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Selectivity of upper limb posterior root muscle reflexes via cervicothoracic spinal cord stimulation.

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Abstract— **Recent studies have reported that transcutaneous spinal stimulation (tSCS) may facilitate improved upper limb motor function in those with incomplete tetraplesia. However, little is known about how tSCS engages upper limb motor pools. This study aimed to explore the extent to which discrete upper limb motor pools can be selectively engaged via altering stimulus location and intensity. 14 participants with intact nervous systems completed two test visits, during which posterior root-muscle reflexes (PRMR) were evoked via a 3x3 cathode matrix applied over the cervicothoracic spine. An incremental recruitment curve at C7 vertebral level was initially performed to attain minimal threshold intensity (MTI) in each muscle. Paired pulses (1ms square monophasic with inter-pulse interval of 50ms) were subsequently delivered at a frequency of 0.25Hz at two intensities (MTI and MTI+20%) across all nine locations. in a random order. Evoked response to the 1st ($PRMR_1$) and 2nd ($PRMR_2$) stimuli were recorded from four upper limb muscles. A significant effect of spinal level was observed in all muscles for $PRMR_1$ with greater responses recorded more caudally. Unexpectedly, contralateral cathode placement significantly increased $PRMR_1$ in *Biceps Brachii* (P=0.012), *Flexor Carpi Radialis* (P=0.035) and *Abductor Pollicis Brevis* (P=0.001). Post-activation depression (PAD) was also significantly increased with contralateral cathode placement in *Biceps Brachii* (P=0.001), *Triceps Brachii* (P=0.012) and *Flexor Carpi Radialis* (P=0.0001). These results suggest that some level of unilateral motor pool selectivity may be attained via altering stimulus intensity and location during cervicothoracic tSCS.**

I. Introduction

A growing body of clinical research has used transcutaneous spinal cord stimulation (tSCS) to generate motor output and improve function in previously paralysed individuals [1-3]. While the majority of therapeutic studies have focused on lumbothoracic tSCS for improving gait and standing, more recent applications using cervical tSCS have reported improvements in grip strength, pinch strength and overall upper limb function in individuals with chronic SCI [3-6]. Therapeutic techniques typically involve delivery of 1ms pulses at a frequency of 30Hz and a current density of less than 20mA.cm^{-2} [7]. The cathode is placed on the skin overlying vertebral spinous processes, with a larger anode electrodes placed ventrally, sometimes at great distances from the cathode. Electrode location, stimulation characteristics and polarity remain highly variable, particularly with respect to cervical tSCS. Computational and experimental data suggests that tSCS stimulates medium to large sensory afferents within the dorsal roots [8-10], resulting in mono-synaptic reflex activation of the corresponding motor pools. Such responses are termed posterior root-muscle reflexes (PRMR) [10]. By modulating reflex excitability at a spinal level, it is thought that tSCS can supplement tonic sensory and supraspinal inputs, leading to enhanced recruitment of locomotor and/or postural control circuitry [11]. However, a critical assumption with this mechanism, is that tSCS operates via trans-synaptic reflexes and not direct stimulation of the motor pools.

The reflex nature of tSCS is typically verified using paired stimuli delivered with a short (40-50ms) inter-pulse interval (40-50ms), such that the 2nd response is attenuated or absent, due to monosynaptic depression. By comparing the conditioning ($PRMR_1$) and test ($PRMR_2$) motor responses, post-activation depression (PAD) can be quantified, allowing researchers to evaluate the effectiveness of tSCS at engaging spinal reflex pathways. While PAD has been widely confirmed in lumbo-thoracic tSCS [8-10], there is still debate regarding the reflex nature of tSCS delivered at cervical level. While de Freitas et al. [12] argue a predominant reflex origin for tSCS delivered at multiple segments (C6-T1), Wu et al. [13] demonstrated that preferential excitation of upper limb 1a afferents is highly dependent on stimulus intensity. Experimental data has also shown that lower limb motor pools can be selectively activated via rostro-caudal [14] and medio-lateral [15] changes in electrode position. More recently, de Freitas et al. [12] confirmed bilateral selectivity of upper limb motor pools via stimulation of C6, C7 and T1 vertebral levels, with higher stimulus currents required to elicit responses in the distal motor pools. However, the level of unilateral selectivity which can be obtained via cervical tSCS remains unknown.

The primary aim of this study was therefore to quantify the selectivity of upper limb motor pool excitation via tSCS stimulation. This study aimed to identify whether significant differences exist in PRMRs evoked from nine different locations along a rostro-caudal and medio-lateral axis.

II. Methods

A. Study design

A total of 14 participants (9 male, 5 female; aged 27 ± 4 years; height, 176 ± 86 cm, weight, 73.9 ± 12.5 kg) with intact nervous systems completed two test visits, during which tSCS was applied to various locations on the cervicothoracic spine. During Visit-1, a recruitment curve was conducted with a single stimulation configuration. During Visit-2, the same recruitment curve was initially conducted, prior to the application of a 3x3 cathode matrix (Fig.1). A series of three

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paired pulses were subsequently applied at each location and at two intensities in a randomized order.

B. Stimulation Protocol

Cathode electrodes (ø 3.2cm2, Axelgaard, Fallbrook, CA) were placed in a 3x3 montage centrally over C5-C6, C6-C7 and C7-T1 intervertebral spaces and ~3.2cm laterally on either side (Fig.1). These locations were assumed the most proximal to C5/6, C7 and C8 spinal nerves, respectively. A fixed anode (5x10cm, Axelgaard) was placed centrally on the anterior neck with the caudal border at the level of C7. During Visit-1 and Visit-2, recruitment curves were performed via incremental stimulation of the C7 central cathode. This test involved a series of three paired pulses (1ms monophasic square wave, 50ms IPI) delivered at 0.25Hz with 5mA increments from 10mA up to 80mA (or maximal tolerance). Minimal threshold intensity (MTI) was subsequently determined as the lowest stimulus intensity in which PRMRs were evoked in two or more muscles. Criteria for PRMR was set at peak-to-peak amplitude of 50µV [13]. Following determination of MTI, individualised stimulation intensities for testing across the 3x3 cathode array were calculated (Lo=MTI, Hi=MTI+20%). A series of three paired-pulses (1ms monophasic, IPI=50ms) were applied at a frequency of 0.25Hz for each of the two stimulus intensities across all nine cathodal locations, in a randomised order, using a constant current stimulator (DS8R; Digitimer Ltd, UK).

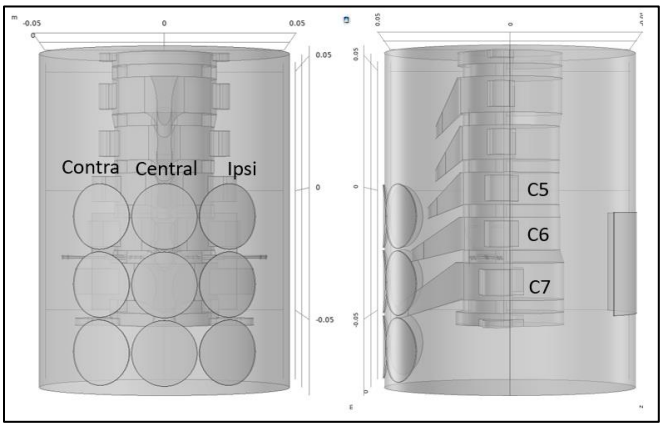

Figure 1: *3-dimensional model of electrode array in the coronal (left) and sagittal (right) planes. A 3x3 cathode matrix was placed at the approximate level of C5/6, C7 and C8 spinal nerves in a contralateral, central and ipsilateral arrangement. A rectangular 5x10cm anode was placed ventrally.*

C. Electromyography

Surface-electromyographic (EMG) recordings were acquired from *Biceps Brachii* (BB), *Triceps Brachii* (TB), *Flexor Carpi Radialis* (FCR) and *Abductor Pollicis Brevis* (APB) on the right arm using pairs of pre-gelled Ag/AgCl electrodes (Kendall, Mansfield, MA). The skin sites were shaved and cleaned with isopropyl alcohol wipes prior to electrode application. Recording electrodes were placed centrally over the muscle belly with longitudinal alignment, in accordance with the SENIAM recommendations. EMG signals were acquired using an Octal Bioamp integrated into a Powerlab 16/35 system (ADInstruments, Sydney, Australia). Signals were recorded at 10kHz, amplified (CMMR >60dB), bandpass filtered (10–500 Hz) and digitized. Recordings were subsequently exported to Matlab (MATLAB 2020b, The MathWorks Inc., Natick, MA) for processing and analysis. All recordings were conducted with the participants seated comfortably in a chair, arms supported symmetrically on both sides via arm rests and neck in a neutral position.

D. Data Processing

Evoked responses were recorded into LabChart (V8, ADInstruments, Oxford, UK) and exported to Matlab (Mathworks Inc. Natick, MA) for subsequent processing and analysis. Data were initially DC offset, and band-pass filtered between (20-500Hz) prior to stimulus artefact removal using a customised curve fitting programme. Peak-to-peak response amplitude was quantified in all EMG traces in the range of 6-40ms after both 1st ($PRMR_1$) and 2nd ($PRMR_2$) pulses and averaged over three consecutive paired pulses for all nine cathode locations and two stimulation intensities.

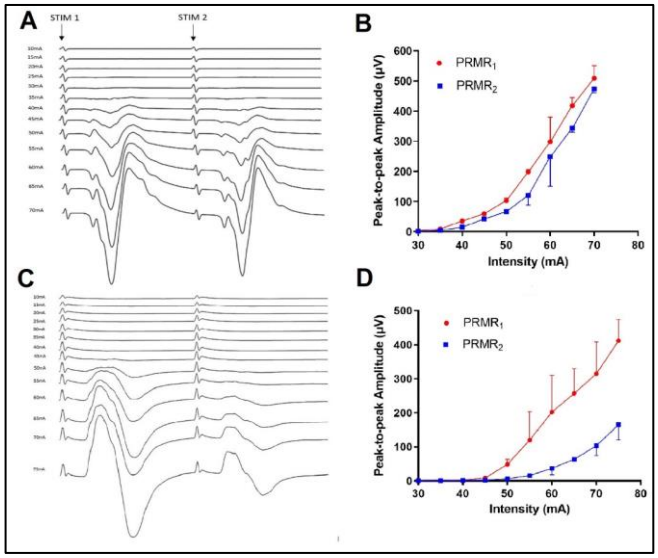

Figure 2: *Incremental EMG traces (A & C) and the corresponding intensity-response curves (B & C) from FCR muscle in two participants. Note the large variation in $PRMR_2$ response between individuals, suggesting stimulation of ventral rootles (A & B) and dorsal rootlets (C & D) respectively.*

Outcome variables quantified for the purposes of comparing stimulus intensity and location were $PRMR_1$ and PAD. $PRMR_1$ was normalised to the maximal PRMR recorded in any location or intensity. PAD was measured in each muscle as previously described [13]:

$$PAD\ (\%) = [1 - PRMR_1/PRMR_2]*100$$

MTI was defined as the minimal current (in mA) which elicited a PRMR>50uV within a muscle during recruitment curves. PAD_{max} was quantified as the maximal PAD attained from the associated C7 recruitment curve [12].

D. Statistical Analysis

Data for each muscle were assessed for normality via Kolmogorov Smirnov tests. Non-normally distributed data were transformed via log or antilog prior to further analysis. The effect of spinal level (C5/6, C7, C8 spinal nerves), lateral location (contralateral, central and ipsilateral) and stimulation intensity (MTI and MTI+20%) on the magnitude of $PRMR_1$ and PAD were evaluated using a 3 x 3 x 2 repeated measures

ANOVA (row x column x intensity). Violations of Sphericity were corrected via Greenhouse Geisser. A priori of $P<0.05$ inferred statistical significance at all times and Cohen's descriptors were used for quantifying effect size ($\eta 2$, Trivial 0-0.19; Small 0.2-0.49; Moderate 0.5-0.79; Large>0.8). Test-retest reliability of MTI, PAD_{max} and X_D were evaluated and compared across muscles using Bland-Altman analysis. Absolute reliability was expressed in terms of technical error of the measure (TEM) and 95% LOA. Relative reliability was expressed as intraclass correlation coefficients (ICC). Munro's descriptors describe the degree of repeatability.

III. RESULTS

The effect of spinal level, lateral location and stimulation intensity on $PRMR_1$ and PAD are summarized in Table 1 and Fig. 3. A significant effect of spinal level ($\eta 2=0.397$, $P<0.05$) and stimulation intensity ($\eta 2=0.725$, $P<0.001$) were observed in BB. However, the lateral location of the cathode electrode did not significantly impact $PRMR_1$ in BB. No interactions between spinal level, lateral location or stimulation intensity were observed. Similarly, in TB, a significant overall effect of spinal level ($P<0.001$, $\eta 2=0.784$) and intensity ($P<0.001$, $\eta 2=0.789$) was observed with no effect of lateral location. There were no interactions between factors. The muscles below the elbow (FCR and ABP) were significantly affected by both spinal level and lateral location of stimulation. In both cases, contralateral placement of the cathode significantly increased evoked response (see Table 1 and Fig. 3).

For FCR, spinal level ($P<0.001$, $\eta 2=0.77$), lateral location ($P<0.05$, $\eta 2=0.288$) and stimulation intensity ($P<0.001$, $\eta 2=0.85$) all significantly affected $PRMR_1$. A significant interaction between lateral location and stimulation intensity was also observed ($P<0.05$, $\eta 2=0.24$), with greater lateral effect observed caudally at C8 (Fig.3).

	$PRMR_1$				PAD			
	BB	*TB*	*FCR*	*APB*	*BB*	*TB*	*FCR*	*APB*
Lateral Effect	F=4.9 P=0.012 $\eta 2=0.29$	-	F=4.9 P=0.035 $\eta 2=0.28$	F=8.9 P=0.001 $\eta 2=0.43$	F=9.3 P=0.001 $\eta 2=0.44$	F=5.4 P=0.012 $\eta 2=0.31$	F=17.4 P=0.000 $\eta 2=0.59$	-
Spinal Level	F=39.7 P=0.000 $\eta 2=0.77$	F=43.4 P=0.000 $\eta 2=0.79$	F=39.8 P=0.000 $\eta 2=0.77$	F=107.0; P=0.000 $\eta 2=0.90$	-	-	-	F=7.7 P=0.003 $\eta 2=0.39$
Intensity	F=65.6 P=0.000 $\eta 2=0.85$	F=44.9 P=0.000 $\eta 2=0.79$	F=65.6 P=0.000 $\eta 2=0.85$	F=145.6 P=0.000 $\eta 2=0.92$	F=6.5 P=0.026 $\eta 2=0.35$	F=22.6 P=0.000 $\eta 2=0.65$	-	-

TABLE 1: ANOVA RESULTS

The most profound effects of both spinal level ($P<0.001$, $\eta 2=0.90$), lateral location ($P<0.01$, $\eta 2=0.43$) and stimulation intensity ($P<0.001$, $\eta 2=0.92$) were observed for *ABP*. A significant interaction between spinal level and lateral location ($P<0.001$, $\eta 2=0.53$) was observed, with greater lateral effect observed caudally at C8 (Fig. 3). An additional interaction between spinal level and intensity ($P<0.001$, $\eta 2=0.84$) was also observed, with stimulus intensity affecting the magnitude of $PRMR_1$ to a greater extent caudally (Fig.3). No significant effect of spinal level was observed for PAD in BB, TB or FCR. However, lateral location significantly affected the magnitude of PAD responses in BB ($P<0.01$, $\eta 2=0.44$), TB ($P<0.05$, $\eta 2=0.31$) and most profoundly in FCR ($P<0.001$, $\eta 2=0.59$). In all three muscles, contralateral stimulation increased the level of reflex-induced response. In contrast, ABP showed consistency in PAD across lateral location, but a significant effect of spinal level was observed ($P<0.01$, $\eta 2=0.39$). An effect of stimulation intensity was observed in the larger proximal muscles with both BB ($P<0.05$, $\eta 2=0.35$) and TB ($P<0.001$, $\eta 2=0.65$) demonstrating greater reflex responses at higher stimulus intensity.

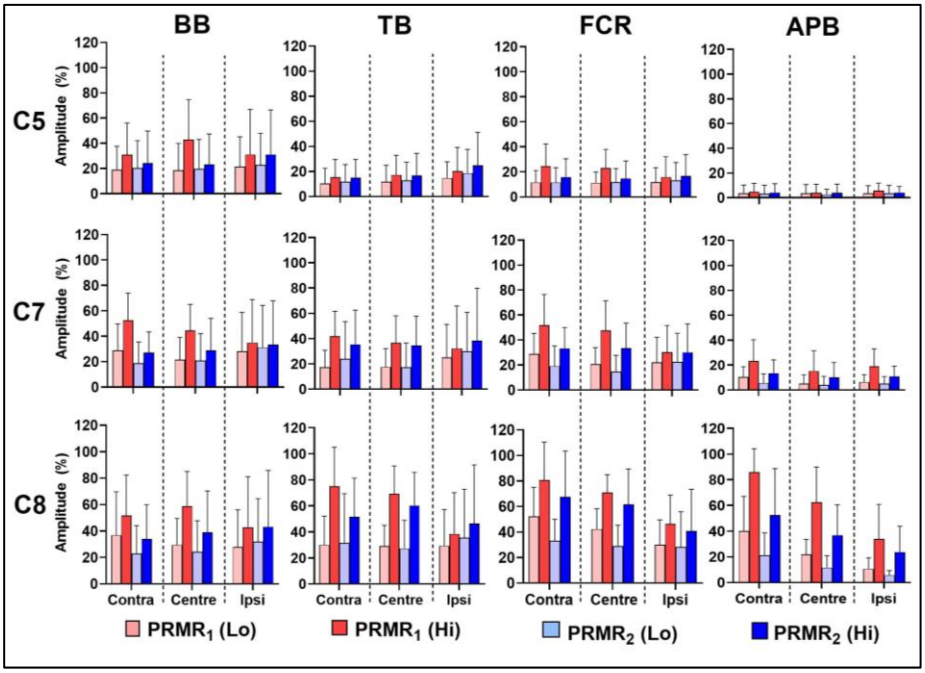

Figure 3: *Group mean ± SD amplitude of $PRMR_1$ (red) and $PRMR_2$ (blue), across spinal level (C5/6, C7, C8), location (contralateral, central, ipsilateral) and intensity (Lo = light; Hi = dark) in BB, TB, FCR, APB. Amplitude data were normalised to maximal evoked response recorded at any location or intensity.*

In contrast, the reflex nature of the response in muscles distal to the elbow was not significantly altered by stimulation intensity, although muscles exhibited greater PAD at lower intensity over C8 level

IV. Discussion

A. Selectivity of upper limb motor pools via tSCS

Medio-lateral adjustments to cathode location significantly altered the resultant PRMR responses from upper-limb muscles. Unexpectedly, stimulation from the contralateral side not only increased the magnitude of $PRMR_1$ in BB, FCR and APB (Fig. 3), but also enhanced the sensory reflex origin in BB, TB and FCR, as highlighted by significantly increased PAD. These findings disagree with previous research reporting increased PRMR response with ipsilateral stimulation of the lumbo-thoracic spine [15]. This may be in-part explained by regional variations in vertebral architecture, along with differing curvature and orientation of the spinal nerves emanating from the intervertebral foramina. In terms of the spinal level, research has already highlighted that upper limb PRMR response alters significantly when cathode location is moved rostro-caudally [12]. Our results support these findings and highlight that placement of cathodes at levels above C7 may be sub-optimal, even for muscles proximal to the elbow (i.e. BB and TB). Stimulation more caudally on the upper thoracic spine may allow further motor pool selectivity, however, this was beyond the scope of the current study.

B. The sensory reflex origin of tSCS

A critical assumption regarding the use of tSCS as a neuromodulation technique is the preferential stimulation of large diameter sensory afferents within the dorsal roots [12]. This has been demonstrated via the appearance of PAD when paired stimuli are applied dorsally [8-10]. The magnitude of PAD observed in the current study was highly variant between individuals (Fig.1) and in general less than previously reported for cervical tSCS [12,13]. In some cases, potentiation rather than depression of $PRMR_2$ was observed (Fig.4), the mechanism of which remains unknown. Variations in seated posture and/or neck curvature can alter the subcutaneous electrical field, and may explain the inconsistencies observed. Root fibre pathways are thought to be altered with flexion and extension of the spine, thus impacting upon PRMR response at the lumbar spine [16]. More complex computational models of the cervical spine which account for vertebral articulation may help explain these findings. APB and FCR demonstrated consistent PAD with low intensity stimulation over C8 (Fig.4). While higher intensity stimulation significantly increased PAD in both proximal muscles, the distal muscles favoured low intensity stimulation at MTI, which is in agreement with previous research [13]. Finally, this study provides additional data on the repeatability of tSCS at cervicothoracic level. MTI and X_D demonstrated moderate to high repeatability, which may be useful for future clinical researchers using tSCS in electrophysiological assessment and therapeutic prescription.

V. Conclusion

The results of this study highlight that some degree of targeted upper-limb activation is feasible with cervicothoracic tSCS, albeit the optimal combination of parameters (location vs. intensity) appears highly variable between individuals.

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