Effect of thoracic spinal cord injury on forelimb somatosensory evoked potential

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ABSTRACT

In this paper, we investigate the forelimbs somatosensory evoked potential (SSEP) signals, which are representative of the integrity of ascending sensory pathways and their stability as well as function, recorded from corresponding cortices, post thoracic spinal cord injury (SCI). We designed a series of distinctive transection SCI to investigate whether forelimbs SSEPs change after right T10 hemi-transection, T8 and T10 double hemi-transection and T8 complete transection in rat model of SCI. We used electrical stimuli to stimulate median nerves and recorded SSEPs from left and right somatosensory areas of both cortices. We monitored pre-injury baseline and verified changes in forelimbs SSEP signals on Days 4, 7, 14, and 21 post-injury. We previously characterized hindlimb SSEP changes for the abovementioned transection injuries. The focus of this article is to investigate the quality and quantity of changes that may occur in the forelimb somatosensory pathways post-thoracic transection SCI. It is important to test the stability of forelimb SSEPs following thoracic SCI because of their potential utility as a proxy baseline for the traumatic SCIs in clinical cases wherein there is no opportunity to gather baseline of the lower extremities. We observed that the forelimb SSEP amplitudes increased following thoracic SCI but gradually returned to the baseline. Despite changes found in the raw signals, statistical analysis found forelimb SSEP signals become stable relatively soon. In summary, though there are changes in value (with $p > 0.05$), they are not statistically significant. Therefore, the null hypothesis that the mean of the forelimb SSEP signals are the same across multiple days after injury onset cannot be rejected during the acute phase.

1. Introduction

Spinal cord injury (SCI) is characterized by the disruption of neuropathways and surrounding parenchyma at and around the injury site (Agrawal et al., 2008; Bellardita et al., 2018; Maynard et al., 1997). Previous studies have shown that some functional recoveries are achievable despite the central nervous system's lack of ability for proper endogenous repair and regeneration (Maybhate et al., 2012; Teh et al., 2018). These recoveries could be attributed to post-injury cortical and neuronal reorganization near the site of injury as well as neural plasticity in the higher structures of cortices (All et al., 2019; Bazley et al., 2014a, 2014b; Bazley et al., 2011; Ghosh et al., 2010; Vipin et al., 2016).

Recognizing early neuronal plasticity and reorganization plays a pivotal role in rehabilitation and treatment post-SCI, especially during the acute phase. The post-SCI changes in SSEP signals are associated with the plasticity in the higher structures of the nervous system as well as the sprouting and rewiring of surviving neurons through reorganization around the epicenter of trauma (Ghosh et al., 2010; Sydekum et al., 2014). All together, these changes may be the key factors facilitating adaptive endogenous recovery (Ramer et al., 2014).

Somatosensory Evoked Potential (SSEP) enables us to quantitively assess the changes in injured and uninjured sensory pathways after SCI, which is also widely adopted in clinical settings (Hyun et al., 2009). SSEPs are the cortical electrical responses elicited by an external sensory stimulus (All et al., 2010; Dawson, 1947). As electrical measurements of the integrity for the sensory pathway, SSEPs have been used to discern

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the severity of SCI as well (Agrawal et al., 2009a,2009b,2009c; Fatoo et al., 2007). SSEPs are commonly obtained by stimulating the tibial and median nerves in the lower and upper limbs for the assessments of SCIs (All et al., 2009; Bazley et al., 2012, 2014a, 2014b;Mir et al., 2010a, 2010b;Mir et al., 2010a). In addition, the forelimb SSEPs could also be used to provide replacement for the baseline traces in longitudinal SCI monitoring, where the baseline recordings are absent, particularly in clinical cases (Al-Nashash et al., 2009, 2020).

Novel forms of signal processing techniques such as linear modeling (Mir et al., 2015), shape analysis (Agrawal et al., 2009a, 2009b, 2009c), slope analysis (Agrawal et al., 2010a, 2010b), sparse modeling (Mir et al., 2017), spectral coherence (Al-Nashash et al., 2009), adaptive coherence (Sherman et al., 2010) and chirp modeling (Väyrynen et al., 2016) have empowered both physicians and scientists to use the SSEP signals for detecting even minuscule changes.These SSEP signals for ascending and Motor Evoked Potentials (MEPs) for descending neuropathways monitoring (Agrawal et al., 2009a, 2009b, 2009c; Iyer et al., 2010; Mir et al., 2011) are also employed to detect the onset of trauma, its progression (Agrawal et al., 2010a, 2010b) as well as endogenous and therapeutic recoveries such as stem cell replacement therapy (All et al., 2015, 2012; Kerr et al., 2010; Walczak et al., 2011) and neuroprotective hypothermia (Bazley, Pashai, et al., 2014; Vipin et al., 2015).

Although it is known that a cervical SCI would cause changes in SSEP and MEP signals in both upper-limbs and lower-limbs, it is imperative to also investigate possible changes in the upper-limbs signals after thoracic SCI, where the trauma mainly envolves the lower-limbs neuropathways. As we previously reported (Al-Nashash et al., 2020), upper-limb SSEP signals could be used for daily comparison of the changes that occur in the lower-limbs SSEP signals in order to detect both progress of injury and range of recovery. Hence, detecting changes that could occur in the forelimbs SSEPs after thoracic SCI is critical.

Here, we report the effect of thoracic SCI on forelimb SSEP signals using rodent transection SCI models.This study shows that even in the case of thoracic SCI, the otherwise healthy forelimbs will be subject to temporarily transient changes in their SSEP amplitudes, which could be related to the neural plasticity and reorganization of the neuropathways (Blesch and Tuszynski, 2009; Endo et al., 2007). Nevertheless, the upper extremities SSEPs exhibit long term stability and, as a result, render them valid to be used as proxy baselines to measure the long-term recovery of lower extremities SSEPs.

2. Materials and methods

We have previously published the transection SCI experimental procedures and the electrophysiological monitoring in details (Al-Nashash et al., 2020; All et al., 2019). Here we intend to report a brief summary of the main concepts.

2.1. Experiment setup

2.1.1. Animals and transection injury

The guidelines for Rodent Survival Surgery and *in vivo* experiments were followed and approved by the Institutional Animal Care and Use Committee at the National University of Singapore. 20 adult (200−225 g) male and female Sprague-Dawley rats were used for three injury groups plus one control group (n = 5): (i) right T10 hemi-transection (RxI), (ii) left T8 and right T10 double hemi-transection (DxI), (iii) T8 complete transection (CxI) and (iv) laminectomy with no injury (control). After laminectomy and exposing the spinal cord, the transection injury was performed by one clean, sharp transverse incision using a small-size N⁰. 11 scalpel (Swann-Morton) under microscope. The ip injection of 0.2−0.3 ml cocktail of Ketamine (50 mg/kg), Xylazine (5 mg/kg) and Acepromazine (1 mg/kg) was used for anesthesia. Rats' body temperature was kept stable at 37 +/- 0.5 °C at all times. Analgesics buprenorphine (0.06 mg/kg) and antibiotic gentamicin (8 mg/kg) were given to all rats and bladder expression was performed until
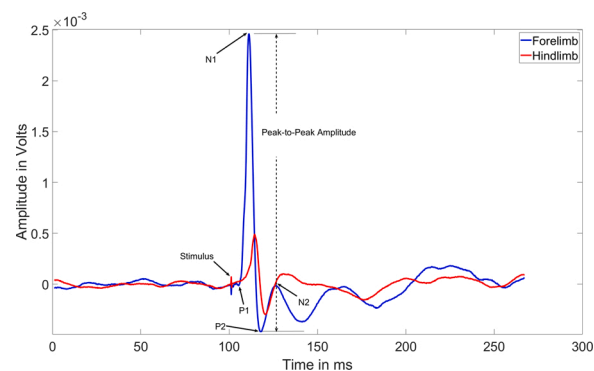

Fig. 1. An example of an averaged baseline SSEP signal obtained from both forelimbs and hindlimbs prior to the spinal cord injury.

rats regained their ability of urination by themselves.

2.1.2. Skull electrode implantation

One week before injury day, five SSEP screw electrodes (E/363/20/SPC; Plastic One, Inc) were implanted on the skull of rats, corresponding to the forelimbs (left and right hemispheres at 0.2 mm posterior and 3.8 mm lateral to the bregma), hindlimbs (left and right hemispheres at 2.5 mm posterior and 2.8 lateral to the bregma), a reference (right hemisphere at 3.0 mm lateral to lambda) and fixed with a small amount of dental cement (Jet Denture Repair Package; Lang Dental Manufacturing Co., Inc).

2.1.3. Multi-limb SSEP recording

An isolated current stimulator (Letchworth DS3; Digitimer Ltd., Welwyn Garden City, UK) was used to deliver electrical stimulations to a pair of subdermal needle electrodes (RI Safelead F-E3−48; Grass Technologies, West Warwick, RI) that were placed near the Tibial and Median nerves of both limbs. A Tucker-Davis Technologies (TDT; Tucker-Davis Technologies Inc., Alachua, FL) with 64-channel head-stage amplifier (RA64LI) was used for SSEP monitoring. A digital pre-amplifier (RA4PA) and a Bio-amplifier processor (RZ5) were used for data acquisition. The skull screw electrodes were connected to an amplifier and the OpenEx software controlled the stimulator. The Stimulator was set to trigger the Bioamp processor at 0.5 Hz, 3.5 mA pulse intensity, 200 μsec pulse width at 1 Hz. Then, the SSEP signals were recorded in 1-sec epochs at a sampling rate of 4882 Hz. This enabled us to collect 150 epochs of SSEPs of 1-sec length each from the corresponding somatosensory cortices for each of the four limbs (Al-Nashash et al., 2020; All et al., 2019). It is noteworthy that Isoflurane gas anesthesia (1.5 % Isoflurane plus 90 % oxygen and room air at the flow rate of 1.5 L per minute) via isoflurane vaporizer (using a diaphragm with a C-pram circuit mask) is the most desirable drug for use in SSEP recordings. Since it is critical for these experiments, the anesthesia level and body temperature have always been kept constant in all rats. SSEPs were obtained for the baseline data before that injury and then on days 4, 7, 14 and 21 post-SCI.

2.1.4. Definitions

Definitions used in the following sections: **RxI (**Right T10 hemi-transection injury); **DxI (**Left T8 and Right T10 double hemi-transection injury); **CxI** (T8 complete transection injury); **RFxS** (Right forelimb stimulation); **RHxS** (Right hindlimb stimulation); **LFxS** (Left forelimb stimulation); **LHxS** (Left hindlimb stimulation)

2.2. Signal processing

All signal processing was performed in MATLAB R2018b from MathWorks Inc. The raw SSEP signal was first bandpass filtered with a frequency bandwidth of 20 Hz to 1 K Hz. The 50 Hz power line
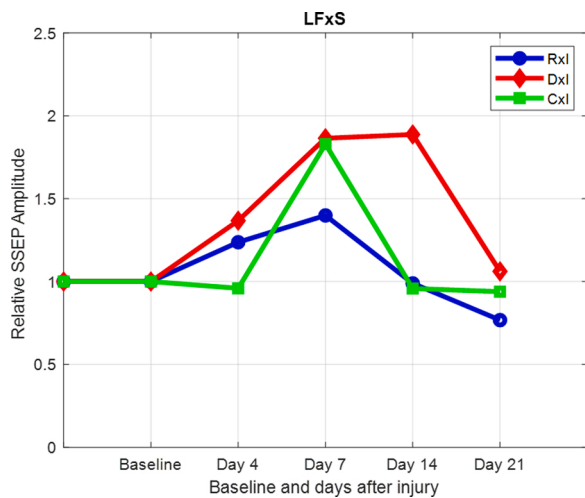
Fig. 2. Mean relative SSEP amplitude recorded from the right hemisphere with left forelimb stimulation for the three injury groups on different days.

Fig. 3. Mean relative SSEP amplitude recorded from the left hemisphere with right forelimb stimulation for the three injury groups on different days.

interference was minimized using notch filtering. The SSEP signal was then extracted from the raw SSEP signal epochs using ensemble averaging. Ensemble averaging was performed with the help of the 1 Hz stimulation pulse. This procedure improves the signal-to-noise ratio of the SSEP signal. Fig. 1 depicts a typical averaged baseline window of 260 msec SSEP signal obtained from both forelimbs and hindlimbs prior to spinal cord injury. Although the wave shape may vary among different animals, the main signal components are identified as P1 for the first positive peak following the stimulus pulse, N1 for the first negative peak, P2 for the second positive peak and N2 as the second negative peak. Peak detection was then applied to locate the N1 and P2 peaks followed by measuring the peak-to-peak amplitude between them. The SSEP averaged signals were then normalized relative to the respective or corresponding baseline signal. This was computed by dividing the N1-P2 peak-to-peak amplitude of the SSEP by the N1-P2 peak-to-peak of the corresponding baseline.

2.3. Statistical analysis

The software package Minitab® 18.1 was used for statistical data analysis. Alternative statistical tests were performed on the SSEP data. Our SSEP data are defined as the following: n = 5, one control and three types of SCI (RxI, DxI and CxI), one SSEP baseline recording prior to injury and then recordings on days 4, 7, 14 and 21 after SCI. In total, we collected and analyzed 300 SSEP data records corresponding to the three injury groups, 5 animals in each group, 5 days (including baseline, Days 4, 7, 14, and 21) of recordings. The four SSEPs correspond to two from the right somatosensory cortex receiving projections from the left forelimb and left hindlimb (LFxS & LHxS) and two from the left somatosensory cortex receiving projections from right forelimb and right hindlimb (RFxS & RHxS).

We compared the relative SSEP amplitude using a simple main-effect analysis of variance (ANOVA). The relative amplitude value is adopted as the response variable while the injury type as the factor. This was followed by pairwise tests using Fisher's Least Significant Difference method for multiple comparisons between relative amplitudes on different days. The null hypothesis was that the relative amplitudes are the same on different days before and after injury.

3. Results

3.1. SSEP analysis

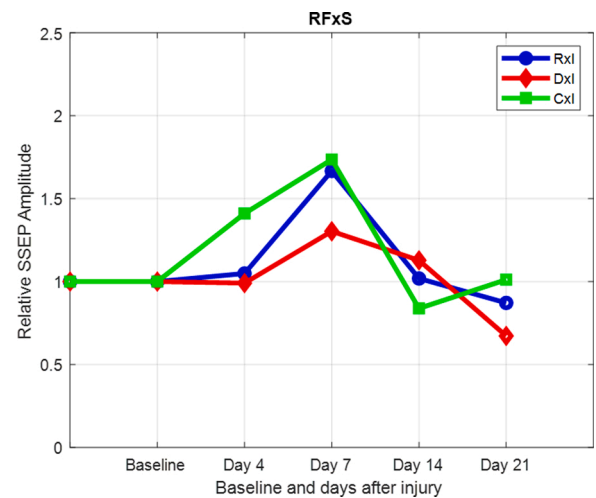Rats were randomly divided into three injury and one control groups:

right hemi-transection at T10 (RxI), double hemi-transection at left T8 and right T10 (DxI), complete transection at T8 (CxI), and only laminectomy with no transection (dura remained intact).

Fig. 2 shows the mean relative SSEP amplitude recorded from the right hemisphere with left forelimb stimulation (*LFxS*) for the three RxI, DxI and CxI injury groups on different days. The mean relative amplitude was obtained by averaging the SSEP from all 5 rats within the same injury group. Value of 1 corresponds to the normalized baseline relative SSEP amplitude. The SSEP signals of rats in the control group showed no changes and their relative amplitudes remained 1 throughout the monitoring (data not reported). We observed an increase in relative amplitude of forelimbs SSEP signals reaching more than 1.5 following thoracic injury on day 7 before recovering back to values close to the baseline (more than 0.7) and stabilizing.

Similarly, Fig. 3 shows the mean relative SSEP amplitude recorded from the left hemisphere with right forelimb stimulation (RFxS) for the three injury groups on different days. We observed a similar pattern indicating various degrees of increased relative amplitudes depending on different severities of the injury mainly on day 7 before recovering back and stabilizing to the values close to the baseline. Considering neuropathways from forelimbs project well-above the site of injury, the phenomena of temporary increase in forelimbs SSEP amplitude, particularly soon after the thoracic SCI, is noteworthy. As we reported previously for the contusive thoracic SCI, this could be attributed to the plasticity that happens within the cortices post-SCI (Bazley et al., 2011) and is not related to the re-organization of neuropathways surrounding the epicenter of injury.
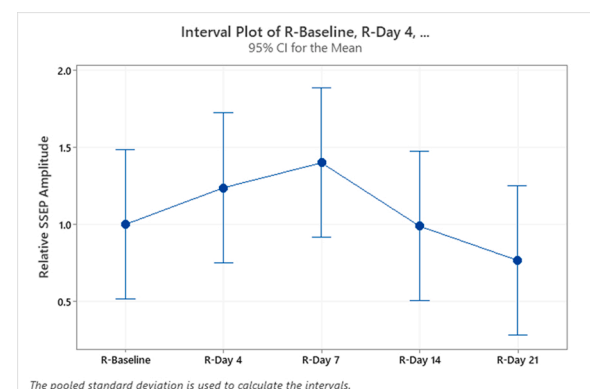

Fig. 4. Interval plot of the relative SSEPs from right hemisphere recording with left forelimb simulation vs days before and after injury.
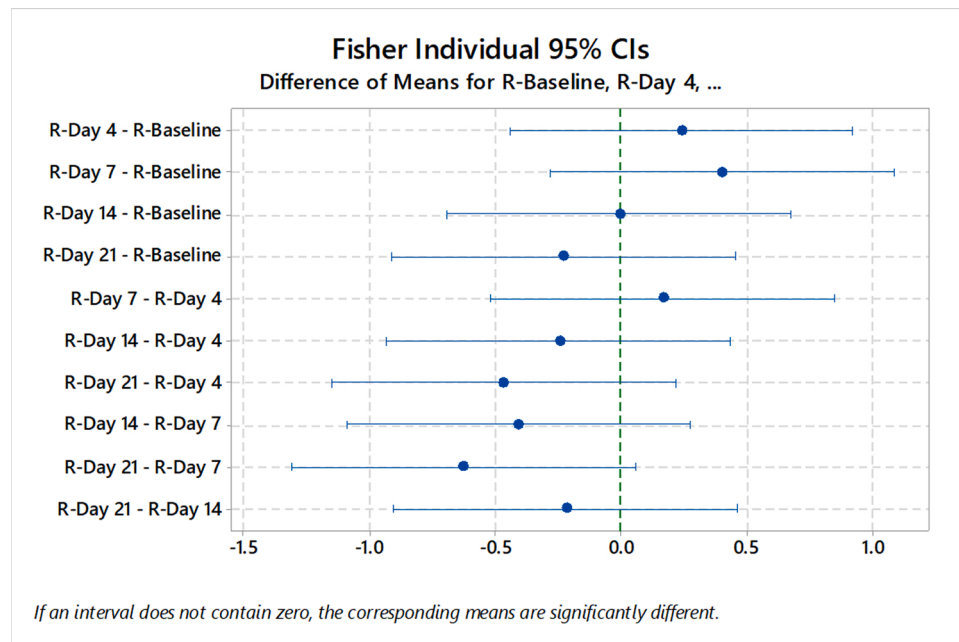
Fig. 5. Pairwise multivariate test results according to Fisher's Least Significant Difference method for multiple forelimb SSEP amplitude comparisons for RxI on.
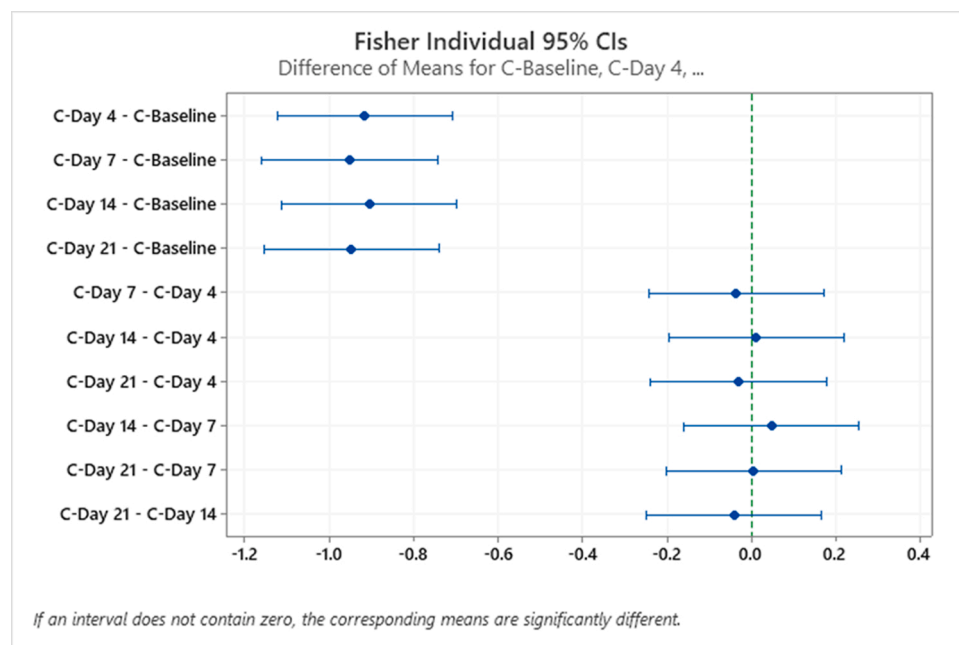

Fig. 6. Pairwise multivariate test results according to Fisher's Least Significant Difference method for multiple hindlimb SSEP amplitude comparisons for CxI on.

3.2. Histological examination

The results for the histological examinations of the regions of interest for the three abovementioned injury groups have been reported previously (All et al., 2019).

3.3. Statistical analysis

To characterize the degree of changes in SSEPs when different limbs are stimulated before and after injury, we compared the SSEP relative amplitude using a simple main-effect analysis of variance (ANOVA). We also performed a pairwise test using Fisher's Least Significant Difference method to compare the relative SSEPs on different days. The null

hypothesis was that the relative amplitudes are the same on different days before and after injury.

Fig. 4 shows the 95 % confidence interval plot of the relative SSEP amplitudes obtained from the right hemisphere with left forelimb stimulation for the RxI (right T10) injury group on different days. Despite the apparent variations in the SSEP relative amplitudes, ANOVA test did not reject the null hypothesis that all means are the same with $p > 0.05$.

We repeated the ANOVA test on the relative SSEP amplitude recorded from the left hemisphere with right forelimb stimulation for the RxI injury group on different days – and again, the ANOVA test did not reject the null hypothesis that all means are the same with $p > 0.05$. We then performed the ANOVA test on the relative SSEP amplitude recorded

from the left and right forelimbs for the other two injury groups DxI (double) and CxI (complete) transection. None of the test results rejected the null hypothesis that all means are the same with $p > 0.05$.

We further performed a pairwise test using Fisher's Least Significant Difference method and compared the relative SSEPs recorded from the left and right hemisphere with left and right forelimbs stimulation for the three injury types on different days. Fig. 5 shows the intervals of the mean difference between the SSEPs obtained when stimulating the forelimbs of the RxI injury group. The mean difference between the baseline and the days following RxI do indeed include zero. Therefore, the difference between these means did not reject the null hypothesis with $p > 0.05$. On the other hand, Fig. 6 shows the intervals of the mean difference between the hindlimb baseline SSEPs and the 4 recording days following CxI injury. The mean difference between the baseline and days following CxI do not include zero. Therefore, the difference between these means was statistically significant with $p < 0.05$, indicating the severity of the injury and lack of any recovery.

Fig. 6, which is a sample analysis of the hindlimb SSEP signals, was reported here for the comparison purposes to demonstrate the transient nature of the changes of the forelimb SSEP signals (Fig. 5) within the same time periods.

4. Discussion

Since the injury is in the lower part of the thoracic area and consequently the neuropathways of the forelimbs are not directly affected, the possibility of re-organization of neuropathways are remote (All et al., 2019). On the other hand, we also described that there are both adaptive and compensatory mechanisms, defined as neuroplasticity, within the adjacent forelimbs and hindlimbs somatosensory areas of the same and contra-lateral cortices (Bazley et al., 2014a, 2014b; Bazley et al., 2011). Such plasticity was mainly contributed to the lack of input from corresponding hindlimb somatosensory pathways, enabling forelimbs for adaptation and higher functional activities. The monitoring of forelimb SSEPs did not reveal any long-term statistically significant variations, despite the temporary transient increases in SSEP amplitudes.

As we showed previously (Al-Nashash et al., 2020), the forelimb SSEP signals are robust and stable after thoracic SCIs, with one exception during a short time soon after the onset of the injury. Interestingly, during this acute phase post-thoracic SCI, the amplitude of the forelimb SSEPs temporarily (not permanently) increases, but quickly normalizes, stabilizes and returns to the pre-injury baseline values. Their nature is transient and overall carry no statistically significant impact. Moreover, as reported by us and others (Bazley et al., 2014a, 2014b; Bazley et al., 2011; Mir et al., 2015), such temporary increases in forelimbs SSEPs were also present during the early acute phase of thoracic contusive SCI. Supported by the f-MRI data, we described that this phenomenon could be related to the plasticity within the higher structures of the somatosensory neuropathways of the corresponding cortices. In this article, we intended to highlight the presence of the similar transient changes soon after the thoracic transection SCI. Undoubtedly, timely recognition of neuronal plasticity post-injury could enable scientists and physicians to reinforce the therapeutic actions by exploiting it for more effective rehabilitation of patients suffering from SCI. Nevertheless, the results support the fact that the SSEP signals obtained from the forelimbs, in combination with the hindlimbs for comparison, would indeed be an excellent monitoring tool to assess the natural history (onset, progress and recovery) of transection thoracic SCI as well.

Moreover, we like to ponder the idea of considering the clinical relevance of this study. Since the upper limbs SSEPs show long term stability, thus it is justified to use them as proxy baselines in traumatic thoracic SCI wherein no lower extremity pre-injury baselines are possible to establish.

In conclusion, this study reports that an increase in forelimbs' SSEP amplitudes following onset of thoracic SCI and a subsequent prompt return to the baseline values could be expected. Yet, it also confirms the long-term stability of forelimbs SSEP signals post-SCI with no statistically significant changes. Since the forelimb SSEPs have been suggested as a potential baseline candidate in longitudinal studies in lieu of pre-injury baseline recordings, this study provides crucial insights into the transient dynamic but overall stable nature of the forelimb SSEP signals.

Author contribution

Angelo All (A.A.) and Hasan Al Nashash (H.A.) contributed to the conception and experimental design. H.A. completed data analysis. A.A., H.A. and Shiyu Luo (S.L.) drafted the paper. A.A. and S.L. performed literature search. A.A., H.A. and Xiaogang Liu (X.L.) supervised and provided critical revision.

Declaration of Competing Interest

The authors state that they do not any conflict of interest to report here.

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