Final Report

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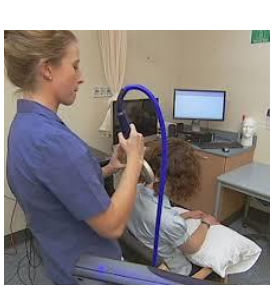
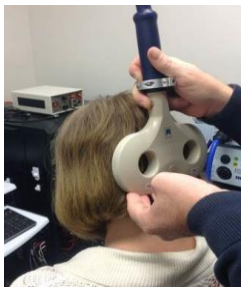
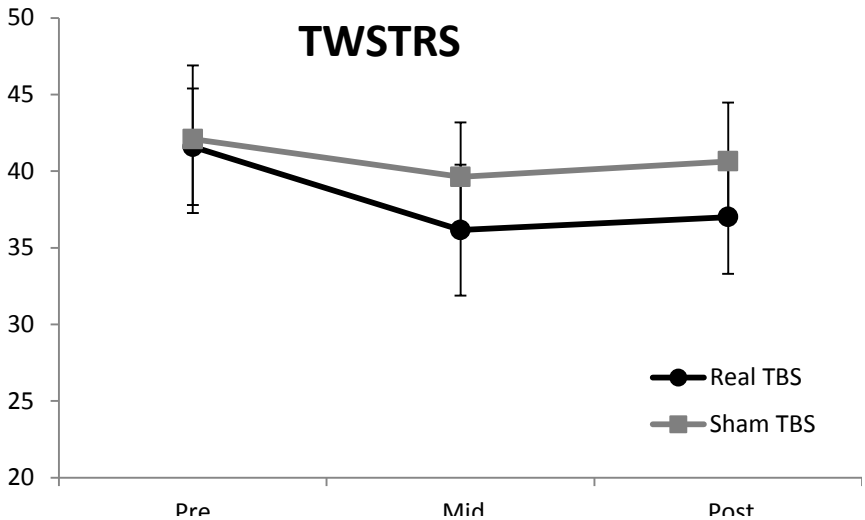
Title of Project: Multimodal treatment of cerebellum for cervical dystonia

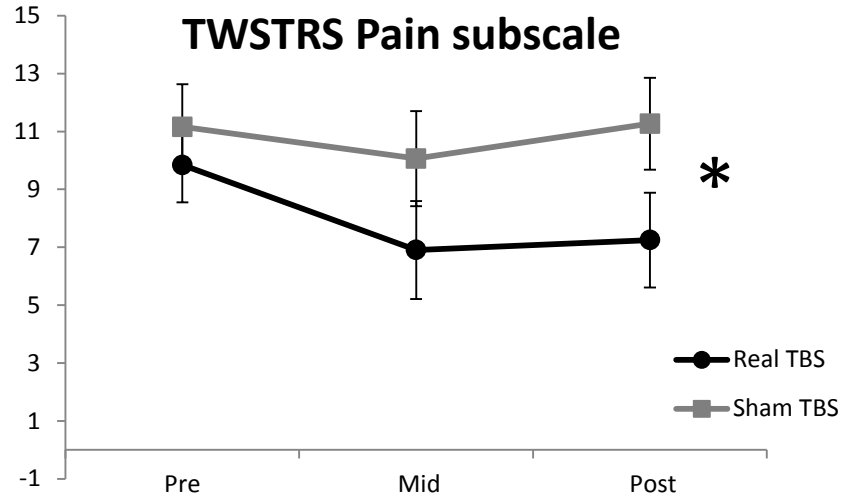
Summary: (approximately 1,000 words)
The Brain Foundation gift awarded in 2012 was used to begin a small randomized controlled trial of repeated sessions of non-invasive stimulation to cerebellum combined with motor and cognitive tasks in people with cervical dystonia (CD). Recruitment commenced in February 2013 and was completed in December 2014 with a total of 16 patients. Participants were randomized into either a real or sham stimulation group. The stimulation was delivered as intermittent theta-burst stimulation (iTBS) which is a pattered form of repetitive transcranial magnetic stimulation (TMS) known to promote synaptic plasticity and learning in the brain. Participants who had botulinum toxin injections for their CD were recruited 10 weeks post injections. All participants underwent measures of corticomotor excitability of their neck muscles using single-pulse TMS and a battery of tasks testing motor and cognitive sequencing and motor control. The primary outcome measure was the Toronto Western Spasmodic Torticollis Scale (TWSTRS); and the CD-specific quality of life assessment, the cervical dystonia questionnaire 24 (CDQ-24). Sequencing ability was tested by a mental rotation task and working memory and executive function by a random number generation test. Following baseline assessments, participants attended for 10 consecutive sessions of either real or sham iTBS directed to the posterior skull over the cerebellum. The stimulation was followed by motor and cognitive training tasks designed to challenge cerebellar function (implicit learning, action observation, cueing). Participants were tested again at the end of the 10 intervention sessions and the CDQ24 was assessed at 4 and 12 weeks after the last iTBS session.
The primary outcome measure, TWSTRS score at POST 1, was significantly reduced in the real iTBS group (X^2 (2) = 8.86, P = 0.012), but not in the sham iTBS group (X^2 (2) = 0.67, P = 0.72) as revealed by the Friedman test. A Wilcoxon post hoc test revealed the TWSTRS was reduced by iTBS at MID (-5.7 ± 0.9, P = 0.018) and POST 1 (-4.4 ± 1.2, P = 0.042). Comparison between Groups (Kruskal-Wallis) revealed no difference at baseline or either follow-up point (all P > 0.66). The pain subsection of the TWSTRS found a significant difference over time for iTBS (X^2 (2) = 9.74, P = 0.008), but not for sham TBS (X^2 (2) = 4.26, P = 0.12). Post hoc tests showed a significant reduction in pain at both MID and POST 1 (both P < 0.018). Comparison between groups found a significant difference at POST 1 (P = 0.040) but not at PRE or MID (both P > 0.18). For the CDQ-24, there was a difference across time for iTBS (X^2 (4) = 11.14, P = 0.025), but not sham TBS (X^2 (4) = 4.69, p = 0.32). Post hoc tests revealed a reduction by iTBS compared with baseline at each assessment point (all P < 0.01). The group comparison revealed a significant difference between real and sham iTBS at POST 3 (P = 0.04), but no difference between Groups at PRE, MID or POST 1 (all P > 0.16). Repeated measures ANOVA revealed no effect of GROUP, SIDE or TIME for MEPs or CSPs recorded from the upper trapezius (all P > 0.21).

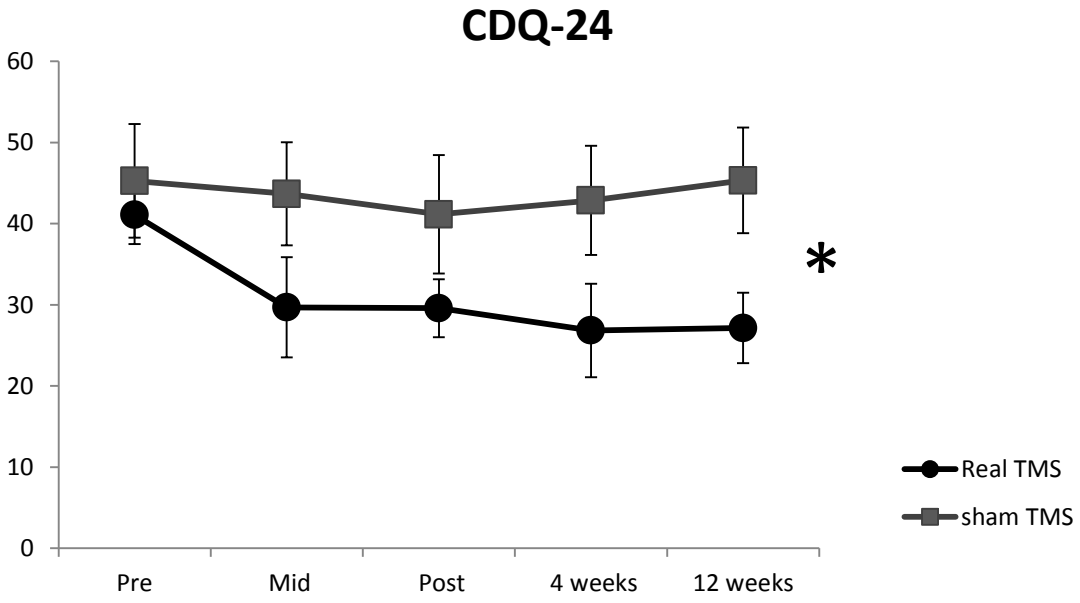
Figures illustrate the position of the stimulation coil over the posterior skull to stimulate the lateral cerebellum, the TWSTRS and CDQ-24 results. While there is a small improvement on the TWSTRS only the pain subsection demonstrated a significant difference between groups.











The strongest result at this stage is from the CDQ-24 quality of life measure, which demonstrates a difference between groups at the 12 week follow up. These data indicate the effects of 10 sessions of iTBS on quality of life last beyond the treatment period. Furthermore, since most participants had botulinum toxin injections immediately after the intervention, if may be possible that iTBS just prior to injections improves their efficacy, although this hypothesis would need to be tested empirically. The 14 point reduction in CDQ-24 at week 12 after the interventions greater than the 95% confidence interval boundary for effects of botulinum toxin injections alone 12 weeks post injection (mean 11.8; CI -13.1 to -10.4), showing a good effect of stimulation (Heftner et al 2013).

Hypothesis vs Findings

Our data support our hypothesis that cerebellar iTBS can improve symptoms of dystonia. The new finding is that a reduction in pain and improvement in quality of life are the most positive outcomes of this novel therapy.

Unanswered Questions
What are the mechanisms underlying improvement?
What is the optimum dose of iTBS for best effect?
Do some patient types (eg fixed vs mobile dystonia) respond better to iTBS?
Can treatments be combined with other interventions e.g. physiotherapy to improve efficacy?
What is the best time to deliver iTBS in relation to the botulinum toxin injections

What these research outcomes mean
There may be an alternative non-invasive treatment intervention for some types of cervical dystonia, or a treatment that can work synergistically with botulinum toxin injections or physiotherapy to improve their efficacy. Futher research in larger numbers of patients is required, with a greater range of neurophysiologic outcome measures to help understand the mechanisms underlying the improvements.

Please include any appropriate photos or diagrams.

Please submit this report as a PDF using the following naming convention:

Lastname Firstname – Simplified Project Title

For example: Smith Jane – The anatomy of the Brain.PDF