

# Pilot Study of Supplementary Motor Area rTMS for Tourette's Syndrome in Children

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## Background

- Tourette's syndrome (TS)** is a neuropsychiatric disorder, characterized by brief, repetitive movements and vocalizations called **tics**.
- Current treatment options (antipsychotics, behavioral therapy) are limited both in scope and efficacy.
- There is a need for new safe interventions to help youth who are suffering.
- A maturational reduction in tic frequency from conscious tic suppression is associated with an increase in tonic inhibition in the **supplementary motor area (SMA)**.
- 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.

**Aim 1:** To characterize the effect of low frequency rTMS of the SMA on TS symptoms.

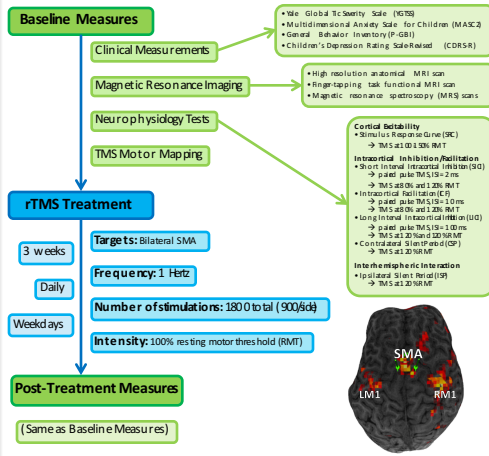
**Hypothesis 1:** Tourette's syndrome symptom severity will decrease with low frequency rTMS targeting the SMA bilaterally in children with TS.

**Aim 2:** To identify TMS-mediated alterations in brain metabolites and functional connectivity that serve to normalize cortical activity.

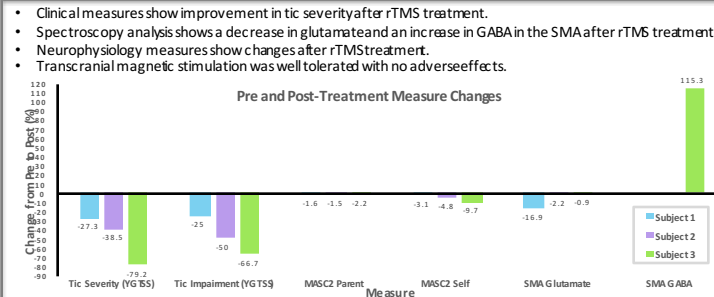
**Hypothesis 2:** Improvement in TS symptoms will be moderated by (1) TMS-induced changes in GABA and glutamate in the SMA and (2) potentiation of GABAergic neurotransmission.

## Methods

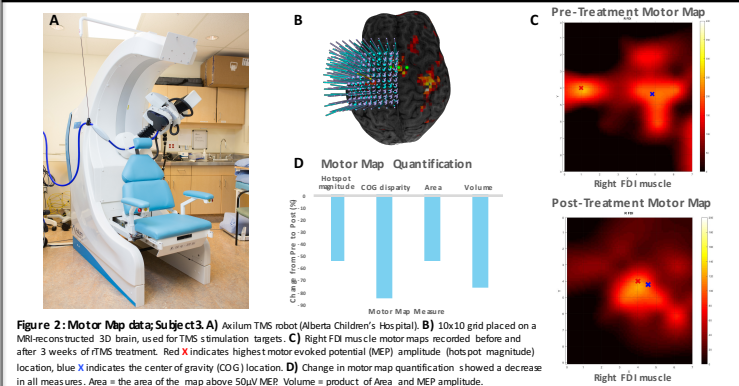
**Sample:** First three right-handed male participants (age 7-12) with moderate to severe tics were recruited through the Calgary Tourette's Syndrome Clinic.



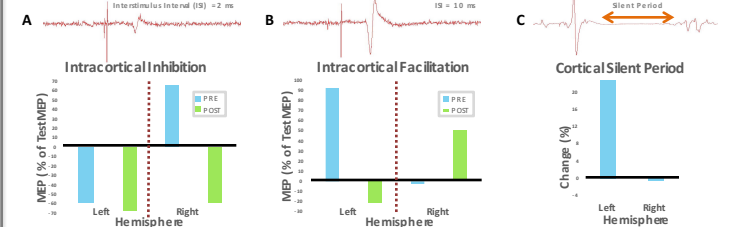
## Preliminary Results



**Figure 1:** Tic Severity scores and Tic Impairment scores decreased for all three participants (YGTSS). Anxiety scores decreased for all three participants (MASC2 Parent and Self). Glutamate concentrations in the supplementary motor area (SMA) decreased for all three participants (MRS). GABA concentrations, only measured for Subject 3, showed a concentration increase (MRS) after rTMS treatment.

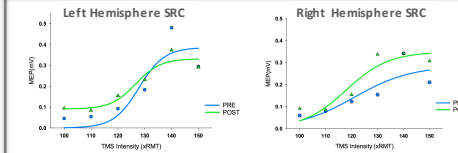


**Figure 2: Motor Map data; Subject 3.** A) Avium TMS robot (Alberta Children's Hospital). B) 10x10 grid placed on a MRI-reconstructed 3D brain, used for TMS stimulation targets. C) Right FDI muscle motor maps recorded before and after 3 weeks of rTMS treatment. Red X indicates highest motor evoked potential (MEP) amplitude (hotspot magnitude) location, blue X indicates the center of gravity (COG) location. D) Change in motor map quantification showed a decrease in all measures. Area = the area of the map above 50µV MEP. Volume = product of Area and MEP amplitude.



**Figure 3: Neurophysiology data; Subject 3.** A) Intracortical inhibition increased after treatment; more in the right hemisphere. B) Intracortical facilitation change varied between hemispheres. C) Silent period elongated in the left hemisphere. Speculatively, this shows an increase in intracortical inhibition and decrease in facilitation.

## Preliminary Results



**Figure 4: Stimulus response curves; Subject 3.** The stimulus response curve shifted after rTMS treatment, different in both hemispheres.

## Discussion

### Clinical Measures

- The preliminary results indicate a substantial improvement in tic severity for the first three participants of this pilot study following treatment.
- Quality of life factors, such as anxiety and depression, also improved after the rTMS treatment.

### Magnetic Resonance Spectroscopy Measures

- The observed decrease in glutamate and increase in GABA concentrations coincide with the brain metabolite changes observed in Tourette's patients that show a reduction in tic severity and frequency from years of conscious tic suppression.

### TMS Neurophysiology Test Measures

- Neurophysiology testing can be used to measure intra- and inter-cortical changes in children with Tourette's syndrome.
- The changes seen in intracortical inhibition and facilitation are in line with the clinical and MRS measures that were observed.

### TMS Motor Mapping Measures

- Motor mapping from Subject 3 shows the map becoming more defined after rTMS treatment.
- The preliminary data shows an overall improvement in Tourette's syndrome symptoms, and implies an improvement in cortical activity, and cortical connectivity.
- More participants are being recruited to determine significance, validity, and reliability of the various measures of treatment response.

## Conclusion

- Robot-driven, personalized, neuro-navigated repetitive transcranial magnetic stimulation interventions appear feasible and well-tolerated in children with moderate to severe Tourette's syndrome.
- Transcranial magnetic stimulation appears to be a safe form of neuromodulation technology for children with Tourette's syndrome.
- Treatment combined with transcranial magnetic stimulation and neuroimaging may inform mechanisms of action and predictors of response.