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# Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury

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HIGHLIGHTS

- Five-Hertz rTMS produced modest functional improvement but no clinical change in chronic, stable spinal cord injury subjects.
- Changes in cortical motor threshold measures may accompany functional gains to rTMS in spinal cord injured subjects.
- Electrophysiological measures may provide a useful adjunct to American Spinal Injury Association impairment scales.

ABSTRACT

*Objective:* To assess the effectiveness of physiological outcome measures in detecting functional change in the degree of impairment of spinal cord injury (SCI) following repetitive transcranial magnetic stimulation (rTMS) of the sensorimotor cortex.
*Methods:* Subjects with complete or incomplete cervical (or T1) SCI received real and sham rTMS in a randomised placebo-controlled single-blinded cross-over trial. rTMS at sub-threshold intensity for upper-limb muscles was applied (5 Hz, 900 stimuli) on 5 consecutive days. Assessments made before and for 2 weeks after treatment comprised the ASIA (American Spinal Injuries Association) impairment scale (AIS), the Action Research Arm Test (ARAT), a peg-board test, electrical perceptual test (EPT), motor evoked potentials, cortical silent period, cardiovascular and sympathetic skin responses.
*Results:* There were no significant differences in AIS outcomes between real and sham rTMS. The ARAT was increased at 1 h after real rTMS compared to baseline. Active motor threshold for the most caudally innervated hand muscle was increased at 72 and 120 h compared to baseline. Persistent reductions in EPT to rTMS occurred in two individuals.
*Conclusions:* Changes in cortical motor threshold measures may accompany functional gains to rTMS in SCI subjects.
*Significance:* Electrophysiological measures may provide a useful adjunct to ASIA impairment scales.


## 1. Introduction

The ability to detect physiological change associated with rehabilitation or treatments to effect axonal regeneration in spinal cord injury (SCI) will be challenging using the widely employed American Spinal Injuries Association (ASIA) impairment scales (AIS) for sensory and motor function (ASIA, 2002; Marino et al., 2003). Despite many revisions to the AIS standard neurological assessment there remains a perceived need for more sensitive, quantitative and objective outcome measures. The aim of this study (Stage 2 of the ISRT Clinical Initiative) was to examine the ability of identified physiological tests (Ellaway et al., 2004) to reveal functional improvements in SCI and compare them with AIS measures. As an intervention that was expected to improve functional outcome, repetitive transcranial magnetic stimulation (rTMS) was applied to the motor cortex in stable (chronic) SCI subjects who were at least

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>1 year post-injury (see Fawcett et al., 2007). rTMS induces short lasting modulation of cortical circuitry (Pascual-Leone et al., 1994b) that tends to produce depression of corticospinal output at low frequencies (<1 Hz) (Chen and Seitz, 2001) and facilitation at higher frequencies (>5 Hz) (Peinemann et al., 2004), although the effects appear inconsistent and depend upon stimulation parameters other than frequency (Fitzgerald et al., 2006; Hiscock et al., 2008; Rothkegel et al., 2010).

rTMS has been used extensively as a potential therapeutic intervention in neurological disorders including motor conditions, such as stroke (Fregni et al., 2006; Talelli et al., 2007), spasticity in multiple sclerosis (Centonze et al., 2007) and Parkinson's disease (Pascual-Leone et al., 1994a; Siebner et al., 2000) with some short term but inconsistent (Ghabra et al., 1999) functional improvements (for review, see Ridding and Rothwell, 2007). Application of rTMS in spinal cord injury has produced inconsistent results regarding amelioration of pain (Defrin et al., 2007; Kang et al., 2009). Belci et al. (2004) examined somatomotor functional recovery in SCI and showed a short term reduction in cortical inhibition during treatment with improved AIS measures of sensory and motor function and improved hand function that lasted into a recovery period. Reductions in spasticity have also been reported in SCI with the effect outlasting the period of rTMS application (Kumru et al., 2010).

## 2. Methods

### 2.1. Subjects

Twenty-three adult volunteers with chronic, stable spinal cord injury (SCI) were recruited for the study. Of those, 15 subjects completed the study (12 male, 3 female: age range 26–59 years). Eight recruits dropped out of the study for a variety of reasons including onset of illness un-related to the treatment (rTMS) or assessments, and un-anticipated personal time constraints. Inclusion criteria for the study were chronic (>9 months) and stable complete or incomplete spinal cord injury and a lesion level of T1 or above with residual hand and arm function. Exclusion criteria: neurological disorders, ferromagnetic implants in the head or neck, pregnancy, diabetes, cardiac pacemaker. Demographic details of the subjects are shown in Table 1. Ethics (Oxford Research Ethics Committee, REC 04/Q1606/48) and site specific (Royal National Orthopaedic Hospital) approvals were obtained. All subjects provided written, informed consent to participate in the study.

### 2.2. Study design

The study constituted a randomised placebo-controlled single-blinded (subject) cross-over trial of an intervention.

### 2.3. Intervention

The intervention consisted of repetitive transcranial magnetic stimulation (rTMS) (Magstim Super Rapid$^2$, The MagStim Co., Dyfed, Wales) using either a real coil or sham coil. Real rTMS stimulation was applied using a figure-of-eight coil with the handle pointing antero-medially over the sensorimotor cortex on one side. The initial current induced by the biphasic pulse of the magnetic stimulator would have flowed postero-laterally (Balslev et al., 2007). The junction of the coil was placed over the lowest threshold spot (see below) for eliciting a motor evoked potential (MEP) contralaterally in first dorsal interosseous (FDI), thenar eminence or extensor carpi radialis (ECR) muscles. The muscle with the lowest TMS threshold, left or right side, was selected as the reference muscle for applying rTMS and determined the hemisphere to be stimulated. The rationale for selecting the muscle with the lowest threshold is that from prior experience with TMS and SCI we expected some muscles to be out of range of the stimulator, i.e. thresholds >100% maximum stimulator output (MSO). We included three muscles in the study with the aim of finding at least one or more within range. Selecting the muscle with the lowest threshold also provided the opportunity of a wider range of responses (either increases or decreases) to test TMS. Selecting different target muscles was not thought to be significant confounding factor in design of the study. The difference in hot-spot location for the three limb muscles is small compared to the size of the delivery coil. The size of the coil and intensity of the rTMS would have affected a large part of the motor cortex, albeit concentrated over the low threshold site (hot-spot) for a particular muscle.

Subjects were seated with their upper limbs relaxed and rTMS delivered at 5 Hz as 2 s trains separated by 8 s for 15 min. Stimulation was applied at 80% of the active motor threshold (AMT) for eliciting a MEP during a weak (approximately 10%) voluntary contraction. The same strength, frequency and duration of stimulation were applied on 5 consecutive days. Sham stimulation was provided using a circular sham coil placed over the vertex. The stimulation was set to the same intensity for both real and sham stimulation but the sham coil delivered only 5% of real stimulator output. The output of the sham coil was always an order of magnitude below that regarded as necessary (70% of AMT) either for MEP generation (Todd et al., 2006) or to excite inhibitory circuits in the motor cortex (Rizzo et al., 2004). Both coils produced an audible click the intensity of which was similar or identical for real and sham stimulation. Neither real nor sham stimulation elicited a muscle twitch. Neither could be felt or distinguished by any subject.

### 2.4. Protocol

The subjects were screened for any current medication and asked to maintain it throughout the study. They did not undertake

**Table 1**
Subject demographics. Injury – time since injury. Level – level of injury (zone of partial preservation in brackets). Cause – RTA, road traffic accident. Medication – all oral.

| Subject | Gender | Age | Injury | ASIA | Level | Cause | Medication |
|---|---|---|---|---|---|---|---|
| 1 | F | 53 | 28y 7m | A | C8 (T3) | RTA | Baclofen |
| 2 | M | 34 | 13y 6m | A | C4 (C6) | Diving | Baclofen |
| 3 | M | 26 | 5y 1m | A | C5 (T3) | Diving | Baclofen, Nifedripine, Tizanidine, Oxybutynin |
| 4 | M | 31 | 12y 9m | B | C6 | RTA | Gabapentin, Diclofenac, Alfuzocin, Amitryptyline |
| 5 | F | 42 | 7y 0m | B | C5 | RTA | Oxybutinin |
| 6 | M | 29 | 8y 1m | B | C6 | Diving | Oxybutinin |
| 7 | F | 31 | 3y 0m | C | C4 | RTA | Baclofen, Tolterodine |
| 8 | M | 42 | 5y 9m | C | C4 | Diving | Baclofen |
| 9 | M | 38 | 16y 11m | C | C4 | Fall | Baclofen |
| 10 | M | 37 | 4y 1m | C | C6 | RTA | Baclofen, Oxybutinin, |
| 11 | M | 50 | 4y 5m | D | C2 | RTA | Oxybutinin, Alfuzosine |
| 12 | M | 31 | 4y 11m | D | C7 | RTA | Alfuzosin, Baclofen, Nifedipine |
| 13 | M | 50 | 13y 5m | D | C4 | RTA | Baclofen, Carbamazepine, Diclofenac, Diazepam |
| 14 | M | 59 | 10y 8m | D | C5 | Stenosis | Baclofen, Propiverine, Atenolol, Doxazosin |
| 15 | M | 42 | 16y 11m | D | C5 | RTA | Baclofen, Oxybutinin |