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Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia

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ABSTRACT

Background: Early invasive electrical stimulation studies suggested that enhancement of cerebellar vermal activity might prove valuable in symptomatic treatment of refractory neuropsychiatric diseases via modulation of emotion and affect. This proof of principle study aimed to test this hypothesis using noninvasive brain stimulation, and to explore the safety of this protocol in schizophrenia.
Methods: Eight treatment-refractory patients with schizophrenia underwent ten sessions of intermittent theta burst stimulation (TBS) to the cerebellar vermis using MRI-guided transcranial magnetic stimulation (TMS). Assessments included side effect questionnaires, cardiovascular monitoring, psychiatric evaluations and comprehensive neuropsychological testing before and after TBS and at one-week follow-up.
Results: Overall, TBS was tolerated well with mild side effects primarily comprising neck pain and headache. No serious adverse events occurred. Diastolic blood pressure (BP) showed mild decreases for five minutes post-TBS; no significant changes were detected for systolic BP or pulse. PANSS negative subscale showed significant improvements following TBS and during the follow-up. Calgary Depression Scale and self-report visual analog scales for *Happiness* and *Sadness* pointed to significant mood elevation. Neuropsychological testing revealed significantly fewer omissions in working memory and interference conditions of a Continuous Performance Test, a longer spatial span and better delay organization on the Rey–Osterrieth Complex Figure during follow-up. No significant worsening in psychiatric or neuropsychological measures was detected.
Conclusions: Theta burst stimulation of the cerebellar vermis is safe and well-tolerated, while offering the potential to modulate affect, emotion and cognition in schizophrenia. Future randomized, sham-stimulation controlled studies are warranted to support the clinical efficacy of this technique.

1. Introduction

The possibility of a pathophysiogical role for cerebellum in schizophrenia has become increasingly likely (Weinberger et al., 1979; Snider, 1982; Schmahmann, 1991; Andreasen

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et al., 1996). Clinical reports of patients with cerebellar pathology provide evidence for a cerebellar role in cognition, affect and psychosis (Keschner et al., 1937; Rubinstein and Freeman, 1940; Courville and Friedman, 1940; Keddie, 1969; Smith, 1975; Hamilton et al., 1983; Schmahmann, 1991, 1997, 2000; Sandyk, 1993; Jurjus et al., 1994; Schmahmann and Sherman, 1998; Spranger et al., 1999; Tashiro et al., 1999; Turner and Schiavetto, 2004; Duggal, 2005; Schmahmann et al., 2007; Tavano et al., 2007). Neuroimaging and postmortem studies in schizophrenia report cerebellar dysmorphology, and altered gray–white matter proportions in the vermis (Nopoulos et al., 1999; Loeber et al., 2001; Ichimiya et al., 2001; Okugawa et al., 2002, 2003; Joyal et al., 2004; Levitt et al., 1999; Lee et al., 2007; Lawyer et al., 2009), decreased Purkinje cell (PC) input to the deep nuclei and reduction in size and linear density of the PC layer (Eastwood et al., 2001; Tran et al., 1998; Reyes and Gordon, 1981). Further, accumulating evidence indicates prominent cerebellar dysfunction within the cerebello-thalamo-cortical networks in schizophrenia and points to lower N-acetylaspartate levels and volumetric reductions in cerebello-thalamo-cortical networks (Rusch et al., 2007; Deicken et al., 2001; Ende et al., 2005), disrupted connectivity in the middle and superior cerebellar peduncles (Okugawa et al., 2004, 2005, 2006; Kyriakopoulos et al., 2008; Magnotta et al. 2008), and disruption of the interactions between cerebellum and cerebral cortex by way of the thalamus as shown by transcranial magnetic stimulation (TMS) and positron emission tomography (PET) (Daskalakis et al., 2005; Andreasen et al., 1996, 1998).

It now appears that cerebellum is a critical neuromodulator not only of motor control but also of intellect and mood, optimizing these functions that are represented with topographic precision in distinct regions of the cerebellum (Stoodley and Schmahmann, 2010). The cerebellar vermis and fastigial nucleus (the limbic cerebellum [Snider, 1976; Heath, 1977; Schmahmann, 1991]) seem to be particularly involved in the regulation of emotion and affect (Stoodley and Schmahmann, 2009). They are connected with limbic/paralimbic regions in the frontal and temporal lobes, amygdala hippocampus, septal region, hypothalamus, periaqueductal gray matter and monoamine brainstem nuclei (Anand et al., 1959; Riklan et al., 1974; Cooper et al., 1976; Tolbert et al., 1976; Batini et al., 1978; Heath et al., 1978; Snider, 1982; Schmahmann, 2001), and manipulation of the vermis in animals and humans produces alterations in complex behaviors and mood (Reis et al., 1973; Heath, 1977; Berman et al., 1978).

In the 1970s Cooper (Riklan et al., 1974; Cooper et al., 1976) implanted stimulators on the cerebellar surface to treat epilepsy, hypothesizing that cerebellar cortical stimulation would induce upstream inhibition of cerebral cortex via inhibition of thalamus. In addition to improvements in epilepsy, patients demonstrated improved attention and amelioration of aggression. Heath and colleagues (Heath, 1977; Heath et al., 1980) followed up their observations of abnormal electrical activity within the cerebellar vermis and limbic sites in emotional disorders, by high frequency electrical stimulation of cerebellar vermal–paravermal regions for the treatment of schizophrenia, severe neurosis and uncontrollable aggression; and reported clinical improvements. These invasive manipulations suggested a direct relationship between cerebellum, mood and psychosis, but they have not been replicated.

In the current era, repetitive TMS (rTMS) is a promising therapeutic tool for refractory neuropsychiatric diseases on the basis of neural network modulations, and is a noninvasive analogue to electrical stimulation (Pascual-Leone et al., 1996; George et al., 2000; Kobayashi and Pascual-Leone, 2003). Theta burst stimulation (TBS) is a relatively new rTMS protocol that modulates activity in the underlying region in a shorter period of time, enabling more potent and longer-lasting post stimulation effects compared with standard rTMS (Huang et al., 2005; Stefan et al., 2008). Consecutive sessions of TBS have been employed safely and with promising clinical efficacy in schizophrenia (Bor et al., 2009; Sidhoumi et al., 2010), levodopa induced dyskinesias (Koch et al., 2009), spasticity (Mori et al., 2010) and depression (Chistyakov et al., 2010). Notably, ten sessions of TBS to lateral cerebellar hemispheres have led to improvement in levodopa-induced dyskinesias, highlighting the capability of TBS to augment long lasting plasticity via modulation of the cerebello-thalamo-cortical circuits (Koch et al., 2009).

Here, we conducted the first clinical trial to test whether enhancing cerebellar vermal activity using intermittent TBS (iTBS) may be a safe noninvasive method for augmenting the cerebellar modulation of the putatively dysfunctional neural networks in schizophrenia. The primary objective of this study was to determine the safety and tolerability of repeated sessions of iTBS over the cerebellar vermis. As a secondary aim, we explored the potential therapeutic efficacy in an effort to provide an early proof of principle for this novel approach.

2. Methods

2.1. Patients

Eligible subjects were ≥18 years of age, with a DSM-IV diagnosis of schizophrenia diagnosed by a board-certified psychiatrist using the clinician-administered Structured Clinical Interview for DSM-IV Axis I Disorders. For the month before enrollment they received outpatient care, with no visits to emergency psychiatry departments, and on stable doses of psychotropic medications. Exclusion criteria were alcohol or drug abuse in the prior six months, a history of seizures, head injury or prior neurosurgical procedures, DSM-IV diagnosis of other Axis I disorders, contraindications to TMS or MRI, gross organic pathology on neuroimaging, and pregnancy in females.

Eight patients were included in the study (Table 1). All had treatment-refractory schizophrenia, having failed at least three trials of therapeutic doses of antipsychotic use during their lifetime. All had a baseline PANSS score of ≥58, indicating moderate to severe illness at the time of study (Leucht et al., 2005). With one exception, all had been hospitalized several times in the past. Two were medication-free at time of study as a result of self-reported noncompliance. Medications remained unchanged for the duration of the study. Five were smokers; two used alcohol occasionally; all denied substance abuse. All participants were right-handed as confirmed by the Annett's Handedness Inventory (Annett, 1970).

The study was approved by the Institutional Review Board and Scientific Advisory Committee of the Harvard–Thorndike Clinical Research Center (CRC) at Beth Israel Deaconess Medical Center (BIDMC). The approval of the Massachusetts Department of Mental Health was granted by the Central Office

Table 1
Demographic and clinical characteristics of patients with schizophrenia.

	Patients (n = 8)
Gender	
Male	7
Female	1
Age at study entry	
Mean	41 ± 9.2
Min–max	29–54
Education	13 ± 2.1
Age at disease onset	22.5 ± 2.14
Duration of disease	18.9 ± 8.3
Premorbid IQ estimate (WTAR)	103.0 ± 11.6
Current IQ (WASI, Full Scale IQ)	91.5 ± 14.2
Handedness	
Right	8
Race	
Caucasian	8
Schizophrenia subtypes	
Paranoid	4
Undifferentiated	3
Disorganized	1
Medications	
Atypical antipsychotics	8
Antianxiety (benzodiazepines, buspiron)	4
Antidepressant (SSRI)	3
Mood stabilizer (lamotrigine, sodium valproate)	2
Unmedicated	2

Abbreviations: WTAR: Wechsler Test of Adult Reading (Wechsler, 2001); WASI: Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Full Scale IQ derived from Two-Subtest Form (Vocabulary and Matrix Reasoning).

Research Review Committee. Two study investigators explained the study protocol, assessed competency to sign informed consent and discussed potential risks of the study with patients before enrollment. All participants provided written informed consent.

2.2. TBS applications

Anatomical brain MRI (Philips 3T-scanner, 0.5 mm resolution) was performed prior to baseline assessment to enable use of the Brainsight frameless stereotaxic system (Rogue Research, Montreal, Canada) that effectively localizes the area of stimulation throughout the TBS application and ensures consistency of coil placement across days. The precise location of stimulation is illustrated in Fig. 1.

Participants received 10 sessions of TBS to the cerebellar vermis. TBS sessions were administered twice daily (8.30 am and 1.30 pm) on five consecutive days. TBS was applied via a MagPro X100 stimulator and a figure-of-eight cool coil (Tonica, Farum, Denmark) held tangentially to the scalp with the handle pointing upwards. TBS was applied at 100% of active motor threshold (AMT) intensity (*A*/μs) with the standard iTBS burst pattern described by Huang et al. (2005) (3 pulses at 50-Hz repeated at a rate of 5-Hz; 20 trains of 10 bursts given with 8-s intervals; 600 pulses).

2.3. Safety

All patients were admitted to the inpatient CRC of BIDMC during the week of TBS to maximize observation and subject protection (Fig. 2). Animal studies suggest a role for posterior vermis in cardiovascular control (Bradley et al., 1991), therefore

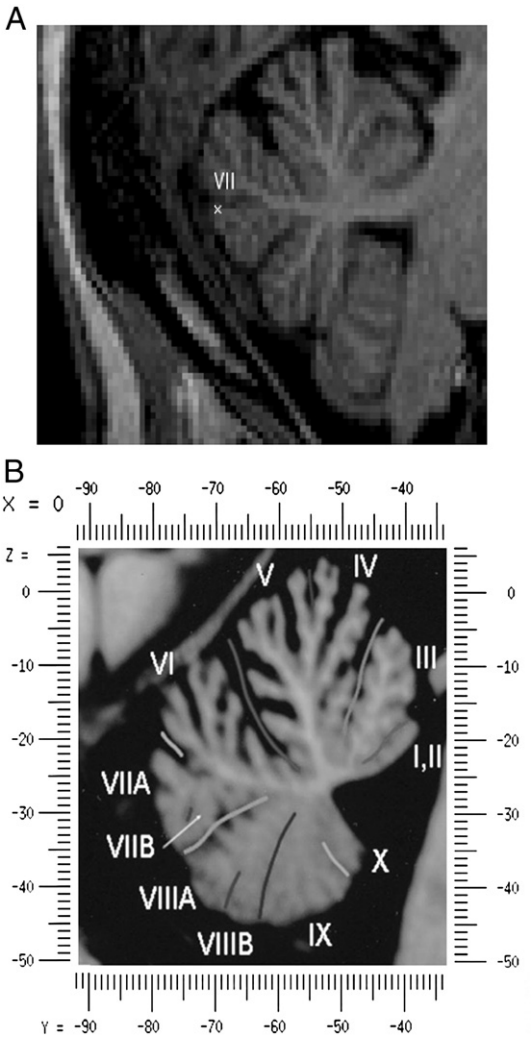

Fig. 1. (A) Location of stimulation in a patient (Talairach coordinates x = 0, y = −82, z = −30). Stimulation was performed using frameless stereotaxic system enabling precise targeting in all patients. (B) Vermis warped into the proportional stereotaxic space of Talairach, midsagittal plane.
Adapted from Schmahmann et al. (1999).

all participants underwent cardiovascular monitoring before and after every TBS application with systemic blood pressure (BP) and heart rate measurements every 5 min for a total of nine times during one session. To avoid possible BP surges potentially influenced by diet, participants were not permitted caffeine, and they were given a low-sodium diet.

Adverse events were recorded using standard adverse event forms, from the start of TBS treatment through the end of study participation. Patients reported pain/discomfort level on a visual analog scale (VAS) before and after each TBS session. Neurological examination focused on cerebellar signs and was repeated after every session. Patients were followed by telephone every other day after discharge to their follow-up visit.

2.4. Assessments

Serial clinical assessments included psychiatric evaluations and neuropsychological testing performed on three

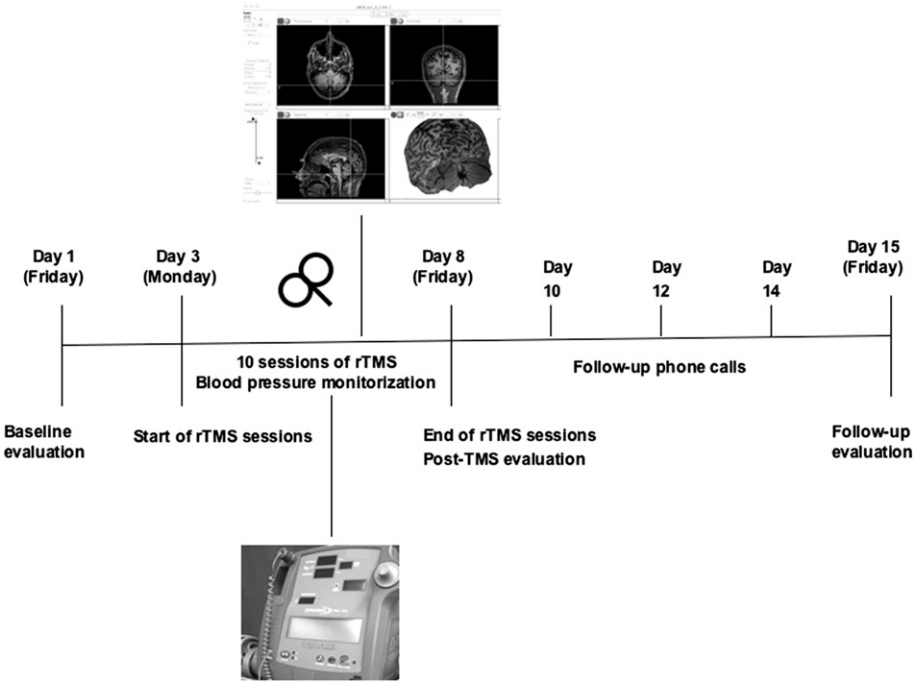

Fig. 2. Schematic representation of the experimental design. Clinical safety evaluations comprised psychiatric and neuropsychological assessments at three time points: prior to and following the application of 10 sessions of TBS, and one week later for follow-up purposes. Blood pressure was monitored throughout each TBS session.

consecutive weeks. Psychiatric evaluations were carried out by an experienced board-certified psychiatrist, a certified rater for Positive and Negative Symptom Scale (PANSS) (LS). Outcome measures for clinical efficacy comprised standardized ratings using the PANSS and Clinical Global Impression (CGI) for rating the symptoms of Schizophrenia, and Calgary Depression Scale for Schizophrenics (CDSS) to index effects on mood. Subjects rated themselves on self-administered scales, including the Profile of Mood States (POMS) test and VAS for dimensions of mood (Happiness, Sadness, Calmness, Anxiety, Wellbeing, Anger, Self-confidence, Fear, Alertness, and Energy).

Table 2 summarizes the neuropsychological battery with emphasis on attention, working memory, long-term memory, speed of processing, executive functions, visuospatial skills, and motor functions. For all time points, tests were administered in the same session by a post-doctoral fellow in clinical neuropsychology (JRC) supervised by neuropsychologists experienced with clinical assessment of individuals with schizophrenia (LJS, WSS). To minimize practice effects, alternative versions were used where possible. Raw or standardized scores were used, depending upon the particular measure.

2.5. Statistical analysis

Nonparametric statistical analyses were performed due to the small cohort. Baseline, post-TBS and follow-up evaluation scores were compared using nonparametric Friedman's ANOVA. When appropriate, post-hoc comparisons were performed using Wilcoxon signed-rank test. Spearman's rho was employed for nonparametric correlational analyses to explore possible associations. Given the exploratory character of the study, the alpha level was not lowered using Bonferroni's correction. Resulting p-values <0.05 were considered statistically significant while p-values of <0.1 were reported to show a trend. Cohen's *d* effect sizes were computed to estimate effects that might be overlooked due to the small sample size and to compare magnitude of change in a standardized way across disparate measures (Cohen, 1994). Analyses were carried out using STATA statistical software (version 9.1).

3. Results

3.1. Safety

All patients completed the protocol without complications. Side effects were mild including neck pain and headache (both responded to acetaminophen), discomfort at the location of stimulation, and light-headedness. The pre- and post-TBS VAS for pain/discomfort did not detect a significant change ($p>0.05$). Inpatient stay with low-sodium and caffeine-free diet was tolerated by all patients but one; our last patient received eight of ten sessions of TBS because he refused to stay more days at the CRC unit. No seizures occurred. Neurological examination did not change. Patients reported no new symptoms or worsening of existing symptoms.

3.1.1. Cardiovascular monitoring

There were no cardiovascular adverse events. Friedman tests yielded a significant effect of TBS on diastolic BP ($\chi^2=26.19$, $p<0.001$) but not for systolic BP or pulse rate. Diastolic BP measured immediately post-TBS and five minutes later showed mild decreases ($p<0.01$), with a tendency to return to the baseline thereafter.

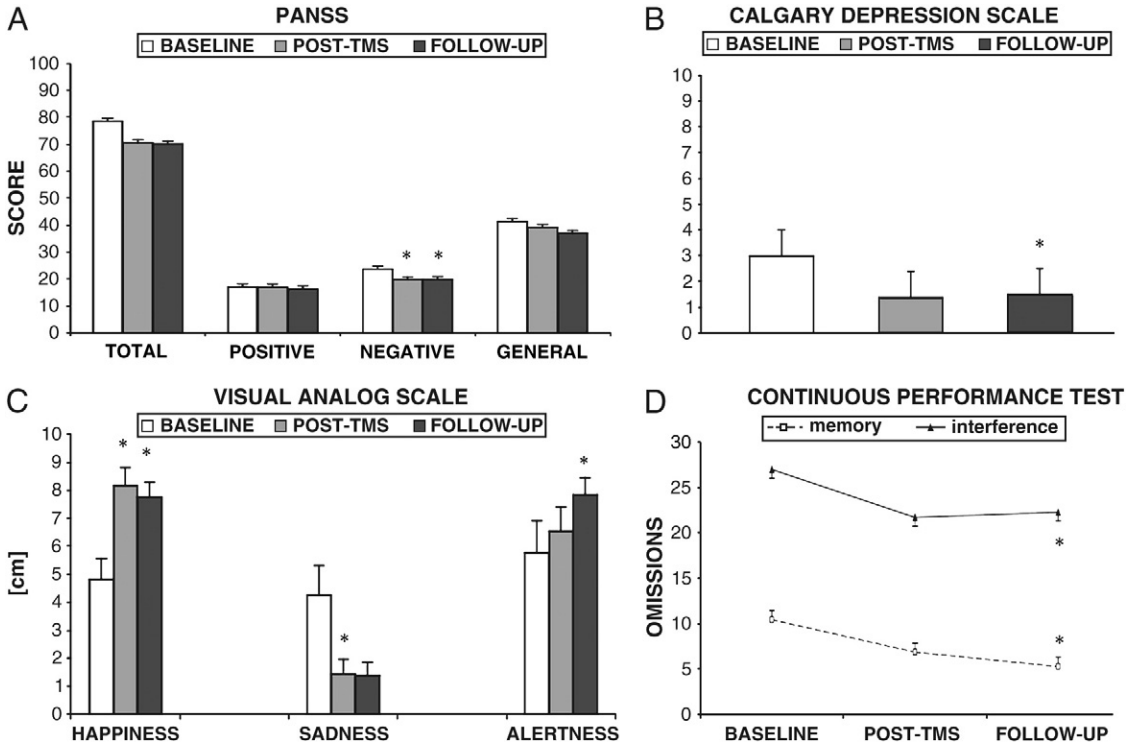

Fig. 3. The graph demonstrates the changes in (A) PANSS and subscales, (B) Calgary Depression Scale, (C) Visual Analogue Scales (*Happiness*, *Sadness* and *Alertness*) and (D) Continuous Performance Test (omissions during memory and interference conditions) for all time points. Significant changes are marked *.

Highest and lowest BP values for each day were identified to investigate possible trends or fluctuations throughout the study. Changes varied and revealed elevation (N = 3), no change (N = 2), or a decrement (N = 3). Elevation of BP was remarkable in only one patient with a history of hypertension. Overall, the group showed a 6 ± 19 mm Hg mean increase in systolic and 4.85 ± 13 mm Hg increase in diastolic BP ($p > 0.05$).

3.2. Clinical psychiatric data

Friedman test revealed no significant changes between baseline, post-TBS and follow-up PANSS total scores ($\chi^2 = 3.56$, $p = 0.16$). However, when analyzed separately in positive, negative, and general subscales, a significant condition effect of TBS on PANSS negative subscale was detected ($\chi^2 = 9.2$, $p < 0.01$) (Fig. 3). Post-hoc comparisons showed significant differences between baseline vs. post-TBS ($p < 0.05$, $d = 0.69$), and baseline vs. follow-up ($p < 0.01$, $d = 0.60$). The mean peak reduction of the baseline score for negative symptoms was 19.3 ± 12.3% (7.1%–43.8%) and was ≥15% in six patients. Improvement of symptoms showed no correlation with age, age at disease onset, duration of disease or IQ. There was no significant effect of TBS on either positive or general subscales of PANSS, or CGI scale ($p > 0.05$).

CDSS revealed significant increases in mood following TBS ($\chi^2 = 6.8$, $p < 0.05$). Post-hoc tests showed a significant difference only for baseline vs. follow-up ($p < 0.01$, $d = 0.72$) while a trend was present between baseline vs. post-TBS ($p = 0.077$, $d = 0.64$). Parallel results were noted in the POMS; however, comparisons did not reach statistical

Table 2
Neuropsychological battery according to cognitive domains.

Cognitive domain	Neuropsychological test
Attention/vigilance	Auditory Continuous Performance Test (CPT; Seidman, vigilance condition; Seidman et al., 1998)
Working memory	Auditory CPT (Seidman, memory and interference conditions; Seidman et al., 1998)
	Letter–Number Span (Gold et al., 1997)
	Wechsler Memory Scale, 3rd Edition (WMS-III) — Spatial Span (Wechsler, 1997)
Speed of processing	Phonemic/Letter Fluency (FAS; Benton and Hamsher, 1978)
	Category Fluency (Animals; Spreen and Strauss, 1991)
	Brief Assessment of Cognition in Schizophrenia (BACS)-Symbol Coding (Keefe, 1999)
	Trail Making Test: Parts A&B (Reitan and Wolfson, 1985)
Executive functions/	Wisconsin Card Sorting Test (WCST; Heaton, 1981)
Abstract thinking	Delis–Kaplan Executive Function System (D-KEFS) — Proverbs Test (Delis et al., 2001)
Verbal learning	California Verbal Learning Test, 2nd Edition (CVLT-II; Delis et al., 2000)
Visual learning	Rey Osterrieth Complex Figure Test (Denman, 1984)
Motor Functions	Grooved Pegboard (Matthews and Klove, 1964)

significance. A Friedman test for *Happiness* showed a significant overall effect ($\chi^2 = 9.43$, $p < 0.01$). Post-hoc tests revealed significant paired comparisons for baseline vs. post-TBS ($p < 0.01$, $d = 1.39$) and baseline vs. follow-up ($p < 0.05$, $d = 1.2$), with ratings increasing following TBS. There was a significant decrease in *Sadness* ($\chi^2 = 7$, $p < 0.05$); the sole statistically significant difference was observed between baseline and post-TBS conditions ($p < 0.05$, $d = 1.15$) while a trend was present between baseline and follow-up ($p = 0.06$, $d = 1.05$). Friedman test for *Alertness* showed a significant difference ($\chi^2 = 6.2$, $p < 0.05$) and post-hoc comparisons pointed to an increase at follow-up only ($p < 0.05$, $d = 0.8$). Other VAS ratings showed no significant effects; however, the *Anxiety* ($\chi^2 = 4.7$, $p = 0.093$, baseline vs. follow-up $d = 0.84$) and *Fear* ($\chi^2 = 4.68$, $p = 0.096$, baseline vs. post-TBS $d = 0.96$) categories showed a trend toward a reduction.

3.3. Neuropsychological data

Neuropsychological data indicated no significant negative effects of cerebellar TBS on the tested domains (Table 3). Four tests revealed improved performance during post-TBS and follow-up assessments compared to baseline. Continuous performance test (CPT) results revealed significantly fewer omissions during the memory and interference conditions ($\chi^2 = 7.1$, $p < 0.05$). Post-hoc comparisons showed a significant difference only between baseline vs. follow-up time points for both conditions ($p < 0.05$, $d = 0.78$ and $d = 1.04$, respectively). Spatial span forward performance improved significantly between baseline ($\chi^2 = 6.06$, $p < 0.05$) and both post-TBS and follow-up assessments ($p < 0.05$, $d = 0.69$). The delay organization score of the Rey–Osterrieth Complex figure also showed improvement ($\chi^2 = 7.56$, $p < 0.05$) and this was significant for the follow-up assessment ($p < 0.05$, $d = 0.68$).

No test showed significant decline during the study, although Wisconsin Card Sort categories score showed a nonsignificant decrement compared to baseline ($\chi^2 = 1.5$, $p > 0.05$, $d = 0.68$). Overall, we note that 70% of the neuropsychological variables tested were in the direction of improvement (mean $d = +0.33$), 4% showed zero effect sizes, and 26% showed negative effects (mean $d = -0.18$). Thus, this pattern, combined with four significant results indicating improvement, suggests a trend toward improvement in neuropsychological function.

4. Discussion

We have investigated the safety of repeated applications of iTBS over the cerebellar vermis in patients with schizophrenia, and have observed no cognitive decline, psychiatric worsening, or serious systemic adverse events. No seizures occurred; indeed, previous reports indicate reduced seizure activity following electrical stimulation of the cerebellar cortex (Cooper et al., 1976; Heath, 1977; Brighina et al., 2006). Side effects of mild occipital headache were similar to those reported following single cerebellar TBS sessions (Koch et al., 2008). Fluctuations in BP were noted and were generally mild except in one patient with hypertension. The posterior vermis (lobules VI–VII) and fastigial nucleus constitute a “cardiovascular module” in cerebellum (Bradley et al., 1991), and we consider it likely that the BP changes were related to the cerebellar stimulation.

Serial psychiatric assessments and neuropsychological testing revealed no safety concerns. On the contrary, evidence of efficacy was detected for negative symptoms, mood, and cognition, in agreement with earlier reports following invasive electrical stimulation (Cooper et al., 1976; Heath, 1977). Increased cerebellar activity in PET studies has been considered a compensatory mechanism for dysfunctional cerebrocerebellar circuitry in patients with hypofrontal/negative symptoms (Andreasen et al., 1997; Kim et al., 2000; Potkin et al., 2002) and, given the changes in frontal gamma spectrum following excitatory stimulation of the vermis (Schutter et al., 2003), it is theoretically plausible that potentiation of cerebellar inhibitory output via excitatory iTBS may modulate impairments in frontal gamma activity (Farzan et al., 2010; Cho et al., 2006). While the mechanism of improvement remains to be shown, our findings provide empirical support for the dysmetria of thought theory (Schmahmann 1991, 1996, 1998, 2000), that cerebellum acts to correct errors in the realms of thought and emotion maintaining behavior around a homeostatic baseline, and loss of the universal cerebellar transform in schizophrenia.

In this study, stimulation intensity was set at 100% AMT, with a slight modification from the original protocol described by Huang et al. (2005), because the estimated vermis-coil distance is approximately 2.5 cm (Schmahmann et al., 1999). However, the applicability of motor threshold intensities to cerebellum is still under debate (Del Olmo et al., 2007), and future studies employing cerebellar TBS should specifically address this issue. We chose a twice-daily regimen of iTBS to minimize length of inpatient stay and maximize patient compliance, but other combinations of TBS protocols may also prove effective. It is now well established that TBS can be safely performed using a range of stimulation parameters. Twice daily iTBS each comprising 1800 stimuli, performed at 100% AMT over the dorsolateral prefrontal cortex (DLPFC) in patients with depression was reported to be safe without significant adverse effects (Chistyakov et al., 2010), and twice daily iTBS over the DLPFC at 80% MT resulted in improvement of negative symptoms in a patient with schizophrenia (Bor et al., 2009). EEG recordings of standard TBS protocols over the DLPFC proved safe with no epileptiform activity in normal subjects (Grossheinrich et al., 2009). Standard TBS protocols targeting the motor cortex in patients with multiple sclerosis and amyotrophic lateral sclerosis did not produce serious adverse events (Mori et al., 2010; Di Lazzaro et al., 2009), and weekly use of TBS for up to 12 consecutive months has provided evidence in favor of its long-term safety (Di Lazzaro et al., 2009). Finally, ten consecutive sessions of TBS to lateral cerebellar hemispheres in levodopa-induced dyskinesias reported no adverse events (Koch et al., 2009).

It is not possible to know whether cerebellar vermal iTBS could be more effective in schizophrenia than invasive electrical stimulation; early data on electrical stimulation are limited. Invasive stimulation offers the advantage of being able to stimulate any desired location while TBS is mostly limited to more superficial structures. The major advantage of TBS, however, lies in its noninvasive, morbidity-free application and its safe use within a range of stimulation parameters.

Table 3
Neuropsychological functioning in patients with schizophrenia during baseline, post-TBS and follow-up.

	N	Baseline (B)	Post-TBS (P)	Follow-up (F)	*d* B = P	*d* B = F	χ^2	*p* value	Pairwise Comparisons
Attention — vigilance									
Seidman Auditory Continuous Performance Test (Omission errors)									
Vigilance	7	7.57 ± 12.2	5.71 ± 6.6	3.29 ± 2.8	0.19	0.49	2	0.36	ns
Working memory									
Seidman Auditory Continuous Performance Test (Omission errors)									
Memory	7	10.5 ± 8.2	6.9 ± 5.4	5.3 ± 4.5	0.52	0.78	7.14	0.028	F<B
Interference	7	27.0 ± 5.6	21.7 ± 7.6	22.3 ± 3.2	0.79	1.04	6.5	0.039	F<B
Wechsler Memory Scale, 3rd Edition (WMS-III)									
Spatial Span Forward	8	7.4 ± 1.5	8.6 ± 1.9	8.4 ± 1.4	0.74	0.69	6.06	0.048	P>B F>B
Spatial Span Backward	8	6.1 ± 3.0	6.3 ± 3.0	6.1 ± 3.0	0.04	0.00	0.19	0.91	ns
University of Maryland Letter–Number Span	7	13.0 ± 3.2	13.6 ± 3.1	13.0 ± 2.9	0.18	0.00	0.5	0.77	ns
Speed of processing									
Phonemic Fluency (FAS)	8	33.1 ± 10.8	35.3 ± 12.5	35.6 ± 13.0	0.18	0.21	1.75	0.42	ns
Category Fluency (Animals)	8	18.1 ± 5.0	17.6 ± 5.8	19.8 ± 6.2	−0.09	0.29	2.44	0.3	ns
Brief Assessment of Cognition in Schizophrenia									
Symbol Coding	8	36.0 ± 7.9	36.3 ± 11.0	36.3 ± 10.8	0.03	0.03	0.25	0.88	ns
Trail Making Test (seconds)									
Time Part A	8	31.5 ± 11.1	34.1 ± 18.6	35.3 ± 18.8	−0.17	−0.24	0.25	0.88	ns
Time Part B	8	94.6 ± 33.8	96.3 ± 83.7	105.9 ± 81.9	−0.03	−0.18	1	0.6	ns
Executive functioning									
Wisconsin Card Sorting Test									
Categories Completed	7	3.9 ± 2.3	2.9 ± 3.0	2.4 ± 1.8	−0.37	−0.68	1.5	0.47	ns
Perseverative Errors	7	17.6 ± 13.5	19.3 ± 9.7	21.3 ± 9.5	−0.15	−0.32	1.79	0.4	ns
Delis–Kaplan Executive Function System (D-KEFS), Proverbs Test									
Accuracy	7	7.7 ± 5.4	7.4 ± 5.3	8.0 ± 4.7	−0.05	0.06	0.29	0.87	ns
Abstraction	7	9.4 ± 5.6	10.3 ± 3.9	9.7 ± 4.7	0.18	0.06	1.36	0.5	ns
Achievement	7	14.9 ± 8.8	17.7 ± 8.8	17.7 ± 9.0	0.33	0.32	3.7	0.16	ns
Verbal learning									
California Verbal Learning Test, 2nd Edition (CVLT-2) (Number of words recalled)									
Total 1–5 standard score	8	35.3 ± 9.7	34.4 ± 11.9	40.0 ± 12.6	−0.08	0.42	3.06	0.21	ns
Short delay free recall	8	6.0 ± 3.6	6.6 ± 3.1	7.9 ± 4.1	0.19	0.49	4.19	0.12	ns
Long delay free recall	8	6.3 ± 3.5	7.3 ± 4.3	8.3 ± 4.6	0.29	0.49	6.06	0.048	ns
Short delay cued recall	8	6.8 ± 3.6	7.8 ± 3.8	8.0 ± 4.6	0.27	0.30	3.56	0.17	ns
Long delay cued recall	8	6.8 ± 3.5	7.7 ± 3.6	8.3 ± 3.7	0.24	0.45	2.69	0.26	ns
Visual learning									
Rey–Osterrieth Complex Figure									
Copy Organization	8	63.1 ± 12.9	62.0 ± 15.3	63.0 ± 13.5	−0.08	−0.01	0.06	0.96	ns
Delay Organization	8	21.9 ± 13.7	27.9 ± 16.9	32.9 ± 18.5	0.39	0.68	7.56	0.02	F>B
Motor functions (seconds)									
Grooved Pegboard Right	7	85.4 ± 16.1	82.4 ± 6.8	80.6 ± 8.5	0.01	0.02	0.92	0.63	ns
Grooved Pegboard Left	7	98.0 ± 19.7	94.0 ± 14.1	95.6 ± 16.4	0.02	0.01	0.64	0.72	ns

Abbreviations: B: baseline; P: post-TBS; F: follow-up; *d*: Cohen's *d* effect size measurement; χ^2: Friedman's ANOVA; ns: nonsignificant, p>0.05. Higher scores indicate improvement except for the following variables: Auditory CPT omission errors, Trail Making Test seconds, Wisconsin Card Sorting Test perseverative errors, Grooved Pegboard seconds.

Future modifications of TBS may result in clinically significant changes in efficacy, but the safety of such protocols could differ (Rossi et al., 2009).

The strengths of this study include the novel hypothesis-driven approach of stimulating the cerebellum and particularly the vermis in this disorder, the precise targeting of the vermis and minimized interindividual anatomical variability achieved via the use of neuronavigation, and continuous monitoring of the patients in the CRC unit to ensure their safety. There are notable limitations in this exploratory study. The principal limitation is the open-label nature and the absence of a control intervention; this was not included because of our primary focus on safety. Whereas our results demonstrate the safety and tolerability of repeated sessions of rTMS over the vermis in schizophrenia and provide early proof of principle to proceed further, future placebo controlled trials will need to define clinical efficacy. Electroencephalography and functional neuroimaging may help characterize changes in neural circuitry

induced by cerebellar stimulation, and shed light on the neurobiology of this disorder. A second limitation is the number of patients studied which can lead to type II errors. Despite the small *n*, psychiatric and cognitive results actually showed improvement in some functions. Lastly, smoking habits, caffeine restriction and medications may have influenced our results. The refractoriness of our patients precluded withdrawal or changing their existing medications in favor of one antipsychotic, although it would be desirable to study medication-free patients because psychotropics may affect the response to TBS.

In sum, this study demonstrates that repeated sessions of iTBS to the cerebellar vermis in patients with refractory schizophrenia are safe and well-tolerated. Improvement in negative symptoms, mood and cognition represents an encouraging initial step towards treatment of refractory schizophrenia through noninvasive neuromodulation of the cerebellum. These findings are potentially important because available treatments for negative symptoms of schizophrenia remain only partially effective (Alphs, 2006). Further studies of clinical efficacy and mechanisms of cerebellar TBS are warranted. By demonstrating the safety of cerebellar vermal iTBS in schizophrenia, it may be possible to perform future studies in the outpatient setting, although caution is warranted in patients with hypertension.

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Contributors

JDS conceptualized the initial idea. ADT, JDS, LJS, WSS, CF and APL designed the study. ADT, JDS and APL wrote the protocol. DO was involved in patient screening and recruitment. ADT, CF, JRC and LS collected the data. ADT, JDS and APL oversaw and coordinated data analysis and interpretation. JRC participated in statistical analyses and LJS, WSS and DO contributed to interpretation of the data. ADT wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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