Hotchkiss Brain Institute / Mathison Centre Pilot Research Fund Program (PFUN)
Application Form
Funding Competition 2014
Deadline: December 17, 2014

Instructions: Please complete all relevant sections and submit this form electronically to csjahrau@ucalgary.ca and meredith.maloney@albertahealthservices.ca in either PDF or Word format. Please also include with your application a Letter of Support from the Mathison Centre Director, outlining the benefits of the proposed research to their program, and the roles of the pilot study within the larger research program.

Project Title: TICS: Transcranial Magnetic Stimulation for Children with Tourette's Syndrome

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***** The signature of each team member is required to indicate their willingness to participate in the project. This requirement can also be met through the submission of a separate letter from the team member confirming their involvement.

Department Head:

Name: Dr. Beverly L. Adams **Signature**:

***** My signature above acknowledges and accepts the impact (clinical, financial, or otherwise) of this research on my department/division/program/portfolio and I agree with the costs itemized in the study budget.

1. Objectives: Tourette's Syndrome (TS) is a neuropsychiatric disorder characterized by brief, repetitive movements and vocalizations called tics. The effects of TS in children and youth are far-reaching, with academic, occupational, and social implications. Current treatments for TS remain limited, both in scope and efficacy. Pharmaceuticals prescribed to control tics often have severe side effects with suboptimal benefit [1]. Behavior therapy has limited efficacy in children and is difficult for patients to access. Hence, there exists a salient need for the development of safe, accessible, and effective treatments for young people with TS. Indeed, a recent study has suggested that the maturational reduction in tic frequency that is sometimes seen in TS is due to a conscious effort directed at tic suppression, which develops over time. Tic suppression is associated with an increase in tonic inhibition in the supplementary motor area (SMA), and correlates with increased GABA neurotransmission and levels [2]. Consequently, the SMA is a direct target for therapeutic intervention. Repetitive transcranial magnetic stimulation (rTMS) involves a safe, non-invasive application of a magnetic field to a target brain area in order to change its activity and function. Our central hypothesis is that low frequency rTMS, targeted to the SMA, will reduce tic severity through the potentiation of cortical GABAergic neurotransmission. We propose the following **specific objectives**:
(Aim 1) **To characterize the effect of low frequency rTMS of the SMA on TS symptoms**. *We hypothesize that TS symptom severity (as measured by the Yale Global Tic severity Scale or YGTSS) will decrease with low frequency rTMS targeting the SMA.*
(Aim 2) **To identify TMS-mediated alterations in brain metabolites and functional connectivity that serve to normalize cortical activity.** *We further hypothesize that improvement in TS symptoms will be moderated by TMS-induced changes in GABA and glutamate in the SMA assessed with proton magnetic resonance spectroscopy (^{1}HMRS), potentiation of GABAergic neurotransmission assessed with short-interval cortical inhibition (SICI), and changes in the functional connectivity between the SMA and primary motor cortex.*

2. Background: Tics in TS are thought to arise from 1) dysregulation of excitation/inhibition in brain regions related to motor function, and 2) alterations in specific brain chemistry that potentiates overexcitability in the primary motor cortex (M1), via input from the SMA. This results in the activation of striatal neurons, and hyper-excitation of the M1, leading to the expression of tics. It is hypothesized that TS is also associated with a reduction in GABA transmission within the SMA and M1 [3]. One technique that has shown promise in normalizing brain function and reducing symptoms of TS in children and adults is rTMS. While initial experiences with varied approaches were not encouraging [4] [5] an effective approach is emerging [6] [7] [8]. Furthermore, it is not known what effects this technique has on the concentration of brain metabolites that mediate cortical hyperactivity and inhibitory neurotransmission. In this study, we aim to investigate whether low frequency rTMS can improve TS symptoms in a pediatric population, and what effects this technique has on the concentration of brain metabolites that mediate cortical hyperactivity.

3. Novelty (What will we learn that we don't already know?): The neurobiological study of the novel application of rTMS in pediatric TS allows us to map the trajectory of adaptive changes in the brains of children with TS, and to attempt to speed up these processes as they relate to decreasing cortical hyper-excitability, modulating GABAergic neurotransmission, increasing inhibitory metabolite levels within affected brain regions. Our multimodal approach allows us to gain critical insight into the structural, functional, and metabolic correlates of TS symptoms within the pediatric brain, an area that currently remains underexplored.

4. Methods
Sample: A pilot cohort of 11 males with TS (7-12 years, right handed, no comorbid ADHD) will be recruited through the Calgary Tourette Syndrome Clinic (Alberta Children's Hospital, Calgary, Alberta). Participants will continue prescribed medication regimes during the trial at the discretion of individual medical care professionals.
Measurements: To establish diagnosis and ascertain treatment response, we will conduct assessments at baseline, weekly during treatment (including the final week) and at 8 week and 6 month follow-ups. Measures used include the Yale Global Tic severity Scale (YGTSS), Present and Lifetime version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL), Multidimensional Anxiety Scale for Children, the Children's Depression Rating Scale-Revised, and the General Behavior Inventory (P-GBI).

MRI Acquisition: Participants will undergo both baseline and post-treatment MRI scans. MR data will be acquired on a GE 3T Discovery 750W scanner, and include a high-resolution anatomical scan for use in the rTMS procedure. Voxels within the M1 and SMA will be targeted by short echo (TE= 30msec, TR = 2000 msec) and MEGA PRESS proton magnetic resonance spectroscopy (1H-MRS) protocols. Analysis of MRS will be completed using the LCModel method, which converts the in vivo spectrum to a linear combination model for each metabolic solution [9, 10]. The SMA will be confirmed during the scan with a brief right and left finger tapping functional magnetic resonance imaging (fMRI) task [11]. We will also collect resting state fMRI and diffusion tensor imaging (DTI). Total time in the scanner is less than 60 minutes. Our established acquisition is well tolerated from ages 5 through adulthood.
Single and Paired-Pulse TMS (Neurophysiology): Using established lab protocols, the following motor neurophysiology measures (and their possible neurotransmitter system correlates) will be defined for M1 bilaterally at baseline and 1 week post-intervention: rest and active motor thresholds (RMT, AMT), stimulus response curve (100-150%RMT), short-interval intracortical inhibition (SICI, $GABA_A$), cortical silent period (cSP, $GABA_B$), ipsilateral silent period (iSP, interhemispheric inhibition), and intracortical facilitation (ICF, glutamatergic NMDA)[12].
Low-Frequency rTMS (Neuromodulation): Baseline T1 MR images will allow individualized neuronavigation (Brainsight 2, Rogue Research, Montreal QC) to coregister the rTMS Airfilm coil (Magistim, UK) precisely to the SMA as defined by fMRI. Interventional rTMS parameters will be: intensity 100% RMT, frequency 1Hz, duration 20 minutes (1200 stimulations). Treatments will occur on each weekday at the same time of day for three weeks (15 total).
Analysis: Statistical analyses will be performed using SPSS for Windows 22.0 (SPSS Inc., Chicago, IL). For aim 1, to test for differences in tic symptoms (YGTSS) with rTMS, a repeated measures analysis of variance (rmANOVA) will be performed. A similar approach will be used for assessing glutamate concentration in the SMA, SICI, ICF, CSP (Aim 2). Furthermore for Aim 2, functional connectivity changes with rTMS will be examined using Statistical Parametric Mapping (SPM) approaches. Pearson correlations between clinical and neurobiological variables controlling for age will be explored.

5. Sample size with justification: Estimating the sample size needed was based on similar studies. For the primary outcome measure (aim 1) of a reduction in tic severity (Yale Global Total Tic Severity Scale), we set $p < 0.05$ (two tailed), $d = 0.47$, power = 0.80, rendering a need for a minimum of 10 subjects. Clinically meaningful change in the YGTSS will be defined at a 23% or greater reduction in total score [13].

6. Anticipated Results: We predict this novel treatment will demonstrate reduction in tic severity and intrusiveness. Potential pitfalls include (1) intolerance to rTMS, (2) inadequate MRI data quality and (3) non-response to treatment. For TMS tolerability, most do very well, with a low incidence of side effects [14]. Moreover, low frequency rTMS is the most well tolerated type of rTMS. With regard to motion during the MR scan, our group has scanned over 200 subjects at the Alberta Children's Hospital to date. Data loss from motion accounts for less than 5%. To improve data quality, we have a mock scanner that helps acclimatize children to the scanning procedure. Given our collaboration with the Calgary Tourette Syndrome clinic, we anticipate robust recruitment (over 1,000 patients associated with the clinic).

7. Likelihood of Generating New Funding: In Canada, there are only 5 active operating CIHR grants with any conceptual relationship (however remote) with TS. Only two examine treatment (both behavioral interventions) and only one targets children, but simply as a sub-population. ClinicalTrials.gov has only two actively recruiting studies of TS listed in Canada as well (physical activity, pharmacological). **Despite the severity, prevalence, onset in childhood, and limitations of current interventions, there is little active research in TS in children.** Furthermore, despite the recent evidence described above implicating the SMA and indicating the promise of rTMS, no study is currently combining neurobiological measures with brain stimulation to target symptoms in TS. We believe, given our infrastructure and expertise, we are well suited to take leadership in this area internationally. Initial data will be applied to funding applications for the Thrasher foundation ($300,000 over 3 years) and the Tourette Syndrome Association Research Grant ($150,000 over 2 years). Similar funding will be sought from CIHR, AIHS, and NIH as appropriate. We have also formed a new collaboration with the Mayo Clinic, University of Cincinnati, CAMH, and others through our CAIRNS (Child and Adolescent International Research into Neuro-Stimulation) research program. This collaboration can help in developing larger scale trials.

Budget (How will the funds be spent? Include discussion of overlap with existing projects, if appropriate. Provide a justification and indicate the amount to be spent on each budget item).

Personnel

[redacted]

Overlap

There is no overlap with existing projects. This direction into Tourette's Syndrome is entirely novel.

Please note that supplementary or "top-up" funding is not permitted for this competition; projects must explore a new avenue of research for the investigator.

Are there any other sources of funding? Yes: X - If yes, from where: Dr. MacMaster's start up funds ($4,950)

References:

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