Exp Brain Res (2016) 234:1807–1818
DOI 10.1007/s00221-016-4580-1

RESEARCH ARTICLE

Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex enhances working memory

Yasaman Bagherzadeh[1,4] · Anahita Khorrami[1] · Mohammad Reza Zarrindast[1,2] · Seyed Vahid Shariat[1,3] · Dimitrios Pantazis[4]

Received: 4 August 2015 / Accepted: 30 January 2016 / Published online: 16 February 2016

Abstract Neuroimaging and electrophysiological studies have unequivocally identified the dorsolateral prefrontal cortex (DLPFC) as a crucial structure for top-down control of working memory (WM) processes. By modulating the excitability of neurons in a targeted cortical area, transcranial magnetic stimulation (TMS) offers a unique way to modulate DLPFC function, opening the possibility of WM facilitation. Even though TMS neuromodulation effects over the left DLPFC have successfully improved WM performance in patients with depression and schizophrenia in a multitude of studies, raising the potential of TMS as a safe efficacious treatment for WM deficits, TMS interventions in healthy individuals have produced mixed and inconclusive results. Here, we stimulated the left DLPFC of healthy individuals using a high-frequency repetitive TMS protocol and evaluated behavioral performance in a battery of cognitive tasks. We found that TMS treatment enhanced WM performance in a verbal digit span and a visuospatial 2-back task.

Keywords Cognitive enhancement · Repetitive transcranial magnetic stimulation · Working memory · Dorsolateral prefrontal cortex

Introduction

The past decade has seen a growing interest in effective and safe methods to augment mental abilities through direct intervention in the human brain (Dresler et al. 2013). Many of these strategies have relied on pharmacological interversions (Sandberg and Bostrom 2006) and targeted the dopaminergic and adrenergic systems. So far their efficacy has been limited, with present data indicating a vigilance enhancement rather than specific improvement in cognitive performance, such as working memory or executive function (De Jongh et al. 2008; Quednow 2010).

Using brain stimulation techniques as a means of improving brain function has a long and successful history. Transcranial magnetic stimulation (TMS), introduced nearly 20 years ago, offers a promising alternative for cognitive enhancement in healthy individuals (Luber and Lisanby 2014). While most TMS protocols were originally developed for therapeutic purposes in psychiatry and neurology (Hoy and Fitzgerald 2010; McKinley et al. 2012), studies on healthy individuals have demonstrated success in facilitating visual spatial attention (Hilgetag et al. 2001; Thut et al. 2005), visual search (Hodsoll et al. 2009), mental rotation (Klimesch et al. 2003), analogical reasoning (Boroojerdi et al. 2001), phonological recall (Kirschen et al. 2006), and abilities in drawing (Snyder et al. 2003; Young et al. 2004), and mathematics, calendar calculating and proofreading (Young et al. 2004).

Although working memory (WM) has been a frequent target of cognitive enhancement strategies (Dresler et al.

Electronic supplementary material The online version of this article (doi:10.1007/s00221-016-4580-1) contains supplementary material, which is available to authorized users.

✉ Anahita Khorrami
khorramiaanahita@gmail.com

1 Institute for Cognitive Science Studies, Tehran, Iran

2 Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran

3 Mental Health Research Center, Tehran Institute of Psychiatry-School of Behavioral Sciences and Mental Health, Iran University of Medical Sciences, Tehran, Iran

4 McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA

2013; Fregni et al. 2005; Andrews et al. 2011), there is still conflicting evidence of TMS-facilitated WM enhancement in healthy individuals. Relatively few studies to date have demonstrated such effects (Preston et al. 2010; Esslinger et al. 2014; Hoy et al. 2015), with others finding no significant effects (Gaudeau-Bosma et al. 2013; Guse et al. 2013). Given the large variability in cognitive tasks, stimulation protocols, and targeted cortical sites in these studies, the effectiveness of TMS in enhancing WM remains an open question.

The efficacy of a TMS treatment depends critically on the pulse protocol. Single-pulse TMS delivers a brief, focal magnetic pulse over the head every 5–10 s and induces a transient electrical current in the underlying brain tissue, modulating neural activity in the targeted region for a short time. Single-pulse TMS enhancement effects on cognitive function (Grosbras and Paus 2002; Koski et al. 2005; Walsh et al. 1998) are typically transient, lasting only during online TMS application. A train of TMS pulses applied at a given intensity and frequency (1–20 Hz) is known as repetitive TMS (rTMS). The higher the stimulation frequency and intensity, the more the stimulation train disrupts cortical function. However, beyond these immediate effects, an rTMS pulse train can also modulate cortical excitability. This long-lasting effect may be inhibitory or facilitatory, depending on the stimulation variables (particularly the stimulation frequency). For example, motor cortex appears to be less excitable following stimulation at lower rTMS frequencies, in the 1 Hz range, and more excitable following stimulation by 10 Hz trains (Pascual-Leone and Hallett 1994). The lasting modulatory effects of rTMS have been extensively demonstrated (Maeda et al. 2000; Tegenthoff et al. 2005; Fregni and Pascual-Leone 2007; Brunoni and Vanderhasselt 2014) and make it a suitable methodological choice for WM enhancement studies (Esslinger et al. 2014; Brunoni & Vanderhasselt 2014; Gaudeau-Bosma et al. 2013; Guse et al. 2013).

Here, we conducted a high-frequency rTMS study employing offline stimulation of the left DLPFC. Human and animal research has provided key insights into the neuronal and neurotransmitter basis of WM, with the dorsolateral prefrontal cortex (DLPFC) assuming an executive role by exerting top-down control over other WM-related brain areas, including the intraparietal sulcus and posterior parietal cortex (Gazzaley and Nobre 2012; Zanto et al. 2011; Edin et al. 2009; Kojima and Goldman-Rakic 1982). Brain imaging studies in humans using functional magnetic resonance imaging (fMRI) and positron emission tomography have shown increased activation of the DLPFC in WM tasks (Owen et al. 1996; Wager and Smith 2003; Cho & Strafella 2009). Furthermore, DLPFC activation was accompanied by the recruitment of a network of regions, including an increase in connectivity between DLPFC and parietal areas (Owen et al. 2005; D'Esposito et al. 1998).

We explored the effects of rTMS on left DLPFC on a range of behavioral tasks. The study had two aims: (a) to investigate whether rTMS can induce WM enhancement in healthy subjects and (b) to elucidate the specificity of left DLPFC to different cognitive domains and clarify the relation of the stimulated site with different cognitive tasks. We used cognitive tests evaluating a range of cognitive abilities, including verbal, visuospatial, and object memory skills. We applied rTMS on the left DLPFC in multiple sessions at 10 Hz stimulation, a protocol known to produce long-lasting facilitation effects that persist past the initial period of stimulation (Fregni and Pascual-Leone 2007; Brunoni and Vanderhasselt 2014).

Materials and methods

Participants

Thirty healthy subjects (20 females; age mean ± S.D. = 36.8 ± 13.5 years) with no contraindications to receive TMS (Rossi et al. 2009) participated in the experiment. Subjects were suitable to participate in the study if they fulfilled the following criteria: (1) were mentally and physically healthy, as evaluated by a self-report and a General Health Questionnaire-28 (GHQ-28) score of 22 or lower (Taghavi 2002); (2) had normal or corrected-to-normal vision; and (3) were right-handed based on a modified version of the Edinburgh Handedness Inventory (Oldfield 1971). After passing the preliminary screening, participants were randomly assigned to either the active or sham group with 15 subjects per group. The members of the two groups had balanced demographic data with no statistical differences across age, education, and gender (Table 1). The study was conducted according to the Declaration of Helsinki

Table 1 Participant demographic data for active and sham TMS groups

Test	Active TMS group	Sham TMS group	*p* value
Age (years)	39.1 (4.1)	34.5 (3.36)	0.35 (two-sided *t* test)
Education (years)	16.9 (0.83)	16.9 (0.45)	1 (two-sided *t* test)
Gender	12 females; 3 males	8 females; 7 males	0.25 (Fisher's exact test)

Values for age and education are means across participants with standard deviation in brackets

and approved by the local ethics committee (Institutional Review Board of the Tehran University of Medical Science, Iran).

Experimental design

The study consisted of three main phases: (1) baseline behavioral evaluation; (2) ten TMS sessions applied in different days over a period of 2 consecutive weeks; and (3) post-intervention behavioral evaluation within 5 days after the final TMS session (Fig. 1a). Participants were informed before the beginning of the study that they would receive either active or sham TMS stimulation, and were only told their true assignment at the end of the 3 study phases. Participants completed a visual analog scale questionnaire before the start of each TMS session, enquiring about any notable changes in appetite, sleep, mood, and ability to concentrate (Supplemental Figure 1). Within the TMS group, 5 participants withdrew from the experiment after reporting headache (one participant), sleep disturbances (one participant), and mood changes (three participants). These 5 participants were substituted with new individuals for a total of the 30 subjects listed above.

Behavioral evaluation

Behavioral evaluation consisted of well-validated tests selected mainly from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd, Cambridge, UK) (version 3), as well as a

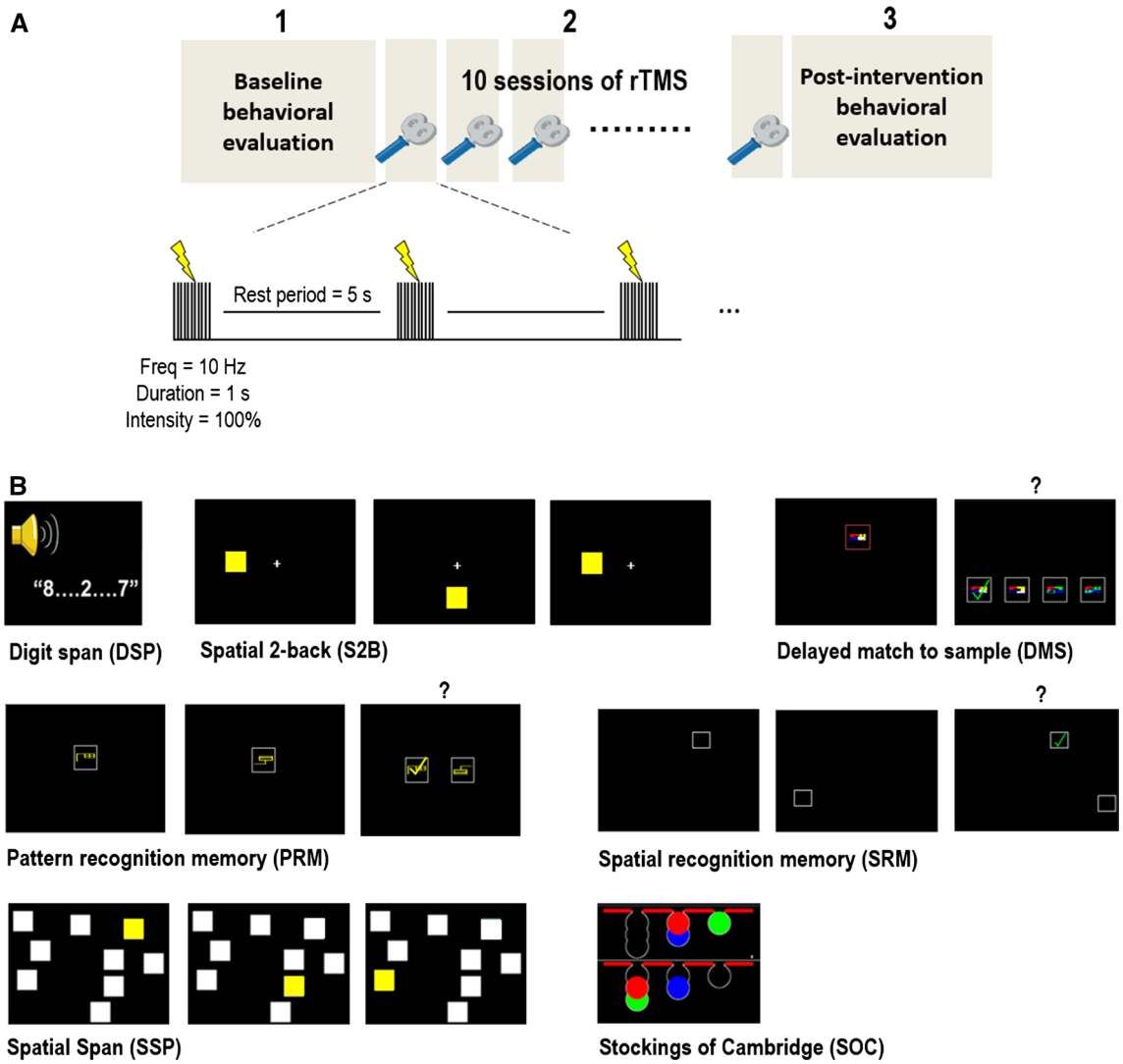

Fig. 1 **a** Experimental design and rTMS stimulation. The study consisted of 3 phases with behavioral evaluation prior and subsequent to 10 sessions of rTMS stimulation; **b** behavioral evaluation tasks. Most tasks were obtained from the CANTAB battery, with the exclusion of the DSP and S2B task, and engaged different aspects of maintenance and manipulation of information

Wechsler forward digit span test and a 2-back task (both by Sina Psycho lab Institute, Tehran, Iran) (Fig. 1b). The battery of tasks differed in material (verbal, spatial, and object patterns), storage capacity, attentional demands, processing speed, and strategy. The testing environment was a quiet and semi-dark room (neuropsychology lab at the Institute for Cognitive Science Studies, Tehran, Iran) equipped with a touch screen computer. Participants were given oral instructions and an option for a short break (1–5 min) before the beginning of each test, and were alone in the experimental room while performing the tests. All tests were completed in approximately 60 min and were repeated for all participants for both the pre-treatment (baseline) and post-treatment assessment phases in the same order as listed below.

Digit span task (DSP)

This task, obtained from the Wechsler Adult Intelligence Scale (Wechsler 1981), measures the capacity of verbal short-term memory. Participants were asked to repeat in the same order increasingly longer sequences of digits presented verbally with an inter-stimulus interval of 1 s. Sequences started at two digits and went up to a maximum of nine. For each sequence length, two different series of digits were presented and the test terminated early when the participant failed two sequences of same length. Administration time was approximately 8 min.

Spatial 2-back task (S2B)

This task presented a sequence of 48 stimuli, each consisting of the same visual object (square) randomly presented in one of eight possible locations of the screen. The locations were arranged on a 3 × 3 regular grid excluding the center of the screen, and each stimulus was presented for 0.5 s with inter-stimulus interval 1.5 s. Participants responded by pressing a button indicating whether the position of the current stimulus matched the one from 2 steps earlier in the sequence. The same presentation sequence was used for all participants. The 2-back task evaluated storage and executive processes, including selective maintenance, monitoring, and updating of spatial information in WM. (Owen et al. 2005). Administration time was approximately 8 min.

Delayed match-to-sample task (DMS)

In this task, a complex abstract pattern (the sample) was presented on screen, followed by four similar stimuli (Robbins et al. 1994). Participants were instructed to select the stimulus that matched the sample. The sample either remained visible for the entire duration (simultaneous condition) or was covered, and the stimuli were presented after a brief delay (0, 4, or 12 s intervals). DMS tested the visual domain of memory and forced decision-making. Administration time was approximately 10 min.

Pattern recognition memory task (PRM)

This task is a two-choice test of abstract visual pattern recognition. After a sequence of test patterns was shown on screen, participants were presented with pairs of patterns, one novel and one previously shown (selected opposite to the order of first presentation). They were instructed to identify which pattern was shown before. The task was repeated 12 times with approximately 5 min administration time.

Spatial recognition memory task (SRM)

This is a two-choice test of spatial recognition memory. A sequence of 5 squares was shown at different locations on the screen. Participants were then presented with pairs of squares, one at a novel location and one at a previously presented location (selected opposite to the order of presentation) and were instructed to identify which squares were in the same location as before. Administration time was approximately 5 min.

Spatial span task (SSP)

This test assesses the ability to remember a sequence of visual stimuli presented on screen. Nine white squares were shown simultaneously in random positions. Some of the squares then started changing color one by one, and the participant had to then indicate which squares changed color in the same order. The sequence progressively increased from 2 to 9 squares with 3 random trials in each length, and the test terminated if the participant failed all 3 trials of a given length. Administration time was approximately 6 min.

Stockings of Cambridge task (SOC)

This is a modified version of the Tower of London (Hill 2004), with the participants presented with 3 colored balls placed on vertical columns. The participants were instructed to plan and then initiate a sequence of moves to position the balls into a final arrangement as presented on the top of the screen. This test measured executive function and required spatial abilities and strategic planning. Administration time was approximately 10 min.

TMS application

Transcranial magnetic stimulation was performed with a Double Air Film Coil and Magstim Rapid2 stimulators (The Magstim Company Ltd, Whitland, Carmarthenshire, UK). The stimulation site was the left DLPFC, determined according to the Beam F3 system (Beam et al. 2009), with the coil positioned tangential to the scalp with the handle pointing back and away from the midline at 45° (as in Gaudeau-Bosma et al. 2013). We used a high-frequency repetitive TMS protocol at 10 Hz stimulation, known to induce facilitation effects in motor cortex (Pascual-Leone et al. 1998; Maeda et al. 2000). Every TMS session lasted 6 min and comprised 60 trains of 1 s stimulation (10 pulses each) separated with 5 s rest period in between. TMS stimulus intensity was set at 100 % of motor threshold on the left hemisphere, defined as the lowest TMS stimulation applied on the left motor cortex that produced a visible contraction of the right thumb in 10 consecutive stimulations.

Stimulation for the sham TMS group was delivered using the same parameters as the active TMS group; however, the coil was turned 45° away from the skull in a single-wing tilt position toward the anterior (same as in Fig. 1: 2-wind 45° in Lisanby et al. 2001), and stimulus intensity was set at the lowest setting. This placement evoked a sensation similar to those of active stimulation, but with minimal neuronal stimulation. Participants were not asked whether they thought they received active or sham TMS at the end of the study. However, the sham condition was reasonably convincing to the participants, with no participant spontaneously reporting any suspicions they were in the sham TMS group. All participants were naïve subjects with no prior experience in TMS studies.

Data analysis

The behavioral evaluation measures of the active and sham TMS groups were first compared using a two-sample *t* test in the baseline period. We expected no consistent difference in baseline performance given the two groups had balanced demographic data in age and education. To examine TMS effects on behavior, we then conducted analyses of variance (ANOVA) contrasting the two subject groups with different TMS treatments. We used mixed-design ANOVAs in a full-factorial design available on SPSS Software, Version 22 (IBM Corp, New York, USA). Between-subject factor was *Treatment* (active TMS vs. sham TMS). Within-subject factor was *Time* (prior vs. subsequent to TMS treatment). Dependent variables were the behavioral evaluation measures obtained separately for each task. These included the maximum span length for the DSP task, the accuracy for the S2B task, the accuracy and latency of correct responses for the DMS, PRM, SSP, and SRM tasks, and the percent problems solved with minimum moves and mean initial thinking time for the SOC task.

All statistical test *p* values were corrected for multiple comparisons using false discovery rate (Yekutieli and Benjamini 1999) at a 0.05 level. This included both the baseline *t* tests, and the main effect and interaction *p* values in the ANOVA analyses.

Results

The outcomes of all the behavioral evaluation tasks are presented in Table 2. The DMS task had a simultaneous condition and 3 delay periods (0, 4, and 12 s), depending on the presentation of the sample stimulus, and results were also averaged across these four conditions.

Accuracy varied considerably across the tasks, from around 30 % for the S2B task to close to 100 % for the DMS task (simultaneous condition). Performance improved for nearly all tasks from the baseline behavioral evaluation to the follow-up behavioral evaluation after TMS intervention. This includes improvements in accuracy and reduction of most latencies. The only 3 cases with no improvement in accuracy were the DSP task for the sham TMS group with unchanged performance (5.47 span length), the DMS task for the active TMS group with a slight drop in performance (from 98 to 97.33 %; simultaneous condition), and the DMS task for the sham TMS group with unchanged performance (82 %, 0 s delay condition). The only 3 cases with no improvement in latency were the DMS task for both the active TMS group (3.71 s unchanged; simultaneous condition) and the sham TMS group (from 3.78 to 3.91 s for the simultaneous condition; and from 3.70 to 3.75 s for the 0 s delay condition).

None of the baseline *t* tests were statistically significant, indicating no performance difference between the active and sham TMS groups in the baseline period (Supplemental Table 1). As expected, the two groups had comparable baseline behavioral evaluation given their matched demographic information.

Outcome measures were then used as independent variables for mixed-designs ANOVAs with between-subject factor Treatment (Active vs. Sham TMS) and within-subject factor Time (baseline vs. post-intervention measurement). Table 3 lists *F* tests and significance values for all main effects and interactions. Supplemental Table 2 lists detailed results on all DMS conditions (averaged, simultaneous, and 3 delay periods). Participants had significant Time main effects of improved performance in several tasks, both for accuracy (DSP, S2B, PRM, SRM, DMS) and latency of response (PRM, SRM). Results had no significance only for the SSP and SOC task.

TMS intervention affected behavior only if the interaction Time × Treatment was significant. We found two such tasks with significant Time × Treatment interactions, the

Table 2 Outcome measures of behavioral evaluation tasks

Test	Outcome measure	Active TMS group		Sham TMS group	
		Baseline	Post-intervention	Baseline	Post-intervention
DSP	Span length	5.47 (0.34)	6.60 (0.36)	5.47 (0.40)	5.47 (0.36)
S2B	Accuracy (%)	32.67 (7.88)	47.17 (9.32)	28.67 (5.21)	30.00 (5.37)
DMS (ave)	Accuracy (%)	87.80 (1.77)	91.17 (1.56)	80.80 (3.49)	87.17 (2.35)
	Latency (s)	4.15 (0.45)	3.78 (0.31)	4.03 (0.47)	3.94 (0.40)
DMS (simult.)	Accuracy (%)	98.00 (1.07)	97.33 (1.53)	92.67 (3.30)	96.67 (1.59)
	Latency (s)	4.13 (0.55)	3.52 (0.38)	3.78 (0.49)	3.91 (0.56)
DMS (0 s)	Accuracy (%)	85.33 (2.74)	87.33 (2.28)	82.00 (4.70)	82.00 (3.55)
	Latency (s)	3.71 (0.51)	3.71 (0.30)	3.70 (0.47)	3.75 (0.59)
DMS (4 s)	Accuracy (%)	88.00 (2.96)	90.67 (2.67)	77.33 (4.19)	83.33 (3.19)
	Latency (s)	4.17 (0.38)	3.59 (0.35)	3.92 (0.43)	3.65 (0.39)
DMS (12 s)	Accuracy (%)	80.67 (4.31)	88.00 (2.62)	72.00 (4.70)	85.33 (3.89)
	Latency (s)	4.62 (0.47)	4.34 (0.26)	4.64 (0.58)	4.32 (0.56)
PRM	Accuracy (%)	85.60 (1.73)	89.69 (1.67)	85.60 (2.17)	89.14 (2.15)
	Latency (s)	2.31 (0.14)	1.93 (0.11)	2.21 (0.20)	1.83 (0.18)
SRM	Accuracy (%)	74.67 (4.04)	79.33 (3.96)	73.67 (3.18)	79.00 (3.02)
	Latency (s)	2.87 (0.27)	1.80 (0.11)	2.37 (0.28)	1.82 (0.20)
SSP	Span length	6.20 (0.37)	6.53 (0.42)	5.87 (0.38)	6.00 (0.38)
	Total error	14.40 (1.25)	14.07 (2.22)	13.53 (1.19)	11.27 (0.60)
SOC	Problems solved with minimum moves (%)	59.05 (3.23)	66.67 (2.58)	58.10 (3.81)	61.90 (3.39)
	Mean initial thinking time (s)	4.70 (0.75)	3.60 (0.55)	2.78 (0.37)	2.21 (0.41)

Values are means across participants with standard errors in brackets

DSP digit span task, *S2B* spatial 2-back task, *DMS* delayed match to sample task, *PRM* pattern recognition memory task, *SSP* spatial span task, *SRM* spatial recognition memory task, *SOC* stockings of Cambridge task

DSP task ($F_{(1,28)} = 13.669$, $p = 0.008$, FDR corrected) and the S2B task ($F = 7.085$, $p = 0.049$, FDR corrected). Post hoc *t* tests presented in Fig. 2 showed that participants benefited with TMS intervention for both the DSP and S2B tasks, while the sham TMS group had no or minor change in performance, respectively. No other Time × Treatment interactions were significant.

In some behavioral tests, the observed variables included both response speed and response accuracy. To examine for possible speed–accuracy trade-offs, we designed new dependent variables by dividing latencies by accuracy outcomes within each task and repeated the same mixed-design ANOVA analyses. Results showed no significant Time × Treatment interactions (Supplemental Table 3), and thus, we did not proceed with further investigation using diffusion model analysis (Wagenmakers et al. 2007).

Discussion

We have shown that high-frequency rTMS treatment of the left DLPFC enhanced cognitive performance in healthy individuals in two cognitive tasks: the digit span (DSP) and the spatial 2-back (S2B) tasks. We observed practice effects but no TMS effects in the rest of the investigated cognitive tasks.

For the DSP task, we administered the verbal span-forward version, which is a measure of attention and capacity of short-term memory (Aben et al. 2012). Thus, the improved DSP performance reflects enhanced verbal WM capacity following TMS stimulation of left DLPFC. In contrast, we observed no capacity enhancement for the SSP task, which is also a span task but on visuospatial material. This verbal/visuospatial distinction is consistent with the *dual-coding theory*, which postulates left hemisphere dominance in verbal processing, while the right hemisphere has an advantage in nonverbal tasks (Paivio 1991). In support, several authors have reported that the right but not left DLPFC facilitates the encoding of visuospatial and visual object associations (Epstein et al. 2002), and the left but not right DLPFC facilitates the encoding of verbal material (Floel et al. 2004; Skrdlantova et al. 2005).

For the S2B task, which also showed significant TMS-related performance enhancement, we administered a visuospatial version with possible stimulus locations arranged in a regular grid on the screen. The n-back task is thought to

Table 3 TMS treatment effects on behavioral outcomes

Dependent variable	Effect	$F_{(1,28)}$	p value	p adjusted (FDR)	Observed power
DSP: span length	Time	13.669	0.001	**0.008***	0.946
	Treatment	1.31	0.262	0.542	0.198
	Time × Treatment	13.669	0.001	**0.008***	0.946
S2B: accuracy	Time	10.246	0.003	**0.018***	0.871
	Treatment	1.162	0.290	0.544	0.180
	Time × Treatment	7.085	0.013	**0.049***	0.729
PRM: accuracy	Time	9.969	0.004	**0.020***	0.862
	Treatment	0.012	0.913	0.945	0.051
	Time × Treatment	0.051	0.823	0.945	0.055
PRM: latency	Time	25.827	<0.001	**0.008***	0.998
	Treatment	0.246	0.624	0.780	0.077
	Time × Treatment	<0.001	0.984	0.984	0.050
SRM: accuracy	Time	7.787	0.009	**0.039***	0.768
	Treatment	0.020	0.889	0.945	0.052
	Time × Treatment	0.035	0.854	0.944	0.054
SRM: latency	Time	26.883	<0.001	**0.008***	0.999
	Treatment	0.735	0.399	0.640	0.131
	Time × Treatment	2.904	0.099	0.248	0.377
SSP: span length	Time	1.260	0.271	0.542	0.192
	Treatment	0.377	0.544	0.710	0.091
	Time × Treatment	0.140	0.711	0.853	0.065
SSP: total error	Time	1.075	0.309	0.545	0.170
	Treatment	1.313	0.262	0.542	0.198
	Time × Treatment	0.595	0.447	0.640	0.116
SOC: problems solved	Time	5.929	0.022	0.060	0.652
	Treatment	0.509	0.481	0.656	0.106
	Time × Treatment	0.659	0.424	0.640	0.123
SOC: initial thinking time	Time	5.886	0.022	0.060	0.649
	Treatment	5.879	0.022	0.060	0.648
	Time × Treatment	0.592	0.448	0.640	0.115

Mixed-design ANOVA results show main effects and interactions on factors Treatment and Time. The symbol (*) indicates statistical significance corrected with false discovery rate at a 0.05 level

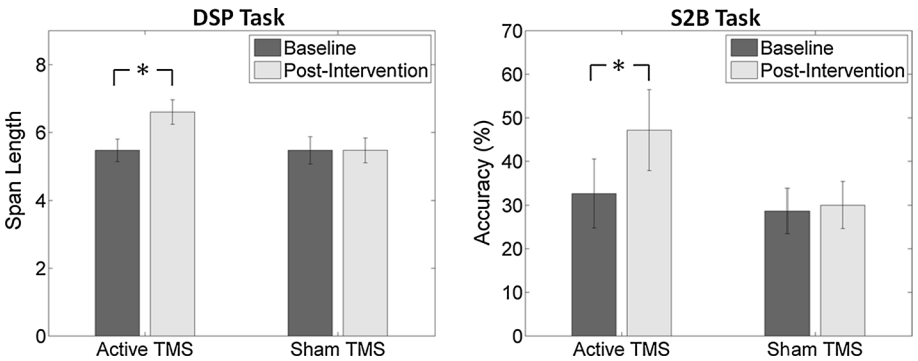

Fig. 2 Active TMS treatment significantly improved behavioral outcomes in both the DSP and S2B tasks. For the DSP task, the active TMS group significantly increased span length [one-sample two-sided t test $t_{(14)}$ 4.79; 95 % CI for difference (0.62, 1.64); p <0.001], whereas there was no change in the sham TMS group [$t_{(14)}$ 0; 95 % CI (−0.42, 0.42); p 1]. For the S2B task, the active TMS group significantly increased accuracy [$t_{(14)}$ 3.08; 95 % CI (4.39, 24.61); p 0.008], whereas there was no significant change in the sham TMS group [$t_{(14)}$ 0.89; 95 % CI (−1.88, 4.55); p 0.39]

tap into processes involving manipulation and maintenance of information in WM. Although it is widely assumed that the verbal and spatial versions of the task recruit verbal and spatial cognitive processes, respectively, such strict domain distinction has been challenged. In particular, task analysis has shown that the n-back task may always recruit both verbal and spatial processes (Meegan and Honsberger 2005; Chen and Mitra 2009). In our S2B task, stimulus locations could have been verbalized, making the task less of a pure assessment of spatial WM. Thus, S2B task enhancement would still be consistent with left DLPFC dominance for verbal content posited by the dual-coding theory.

In our study, performance enhancement effects in most tasks were explained by practice effects (Time factor main effect). The reasons we did not observe significant TMS effects in these cognitive tests could be twofold: (a) type of material and (b) cognitive load.

First, regarding the type of material, the tasks with no TMS effects involved visuospatial or visual object memory, which according to the dual-coding theory are not supported by the left DLPFC (Paivio 1991).

Second, it is possible that tasks demanding higher cognitive load, such as DSP and S2B, may be more amenable to cognitive enhancement than tasks with low cognitive load which already have near ceiling performance. In our study, the tasks from the CANTAB battery, showed no significant TMS effects. Neurophysiological test batteries, such as CANTAB, are optimized to evaluate neuropsychiatric patients and clinical interventions rather than healthy individuals (Lowe and Rabbitt 1998). As a result, they are designed for high baseline performance by healthy controls to maximize detection of cognitive deficits and limit significant practice effects that compromise comparisons on repeated testing (Lowe and Rabbitt 1998). Indeed, Table 2 lists high accuracy for most of the CANTAB tests, close to or exceeding 90 % for the DMS and PRM tasks, 75–80 % for the SRM task, and ceiling for the SSP. Though most tests showed practice effects, they were small not even reaching statistical significance for some tasks. Repetitive TMS may prove more effective on performance enhancement as task difficulty increases (Barr 2013), as in the case of the DSP and S2B tasks. We note that CANTAB test performance reported here was comparable to prior studies for all tests (Lowe and Rabbitt 1998; Dickstein et al. 2004; Tavares et al. 2007).

Despite mixed results for healthy participants, a number of promising rTMS studies have shown beneficial WM effects in neuropsychiatric patients, both for depression (O'Connor et al. 2003; Fabre et al. 2004; Hausmann et al. 2004; Schulze-Rauschenbach et al. 2005; Boggio et al. 2005; Kuroda et al. 2006; Bloch et al. 2008; Vanderhasselt et al. 2009; Guse et al. 2010) and schizophrenia (Demirtas-Tatlidede et al. 2013; Levkovitz et al. 2011; Barr et al. 2013). Compromised cortical activity of neuropsychiatric patients, associated with hypo-dopaminergic states (Stahl 2013) and neurophysiological inhibitory deficits (Radhu et al. 2013), may explain these findings. It thus remains possible that TMS primarily offers neuronal modulation of cortical networks only when abnormal activation patterns exist.

This could point to the inverse-U pattern, a general principle found in several neural systems (Quednow 2010). According to this principle, enhancement is only possible if the neuronal system is in a compromised or suboptimal state, such as reduced arousal, vigilance, or neurotransmitter levels. Interventions can enhance performance, but beyond a point they may also have adverse effects. For example, very low doses of D1 agonist improve working memory performance in monkeys, while higher doses worsen performance (Arnsten and Li 2005). A healthy brain is already optimally tuned and thus difficult to enhance, with effects generally weak and difficult to detect as in the present study.

Demonstrating WM enhancement in healthy individuals through rTMS stimulation of the DLPFC has been an elusive goal with prior studies offering mixed results. Guse et al. (2013) found no significant 10 Hz rTMS-related effects on a verbal 2-back task for either schizophrenic or control subjects. Similarly, Gaudeau-Bosma et al. (2012) found no significant 10 Hz rTMS-related effects on a verbal 2-back task though they identified neural correlates in the bilateral middle frontal gyrus and in the left caudate nucleus. Although both of these studies targeted the left DLPFC with more intensive TMS protocols than our study (higher intensity pulses; more pulses/session; equal or more sessions), they reported negative findings, which could be explained by the lower cognitive load necessitated by their 2-back tasks (slower stimulus presentation adapted for fMRI acquisition; and near ceiling performance). In contrast, Esslinger et al. (2014) reported significantly shorter reaction times during an n-back task after 5 Hz rTMS on the right DLPFC; Preston et al. (2010) reported faster performance on a Sternberg task (verbal WM task) after 10 Hz rTMS of both left and right DLPFC, and Hoy et al. (2015) reported improved accuracy on a verbal 2-back task following a theta-burst stimulation protocol. All these studies used a single-session TMS protocol, and the cognitive load of the tasks in at least two of these studies is comparable to ours [same stimulus presentation times for Esslinger et al. (2014) and Hoy et al. (2015)].

The exact functional specialization of DLPFC remains controversial, though it is widely accepted that DLPFC exerts executive control on the WM system. DLPFC has been associated with the encoding and retrieval phases of WM tasks (Balconi 2013), and consistent evidence implicates parietal areas in the actual storage of information

(Edin et al. 2009). DLPFC may regulate the signal-to-noise ratio of the parietal cortex to enable increased storage capacity (Edin et al. 2009). Prior electrophysiological studies have shown that high-frequency rTMS can entrain endogenous alpha frequency in the stimulated area, which then leads to suppression of distracters and thus enhancement of WM capacity (Sauseng et al. 2009; Hamidi et al. 2009; Thut and Miniussi 2009; Klimesch et al. 2003). Other evidence points to the executive role of DLPFC in suppressing interfering task-irrelevant information (Sandrini et al. 2008) and updating goal representations based on context information or task-related demands (Brunoni 2014; Barch et al. 2003). Our study design used offline rTMS stimulation, aiming to demonstrate WM improvements after multiple sessions of TMS treatment in healthy individuals. Our results indicate that stimulation of left DLPFC improved performance of updating and monitoring of spatial information in the S2B task, confirming the central executive role of DLPFC in WM. Importantly, we also observed enhanced capacity in the DSP task, suggesting that left DLPFC might also be involved in the control of pure storage by filtering out distracters and top-down control.

The time scale during which TMS produces detectable neuronal effects can vary considerably. Immediate neural effects include acute and transient changes in the electrical state of the stimulated neurons (Chervyakov et al. 2015). In addition, repetitive TMS causes slow and long-lasting neuroplastic changes of the stimulated area following multiple TMS treatment sessions. These include neurotransmitter regulation of the dopaminergic (Strafella et al. 2001; Cho and Strafella 2009; Ko et al. 2008) and adrenergic system (Lisnaby and Belmaker 2000), as well as gene expression (Hausmann et al. 2000; Funamizu et al. 2005) and morphological regulation (Fujiki et al. 2003). TMS stimulation causes not only local physical effects, but also excitation of remote brain areas and modulation of long-distance functional connectivities. For example, studies have reported increases in fronto-parietal theta synchronization and parietal gamma band power (Hoy et al. 2015), and anterior cingulate cortex activation (Gaudeau-Bosma et al. 2013; Esslinger et al. 2014) following stimulation of the left DLPFC using TMS protocols similar to our study. Such network changes confound direct interpretation of results, since stimulation of a single cortical site can influence entire brain networks.

Finally, even when following the strict safety guidelines for TMS, general and transient side effects such as headache, mood changes, and tinnitus have been reported (Krishnan et al. 2015). The most serious adverse event of TMS is the risk of triggering epileptic seizures (Bostrom and Sandberg 2009) which can be less than 1/1000 (Machii, et al. 2006) in healthy subjects (Machii et al. 2006; Rossi et al. 2009; Krishnan et al. 2015). In this study, we used previously established safe TMS protocols (10 Hz frequency; 100 % motor threshold intensity; long inter-train interval). Though we observed some cognitive enhancement effects, we also recorded side effects in some participants, most prominently higher mood in 3 participants following a few repeated stimulation sessions. Given that all medical interventions carry some risk, and that the enhancement benefits may often be more subjective and value-dependent than the benefits of being cured of a disease, this can raise the issue of ethical relevance for TMS cognitive enhancement strategies in healthy subjects.

Conclusion

We have successfully demonstrated working memory beneficial effects with offline rTMS on the left DLPFC of healthy individuals. Performance improvements were observed in tasks involving both verbal and visuospatial material. Our encouraging results will hopefully motivate more comprehensive studies aiming to conclusively validate TMS as a beneficial intervention for WM enhancement in healthy individuals.

Acknowledgments We are grateful to Santani Teng for assistance in editing this manuscript.

References

Aben B, Stapert S, Blokland A (2012) About the distinction between working memory and short-term memory. Front Psychol 3(301):1–9

Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 4(2):84–89

Arnsten AF, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 57(11):1377–1384

Balconi M (2013) Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. Neurosci Bull 29(3):381–389

Barch DM, Sheline YI, Csernansky JG, Snyder AZ (2003) Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol Psychiatry 53(5):376–384

Barr MS, Farzan F, Rajji TK, Voineskos AN, Blumberger DM, Arenovich T, Fitzgerald PB, Daskalakis ZJ (2013) Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. Biol Psychiatry 73(6):510–517

Beam W, Borckardt JJ, Reeves ST, George MS (2009) An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2(1):50–54

Bloch Y, Grisaru N, Harel EV, Beitler G, Faivel N, Ratzoni G, Stein D, Levkovitz Y (2008) Repetitive transcranial magnetic stimulation

in the treatment of depression in adolescents: an open-label study. J ECT 24(2):156–159
Boggio PS, Fregni F, Bermpohl F, Mansur CG, Rosa M, Rumi DO, Barbosa ER, Rosa MO, Pascual-Leone A, Rigonatti SP, Marcolin MA, Araujo Silva MT (2005) Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord 20(9):1178–1184
Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J (2001) Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology 56(4):526–528
Bostrom N, Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges. Sci Eng Ethics 15(3):311–341
Brunoni AR, Vanderhasselt MA (2014) Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 86:1–9
Chen YN, Mitra S (2009) The spatial-verbal difference in the n-back task: an ERP study. Acta Neurol Taiwanica 18(3):170–179
Chervyakov A, Sinitsyn D, Chernyavsky A, Piradov M (2015) Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. Front Hum Neurosci 9:303
Cho SS, Strafella AP (2009) rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS One 4(8):e6725
D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J (1998) Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res 7(1):1–13
De Jongh R, Bolt I, Schermer M, Olivier B (2008) Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. Neurosci Biobehav Rev 32(4):760–776
Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A (2013) Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 64:566–578
Dickstein DP, Treland JE, Snow J, McClure EB, Mehta MS, Towbin KE, Pine DS, Leibenluft E (2004) Neuropsychological performance in pediatric bipolar disorder. Biol Psychiatry 55(1):32–39
Dresler M, Sandberg A, Ohla K, Bublitz C, Trenado C, Mroczko-Wąsowicz A, Kuhn S, Repantis D (2013) Non-pharmacological cognitive enhancement. Neuropharmacology 64:529–543
Edin F, Klingberg T, Johansson P, McNab F, Tegnér J, Compte A (2009) Mechanism for top-down control of working memory capacity. Proc Natl Acad Sci 106(16):6802–6807
Epstein CM, Sekino M, Yamaguchi K, Kamiya S, Ueno S (2002) Asymmetries of prefrontal cortex in human episodic memory: effects of transcranial magnetic stimulation on learning abstract patterns. Neurosci Lett 320(1):5–8
Esslinger C, Schüler N, Sauer C, Gass D, Mier D, Braun U, Ochs E, Schulze T, Rietschel M, Kirsh P, Meyer-Lindenberg A (2014) Induction and quantification of prefrontal cortical network plasticity using 5 Hz rTMS and fMRI. Hum Brain Mapp 35(1):140–151
Fabre I, Galinowski A, Oppenheim C, Gallarda T, Meder JF, De Montigny C, Olie JP, Poirier MF (2004) Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: an open trial. Int J Geriatr Psychiatry 19(9):833–842
Floel A, Poeppel D, Buffalo EA, Braun A, Wu CWH, Seo HJ, Stefan K, Knecht S, Cohen LG (2004) Prefrontal cortex asymmetry for memory encoding of words and abstract shapes. Cereb Cortex 14(4):404–409
Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 3(7):383–393
Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcoli MA, Rigonatti SP, Silva MTA, Paulus W, Pascual-Leone A (2005) Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166(1):23–30
Fujiki M, Kobayashi H, Abe T, Kamida T (2003) Repetitive transcranial magnetic stimulation for protection against delayed neuronal death induced by transient ischemia. J Neurosurg 99(6):1063–1069
Funamizu H, Ogiue-Ikeda M, Mukai H, Kawato S, Ueno S (2005) Acute repetitive transcranial magnetic stimulation reactivates dopaminergic system in lesion rats. Neurosci Lett 383(1):77–81
Gaudeau-Bosma C, Moulier V, Allard AC, Sidhoumi D, Bouaziz N, Braha S, Volle E, Januel D (2013) Effect of two weeks of rTMS on brain activity in healthy subjects during an n-back task: a randomized double blind study. Brain Stimul 6(4):569–575
Gazzaley A, Nobre AC (2012) Top-down modulation: bridging selective attention and working memory. Trends Cogn Sci 16(2):129–135
Grosbras MH, Paus T (2002) Transcranial magnetic stimulation of the human frontal eye field: effects on visual perception and attention. J Cogn Neurosci 14(7):1109–1120
Guse B, Falkai P, Wobrock T (2010) Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J Neural Transm 117(1):105–122
Guse B, Falkai P, Gruber O, Whalley H, Gibson L, Hasan A, Obst K, Dechent P, Mclntosh A, Suchan B, Wobrock T (2013) The effect of long-term high frequency repetitive transcranial magnetic stimulation on working memory in schizophrenia and healthy controls—a randomized placebo-controlled, double-blind fMRI study. Behav Brain Res 237:300–307
Hamidi M, Slagter HA, Tononi G, Postle BR (2009) Repetitive transcranial magnetic stimulation affects behavior by biasing endogenous cortical oscillations. Front Integr Neurosci 3(14):1–12
Hausmann A, Weis C, Marksteiner J, Hinterhuber H, Humpel C (2000) Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus. Mol Brain Res 76(2):355–362
Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler K, Lechner T, Walsh T, Deisenhammer EA, Kofler M, Rupp CI, Hinterhuber H, Conca A (2004) No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. J Neurol Neurosurg Psychiatry 75(2):320–322
Hilgetag CC, Théoret H, Pascual-Leone A (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 4(9):953–957
Hill EL (2004) Executive dysfunction in autism. Trends Cogn Sci 8(1):26–32
Hodsoll J, Mevorach C, Humphreys GW (2009) Driven to less distraction: rTMS of the right parietal cortex reduces attentional capture in visual search. Cereb Cortex 19(1):106–114
Hoy KE, Fitzgerald PB (2010) Brain stimulation in psychiatry and its effects on cognition. Nat Rev Neurol 6(5):267–275
Hoy KE, Bailey N, Michael M, Fitzgibbon B, Rogasch NC, Saeki T, Fitzgerald PB (2015) Enhancement of working memory and task-related oscillatory activity following intermittent theta burst stimulation in healthy controls. Cerebral Cortex doi:10.1093/cercor/bhv193
Kirschen MP, Davis-Ratner MS, Jerde TE, Schraedley-Desmond P, Desmond JE (2006) Enhancement of phonological memory following transcranial magnetic stimulation (TMS). Behav Neurol 17(3–4):187–194

Klimesch W, Sauseng P, Gerloff C (2003) Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur J Neurosci 17(5):1129–1133

Ko JH, Monchi O, Ptito A, Bloomfield P, Houle S, Strafella AP (2008) Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task—a TMS-[11C] raclopride PET study. Eur J Neurosci 28(10):2147–2155

Kojima S, Goldman-Rakic PS (1982) Delay-related activity of prefrontal neurons in rhesus monkeys performing delayed response. Brain Res 248(1):43–50

Koski L, Molnar-Szakacs I, Iacoboni M (2005) Exploring the contributions of premotor and parietal cortex to spatial compatibility using image-guided TMS. Neuroimage 24(2):296–305

Krishnan C, Santos L, Peterson MD, Ehinger M (2015) Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul 8(1):76–87

Kuroda Y, Motohashi N, Ito H, Ito S, Takano A, Nishikawa T, Suhara T (2006) Effects of repetitive transcranial magnetic stimulation on [11 C] raclopride binding and cognitive function in patients with depression. J Affect Disord 95(1):35–42

Levkovitz Y, Rabany L, Harel EV, Zangen A (2011) Deep transcranial magnetic stimulation add-on for treatment of negative symptoms and cognitive deficits of schizophrenia: a feasibility study. Int J Neuropsychopharmacol 14(7):991–996

Lisanby SH, Belmaker RH (2000) Animal models of the mechanisms of action of repetitive transcranial magnetic stimulation(RTMS): comparisons with electroconvulsive shock(ECS). Depress Anxiety 12(3):178–187

Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA (2001) Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry 49(5):460–463

Lowe C, Rabbitt P (1998) Test re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Neuropsychologia 36(9):915–923

Luber B, Lisanby SH (2014) Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 85:961–970

Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A (2006) Safety of rTMS to non-motor cortical areas in healthy participants and patients. Clin Neurophysiol 117(2):455–471

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000) Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 133(4):425–430

McKinley RA, Bridges N, Walters CM, Nelson J (2012) Modulating the brain at work using noninvasive transcranial stimulation. Neuroimage 59(1):129–137

Meegan DV, Honsberger MJ (2005) Spatial information is processed even when it is task-irrelevant: implications for neuroimaging task design. NeuroImage 25(4):1043–1055

O'Connor M, Brenninkmeyer C, Morgan A, Bloomingdale K, Thall M, Vasile R, Leone AP (2003) Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk–benefit analysis. Cogn Behav Neurol 16(2):118–127

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1):97–113

Owen AM, Evans AC (1996) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cerebral Cortex 6(1):31–38

Owen AM, McMillan KM, Laird AR, Bullmore E (2005) N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25(1):46–59

Paivio A (1991) Dual coding theory: retrospect and current status. Can J Psychol 45(3):255

Pascual-Leone A, Hallett M (1994) Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. NeuroReport 5(18):2517–2520

Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD (1998) Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 15(4):333–343

Preston G, Anderson E, Silva C, Goldberg T, Wassermann EM (2010) Effects of 10 Hz rTMS on the neural efficiency of working memory. J Cogn Neurosci 22(3):447–456

Quednow BB (2010) Ethics of neuroenhancement: a phantom debate. BioSocieties 5(1):153

Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ (2013) A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clin Neurophysiol 124(7):1309–1320

Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P (1994) Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dement Geriatr Cogn Disord 5(5):266–281

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12):2008–2039

Sandberg A, Bostrom N (2006) Converging cognitive enhancements. Ann N Y Acad Sci 1093(1):201–227

Sandrini M, Rossini PM, Miniussi C (2008) Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: rTMS evidence. Neuropsychologia 46(7):2056–2063

Sauseng P, Klimesch W, Heise KF, Gruber WR, Holz E, Karim AA, Hummel FC (2009) Brain oscillatory substrates of visual short-term memory capacity. Curr Biol 19(21):1846–1852

Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M (2005) Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. Br J Psychiatry 186(5):410–416

Skrdlantova L, Horacek J, Dockery C, Lukavsky J, Kopecek M, Preiss M, Novak T, Hoschl C (2005) The influence of low-frequency left prefrontal repetitive transcranial magnetic stimulation on memory for words but not for faces. Physiol Res 54(1):123–128

Snyder AW, Mulcahy E, Taylor JL, Mitchell DJ, Sachdev P, Gandevia SC (2003) Savant-like skills exposed in normal people by suppressing the left fronto-temporal lobe. J Integrat Neurosci 2(02):149–158

Stahl SM (2013) Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge University Press, Cambridge

Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 21(15):1–4

Taghavi SMR (2002) Validity and reliability of the general health questionnaire (ghq-28) in college students of Shiraz University. J Psychol 5(4):381–398

Tavares JVT, Clark L, Cannon DM, Erickson K, Drevets WC, Sahakian BJ (2007) Distinct profiles of neurocognitive function in unmedicated unipolar depression and bipolar II depression. Biol Psychiatry 62(8):917–924

Tegenthoff M, Ragert P, Pleger B, Schwenkreis P, Forster A, Nicolas V, Dinse HR (2005) Improvement of tactile discrimination performance and enlargement of cortical somatosensory maps after 5 Hz rTMS. PLoS Biol 3(11):2031

Thut G, Nietzel A, Pascual-Leone A (2005) Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. Cereb Cortex 15(5):628–638

Thut G, Miniussi C (2009) New insights into rhythmic brain activity from TMS–EEG studies. Trends in Cognitive Sciences 13(4):182–189

Vanderhasselt MA, De Raedt R, Leyman L, Baeken C (2009) Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. J Psychiatry Neurosci 34(2):119

Wagenmakers EJ, Van Der Maas HL, Grasman RP (2007) An EZ-diffusion model for response time and accuracy. Psychon Bull Rev 14(1):3–22

Wager TD, Smith EE (2003) Neuroimaging studies of working memory. Cogn Affect Behav Neurosci 3(4):255–274

Walsh V, Ellison A, Battelli L, Cowey A (1998) Task–specific impairments and enhancements induced by magnetic stimulation of human visual area V5. Proc R Soc Lond B Biol Sci 265(1395):537–543

Wechsler D (1981) The psychometric tradition: developing the Wechsler adult intelligence scale. Contemp Educ Psychol 6(2):82–85

Yekutieli D, Benjamini Y (1999) Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. J Stat Plan Infer 82(1–2):171–196

Young RL, Ridding MC, Morrell TL (2004) Switching skills on by turning off part of the brain. Neurocase 10(3):215–222

Zanto TP, Rubens MT, Thangavel A, Gazzaley A (2011) Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. Nat Neurosci 14(5):656–661