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The Effects of Transcranial Magnetic Stimulation (TMS) Over Prefrontal Cortex, Temporal Lobe and Cerebellar on Verbal Working Memory: A Systematic Review

Weiqi Li[1,a]

[1] *Department of Psychology, Durham University, Durham, United Kingdom*

[a] *862076453@qq.com*

ABSTRACT
Transcranial magnetic stimulation (TMS) is a safe and non-invasive brain stimulation technique, which has been widely used to draw causal links between brain regions and specific behaviours during the past decades. By using TMS, recent studies have demonstrated that prefrontal cortex, temporal lobe and cerebellar are taking part in processing verbal working memory. However, inconsistent results were reported from such experiments. The current study aimed to perform a systematic review on the use of TMS exploring the involvements of prefrontal cortex, temporal lobe and cerebellar in verbal working memory. The databases we used were Web of Science, PubMed and Google Scholar. We searched for the studies that applied TMS over the prefrontal cortex, temporal lobe or cerebellar published from 2000 January. In total, ten studies were included. Result showed that temporal disruption of prefrontal or temporal cortex induced by low-frequency rTMS significantly impaired verbal working memory performance, while high-frequency rTMS applied over dlPFC. Significantly improved verbal working memory performance. The studies on cerebellar were limited, so only one study was included. It showed that participants made more error responses after theta burst stimulation. Overall, these results indicated that the engagement of prefrontal cortex, temporal lobe and cerebellar was indispensable to verbal WM performance. However, the results in cerebellar must be interpreted cautiously given limited results and uncomfortable feeling of participants.

***Keywords**: Repetitive transcranial magnetic stimulation, verbal working memory, prefrontal cortex, temporal lobe, cerebellar*

1. INTRODUCTION

Working memory (WM) is a memory system and active processor which has been often considered to include visual and verbal components and has limited capacity. Baddeley and Hitch developed a working memory model constituted by three parts: Central Executive, Phonological Loop， and Visuo-Spatial Sketchpad (Baddeley & Hitch, 1974) [1]. Central Executive has been usually considered as a “leader” for controlling and manipulating information. Visuospatial Sketchpad has been considered processes spatial information. Phonological loop has been considered processing acoustic information (i.e., verbal working memory) and divides into the subvocal rehearsal system and phonological store which can rehearse the verbal information by repeating it for preventing the verbal information decay over time. In 2000, Baddeley [2] added a new part called Episodic Buffer for keeping and gathering the information from the other parts.

Existing neuroimaging studies already provided some evidence about the role of brain areas in prefrontal cortex (PFC), temporal lobe and cerebellar (e.g., Mottaghy et al., 2000; Tomlinson et al., 2014; Acheson et al., 2011) [3], [4], [5].

Previous studies have demonstrated that the prefrontal cortex plays a critical role in several cognitive functions, such as memory, sensory, and attention (for review, see Miller, 2000) [6]. For example, Barbey et al. (2013) [7] investigated 19 patients who got damage in the dorsolateral prefrontal cortex (dlPFC). The result showed that there was no significant group difference in most tasks (e.g., 0,1,2,3 Back, Spatial and Digit Span Forward). However, they found that patients with dlPFc damage were shown the deficiency in the verbal WM tasks such as mental arithmetic test. Therefore, they assumed that impaired verbal and spatial WM is associated with dlPFC damage.

Previous studies also found that the temporal lobe may associate with verbal working memory (e.g., Smith & Jonides, 1999) [8]. Functional imaging studies have reported the activation in supramarginal gyrus (SMG) during verbal working memory tasks (e.g., Yen & DeMarco &Wilson, 2019) [9]. Left SMG showed a stronger correlation than the right SMG. According to Oberhubber et al. (2016) [10], they applied fMRI over the SMG with 85 healthy subjects. They concluded when the subjects were doing the verbal working memory tasks, activation was detected. Although these studies gave the evidence of temporal lobe taking part in verbal working memory, it is hard to speculate the absolute correlation without the supporting from further study.

The cerebellar is a softball-sized structure attached to the bottom of the brain, which is involved in a wide range of tasks, including sensorimotor control, language, emotional processing, and spatial and higher-level cognitive functions (see Ackermann, Mathiak, & Riecker, 2007; Stoodley & Schmahmann, 2009 for reviews) [11], [12]. More recently, some brain imaging studies have found that the cerebellar might contribute to language processing (e.g., Desmond & Chen & Shieh, 2005; Pleger & Timmann, 2018) [13], [14]. One of the functional imaging studies found that the right cerebellar hemisphere may take part in verbal information processing (e.g., Stoodley and Schmahmann, 2009) [11]. Furthermore, Baillieux et al. (2010) [15] claimed that the patient with cerebellar damage in the right hemisphere showed less accuracy than the other cerebellar damage patient in verbal working memory tasks. Its worthy to mention that the left cerebellar hemisphere takes part in some auditory information process including verbal working memory (Hokkanen et al.,2006; Scott et al., 2001; Marine et al.,2001) [16], [17], [18]. One of the possible reasons is left cerebellar hemisphere can be the 'cannel' for transport verbal working memory. All in all, the cerebellar (particularly the right cerebellar hemisphere) seems like taking part in verbal working memory.

Recently, repetitive transcranial magnetic stimulation (rTMS) provided the new opportunities to investigate working memory. rTMS has been demonstrated to successfully cause temporal interference (lesion) in the target brain area. In most of the brain area, when applying rTMS with high frequency (>1Hz), or low frequency (≤1Hz) in the particular brain area, the corresponding area could be increased or decreased (for further information, see Groppa et al., 2012) [19].

Relevant rTMS studies showed different and mixed result in investigating verbal working memory. This review paper aimed to review previous research and discuss the possible role of three different brain areas (PFC, cerebellar and temporal lobe) in verbal working memory.

2. METHODS

This paper carried out a systematic review by following the data checklist based on the PRISMA guidelines (checklist provided by The PRISMA Group, Liberati et al., 2009) [20]. The method section involved three parts: literature review, eligibility criteria and quality assessment.

2.1. Literature review

A search was conducted of papers in PubMed, Web of Science published and Google Scholar. Only the papers that were available to view online were reviewed. Following keywords were used: ('Verbal Working Memory' or 'WM' or 'Working Memory') and ('non-invasive brain stimulation' or 'transcranial magnetic stimulation' or 'TMS') and ('prefrontal cortex' or 'PFC' or 'temporal lobe' or 'cerebellar')

2.2. Eligibility criteria

The articles' standard: (1) The full text is in English; (2) All the participants are healthy control; (3) Apply rTMS over prefrontal cortex, temporal lobe or cerebellum (i.e., not included research using rTMS testing in other brain areas); (4) Only involves human being subjects; (5) Use verbal WM task.

2.3. Quality assessment

For ensuring the research quality, we assessed some criteria for controlling the extraneous variables which could cause the results confounded: (1) Navigation - whether the experimenters used suitable function/technology to localize the brain areas which will be stimulated; (2) Ethic - whether the examiner considered all the ethnic factors (e.g. informed consent); (3) Using random assignment- whether the participants are randomly allocated to different conditions; (4) Sample size– whether all the samples are representative(have suitable sample size) and over eighteen years old; (5) Type of tasks-whether the examiner used suitable tasks for detecting verbal working memory; (6) Not a case study.

3. RESULT

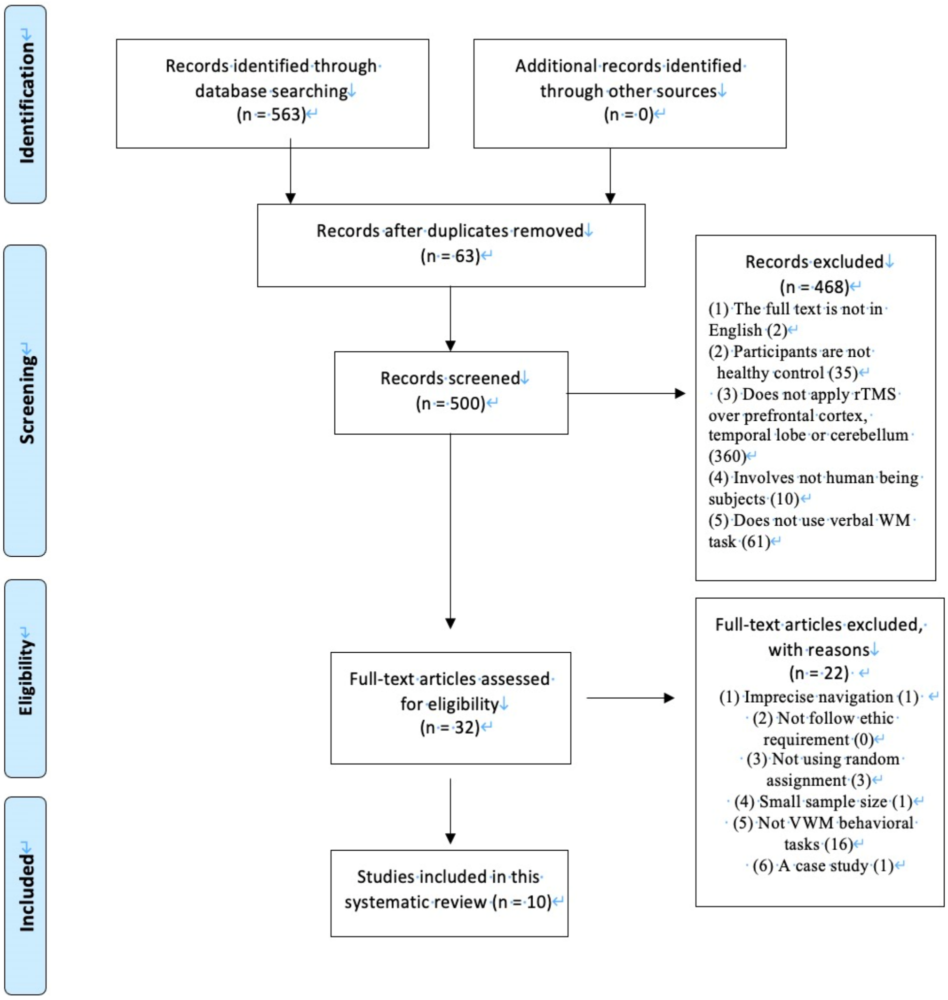

Figure 1 Data checklist

Table 1 Ten papers were included

The author and years	Design	Frequency	Target area	Number of experiments	Task	Sham	N Participants (Female)
Shields et al. (2018)	Between-subjects	1 HZ	PFC	1	n-back	Y	71(36)
Mottaghy et al. (2000)	Within-subjects	4 HZ	PFC	1	n-back	Y	14(0)
Fried et al. (2014)	Within-subjects	1 HZ	PFC	2	n-back	Y	20(17)
Turriziani et al. (2010)	Between-subjects	1 HZ	PFC	2	Study phase and a test phase	Y	62(36)
Feredoes et al. (2006)	Within-subjects	8 HZ	PFC	1	Recent Probes Task	Y	12(6)
Nixon et al. (2004)	Between-subjects	10 HZ	PFC	3	Delayed homophone test.	Y	12(6)
Soto et al. (2011)	Within-subjects	1 HZ	Temporal lobe	2	Study and memory-test phases	Y	8(4)
Acheson et al. (2011)	Within-subjects	10 HZ	Temporal lobe	2	Pace reading, Delayed serial recal and Picture naming.	Y	14(7)
Deschamps et al. (2013)	Within-subjects	1 HZ	Temporal lobe	2	n-back	Y	16(11)
Tomlinson et al. (2014)	Within-subjects	50 HZ	Cerebellar	2	Sternberg tasks	Y	16(10)

3.1. Overview

According to Figure 1, our search criteria identified 563 papers in the Web of Science/Google Scholar/PubMed database. 468 papers were excluded after the review of abstract or title because they were: (1) The full text is not in English (2); (2) Participants are not healthy control (35); (3) Does not apply rTMS over prefrontal cortex, temporal lobe or cerebellum (360); (4) Involves not human being subjects (10); (5) Does not use verbal WM task (61). Therefore, we examined the full text of 32 papers. 22 papers were excluded because they were: (1) Imprecise navigation (1); (2) Not follow ethic requirement (0); (3) Not using random assignment (3); (4) Small sample size (1); (5) Not VWM behavioral tasks (16); (6) A case study (1). Finally, 10 papers were included in this review. Most studies used a Within-subjects design. Half of the studies used low frequency of rTMS and the other half used high frequency of rTMS. Offline rTMS was chose in all the studies. The total number of participants is 245. Most of them are right-handed subjects. All the subjects were adults and above 18 years old. Based on these criteria, we assumed that the included studies could be considered of good quality.

3.2. Main Result

Three main themes emerged from our systematic review of the 10 papers (Table 2):

1) Prefrontal Cortex
2) Temporal Lobe
3) Cerebellar

3.2.1. Prefrontal Cortex

Previous studies showed that low-frequency rTMS over PFC impaired verbal WM performance. For example, Shields et al. (2018) [21] investigated the influence of rTMS over dlPFC on the n-back task performance. Shields et al. (2018) [21] claimed that in the 0-back task, participants showed no difference between absent vs. present group in zero-back task in accuracy, but there was an overall improvement in the two-back task. The study revealed a decreased reaction time (RT) in participants (Shields et al., 2018) [21]. Shields et al. (2018) [21] suggested that these results may be influenced by the practice effect (i.e., participants got practice from doing the task more than once). In further analysis (within groups analysis), participants did not show any change after receiving left stimulation but showed improvement in accuracy following sham ($p = 0.007$) and right stimulation ($p=0.001$). Furthermore, no difference was presented in RT or accuracy between the right, sham and left post-stimulation conditions (Shields et al., 2018) [21]. In addition, around 83.3% of participants exhibited impaired performance in accuracy following left post-stimulation. In contrast, one group showed impairment while the other two groups showed improvement. (Shields et al., 2018) [21]. All in all, applying rTMS over left dlPFC leaded to impaired performance of verbal working memory task. This result was also supported in the other studies. Mottaghy et al. (2000) [22] reported that participants revealed a significant increased performance in 2-back task in accuracy after receiving rTMS over right and left dlPFC. Turriziani et al. (2010) [23] reported a significant effect of rTMS on recollection. Post-hoc comparison indicated that the performance of recollection was decreased when applying rTMS over left dlPFC at the phase of encoding, but not difference was presented after applying right dlPFC. However, one study suggested the opposite results in the impact of rTMS. Fried et al. (2014) [24] reported not significant main effect of TMS, but significant interactions were found in the factors rTMS condition (i.e., vertex, left and right dlPFC) x task domain (i.e., verbal and spatial) x time (i.e., pre-stimulation and post-stimulation), thus rejecting the null hypothesis of TMS. Post-hoc comparison showed that temporally impact was not showed in rTMS of the left dlPFC or the vertex but presented in the rTMS of the right dlPFC (Fried et al., 2014) [24]. Accuracy increased on the verbal task, whereas decreased in spatial task (Fried et al., 2014) [24]. With regard to RT, there were no significant effect or TMS or task (Fried et al., 2014) [24]. Post-hoc comparison indicated that the RT of post-stimulation was quicker that pre-stimulation (Fried et al., 2014) [24].

Studies in investigating inferior frontal gyrus (IFG) also revealed that rTMS impaired verbal WM performance. For example, Feredoes et al. (2006) [25] used recent probes task and response-level conflict (RC) task for investigating the causal contribution of left IFG and left postcentral gyrus to verbal WM. In the recent probes task, accuracy data indicated that only the participants who received the rTMS over left IFG made more error responses (Feredoes et al., 2006) [25]. Three-way interaction of validity (positive, negative), region (left IFG, left postcentral gyrus, primary motor cortex and supplementary motor area) and rTMS (present, absent) was reported (Feredoes et al., 2006) [25]. Further analysis revealed that compared to rTMS over postcentral gyrus, rTMS over the left IFG impaired accuracy of recency negative probe (Feredoes et al., 2006) [25]. Feredoes et al. (2006) [25] also collected the RT data, but he did not find significant main effect or interaction of rTMS. In RC task, no significant main effect of rTMS and region was found in both RT and accuracy. However, significant two-way interaction of region (left IFG, left supplementary motor area) x rTMS (present, absent) was observed in omnibus ANOVA of the RT data. (Feredoes et al., 2006) [25]. For accuracy data, no significant interaction was found, but omnibus ANOVA showed the main effect of validity. Nixon et al. (2004) [26] looking at left IFG as well, he reported that the participants who received rTMS over left IFG revealed a significantly lower degree of accuracy on the homophone task during the delay than the participants in the control condition, but not significant at the time of the response, both tasks revealing significant higher RT in the delay and response homophone. All in all, results gave that applying rTMS over PFC leaded to an overall impaired performance in verbal working memory tasks. This supported that PFC in was very likely to take part in processing verbal working memory.

3.2.2. Temporal Lobe

In general, previous studies showed that rTMS over temporal lobe significantly affected verbal WM. For instance, one study used paced reading tasks, delayed serial recall and picture naming tasks with rTMS for testing the causal relationship in posterior superior temporal gyrus (pSTG), middle temporal gyrus (MTG) and verbal WM (Acheson et al., 2011) [27]. The result in raced reading tasks showed a TMS x Region interaction on accuracy proportion, but no main effect of region was found (Acheson et al., 2011) [27]. Post-hoc comparison showed that participants made more error after receiving rTMS over pSTG, but not in the participants who received rTMS over MTG (Acheson et al., 2011) [27]. For delayed serial recall task, ANOVA revealed that a significant TMS x Region significant interaction (Acheson et al., 2011) [27]. Post-hoc comparison revealed participants who received rTMS over pSTG were more likely to make errors, but not in the participants who received over MTG (Acheson et al., 2011) [27]. For picture naming task, the interaction did not reach significance in the study of Acheson et al. (2011) [27], but did in Mottaghy et al. (2006) [28]. Mottaghy et al. (2006) [28] suggested that rTMS decreased the RT in picture naming task. The evidence from a study of supramarginal gyrus (SMG) also supported that temporal lobe took part in processing verbal WM. Deschamps et al. (2013) [29] found a significant main effect of TMS in 2-back task, which revealed that the response accuracy in sham blocks was higher than the TMS present blocks. Significant interaction was found in Hemisphere x Group (Deschamps et al., 2013) [29]. Further analysis showed that the participants who received TMS over right SMG were significantly less accurate than the participants who received TMS over left SMG (Deschamps et al., 2013) [29]. Besides, the participants were more accurate when received Sham TMS to the left SMG as compared to real TMS to the left SMG (Deschamps et al., 2013) [29]. Main effect of TMS also found in the RT for 2-back task. Sham TMS blocks revealed significantly shorter mean RTs than the real TMS blocks (Deschamps et al., 2013) [29]. Significant interaction was observed in Hemisphere x Group. Further analyzing showed that participants who received TMS over right SMG were significantly shorter than the participants who received TMS over left SMG (Deschamps et al., 2013) [29]. All in all, these results confirmed that rTMS significantly decreased the function of temporal lobe to processing verbal working memory. The view that temporal lobe was taking part in processing verbal working memory could be made.

3.2.3. Cerebellar

For cerebellar, only one study met our review criteria. Tomlinson et al. (2014) [4] used Sternberg tasks and Theta Burst Stimulation (50Hz, cTBS) for testing both verbal and visual WM in cerebellar. Participants who received cTBS in right cerebellar performed significantly lower accuracy in the verbal task, but the participants who received cTBS in left cerebellar did not show significantly functional changing (Tomlinson et al., 2014) [4]. A significant three-way interaction between Task x Time x Site were found (Tomlinson et al., 2014) [4]. Besides, slight improving in RT was observed in the verbal task after applying the cTBS over right hemisphere, but it failed to reach significant (Tomlinson et al., 2014) [4]. The view that cerebellar takes part in processing or encoding verbal working memory cannot be confirmed by one single rTMS study. For this reason, we expected to find more studies supporting the result that Tomlinson et al. found in 2014 [4], but we cannot. The possible reason could be some of the research reported discomfortable from participants presented in the experiment's participants. For example, in one of the rTMS studies for investigating side effects of cerebellar, 1/4 subjects induced nausea (Satow et al., 2002) [30]. A similar study from Brighina et al. (2009) [31] reported mild muscular neck stiffness from 2 out of 17 participants. All in all, the uncomfortable feeling of the participants could be the main reason why the rTMS studies of cerebellar were scarcity.

4. CONCLUSION

Overall, in this review paper, we found that repetitive transcranial magnetic stimulation over prefrontal cortex and temporal lobe leaded to functional changing in verbal working memory. Most of the studies reported low-frequency rTMS significantly impaired verbal working memory performance. Besides, although a study in cerebellar suggested that right hemisphere took part in processing verbal working memory, the uncomfortable felling of the participants made this study having low reliability and validity. Thus, the view that cerebellar associates with verbal working memory cannot be confirmed.

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