Measuring a broad spectrum of clinically relevant outcomes after experimental spinal cord injury

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Measuring recovery of function after central nervous system injury is an important aspect of experimental models of brain and spinal cord injury. Our laboratory has been focused on developing models, especially for spinal cord injury, for many years. The purpose of the models is to mimic the neurological condition in humans and to provide a test ground for evaluating treatments which then could be brought to clinical trials. For spinal cord injury, the consequences for humans include loss/reduced motor function with altered reflexes and spasticity, sensory loss and aberrant sensations (e.g. pain syndromes), and autonomic dysfunctions including autonomic dysreflexia, and altered eliminative and sexual functions. These functional changes significantly affect a person's quality of life and ability to work, therefore the full range of these deficits should be modeled, and treatments focused on the multiple endpoints they represent. In a recent survey by Anderson [1], people with SCI rated bladder and bowel function most highly as a critical target for treatment; those with paraplegia also rated recovery of sexual function as a very high priority, whereas those with quadriplegia rated return of hand function as their highest priority. The experimental spinal cord injury literature has only recently begun to recognize these functions as important targets and most studies still evaluate locomotor function as the primary outcome measure, as this is the most easily tested and quantified.

There are many ways to measure locomotor function. The simplest is an open field evaluation using an observational rating scale (BBB) that covers the gamut of possible locomotor functions from total paralysis (no movement) to normal function. The usefulness of this measure is that it provides a general categorization of functional ability. The test has good inter-rater and inter-laboratory reliability, and it can be used to determine when other tests which require a specific level of recovery may be applied. For example, if animals are able to step, runway tests with solid floors (e.g. the CatWalk [2]), or horizontal ladder tests or grid walking tests can be used to measure more refined locomotor abilities. Other tests with a broad range of performance outcomes include swimming tests (e.g. the Schnell swimming test and the Louisville swim score), and the inclined plane test which measures the ability of an animal to maintain position on a platform oriented at increasingly steep angles. Locomotor ability on a treadmill moving at different speeds is also frequently used for kinematic analysis of recovery of hindlimb function, and correlated with EMG patterns. Such analyses frequently show dysregulation of muscle activity which alters the kinematic pattern, even in humans after SCI (e.g. Maegele et al., [3]).

Following thoracic contusion spinal cord injury in rats, in addition to locomotor dysfunction, significant disruption of bladder, bowel and sexual function occurs and can be measured. Hyperactivity/spasticity in external urethral and anal sphincter muscle activity leads to a dyssynergia with autonomically innervated smooth muscle activity, and a concomitant disruption of bladder and bowel function (e.g. [4,5]). Interestingly, these and other functions exhibit recovery profiles over time courses comparable to the more commonly tested locomotor function [4]. However, measuring such functions in freely moving animals is difficult at best. Recently, we have developed methods for measuring autonomic outcomes after injury in awake freely moving animals using implantation of telemetric pressure transducer devices in collaboration with Dr. Markus Schmidt [6,7]. If placed in the corpus spongiosum of the penis, patterns of pressure changes can be correlated with not only penile reflex activity, but micturition as well. Pressure measurements in a variety of behavioral contexts (ex copula reflex testing, non-contact erection test, copulatory test) and video-monitoring of micturition over 24 hr testing periods were recorded and matched to observed erectile and micturition events. There was excellent correspondence between the pattern of pressure recordings and observed erectile and micturition events suggesting that telemetric recordings of CSP pressure can provide quantitative assessments of these events in freely moving animals. In addition, the pattern was affected by spinal cord injury, initially showing a significant reduction in activity which recovered over time, paralleling the recovery of the behaviors. However, the patterns recorded indicated development of hyperactivity in the bulbospongiosus muscle similar to that seen in the external urethral and anal sphincter muscles observed after spinal cord injury. These studies as well as those to be described subsequently in this symposium, show the feasibility of measuring a broad variety of functional outcomes after experimental SCI and suggest alternative analytic approaches to measuring improved recovery after spinal cord damage.

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