Research report

The cerebellum and its role in word generation: A cTBS study

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ABSTRACT

The purpose of this study was to investigate the role of the cerebellum in the executive control of word generation using a phonemic and semantic fluency task. Phonemic fluency tasks require novel strategy to organize verbal output, and are more effortful than semantic fluency tasks. The number of category switches made between subcategories of words is a measure of mental flexibility, and is greatest during the early phase of the task (first 15 sec). Both tasks were tested on healthy participants, before and after the application of transcranial magnetic stimulation using continuous theta burst stimulation (cTBS) applied over the left or the right posterior/lateral cerebellar cortex in separate groups. We hypothesized that the number of category switches and number of words produced within the first 15 sec would be reduced after cTBS to the right, posterior-lateral cerebellum during phonemic fluency tasks. The results from the study were consistent with the hypothesis. Within the first 15 sec of each trial, right cTBS participants displayed significantly lower switching scores ($p = .05$) after stimulation. Previous studies have illustrated similar impairments in switching between categories during phonemic fluency performance in patients with damage to the left frontal cortex. Our findings support the general hypothesis of cerebellar involvement in executive control through connections to the frontal cortex.

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1. Introduction

Clinicians typically assess lexical access using standardized language tests such as word generation tasks. These tests measure the ability to generate as many words as possible within specific parameters and time constraints. Semantic and phonemic fluency tests are word generation tasks with a pre-determined word retrieval cue. Semantic fluency cues are category based and provide a template for the list of words that can be generated. For example, an appropriate response to the semantic cue “Animals” would be “dog”, “cat” or “bear”. Phonemic fluency tasks demand more executive control than semantic tasks, as they require novel strategic organization of words for correct output (Lezak, 1983). For example, the phonemic cue “F” can generate a far more exhaustive list of words than the semantic cue “Animals” and the task itself has more restrictions, such as no proper nouns and no sequential derivations.

Maximizing performance requires the ability to strategically organize words into meaningful groups (clusters), and

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the flexibility to make quick shifts (switches) to search and retrieve new clusters. Category switching, in this context, reflects executive and strategic mental processes (Troyer et al., 1998). The more category switches that occur within a trial, the higher the likelihood of increasing the total number of words generated. Typically most words are generated during the early phase (first 15 sec) of a trial, which includes the greatest scope of subcategories (Troyer et al., 1998). During this phase search and retrieval strategies are most flexible. As the time for the test elapses however, the number of correct selections begins to decline, strategic flexibility weakens, and words are produced less frequently (Troyer et al., 1998). Words generated within the early phase reflect an increased facilitation of a neuronal network to optimize speed of information processing (Stuss and Alexander, 2007). Based on this phenomenon, performance in the early phase of semantic and phonemic (verbal) fluency trials (e.g., first 15 sec) can be scored separately from performance in the late phase (e.g., last 45 sec).

Word generation deficits have been reported in cerebellar patients (Leggio et al., 2000; Akshoomoff et al., 1992; Appollonio et al., 1993; Silveri et al., 1994; Molinari et al., 1997; Richter et al., 2007). A probable basis for such effects is the reciprocal connections between the cerebellum and contralateral regions of the frontal lobes (Middleton and Strick, 2000). For example, verb generation tasks require the linguistic ability to generate a verb in response to a cue that is always a concrete noun. Although linguistic functioning is left lateralized, the right lateral cerebellum is activated during verb generation (Petersen et al., 1989). This contralateral connection is supported by Fiez et al. (1992) in a case study of a patient with an infarct to the right posterior inferior cerebellar artery who performed significantly worse than healthy controls at a verb generation task. Debate however does exist over whether the right lateral cerebellum is involved in verb generation, as studies using cerebellar degenerative patient report no deficit in linguistic functions (Helmuth et al., 1997; Richter et al., 2004). Verb and word generation tasks are both heavily lateralized because of their language component. Not surprisingly, impaired switching and reduced word output during phonemic (Lezak, 1983; Troyer et al., 1998) and semantic (Troyer et al., 1998; Henry and Crawford, 2004) fluency tests are found in left frontal patients. Cerebellar patient studies however have conflicting results concerning laterality (left or right, both) and specificity (phonemic or semantic fluency, both) as they are based on patients with varying etiologies – cerebellar tumors, degeneration and lesions. Studies that restricted patients to one etiology, such as focal vascular lesions, had more consistent results and narrowed word generation deficits to Crus II of the right cerebellum (Richter et al., 2007; Schweizer et al., 2010). Schweizer and colleagues (2010) reported reduced word output and a decreased number of category switches during phonemic fluency trials in patients with right unilateral lesions of the cerebellum. The greatest impairment occurred during the early phase of the task (first 15 sec), compared to patients with left, unilateral cerebellar lesions, and age-matched controls. Because of the specificity of the fluency impairment, it is likely that the deficits in the cerebellar population are not attributed to disturbed motor performance, but may be caused by impaired executive processes necessary for organizing and monitoring word output. A meta-analysis of neuroimaging studies also revealed that the cerebellar regions most identified during word generation tasks were the posterior-lateral areas of the right cerebellar hemisphere – lobule VI, Crus I/II (Stoodley and Schmahmann, 2009). Lacking from these studies is the separation of the early and late phase of the word generation tasks, thus neuroimaging studies have yet to disentangle the contribution of the cerebellum to word generation.

There is converging evidence from patient and neuroimaging studies that the left prefrontal cortex and right cerebellum are both involved in word generation tasks. Together these different methodologies elucidate the potential role of the cerebellum during non-motor functions. Another potentially useful technique, transcranial magnetic stimulation (TMS), may also prove effective in revealing the role of cerebellar-frontal connections in verbal fluency. TMS is a non-invasive technique that can be used for mapping neurological functions. It involves passing an electric current through a magnetic coil placed on the scalp to induce a secondary electric current that disrupts the excitability of a focal population of neurons. The temporal precision of TMS is superior to functional imaging techniques and the spatial accuracy of induced inhibition allows for clearer interpretation than patient studies with inconsistent etiologies. As a result, TMS can provide unique support to imaging and lesion studies by transiently inhibiting focal areas of the cortex in healthy participants. TMS can be used to investigate cerebello-thalamo-cortical pathway integrity (Ugawa et al., 1995). Repetitive application of the current to the cerebellum has induced significant behavioral changes in healthy participants, such as decreasing performance accuracy during paced-finger-tapping-tasks (Theoret et al., 2001), and disrupted performance of cognitive tasks, such as time perception (Koch et al., 2007; Olivi et al., 2007). A relatively new form of TMS, continuous theta burst stimulation (cTBS), uses a very low current to transiently decrease cortical excitability for several minutes following stimulation. In the motor cortex inhibitory effects can last up to an hour in healthy participants (Huang et al., 2005) and when this protocol is applied to the contralateral, posterior-lateral cerebellum, it can modulate intracortical circuits of the human motor cortex (Koch et al., 2008). It is feasible then, that cTBS to the cerebellar cortex can also induce focal, transient cortical changes that influence the activity of the prefrontal cortex during tasks that require cognitive processing. In the current study we address whether the cerebellum is critical in the executive control processes involved in word generation and whether there is a laterality effect following cTBS. Based on lesion and imaging studies that suggest involvement of the right, posterior-lateral cerebellar cortex (Crus I/II) during word generation tasks (Stoodley and Schmahmann, 2009), we hypothesized that cTBS would have an effect on verbal fluency performance. This effect will be specific to phonemic fluency as phonemic cues demand greater executive control and rely more heavily on the frontal lobes than semantic cues, which require semantic memory (Baldo et al., 2006). Behavioral changes from cTBS will be specific to the right cerebellar hemisphere, contralateral to the left prefrontal cortex, and represented by a decrease in the

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number of category switches and number of words produced, during the early phase of the task (first 15 sec), as this time period demands the greatest strategic organization for executing the task. We also hypothesized that cTBS would have little effect on performance when applied over the left cerebellar hemisphere.

2. Methods

2.1. Participants

Twenty-seven (18 female) healthy, self-reported right-handed participants (age range 20–35 years, mean = 23.8; education range 15–21 years, mean = 16.6) with no reported history of neurological problems were recruited for this study. All participants were fluent in English. Participants were randomly assigned to one of two groups for application of cTBS to the posterior-lateral cerebellum, left hemisphere (LH) or right hemisphere (RH). There were 14 participants for the LH and 13 participants for the RH group. All participants provided written informed consent prior to testing. Experimental procedures were approved by the Office of Research Ethics at the University of Waterloo.

2.2. Stimulus and apparatus

Prior to application of cTBS over the cerebellum, motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous (FDI) muscle using electromyography (EMG) with Ag–AgCl surface cup electrodes (9 mm diameter). The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the right index finger. EMG signals were amplified (1000×) and sampled at 1000 Hz using a custom program written in LabVIEW software (version 8.5, National Instruments). Participants were seated with their hands resting on the chair arms and instructed to remain relaxed while a figure eight TMS coil (MCF-B65) of a Medtronic stimulator (Model: MagPro x100, Medtronic, Minneapolis), was placed against the upper left surface of the participant’s scalp at the optimal position for eliciting MEPs from the contralateral FDI muscle. Single pulse stimulations were applied with increasing intensity until a MEP of 200 μV peak-to-peak was elicited in the right FDI during an isometric contraction at 10% of their maximum voluntary contraction on five out of 10 trials. This intensity was taken as the active motor threshold (AMT).

Once the AMT was established, participants completed the “pre-stimulus” condition as described below. After this condition, participants were instructed to rest their forehead on a stability cushion so that their head is supported and comfortably positioned in a forward flexed posture. TMS was then applied at 80% of AMT using a cTBS pattern in which three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 sec (a total of 600 pulses). Stimulation over the lateral (left or right) cerebellum was positioned using pre-determined coordinates with the handle pointing superiorly (Koch et al., 2008). The intended target for these coordinates were lobules Crus I and Crus II of the cerebellum. For stimulation of the left cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm to the left of the inion. For the RH the coil was placed 1 cm below and 3 cm to the right of the inion (Theoret et al., 2001). After the cTBS, the “post-stimulation” condition followed.

2.3. Procedure

Fluency tasks are designed such that a participant is given a minute to generate as many words as they can in response to a verbal cue. In our study, participants performed this task before and after cTBS application to the posterior-lateral cerebellum. The pre-stimulation condition consisted of four trials that took place before cTBS was applied to the cerebellum. The first three trials pertained to letter category, phonemic fluency. Subjects were instructed to generate as many words as possible that start with a particular letter. For the last trial, participants were instructed to generate a list of words that belong to a semantic category, semantic fluency. The semantic fluency trials always followed the phonemic trials. Trials were each 1-min in duration, except for the last phonemic category trial, which was 2 min – this was to test the time constraints of the task (Lezak, 1983). The post-stimulation condition followed the same standardized procedure, however with different phonemic and semantic categories.

Phonemic categories were always paired as F, A, S or P, R, W. These sets of letters are well matched in the literature, reducing the influence of task difficulty (Ross et al., 2006). Semantic categories were either ‘animals’ or ‘groceries’. There were less semantic trials than phonemic because there are less semantic categories that are equivalent in terms of task difficulty. However both ‘animals’ and ‘groceries’ are often used clinically and have normative data (Troyer, 2000). Phonemic and semantic categories chosen for test and retest were counterbalanced across groups (half of each group started with letters F, A, S and ‘animals’ first, the other half started with P, R, W and ‘groceries’) to ensure there was no difference in performance due to the phonemic and semantic categories chosen. For this study we used the same scoring criteria previously reported by Troyer et al. (1997). In brief, category switches were defined as the exhaustion of a phonemic or semantic cluster and the shifting to another. Phonemic clusters consisted of specific characteristics. Words could rhyme, begin with the same first letter, have the same first sound (i.e., school and skate), or be homonyms. Errors for phonemic fluency trials consisted of proper nouns, sequential derivations (i.e., feel, feeling), intrusions (words that do not begin with the appropriate letter cue) and word repetitions. For semantic fluency, successful clusters consisted of words within the same subcategory. For example, subcategories for “animals” consisted of farm animals, zoo animals, and domestic pets, and some subcategories for “groceries” encompassed fruits, dairy, and non-perishables. Semantic words that deviated from the semantic category or repeated words were considered errors and corrected for. All trials in the pre-stimulus and post-stimulation conditions were audio-recorded on computer for offline scoring. A standardized script was read at the beginning of each condition, explaining the specifics of the task.

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2.4. Statistical analysis

The initial analysis used a 2×2 analysis of variance (ANOVA) with a within-subject factor of condition (pre-cTBS, post-cTBS) and a between group factor of hemisphere (left, right), for both the number of switches and words generated during the first 15 sec and last 45 sec of the phonemic fluency task. Specific a priori hypotheses were then tested by using one-tailed, t-tests.

Specifically for the first 15 sec of the phonemic fluency task, baseline values for category switches and words generated pre-cTBS were compared to ensure that there were no between group differences prior to cTBS. The baseline means acted as a control to test the specific hypothesis that these measures during the first 15 sec of the task would decrease following cTBS to the RH but not the LH. Post-cTBS means of the LH were also compared to the control, and to the post-cTBS means of the RH group. Comparisons between groups were made using one-tailed independent t-tests.

In order to control for possible individual differences, change scores were calculated by taking the mean difference of the scores between the within-subject factor of condition (pre-cTBS, post-cTBS). The number of category switches and the number of words generated were the dependent measures of the phonemic and semantic fluency tasks. Scores for each measure were summed across trials. Separate comparisons were made for phonemic and semantic fluency tasks with two-way ANOVA using the between-subject factor of LH and RH, and within-subject factor of time period (First 15 sec, and Last 45 sec of the trial). ANOVAs were performed with an α level of .05. Where a significant interaction occurred between hemisphere and time period, two-tailed independent t-tests were used to test a priori hypotheses comparing the two groups at each time period. Demographic differences between hemisphere groups were compared using one-way ANOVAs with age and education as between-subject factors.

3. Results

Analyses of the demographic data for the participants revealed no significant differences between groups on age [F(1,26)=.08, p = .78], or education [F(1,26)=.06, p = .82].

3.1. Phonemic fluency

For the number of switches produced in the first 15 sec, there was no interaction between condition and hemisphere [F(1,54)=.36, p = .55]. While there was no effect of condition [F(1,54)=.78, p = .38], a main effect of hemisphere approached significance [F(1,54)=3.77, p = .06]. For the number of switches generated in the last 45 sec of the phonemic fluency trial, there was also no interaction between condition and hemisphere [F(1,54)=1.33, p = .26]. There was however a main effect of condition [F(1,54)=4.32, p = .04], and hemisphere [F(1,54)=3.94, p = .05].

For the number of words generated within the first 15 sec of the phonemic fluency task, there was neither interaction between condition and hemisphere [F(1,54)=.29, p = .60], nor was there an effect of condition [F(1,54)=.82, p = .37], or hemisphere[F(1,54)=3.77, p = .08], this value did however approach significance. In the last 45 sec of the phonemic fluency task, there was no interaction between factors [F(1,54)=2.04, p = .16]. There was an effect of condition [F(1,54)=6.60 p = .01] but not of hemisphere [F(1,54)=1.86, p = .18].

A priori comparisons revealed no significant difference for the number of category switches [t(25)=1.12, p = .14], and for the number of words generated [t(25)=.93, p = .18] pre-cTBS for the first 15 sec of the task. As a result, pre-cTBS scores of the LH and RH groups were used as a control group for comparing the mean number of category switches generated after cTBS. These values can be seen in Fig. 1. There was no significant difference between post-cTBS scores of the LH group and the pre-cTBS scores of the control [t(38)=−1.12, p = .26]. There was however a significant difference between the post-cTBS scores of the RH group and the pre-cTBS scores of the control [t(39)=1.84, p = .04]. There was also a difference between the LH and RH groups, however it only approached significance [t(25)=1.58, p = .06].

For the number of words produced within the first 15 sec of the phonemic fluency task there was a significant difference between the LH group and control [t(38)=−1.71, p = .04] but not between the RH and control [t(39)=.20, p = .4]. The difference between LH and RH groups also only approached significance [t(25)=1.59, p = .06].

Change scores analysis revealed a significant interaction between hemisphere group and time period for the differences in the mean number of category switches produced post-cTBS relative to pre-cTBS [F(1,27)=4.34, p = .01]. Driving this interaction is the difference of the mean number of category switches made by the LH and RH groups during the first 15 sec of the trial. We found that the number of category switches was reduced for the RH group and increased for the
LH group and this difference was significant in the first 15 sec of the trial \( t(25) = 2.03, p = .05 \) (Fig. 2). There was no significant difference between the RH and LH groups in the number of category switches produced in the last 45 sec of the trial \( t(25) = /C0 1.64, p = .12 \).

The ANOVA for the number of words generated also revealed a significant interaction between hemisphere and time period \( F(1,27) = 4.7, p = .01 \). Fig. 3 summarizes the change scores for word generation during the phonemic fluency task. Participants within each hemisphere group increased their word output during the last 45 sec of the task, the RH group statistically more than the LH \( t(25) = -2.44, p = .02 \).

3.2. Semantic fluency

There were no significant effects for semantic fluency trials. No significant effects between hemisphere and time period were found on the change score of the number category switches \( F(1,27)=2.26; p = .14 \), and no main effect of hemisphere \( F(1,27)=3.35; p = .07 \) or time period \( F(1,27)=.38; p = .54 \). For the measure of number of words produced, there was no significant interaction between factors \( F(1,27)=.83; p = .37 \) and no main effect of hemisphere \( F(1,27)=3.02; p = .09 \) or time period \( F(1,27)=2.26; p = .14 \).

4. Discussion

The behavioral effects of cTBS over the posterior-lateral cerebellum on word generation were hemisphere and task specific. For the RH group, the number of category switches was reduced during word generation tasks. This effect was specific to phonemic fluency, and restricted to the early phase. These findings are consistent with those reported by Schweizer et al. (2010) using focal, unilateral cerebellar lesion patients. In that study, RH patients produced fewer category switches compared to the LH patients during the first 15 sec of phonemic fluency. Thus, the main results of this study support our hypothesis. The transient inhibitory effects of cTBS reduced the number of category switches during the early phase of phonemic fluency in only the RH group. This suggests the putative role the right cerebellum plays at the early phase of phonemic fluency tasks, when executive processes are required to optimize performance.

Recent clinical studies support the hypothesis that focal cerebellar injury disrupts some aspects of attention and executive functioning (Schweizer et al., 2008; Schweizer et al., 2007a; Schweizer et al., 2007b). In the current study, we posit that the cerebellum is recruited during the early phase of phonemic fluency when the novelty of the task requires a larger neural network to maximize performance. It is possible that when cerebellar excitation is modulated it may disrupt tonic facilitation to cortical areas and consequently reduce category switches; this however is purely speculative. During the late phase, executive control is in less demand and does not require as large of a network to perform the task. Thus it is possible that distinct neural networks may be performing the same collective task.

Maximizing word output is the ultimate goal of verbal fluency, but not the main measure of executive processing. We did not find a reduction in the number of words generated by the RH group during the early phase of the phonemic fluency task after cTBS. One possible explanation for the discrepancy between our study and patient data that have shown word generation deficits during the initial 15 sec phase (Schweizer et al., 2010), may be the difference between cTBS inhibition and structural damage as they affect cerebellar function. The transient, inhibitory effect of cTBS is much less and this may...
reflect the sensitivity of the category switch measure. While we did not have an a priori hypothesis as to what the effects of cTBS would be on the late phase of the task, we did find a difference in the number of phonemic words produced by each hemisphere group in the late phase of the task. The RH group had a larger change in word output, however in the same direction as the LH group. The difference between groups remains unclear. We speculate that for the RH group the change in the late phase of the phonemic fluency task is a result of the neural manipulation from cTBS over the early phase. The negative change in category switches may have influenced the positive change in word output, as more words were likely generated once the task goal was sustained. Future studies are required to investigate the difference in performance during the late phase of the task, perhaps by applying cTBS to the prefrontal cortex and probing whether the disruption is specific to a time period of the task or is generalized.

This is the first TMS study using cTBS to probe the effects of cerebellar stimulation on the executive control of word generation. Results of this study are consistent with cerebellar focal lesion patient and imaging studies, suggesting TMS as a potentially powerful tool for mapping cognitive functions. Like all methodologies, cTBS has its limitations. Between-subject variability is difficult to control and direct output measures are limited. For example, the output measure for this study was strictly behavioral, making our findings less concrete since no physiological data was recorded. Using standard measurements for localizing the site of stimulation may have been a limitation to the study due to variability in head size. The efficacy of cTBS over the cerebellum as a non-invasive assessment of cerebellar function has been recently questioned. It is possible that stimulation to the posterior-lateral cerebellum could have directly activated corticospinal neurons (Fisher et al., 2009), however if such activation occurred it is not likely that it contributed to the results of our study. Activation of corticospinal neurons would have influenced the motor component of the task, specifically the initiation of speech, however; neither group showed any deficit for generating word output. Since cTBS modulation was hemisphere and task specific, it is more likely that the cerebellum-thalomo-cortical pathway was activated or interrupted, as cTBS influenced the executive control of word generation.

The converging evidence from studies using different methodologies makes an argument for the benefits of using cTBS in future studies, as it is a technique that on its own can provide the spatial acuity necessary for mapping the functional organization of the cerebellum via non-invasive, transient interneuronal inhibition. Our results map onto previous findings implicating the involvement of the cerebellum during tasks that require attention and executive control.

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References


