Transient inhibition of the cerebellum impairs change-detection processes: Cerebellar contributions to sensorimotor integration

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Pages in Manuscript: 36
Number of Figures: 4

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Abstract:

Patients with cerebellar lesions have shown altered responses to unpredictable stimuli. This finding has led to the belief that the cerebellum is involved in comparing incoming stimuli with previously experienced stimuli in order to predict and coordinate responses. The role of the cerebellum is thought to extend beyond motor control to higher-order executive functions, which allow for the evaluation of stimuli that influence our personal reactions, emotions, and thoughts. This current study tested the role of the cerebellum on cognitive function by examining incoming sensory stimuli being unattended by the participant. Median and ulnar nerve somatosensory evoked potentials (SEPs) were elicited by electrical stimulation via surface electrodes. Nerve stimulation was presented in an oddball fashion where median and ulnar stimulation were presented as frequent and deviant stimuli, respectively. Electroencephalography (EEG) was used to measure participants' cortical responses both before and after either continuous theta burst stimulation (cTBS) used to transiently inhibit cerebellar activity, or a sham condition. The N140 was shown to be modulated in response to deviant stimuli, resulting in a large negativity pre-cTBS, referred to as the mismatch-negativity (MMN). Following cTBS, the MMN was reduced, resulting in similar waveform patterns in response to both the frequent and deviant stimuli. The mechanisms that are thought to modulate this change within the N140 in response to deviant stimuli are believed to be different from those that govern its response to frequent stimuli. The cerebellum may be involved in attentive change-detection processes that are critical for a wide-range of everyday processes.

Keywords: cerebellum; sensorimotor integration (SMI); oddball; continuous theta burst stimulation (cTBS); evoked potentials

Highlights

- Presentation of a deviant somatosensory stimulus interspersed amongst frequent stimuli elicits a large negativity present within the 140-200 ms latency range, referred to as the mismatch negativity.
- Transient inhibition of the cerebellum using cTBS modulates this negativity such that, over time, cortical responses to deviant stimuli become similar to the responses to frequent stimuli.
- The cortical response seen in the deviant stimulus post cTBS, which was not observed in the frequent stimulus, suggests the potential critical role of the cerebellum in higher-order cognitive processes.
- This supports work that indicates that the cerebellum is involved in the processing of sensory information without the need for an explicit motor goal.

1.0 Introduction

Communication between the central nervous system (CNS) and the periphery creates a fundamental feedback loop wherein sensory input is integrated and used for assisting in the execution of appropriate motor outputs; this dynamic process is sensorimotor integration (SMI). SMI is flanked by the proponents of variability reduction and prediction estimates where with continued exposure to certain stimuli, error (or variability) can be reduced due to state predictions that are based on incoming sensory information and previous exposure to stimuli [1, 2]. Behavioural training has been shown to induce resulting SMI use-dependent cortical changes necessary for skill acquisition [3, 4, 5]. While these adaptive changes are necessary, studies have shown that in various injuries and neurologic disorders, anatomical changes are correlated with unfavourable behavioural motor performance [6, 7, 8, 9].

The cortical structures contributing to the learning of motor skills have been the focus of research in this area for years, however recent investigations have focused on the contributions of subcortical areas [10, 11, 12, 13]. Traditionally, the cerebellum has been regarded as an accessory motor structure in that its purpose was to receive massive amounts of somatosensory input and exclusively optimize and fine tune the regulation of voluntary movement [14]. This idea of the cerebellum functioning solely as an accessory motor structure was supported by research which demonstrated that cerebellar lesions produce uncoordinated movements, not gross sensory deficits [15]. This traditional view is now challenged as cerebellar activity has been observed following tasks that are not inherently motor in nature such as cutaneous discrimination, auditory, visual, and working memory tasks [16, 17, 18]. Specifically, the role of the cerebellum with regard to learning has long been debated, and recently it has emerged as a main candidate of stimuli integration and internal feedback, which are critical for the

coordination and adaptation that occurs within SMI [11, 19, 20, 21]. However, the concepts of adaptation and coordination are very large, overarching conditions that may have multiple, smaller underlying mechanisms or processes which extend beyond the realm of motor control only. SMI processes have been largely studied using learning adaptations based on simple upper limb movements. These adaptations have generated rich discussions surrounding the potential mechanisms that govern this gradual change in efficiency and ability to recall skills. Specifically, changes within cortico-cerebellar circuits have been of interest with their hypothesized use of internal models. It is thought that the formation and alteration of these models allow us to adjust our behaviour depending on changes in environmental dynamics; for example: changing our gait when transitioning to walking on concrete to walking on ice, adjusting the effort required to lift a drink to our mouths as we consume its contents, or even changing our tone of voice and body language depending on how we interpret the experiences of others that we encounter [22, 23]. This is further supported by cerebellar communication and its influence on information processing in multiple regions of the cortex; it has dense connections with the thalamus that project to motor, prefrontal and parietal cortices, which are involved in cognitive and emotional processes [24, 25]. The uniform structure of the cerebellum paired with its diverse cortical connections has led to the creation of theories about how the cerebellum may be involved in these higher order processes. Such theories posit that just as the cerebellum regulates the rate, force and accuracy of movements, it may also regulate the speed, consistency and appropriateness of cognitive processes [26, 27]. Combined imaging and multi-domain task studies have shown that there are functionally distinct areas of the cerebellum which are dependent on the input they receive [28, 29].

Past research has shown that the cerebellum is able to modulate the excitability of the primary somatosensory cortex (S1) at early stages of somatosensory input processing [30]. Investigation of early latency evoked potentials in patients with lateralized cerebellar lesions has revealed that cortical inhibitory circuitries are low-functioning in cerebellar patients, suggesting that the cerebellum influences the inhibitory circuitries of S1. This may in turn modulate receptive fields and affect sensory discrimination, causing decreases in early somatosensory peaks due to the inability to correctly process incoming sensory stimuli [30, 31]. Observations of somatosensory deficits such as difficulty in weight perception or kinesthesia have been reported in patients with cerebellar lesions [32]; this in combination with evidence of widespread cerebellar connections with sensory and associative cortical areas, it is now thought that the cerebellum participates in higher-level cognitive processes, such as planning, memory and attention [18]. The function of the cerebellum in coordinating skill acquisition during motor learning tasks may operate in the same way for sensory and even cognitive tasks; this possibility is supported by the uniform cytoarchitecture of the cerebellum and the belief that this symmetry of organization facilitates a common function of the cerebellum for various tasks. It is still argued that the purpose of the cerebellum is inherently motor related since its activation during perception or memory tasks may involve motor imagery. Still, widespread evidence of the cerebellum's influence over S1's activity warrants further investigation of its ability to predict incoming sensory stimuli and determine how this may extend into the realm of higher-order functions.

The mismatch negativity (MMN) is a cortical event related potential (ERP) which is generated by an automatic cortical change-detection process, where a difference is found between the current input and the expected input or a representation of the regular aspects of the

preceding input [33, 34]. Research has tested this process by interspersing unattended, deviant stimuli between regular, frequent stimuli. This work is typically performed with the use of an auditory stimuli, but has also been shown with visual and olfactory stimuli [35, 36, 37]. Deviant stimuli have been shown to elicit a fronto-temporal negative response in the 120-180 ms latency range, the MMN. It is thought that the MMN can only be seen if a representation of the standard or expected input is available for comparison with the current input. Due to the location patterns of the negativity, researchers believe it reflects a distributed network involving the prefrontal and parietal cortices [38]. These areas of the cortex have been implicated in higher-order executive functioning [39, 40]. Transneuronal tracing techniques have provided evidence that there are reciprocal circuits between the cerebellum and both frontal and parietal areas from regions that do not have overlap with cerebellar motor circuitry [25]. This, paired with evidence that the cerebellum has the ability to modulate accessory cortical regions and high-order processes such as attention, leads to the questioning of whether the cerebellum acts as a regulator for these regions that are thought to hold the main responsibility of higher-order processes [41]. Functional topography studies have suggested that there are distinct areas of the cerebellum which receive dominant input from different cortical areas leading to regional distinctions; the anterior lobe is principally involved in motor control, the vermis is involved in affective processing and the posterior cerebellum contributes to higher-order and cognitive operations [42, 43, 44, 45]. Within such studies, there are still contradictory results due to the differences in task demands and outcome measures, therefore there is value in trying to understand the role of the cerebellum outside of the motor domain through the use of simple sensory stimuli.

In an effort to assess the cerebellum's capacity to evaluate sensory stimuli and modulate cortical activity, Restuccia et al. performed an OB paradigm using stimulation of the first and

fifth digits of the hands ipsilateral to a cerebellar lesion in patients and found abnormal responses as measured by EEG when compared to healthy controls [30]. Specifically, this study found that there was a lack of the change-detection mechanism (MMN) on the lesioned side which may indicate that the cerebellum is a key evaluator of stimuli in a predictive way, however more work is needed to confirm this [30, 31].

The use of a unilateral cerebellar lesion group provides a unique opportunity to investigate both the affected and unaffected sides in the same individual; however, it does provide difficulties when considering the heterogeneity of lesion depth and location. Continuous theta burst stimulation (cTBS), a type of non-invasive brain stimulation, provides a useful tool to investigate the involvement of specific cortical areas within a task or process of interest. cTBS has been widely studied within the motor cortex (M1) and is known to induce transient changes, specifically a reduction in motor evoked potential (MEP) amplitudes [46]. Targeting the cerebellum with this same technique is appealing as it provides a means for establishing a relationship between a specific area and its influence over other cortical regions and processes due to its extensive connections with the cortex. Following cerebellar cTBS, decreased MEP amplitudes have been observed in the contralateral M1 [47]. It is postulated that cTBS acts on the cells of the superficial cerebellar cortex layer which in turn have inhibitory synapses onto Purkinje cells (PC), therefore, decrease in inhibition of the PC occurs. The axons of the PC are inhibitory in nature and are the sole output of the cerebellar cortex that influence deep cerebellar nuclei (DCN); a decrease in the inhibition of these cells would cause increased inhibitory drive onto the dentate-thalamo-cortical pathway, which is excitatory in nature [48]. Studies in both patients and healthy populations have demonstrated the ability of the use of non-invasive brain stimulation to influence these pathways, which stem from the cerebellum to the cortex, although

many focus on resulting M1 excitability [49, 50]. Given its unique structure when compared to the cerebral cortex, it is difficult to discern the spread of the cTBS within the cerebellum given the patterns of the folia and the distinct motor and non-motor networks that are formed based on the outputs and reciprocal inputs. A functional connectivity study which employed the use of TBS sought to investigate the specificity of stimulation and its ability to affect differing networks [51]. This work found that both right lateral and midline stimulation did not alter functional connectivity within the motor network [51]. Targeting cerebellar regions thought to be involved in specific processes (ie. cognition) and observing the potential changes in task performance can help to break down what exactly it is the cerebellum does with sensory information and how it communicates with widespread cortical areas beyond M1.

Through the use of cTBS in this present study, it is hypothesized that following transient inhibition of the cerebellum, the MMN present at fronto-parietal sites in response to deviant stimuli will be blunted so that the cortical activity in response to deviant stimuli post transient inhibition will mimic that which is seen in response to frequent stimuli.

2.0 Materials and Methods

2.1 Participants

Twenty healthy, right-handed participants with no known neurological conditions were recruited from the University of Waterloo community (10 males, 10 females; mean age +/- SD = 26 +/- 4.1). The participants were randomly assigned to either the cTBS or sham stimulation group resulting in ten volunteers within each group. All participants provided informed written consent to participate in the study. The University of Waterloo Office of Research ethics approved all experimental procedures.

2.2 Experimental Design

All participants entered a single-blind pre-post experimental design which required them to attend one session. Each participant was administered the Edinburgh Handedness Questionnaire [52] and a transcranial magnetic stimulation (TMS) safety checklist to ensure they were all right-handed and had no contraindications to receiving TMS, respectively. Participants' responses to electrical nerve stimulation were evaluated before and after the application of either cTBS or sham stimulation to the right lateral cerebellum (sham: stimulation coil placed at a 90 degree angle away from the scalp and stimulus intensity at 10%). Participants in the sham group were naïve to both cTBS and TMS procedures. Nerve stimulation was presented in an odd-ball paradigm where there were two types of stimuli, median and ulnar nerve stimulation. The median nerve stimulation served as the frequent stimulation and the ulnar nerve stimulation served as the deviant stimulation. The stimuli were represented in an 80/20 fashion such that the median nerve stimulation occurred 80% of the time and the ulnar nerve stimulation occurred the remaining 20% of the time.

2.3 Experimental Paradigm

Participants were randomly assigned to either the experimental stimulation (cTBS) or sham stimulation group, with both groups participating in the same oddball stimulation paradigm pre- and post-stimulation. TMS thresholding was conducted after EEG cap preparation to ensure appropriate intensity of TMS stimulation was achieved for cTBS, this was followed by nerve stimulation thresholding and set up. The participant was seated comfortably at a desk with a partition placed between them and the experimenter during the nerve stimulation conditions, in order to isolate the participant from distractors. In all conditions participants passively received

nerve stimulation to the right upper extremity while gazing at a white fixation cross in the centre of a computer screen in front of them. The oddball nerve stimulation paradigm was delivered to the right wrist and hand pre- and post-cTBS to the right lateral cerebellum. The pre-cTBS nerve stimulation trials consisted of two blocks of nerve stimulation, each consisting of 240 total stimuli with frequent and deviant stimuli presented in an 80/20 ratio. Therefore, in a block of 240 stimuli, 197 median nerve or frequent stimuli and 43 ulnar nerve or deviant stimuli occurred. Each block lasted approximately 6 minutes, with the stimuli occurring at an average of 1.36 seconds apart (range of 1.26-1.46 seconds); having a range of interstimulus interval times was used to decrease predictability of the stimuli. Following administration of cTBS to the right lateral cerebellum, the post-cTBS nerve stimulation trials began. The oddball stimulation paradigms were identical to that of the pre-cTBS trials, however there were more blocks performed in an effort to quantify the timeline of the effects of cTBS on cerebellar function. For the post-trials, nerve stimulation was performed at 3 time points following cTBS (Post 1, 2, 3 – beginning at 0, 15, 30 min post-cTBS). During each post-cTBS time point, two blocks of nerve stimulation were delivered as in the pre-cTBS trials to ensure that there were a sufficient number of deviant trials to average as they were significantly less in number than the frequent trials and lasted a total of 36 minutes. This same protocol was conducted pre- and post-sham stimulation.

In order to ensure that the response being measured to deviant stimuli is in fact due to a change-detection process, rather than activating different afferents due to the difference in stimulation parameters, a standard omitted (SO) protocol was also performed for one block before cTBS stimulation. This trial consisted of only the ulnar nerve stimulation identical to that used in the oddball paradigm (approximately 240 ulnar nerve stimuli).

2.4 Stimuli

Electrical stimuli were delivered to the median and ulnar nerve at the right wrist and 5th digit respectively. The stimuli consisted of electrical pulses which were 0.1 ms in duration delivered at a rate of 0.98 Hz (GRASS, S88X stimulator, West Warwick, Rhode Island, USA). The nerve stimulation was delivered through a custom LABVIEW program (National Instruments, Austin, TX, USA). The stimuli delivered to the median nerve were done so through two Ag/AgCl ECG conductive adhesive skin electrodes (MEDITRACE™ 130, Ludlow Technical Products Canada Ltd., Mansfield, MA). These electrodes were placed over the median nerve on the skin 2-3 cm proximal to the distal wrist crease, between the tendons of the flexor pollicis longus and palmaris longus with the anode distal. To familiarize participants to the stimulus and set an appropriate intensity, motor thresholding was performed and the recurring stimuli were delivered at this intensity for the median nerve. Motor thresholding is defined as the lowest possible intensity at which a visible muscle contraction of the abductor pollicis brevis (APB) was elicited. The stimuli delivered to the ulnar nerve was done via ring electrodes placed on the fifth digit (anode distal) to stimulate a digital nerve in the ulnar nerve distribution. Intensity for the ulnar nerve stimulation was determined by sensory thresholding. The intensity was slowly increased until the participant reported a consistent sensation (lowest perceptual threshold) at which point the intensity was increased 2.5 times this and the stimuli to the ulnar nerve was delivered at this intensity for the remainder of the experiment (ie. 2.5x perceptual threshold).

2.5 cTBS Parameters

Application of cTBS was performed using a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure eight coil (MCF-B65). Stimulation intensity was set at 80% of the active motor threshold (AMT) for the right APB, according to the stimulation protocol as

outlined by Huang et al. [53]. To determine AMT, the stimulation coil was placed on the participant's scalp (over the EEG cap) at the optimal location over the left M1 that would elicit motor evoked potentials (MEPs) from the contralateral APB. This was done by placing the centre of the coil around the C3 electrode of the EEG cap, which aligns with the approximate location of M1 according to the 10-20 system; the coil was manipulated from this position in order to find the optimal location to stimulate the APB. Coil placement and orientation was continuously monitored using Brainsight (Brainsight 2; Rogue Research, Montréal, QC, Canada), a TMS neuronavigation system that displays real-time coil placement and target location on an anatomical magnetic resonance image (MRI), a standardized MRI template was used to ensure that the coil placement and orientation were consistent. The coil was oriented tangential to the scalp with the handle pointing posterior and 45° away from the midline to activate the corticospinal system. MEPs were measured using surface EMG over the right APB using two surface electrodes (MEDITRACE), two active electrodes were placed over the muscle belly and a ground was placed over the right radial styloid process. AMT was defined as the lowest stimulator output required to produce a MEP of >200 microvolts in 5 out of 10 trials during a 10% maximum voluntary isometric contraction as measured using an oscilloscope which was situated in front of the participant so that both the participant and experimenter could monitor the constant contraction intensity.

For the sham condition, the TMS unit was set to 10% of maximum stimulator output. The participants could hear the stimulator pulses, but the coil was oriented at 90° up and away from the scalp. It is important to note that the individuals in the sham group still received the protocol to determine the active motor threshold. During cTBS, bursts of three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 seconds, which yields a total of 600 pulses [53].

In order to stimulate the right cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm lateral to the right of the inion [54, 55, 56].

2.6 EEG Parameters

EEG data was recorded using a full 64-channel EEG cap (Quick-Cap, Neuroscan, Compumedics, NC USA) to measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement and referenced to the linked mastoids. Impedances were maintained < 5 kΩ and continuous EEG data was collected, filtered (0.2-1000 Hz), digitized at 1000 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC USA) and stored on a computer for offline analysis. EEG analysis began with epoching to the nerve stimuli followed by baseline correction to the pre-stimulus interval. Epochs were 400 ms in length, beginning 100 ms before stimulus onset and epochs contaminated by muscle contractions, eye movements or blinks were removed by visual inspection before averaging. The final averaged traces for each block for frequent stimuli contained on average, 237 artifact-free epochs, minimum 132; and for deviant stimuli, 94 artifact-free epochs, minimum 57.

2.7 Data Analysis

The amplitudes of evoked potentials were measured peak-to-peak, from the peak of interest to the preceding potential of opposite deflection. As two separate groups were being compared to one another (cTBS and sham stimulation), the data was expressed as a proportion of the pre-stimulation baseline values so as to make the magnitude of individual amplitude measurements comparable. All 20 participants who took part in this study were included in the analysis of EEG data.

The goal of this study was to test the hypothesis that the cerebellum is involved in the processing of purely sensory stimuli and to further investigate its role in modulating the cortical change-detection process in response to deviant stimuli. The goals of the statistical analysis were to test the specific hypotheses of (1) the presence of a much larger negativity in response to deviant stimuli versus frequent stimuli and (2) whether this large negativity was modulated by cTBS over the cerebellum in a way that decreased its amplitude in response to deviant stimuli post-cTBS. To do this, a three-factor mixed-model analysis of variance (ANOVA) was performed in SPSS (IBM, Version 25) to compare mean peak amplitude changes with factors of TIME (pre, post 1, post 2, and post 3) and STIMULUS (frequent, deviant) as within factors and a factor of GROUP (cTBS, sham) as the between factor. Statistical significance was set at $p=0.05$. Data was checked for normality to ensure that assumptions for performing the ANOVA were upheld.

A t-test was used to compare pre-cTBS amplitudes of the ulnar nerve stimulation in both the SO protocol and oddball paradigm. Amplitudes for the pre-cTBS time point of SO and oddball were compared. An alpha level of 0.05 was used to define statistical significance for any effects.

3.0 Results

The EEG traces demonstrated a clear N140 component in response to nerve stimulation, which was maximal parieto-occipitally, in the 140-200 ms latency range. As stimulation of the cerebellum was delivered over the lateral right side, amplitude and latency measurements for the N140 were reported from electrode PO3. A small but reliable N60 was also observed parieto-occipitally and was maximal at the CP3 electrode in the 50-90 ms latency range and was therefore measured from this electrode site. Prior to cTBS stimulation of the cerebellum, there

was a much larger cortical negativity parieto-occipitally in response to the deviant nerve stimulations when compared to the frequent nerve stimulations, taken to be the mismatch negativity response (MMN). Additionally, the P100 was also reliably observed within the 90-150 ms latency range and measured within parieto-occipital electrode, PO3 of the left hemisphere. These components were visible in both cTBS and sham control groups as seen within Figures 1 and 2.

For the N60 peak, the three-factor mixed design ANOVA showed no significant interaction effects between any within-subjects factors (stimulus, or time), nor were any main effects observed. Furthermore, no main effects were observed for the between-subjects factor of group.

For the P100 peak, the ANOVA revealed a significant interaction of stimulus by time ($F_{3,54}$=8.658, p=0.011, η^2= 0.062, 1-β=0.082). To investigate this interaction further, two separate one-way ANOVA analyses were performed for the stimulus types, frequent and deviant across the four time points. The ANOVAs revealed that there was a significant difference between time and the frequent stimuli ($F_{3,79}$=8.561, p=0.037; for post 1 η^2= 0.26, 1-β=0.068; for post 2 η^2= 0.17, 1-β=0.073, for post 3 η^2= 0.31, 1-β=0.076). Post-hoc testing showed that this difference was specifically between time point one (pre) and time point four (post 3) for the frequent stimuli (p=0.05). Qualitatively, the peak amplitude of the P100 in response to frequent stimuli slightly decreased from baseline values when measured at the third timepoint.

For the N140 peak, the ANOVA demonstrated a significant 3-way interaction between factors of time by group by stimulus ($F_{3,54}$=35.056, p<0.0001, η^2= 0.45, 1-β=0.09). To further explore the interactions present and better represent the overall group difference that was

observed for the N140 peak, separate two-way ANOVAs were performed, separated by group, cTBS and sham respectively. Within the cTBS group, the ANOVA showed that there was a significant interaction between frequent and deviant stimuli types for the N140 peak amplitude across the time points ($F_{3,36}$=36.377, p<0.001, η^2= 0.27, 1-β=0.082). Post hoc testing using Tukey's test revealed that these differences were not present across all time points, but specifically during the pre (p<0.001) and post 1 (p=0.001) time points. This demonstrates that the MMN was diminished over time post cTBS in response to deviant stimuli. Figure 1 shows the grand average traces which demonstrate these changes in peak amplitude that occur between frequent and deviant stimuli from the baseline trials (1.A) to the post 3 time point for the cTBS group (1.B).

For the sham group, the ANOVA showed a significant difference between frequent and deviant stimuli types for the N140 peak amplitude across the timepoints ($F_{3,36}$=13.397, p<0.0001, η^2= 0.056, 1-β=0.076). Post hoc testing using Tukey's test revealed that these differences between deviant and frequent stimuli were present across all time points pre (p<0.0001), post 1 (p<0.0001), post 2 (p<0.0001) and post 3 (p=0.0001). Comparison between the two groups can be observed in Figure 2, which shows the grand average traces of frequent and deviant stimuli across time points for the Sham group. This demonstrates that the MMN remained present in response to deviant stimuli post cTBS for the duration of the experiment.

These between and within group differences are further demonstrated in Figure 3, which depicts the mean amplitude difference between stimulus types for the cTBS and sham groups. The mean amplitude differences were calculated by subtracting the amplitude of the N140 peak in response to frequent stimuli from the amplitude of the N140 peak in response to the deviant stimuli. It is clearly seen here that within the cTBS group, that the mean amplitude difference is

large during the pre-cTBS time point and that the presence of this difference deteriorates as time continues post cTBS. However, within the sham group, it can be seen that the presence of this large mean amplitude difference stays constant throughout all time points. It is quite clear that prior to cTBS stimulation, a large peak amplitude presents in concordance with a change detection mechanism required to identify a deviant stimulus, and following cerebellar cTBS, this mechanism may be affected as there is a loss of amplitude difference between the two stimuli. No significant differences in latency were observed for any of the peaks.

In order to ensure that the differences seen in amplitudes between the frequent and deviant stimuli were in fact due to a change detection mechanism and not due to different afferents being activated in response to the altered stimuli, trials in which the ulnar nerve stimulation was the sole stimuli provided (SO) were compared to trials in which the ulnar nerve stimulation was delivered in the context of deviant stimuli (OB). For the comparison, amplitude averages of the N140 from baseline (pre) SO trials were compared to the baseline (pre) trials of the cTBS group. The t-test indicated that there was a significant difference in amplitude ($p<0.001$). There was also a significant difference in latency ($p=0.04$) between the two groups, with OB trials having a longer latency than SO trials. These differences are demonstrated in Figure 4.

4.0 Discussion

This work adds to the body of research, which posits that at some level, the cerebellum plays a role in the processing of sensory stimuli that is not needed for the purpose of a motor action or goal. The major findings of this study were (1) that interspersing deviant somatosensory stimuli amongst frequent stimuli elicits a clear parieto-occipital negativity, the

MMN and (2) that the characteristic MMN is modulated following transient inhibition of the right lateral cerebellum.

As previously mentioned, the MMN is defined as an electrical response evoked by a discriminable change in any regular or repeated somatosensory stimulation elicited in the absence of attention [57]. Although this response has been routinely explored following exposure to auditory stimuli, it has also been elicited in response to visual, olfactory and somatosensory stimuli [58, 59, 60]. The MMN responses evaluated in response to somatosensory stimuli have historically been studied the least. Furthermore, replicating the MMN has not been consistent, potentially due to the nature of the stimuli used and variability in study participants (ie. vibrotactile stimuli, two-point discrimination tasks, lesion locations). This is why the use of a healthy population and a control group are so critical to the design of this study to further our knowledge on the role of the cerebellum in modulating the MMN during a controlled somatosensory stimulation task. Following the application of cTBS specifically to the right lateral cerebellum, the presence of a large negativity in response to deviant stimuli is gradually reduced, becoming maximally reduced 30 minutes following stimulation. This finding is further strengthened via the continuous presence of the large negativity in response to deviant stimuli across all time points in the Sham group.

In order for a change to be detected, there must be a preserved sensory representation of the regular or repeating stimuli. In observing that there is a clear difference in response to the deviant stimuli compared to the frequent stimuli, this provides evidence for the presence of a cortical mechanism responsible for recalling past events used in order to predict future events. While the neural correlates of this mechanism are still not fully known, it is thought that it differs from those circuits which are involved in the cortical responses seen as the N140 in frequent

stimuli trials [14]. This thought is supported by the current study as the cortical responses to the ulnar nerve stimulation in the standard omitted trials differed from that of the responses to the same stimuli following its presentation as a deviant stimulus in the oddball paradigm. This is also supported by the distribution of activity seen with the MMN maximal at parieto-occipital electrodes as opposed to a more frontal N140 distribution; this has been observed in previous studies which have presented somatosensory stimuli in an oddball paradigm [31, 35].

The cerebellum has long been discussed as having a comparator function in order to facilitate coordination in motor behaviour. The way in which the cerebellum is able to control these functions smoothly is thought to be via efference copies of the planned movement with the sensory feedback that is produced by the actual or current movement [61, 62]. The major route for information access to the cerebellum, the climbing fibres and the interactions with the mossy fibre system are considered to be the basis of this comparator function that the cerebellum is responsible for [61]. During active, self-generated movements, transmission of major input to the cerebellum is found to be gated; however, the presence of altered or unpredictable stimuli increases the transmission of information in the cerebellum [63]. This pattern of information flow within the cerebellum would serve to store initially, the expected outcome from a stimulus following repeated exposure to it and then update this previously stored event following the occurrence of an unfamiliar stimulus. A prominent feature of the cerebellum is its uniform organization that is repeated throughout its cortex [64]. It is known that the cerebellum receives input from a variety of higher-order, non-motor areas such as the cingulate cortex, posterior parietal cortex and frontal cortex and viral tracing techniques have demonstrated that there is a significant amount of output from the cerebellum to these non-motor areas [16]. Based on the ubiquity of the cerebellum's organization and the presence of non-motor loops, perhaps the same

processing role that the cerebellum performs for motor input is extended to input for these non-motor association areas.

A major aspect of the oddball paradigm was the requirement of participants to receive nerve stimulation passively, without having to overtly respond to the presence of the stimuli. The experiment was designed in this way in order to evaluate the cerebellum's role in the processing and integration of sole sensory stimuli. Measuring the MMN is best recorded using passive conditions where the individual's attention is not focused on the stimuli [65]. One caveat however, is that in order to elicit the MMN response desired in this experiment the stimuli presented must differ substantially and it is therefore difficult to discern whether the participant's attention is covertly shifted to the stimuli as the sheer difference in stimuli may attract attention beyond the control of personal will and instructions. Attention is critical for all aspects of daily living and research has demonstrated that attentional deficits are related to sensory processing issues, demonstrating there is an overlap between the processes of sensory integration and attention [66, 67, 68]. This therefore poses a larger question with regards to the cerebellum's role in the processing of sensory information and its comparator responsibility. The relatively stable nature of N60 and P100 throughout the experiment in comparison to the N140/MMN lends support to the pre-attentive mechanism of the change detection as these peaks have been shown to be modulated by changes in attention [69, 70]. The interaction effect that is observed for the P100 in response to deviant stimuli between the two groups at the Post 3 time point may be indicative of a stronger gradual shift of attention within the Sham group over time, although the slight difference in change of amplitude direction may be the main driving force behind this finding.

There are distinct networks that have been implicated in attention, namely the dorsal attention network (DAN), which is comprised of mainly frontal and parietal regions [39, 40]. Functional connectivity work has demonstrated that there are also cerebellar nodes involved in the DAN and that when these cerebellar nodes of the DAN are targeted with non-invasive stimulation techniques which have been shown to transiently facilitate neural activity, improvements in attentional lapses alongside enhanced DAN activity are observed [41, 71]. This is perhaps not surprising given the known presence of connections between the cerebellum and non-motor association areas, however more work needs to be performed to understand how the cerebellum may be exerting these effects upon distal cortical areas. Functional imaging has shown the presence of cerebellar activity during a visual attention task in an area completely distinct from areas of activation during motor performance [72]. Cerebellar patients have presented with impaired verbal fluency although, as mentioned, patient studies are often conflicting due to the nature of variability stemming from differences in cerebellar tumors, degeneration and lesions [31, 73]. A study by Arasanz et al. [55] administered cTBS over the right lateral cerebellum in a fashion similar to the current experiment and found that following cTBS, there was a reduction in phonemic fluency with specific regard to category switches. Category switches allow for the meaningful organization of word groups or clusters, this is reflective of executive and strategic mental processes [74]. An increased amount of category switches allows for increased word generation, generally within such tasks, most words are generated within the first 15 seconds, referred to as the early phase. Following cTBS, this ability to switch categories was found to be the most impaired during the early phase of the task, once again supporting the role of the cerebellum in executive functioning and cognition, which is heavily relied on in the early moments of category switches [55]. The ability to switch categories

in a time sensitive manner can be linked back to the concept of attention and the cerebellum's potential role in this higher order function. Another study by Arasanz et al. [54] found that following cTBS to the right lateral cerebellum, there was a decrease in accuracy to detect a second target in a string of letters when the second target was presented in a shorter time frame following the first or initial target (120-400 ms), this interference is known as the attentional blink phenomenon (AB). Studies have posited that the AB is predicted by the magnitude of attention resources that an individual places on the initial target [8, 54]. It is possible that the cerebellum plays a role in modulation of attentional resources that are required to switch and detect the next target or event rapidly, a concept reminiscent of the rapid switch in attention needed for word generation as well [54, 55].

These alterations in cerebellar activity during cognitive tasks clearly demonstrate that the cerebellum is not solely functioning during motor control activities. There is growing evidence in the literature and in this present study that lends support to the cerebellum having separate modules influencing different behavioural functions such as cognition and attention. These facets of behaviour work alongside movement in order to form meaningful actions in an ever-changing multisensory environment. Therefore, a study which includes both transient modulation of cerebellar output in conjunction with directly orienting and/or manipulating a participant's attention towards target stimuli would allow for a better understanding of how the cerebellum can aid in facilitating higher-order processes. It could be possible that the cerebellum's role in comparison serves to act as the regulator of other cortical regions which are involved in execution of more specific functions. Using multiple groups and larger sample sizes in future studies would be beneficial in garnering a more stable understanding of which critical parts of processing the cerebellum is involved in. Although the sample size within this study is smaller,

the use of the control group and SO condition aid in strengthening the concept of the cerebellum's role in distinguishing pertinent stimuli based on past experience and context.

Given the unique cytoarchitecture and connections of the cerebellum, it is challenging to confirm whether what we know about the mechanism of cTBS as it pertains to M1 holds true for when stimulating over the cerebellar cortex. Studies have aimed to test the efficacy of TBS protocols on the cerebellum by measuring its influence on M1 excitability and have found that following cerebellar cTBS there is a resulting decrease in thalamocortical drive, as demonstrated by suppressed M1 excitability and reductions in MEP amplitudes [46]. Imaging studies also provide evidence for the efficacy of TBS as they have demonstrated bidirectional changes in network connectivity between the cerebellum and associative cortical areas depending on whether the TBS protocol delivered transiently increased (iTBS) or decreased (cTBS) cerebellar activity [51, 75]. Although these changes in network connectivity show a clear effect of TBS, it is unclear as to where in the network these changes are greatest, especially when considering the connections that exist between the cerebellum and subcortical areas. Although these structures are distant from the stimulation site, longer lasting effects may be a product of altered communication with areas such as the inferior olive or basal ganglia [76]. Continued investigation into exactly how these changes are mediated and whether they affect other widespread areas equally using TBS need to be performed and prudent attention to coil placement and orientation is needed due to the compact topography of the cerebellum. Studies which alter the stimulation intensity and which investigate location specificity through stimulation of both cerebellar hemispheres would help to elucidate this.

Lastly, the current study did not include any behavioural measures; a critical next step would be to alter participant's attention while having them respond to target stimuli in a sensory

task. Combining cortical responses and behavioural measures provides an avenue for us to better understand how the cerebellum may be involved in linking information that is required when we engage in higher-order processes. This has the potential to increase our understanding of some of the challenges and deficits seen in attentional and behavioural disorders.

5.0 Conclusions

This work demonstrates that even during an unattended condition, when deviant electrical somatosensory stimuli are interspersed amongst frequent stimuli they elicit a modulation of the N140 SEP peak. The use of cTBS to inhibit the cerebellum transiently validates the presence of cerebellar input to this cortical peak, as abnormalities are seen following cTBS. Specifically, this work strengthens the current theories and evidence that support the role of the cerebellum in somatosensory processing. Following transient inhibition of the cerebellum, there is a removal of the change detection that was seen pre-inhibition. This is further supported by the findings of the standard omitted protocol which strengthened the evidence that the changes seen during the oddball were due to the deviant stimuli and not the type of nerve stimulation. Also, the N60 which is attentionally driven and related to frontal areas, remains relatively stable throughout all paradigms. This further supports that across all conditions even though the sensory information is still reaching the cortex, with abnormal cerebellar input there is limited context relevance since the cerebellum is less efficiently able to perform its pre-attentive assessment of incoming information. Further work must be performed in order to understand the behavioural implications that cerebellar input, or the lack thereof has on performance, learning and potentially higher-order executive processes.

Acknowledgements

The authors would like to acknowledge the following organizations for support and funding: Natural Sciences and Engineering Research Council of Canada (NSERC) for a research grant to WRS and the Ontario Graduate Scholarship Fund (OGS) for scholarship support for DA.

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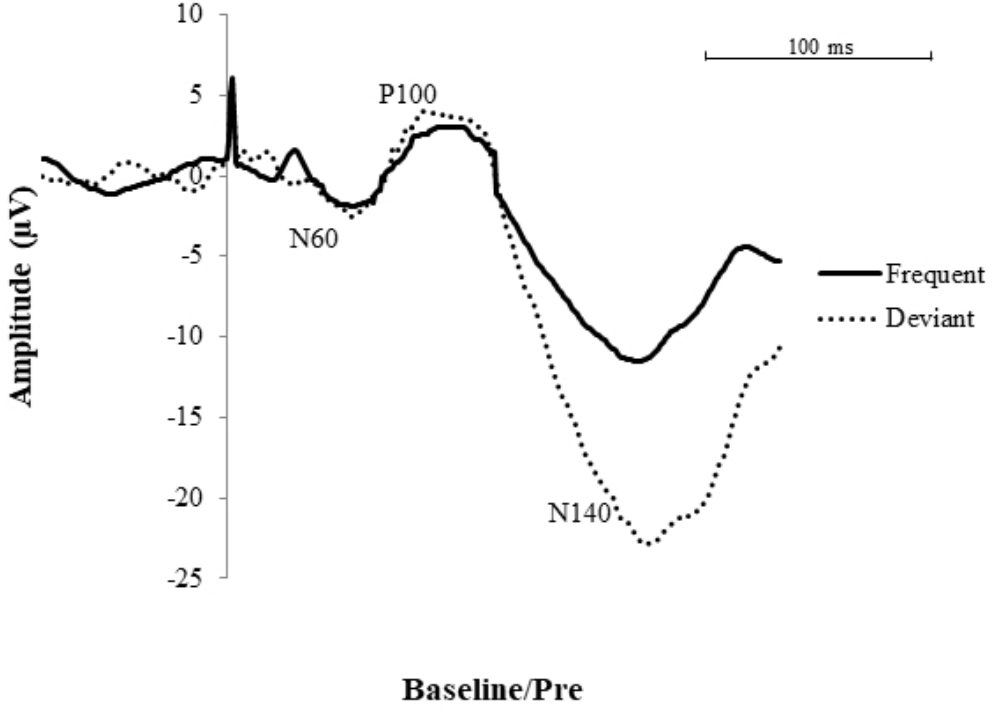
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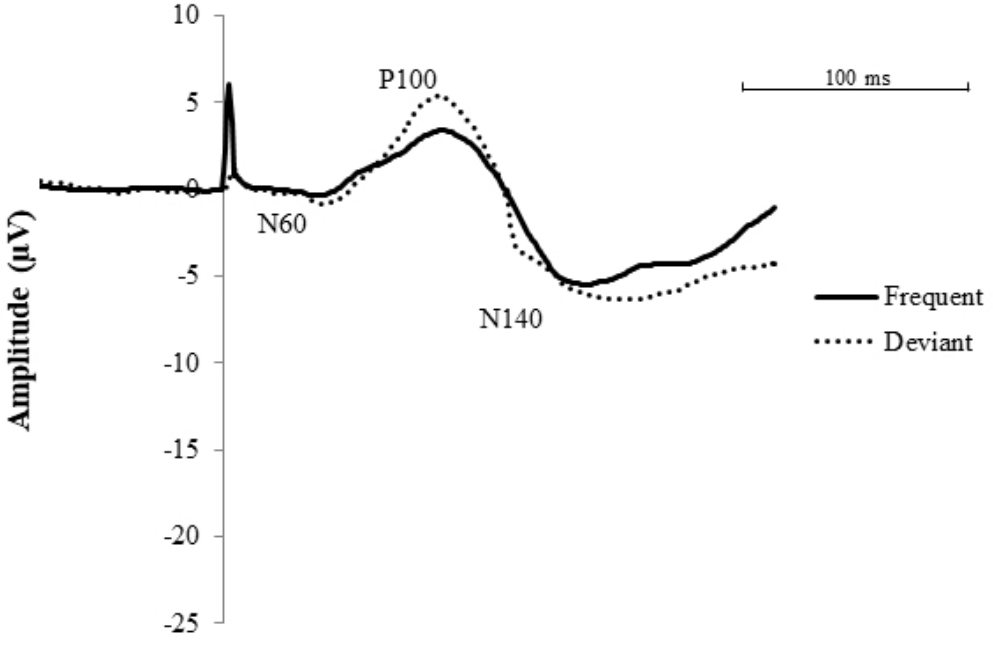
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1.A

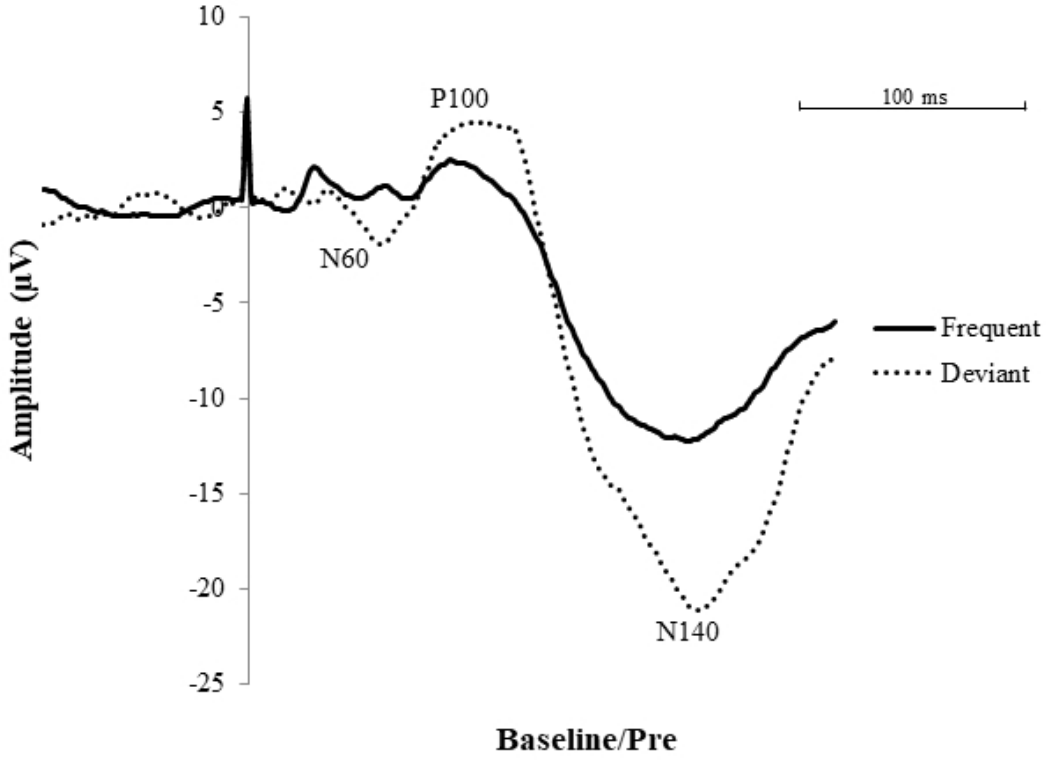

10
5
0
-5
-10
-15
-20
-25
100 ms
P100
N60
N140
Amplitude (μV)
Frequent
Deviant
Baseline/Pre

1.B

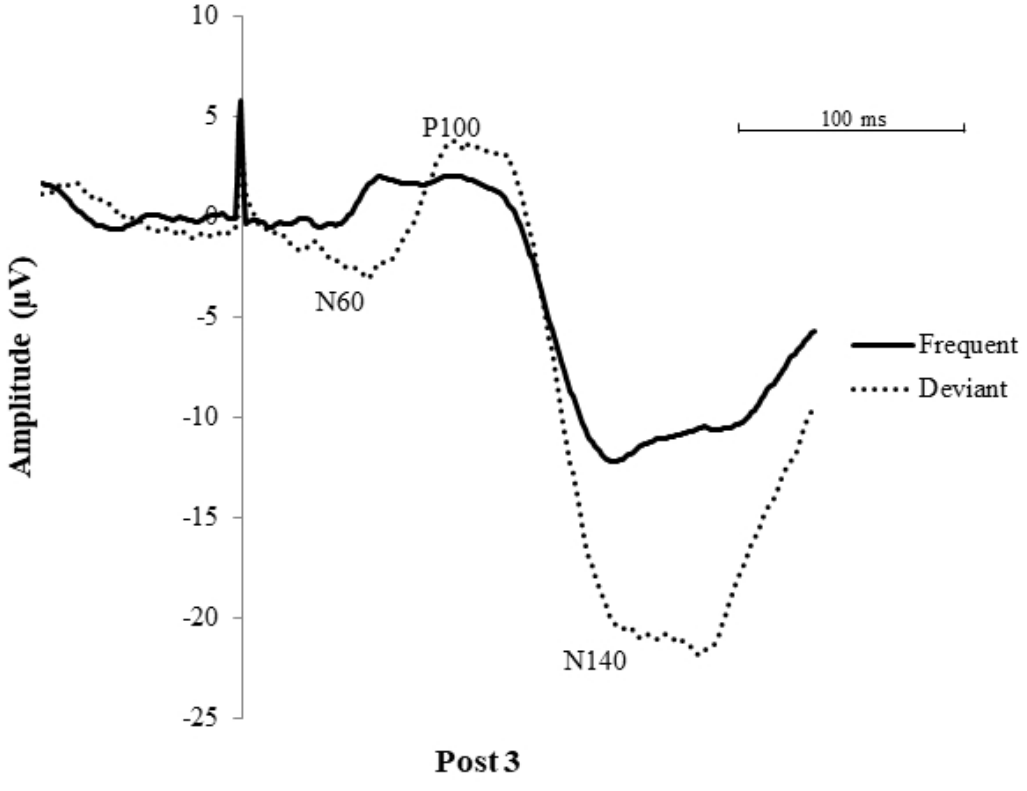

10
5
0
-5
-10
-15
-20
-25
Amplitude (µV)
P100
N60
N140
100 ms
Frequent
Deviant

Post 3

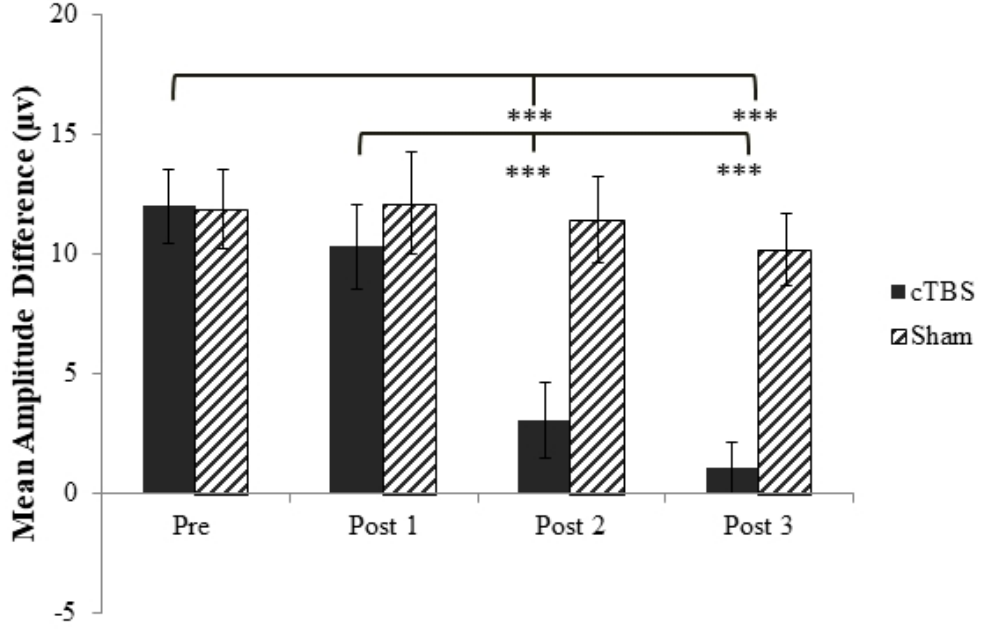
2.A


10
5
0
-5
-10
-15
-20
-25
Amplitude (µV)
P100
N60
N140
100 ms
Frequent
Deviant
Baseline/Pre

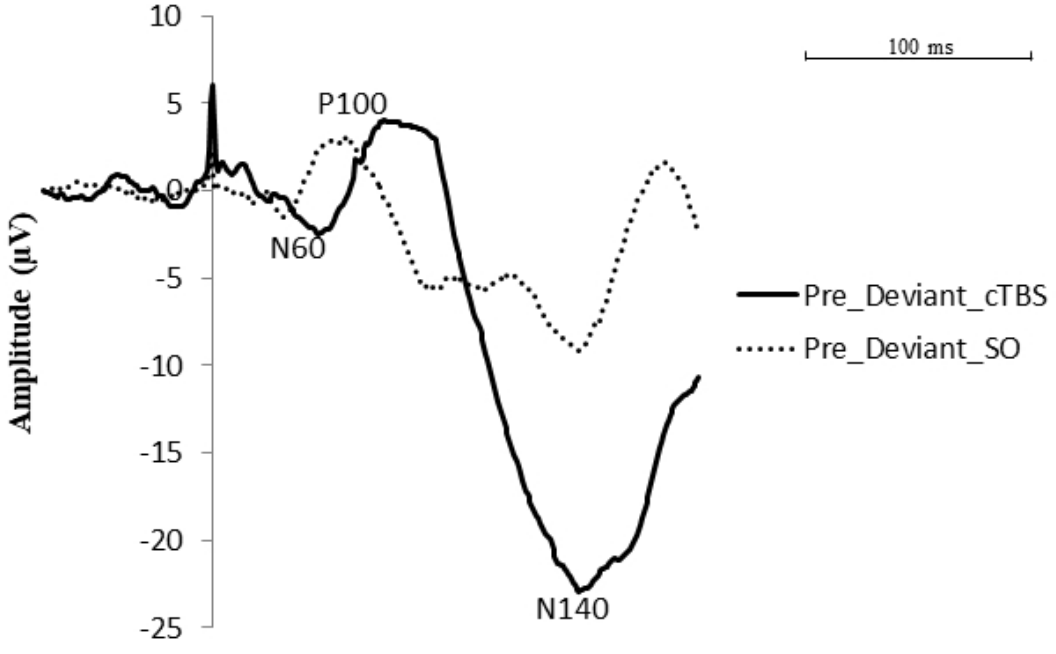
2.B


10
5
0
-5
-10
-15
-20
-25
Amplitude (µV)
P100
N60
N140
100 ms
Frequent
Deviant
Post 3

3.


20
15
10
5
0
-5
Mean Amplitude Difference (μv)
***
***
***
***
Pre
Post 1
Post 2
Post 3
cTBS
Sham

4.


10
5
0
-5
-10
-15
-20
-25
Amplitude (μV)
100 ms
P100
N60
N140
Pre_Deviant_cTBS
Pre_Deviant_SO