Effect of rTMS over the Medial Cerebellum on Positive and Negative Symptoms and Cognitive Dysmetria in subjects with treatment refractory Schizophrenia

Robert J. Buchanan, M.D.

Zoltan Nadasdy, Ph.D.

James Underhill, Psy.D.

Seton Brain and Spine Institute

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Hypotheses:

1) **Cerebellar stimulation will cause activation of thalamic and frontal cortical networks associated with attentional processes. These attentional processes are a component of the "distracted" affect of schizophrenia (part of both positive and negative symptoms).**
2) **Cerebellar stimulation will cause activation of the reticular activating system (RAS), and this will allow the "mutism", which is a negative symptom, to be partially improved.**

Purpose of Study, Anticipated Benefits

The etiology of negative symptoms in schizophrenia which includes social withdrawal, affective flattening, poor motivation, and apathy is poorly understood. Symptomatic treatment of these negative symptoms with medications and psychotherapy are almost non-existent, whereas treatment of the positive symptoms (hallucinations and delusions) has been more effective with psychotropic medications. New methods of treating negative symptoms are needed.

Background and Significance

There is increasing evidence from neuropsychological and imaging studies that cerebellar function is relevant not only to motor coordination, but equally to cognition and behavior (M. Rapoport et al 2000). Selective modulation of cerebello-thalamocortical pathways, in turn, is believed to provide an additional means of modulating cortical function. Repetitive transcranial magnetic stimulation (rTMS) can modulate cortical excitability focally in conscious subjects. Trains with slow frequency (i.e.,1 Hz) are known to suppress cortical excitability (Chen et al 1997), whereas facilitation occurs if frequencies higher than 5 Hz are used (Berardelli et al 1998). With respect to rTMS of the cerebellum, a major impact on cognitive function Oliveri et al. 2007) has been described.
The cerebellum is a very good candidate to be the generator for intracortical inhibition; its stimulation can modulate the cortical inhibition. Invasive studies by

Robert Heath at Tulane University revealed that the cerebellum is strongly connected to 2 structures at the core of the proposed abnormal circuitry in schizophrenia, the septal nuclei and the hippocampus (HC). According to his theory and findings, the septal nuclei are involved in positive mood regulation, pleasure. The firing of the HC was correlated with negative affect and sadness (Heath et al, 1980). By stimulating the fastigial nucleus and vermis of the cerebellum, the septal nuclei were facilitated to fire and the HC was inhibited. The other component of what Heath referred to as the “aversive system”, the amygdala was also inhibited. This central role of the cerebellum in this circuit is analogous to its role in “smoothing” the flow of movements. When considering emotion and cognition, the cerebellum has a smoothing function. Aside from direct monosynaptic connections between these sites, there is evidence that the deep cerebellar nuclei are connected to the parietal cortex, temporal cortex, as well as the cingulate gyrus. These are all areas that have limbic function. The cerebellum is also directly connected to the midbrain reticular activating system (RAS). This region is responsible for levels of consciousness and arousal. By potentiating the activation of the RAS, we can increase the decreased level of arousal, which in many schizophrenic patients is akin to psychomotor retardation and mutism (catatonic). Midline deep cerebellar nuclei efferents have been traced to the hypothalamus, central nuclei of the thalamus, which are also associative (cognitive) and limbic in function. The Locus Ceruleus and the substantia nigra, in the brain stem are also monosynaptically connected to the cerebellum.

The cerebellum is connected to thalamus and motor cortex (frontal cortex) through cerebello-thalamo-cortical pathway (fig 1). And as stated above it is also connected to a vast array of limbic structures, making it a good choice to use to modulate abnormal activity in these structures.

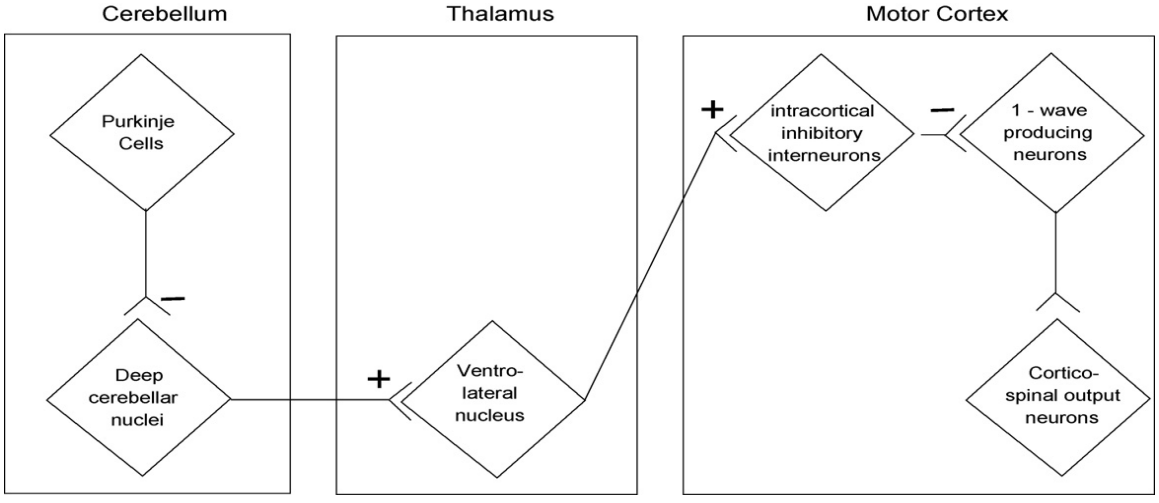

Fig 1. Purkinje cells, the output neurons of cerebellar cortex reduce the excitatory drive from the deep cerebellar nuclei via the ventrolateral thalamus to inhibitory neurons in the motor cortex. Interestingly, the activity of those intracortical

inhibitory neurons may be assessed by measuring cortical inhibition of Short inetracortical inhibition (SICI) using paired pulse Trans cranial magnetic stimulation. (TMS) (Langguth et al 2008). SICI reflects intracortical GABA (A)ergic function.

Following this model, activation of Purkinje cell will inhibit the thalamic drive to intracortical inhibitory neurons, therefore, decrease the intraccortical inhibitory interneuron and decrease in SICI and CSP. On the other hand, inhibition of purkinje cerebellar cells is expected to have opposite effect and release the thalamus from inhibitory control, increase the thalamic drive to stimulate the inhibitory interneurons which can be demonstrated by increase in SICI and CSP Indeed, applying inhibitory rTMS at frequency of 1 Hz resulted in increase SICI (Langguth et al 2008).
The midline deep cerebellar nuclei, those that are anatomically and phylogenetically, related to the vermis also send collaterals to the reticular activating system (RAS) of the brain stem. By increasing the excitatory (Glu) drive on the RAS, the subject will experience increased awareness and connection to their environment.

For decades, the cerebellum has been thought to be predominantly involved in motor performance and cognitive operations. Recently, however, a growing body of evidence indicates that the cerebellum is also involved in emotion. The first evidence for cerebellar involvement in emotion came from the work of Robert G. Heath during the early fifties. Although his initial work predominantly involved the electrical stimulation of the septum, he then began research on stimulation of the cerebellum, thinking that it might provide a better entry to the emotional circuitry of the brain. Several cerebellar pacemaker studies by Heath did indeed demonstrate positive effects on mood and personality in patients with psychiatric illness after electrical stimulation of the cerebellum. Moreover, Schmahmann and Sherman provided clinical support for the role of the cerebellum and particularly the vermis in the regulation of emotion and mood. Given its modulatory role on emotion, the midline cerebellar vermis together with the fastigial nucleus and the flocculonodular lobe have been designated the limbic cerebellum (Schutter and van Honk 2005). Furthermore, additional evidence for the involvement of the cerebellum in schizophrenia was supported by genetic, structural and functional imaging data (Sandyk et al., 1991; Nopoulos et al., 1999; Ichimiya et al., 2001; Varnas et al., 2007) as well as by clinical evidence (Deshmukh et al., 2002; Ho et al., 2004; Varambally et al., 2006). For example, in an animal model for schizophrenia using prenatal infection of mice with human influenza virus, the animal developed behavioral changes similar to those of schizophrenia and was associated with altered expression of cerebellar genes (Fatemi SH, et al. 2008). Some studies reported smaller bilateral cerebellar volumes as compared to controls in first episode schizophrenia patients (Bottmer et al., 2005). One of the first studies to demonstrate the importance of a dysfunctional cerebellar circuitry in schizophrenia was a positron emission tomography (PET) study (Andreasen et al., 1996). The authors examined memory performance in schizophrenic patients

and correlate it to blood flow in cerebello-thalamo-cortical pathway. They used two tasks for memory, namely an easy and a relatively difficult one. While patients with schizophrenia showed normal performance on the easy practiced memory task they already demonstrated decreased blood flow in the cerebello-thalamo-cortical pathway. By contrast, in the relatively more difficult memory task, schizophrenic patients performed worse than healthy controls and displayed significantly lowered frontal and cerebellar blood flow (Andreasen et al., 1996).

Consistent with the assumed disruption of the cerebellothalamo- cortical pathway in schizophrenia is evidence from two proton magnetic resonance spectroscopic imaging (HMRS) studies. Lower levels of N-acetylaspartate (NAA), a marker for neuron density and viability, were found in the thalamus and cerebellar vermis (Deicken et al., 2001) in patients with schizophrenia. In keeping with these findings, lower NAA levels in the vermis and cerebellar cortex have also been found (Ende et al., 2005) as well as in mediodorsal region of the thalamus (Ende et al., 2001). In addition, poor executive functioning in patients with schizophrenia was associated with volumetric reductions in the cerebello-thalamo-cortical network (Rusch et al., 2007). Moreover, a diffusion tensor imaging (DTI) study has shown that patients with schizophrenia demonstrate abnormality in the connectivity between cerebellum and thalamus with possible difference between the right and left cerebellum. (Magnota et al 2008) psychiatry research: Neuroimaging 163 (2008) 193-200 Investigating connectivity between the cerebellum and thalamus in schizophrenia using diffusion tensor tractography: A pilot study). Another DTI study found neuronal disorganization in the superior peduncle with neuronal disorganization being associated with poor cognitive performance (Okugawa et al., 2006). Finally, the activity of right and left cerebellum may not be the same. For example, impaired working memory in schizophrenia is associated with over and under-activation along the cerebellothalamo- cortical pathway with under-activation of the left DLPFC and right cerebellum and over-activation of the left cerebellum (Mendrek et al., 2005).

To date, cerebellar involvement in schizophrenia remains a subject of ongoing study. It was shown that motor impairments in schizophrenia are related to cerebellar malfunction. Several studies report that the cerebellum is indeed involved in cognitive (Eyler et al., 2004; Aasen et al., 2005; Kiehl et al., 2005) and affective (Paradiso et al., 2003; Takahashi et al., 2004; Stip et al., 2005) impairments. This study aims to clarify the role of the cerebellum in development of negative symptoms through its regulation of cortical inhibition, activation of the septal region with reciprocal inactivation of the hippocampus, and RAS activation.

All subjects will have a DSM IV TR Axis I diagnosis of Schizophrenia (295). They will be screened to determine that they do not have co-morbid AXIS I disorders, and if they do, that they are in remission. Patients with AXIS II disorders will be excluded. The patients must also be able to communicate with the examiner and also be able to cooperate during the administration of the rating scales. We will also ask both the patient and the care-giver if appropriate, to keep a brief Journal

of both their positive, negative, and mood symptoms daily. The patient must also be able to sit in the TMS chair for a 20 minute treatment. This will be determined by the Board Certified Psychiatrist, who is also the PI.
Patients enrolling to the study

A. must be stable on their medications at the start of their enrollment in the study and throughout the duration of the study.
B. must have no history of substance use of substance-dependence issues over at least the past six months,
C. must be able to and have the capacity to provide consent,
D. and if older patient, he/she must be able to participate without a safeguard to be present.

Patients excluded from the study are:

A. Patients with typical clinical considerations that exclude them from treatment with TMS (i.e., patients who have had head injuries, patients with metal implants, patients with a history of seizures, patients with elevated risk of seizures, patients who are taking medications that may interfere with TMS or potentiate the related side effects, etc.).
B. Patients who have had changes in their medications (i.e., patients must be stable on their medications throughout their participation in the study).
C. Patients with history of substance abuse or substance-dependence anytime over the past six months.
D. Patients who are unable (i.e., do not have the capacity) to consent.

In addition, we require a third-party psychiatrist *who is not involved in this study* making the determination of whether or not the patient has the capacity to consent to participate in the research study. For example, the referring or primary psychiatrist can state this in their referral letter for the patient.

In order to keep the patients in the study, we will provide taxi rides to the TMS lab and back. In addition, we will contact them by phone before the day of their appointment, and every day during the experiment to remind them to their appointment. Moreover, we will follow up with every patient after they completed the TMS sessions to make sure that they keep record of their status in their journal. We also provide them with a flyer containing their appointment dates, times, location and contact information. The patients can cancel their appointment by phone.

Experimental Design and Methods/Procedures

1) rTMS over the vermis of the cerebellum
2) 3 sessions/week for 1 month
3) Randomization as explained below.
4) Patients/subjects will receive pre-treatment protocol neuropsychiatric measures. These rating scales are accepted and standardized.

a. Brief Psychiatric Rating Scale
b. Scale for the Assessment of Negative Symptoms (SANS)
c. Scale for the Assessment of Positive Symptoms (SAPS)
d. Thought Disorder Index
e. Barnes Akathisia Rating Scale (BARS)

Patients will be randomly assigned to either the high frequency or low frequency Medial Cerebellum Target Treatment protocol. Each group will then be entered into a randomized, double-blind, sham-controlled, parallel-design clinical trial that consists of three main phases: (1) Baseline Psychiatric and Psychometric Testing Exam; (2) 8 rTMS treatments, double-blind, that in 2 treatment sessions/week with sham or active rTMS for over period of 4 weeks; and (3) a follow-up period of 1 month. The patients will then be reassigned to the other Frequency (either high or low) Arm of the study (Table 1). The protocol will then be repeated. Patients and the investigators, except the investigator who applied rTMS, will be blinded to the treatment arm. During the baseline period, patients will be randomized in a) a 3:4 ratio to receive sham (3 in each 7 patients) or b) an active (4 in each 7 patients) rTMS. We chose this randomization strategy (3:4) to increase the sample size of the active treatment. This strategy of randomization is advocated in small sample size phase II trials that do not have adequate information on the efficacy of a new treatment (Peto, 1978). The disadvantage of this strategy is that it decreases the power of the study (because less information from the sham group is provided). However, we accounted for this decrease of power (that is minimal with the 3:4 ratio) in our sample size calculation. Randomization was performed using the order of entrance in the study and a randomization table previously generated by a computer using randomization blocks of seven (for each seven patients, three were randomized to sham and four to active rTMS) to minimize the risk for unbalanced group sizes. To determine the sample size, we assumed a mean reduction in seizures of at least 50% in the active group. We chose this effect size from our preliminary data and because our aim was to assess whether rTMS may have a truly clinically meaningful impact. In the sham rTMS group, we assumed mean reduction of seizure frequency of 15%. This was based on the placebo effect reported in Theodore et.al

PHASE I (Vermis, High Frequency 10 Hz)	
I	TMS lab - rTMS treatment (20 minutes, 1 Hz).
II	The above protocol is repeated on Tuesday and Thursday, for 4 weeks (8 treatments).
III	Record in Psychiatric Journal over the 4 week treatment period.
IV	Pre and Post rTMS treatment Psychometrics and Journals will be analyzed for a change in ratings and behaviors respectively
1 month washout period. New Neuropsychological Testing (Psychometrics)	
PHASE II (Vermis) (Low Frequency 1Hz)	
I	TMS/lab - Pre rTMS, Repeat Psychometric Scales. - rTMS treatment (20 minutes, 1 Hz).
II	The above protocol is repeated on Tuesday and Thursday, for 4 weeks (8 treatments).
III	Record Psychiatric Journal over the 4 week treatment period.
IV	Pre and Post rTMS treatment Psychometrics and Journals will be analyzed for a change in ratings and behaviors respectively.

Cerebellar stimulation:

1) At each session, 1000 stimuli rTMS will be delivered at an intensity of 120% of resting motor threshold (RMT) by a figure of eight coil (double circular 90 mm coil), connected to a Magstim Rapid 2 stimulator (Magstim Company, Dyfed, UK). This relatively high stimulation intensity is chosen in order to ensure that the magnetic field reaches the cerebellum in spite of the higher distance from the coil compared to motor cortex stimulation. Medial cerebellum (vermis) will be targeted based on individual MRI data. The coil will be positioned over the cerebellar vermis (lobule VII At; Fig. 2a), A neuronavigational system (Brainsight, Montreal, Canada) will be used to navigate the coil on the surface of the skull over the targeted brain region.

Once the optimal coil position is found, the coil will be held with a mechanical arm and its position over the target region will further monitored by the neuronavigation system. The handle of the coil will be pointed upwards. The current in the coil will be directed downward during the reversal phase of the biphasic stimulus, thus inducing an upward current in the region of interest. This current direction is considered optimal for cerebellar stimulation (Figure 3). In each of the treatments session, a Magstim rapid 2 air cooled 9-cm circular coil will be placed on the area of abnormal cerebellar activity. Stimulation will be

given 2 seconds per minute for 20 consecutive minutes per session at an intensity of 120% motor threshold, a minimal magnetic pulse that reliably induced visible contra lateral thumb movement. The frequencies for the active stimuli will be 1 Hz, individualized alpha (8–13 Hz). Sham stimulation will be given by applying the “sham coil” to the same cerebellar area. All rating scales were administered at screening, baseline (immediately prior to first treatment), immediately following the final treatment, and after 4 weeks of washout for each condition.

While the technician administering the rTMS procedures could not be blinded, the evaluating physician and patients remained unaware of the type of treatment throughout the duration of the study.

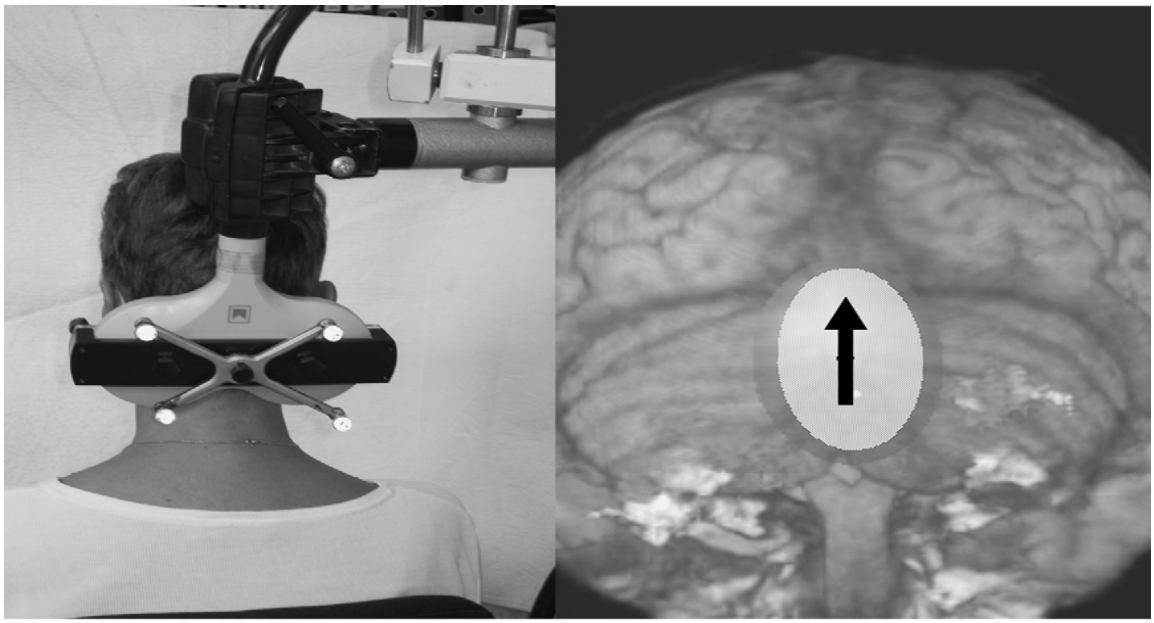

Figure 3. Left side a figure of eight TMS coil is positioned to point to the cerebellum. When the coil is positioned exactly orthogonal to the mid-sagittal plane the largest magnetic current is applied to the vermis.

Subject Population

Patients diagnosed with schizophrenia (age: 18-80 years old) presenting predominantly with negative symptoms and stabilized on current antipsychotic

medications for at least 30 days will be enrolled in the study. Severity of symptoms will be evaluated by the Positive and Negative Syndrome Scale (PANSS). During the subject recruitment, a minimum score of 20 on the PANSS negative symptom subscale and a maximum score of 19 on the positive symptoms subscale are required at baseline.

Statistical Analyses

Apriori categorical definition for clinical response will be > 30% baseline-to posttreatment reduction, or < 16 at the end of second phase treatment when baseline score is lower than 20 on PANSS negative symptom subscale.

Clinical data were analyzed on an intent-to-treat basis with the last observation carried forward. Patients with a baseline and at least 1 additional set of completed assessments (at least 5 treatment sessions) were included in the analysis of mean treatment effect. Efficacy in clinical ratings was evaluated by using analyses of variance (ANOVA). The models included 1 between-subjects factor of treatment, and 2 within-subjects factors of time and treatment order. Covariance for the baseline was used when significant group difference was found at the baseline.

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