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# Trigemino-cervical-spinal reflexes after traumatic spinal cord injury

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## HIGHLIGHTS

- Trigemino-cervical reflex (TCR) and trigemino-spinal reflex (TSR) responses can be recorded from upper limb muscles only in SCI patients.
- These EMG responses in the neck muscles were significantly higher in SCI patients.
- Synaptic plasticity and sprouting processes may contribute to the findings.

## ABSTRACT

*Objective:* After spinal cord injury (SCI) reorganization of spinal cord circuits occur both above and below the spinal lesion. These functional changes can be determined by assessing electrophysiological recording. We aimed at investigating the trigemino-cervical reflex (TCR) and trigemino-spinal reflex (TSR) responses after traumatic SCI.
*Methods:* TCR and TSR were registered after stimulation of the infraorbital nerve from the sternocleidomastoid, splenius, deltoid, biceps and first dorsal interosseous muscles in 10 healthy subjects and 10 subjects with incomplete cervical SCI.
*Results:* In the control subjects reflex responses were registered from the sternocleidomastoid, and splenium muscles, while no responses were obtained from upper limb muscles. In contrast, smaller but clear short latency EMG potentials were recorded from deltoid and biceps muscles in about half of the SCI patients. Moreover, the amplitudes of the EMG responses in the neck muscles were significantly higher in patients than in control subjects.
*Conclusion:* The reflex responses are likely to propagate up the brainstem and down the spinal cord along the reticulospinal tracts and the propriospinal system. Despite the loss of corticospinal axons, synaptic plasticity in pre-existing pathways and/or formation of new circuits through sprouting processes above the injury site may contribute to the findings of this preliminary study and may be involved in the functional recovery.
*Significance:* Trigemino-cervical-spinal reflexes can be used to demonstrate and quantify plastic changes at brainstem and cervical level following SCI.

## 1. Introduction

Adaptive changes within spared neuronal circuitries reflect the reorganization of nervous system after SCI and may occur at cortical, brainstem, or spinal levels. Reorganization of intraspinal circuits may occur both above and below a spinal lesion (Raineteau and Schwab, 2001; Bareyre et al., 2004). This ability

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of the adult central nervous system to reorganize its circuits over time following injury is the key to understand the functional improvement in patients with SCI.

Changes in the sensorimotor system after SCI can be reliably determined by assessing electrophysiological recordings. Electrical stimulation to the supraorbital and infraorbital branches of the trigeminal nerve induces early and late reflex evoked responses in neck and upper limb muscles, termed trigemino-cervical reflexes (TCR) and trigemino-spinal reflexes (TSR) (Sartucci et al., 1986; Di Lazzaro et al., 1995, 1996, 2006; Ertekin et al., 1996, 2001; Leandri et al., 2001; Serrao et al., 2005, 2011; Bartolo et al., 2008; Nardone et al., 2008; Kiziltan et al., 2014). These responses probably have a different functional significance. The early responses are mediated by non-nociceptive afferents and functionally resemble the R1 component of the blink reflex (Shahani and Young, 1972), while the late responses have been related to movements of head retraction as a protective mechanism against a nociceptive stimulus on the face (Sartucci et al., 1986; Ertekin et al., 1996).

A polysynaptic pathway provides the neural network required for these highly integrated motor responses influenced by converging sensory inputs. The nucleus reticularis pontis caudalis and from there efferent projections in the reticulobulbar and reticulospinal tracts are the central structure mediating the neural circuitry underlying these reflex responses. Reticulospinal fibers in general do not form well-defined tracts, but are scattered throughout the anterior and lateral columns and are known to project directly to the PNs (Nathan et al., 1996). The PNs are a population of spinal cord interneurons that connect multiple spinal cord segments and participate in complex or “long” motor reflexes (Flynn et al., 2011).

These neuronal pathways may represent an important substrate for recovery from SCI and contribute to plastic reorganization of spinal circuits. Since these neuronal circuits may undergo an extensive remodelling after SCI, in this study we aimed at evaluating the early TCR and the TSR responses in subjects with incomplete chronic cervical SCI. We hypothesize that the reorganizational processes following SCI may induce changes in the polysynaptic pathways that mediate the reflex interaction between trigeminal afferents and cervical spinal cord motoneurons, resulting in reflex responses that are different from those of healthy subjects.

## 2. Materials and methods

### 2.1. Subjects

Ten subjects (mean age 44.8 years, range 24–62, seven men and three women) with chronic cervical SCI and bilateral limb involvement, classified as grades B, C or D according to the American Spinal Cord Injury Association Impairment Scale (Marino et al., 2003), were enrolled in the study. Ten healthy volunteers (mean age 44.2 years, range 24–58, seven men and three women) participated as sex- and age-matched controls. Clinical and demographic features of the patients are shown in Table 1.

Patients and control subjects provided informed consent before participation in the study, which was performed according to the declaration of Helsinki and approved by the Ethics Committee. Inclusion criteria were: (a) ability to activate the above mentioned muscles against gravity; (b) ability to give informed consent and comprehend instructions. Exclusion criterium was the presence of other neurological conditions, including traumatic brain injury and any history of cervical radiculopathy or polyneuropathies.

### 2.2. Experimental procedure

Surface EMG activity was recorded bilaterally using 0.9 cm. diameter Ag/AgCl electrodes.

For the sternocleidomastoid (SCM) muscle the active electrode was placed over the upper half of the muscle, approximately 8 cm above a reference electrode on the clavicle; for splenius capitis the active electrode was placed approximately 6–8 cm lateral to C4, where the muscle can be palpated, with a reference on the spinous process of C7; for deltoid the active electrode was placed over the anterior part of the muscle belly, with the reference on the acromion; for biceps the active electrode was placed over the mid-region of the muscle and the reference on the tendon; for the first dorsal interosseous (FDI) the active electrode was placed over the motor point and the reference over the metacarpophalangeal joint (Di Lazzaro et al., 1995). Patients and controls were asked to contract the muscles at 30% of the maximum strength so as to facilitate the appearance of reflex responses.

The EMG was amplified (Digitimer, D150), bandpass filtered (30–3000 Hz) and averaged (512 trials) using a sampling rate of 5 kHz from 20 ms before the stimulus to 80 ms afterwards.

Electrical stimuli (50 μs duration) were applied to the left infraorbital nerves via bipolar surface electrodes fixed near their point of exit from the skull. The intensity was adjusted to be 3 times of the perceptual threshold, which most subjects regarded as strong but not painful. The repetitive rate was usually 3 Hz. Amplitude where measured peak to peak in the unrectified mean. Because the size of the EMG responses is linearly related to the degree of background muscle contraction (Di Lazzaro et al., 1995, 1996), the size of the potentials was expressed as a ratio to the mean rectified surface EMG activity preceding the stimulus. Since the size of the responses varied considerably from subject to subject, we took the square root of the amplitude values to transform the distribution of the data into a Gaussian form.

### 2.3. Statistical analysis

Statistics were carried out using the software environment R (R Core Team, 2014). We ensured that the data was normal distributed by calculating a Shapiro–Wilk-test for each response variable. Since results of all tests for normal distribution yielded a $p > .05$, we calculated three ANOVAs (function aov) for each of the measures amplitude, onset latency and first peak latency. Each of these ANOVAs included the between-subject factor group (controls vs. patients), and the within-subject factors muscle (SCM vs. splenius capitis) and side (ipsi- *vs.* contralateral). The resulting p-values were corrected for multiple comparisons with the Bonferroni correction. Thus, a *p*-value of $p < 0.016$ was considered as significant.

## 3. Results

As previously described (Di Lazzaro et al., 1995, 1996), in the healthy subjects the clearest responses were obtained in the SCM when they were activated bilaterally by holding the head raised in the supine position. Stimulation of the left infraorbital branch of the trigeminal nerve produced in the unrectified, averaged surface EMG a bilateral response, which consisted of positive/negative wave with a mean onset latency of about 13 ms, the positive peak at about 19 ms and the negative peak at about 31 ms. Short-latency EMG potentials were also recorded in the splenius capitis when the muscle was activated by extending the neck. No responses were observed in deltoid, biceps, or FDI muscles.

In SCI patients, stimulation of the left infraorbital nerve induced responses in the SCM and splenius muscles of similar onset and first peak latencies, but of significantly increased peak-to-peak size compared to healthy controls ($F_{(1,66)} = 6.11$; $p = .016$). Moreover, a clear response was registered from tonically active deltoid in 6 of the 10 patients (bilaterally in 5 patients, only ipsilateral in one patient), and from biceps in 5 out of the 10 patients (bilaterally in all patients) (see example in Fig. 1).