Spinal cord concussion: studying the potential risks of repetitive injury

What is spinal concussion? Spinal cord concussion is a variant of mild spinal cord injury, clinically designated as transient paraplegia or neurapraxia, and characterized by variable degrees of sensory impairment and motor weakness that typically resolve within 24–72 hours without permanent deficits (Del Bigio and Johnson, 1989; Zwimpfer and Bernstein, 1990; Torg et al., 1997). Accordingly, a grading system was developed based on the duration of symptoms, ranging from Grade I (< 15 minutes) to Grade III (> 24 hours) (Zwimpfer and Bernstein, 1990; Torg et al., 1997). Spinal cord concussion is predominant-ly a sport-related injury occurring in a wide variety of contact sports in adult and pediatric athletes including wrestling, hockey, gymnastics, and diving, but most commonly in American football, although spinal concussions can also occur after minor car accidents as “whiplash injuries” and falls (Zwimpfer and Bernstein, 1990). In contact sports, the cervical spine is particularly susceptible to injury because of axial loading forces to the head with the neck in flexion or extension. In these circumstances, injury may occur due to disc herniation, buckling of the ligamentum flavum or the posterior longitudinal ligament, or by compression of the spinal cord between vertebral bodies. There appears to be a mechanistic difference in the injury between adult and pediatric age groups. In the adult, a stenotic spinal canal or a diminished spinal canal to vertebral body diameter predisposes patients to cervical concussion at the level of stenosis after hyperextension, hyperflexion, or axial loading. The pediatric spine, in contrast, has increased mobility, predisposing the spinal cord to contact with bony elements even in absence of focal stenosis (Clark et al., 2011). Guidelines regarding return to play have been developed based upon the duration of neurological symptoms, neurapraxia, and MRI analysis, but they are based on a limited number of small-scale retrospective studies (Tempel et al., 2015). Given the lack of randomized trials, medical clearance of athletes for resumption of activities is a highly controversial topic without consensus opinion (Cantu, 1998; Morganti, 2003; Mayers, 2008; Harmon et al., 2013). Furthermore, many individuals may experience multiple episodes of spinal cord concussion with recurrence of symptoms (Zwimpfer and Bernstein, 1990; Torreman et al., 1996; Clark et al., 2011). It has therefore been important to develop animal models of spinal cord concussion to elucidate the histological and functional deficits of single and repeated injuries. This perspective presents our recent efforts in developing such a model and the consequences of repetitive injury (Jin et al., 2014, 2015).

Lessons from brain concussion: Unlike spinal cord concussion, brain concussion or mild traumatic brain injury (mTBI) following contact sports has been extensively studied both clinically and with a variety of animal models. These studies have indicated that a single concussion not only increases the vulnerability to a subsequent injury, especially if the injury occurs before symptoms have completely resolved (Bailes et al., 2014), but also results in greater neurological deficits. Moreover, repetitive brain concussions may have a variety of additional neurocognitive effects, not limited to motor and sensory deficits, increasing the risk in later life for dementia, Parkinson’s disease, and depression (Gardner and Yaffe, 2015). A key clinical question following mTBI pertains to the duration of physical and mental rest and the resumption of activity before returning to play. Most symptoms of brain concussion resolve spontaneously within days, but persistent post-concussive symptoms have been reported in a subgroup of patients with mTBI who continue to have both physical symptoms and lower cognitive test performance, even after 90 days (Spira et al., 2014). While it is generally accepted that athletes who sustain a head injury do not return to play without medical clearance by a team doctor or neurological consultant, the symptoms of mTBI are not always reported by athletes. As a result, athletes with mTBI may return to play before resolution of symptoms or during vulnerable periods in which a subsequent injury may exacerbate initial symptoms. The importance of this issue has been underscored by the multitude of recent media and scientific reports highlighting events such as increased suicide and depression among retired professional athletes and increases in neuropsychological sequelae such as depression, anxiety, and substance abuse, among others, in both adults and adolescents (Guskiewicz et al., 2007; Semple et al., 2015).

A variety of animal model systems have been used to characterize the histological and functional effects of mTBI. It is important to recognize, however, that there exists a great degree of variability in the specific parameters of the repetitive injury models—the model system used for injury, location of injury, type of impactor tip, duration between injuries, and number of injuries. The length of time between injuries remains a key point of debate as it is unclear how much time between injuries is necessary to prevent further aggravation of symptoms. Previous studies have shown that multiple injuries, typically sustained 24 to 72 hours apart, lead to increased glial activation, axonal injury, and neuroinflammation, resulting in impaired learning and depressive-like behavior (Longhi et al., 2003; Mannix et al., 2013; Luo et al., 2014). Furthermore, inter-injury intervals of 24 hours to 5 days duration have been shown to increase cognitive or behavioral deficits and cellular damage and dysfunction, although other reports have suggested that inter-injury intervals longer than 24 hours do not appear to exacerbate brain damage (Longhi et al., 2005; Bolton and Saatman, 2014).

A spinal concussion injury model: In contrast to mTBI, relatively little is known about the immediate consequences and long-term effects of spinal cord concussion. It is a poorly understood phenomenon that has remained underreported and understudied, with sparse data on repeated injury, limited to clinical case reports with no adequate experimental animal models. To address this issue, our first study (Jin et al., 2014) focused on the development of an animal model of spinal cord concussion with an emphasis on repetitive injury, using the commonly accepted “mild SCI” model (Basso et al., 1995) at the thoracic level generated by the NYU impactor (10 g weight dropped from a height of 6.25 mm). The results indicated that functional deficits worsened with a second injury and resulted in increased tissue damage, inflammation, and cell death. Assessment of motor activity with the Basso Beattie Bresnahan scale (BBB) showed that mild contusion at T10 resulted in functional deficits of single and repeated injuries. This perspective presents our recent efforts in developing such a model and the consequences of repetitive injury (Jin et al., 2014, 2015).
Figure 1 Analysis of locomotor function in two injury models. (A) Locomotor function assessed by Open Field BBB following "Mild SCI." The BBB scores decreased 2–3 days post-T10 injury, followed by a recovery period of 3 weeks. Following the second injury, the BBB scores decreased again 2–3 days post-injury, but the 2-contusion group demonstrated significantly less recovery. *P < 0.05, 2-contusions compared to 1-contusion at all time points following the second injury. Modified from Jin et al., 2014. (B) Locomotor function assessed by Open Field BBB following "Very-mild SCI." This injury resulted in a minor decrease in BBB scores 2–3 days post-injury with a rapid recovery within a week. The 2-contusion group showed a small deficit 2–3 days post-injury, which was significantly different from their baseline value (*P = 0.0008), but recovered within a week to near-normal levels with no differences compared to the 1-contusion group. Modified from Jin et al., 2015.

showed acute functional deficits two to three days post-injury, which recovered only to a BBB score of 17, significantly worse than the recovery levels obtained after the first contusion (Figure 1). Although the results demonstrated the detrimental effects of repeated injury, the standard "mild SCI" produced in that study resulted in major tissue damage at the lesion epicenter and a slow functional recovery that lasted 3 weeks post-injury, drastically different from the clinical presentation of spinal cord concussion.

Given the extent of morphological damage in our original study (Jin et al., 2014), we concluded that the available "mild SCI" model did not faithfully reproduce the clinical presentation of spinal cord concussion, which is characterized by minimal tissue damage and rapid functional recovery. We therefore developed a new spinal cord concussion model that generates a very mild contusion using the Infinite Horizon (IH) impactor (50 kilodynes) and referred to this injury model as a Minimal Cervical Contusion, MCC (Jin et al., 2015). Rats received this MCC injury at C5 and were randomized into two groups 3 weeks after the initial injury – Group 1, which received a second sham surgery, and Group 2, which received a second MCC at the same site. The degree of functional recovery was examined weekly using a variety of motor and sensory analyses – BBB, CatWalk™, cylinder test, and the Von Frey mechanical sensory test. BBB analysis demonstrated rapid locomotor recovery within 2–3 days post-injury, which reached normal levels by 1 week after the initial injury (Figure 1). The Cylinder test, which measures forelimb paw use, showed no changes in paw preference compared to the baseline. Similarly, sensory function, assessed by CatWalk™ and Von Frey, indicated no significant changes post-injury compared to baseline. Taken together, the behavioral data suggests that the minimal cervical contusion injury model mimicked clinical spinal cord concussion, with minimal tissue damage and transient effects on motor and sensory function. This Minimal Cervical Contusion spinal cord concussion model can therefore be used as a new experimental system of minimal cervical injury that closely resembles clinical spinal cord concussion.

In order to shed light on clinical decision-making models pertaining to spinal cord susceptibility post-injury, our study (Jin et al., 2015) also examined the vulnerability of the spinal cord following full recovery from the MCC injury. To examine these issues, Group 2 was subjected to a second MCC injury at the same location, following full recovery from the initial injury, whereas Group 1 received a sham surgery, serving as a control. Interestingly, BBB scores followed a similar pattern as observed for the initial injury, with decreased BBB scores 2–3 days after the second injury and a return to normal levels by 1 week, with no significant differences between the two groups (Figure 1). In contrast to motor analyses, sensory analyses derived from the CatWalk™ platform showed significant changes in all 4 paws in pressure applied during stance and swing phase duration during stepping in Group 2. These analyses indicated changes in weight bearing and an increased sensitivity of not only the affected limb, but also the contralateral forelimb and both hind limbs. Importantly, the Cylinder test showed that while a single contusion did not induce significant deficits of the affected limb, a repeated injury resulted in significant alteration in paw preference. These results indicate that repeated minimal cervical contusion injuries of spinal concussion result in an accumulation of functional deficits even after full recovery from the initial injury. Anatomical analyses revealed that while the lesion volume of both groups was minimal, the area of spared white matter in Group 2 was significantly reduced 1 and 2 mm rostral to the lesion epicenter. Reactive astrocytes were present in both groups, with the majority found at the lesion epicenter in the Group 1, whereas Group 2 showed increased reactive astrocytes extending 1 mm caudal to the lesion epicenter. Macrophages accumulated within the injured, dorsal and ipsilateral spinal cord, with significant increases at 2 and 3 mm rostral to the epicenter in Group 2 (Jin et al., 2015).

We believe that the study of repetitive injuries will allow for an examination of the relationship between the lesion/spared tissue and the capacity for recovery to determine conditions that will augment spontaneous recovery. A similar approach has been recently tested in a combination SCI and TBI model to elucidate the mechanistic framework of dual injuries (Inoue et al., 2013). The results showed that SCI together with contralateral TBI often produced profound deficits that failed to demonstrate spontaneous recovery. For example, in the grooming test, the dual SCI/contralateral TBI model demonstrated worse recovery than either lesion alone. These findings emphasize...
the complexity of recovery from combined CNS injuries and the possible role of plasticity in recovery, providing impetus towards a preclinical model for evaluating effective therapies for combined injuries.

Conclusions: Ideally, a model of spinal concussion should use a closed injury to more accurately model the stretching or axial loading seen in clinical cord concussion, as injuries typically occur as a result of hyperextension or hyperflexion of the spinal cord exacerbated by smaller cervical canals or stenosis (Torg et al., 1997). The need for reproducible, quantitative injury models, however, makes the direct application of forces on the exposed spinal cord a necessary trade off for most animal models of SCI. Our model is designed to represent spinal cord concussion, and to highlight the susceptibility and functional consequences of repeated injury. This study, however, is only a first step in preclinical work on the risks associated with spinal concussion, which will provide a mechanistic framework for understanding the etiology of the injury as well as better guide clinical decision-making for return to play following contact sports injuries. We anticipate that future work from our laboratory and others will elucidate the key parameters of spinal vulnerability following spinal concussion with respect to the time, location, and severity of the injury. To maximize the effectiveness of this work, the basic research with animal models should be coordinated with clinical observations and studies of both spinal and brain concussion injuries.

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