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RESEARCH

Cerebellar Theta Burst Stimulation Impairs Working Memory

Nasem Raies[1,2] · Jean-François Nankoo[2] · Christopher R. Madan[3] · Robert Chen[1,2,4]

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Abstract
Working memory refers to the process of temporarily storing and manipulating information. The role of the cerebellum in working memory is thought to be achieved through its connections with the prefrontal cortex. Previous studies showed that theta burst stimulation (TBS), a form of repetitive transcranial magnetic stimulation, of the cerebellum changes its functional connectivity with the prefrontal cortex. Specifically, excitatory intermittent TBS (iTBS) increases, whereas inhibitory continuous TBS (cTBS) decreases this functional connectivity. We hypothesized that iTBS on the cerebellum will improve working memory, whereas cTBS will disrupt it. Sixteen healthy participants (10 women) participated in this study. Bilateral cerebellar stimulation was applied with a figure-of-eight coil at 3 cm lateral and 1 cm below the inion. The participants received iTBS, cTBS, and sham iTBS in three separate sessions in random order. Within 30 min after TBS, the participants performed four working memory tasks: letter 1-Back and 2-Back, digit span forward, and digit span backward. Repeated measures analysis of variance revealed a significant effect of the type of stimulation (iTBS/cTBS/Sham) on performance in the digit span backward task ($p = 0.02$). The planned comparison showed that the cTBS condition had significantly lower scores than the sham condition ($p = 0.01$). iTBS and cTBS did not affect performance in the 1- and 2-Back and the digit span forward tasks compared to sham stimulation. The findings support the hypothesis that the cerebellum is involved in working memory, and this contribution may be disrupted by cTBS.

Keywords Cerebellum · Working memory · Repetitive transcranial magnetic stimulation · Theta burst stimulation

Introduction

Working memory refers to the process responsible for temporarily storing and manipulating information. The Baddeley and Hitch [1] working memory model contains several components: the phonological loop for holding and manipulating auditory and language-related information, the visuospatial sketchpad for visual stimuli, the episodic buffer for the inter-modal transfer of information between the sketchpad and the loop, and the central executive for organizing the working memory process and controlling the other subordinate components. Lesion and functional magnetic resonance imaging (fMRI) studies have attempted to localize brain areas responsible for working memory. A study involving 158 patients with lesions in different brain areas found that performance on the N-Back task was impaired in patients with lesions to the right ventrolateral prefrontal cortex, right inferior parietal cortex, and right middle temporal gyrus [2]. Moreover, performance on the digit span test was impaired in patients with lesions in the right dorsolateral prefrontal cortex, left angular gyrus, left superior parietal cortex, and left superior temporal gyrus [2]. A meta-analysis of 24 fMRI studies that used the N-Back as a working memory task identified the key activated brain regions as bilateral premotor cortex, supplementary motor area, bilateral rostral and dorsolateral prefrontal cortex, mediolateral prefrontal cortex, bilateral posterior parietal cortex, and the medial cerebellum [3].

The cognitive and executive functions of the cerebellum have received considerable attention [4]. Schmahmann

✉ Nasem Raies
raies@ualberta.ca

1 Institute of Medical Science, University of Toronto, Toronto, Canada

2 Krembil Research Institute, University Health Network, Toronto, Canada

3 School of Psychology, University of Nottingham, Nottingham, UK

4 Division of Neurology, Department of Medicine, University of Toronto, Toronto, Canada

and Sherman coined the term cerebellar cognitive affective syndrome (CCAS) [5]. Patients with CCAS resulting from lesions to the cerebellum showed impairments in setting plans, abstract reasoning, and working memory [5]. Previous studies suggest that the cerebellum is involved in the phonological loop of Baddeley's working memory model [6, 7]. Patients with cerebellar lesions have shorter forward and backward digit spans compared to healthy controls [7]. In healthy individuals, working memory tasks activated lobules VI/Crus I and lobules Crus II/VIIB of the cerebellum [8]. Thus, there is evidence that the cerebellum contributes to working memory. While there is evidence suggesting lateralized roles of the cerebellum, particularly the right cerebellum's involvement in verbal working memory through its connections with the left prefrontal cortex, it is important to note that the full extent and implications of cerebellar lateralization are not yet completely understood. A study demonstrated that cerebellar activity associated with increasing verbal working memory load involves widespread regions, including bilateral Crus I, right Crus II, and right Lobules VI and VIII [9]. This widespread activation suggests that bilateral cerebellar stimulation could modulate these extensive cerebellar-cortical networks more effectively than unilateral stimulation.

Theta burst stimulation (TBS) is a type of repetitive transcranial magnetic stimulation (rTMS) that demonstrates high effectivity in inducing neuronal plasticity by means of long-term potentiation and long-term depression like mechanisms [10]. Compared to regular rTMS, the required stimulation time for TBS is shorter, making it more practical when used in treatment protocols [11]. Studies have investigated two types of TBS: continuous TBS (cTBS), which decreases brain excitability, and intermittent TBS (iTBS), which increases brain excitability [12]. A few studies have investigated the effects of TBS of the cerebellum. Applying cTBS to the lateral cerebellum decreased its functional connectivity with cognitive regions in the prefrontal and parietal cortices [13], whereas iTBS to the lateral cerebellum increased its functional connectivity with the default mode network [14]. Therefore, stimulating the lateral cerebellum with TBS may change the influence of the cerebellum on cognitive functions due to alterations in functional connectivity with the cognitive areas of the prefrontal cortex. Regarding behavioral effects, cTBS of the right lateral cerebellum reduced category switching, which is an indication of impairment in mental flexibility [15]. cTBS of the left lateral cerebellum interfered with the encoding and retrieval of spatial information [16], whereas targeting the right lateral cerebellum with cTBS reduced accuracy in a verbal working memory task [17]. The authors attributed this effect to the role of the cerebellum in phonological working memory. To our knowledge, no studies have explored the effects of cerebellar iTBS on cognitive functions.

The present study aimed to examine the role of the cerebellum in working memory by manipulating the cerebello-thalamo-cortical circuit using iTBS and cTBS. Since it was expected that cTBS has inhibitory effects and iTBS has facilitatory effects, we hypothesized that iTBS of the lateral cerebellum would improve while cTBS of the lateral cerebellum would impair performance on working memory tasks compared to sham TBS.

Materials and Methods

Participants

Sixteen right-handed healthy volunteers (ages 42–79, 10 women and 6 men) participated in this study. The age of participants was 65.1 ± 13.1 (mean ± SD) years. Handedness was determined using the Edinburgh handedness inventory [18]. Participants underwent a neurological assessment by a neurologist and were screened to ensure the absence of seizures, neurological disorders, intracranial implants, and cardiac pacemakers. The assessment included evaluating handedness, previous or current medical history, current medications, pregnancy status, and examinations of cranial nerves, motor functions, reflexes, coordination, and sensory functions. Participants provided written informed consent approved by the University Health Network Research Ethics Board.

Procedures

The N-Back Task

In the N-Back paradigm, participants monitor a series of stimuli and are required to respond if the current stimulus (trial) is the same n trials before [3]. We employed the letter 1- and 2-Back conditions. In the 1-Back condition, participants were required to respond by pressing the space bar if the current stimulus was the same 1 trial earlier (i.e., the previous trial). For the 2-Back condition, participants were required to respond by pressing the space bar if the current stimulus was the same 2 trials earlier. The stimuli were letters (A to Z) generated randomly using a randomization website [19]. The task was administered on a laptop computer running MATLAB software (MATLAB R2021R, MathWorks, Inc.). The letters were presented in black font on a white background. Each letter was presented for 500 ms with a 1500 ms interval between stimuli [20]. The response was captured and assigned to a particular trial if the participant responded during the letter presentation or the interstimulus period following that trial, i.e., the participant had 2000 ms to respond in a trial. Each block consisted of 40 trials which included 10 target trials that participants had to respond to. Participants read an instructions sheet and completed a practice block for the 1-Back followed by a practice block for the 2-Back condition. The recorded blocks consisted of three 1-Back blocks followed by three 2-Back blocks. Thus, each condition (1-Back or 2-Back) contained a total of 30 target trials and 90 non-target trials. The performance was measured based on the overall scores. Following the signal detection theory [21], a response to a target trial is considered a hit, whereas a response to a non-target trial is considered a false alarm. For each N-Back condition in each visit, we calculated the discriminability index (D-Prime), which takes into account both the hits ratio (H) and the false alarms ratio (FA) following the formula: d' = z(H) - z(FA) [22]. Thus, D-Prime is the difference between the z transforms of hits and false alarms ratios. To deal with extreme values representing hit ratios of 1 (all targets detected) and zero false alarms (no response to any non-target trial) in which we cannot perform the z transformations, we transformed the data using the log-linear correction [23].

Digit Span Test

The digit span test closely mirrored that of the Wechsler Memory Scale III [24]. Participants performed the forward followed by the backward digit span tests. The experimenter faced the participant and read a list of digits at a rate of 1 digit per second. In the forward condition, the participant had to repeat the list in the same order. In the backward condition, the participant had to repeat the list in the backward order starting with the last digit in the list. The lists contained digits in the range of 1–9 and were generated using a randomization website [19]. There were 2 trials for each number of digits (i.e., 2 trials of 2 digits, 2 trials of 3 digits, and so on). The list started with 2 digits, and the number of digits increased by 1 until a maximum of 9 digits in the forward condition or 8 in the backward condition. The test ended when the participant failed to correctly reproduce the lists in both trials of the same number of digits. Participants had a practice run for the forward followed by the backward test. For each digit span condition, we measured the total score, which is the number of lists (trials) that the participant correctly reproduced. Since there were 2 trials for each number of digits, the maximum possible score was 16 for the forward and 14 for the backward condition [25].

Theta Burst Stimulation (TBS) and Neuro-Navigation

Transcranial magnetic stimulation (TMS) was delivered using a Magstim Super Rapid² Plus¹ system (The Magstim Company Ltd., UK) equipped with a 70 mm figure-of-eight air-cooled coil. Single pulse TMS to the left M1 was used to determine the active motor threshold (AMT) for activating the right first dorsal interosseous (FDI) muscle. The coil handle pointed in the backward direction at 45 degrees from the midsagittal line [13]. The hot spot for activating the FDI muscle of the right hand was identified. AMT was defined as the lowest intensity that elicits motor evoked potentials (MEPs) of ~200 µV peak-to-peak amplitude in at least 5 of 10 trials when the right FDI muscle was contracted isometrically at 20% of maximum voluntary contraction [13]. MEPs were visualized using Signal software (Cambridge Electronic Design, Cambridge, UK). After determining the AMT and calculating the TBS intensity, TBS was applied to the cerebellum bilaterally, starting with the left hemisphere. The target point for TBS was 1 cm below and 3 cm laterally to the inion, which corresponds to Crus 1 of the cerebellum [13]. We also used a frameless stereotaxic neuro-navigation system (BrainSight Rogue Research Inc., Canada) to validate the target location in 5 participants with available magnetic resonance imaging (MRI) scans [13]. The rTMS coil during the TBS delivery was held in a vertical orientation, with the handle pointing upwards.

iTBS, cTBS, and sham iTBS were delivered on three separate days (3 study visits) at least a week apart. The TBS intensity was set as 80% of AMT [13]. The iTBS protocol consisted of trains of pulses (600 pulses) delivered in an intermittent pattern with inter-block interval of 10 s (20 blocks in total). Each block consisted of 10 trains with inter-trial interval (ITI) of 200 ms (5 Hz). Each train consisted of three pulses with interstimulus interval (ISI) of 20 ms (50 Hz) [12]. The cTBS pattern consisted of trains of pulses (600 pulses) delivered in a continuous pattern with ITI of 200 ms (5 Hz). Each train consisted of three pulses with ISI of 20 ms (50 Hz) [12]. For the sham condition, a sham 70 mm figure-of-eight air-cooled coil was used. We chose sham iTBS as the sham condition as we expected real iTBS stimulation to improve working memory.

During the procedures, participants were seated in a comfortable chair and with a pillow on their lap to rest their hands on. Participants were instructed to stay awake and not to talk, move excessively, or use electronic devices.

Experimental Design

All participants attended three study visits at least one week apart to avoid the carryover of the TBS effects. In each session, one type of cerebellar stimulation (iTBS/cTBS/sham iTBS) was delivered, and the order was randomized. The order of procedures in each visit was as follows: practice runs for the N-Back and digit span tests, determining M1 hotspot and AMT, TBS protocol, and recorded blocks for

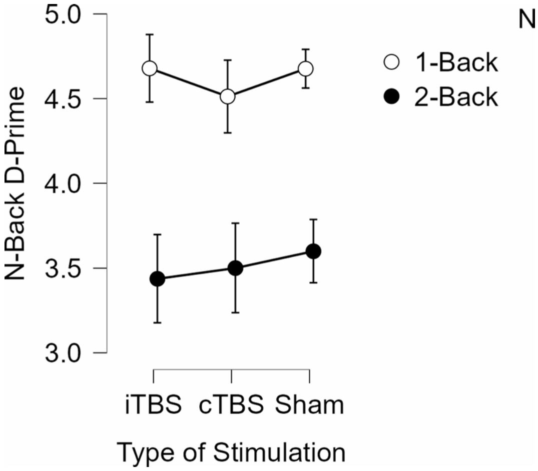

Fig. 1 Results for the 1-Back and 2-Back discriminability index (D-Prime). Error bars represent 95% confidence intervals. iTBS: intermittent theta burst stimulation; cTBS: continuous theta burst stimulation

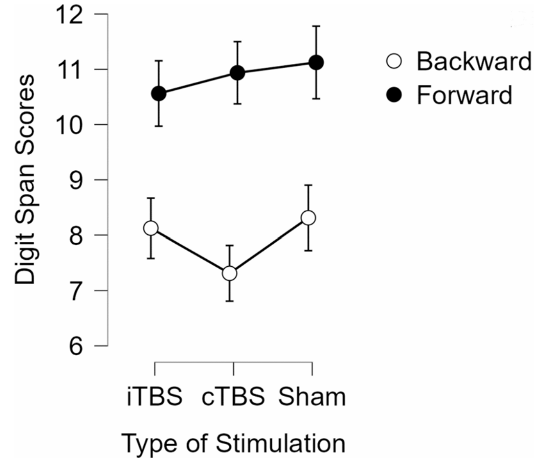

Fig. 2 Results for the forward and backward digit scores. Error bars represent 95% confidence intervals. iTBS: intermittent theta burst stimulation; cTBS: continuous theta burst stimulation

N-Back and digit span tests. The post-TBS testing was limited to a maximum of 30 min to avoid the washout of TBS effects [12].

Data and Statistical Analyses

We calculated descriptive statistics for participants' age and sex. The dependent variables for each visit were the 1-Back D-Prime, 2-Back D-Prime, forward digit span score, and backward digit span score. Statistical analyses were performed using the JASP software, version 0.15 [26]. For each dependent variable, the main analysis used a 2-way repeated measures analysis of variance (ANOVA) with type of stimulation (iTBS/cTBS/sham TBS) as within subject factor. We conducted non-parametric analyses (Friedman Test) if the data was not normally distribution as determined by Shapiro-Wilk test of normality.

Results

Neuro-Navigation

We recorded the target location on MRI in 5 participants. The mean (x, y, z) MNI coordinates for the target location were (-30.67, -102.59, -36.02) for the left cerebellum and (29.02, -99.87, -38.37) for the right cerebellum.

1-Back Task

Repeated measures ANOVA revealed no effect of the type of stimulation (iTBS/cTBS/Sham) on 1-Back D-Prime scores. Mauchly's test of sphericity showed that the sphericity assumption was violated ($p < 0.05$). Thus, we performed the Greenhouse-Geisser correction (corrected F = 1.25; corrected $p = 0.29$). Moreover, the Shapiro-Wilk test of normality showed a violation of the normality assumption in iTBS, cTBS, and sham scores ($p < 0.05$). Thus, we conducted non-parametric analysis (Friedman Test), and it revealed no significant effect of the type of stimulation ($p = 0.30$). Figure 1 shows the results for the 1-Back discriminability index (D-Prime).

2-Back Task

Repeated measures ANOVA revealed no effect of the type of stimulation (iTBS/cTBS/Sham) on 2-Back D-Prime scores (F (2, 30) = 0.54; $p = 0.59$; $\eta_p^2 = 0.03$). Figure 1 shows the results for the 2-Back discriminability index (D-Prime).

Forward Digit Span Score

Repeated measures ANOVA revealed no effect of the type of stimulation (iTBS/cTBS/Sham) on the forward digit span score (F (2. 30) = 1.02; $p = 0.37$; $\eta_p^2 = 0.06$). Figure 2 shows the results for the forward digit span score.

Backward Digit Span Score

Repeated measures ANOVA revealed a significant effect of the type of stimulation (iTBS/cTBS/Sham) on the backward digit span score (F (2, 30) = 4.29; $p = 0.02$; $\eta_p^2 = 0.22$). A planned comparison showed that the scores in the cTBS condition were significantly lower than in the sham condition (t = 2.76; $p = 0.01$). iTBS did not differ from sham stimulation (t = 0.52; $p = 0.61$). Figure 2 shows the results for the backward digit span score.

Discussion

The present study assessed changes in working memory performance using multiple working memory tasks as a result of manipulating the cerebello-thalamo-cortical circuits by targeting the cerebellum with the excitatory iTBS and inhibitory cTBS protocols. Our study showed that the cerebellum contributes to working memory as cTBS impaired performance in the backward digit span task, likely due to a virtual lesion effect in the cerebellum. Unlike previous studies that primarily rely on cerebellar lesion and fMRI studies, our study employs both excitatory and inhibitory TBS protocols to investigate the causal role of the cerebellum in working memory. This approach allows for a more direct assessment of cerebellar function and its modulation. While previous research has shown the involvement of the cerebellum in cognitive processes, our study provides direct evidence of how modulation through TMS affects specific working memory tasks. This adds a layer of understanding to the cerebellum's role, providing causal evidence that goes beyond correlative findings from fMRI and lesion studies. Our findings also have potential implications for understanding and treating neurological disorders that affect cognitive functions. For instance, cerebellar dysfunction is implicated in conditions such as schizophrenia [27], autism [28], and ADHD [29], which are associated with working memory deficits. The differential effects of excitatory and inhibitory TMS on working memory performance in our study could inform therapeutic strategies using TMS for these disorders, potentially leading to targeted interventions that modulate cerebellar activity to improve cognitive outcomes.

There was no significant effect of the type of stimulation on the D-Prime results in the 1-Back task. However, the average 1-Back D-Prime score was over 4.0, reflecting near perfect performance. Thus, the 1-Back results had a ceiling effect, which interferes with the ability to detect differences. The 2-Back task was more cognitively demanding than the 1-Back task as its average D-Prime scores were below 4.0. Neither iTBS nor cTBS affected the 2-Back D-Prime scores. Similar findings were seen in the forward digit span score results as iTBS and cTBS did not affect the participants' performance. In contrast, the backward digit span score was significantly lower in the cTBS condition compared to sham stimulation.

The different results for the forward and backward digit span tasks may be explained by the need for information manipulation, task difficulty, and task administration time. In both tasks, participants need to remember all items but the backward task requires participants to manipulate the information to reproduce the items in the reverse order. Thus, it is possible that cTBS significantly interfered with the information manipulation aspect of working memory, whereas iTBS did not. Task difficulty is another factor. Participants generally showed worse performance in the backward compared to the forward task. Thus, the effect of cerebellar cTBS on working memory may be more evident in more difficult tasks. This may also be the reason why there were no significant effects of stimulation on the 1-Back and 2-Back tasks as performance in these tasks had the ceiling effect. The role of the cerebellum in cognitively demanding tasks was explored in the literature: a study found that transcranial Direct Current Stimulation (tDCS) on the right cerebellum resulted in participants performing more challenging cognitive tasks faster and with more accuracy than in easy tasks [30]. These findings, combined with the current study's outcomes, suggest that the cerebellum plays a more significant role in working memory during cognitively demanding tasks. This contribution can be enhanced by tDCS and disrupted by cTBS. Also, participants performed the working memory tasks in a specific order: 1-Back, 2-Back, digit span forward, and digit span backward. As a result, the stimulation effects may have been more pronounced at certain timepoints after TBS, with cTBS having a more pronounced effect at the timepoint when backward digit span test was administered. This explanation, however, is unlikely as the effects of TBS tend to decrease with time [31]. The digit span backward test was administered approximately 20–25 min after stimulation, suggesting that the effect of cerebellar cTBS on working memory was still present at about 20 min after stimulation.

Contrary to our hypothesis, iTBS did not improve performance in any of the working memory tasks despite its excitatory nature. Likely, the cerebro-cerebellar connections were already optimized in healthy participants, and increasing this connectivity by iTBS would not necessarily lead to better working memory functions. Additionally, the reliability of cerebellar iTBS in evoking excitatory effects can vary. Recent studies provide further context: one study demonstrated that at least three sessions of iTBS were required to induce changes in multi-task attentional performance [32], indicating that a single session might be insufficient for measurable cognitive improvements. Another recent study found no evidence that a single session of prolonged iTBS administered to either the left dorsolateral prefrontal cortex or cerebellum caused any cognitive or event-related potentials (ERP) changes compared to sham stimulation in a healthy sample [33]. These findings suggest that cerebellar iTBS may not be effective in enhancing neural activity or cognitive performance with just a single session, particularly in individuals without pre-existing cognitive impairments.

The negative effects of cerebellar cTBS on working memory are congruent with previous research using cerebellar cTBS. These studies tested different cognitive functions, including word generation [15], spatial working memory

[16], and verbal working memory [17]. There was a significant inhibitory effect of cTBS on verbal working memory when using the verbal version of the Sternberg task [17], and our study showed a similar effect in the digit span backward test. Thus, the effects of cerebellar cTBS on verbal working memory may be consistent regardless of the task used. Tomlinson et al. suggested that the right, but not the left, cerebellum contributes to verbal working memory as it is part of Baddeley's phonological loop of working memory due to connections of the right cerebellum with the left prefrontal and premotor cortex [17]. It was also suggested that the cerebellum may contribute to the central executive component of working memory based on findings in the N-Back paradigm, a task that involves the central executive component of working memory [34]. The authors further argued that the cerebellar contribution to the central executive does not show an effect of laterality. We did not study laterality in the current study as we used bilateral cerebellar TBS. Since we found no effect of cerebellar TBS on performance of the N-Back paradigm and an effect of cerebellar cTBS when using the digit span backward test, we provide further support for the cerebellar contribution to the phonological loop but not necessarily the central executive of working memory. This conclusion should be taken with caution as our N-Back results showed a ceiling effect. However, there would have been room to observe performance impairment if cerebellar cTBS were to negatively impact the central executive. In summary, our results suggest that the cerebellum contributes to the phonological loop of working memory but could not provide a definitive link between the cerebellum and the central executive.

As the cerebellum sends projections to cortical areas involved in working memory such as the prefrontal cortex and the posterior parietal cortex [5], the inhibitory effect of cerebellar cTBS on working memory could be explained by changes in the cerebellar output to these brain regions. The finding that cerebellar cTBS affected performance in the digit span but not the N-Back task may be related to cerebellar projections potentially affected by cTBS. A lesion mapping study showed that deficits in the N-Back task were associated with lesions mainly in the right cerebral hemisphere such as the right prefrontal cortex and the right inferior parietal cortex, while impaired performance in the digit span tests was primarily associated with lesions within the left cerebral hemisphere such as the left superior parietal gyrus [2]. Thus, cerebellar cTBS may have impacted the cerebellar projections to the working memory areas in the left superior parietal gyrus but not necessarily the right prefrontal cortex and the right inferior parietal cortex.

Regarding our target location, we applied TBS to the cerebellum using anatomical landmarks and registered the target in 5 participants. It has been demonstrated that TMS-induced currents have a relatively broad spatial distribution, leading to widespread effects beyond the immediate stimulation site [35]. This phenomenon suggests that even in the absence of neuronavigation in some of our participants, the likelihood of missing the target region, such as Crus 1 in the cerebellum, is mitigated by the high degree of current spread associated with TMS. Also, Several published studies on theta burst TMS of the cerebellum did not use neuronavigation [36, 37].

Since cerebellar TBS with a figure-of-eight coil and a low intensity protocol likely affects the cerebellar cortex, the effects of cerebellar cTBS are likely due to modulation of cerebellar Purkinje cells or the local interneurons, especially those with lower excitability thresholds [38]. Cerebellar cTBS was previously found to decrease MEP amplitudes from stimulation of the contralateral primary motor cortex [36]. Given the proposed inhibitory nature of cTBS, the authors argued that this effect of cerebellar cTBS on the motor cortex was due to the inhibition of the local interneurons in the cerebellar cortex, which decreased their inhibitory output to Purkinje cells. Thus, Purkinje cells increased their inhibitory output to the deep cerebellar nuclei. As a result, cTBS may lead to a reduction in the excitatory output of the deep cerebellar nuclei to the thalamus and motor cortex, showing the inhibitory effect of cTBS on the cerebello-thalamo-cortical circuit [36]. The cerebellum also send projections to the prefrontal and posterior parietal cortices via the thalamus through a similar cerebello-thalamo-cortical circuit [39]. Thus, Schmahmann et al. proposed the theory of universal cerebellar transform, which argues that motor and non-motor functions in the cerebellum are performed in the same manner given that the internal circuits across the cerebellum are consistent [40]. With this argument, the effects of cerebellar cTBS on working memory in the present study were likely due to inhibition of the local inhibitory interneurons in the cerebellar cortex.

Lastly, given that our participant pool involved older adults, we acknowledge that age can affect various brain functions, including working memory. However, there is currently limited understanding of how age specifically influences the cerebellar contribution to working memory. This area remains an important subject for further research. Our study aims to contribute to this understanding by investigating these relationships within the context of our participant sample.

Conclusion

Cerebellar cTBS impaired working memory as measured by performance in the backward digit span task, whereas cerebellar iTBS had no significant effect. Cerebellar cTBS may have created a virtual lesion like effect that impaired working memory. These findings showed that the cerebellum plays a role in verbal working memory.

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Data Availability Data are available on request from the authors.

Declarations

Ethical Approval The study was approved by the University Health Network Research Ethics Board (REB#16-5130) and all participants gave written informed consent. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Competing Interests The authors declare no competing interests.

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