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Characterization of Graded MASCIS Contusion Spinal Cord Injury using Somatosensory Evoked Potentials

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Abstract

Study Design—Electrophysiological analysis using somatosensory evoked potentials (SEPs) and behavioral assessment using Basso-Beattie-Bresnahan (BBB) scale were compared over time for graded MASCIS contusion spinal cord injury (SCI).

Objective—To study SEP responses across different contusion injury severities and to compare them with BBB scores.

Summary of Background Data—For any SCI therapy evaluation, it is important to accurately and objectively standardize the injury model. The graded MASCIS contusion injuries on dorsal spine have been standardized using BBB, which is subjective and prone to human errors. Furthermore, dorsal pathway disruption does not always produce locomotor deficits. SEP monitoring provides an advantage of providing a reliable and objective assessment of the functional integrity of dorsal sensory pathways.

Methods—Four groups of Fischer rats received contusion at T8 using NYU-MASCIS impactor from impact heights of 6.25 (mild), 12.5 (moderate), 25 (severe), or 50 mm (very severe). The control group underwent laminectomy only. SEP and BBB recordings were performed once prior to injury, and then weekly for up to 7 weeks.

Results—Graded levels of injury produced concomitant attenuations in hindlimb SEP amplitudes. Following injury, 25 and 50 mm groups together differed significantly from 12.5 and 6.25 mm groups ($p < 0.01$). From week 5, differences between 12.5 and 6.25 mm groups also became apparent ($p < 0.01$), which showed significant electrophysiological improvement. However, no significant differences were observed between 25 and 50 mm groups, which showed negligible electrophysiological recovery. While comparable differences between different groups were also detected by BBB after injury ($p < 0.001$), BBB was less sensitive in detecting any improvement in 6.25 and 12.5 mm groups.

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Conclusion—SEP amplitudes and BBB scores decrease corresponding to increase in injury severity, however these show different temporal patterns of recovery. These results demonstrate the utility of SEPs, in conjunction with BBB, to monitor therapeutic interventions in SCI research.

Key Points

- The SEP amplitudes and BBB scores decrease corresponding to the increase in injury severity in MASCIS contusion SCI model.
- The temporal pattern of recovery of SEP and BBB show different severity-dependent recovery profiles.
- The results demonstrate that assessment of both SEP and BBB outcomes would be crucial to evaluate therapeutic efficacy against contusion SCI using the NYU-MASCIS impactor.

1. Introduction

Initial trauma to the spinal cord triggers a series of complex pathophysiological mechanisms, which results in spreading of injury to surrounding regions, thus causing delayed secondary degeneration. The degree of neurological dysfunction after spinal cord injury (SCI) largely depends on the level of injury and the nature as well as extent of secondary damage produced to the white and gray matter structures.

Depending on the nature and location of the injury, SCI can have significantly different effects on the conduction of axonal pathways, locomotion and tissue morphology^{1,2}. Spared axonal fibers and their degree of demyelination play an important role in determining the amount of residual functionality present after SCI. Studies have demonstrated ‘anatomically incomplete’ SCI in humans^{3–6} with spared demyelinated axons showing physiological continuity across the lesion even when functional responses were absent. Even a small number of spared fibers after SCI, if detected and administered acute therapy, can greatly improve the quality of life of SCI patients. Development of therapeutic strategies to reduce secondary injury, and to remyelinate spared-through-demyelinated axons has generated considerable interest in recent years^{7–9}.

In the evaluation of any therapeutic approach in SCI research, the availability of a suitable animal SCI model and reliable axon monitoring measures is of primary importance to calibrate the severity and progress of injury and the extent of recovery^{1,10}. The contusion model of SCI, performed using the NYU-MASCIS (New York University - Multicenter Animal Spinal Cord Injury Study) impactor¹¹, is a widely used clinically-relevant rodent model for experimental SCI research^{12,13}. The NYU-MASCIS weight-drop model standardizes grades of contusive spinal cord injury¹⁴ by dropping a 10g rod from specific heights of 6.25 (mild), 12.5 (moderate), 25 (severe) or 50 mm (very severe) upon the exposed dorsal surface of the spinal cord.

The graded contusion spinal cord injuries in rat have previously been characterized using the 21-point, open field BBB locomotor score developed by Basso and colleagues^{15,16}. However, specific disruption of dorsal pathways does not produce pronounced deficits in locomotor function in the rat^{17,18}. Moreover, the MASCIS impactor has been extensively employed for the thoracic SCI and it has been shown that substantial gray matter damage to this region with limited white matter pathology does not produce dramatic deficits in BBB scores¹⁹ leading to some limitations in the effectiveness of using locomotor assessment as a measure to standardize graded SCI in the rat. Furthermore evaluation of the open-field locomotor behavioral test is subjective and prone to human error. This is primarily due to the varying abilities of the two examiners to recognize and detect subtle movements in an injured animal in a total of 4 minutes

of observation time. The rat's non-willingness to move around due to the surgery and muscle dissection is also a major issue during the acute phase of injury.

Somatosensory evoked potentials (SEPs), first described in 1947²⁰, provide a reliable, reproducible and objective in-vivo assessment of the functional integrity of the ascending sensory pathways that project in the dorsal spinal cord. Their utility in SCI studies has been previously demonstrated in both animal studies^{1,21} and in humans^{22,23}. However, the SEP response and its comparison with behavioral outcome measures has not yet been characterized and reported for a graded NYU-MASCIS impactor contusion injury model, a model extensively used in experimental SCI mechanistic and therapeutic studies.

Analogously, motor evoked potentials (MEPs), first described by Merton and Morton in 1980²⁴, have also been shown to be objective measures of the functional integrity of the descending motor pathways of the spinal cord²⁵. Indeed, complimentary studies using MEPs along with SEPs and BBB scores warrant future investigations.

In the present study, quantitative analysis of SEP recordings as well as behavioral assessments were employed in a graded contusive SCI induced by the NYU-MASCIS impactor. The purpose was to investigate the relationship between injury severity and electrophysiological responses as measured by SEP, and its comparison to standard open-field locomotor assessment by the BBB score. The results showed that while both SEP and BBB detected severity-dependent changes after injury, these showed different temporal patterns of recovery.

2. Materials & Methods

All experimental procedures used in this study were in accordance with the guidelines provided in the *Rodent Survival Surgery* manual and were approved by the Institutional Animal Care and Use Committee at the Johns Hopkins University. A total of 15 adult female Fischer rats (Charles River Inc.), with an average body weight of 200g, were used in the study. Rats were housed individually per cage and had free access to food and water. All surgical procedures were performed under anesthesia (45 mg/ml of Ketamine, 5 mg/ml of Xylazine) administered via intra-peritoneal injection.

2.1. SEP Electrode Implantation

One-two days prior to injury, an incision was made on the anesthetized rat's head along the midline and five transcranial screw electrodes (E363/20, Plastics One Inc.) were implanted on the somatosensory cortex in each hemisphere receiving input from sensory pathways originating in the hind and forelimbs. On each hemisphere, the forelimb recording electrodes were implanted 0.2 mm posterior to bregma and 3.8 mm lateral to midline, and the hindlimb recording electrodes were implanted 2.5 mm posterior to bregma and 2.8 mm lateral to midline. A fifth electrode on the right frontal bone, situated 2 mm from both the sagittal and coronal sutures, served as the intracranial reference. The electrodes made very light contact with the dura mater, but did not compress the dura or brain structures.

Before proceeding with the study, few animals were randomly selected and euthanized for inspection of dura and electrode placement. In addition, before every SEP recording, the electrode impedance was tested to make sure that it is within the acceptable range ($\leq 1\text{k}\Omega$). At the end of the study, all the rats were deeply anesthetized and euthanized via transcardial perfusion with formaldehyde. Their skull was then opened for macroscopical inspection of the dura, cortex and surrounding tissues, and positioning of the screw electrodes.

2.2. Contusion Spinal Cord Injury

After making an incision on the skin, longitudinal incisions with approximately 2–3 mm depth were made on the left and right side of the spinous processes of the vertebrae T6–T12 using scalpel #10. The paravertebral muscles were then gently pulled away from the spine, without any further incision or damage to the muscles. With retractors holding the muscle aside, laminectomy was performed using a Zeiss operating microscope, by cutting and removing the lamina at T8 to expose the dorsal surface of the spinal cord. Stabilization clamps were placed at the posterior spinous processes of the vertebrae T6 and T12 to support the vertebral column during impact.

The exposed spinal cord was then contused at the thoracic vertebra T8 using the NYU-MASCIS (New York University - Multicenter Animal Spinal Cord Injury Study) weight-drop impactor¹¹. This device consists of a 10g rod with a flat circular impact surface of diameter 2mm, which is slightly less than that of the rodent spinal cord (body weight >200g) to clear the edges of the vertebral canal as the impactor hits the cord. This also ensures that the entire impact surface is in complete contact with the cord during the contusion, so that all the energy from the weight drop is transferred to the spinal cord parenchyma. This impactor rod was directed towards the midline of the exposed spinal cord and was released from a height of 6.25 mm (n=3), 12.5 mm (n=3), 25 mm (n=3) or 50 mm (n=3), producing more severe neurologic injuries with increasing height. The control group (n=3) underwent laminectomy only. The impactor device was connected to a software Impactor v. 7.0 on a computer, which displayed the impact trajectory curves using the impactor and vertebral position sensors and the cord contact sensor¹¹. It also computed the actual height, time and velocity of the impact. Only rats with <0.05% variation in these values were considered for this study.

After injury, the muscles were sutured in layers and the skin closed with metal wound clips. Gentamycin (5 mg/kg, intramuscular; Abbott Laboratories, North Chicago, IL) was administered immediately post-surgery and then daily for 7 days. The analgesic, Buprenex (0.3 mg/kg, subcutaneous; Reckitt Benckiser, Richmond, VI), was delivered post-surgery and daily for 2 days. After surgery, their bladders were expressed regularly with no complications or other infections to report. No sign of autotomy or autophagy were observed. The rats were maintained for 7 weeks after injury.

2.3. Multi-limb SEP Monitoring

Subcutaneous needle electrodes (Safelead F-E3-48, Grass-Telefactor, West Warwick, RI) were used to electrically stimulate the median and tibial nerves of both left and right limbs. Care was taken to avoid direct contact with the nerve bundle, by making sure that only the corresponding limb twitched without tremors on any other limb or area of the animal. An isolated constant current stimulator (DS3, Digitimer Ltd., Hertfordshire, England) was used for the electrical stimulation of the limbs. Custom Intraoperative Neurological Monitoring (INM) software (Infinite Biomedical Technologies, Baltimore, MD) was used to set the stimulation parameters and trigger the stimulator²⁶. Positive current pulses of 3.5 mA magnitude and 200 μ sec duration at a frequency of 1 Hz were used for limb stimulation, which sequentially stimulated each of the four limbs at a frequency of 0.25 Hz using an advanced demultiplexer circuit.

Cortical SEPs from the transcranial electrodes were amplified by an optically isolated biopotential amplifier (Opti-Amp 8002, Intelligent Hearing Systems, Miami, FL) with a gain of 30,000. The signal from each hemisphere was transferred to a personal computer via an optical data acquisition system with four input channels at a sampling rate of 5000 Hz. The electroencephalogram (EEG) of each hemisphere, containing the SEP for the respective

hemisphere, the stimulation pulse signal and the stimulated limb number, were recorded on separate channels for (post-operative) data analysis.

Multi-limb somatosensory evoked potentials were recorded from anesthetized rats, and the level of anesthesia was kept uniform throughout the recording sessions. Body temperature was maintained at 37 ± 0.5 °C by using a heating pad. Prior to surgery, baseline SEP signals were recorded for approximately 60 minutes (900 stimulations per limb). After the laminectomy, a 30 minute recording (450 stimulations per limb) was done to ensure that no insult had been caused to the spinal cord during the procedure. Post-injury SEPs were recorded after day 1, day 4, week 1, week 2, week 3, week 5 and week 7 for about 90 minutes (1350 stimulations per limb) to ensure signal stability.

SEPs contralateral to the side of limb stimulation were used for analysis. The first 200 stimulations per limb were ignored to obtain a consistent SEP response for analysis. The signal to noise ratio was improved by moving averaging of 100 stimulus-locked sweeps, with the averaging window shifting by 20 sweeps each time. All signal processing was performed using Matlab 7.0 (The Mathworks, Inc.).

2.4. Behavioral Assessment

One week prior to surgery, all rats were made familiar with the open field environment and specific research personnel at four different instances. Two days prior to the injury, locomotor functions of all animals were assessed using the open-field Basso, Beattie and Bresnahan (BBB) locomotor rating scale^{15,16}. This is a 21-point scale to assess and analyze the hindlimb movements of a rat in an open-field.

The BBB scores classify the recovery after SCI in rats into 3 phases and rate them on a scale from 0 to 21^{15,16}. *Early Phase* of recovery consists of isolated joint movements and progresses from flaccid hindlimb paralysis (BBB score 0) to the extensive and simultaneous movement of hip, knee, and ankle in hind paws (score 7). *Intermediate Phase* represents BBB scores from 8 to 13 with a gradual improvement from occasional plantar stepping without weight support to weight supported plantar steps and consistent front-hind limbs coordination. *Late Phase* of recovery consists of a further development of plantar steps with parallel paw position, toe clearance, and fine paw coordination with tail balancing off the ground (BBB scores 14–21).

Behavioral assessments were performed after day 4, week 1, week 2, week 3, week 4, week 5 and week 7. All observations were made by two independent observers, who were unaware of the extent or nature of the injury.

2.6. Statistical Analysis

The statistical package SAS, version 9.1 (Statistical Analysis System, Cary, NC) was used for all the statistical analysis, and *p* values of less than 0.05 were considered statistically significant.

Statistical analysis of the SEP data was performed by a repeated measures analysis of variance (ANOVA) over 9 time points, using log-SEP amplitude (average of right and left side) as the input and impactor height as the independent variable. These time points included baseline, post-laminectomy, day 1, day 4, week 1, week 2, week 3, week 5 and week 7, and the impactor heights were 0 (control), 6.25, 12.5, 25 and 50 mm. The log-transform was performed to uncouple the mean and the variance for the data, and SAS version 9.1 procedure GLM (General Linear Model) was utilized for the analysis. Pairwise multivariate t-tests according to Fisher's Least Significant Difference method and compensation for multiple comparisons were also done. Multivariate contrasts were also performed with reference to the baseline measurement.

The behavioral outcomes were compared between groups of animals using a three-way analysis of variance (ANOVA) with Level of Impact (0, 6.25, 12.5, 25 and 50 mm) as a between-group factor and Week of Recovery and Left-Right Limb Comparison as repeated measures. Fisher LSD multiple comparison post-hoc tests were applied to investigate main effects or interactions. To analyze between-group differences at a particular time point after the injury, we applied simple main effect ANOVA with corrected p levels for number of analyses.

3. Results

3.1. SEP Analysis

In the rat, SEP consists of three major identifiable components (Figure 1), although some inter-animal variability exists. Since the injury was induced at T8, the analysis was based on the SEP signals from hindlimbs' injured pathways, whereas, the SEP signals from forelimbs' non-injured pathways were used for internal control purposes to ensure the quality of the recordings and the electrodes. Forelimb SEP signals were expected to stay constant and any change would indicate that other variants, apart from the desired injury, affected the SEP recordings. However, no significant change was observed in the forelimb SEP signals throughout the course of the study.

Figure 2 shows the averaged hindlimb N1-P2 SEP amplitudes (average of right and left side) normalized with respect to the baseline for the four injury groups and the control group. The laminectomy-only control group showed no SEP amplitude attenuation. In the four injury groups, the SEP amplitude reduced corresponding to the increase in injury severity.

Statistical analysis of the SEP data indicated that a differential recovery pattern began to appear after week 1 across the four injury groups. During week 2, there were significant differences between the pair-wise groups of the two higher (25 and 50 mm) and two lower (6.25 and 12.5 mm) injury severities ($p < 0.01$). There were repeated measures contrasts with baseline due to impact height at the $p < 0.05$, $p < 0.01$ and $p < 0.002$ levels for weeks 2, 3 and 5, respectively. The 50 and 25 mm groups together differed from the 12.5 and 6.25 mm groups through week 3. From week 5, differences between the 12.5 and 6.25 mm injury severities were also observed ($p < 0.01$). No significant differences were observed between the 25 and 50 mm severity groups at all post-injury timepoints.

3.2. Behavioral Outcome

Evaluation of open-field locomotor performance using weekly BBB scoring revealed a short-term recovery in the two higher severity injury groups, which was less pronounced in the two lower severity groups (Figure 3). During the first week of injury, the 25 and 50 mm groups showed significant functional deficits indicating the presence of weight support and some plantar stepping. BBB scores for these two groups increased steadily over the first three weeks following injury. The 12.5 mm injury group showed much milder functional deficits immediately after the injury, indicating consistent weight supported stepping and some coordination. There was a more gradual improvement in BBB scores over the ensuing seven weeks. The 6.25 mm injury group showed the least functional impairment immediately after the injury, indicating consistent stepping and coordination. BBB scores for animals of this group were almost steady after the first two weeks of injury. The laminectomy-only control group showed no functional deficits during the course of the study.

To characterize the initial degree of functional impairment after injury, we compared BBB scores at day 4 post injury by using a simple main-effect ANOVA. This analysis revealed a highly significant relationship between the level of impact and the degree of functional impairment ($p < 0.001$). Subsequent three-way analysis of variance (ANOVA) [Level of Impact

x Week of Recovery x Left-Right Limb] revealed significant effects of the level of impact ($p<0.001$), the week of recovery ($p<0.001$) and the week by limb interaction ($p<0.01$).

4. Discussion

To evaluate the efficacy of any SCI therapeutic intervention, it is necessary to have accurate and objective outcome measures. It is also important to standardize the severity and progress of injury in an experimental model using those measures. The MASCIS contusion SCI model has been previously standardized using BBB. However, since the injury is inflicted on the exposed dorsal spinal cord of rats, it does not always produce pronounced deficits in locomotion^{17,18}. Furthermore BBB scores are subjective and prone to human errors. Therefore, we investigated the utility of monitoring SEPs, which can provide a reliable and objective assessment of the functional integrity of dorsal sensory pathways. The current study examined both SEPs and BBB scores following four grades of thoracic contusion injury (impact heights of 6.25, 12.5, 25 and 50 mm) to the dorsal part of the rat spinal cord using the NYU-MASCIS weight-drop impactor.

The degree of attenuation of SEP amplitudes immediately following injury was found to depend upon the injury severity. Additionally, the temporal progression of SEP amplitude recovery differed significantly among the injury groups over the 7 week evaluation period. Our findings demonstrate that in addition to identifying the four levels of injury, SEPs produced two distinct groups: a high injury-severity group (25 and 50 mm), which showed almost no recovery of electrophysiological response after SCI, and a low injury-severity group (6.25 and 12.5 mm), which showed a significant temporal improvement in SEP amplitudes following injury. This may be attributed to the fact that the cortical responses tend to be all or none due to amplification at the cortical level, and will often recover to a maximal level as long as a sufficient number of myelinated axons remain intact²¹. The data indicate that the high injury-severity contusions resulted in major disruption of the sensory pathways in the spinal cord and produced injury of sufficient magnitude that these pathways could not spontaneously recover. In contrast, the low injury-severity groups showed a significant temporal recovery in SEP amplitudes in the time span of week 1 to week 3 following injury. After that, the SEP signals for these groups stabilized, without showing a complete recovery to the pre-injury baseline.

The temporal pattern of the progress of injury over 7 weeks given by traditional subjective BBB scoring was observed to be different from the more objective SEP analysis. The functional outcomes evaluated by the BBB scale for the high injury-severity groups showed a short-term increase in hindlimb motor functionality over the first three weeks, however the BBB scores for the low injury-severity groups did not show significant improvements after the first week following injury. These contrasting results are likely due to differences in injury and recovery patterns of the sensory and motor pathways in the spinal cord. The presence of locomotor recovery with almost no recovery in the SEP response should not be surprising based on the literature. In previous studies^{17,18}, a complete dorsal hemisection, lesioning the ascending sensory pathways mediating the SEPs along with the pyramidal tract, in the case of the rat has resulted in a largely intact locomotor capability. Temporal improvement in locomotor function could also result from subsiding spinal shock²⁷ (disfacilitation of descending reticulo-, vestibulo-, and rubrospinal pathways), or due to plasticity in non-injured descending motor pathways.

In summary, we have reported the characterization of the graded contusion injuries induced by NYU-MASCIS impactor using electrophysiological responses measured by SEPs and compared these responses with behavioral BBB scores over the 7-week observation period after the injury. Clearly, these are two different but complementary measures. In this regard, assessment of both SEP and BBB outcomes would be crucial in future experiments to evaluate

therapeutic efficacy against contusion spinal cord injury using the NYU-MASCIS impactor, an extensively used model in experimental SCI research.

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FIGURE 1.

Three major identifiable components of the somatosensory evoked potential (SEP) waveform in the rat, along with the demonstration of N1-P2 amplitude measurement

FIGURE 2.

Time course of somatosensory evoked potentials (SEPs) following spinal cord contusion at T8 using the NYU-MASCIS impactor, with impact heights of: 6.25, 12.5, 25 and 50 mm. The control group underwent laminectomy only. The N1-P2 SEP amplitudes are normalized with respect to the baseline amplitude (before the injury) for each animal. The mean and standard deviation for each injury group are plotted at various time points over 7 weeks following injury.

FIGURE 3.

Temporal changes in BBB scores following spinal cord contusion at T8 using the NYU-MASCIS impactor, with impact heights of: 6.25, 12.5, 25 and 50 mm. The control group underwent laminectomy only. The mean and standard deviation for each injury group are plotted at various time points over 7 weeks following injury.