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Modulatory Effects of Theta Burst Stimulation on Cerebellar Nonsomatic Functions

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Abstract Clinical and functional imaging studies suggest that the cerebellar vermis is involved in the regulation of a range of nonsomatic functions including cardiovascular control, thirst, feeding behavior, and primal emotions. Cerebello-hypothalamic circuits have been postulated to be a potential neuroanatomical substrate underlying this modulation. We tested this putative relationship between the cerebellar vermis and nonsomatic functions by stimulating the cerebellum noninvasively via neuronavigated transcranial magnetic stimulation. In this randomized, counter-balanced, within-subject study, intermittent theta burst stimulation (TBS) was applied on three different days to the vermis and the right and left cerebellar hemispheres of 12 right-handed normal subjects with the aim of modulating activity in the targeted cerebellar structure. TBS-associated changes were investigated via cardiovascular monitoring, a series of emotionally arousing picture stimuli, subjective analog scales for primal emotions, and the Profile of Mood States test. All 36 sessions of cerebellar stimulation were tolerated well without serious adverse events. Cardiovascular monitoring pointed to a mild but significant decrease in heart rate subsequent to vermal stimulation; no changes were detected in systolic or diastolic blood pressure measurements. Subjective ratings detected a significant increase in Thirst and a trend toward increased Appetite following vermal stimulation. These observations are consistent with existing neurophysiological and neuroimaging data indicating a role for the cerebellum in the regulation of visceral responses. In conjunction with the modulatory function of the cerebellum, our results suggest a role for the vermis in somatovisceral integration likely through cerebello-hypothalamic pathways. Further research is warranted to elucidate the potential mechanisms underlying the cerebellar modulation of nonsomatic functions.

Keywords Transcranial magnetic stimulation (TMS) · Theta burst stimulation (TBS) · Vermis · Cerebellum · Somatovisceral integration · Nonsomatic modulation

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Introduction

Beyond the long-established role of the cerebellum in somatic motor coordination, the cerebellum also appears to be engaged in the integration of cognitive, emotional, and visceral responses and modulation of behaviors around a homeostatic baseline in response to the internal and external environmental stimuli [1–9]. Further, evidence from clinical investigations and functional imaging and resting state connectivity studies corroborate the notion that the cerebellum is topographically and functionally organized for motor, cognitive, and affective behaviors that map

onto the underlying neuroanatomical circuits that subserve these domains [10–17]. Cerebellar histological architecture is essentially uniform throughout [1, 6, 18], and thus, the diverse array of functions with which the cerebellum is involved is likely the consequence of its bidirectional connections with the prefrontal, posterior parietal and superior temporal cortices, limbic system, monoamine producing brainstem nuclei, and the hypothalamus [5, 8, 9, 19–28].

The hypothalamus is a key neuroendocrine structure involved in the control of vegetative and behavioral functions, with a sizeable influence on vital homeostatic functions including thirst, feeding behavior, energy metabolism, thermal regulation, and circadian rhythms in addition to its role in the endocrine system [29]. Further, as an integral component of the limbic system, it participates in the expression of emotion and formation of behavioral responses, mainly by triggering primal emotions related to preservation and/or survival of the species, such as fear, anger, aggression, or sexual excitement.

The cerebellum shares bidirectional connections with the hypothalamus [30–35]. Cerebello-hypothalamic axons originate from all cerebellar nuclei (fastigial, interposed, and dentate nuclei), course in the superior cerebellar peduncle, decussate, and follow the cerebello-thalamic bundle before entering the hypothalamus [36]. Most cerebello-hypothalamic fibers terminate contralateral to their origin while sparse numbers recross and terminate ipsilaterally in the lateral, dorsomedial, ventromedial, and paraventricular nuclei of the hypothalamus [37, 38]. Indirect multisynaptic projections have also been demonstrated between the cerebellum and the hypothalamus through brain stem reticular nuclei [39]. Electrophysiological studies describe evoked potentials in the hypothalamus following stimulation of the cerebellum, notably in vermal regions [19, 40, 41].

It has been proposed that the cerebello-hypothalamic circuits might provide the essential neuroanatomical pathways for cerebellar modulation of visceral activities [42]. Indeed, there is accumulating evidence regarding cerebellar involvement in feeding [43–51], thirst [52, 53], cardiovascular regulation [54–59], sexual function [60–65], fear conditioning [66–72], and nociception [73–76]. These reports suggest a functional relationship between the cerebellum and the hypothalamus in the control of autonomic states relevant to emotional expression.

Given the reciprocal connections between the cerebellum and the hypothalamus, we were interested to determine whether modulating cerebellar activity might lead to changes in nonsomatic functions. In this study, we aimed to examine the cerebellar topographic organization of nonsomatic functions using repetitive transcranial magnetic stimulation (rTMS), which enables the noninvasive modulation of brain activity. TMS can temporarily modulate the activity in the targeted cortical region and can induce distant effects by means of transsynaptic spread along functional networks [77]. Theta burst stimulation (TBS) is a relatively new asynchronous train paradigm of rTMS with shorter application time and longer-lasting neuromodulatory effects than traditional rTMS protocols [78, 79]. The aftereffects of TBS likely involve long-term potentiation (LTP) or long-term depression (LTD)-like synaptic changes depending on the stimulation protocol [80]. Intermittent TBS (iTBS) induces an increase in the cortical excitability of the motor cortex, similar to high frequency rTMS, whereas continuous TBS (cTBS) leads to the opposite effects [78]. In a similar vein, cerebellar iTBS has been shown to result in increased contralateral motor-evoked potential (MEP) amplitudes while cTBS led to decreased MEP amplitudes [81]. TBS of the cerebellar hemispheres seems capable of inducing distant changes as revealed by the modulation in the intracortical circuits of the interconnected contralateral motor cortex [81]. Further, the possibility of TBS-induced long-lasting plastic modification in the cerebello-thalamo-cortical circuits has been highlighted by two recent studies which reported clinically appreciable benefits in patients following ten consequent sessions of cerebellar TBS [82, 83]. The precise mechanisms of the TBS effects on the cerebellum are yet to be elucidated.

In the light of several reports providing evidence for LTP/LTD-like changes in the cerebellum [84, 85] and the possibility that TBS induces lasting changes in cerebellar activity, we aimed to modulate activity in the right, left, or midline regions of the posterior cerebellum using intermittent TBS. We hypothesized that stimulation of the vermal region would result in more robust changes in nonsomatic functions compared with stimulation of the cerebellar hemispheres. In an attempt to search for cerebellar involvement in nonsomatic functions comprising autonomic responses, survival functions, and emotional processes, we measured changes in the cardiovascular system, regulation of food and water intake, defense against attack, sexual arousal, and emotional behavior.

Methods

Participants

Twelve healthy subjects (six males, all right-handed, mean age 28.8±9.94 years) were recruited to participate in these studies. None had a history of neurological or psychiatric disease and all had normal or corrected to normal vision. Subject selection followed the guidelines for TMS research [86, 87]. All participants provided written informed consent before being enrolled in the study in accordance with the

Beth Israel Deaconess Medical Center Institutional Review Board and were paid for their participation. Participants were not informed of the hypotheses of the study.

Experimental Design

Transcranial Magnetic Stimulation

All subjects underwent a T1-weighted whole brain anatomic magnetic resonance imaging (MRI) scan (0.5 mm resolution) performed on a Phillips 3-T scanner (Philips Medical System, Best, The Netherlands). The MRIs were acquired for the use of Brainsight frameless stereotaxic system (Rogue Research Inc., Montreal, Quebec, Canada) during the stimulation in order to enable precise targeting and decrease interindividual variability.

We employed a randomized, counter-balanced, within-subjects experimental design to compare the TBS-induced effects depending on the site of cerebellar stimulation. Each subject received a total of three TBS stimulation sessions over three different cerebellar locations (right, left, and midline). In each session, we applied iTBS pattern (20 trains of 10 bursts given with 8-s intervals, 600 pulses) at 100% of active motor threshold intensity. All stimulations were applied using a MagPro X100 stimulator (Tonica, Farum, Denmark). A figure-of-eight coil connected to the stimulator was held tangentially with the handle pointing upwards. Each TMS session was performed on a separate date with a minimum gap of 24 h, and the order of stimulation sites was counter-balanced across subjects. The precise locations of stimulation included vermal lobules VI and VII, and lobule VII - Crus I of the right and left cerebellar hemispheres [88, 89] (Fig. 1). Consequently, a total of 1,800 stimuli were delivered to each participant throughout the study. These parameters are well within current safety guidelines [87]. Side effects were collected using standard forms, and a visual analog scale for subjective rating of pain was obtained before and after each stimulation.

Assessments

Cardiovascular Functions In order to investigate the cerebellar modulation of cardiovascular functions, we assessed alterations in blood pressure and heart rate, which represent the final outputs of cardiovascular control. Heart rate and blood pressure monitoring comprised a total of 12 blood pressure and heart rate measurements throughout 1 session (6 measurements before and 6 measurements after the TBS with approximately 5 min interval). Measurements were taken from the upper left arm while the participants were sitting comfortably. Automatic digital blood pressure equipment was used at all times.

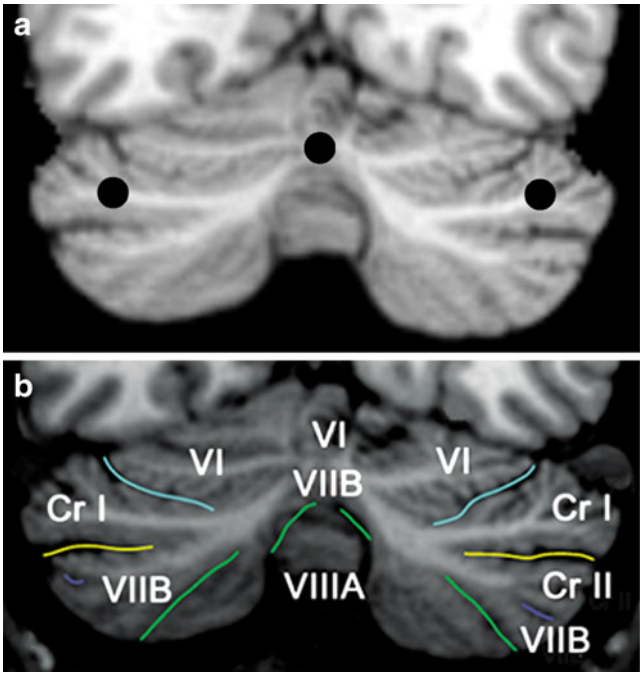

Fig. 1 The illustration depicts the areas of theta burst stimulation. **a** The *black circles* represent the three locations of stimulation comprising vermis lobule VII and right and left crus I. **b** Coronal section of cerebellum indicates the anatomical borders of cerebellar lobules (modified from Schmahmann et al. [89])

Primal Emotions Engendered by Basic Autonomic Systems Visual analog scales comprising subjective ratings of a range of primal emotions were performed before and 10 min after each TBS session in order to investigate the cerebellar influences in the regulation of food and water intake, defense against attack, and sexual arousal processes and to assess whether certain primal emotions would be selectively affected following stimulation of any specific region. Self-report visual analog scales included Thirst, Appetite, Fear, and Libido categories. The scales were presented, on separate pages, as 100 mm horizontal lines (0 = not at all, 100 = extremely). Subjects were asked to mark the point that best represents their perception of their current state. The subjects were not permitted to consume food or beverage during testing.

In addition, subjects were presented a series of emotionally arousing and neutral picture stimuli derived from the International Affective Picture System (IAPS) in order to assess picture-evoked emotions [90]. IAPS presentation comprised 20 picture stimuli equally distributed to five content categories, including Threat, Mutilation, Erotic, Peace, and Neutral scenes. Six different series, equivalent in normative ratings of valence and arousal, were constructed according to the IAPS normative ratings [84]. Participants were asked to fixate on a 24-in. computer screen throughout the 6 s that each picture was displayed and rate how they feel as for arousal (9 = most arousing, 1 = least arousing),

affective valence (9 = most pleasant, 1 = most unpleasant), and dominance (9 = controlled, 1 = in control) during the 12-s gap in between the pictures. The pictures were presented in a pseudorandomized order restricting more than two successive presentations of the same stimulus category. The IAPS presentation was carried out at the end of all assessments in order to avoid possible influence of the visual images on other test measures [91].

Mood and Emotional Expression Self-report Profile of Mood States (POMS), including standard ordinal scales of 65 items and 6 subscales comprising Depression, Tension, Anger, Vigor, Fatigue, and Confusion, was administered. In order to be able to distinguish milder differences that might not be detected by the POMS ordinal scale, the participants were also asked to rate the continuous analog scales, labeled Happiness, Sadness, Anxiety, Anger, Alertness, and Energy.

Data Analysis

Due to the small sample size of the study, the differences in tested variables were computed using nonparametric statistics in order to be more conservative and reduce a priori assumptions [92]. Between variations in cerebellar stimulation locations were tested for significance using nonparametric analysis of variance tests (Friedman ANOVA). If the Friedman test detected a significant difference between the three groups, right, midline, and left areas were compared in pairs via Wilcoxon signed-rank tests. Possible correlations were tested using the Spearman's rho correlation analysis method. Because this study was exploratory in nature, Bonferroni adjustment was not used for statistical inference. In all circumstances, $P<0.05$ was reported to indicate a statistical significance while $P<0.1$ was considered to indicate a trend.

Results

Overall, no serious adverse events occurred in the 36 sessions. All subjects tolerated the TBS well; the only reported side effect was local pain at the stimulation site, which was responsive to acetaminophen. Subjects did not endorse any difference in mood or feelings following stimulation regardless of the TBS site. There was no significant difference in the *Pain* VAS scales between pre- and post-TBS ratings among the three groups (Friedman: $\chi^2=2.94$; $P=0.7$). However, subjects' self reports suggested better tolerability of vermal stimulation and higher pain sensitivity during lateral cerebellar stimulation, likely due to contraction of neck muscles. There was no correlation between subjective ratings for pain and intensity of stimulation.

Analyses for the systolic or diastolic blood pressure showed no significant group differences following TBS. There was, however, a significant interaction between heart rate and the three TBS stimulation conditions (Friedman: $\chi^2=6.29$, $P<0.05$). Between-group comparisons revealed a significant decrease in heart rate following vermal stimulation when compared with the left cerebellum ($P<0.05$) while a trend ($P=0.059$) was present in comparison with the right side (percent change ± SD in heart rate following stimulation of vermis −5.25±1.26, right cerebellum −4.84±1.33, left cerebellum −6.1±2.12) (Fig. 2).

Friedman tests computed separately for each IAPS category detected no significant effects of TBS in response to the Threat, Mutilation, or Erotic scenes categories. In line with this finding, no significant effects of TBS were found on subjective ratings for Fear or Libido. However, the most salient results were detected in the ratings for Thirst. The subjective ratings for Thirst exhibited a clear difference between the three groups following TBS (Friedman: $\chi^2=6.79$, $P=0.034$). Vermal TBS was found to significantly increase thirst compared to the right side ($P<0.01$) and exhibit a trend towards increase when compared to the left ($P=0.09$) (Fig. 2). Likewise, a Friedman test pointed a trend toward increased Appetite following vermal stimulation (Friedman: $\chi^2=5.29$, $P=0.07$). Finally, Friedman tests revealed no significant condition effect of TBS in the total POMS score, its Depression, Tension, Anger, Vigor, Fatigue, and Confusion subscales or corresponding subjective ratings for these emotions.

Discussion

The present study investigated whether modulating cerebellar cortical activity via TBS might induce changes in nonsomatic functions in healthy individuals and whether the cerebellum would show a specific topography for these functions. Our results expand upon the existing neuroanatomical and functional neuroimaging background pointing to a cerebellar influence upon the hypothalamus and provide clinical support that the cerebellum is involved in cardiovascular control, thirst, and feeding behavior. According to our findings, there appears to be topographic arrangement of cerebellar influence on nonsomatic responses, in that the changes were noted after simulation of the cerebellar vermis compared with the cerebellar hemispheres.

In this exploratory study, cardiovascular assessments revealed a significant decrease in heart rate following the theta burst stimulation of the posterior vermis. There is now

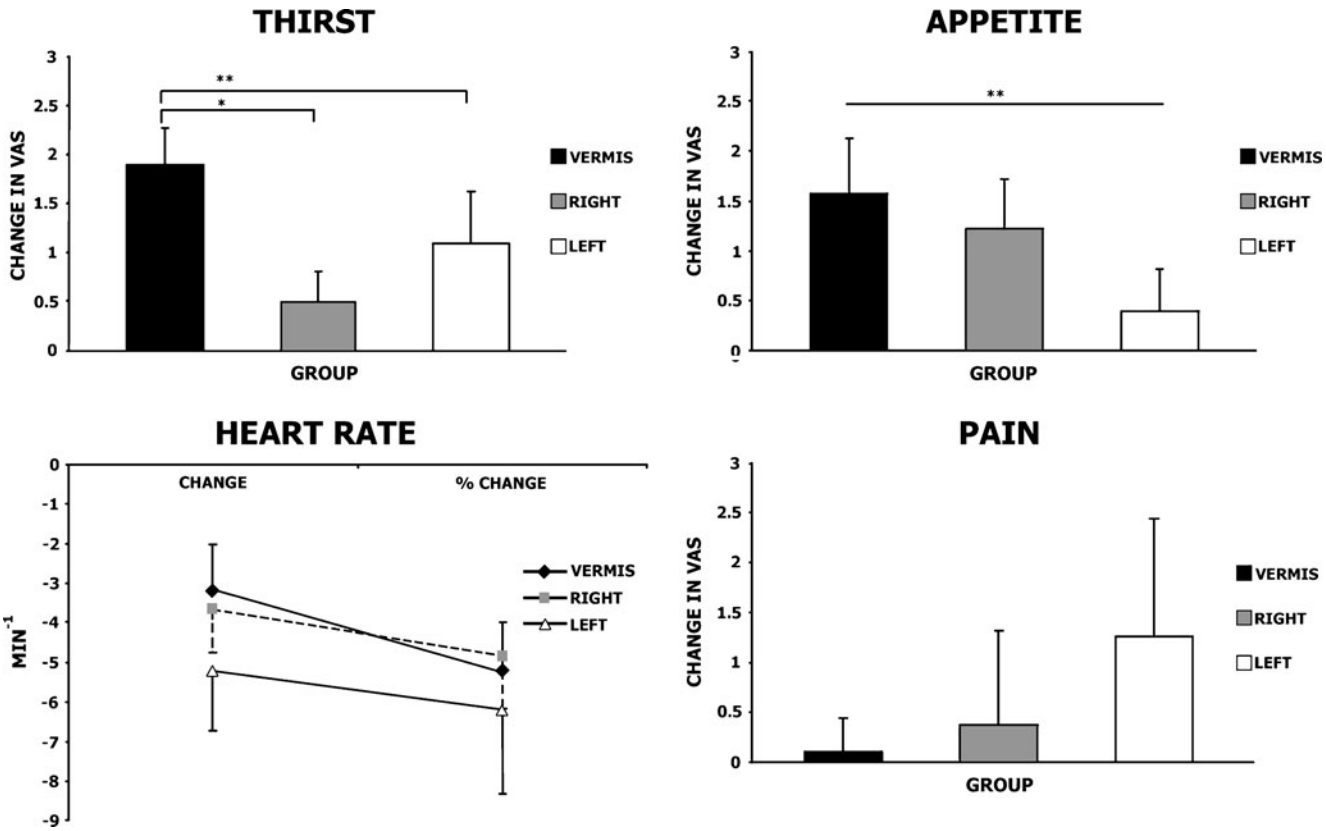

Fig. 2 The graphs demonstrate the elicited effects following intermittent theta burst stimulation of the vermis and the right and left cerebellar hemispheres (*$P<0.05$, **$P<0.1$)

substantial evidence from neuroimaging and animal lesion studies pointing to involvement of the cerebellar vermis in autonomic cardiovascular control [42, 54, 55, 57, 93–95]. Specifically, the medial vermal cortex of lobule VIIA has been demonstrated to receive ipsilateral vagal afferents suggesting that lobule VIIA may participate in the regulation of cardiovascular functions [94]. Further, the medial cerebellum, particularly vermal lobules VI–VII, has been shown to participate in heart rate conditioning and the conditioned bradycardic response [55, 57, 58, 96–98]. The fastigial nucleus may also be involved in autonomic cardiovascular modulation as part of the baroreceptor reflex, and vermal stimulation may lead to changes in arterial blood pressure, heart rate, and regional blood flow [42, 54, 56, 59]. Our observations thus elaborate upon these earlier findings and provide experimental evidence in humans in favor of a role for the posterior cerebellar vermis in nonsomatic cardiovascular regulation.

A significant finding in our study was that modulation of vermal activity via iTBS was associated with increase in subjective ratings of Thirst. This finding is consistent with functional neuroimaging studies, which report involvement of the cerebellum in the emergence of thirst [52, 53]. In particular, the correlation of regional cerebral blood flow with subjective thirst showed activation in the vermal central lobule (lobule III), and hypertonic sodium chloride infusion led to moderate thirst and activation in the lingula (lobules I and II), anterior and posterior quadrangular lobes (lobules IV through VI), and vermal lobules VIIAt and VIIIB [52]. The deep cerebellar nuclei project to the hypothalamic paraventricular nucleus, a plausible neuroanatomical substrate for this effect. Disynaptic pathways to the paraventricular nucleus have been detected following stimulation of neurons in the fastigial nucleus [99–101], and the cerebellar interpositus nucleus also projects to the paraventricular nucleus [102, 103]. Histamine and GABA have been suggested as possible neurotransmitters in hypothalamocerebellar projections, but little is known regarding the neurotransmitters of the cerebello-hypothalamic projection [42, 104]. It is possible that the effects reported here might be mediated through angiotensin II, a peptidergic neurotransmitter abundantly expressed in the cerebellum [105], which has an excitatory influence on the neurons of the paraventricular nucleus [106, 107]. Angiotensin II, together with its derivative angiotensin III, is a potent dipsogenic mediator that induces drinking behavior while regulating sodium and water intake [108–110].

We also observed a trend towards increased appetite following vermal stimulation. In conjunction with the present observations, several animal lesion experiments

and functional neuroimaging studies support the involvement of the cerebellum in feeding behavior [44, 45, 111]. Hunger and appetite are associated with increased blood flow in the cerebellum [44, 111] whereas satiation reduces cerebellar blood flow [112, 113]. Glucose ingestion leads to an initial activation in the anterior cingulate, supplementary motor area, somatosensory cortex, and the cerebellum, followed by a decrease in cerebellar vermal and medial hypothalamic activity during the second peak [45]. In a recent fMRI study, restrained eaters showed activation only in the cerebellum during the fasting state when they were presented highly palatable food [49]. Cerebellectomized animals develop altered feeding behavior patterns and decreased body weight compared to sham-operated and control animals [43]. Paradoxically, hemicerebellectomy in rats was reported to result in worse outcomes than bilateral cerebellar damage, with loss of apparent feeding motivation and high mortality rates [46]. Further, lesions of cerebellar lobule VI or the paramedian lobule lead to decreased caloric intake and body weight [114]. The cerebellar fastigial and interposed nuclei modulate functional activity of the lateral hypothalamus that has been associated with hunger [51], and the cerebellum is rich in critical feeding- and reward-related hypothalamic neuropeptides originating from the medial and lateral hypothalamus, such as orexin, melanin-concentrating hormone, alpha melanocyte stimulating hormone, and neuropeptide Y [98, 115]. Indeed, a recent study reported the involvement of serotonin and neuropeptide Y as neurotransmitters during cerebellar regulation of food intake [48]. Taken together with these observations, our findings provide support for the notion that the cerebellum participates in the regulation of feeding control.

In contrast, the results of this study did not provide evidence in support of our prediction that cerebellar vermal stimulation would lead to alteration in mood state in healthy subjects. We have noted improved mood following ten consequent sessions of cerebellar vermal TBS in patients with schizophrenia [83], and it is possible that the modulatory upregulation of cerebellar neural systems engaged in affect is clinically effective only in pathological states when the internal milieu is not concordant with the external environment. Further, consecutive sessions of TBS might provide more robust effects than a single session of TBS.

We have previously proposed that the computation unique to the cerebellum (the universal cerebellar transform, UCT) is required to maintain behaviors around a homeostatic baseline and that the UCT is applied to different domains of neurological function determined by the anatomically defined cerebrocerebellar connections [5, 8, 9]. Indeed, fundamental mechanisms underlying the cerebellar contribution to non-somatic functions have yet to be elucidated and will need to be addressed in future studies. With regard to the effects elicited through cerebellar TBS, this study for the first time suggests the possibility of plastic modification in cerebello-hypothalamic circuits using TBS, in parallel with two recent studies which have raised the prospect of inducing plasticity in the cerebello-thalamo-cortical circuits via the use of cerebellar TBS [82, 83]. The existence of direct connections from the cerebellar cortex to the hypothalamus has not yet been demonstrated [36]. Hence, it is possible that the effects reported here could be indirect and mediated through vermal projections onto the fastigial and interpositus nuclei [116–118]. Alternatively, direct stimulation of cerebello-hypothalamic axons originating from these inner cerebellar nuclei might have accounted for these findings.

Our study has certain limitations. We attempted to modulate activity in localized regions of the cerebellar cortex by using a figure-of-eight coil that allows greater precision and neuronavigational software that enables accurate and reliable cerebellar targeting. It is possible, however, that there may have been stimulus spread to other nontargeted cerebellar sites by virtue of intrinsic cerebellar functional connectivity [119, 120]. It is also plausible that the measures we assessed could have been influenced not only by the vermis, but also by one or both cerebellar hemispheres. These factors, together with our relatively small *n*, might increase the possibility of a type II error. Further, this was an exploratory study and we did not control for diurnal variations or for subjects' food and liquid consumption and the amount of sleep the night before testing. We used a randomized counter-balanced design to address these limitations, but we cannot completely exclude the possibility that these factors influenced our results. The significant effects that we detected were not consciously reported by the subjects, and the stimulation was well tolerated with no concerns raised regarding the safety of this procedure.

Conclusion

The present results indicate that the cerebellum may have a modulatory influence on several nonsomatic functions including cardiovascular control, thirst, and feeding behavior. In a manner consistent with previous clinical, anatomical, and functional neuroimaging evidence, our findings further implicate the posterior cerebellar vermis as an integral node for somatovisceral integration.

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Conflict of Interest Notification The authors report no conflicts of interest related to this study that might bias this work.

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