Brain Stimulation (2012) 5, 315–9

ELSEVIER

BRAIN
STIMULATION

www.brainstimjrnl.com

SHORT COMMUNICATION

Altered neurophysiologic response to intermittent theta burst stimulation in Tourette syndrome

Steve W. Wu, Donald L. Gilbert

Cincinnati Children's Hospital Medical Center, Division of Neurology, Cincinnati, Ohio

Background
The motor system in Tourette syndrome has been found to be abnormal in previous fine-motor and neurophysiologic studies.

Objective
This novel pilot study uses repetitive transcranial magnetic stimulation as a method to characterize the neurophysiology of the motor system in Tourette syndrome.

Method
We investigated the modulation of cortical excitability in adult Tourette syndrome patients by measuring motor-evoked potential amplitudes before and after applying intermittent theta burst transcranial magnetic stimulation.

Results
Motor-evoked potential amplitude changes over 1 and 10 minutes after intermittent theta burst transcranial magnetic stimulation were greater in 11 healthy controls than 10 adult patients with Tourette syndrome ($P = 0.004$).

The result of this study was presented at the American Academy of Neurology Annual Meeting on April 13, 2010 and also at the Tourette Syndrome Association 5th International Scientific Symposium on June 12, 2009.

This study was funded by the Tourette Syndrome Association-USA and the Division of Neurology at Cincinnati Children's Hospital Medical Center.

Dr. Wu and Dr. Gilbert receive research funding from the Tourette Syndrome Association.

Dr. Wu receives funding from the Tourette Syndrome Association, NIH-NINDS Loan Repayment Program for Pediatric Research, Otsuka Pharmaceuticals, Genzyme Corporation and Psyadon Pharmaceuticals Inc.

Dr. Gilbert serves as a writer for PREP SA (American Academy of Pediatrics), and has received honoraria from the Tourette Syndrome Association, Centers for Disease Control, the Movement Disorder Society, and the American Academy of Neurology. He serves on the medical advisory board for the Tourette Syndrome Association, and receives research support from the NIH [NIMH R01 MH078160 (co-I), NIMH R01 MH08185 (co-I), and NINDS NS056276 (co-I)], Otsuka Pharmaceuticals, Genzyme Corporation, Psyadon Pharmaceuticals Inc., and from Cincinnati Children's Hospital Research Foundation, the University of Cincinnati, and the Tourette Syndrome Association.

Correspondence: Steve W. Wu, MD, Cincinnati Children's Hospital Medical Center, Division of Neurology, 3333 Burnet Avenue, ML 2015, Cincinnati, OH 45229

E-mail address: steve.wu@cchmc.org

Submitted October 26, 2010; revised April 4, 2011. Accepted for publication April 5, 2011.

1935-861X/$ - see front matter
doi:10.1016/j.brs.2011.04.001

Conclusions
This altered neurophysiologic response to intermittent theta burst stimulation may contribute to the understanding of motor cortical mechanisms in Tourette syndrome.

Keywords Tourette syndrome; neurophysiology; neuroplasticity; transcranial magnetic stimulation; theta burst stimulation

The underlying pathophysiology of Tourette syndrome (TS) is thought to involve cortico-striatal-thalamo-cortical circuits, which regulate motor output. Predictably, motor function in TS has been found to be abnormal,[1,2] as well as other motor system measures such as cortical inhibition.[3] In addition to these motor system aberrations, different studies have shown abnormal neostriatal habit-learning, and brain structural changes suggesting abnormal plasticity in TS.[4-6]

Neuroplasticity is the capacity of the brain to adapt, learn, and remember, which is dependent on long-term potentiation (LTP) and long-term depression (LTD). Theta burst stimulation (TBS) is a method of repetitive transcranial magnetic stimulation that induces LTP- and LTD-like processes in the human brain. Given the possible abnormal plasticity in TS, we used intermittent TBS (iTBS) to study the LTP-like process in adult TS and control subjects. Our hypothesis is that the response to iTBS in the primary motor cortex is abnormal in adult TS participants.

Materials and methods

Patient recruitment, diagnosis, clinical assessment

TS adults were recruited from the Tourette Syndrome Clinic at the Cincinnati Children's Hospital Medical Center (CCHMC), and age-matched healthy controls (± 5 years) were recruited by advertisement. Diagnoses were based on DSM-IV-TR criteria using direct physician interview. Pregnant subjects and those with serious medical condition or substance abuse were excluded. All TS and control subjects were right handed, except one left-handed TS patient. Participants gave written informed consent for the study, which was approved by the CCHMC Institutional Review Board. Tic, attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) symptom severities were assessed independent of transcranial magnetic stimulation (TMS) data using Yale-Global-Tic-Severity-Scale[7] (YGTSS), Adult ADHD Self-Report Scale,[8] and Yale-Brown Obsessive-Compulsive Scale[9] (Table 1).

TMS

TMS was performed with a Magstim200 stimulator connected through a Bistim module to a figure-of-eight, 70-mm coil (Magstim Co., Wales, UK). Surface electromyography (EMG) leads were placed over the first dorsal interosseous (FDI) muscle on the right hand. Subjects were seated comfortably, with both arms fully supported on a pillow. Full muscle relaxation was maintained through visual and EMG monitoring. The coil was placed over the left primary motor cortex at the optimal site for obtaining a motor-evoked potential (MEP) in the right FDI, and resting and active motor thresholds (RMT, AMT) were quantified using standard methods.[10] Ten consecutive TMS pulses separated by at least 5 seconds were administered at 120% RMT to obtain MEP amplitudes at three time points: before, and at 1 and 10 minutes after iTBS. ITBS was performed using Magstim Rapid2 (Magstim Co.) with intensity set at 80% of AMT, as per published protocol.[11]

Each surface EMG tracing was reviewed and tracings that contained muscle movements before the TMS pulse were excluded from data analysis.

Statistical analysis

The primary outcome of interest was the Group*Time interaction for mean MEP amplitude change, which is expressed as a ratio of post-iTBS/pre-iTBS MEP amplitudes. Data were subjected to repeated-measures analysis of variance (ANOVA) (PROC MIXED) in SAS v.9.2 (Cary, NC), with two-tailed $P < 0.05$ considered significant. Time (baseline, 1 minute, 10 minutes) was the within-subject and Group (TS, controls) the between-subject factor. To explore confounding effects, the analysis was performed after stratifying for presence of any current neuropsychiatric medication or any comorbid condition. Paired t test was also performed within each group between baseline and 1-minute MEP amplitude change to assess the effect of iTBS.

Results

Ten TS subjects (Table 1) and 11 healthy controls completed this study and did not differ in age ($P = 0.73$) or RMT ($P = 0.81$). The single left-handed TS subject's RMT was 55%, which was in the range of the right-handed TS subjects' RMTs (35-63%).

The mean MEP amplitude changes over 1 and 10 minutes after iTBS were significantly greater in controls than TS adults (repeated-measures ANOVA: Group*Time $F_{2,38} = 6.3$; $P = 0.004$) (Figure 1). Post hoc paired t test showed difference between baseline and 1-minute MEP