstract line drawings for VS n-back) and had to indicate by a key press when the current stimulus matched one presented n items back in the sequence. Sequences were presented in blocks containing $20 + n$ items. There were six target items (matches) in each block. The first block started at 1-back and increased in difficulty by 1 in each subsequent block if less than five errors were made (e.g., increased from 1-back to 2-back). The tasks dis-

continued when five or more errors were made within a block. False alarms (responding to a nontarget) and misses (failing to respond when a match was present) were counted as errors (missing a target). The maximum n-back level reached to this point was scored. For both complex span tasks, participants were presented with a series of storage items (digits for the verbal task and spatial locations for the VS task) interpolated with a same-domain processing task, which was presented for 6 sec in-between the presentation of each storage item. The processing tasks required participants to judge whether two letters rhymed (verbal task) or to decide whether patterns of lines presented inside a pair of hexagons matched (VS task). Participants were required to recall the storage items in serial order at the end of the trial. Trials were presented in blocks of 3. The first block started at a span of 1 (one storage item and one processing episode) and increased by a span of 1 (additional storage item and an additional processing episode) if two or more trials were correct in any block. Trials were scored as correct if all storage items were recalled in the correct serial order and >66% of the processing items were correct. The tasks discontinued if two of the three trials in a block were incorrect. A trial was incorrect if the storage items were recalled incorrectly, accuracy for the processing tasks was <66%, or if there were no responses for the processing tasks. The maximum span reached was scored.

Cognitive Processes Associated with Working Memory

Participants completed a set of tasks that included parallel verbal and VS tests of executive function. Two flanker tasks were administered to provide measures of verbal and VS selective attention. Both tasks consisted of 240 trials: 80 baseline, 80 congruent, and 80 incongruent. Trials were presented in a random order. In the baseline condition, participants were required to click on a button on a computer screen showing a letter (verbal) or arrow (VS) matching the one presented in a box on screen. In the congruent condition, participants were presented with a row of five identical letters (verbal) or a row of five arrows pointing in the same direction (VS). They were required to click on the letter or arrow corresponding to the middle letter/arrow shown below. In the incongruent condition, the central arrow or letter was flanked by incongruent stimuli (e.g., AABAA). Again, participants were asked to respond to the middle stimulus by selecting the appropriate response button shown on screen. RTs for correct trials were recorded for all conditions. The average RT difference between correct congruent and incongruent trials was used to index the Flanker effect.

Indices of inhibitory control were provided by two Stroop tasks. Both tasks consisted of 48 baseline, 48 congruent, and 48 incongruent trials. These were presented in blocks by condition. On baseline trials in the verbal Stroop task, neutral words (e.g., "when") were presented

on screen printed in yellow, blue, green, or red. Participants were required to click on a color block matching the color the word was printed in. On congruent trials, participants were presented with color words printed in the same color as the word (e.g., "yellow" appeared on screen, printed in yellow ink) and were again asked to click on the color the word was printed in. On incongruent trials, color words were presented in different colors to the word itself (e.g., "yellow" was printed in red ink). Participants were required to inhibit the overlearned verbal response of reading the color word and instead click on the ink color. On neutral trials in the VS Stroop task, an arrow appeared in the center of a box, pointing either up, down, left, or right. Participants were required to click on the arrow pointing in the same direction from a choice of four presented in a box below. On congruent trials, an arrow appeared touching the edge of the box at a position congruent with the direction it was pointing (e.g., an arrow pointing right appeared on screen with the arrowhead touching the right hand side of the box). Participants were asked to select the arrow pointing the same way as the one in the box from a choice of four below. On incongruent trials, participants were presented with an arrow in a position in a box that was incongruent to the direction it was pointing (e.g., an arrow pointing right could appear at the left, top, or bottom of the box). Participants were required to inhibit the prepotent response associated with the position of the arrow and instead respond to the direction of the arrowhead by selecting one of four arrows below. For both tasks, RTs for correct trials were recorded for each condition. The Stroop effect was calculated as the difference between the mean RT for correct trials in the incongruent condition and the mean RT for correct trials in the congruent condition.

Information Processing and General Cognitive Abilities

Participants completed two information processing tasks. The verbal processing task required participants to judge whether pairs of letters rhymed. Fifty auditory letter pairs were presented, consisting of monosyllabic English alphabet letter names. Pairs were constrained to avoid successive letters in the alphabet (e.g., J, K), highly confusable fricative letter names (e.g., F, S), and familiar acronyms (e.g., PC, IT, US). A parallel VS processing task required participants to judge whether the line patterns shown on two hexagons presented simultaneously were the same or different. Fifty pairs of hexagons were shown. RTs for correct trials were scored for both tasks.

Two subtests of the Wechsler Abbreviated Scaled of Intelligence (Wechsler, 1999), tests of verbal (Vocabulary) and of nonverbal (Matrix Reasoning) IQ, were also administered. t Scores were derived for each subtest and used to calculate a composite standard score for IQ. The Numerical Operations task of the Wechsler

Individual Achievement Test Second Edition (Wechsler, 2005) was used to measure math ability. The Peabody Picture Vocabulary Test Fourth Edition, a measure of receptive vocabulary (Dunn & Dunn, 2007), was also given.

Cognitive Task with No Memory Load

The Facial Expressions of Emotion test (Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002) is a measure of emotion expression recognition. Participants were presented with 30 morphed faces on an emotional continuum ranging between happiness–surprise, surprise–fear, fear–sadness, sadness–disgust, disgust–anger, and anger–happiness over five blocks. Participants were required to judge which of six emotion labels (happy, sad, anger, fear, disgust, and surprise) best described each facial expression. Only trials with morphed images of 70% or 90% bias toward a particular expression were used to assess performance. Proportion correct across all blocks was scored.

Training

Participants completed 10 sessions of Cogmed Working Memory Training (Cogmed, 2005). Each session lasted approximately 45 min and involved repeated practice on eight training exercises (15 trials on each task totaling 120 trials). Participants completed the same eight tasks in each training session, in one of two counterbalanced task orders. Task order was counterbalanced to ensure all tasks were completed under active stimulation for those in the stimulation group. A mixed ANOVA with order (A or B) and task (gain for each of the eight training tasks) revealed that there were no order effects for either the active stimulation, $F(7, 91) = 1.462, p = .191, \eta_p^2 = .101$, or sham stimulation, $F(7, 91) = .943, p = .478, \eta_p^2 = .068$, groups. Three training tasks required the immediate serial recall of verbal or VS items (Visual Data, Data Room, and Decoder). Five further tasks required mental manipulation (e.g., mental rotation or reversing the sequence) prior to recall (Input Module, Input Module with Lid, Number Grid, Rotating Data Link, and Rotating Dots). Full details about the training program are provided at www.cogmed.com/rm. All training exercises started at a span of two in the first session. An adaptive algorithm was used to calibrate the difficulty of each task to current performance on a trial-by-trial basis. Task difficulty increased by a span of one following three consecutive correct responses and decreased by a span of one following two consecutive incorrect answers. The average span was recorded for each task in each session. Data from Session 1 was not included in the analyses as there was no training in this session (the maximum span participants could reach was below the baseline ability of all participants).

Stimulation

tRNS was applied bilaterally over the DLPFC. Standard 5 × 5 cm rubber electrodes, covered with saline-soaked sponges, were placed on the scalp on areas corresponding to regions F3 and F4 identified using the standard international 10–20 EEG electrode placement procedure. They were fixed by a rubber headband. Stimulation was delivered via a battery-driven electrical stimulator (DC-STIMULATOR-PLUS; NeuroConn). Following Snowball et al. (2013), high-frequency tRNS (101–640 Hz) at a current strength of 1 mA with no DC offset (i.e., varying between −0.5 and +0.5 mA) at a sampling rate of 1280 sample/sec was used. Participants in the active stimulation group received 20 min of tRNS with 15 sec of increasing and decreasing ramps at the beginning and end of stimulation. To maximize opportunities for modulating behavior, stimulation began at the onset of training (Pirulli, Fertonani, & Miniussi, 2013). Stimulation faded in for 15 sec and out over 15 sec at the beginning of each session for the sham group to blind participants to their stimulation condition (Priori, Hallett, & Rothwell, 2009). The stimulation machine display was identical for both groups ensuring both the experimenter and participants were blind to the type of stimulation being applied. Participants were asked to rate the extent to which they experienced any physical sensations from the stimulation on a scale of 1–10 (1 being *not at all*). The ratings were similar (stimulation $M = 1.000$, $SD = 1.363$, sham $M = .9333$, $SD = 1.580$) and did not differ significantly between groups, $t(28) = 1.24$, $p = .902$, Cohen's $d = .046$, indicating that group blinding was effective.

Procedure

This was a double-blind randomized controlled study. Participants completed two pretraining sessions, each lasting approximately 2 hr. They were assigned to either an active (9 women) or sham (10 women) stimulation condition ($n = 15$ per group) after preassessment. Stratified randomization was used to ensure the groups were matched at baseline in terms of age, sex, IQ, and standardized short-term and working memory scores (Table 1). The demand characteristics of the study were identical between the active and sham groups; both completed the same training, were unaware whether they were receiving active or sham stimulation, and were paid for their time. A no-contact control group was not included as they would have been poorly matched in terms of motivation and other demand characteristics (e.g., Shipstead, Redick, & Engle, 2012). Participants then completed 10 sessions of adaptive working memory training with either active or sham stimulation across ~19 days. Training sessions were run individually with each participant. The time taken to complete training did not differ between groups (Table 1). All pretraining tasks were readministered at the end of training.

RESULTS

Training Data

General linear regression models were conducted for each training task to investigate whether there were any group differences in overall gains. For all models, Session 10 scores were entered as the dependent variable, with group (active stimulation or sham) entered as the independent variable. Group did not significantly predict training gains on any task, nor did it predict average gains across the training tasks (Table 2).

Previous studies claiming that cognitive training or brain stimulation are effective have relied on NHST to imply the alternative hypothesis is true; they have rarely quantified the degree to which the evidence supports the null or alternative hypotheses (Sprenger et al., 2013). For this reason, Bayesian methods were employed to quantify the strength of the evidence for the null hypothesis (stimulation does not enhance on-task gains) versus the alternative (stimulation boosts training gains). Bayesian regression analyses conducted in JASP (Love et al., 2015) with default prior scales were conducted for each training task, with group (active stimulation or

Table 1. Group Characteristics

	Stimulation		Sham		Group Comparison		
	M	SD	M	SD	t	p	Cohen's d
Age (years)	25.270	5.509	24.730	4.008	0.303	.764	0.113
IQ	120.667	8.524	119.333	10.834	0.375	.711	0.138
Verbal STM	101.067	15.696	100.600	16.322	0.080	.937	0.029
VS STM	103.733	23.313	106.667	22.064	−0.354	.726	−0.129
Verbal WM	101.000	20.078	101.733	19.282	−0.102	.919	−0.037
VS WM	103.133	22.427	107.867	15.287	−0.675	.505	−0.251
Time to complete training (days)	19.330	4.515	18.333	3.867	0.652	.520	0.238

Table 2. Changes in Training Task Performance by Group

| | Gains from Sessions 2 to 10 | | | | | | | Group by Session | | | | Rate of Change | | | | | | | | | | | |
| | Stimulation | | Sham | | Group Comparison | | | Bayesian Regression BF₁₀ | F | p | Partial Eta | Bayesian ANOVA BF₁₀ | Stimulation | | | Sham | | | Group Comparison | | | Bayesian t Test BF₁₀ |
	M	SD	M	SD	Beta	t	p	BF_{10}	F	p	Partial Eta	BF_{10}	N	M	SD	N	M	SD	t	p	Cohen's d	BF_{10}
Average across all tasks	1.426	0.513	1.346	0.689	−0.068	−0.361	.721	0.36	0.478	.871	0.017	44.202	11	0.194	0.087	8	0.138	0.07	1.48	.157	−0.713	0.345
Visual data link	1.165	0.631	1.167	0.673	0.029	0.156	.877	0.348	0.232	.985	0.008	74.285	10	0.059	0.286	8	0.171	0.149	−1.002	.331	0.515	0.38
Data room	1.028	0.739	0.672	0.647	−0.107	−0.567	.575	0.389	1.136	.34	0.039	8.913	10	0.067	0.134	8	0.157	0.187	−1.2	.248	0.561	0.347
Decoder	0.867	0.761	0.818	0.447	−0.069	−0.368	.716	0.363	0.236	.984	0.008	60.758	12	0.161	0.188	11	0.173	0.128	1.208	.87	0.076	1.352
Input module	2.737	2.078	2.719	2.112	−0.085	−0.451	.655	0.372	0.952	.474	0.033	13.161	12	0.465	0.302	6	0.257	0.081	1.629	.123	−1.086	1.332
Input module with lid	2.611	1.345	2.051	1.511	−0.133	−0.712	.482	0.417	1.123	.349	0.039	8.811	9	0.367	0.217	8	0.153	0.194	2.123	.051	−1.041	0.715
Number grid	1.025	0.804	1.071	0.837	0.059	0.311	.758	0.357	0.43	.902	0.015	40.550	12	0.051	0.456	11	0.21	0.226	−1.041	.31	0.466	0.379
Rotating data link	0.959	0.636	0.955	0.748	−0.062	−0.331	.743	0.359	0.216	.988	0.008	67.100	7	−0.047	0.523	9	0.145	0.139	0.088	.306	0.58	2.135
Rotating dots	1.000	0.686	1.269	0.497	0.008	0.042	.967	0.345	0.74	.656	0.026	22.717	12	0.261	0.488	10	0.277	0.075	−0.101	.92	0.057	0.634

Data from Session 1 were not analyzed as there was no training in this session (the maximum span participants could reach was below the baseline ability of all participants).

sham) entered as an independent variable. Inverse BF (BF_{10}) were used to express the odds in favor of the alternative hypothesis (group has an effect) compared with the null (no effect of tRNS). As a point of reference: BF_{10} of 1–3 indicates weak/anecdotal evidence for the alternative hypothesis; BF_{10} of 3–10 corresponds to positive/substantial support for the alternative hypothesis and $BF_{10} > 10$ indicates positive/strong evidence for the alternative hypothesis (Kass & Raftery, 1995). Bayesian regression analyses, conducted for all training tasks with group entered as the independent variable, yielded no evidence that stimulation influenced gains on the training activities, $BF_{10} < .5$ for all tasks (Table 2).

Mixed effects ANOVAs with Session (2–10) as a within-subject factor and Group (stimulation or sham) as a between-subject factor were conducted to investigate whether there were any group differences in training performance across sessions. These analyses revealed a significant main effect of Session for memory span in both groups on each of the training tasks (all $ps < .01$) and also on span scores averaged across tasks (Figure 1). Neither the main effects of Group or the Group × Session interactions were significant (see Figure 1 for scores averaged across tasks and Table 2 for the Group × Session interaction terms for each task). Bayesian ANOVAs revealed that a simple main effects model in which Group and Session were entered separately was preferred to a model that included a Group × Time interaction for all tasks and for scores averaged across tasks (BF_{10} ranging from 8.913 to 74.285 in favor of the main effects model; Table 2). There was therefore strong evidence for similar training performance across sessions for both groups.
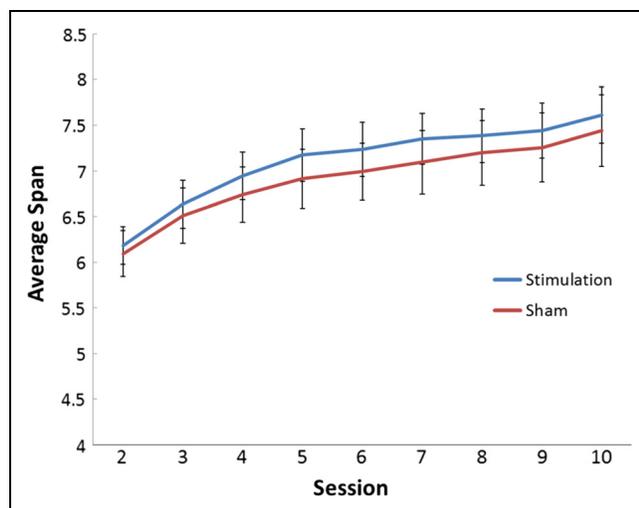

Figure 1. Training data by group, averaged across all eight training tasks. A main effect of Session, $F(8, 224) = 105.114, p < .001, \eta_p^2 = .790$, revealed significant training gains. The absence of a main effect of Group, $F(1, 28) = .201, p = .658, \eta_p^2 = .007$, or Group × Session interaction, $F(8, 224) = .478, p = .871, \eta_p^2 = .017$, indicates that gains were not modulated by stimulation. Data from Session 1 are not displayed as there was no training in this session (the maximum span participants could reach was below the baseline ability of all participants).

Rate of learning on the training activities was estimated by computing a polynomial function that identified the point at which each participant reached asymptotic performance on each task. If stimulation enhances learning, the stimulation group should reach this point faster than the sham group. The functions of the polynomials provided the rate of change to asymptote for each participant on each task. These were computed for each individual training task and for average performance across tasks by approximating each participant's performance with a function that allowed for two turning points; the second corresponded to the point at which they reached asymptote. The functions of the polynomials were then used to calculate how quickly each participant reached their asymptote for each task. This ROC index was calculated as maximum score at asymptote/number of sessions to reach asymptote. Group differences in rate of change values were then compared in a series of independent samples t tests (see Table 2). Data were excluded for curves in which the asymptote was outside the observable training window (i.e., if asymptote <2 or >10). There were no significant group differences in rate of change for any task or for rate of change in scores averaged across tasks. Bayesian independent samples t tests revealed no evidence for group differences in rates of change (all $BF_{10} < 3$), indicating that stimulation did not increase the speed of learning on the training activities (Table 2).

Transfer Tasks

The influences of training and stimulation on transfer were first assessed on the sample as a whole (Table 3). Significant main effects of Training were observed on all working memory tests sharing processes with the training tasks (all $ps < .001$). Bayesian analyses indicated that there was strong evidence for these effects. After family-wise correction for multiple comparisons, there were no significant main effects of Training on memory tasks involving distinct processes to the training activities. The outcomes of Bayesian t tests concurred with this pattern of effects for all measures except VS n-back, where a BF_{10} of 3.322 suggested that there was positive evidence for a training effect. Training gains on verbal and VS information processing tasks and the number operations measure reached significance, with $BF_{10} > 3$ in all cases. There was no evidence for training effects on measures of selective attention, inhibitory control, language, or nonverbal reasoning.

To examine the effect of stimulation on transfer, general linear regression analyses were performed with post-training scores as dependent variables and pretraining scores and group (active or sham stimulation) as independent variables. Stimulation group was a significant predictor of posttraining scores on a verbal n-back task, a memory test that did not share common processes with the trained activities. Training gains were significantly greater for the

Table 3. Training-related Changes in Transfer Tasks

	Pretraining		Posttraining		Pre to Post			
	M	SD	M	SD	t	p	Cohen's d	Bayesian t Test BF_{10}
Process-specific Memory Tasks								
Digit recall	100.833	15.735	108.567	15.85	−4.500	**<.001**	0.490	255.700
Dot matrix	105.2	22.352	120.1	21.865	−6.971	**<.001**	0.674	131219.000
Backward digit recall	101.367	19.345	115.2	15.338	−5.897	**<.001**	0.798	8818.000
Mr X	105.5	19.011	114.733	16.885	−5.541	**<.001**	0.514	3573.000
Verbal storage	7.967	1.351	8.967	1.732	−4.664	**<.001**	0.649	385.700
VS storage	7.267	1.311	8.033	1.752	−3.516	**<.001**	0.500	23.720
Verbal backward	6.567	1.612	8.133	1.548	−4.683	**<.001**	0.991	405.000
VS backward	6.433	1.695	7.367	1.921	−3.006	**.005**	0.517	7.597
Non Process-specific Memory Tasks								
Verbal *n*-back	4.933	1.66	5.4	2.313	−1.304	.203	0.235	0.419
VS *n*-back	3.567	1.547	4.333	1.936	−2.605	**.014**	0.440	3.322
Verbal complex span	6.133	2.3	6.9	2.551	−2.538	**.017**	0.316	2.917
VS complex span	4.667	1.863	4.6	2.061	0.220	.827	−0.034	0.199
Processes Associated with WM								
Verbal Flanker effect	82.774	31.099	79.324	66.107	0.335	.740	−0.071	0.205
VS Flanker effect	75.165	76.888	74.031	66.553	0.064	.949	−0.016	0.195
Verbal Stroop effect	43.349	130.08	76.764	136.27	−1.004	.324	0.251	0.308
VS Stroop effect	124.442	68.5	145.107	114.98	−1.043	.306	0.225	0.319
General Cognitive Abilities								
Verbal processing	2071.47	580.7	1916.78	328.81	2.780	**.009**	−0.340	4.726
VS processing	1221.26	435.74	1017.35	308.9	5.166	**<.001**	−0.548	1374.000
Matrix reasoning	60.667	4.95	62.6	4.223	−2.511	**.018**	0.421	2.766
Vocabulary	61.7	8.125	63.533	8.427	−2.483	**.019**	0.221	2.624
Number operations	112.4	17.047	115.8	15.624	−3.111	**.004**	0.208	9.532
Peabody Picture Vocabulary Test	110.467	14.277	112.567	18.823	−1.467	.153	0.127	0.510
Cognitive Task with No Memory Load								
Emotion hexagon	89.806	8.704	89.698	8.212	0.088	.930	−0.013	0.195

Bold text indicates significant effect at $p < .05$ level; ***bold italics*** denote significant effects after family-wise correction for multiple comparison.

active stimulation group ($p = .046$), but this effect did not withstand correction for multiple comparisons (Table 4). Training-related differences between groups on all other measures were nonsignificant (see Figure 2). Bayesian regression analyses favored the null hypothesis with $BF_{10} < 1$ for all outcome measures, except verbal *n*-back. For this task $BF_{10} = 1.695$, providing equivocal support for the null and alternative hypotheses (Table 4). In summary, these analyses provide no strong evidence that stimulation enhances performance beyond training alone on any outcome measure.

Table 4. Training and Stimulation Effects by Group

| | Stimulation Group | | | | Sham Group | | | | Baseline Group Comparisons | | | Group Comparison in Training Gains | | | Bayesian Regression |
| | Pretraining | | Posttraining | | Pretraining | | Posttraining | | | | | | | | |
	M	SD	M	SD	M	SD	M	SD	t	p	Cohen's d	Beta	t	p	BF$_{10}$
Process-specific Memory Tasks															
Digit recall	101.067	15.696	110.467	15.264	100.600	16.322	106.667	16.723	0.080	.937	0.029	−0.110	−1.019	.317	0.27
Dot matrix	103.733	23.313	120.867	23.676	106.667	22.064	119.333	20.701	−0.354	.726	−0.129	−0.093	−0.966	.343	0.223
Backward digit recall	101.000	20.078	113.867	15.95	101.733	19.282	116.533	15.137	−0.102	.919	−0.037	0.074	0.584	.564	0.249
Mr X	103.133	22.247	110.667	19.667	107.867	15.287	118.800	12.974	−0.675	.505	−0.251	0.136	1.523	.139	0.381
Verbal storage	8.000	1.690	9.067	1.486	7.933	0.961	8.867	1.995	0.133	.895	0.051	−0.040	−0.310	.759	0.231
VS storage	7.533	1.125	8.200	1.699	7.000	1.464	7.867	1.846	1.119	.273	0.412	0.057	0.426	.673	0.243
Verbal backward	7.000	1.512	8.400	1.549	6.133	1.642	7.867	1.552	1.504	.144	0.550	−0.092	−0.491	.627	0.473
VS backward	6.200	1.699	7.200	1.699	6.667	1.718	7.533	2.167	−0.748	.461	−0.273	0.010	0.059	.953	0.323
Non–process-specific Memory Tasks															
Verbal n-back	4.800	1.612	6.000	2.104	5.067	1.751	4.800	2.426	−0.434	.668	−0.159	−0.311	−2.088	**.046**	1.695
VS n-back	3.200	0.862	4.200	1.373	3.933	1.981	4.467	2.416	−1.315	.199	−0.516	−0.077	−0.483	.633	0.337
Verbal complex span	6.600	1.595	6.800	2.541	5.667	2.820	7.000	2.646	1.116	.274	0.423	0.208	1.757	.090	0.286
VS complex span	4.733	1.335	4.467	2.386	4.600	2.324	4.733	1.751	0.193	.849	0.073	0.089	0.613	.545	0.322
Processes Associated with WM															
Verbal Flanker effect	79.551	16.718	74.196	30.288	85.998	41.250	84.452	89.882	−0.561	.579	−0.222	0.024	0.144	.886	0.345
VS Flanker effect	51.239	45.467	84.178	65.175	99.091	94.614	63.883	68.603	−1.766	.088	−0.683	−0.205	−1.033	.311	0.514
Verbal Stroop effect	8.534	45.324	81.750	184.192	78.164	174.354	71.778	66.971	−1.497	.146	−0.634	−0.059	−0.296	.770	0.381
VS Stroop effect	131.600	43.697	159.288	135.996	117.285	87.753	130.926	91.984	0.566	.576	0.218	−0.085	−0.479	.636	0.43

Table 4. (continued)

| | Stimulation Group | | | | Sham Group | | | | Baseline Group Comparisons | | | Group Comparison in Training Gains | | | Bayesian Regression |
| | Pretraining | | Posttraining | | Pretraining | | Posttraining | | | | | | | | |
	M	SD	M	SD	M	SD	M	SD	t	p	Cohen's d	Beta	t	p	BF$_{10}$
General Cognitive Ability															
Verbal processing	1951.487	121.174	1822.971	107.384	2191.454	808.066	2010.594	439.959	−1.137	.265	−0.516	0.101	1.374	.181	0.244
VS processing	1142.336	213.788	946.584	179.034	1300.186	578.135	1088.117	393.530	−0.992	.330	−0.399	0.072	0.805	.428	0.174
Matrix reasoning	62.067	4.847	63.000	3.836	59.267	4.803	62.200	4.678	1.589	.123	0.580	0.079	0.489	.629	0.341
Vocabulary	61.067	7.324	62.800	7.757	62.333	9.069	64.267	9.262	−0.421	.677	−0.154	0.019	0.206	.839	0.135
Number Operations	111.867	18.712	116.867	14.764	112.933	15.85	114.733	16.888	−0.168	.867	−0.062	−0.099	−1.534	.137	0.27
Peabody Picture Vocabulary Test	108.267	13.285	110.533	17.125	112.667	15.342	114.600	20.780	−0.84	.41	−0.307	−0.036	−0.483	.633	0.114
Cognitive Task with No Memory Load															
Emotion hexagon	88.833	9.193	90.135	8.732	90.778	8.389	89.262	7.940	−0.605	.550	−0.221	−0.134	−0.976	.338	0.373

Bold text indicates significant effect at $p < .05$ level.
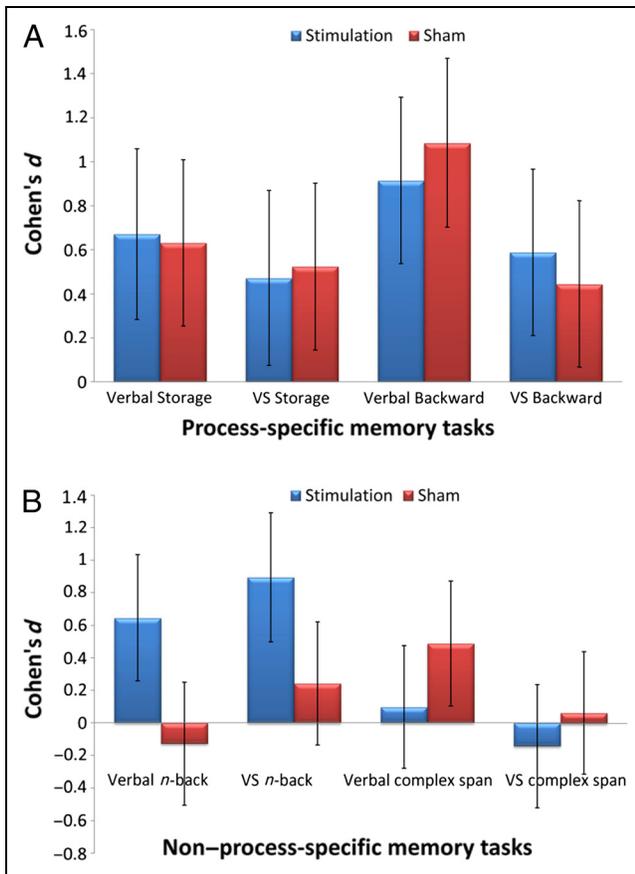
Figure 2. Changes in process-specific (A) and non–process-specific (B) memory tasks by group. Mean effect sizes are displayed. General linear regression models revealed no significant differences in how the groups responded to training (all $ps > .6$; Table 3), demonstrating that stimulation did not enhance transfer to untrained tests of memory.

DISCUSSION

This randomized controlled trial provides the first test of the potential additive benefits of combining tRNS with working memory training. An effective training program (Schwaighofer et al., 2015) was employed in conjunction with stimulation parameters that have been used to enhance training gains in another cognitive domain (Snowball et al., 2013). tRNS did not enhance the rate, magnitude, or degree of transfer of working memory training in an active stimulation group relative to a sham group. Strong training gains were found on trained activities in participants irrespective of stimulation condition, and as in previous research, these effects extended to transfer tests with processing and storage demands in common with the training activities (Melby-Lervåg & Hulme, 2013; von Bastian & Oberauer, 2013; Dahlin et al., 2008).

By contrast, on memory tests with minimal overlap with the training activities there was little evidence for the benefits of training alone. The training tasks involved practice on serial memory paradigms that required either the reproduction of a sequence of verbal or VS items, or mental manipulation of the items prior to recall (e.g.,

reversing a sequence of digits or rotating a sequence of spatial items 90°). No training-related enhancements were found on transfer tests of working memory that involved switching between the storage of memory items and an unrelated processing activity (complex span). There was a small training gain on a VS *n*-back task involving the continuous updating and recognition of a set of items. Although this did not survive a correction for multiple comparisons, Bayesian analyses suggested that there was positive but not strong evidence for this effect. There was no evidence for transfer to a verbal *n*-back task. On balance, this pattern of effects is consistent with previous reports that training induces the learning of task-specific strategies that do not generalize to other categories of working memory task (Dunning & Holmes, 2014; von Bastian & Oberauer, 2013).

There was also no evidence for more distant transfer of working memory training without stimulation to tests of nonverbal reasoning and language ability. Small gains were observed on a test of mathematical ability (three standard score points) and short increases in speed of responses on tests of verbal and VS information processing were also found, but in the absence of a no-intervention test–retest control group, it is impossible to determine whether these reflect genuine training benefits or repetition effects. This pattern of far transfer effects is largely consistent with the working memory training literature, which provides no consistent evidence that training alone ameliorates the everyday difficulties associated with working memory such as problems in attentional focus and learning (Holmes et al., 2015; Dunning et al., 2013; Shipstead et al., 2012; see Simons et al., in press, for a review).

Crucially, the results of the current experiment demonstrate that tRNS does not extend the limited transfer found with working memory training. In line with previous studies that have combined working memory training with a different stimulation technique, tDCS, there were no differences in performance between the active tRNS and sham stimulation groups on any of the transfer tests (Richmond et al., 2014; Martin et al., 2013). Together the results of these studies provide no evidence to support the use of combining training with stimulation as a therapeutic tool to improve working memory function.

There was also no evidence that stimulation modulated the speed of learning or magnitude of gains on the training tasks. These results provide a challenge to the hypothesis that tRNS provides a global facilitation in brain plasticity when combined with a learning task (e.g., Cohen Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012). They are also inconsistent with findings in another cognitive domain, suggesting that tRNS enhances learning when coupled with mathematics training (Cappelletti et al., 2013; Snowball et al., 2013). This may reflect differences in the impact of tRNS on the different interventions, resulting from the malleability of the neural substrates targeted by the working memory and mathematical training

programs, and the complexity of the training programs and their doses. Future research needs to develop a greater understanding of the neurophysiological underpinnings of stimulation and the impact of different stimulation protocols when applied to different scalp regions and combined with different training regimes. Candidate factors for further investigation include the type, duration and intensity of stimulation (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010), the timing of stimulation relative to the task (Pirulli et al., 2013), individual differences in brain anatomy (Opitz, Paulus, Will, Antunes, & Thielscher, 2015), and the functional state of the brain during stimulation (Antal, Terney, Poreisz, & Paulus, 2007).

New interventions that promise cognitive enhancement such as working memory training and brain stimulation are appealing to the scientific community, practitioners, and the general public alike, generating high levels of interest and intense research activity. Their history also shows that they are marked by high levels of early positive results that are typically not sustained over longer periods, probably because of publication bias (Dwan, Gamble, Williamson, & Kirkham, 2013; Scherer, Langenberg, & von Elm, 2007). At this relatively early point in the brain stimulation research field, the clear conclusion from this study is that, when using the most rigorous intervention design and combining training and stimulation protocols that have been shown to be effective in other domains, there is no evidence that tRNS targeting bilateral DLPFC enhances the benefits of Cogmed Working Memory Training.

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