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Leveraging biomedical informatics for assessing plasticity and repair in primate spinal cord injury

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Abstract

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Recent preclinical advances highlight the therapeutic potential of treatments aimed at boosting regeneration and plasticity of spinal circuitry damaged by spinal cord injury (SCI). With several promising candidates being considered for translation into clinical trials, the SCI community has called for a non-human primate model as a crucial validation step to test efficacy and validity of these therapies prior to human testing. The present paper reviews the previous and ongoing efforts of the California Spinal Cord Consortium (CSCC), a multidisciplinary team of experts from 5 University of California medical and research centers, to develop this crucial translational SCI model. We focus on the growing volumes of high resolution data collected by the CSCC, and our efforts to develop a biomedical informatics framework aimed at leveraging multidimensional data to monitor plasticity and repair targeting recovery of hand and arm function. Although the main focus of many researchers is the restoration of voluntary motor control, we also describe our ongoing efforts to add assessments of sensory function, including pain, vital signs during surgery, and recovery of bladder and bowel function. By pooling our multidimensional data resources and building a unified database infrastructure for this clinically relevant translational model of SCI, we are now in a unique position to test promising therapeutic strategies' efficacy on the entire syndrome of SCI. We review analyses highlighting the intersection between motor, sensory, autonomic and pathological contributions to the overall restoration of function.

Keywords

Non-human primate; spinal cord injury; bioinformatics; big-data; syndromics; statistics; translation; plasticity; recovery; motor function; sensory function; autonomic function

INTRODUCTION

Spinal cord injury (SCI) produces a multifaceted disturbance of the CNS that impacts function and neuroplasticity at multiple levels of the neuraxis. The complexity of SCI presents a challenge for translation of therapeutics from well-controlled laboratory preparations into the heterogeneous patient population. Over the past several years there have been a number of successes within the preclinical SCI field (Dubreuil et al., 2003; Ferguson et al., 2008; Fournier et al., 2003; Freund et al., 2006; Lord-Fontaine et al., 2008; Lu et al., 2012; Maier et al., 2009; Pernet and Schwab, 2012; Simonen et al., 2003). Yet, few of these therapies have traversed the translational divide to make their way into standards of patient care (Blesch and Tuszynski, 2009; Dietz and Curt, 2012; Filli and Schwab, 2012). The challenges for translational SCI research include fundamental pipeline questions such as: a) How do we best translate successes from well-controlled small animal studies into more heterogeneous, more complex, and larger models? b) How do we understand the intrinsic variability in promising therapeutic interventions? c) How do we determine the specific conditions under which a given therapy works? These questions have been discussed at great length within the research and clinical SCI community (Kwon et al., 2010; Kwon et al., 2013) as well as within the greater biomedical scientific community (Collins and Tabak, 2014; Landis et al., 2012).

A number of recent surveys among SCI researchers and clinicians identified the need to test emerging therapeutic candidates from rodent studies in a non-human primate model prior to

translation into human clinical trials (Courtine et al., 2007; Kwon et al., 2010; Kwon et al., 2011; Kwon et al., 2013). Parallel efforts are also underway to both standardize data collection (Lemmon et al., 2014) and integrate raw data from preclinical studies into a queryable database available to the SCI community (Nielson et al., 2014). However, variability in SCI data collection methods and models represents a challenge for both scientific reproducibility and translation. In this context, replication and translation boil down to problems of data alignment--how do we best align functional outcomes across multiple scales and multiple species to compare findings? A potential solution is to view translational model development as a 'big-data' challenge that can be addressed in part, through application of data science to SCI translational models (Howe et al., 2008; Marx, 2013; Sejdic, 2014).

In accordance with these translational goals, the California Spinal Cord Consortium (CSCC) has developed a translatable cervical SCI model in non-human primates that is clinically more relevant than small animal studies for unraveling SCI pathophysiology and preclinical trial efficacy with respect to recovery of forelimb and hand function in primates (Nout et al., 2012a; Nout et al., 2012b). The CSCC consists of a multidisciplinary team of scientists and clinicians spanning the fields of anatomy, neurosurgery, neurology, intra-operative monitoring, physiology, behavior, histopathology, bioinformatics and statistics. Our aim is to better understand the intrinsic nature of SCI in non-human primates, and to complement research being done by other groups to optimize therapeutics for clinical application in humans. Previous studies by others have assessed a wide range of important aspects of this translational model, including cortical reorganization and contribution to recovery (Chen et al., 2012; Darian-Smith et al., 2014; Qi et al., 2011), mechanisms of degeneration (Shi et al., 2009; Wu et al., 2013), and cell-therapy transplantation studies (Levi et al., 2002; Nemati et al., 2014). The overarching goal of the CSCC is to integrate as much complementary information as possible in a single translational model. Toward this end, we strive to maximize the use of each experimental subject, including multiple endpoint monitoring across multiple scales of analysis (Jindrich et al., 2011; Nielson et al., 2014; Nout et al., 2012a; Nout et al., 2012b; Rosenzweig et al., 2009; Rosenzweig et al., 2010).

Our research focus has been to optimize post-injury neuroplasticity and understand the relationship between this plasticity and functional recovery (Rosenzweig et al., 2010). However, there is always risk that plasticity after a lesion to the spinal cord can lead not only to beneficial recovery of motor and sensory function, but can also result in maladaptive changes like pain, spasticity, and autonomic dysfunctions (Brown and Weaver, 2012; Cameron et al., 2006; Deumens et al., 2008; Fouad et al., 2011; Weaver et al., 2006). Therefore, therapeutic interventions inducing plasticity warrant caution as beneficial effects could be accompanied by enhanced maladaptive plasticity resulting in the development of intractable sensory and autonomic malfunction (Ferguson et al., 2012; Fouad et al., 2011; Hofstetter et al., 2005). For this reason, and to promote the translational goals of the CSCC, during the course of therapeutic testing studies every subject is monitored to an extent similar to patients in a clinical setting; data are gathered regarding health state, training, surgery, and rehabilitation monitoring, functional recovery, rehabilitation, motor physiology including sensory, bowel and autonomic outcomes, and neuroanatomy. By coupling the non-human primate model development efforts with a coherent big-data collection plan and

statistical science, it becomes possible to maximize knowledge discovery and improve the potential for clinical translation. We believe that the key to unlocking translational information is to simultaneously assess multiple pieces of information in a single subject. This concept has recently materialized in clinical science with the birth of 'precision medicine' (Desmond-Hellmann, 2012; NRC, 2011). Precision medicine re-contextualizes the problem of disease diagnosis and therapeutic testing as a problem for big-data analytics, with the goal of enabling high-level computational approaches to collect, analyze and interpret information to provide insights into patient-level details from multidimensional health information. In the present review we will describe our efforts to re-purpose the goals and methods of precision medicine to assist in *precision translation* for SCI.

Prior publications from our team have outlined the fundamental features of the cervical SCI primate model (Nout et al., 2012b), including novel methods developed to assess forelimb and hindlimb recovery in larger animal species (Nout et al., 2012a), and discovery of novel neurobiological insights related to intrinsic plasticity of the lesioned corticospinal tract (CST) (Rosenzweig et al., 2010). The present review focuses on the role that biomedical informatics and big-data analytics have played in our ongoing efforts to compile multi-scalar, multidimensional data from non-human primate models of SCI (Nielson et al., 2014). We will focus on the unique digital infrastructure resources developed as part of the CSCC to facilitate large-scale data collection, curation, and application of multivariate statistical science to maximize discoveries from the CSCC primate SCI research effort. In addition, we will discuss translational innovations such as our preclinical electronic medical record (EMR), and our development of an array of digital technologies to streamline data collection and data harmonization, across multiple information levels including functional behavior, electrophysiology, kinematics, *in vivo* MRI, postmortem histopathology, and a full medical record from birth to necropsy. To our knowledge, this is the most comprehensive preclinical data record ever assembled for non-human primate SCI studies. By applying sophisticated infrastructure, we are gaining unprecedented access to rich information about each subject to develop a precise view of their functional recovery state across multiple endpoints.

We will review the ongoing evolution of our infrastructure, as well as present examples of data collected using this infrastructure. Most of the data have been previously published in various forms elsewhere and are reprinted here with permission (Nielson et al., 2014; Nout et al., 2012a; Nout et al., 2012b; Rosenzweig et al., 2010). The goal of the present review is not to derive novel insights, but to highlight how we acquire, manage, and integrate multiscale data. The results of leveraging this infrastructure for novel insight discovery are topics of other papers currently in preparation.

Scientific Data Collection

Animals

Data presented in this paper outline the current metrics being collected from non-human primates (Table 1) whose information has been used in previous publications (Nout et al., 2012a; Rosenzweig et al., 2010). Here we present previously published data collected from adult male rhesus monkeys (*Macaca mulatta*, N = 31) mined from the Visualized Syndromic

Information and Outcomes for Neurotrauma-SCI (VISION-SCI) preclinical SCI database (Nielson et al., 2014).

Evolution of Data Collection Standards

Previous methods of data collection of the CSCC studies relied heavily on paper recording sheets to document behavioral recovery, surgical notes, and daily care logs during the entire course of each study. While these methods follow a traditional norm of data collection from most preclinical and some clinical studies, the physical volume and the process of archiving and documenting all of these records into a single data repository requires considerable time and effort (Nielson et al., 2014), particularly when attempting to mine information for analysis, interpretation, and/or running queries. Fortunately in the past several years, CSCC has begun to adopt various forms of electronic data capture in addition to hand-written paper records, including primary data collection through hand-held devices, tablets, and computer interfaces (Fig. 1). Record keeping and collection of behavioral data in this consortium has evolved as the volume and diversity of data-streams being collected has grown and become overwhelming to manage by traditional methods. Initial records were kept in paper logs in the form of behavioral sheets, surgical records, daily care logs, and laboratory tests to monitor the health and well-being of each animal before, during and after experimental SCI. In an attempt to offset the need for data curation and entry from paper records into electronic form, an early version of a handheld data collection device implemented ethology-based forms on a personalized digital assistant (PDA) in a relational database format (HanDbase, DDH software) to collect behavioral data during live experimentation (Siddiqui and Butcher, 2002). However, complications in the implementation of this system, as well as technical errors with real-time PDA-based data collection resulted in the loss of certain data records, spurring the consortium to reconsider electronic data collection. At this time, the group returned to maintaining paper records for behavioral data collection, while parallel efforts were developed to create an online Animal Data Entry and Query Interface (ADEQI) system through MySQL to be used for data entry and storage. ADEQI was implemented through a combination of tablet and computer web-based data entry. During the course of 2 years, paper records were hand entered and error-checked using the ADEQI system, which was queried to present behavioral recovery from a large cohort of non-human primates from multiple behavioral tasks presented previously in a standard primate chair (N = 24) and an open field exercise cage (N = 20) (Nout et al., 2012a; Nout et al., 2012b). We have recently retired the ADEQI systems and moved to a paperless tablet-based digital data collection system. Data are directly entered using digital forms and uploaded into the database by way of automated parsing scripts. Detailed descriptions and public release of the tablet applications and forms will be a topic of an upcoming methods paper.

Data Reuse in the Present Paper

Data plotted in time course recovery curves for vitals during unilateral hemisection (N = 11), weight pre and post injury (N = 18), exercise cage open field behavior (N = 20), reach, grasp and retrieve in the primate chair (N = 20), and kinematics and muscle physiology during treadmill locomotion (N = 3–5) are shown in Figures 2–5, respectively. Graphs in Figures 2–4 and all of Figures 5 and 7B were modified from prior studies and reused with permission (Rosenzweig et al., 2010). Lesion reconstructions in Figure 6A were re-created

from those presented previously (N = 20) (Nout et al., 2012a), and stacked using the multiply function in Adobe Photoshop to illustrate the average lesion size for animals whose behavioral recovery is plotted in Figures 3 and 4. All other illustrations were drawn by hand in Adobe Illustrator (Figures 1, 2A–C, 3A, and 6B).

Data Curation for Multidimensional Assessment

Any type of data collected/scored during live testing and/or from an archived record aims to accurately represent an individual aspect of recovery/impairment of each test subject and is explicitly dependent on detailed animal observations (Fig. 1A). However, there are multiple sources of error intrinsic to any single assessment. Errors can occur at the level of the observer, during transcription of observations, during data management and/or during analysis. The process of screening for these errors and correcting them in the digital record is known as ‘data curation’ (Bandrowski et al., 2012). In the CSCC, functional metrics are collected as the primate performs behavioral tasks designed to encourage voluntary use of the impaired limb(s). Introduction of technological advances to data collection have allowed us to reduce and/or eliminate several data-integrity issues introduced by manually entering large amounts of data. Currently, complete removal of human intervention between data collection and data entry is not a viable option (Fig. 1C), given that some level of processing/knowledge is required to manipulate data into a specific database format. However, we have worked to remove sources of human error through a combination of novel data collection interfaces and ongoing data curation and data quality control measures enabled by fast data queries (Fig. 1D).

Leveraging Biomedical Informatics Infrastructure

We have developed a unified data commons to gain the ability to integrate outcome assessment across multiple endpoint domains and generate full-information statistical reports for each subject. To incorporate healthcare data we have built a preclinical electronic medical records system on the backbone of a HIPAA-compliant biomedical informatics infrastructure hosted within the UCSF-Research Electronic Data Capture (UCSF-REDCap) system (Fig. 2). This approach allows us to manage large volumes of veterinary medical data from our research subjects behind a secure and de-identified firewall. Leveraging these data provides potential for novel insight discovery within animal medical records—a nontraditional data source within basic animal research. Detailed multidimensional medical paper records are collected during the lifespan of each test subject, beginning at birth. These paper medical records are first redacted to remove identifiers regarding the individual investigators, then scanned to PDF for archiving and incorporation into the VISION-SCI database. Data entry technical staff utilize the UCSF-REDcap infrastructure (Fig. 2B–C) (Harris et al., 2009; Obeid et al., 2013) to enter data points from each medical record. To date, we have entered data from 20 test subjects (121.3 ± 25.4 pages per animal; 2425 total pages; 13,204 variables).

By mining these data we have the opportunity to align health information with data from functional tasks providing a data layer and context that is helpful for evaluating functional endpoints for translation. An example of the type of data that can be generated from these

medical records is shown in Figure 2D which highlights the vitals taken during surgery including body temperature, heart rate, respiratory rate, and mean arterial pressure (MAP). These neurocritical monitoring measures are routinely collected manually by anesthesia staff during surgery and can be co-registered with endpoints such as blood oxygenation and anesthesia levels. Similar retrospective analyses can be performed to assess changes in body weight prior to and after SCI (Fig. 2E) as well as other health outcomes within the medical record including, for example, detailed records of appetite, hydration, stool and urine analysis, blood work, and drugs given during the course of recovery from surgery. Any one of these data-streams has potential relevance for replication of therapeutic discoveries and precision translation to humans.

Multidimensional Functional Outcomes

Outcome measures used to assess recovery of forelimb function have been described in detail previously (Jindrich et al., 2011; Nout et al., 2012a; Nout et al., 2012b; Rosenzweig et al., 2009; Rosenzweig et al., 2010) and are outlined in Table 1. Test subjects are assessed during various behavioral tasks including: a) open field locomotion, climbing and object manipulation; b) chair testing designed to isolate movements involving reach, grasp and retrieval of food items; c) electromyography (EMG) recordings in hand and arm muscles monitoring for coordination and co-activation during recovery; and d) treadmill locomotion and kinematics. Additional data now being collected (not presented in this review) include: recovery of fine motor skill and somatosensory function assessed by food retrieval from a Brinkman board (Kaeser et al., 2010); sensory function assessed by von Frey filament stimulation; and bowel function assessed by anal sphincter EMG (Table 1, Fig. 2F).

Multidimensional Assessment of Primate ‘Activities of Daily Living’

One of the important components of the data collected by the CSCC is the assessment of behavioral recovery in an open-field exercise cage (Figure 3). Observation of unconstrained behavior in an open field is a common tool utilized in rodent SCI research (Basso et al., 1995; Basso et al., 2006; Gensel et al., 2006; Irvine et al., 2010; Irvine et al., 2014). Co-development of similar methods for primates (Nout et al., 2012a) and alignment of rodent-to-monkey data (Nielson et al., 2014) can expedite translational therapeutic testing. Figure 3A is an illustration of the exercise cage. Test subjects, enter through the door on the left and have immediate access to the series of 4 perches elevated at varying heights off ground, toys including rubber manipulanda containing food, and baited cups to assess climbing ability. Subjects are filmed as they explore the exercise cage, and behavioral data are simultaneously entered by technicians using structured data-collection ethograms on a tablet computer (see Fig. 1B). Typically, subjects immediately run to the top perch (4^{th}) and interact with forelimb manipulanda. Object manipulation skills are scored while subjects withdraw small food items from a hollow rubber kong toy. Food rewards also are placed inside 5 cups suspended at different heights and subjects are scored based on their ability to climb and retrieve items from these cups. Detailed account of these behavioral tasks and our ongoing scale development methods are described elsewhere (Nout et al., 2012a). Graphical data presented in Figure 3 indicate the degree of functional recovery in test subjects that received a unilateral hemisection at the 7^{th} cervical spinal cord level. Note that assessment

of open field behavior allows for the description of locomotor (Fig. 3D), climbing (Fig. 3I) and object manipulatory (Fig. 3E) skills plotted over time, as an aggregated overall score (Fig 3B) and/or broken down into several subunits isolating forelimb and hindlimb recovery curves (Fig. 3F–G). The data in Figure 3 depict the preliminary results from a summation-based scoring scheme based on forced-choice ratings across a large number of behavioral features. The analysis of metric properties and optimization of this scaling effort is a topic of ongoing study.

Multidimensional Assessment of Constrained Forelimb Reach-and-Grasp

The exercise cage is a useful tool for determining the recovery of gross motor skills. However, the CSCC also has developed tasks that evaluate fine motor skills while subjects are seated in a standard primate chair (Nout et al., 2012a; Rosenzweig et al., 2010)(Figure 4A). We have developed several variations of the reach-and-grasp task including retrieval of food from a stick (Fig. 4B), a handle bar pull (Fig. 4C), and retrieval of food from a platform (Fig. 4D). Each subject is given a series of trials on each of the tasks, providing a multidimensional view of their reach-and-grasp function across a wide dynamic range. Figure 4 depicts data from 20 monkeys as an ordinal ranking score reflecting the full range of responses that the animals display. A portion of these data has been presented previously in the form of % success rate (Nout et al., 2012a; Rosenzweig et al., 2010). Note that animals began to show recovery around 6 weeks post injury, and plateaued around 9 weeks. Although all test subjects were able to attempt to retrieve the food, few subjects could successfully retrieve the food and transfer it to the mouth, as recently highlighted (Nout et al., 2012a). Note that the median response was to reach out and touch the stick from which they were attempting to retrieve food (Fig. 4B), partially pull the handle (Fig. 4C), or grasp the food on a platform (Fig. 4D). This suggests that there is a large residual dynamic range to detect either increases or decreases in function in therapeutic testing.

Multidimensional Assessment of Locomotion

In addition to assessing subjects' responses during food reward tasks, the CSCC records high-resolution kinematics and electromyogram (EMG) data during locomotion on a treadmill and during reaching (Fig. 5). These data, presented in a previous publication (Rosenzweig et al., 2010), give comprehensive details of muscle co-activation and recruitment pre and post SCI. The recovery patterns presented in Figure 5 (N = 11) (Rosenzweig et al., 2010) are from a group of subjects different from those presented in Figure 4 (N = 20) (Nout et al., 2012a).

Multidimensional Assessment of Sensory and Autonomic Function

One important addition to the set of assessments is the monitoring of sensory and autonomic function during the course of recovery. Sensory function is measured by an electronic Von Frey anesthesiometer (Table 1). Stimuli are applied to five different locations on the hairy skin (i.e., shoulder, hand, thorax, knee and foot) on the contralesional and ipsilesional side while the primate is sitting in a primate chair. Every location is randomized and assessed in triplicate. The stimulation protocol includes false alarm trials, wherein no stimulus is applied to the skin. The response to the stimulus is classified into 7 categories: no response, flinch/

skin contraction, withdrawal, activity arrest, orientation towards stimulus, wince or facial response and vocalization. To date these assessments have not revealed evidence of supraspinal pain hypersensitivity.

Bowel dysfunction is another high priority problem for people with SCI (Anderson, 2004). As a surrogate marker of autonomic bowel function the CSCC recently introduced EMG measurement of the external anal sphincter muscle (EAS) (Table 1, Fig. 2F). The EAS consists of striated muscle fibers and is innervated by somatic motoneurons located in Onuf's nucleus or its homologue in the lower lumbar or upper sacral portion of the spinal cord. Supraspinal control of the EAS motoneurons may be interrupted by SCI at both the cervical and thoracic spinal levels. In rodent models of SCI, increased EAS EMG activity can be readily detected in response to a gentle stretch of the rectal wall (Holmes et al., 1998). Evoked EAS EMG responses also may be detected in non-human primates following insertion of a rectal probe (Lee et al., 2012). EMG is recorded during the insertion of glass probes with different diameters into the rectum of the non-human primates under anesthesia. Large amplitude EAS EMG activity is typically observed at the onset of the evoked response; smaller-amplitude EMG activity continues for 1–3 minutes before a quiescent baseline is re-established (Figure 2F). Detailed results from sensory testing and external sphincter EMG will be a topic of future papers.

Multidimensional Assessment of Histopathology

Following termination of each experiment, every animal is humanely euthanized according to the Institutional Animal Care and Use Committee at UC Davis and National Institutes of Health guidelines. The spinal cord is analyzed histologically to determine the lesion size and the extent of pathology in and around the lesion epicenter (Fig. 6A), as described previously (Nout et al., 2012a; Rosenzweig et al., 2009; Rosenzweig et al., 2010). Most of the subjects tested for functional recovery following SCI also receive anterograde tracing of the corticospinal tract (CST) into the hand, arm, trunk, leg and foot regions of the primary motor cortex approximately 6–7 weeks before necropsy (N = 30, 45.3 ± 9.0 days). The tracer surgery and postmortem tissue processing and staining have been described in detail (Rosenzweig et al., 2010). Two different tracers are injected (one into each side of the motor cortex), allowing discrete labeling of the CST axons arising from the left and right hemispheres. Because of the CST projection patterns in primates (Rosenzweig et al., 2009), approximately 90% of the axons arising from the left cortex (and 10% of the axons arising from the right cortex) are severed by the spinal cord hemisection. Labeling of axons arising from the left cortex is shown schematically in Fig. 6B The extensive anatomical plasticity of this system, and its univariate and multivariate relationships to recovery of reaching and locomotion, have been reported previously for some of these animals (N = 11; Fig. 7, (Rosenzweig et al., 2010)). Analyses are ongoing regarding the multivariate relationship of CST plasticity and fine motor skills measured during reach and grasp tasks (Fig. 4), gross motor skills in the open field exercise cage (Fig. 3), sensory and autonomic functional recovery (Table 1), and additional histopathological measures of tissue sparing and neuroinflammation around the lesion site (Fig. 6C).

Leveraging the Full Data Record for Integrated Syndromic Assessment

The ability to collect high resolution data for multiple measures of motor, sensory, and autonomic function as well as histopathology, allow the application of advanced computational and statistical methods to reconcile all data and identify syndromic patterns of functional recovery (Fig. 7) (Ferguson et al., 2011; Ferguson et al., 2013; Nielson et al., 2014; Rosenzweig et al., 2010). For example, we have applied principal component analysis (PCA) on data regarding food retrieval success in the primate chair, locomotor recovery on the treadmill, and stereological quantifications of CST axons anterogradely labeled in the primary motor cortex (N = 11) (Rosenzweig et al., 2009; Rosenzweig et al., 2010). This approach allows us to leverage the patterns of cross-correlations among different outcomes to derive a holistic picture of the syndromic state of each subject. The rationale for this multidimensional view is that a multivariate endpoint can provide a cleaner metric of function that is more robust than any single outcome metric (Ferguson et al,. 2011). In addition, multivariate pattern discovery can identify species-specific substrates for recovery, and can help translation by identifying syndromic outcome sets for SCI that translate across species (Nielson et al,. 2014). Further results of multivariate analyses, including the exercise cage outcomes and their relation to CST sprouting, neuroinflammation, and motor neuron survival are ongoing and will be presented in separate papers currently in preparation.

Discussion and Conclusions

The data presented in this review highlight the methods with which we are conducting non-human primate studies to evaluate recovery following cervical SCI. Due to the large team of experts in anatomy, electrophysiology, behavior, bioinformatics and statistics, our consortium has a unique opportunity to leverage large amounts of useful information from each subject to ensure every effort is being made to maximize knowledge, and limit animal numbers required for translational purposes. Over the past 10–15 years, the CSCC has responded to calls from the SCI community asking for more clinically relevant animal models to study SCI pathophysiology, functional recovery, and preclinical efficacy prior to clinical translation (Courtine et al., 2007; Darian-Smith, 2007). Initial studies in non-human primate models of SCI historically focused on documenting pathological changes at the site of lesion (Bresnahan, 1978), with later studies investigating hindlimb functional deficits (Courtine et al., 2005). However, in recent years we have transitioned our efforts into a cervical model of SCI in the non-human primate (Nout et al., 2012a; Nout et al., 2012b) to address the priority from the SCI patients, most of whom suffer from cervical spinal injuries, and would benefit greatly from regaining hand and arm function (Anderson, 2004).

Our approach to modeling SCI has been to specifically target recovery of hand and arm function, and therapeutic options that will promote CST sprouting and plasticity. Our group has traditionally used hemisection injuries at cervical levels 6/7 to selectively target components of the CST and motor neurons in the cervical enlargement, in order to assess restoration of connectivity and function below the lesion. This focus in recent years on cervical function is based on priorities from the SCI patient population (Anderson, 2004), however the CSCC has assessed thoracic models in the past (Courtine et al., 2005). In the future, we plan to develop the ability to include data from multiple lesion models including

those collected by other researchers (e.g. dorsal column lesions) through our informatics infrastructure. To improve translation, the CSCC is also developing a novel clinically relevant contusion model to extend our translation beyond hemisection models. These ongoing model-development efforts include the development of novel translational metrics for monkeys that will help bridge translation to human recovery. For example fine-digital control measures used in the chair tasks, object manipulation in the exercise cage (Nout et al., 2012a), and quantitative metrics being developed by CSCC are specifically designed to mirror hand tasks used in humans, including the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) task (Kalsi-Ryan et al., 2012; Kalsi-Ryan et al., 2014; Velstra et al., 2014) and others. Data-driven multivariate analytics across measures in rodents and non-human primates are revealing the precise battery of endpoints that will enable rapid cross-species comparisons (Nielson et al., 2014). The long-term goal is to determine what is unique and conserved between species harnessing existing data to accelerate this translation.

Most of our earlier reports, and those by others in the field of SCI, have focused on motor functional recovery, as the restoration of mobility is a high priority for patients living with SCI. A recent study in non-human primates revealed a novel finding of sprouting of the CST from the primary somatosensory cortex, in addition to the primary motor cortex, after a combined peripheral and spinal lesion (Darian-Smith et al., 2014). This study raises the important question about the role of the primary somatosensory cortex in CST plasticity following SCI. Furthermore, during the course of recovery patients often develop sensory dysfunctions such as pain. Pain as a maladaptive sensory symptom represents an important aspect of disturbance after SCI and for individuals who experience pain it can become the most difficult aspect of SCI (Anderson 2004). Understanding and treating neuropathic pain after SCI is a high priority for the SCI research field, given its high prevalence (up to 50%), its tendency to become a chronic condition (Siddall et al., 2003), the devastating consequences for quality of life of the individuals, coupled with the lack of effective treatments (Cardenas and Jensen, 2006; Widerstrom-Noga and Turk, 2003). Yet, sensory functional assessments are a highly underrepresented component of many studies, though they are highly relevant to our translational understanding of recovery of hand/arm function.

On the clinical side, the International Standards for the Neurological Classification of SCI (ISNCSCI) has become a standard clinical tool to assess sensory function after human SCI (Kirshblum et al., 2011; Maynard et al., 1997). Light touch and pinprick sensation are assessed segmentally rostral and caudal to the level of injury and classified into normal, impaired and absent sensory function. Quantitative sensory testing has been proposed to refine sensory outcomes after human SCI (Hayes et al., 2002). This method attempts to measure sensory detection and pain thresholds of different stimulus modalities (e.g., warm, cold, vibration, and touch) and thereby assesses both spinothalamic tract and dorsal column function (Rolke et al., 2006; Shy et al., 2003). Similar approaches have been used in non-human primates to assess subcortical and cortical responses such as withdrawal, escape, flinch, skin contraction vocalization, orientation, facial expression, activity arrest and measures of the responsiveness of the somatosensory cortex have been assessed after various stimulus modalities (e.g., cold, heat, touch, electrical)(Chen et al., 2012; Cooper and Vierck, 1986; Greenspan et al., 1986; Lalonde and Poirier, 1959; Palecek et al., 1992; Qi et

al., 2011; Vierck, 1974; Vierck, 1977; Vierck and Light, 2000). Von Frey filaments are used in non-human primates to assess light touch sensation and mechanical allodynia (Palecek et al., 1992). A comparable measurement in humans is incorporated in the sensory domain of the GRASSP (Kalsi-Ryan et al., 2012; Kalsi-Ryan et al., 2014; Velstra et al., 2014). During testing, calibrated von Frey stimuli (Semmes-Weinstein monofilaments) are applied to the dorsum and palmar side of the hand. We are beginning to address the role of sensory function in our monkey models of SCI (Table 1) by monitoring sensory changes by von Frey testing which will be the subject of future studies by the CSCC.

We have numerous measures to assess motor functional recovery including treadmill kinematics and EMG (Jindrich et al., 2011; Rosenzweig et al., 2010), food retrieval (Nout et al., 2012a; Nout et al., 2012b; Rosenzweig et al., 2010), and open field behavior in the exercise cage (Nout et al., 2012a), with ongoing data being collected using other methods of assessing skilled reach, grasp and retrieval (Kaeser et al., 2010). Additional efforts are underway to address autonomic changes, another clinically relevant but underrepresented research area in the SCI field. Bladder and bowel dysfunction are major concerns for patients to improve quality of life, yet these are often overlooked or not reported in preclinical studies as a prominent outcome. Including human studies, there exists no direct tests of autonomic integrity of the distal bowel function, so the field relies on surrogate evaluation of autonomic control of bowel function. In humans the international standards to document remaining autonomic function after SCI recommend the assessment of voluntary sphincter contraction during anorectal examination (Krassioukov et al., 2012). The external anal sphincter consists of striated muscle fibers and is innervated by somatic motoneurons located in Onuf's nucleus or its homologue in the lower lumbar or upper sacral portion of the spinal cord. Supraspinal control of the EAS motoneurons may be interrupted by injury to, for instance, the cervical or thoracic spinal cord. The CSCC has begun translating autonomic tests from rodent-to-primate models of spinal cord injury including increased EAS EMG activity in response to a gentle stretch of the rectal wall (Holmes et al., 1998). Evoked EAS EMG responses also may be detected in non-human primates following insertion of a rectal probe (Lee et al., 2012), providing a tool for assessing autonomic function in primate SCI.

Several promising interventions are being considered for translation through the non-human primate model based on successful studies in rodent models. These interventions include those aiming to promote recovery of cortically-driven voluntary hand and arm function, such as cell therapy grafts to promote regeneration (Lu et al., 2012; Steward et al., 2014; Tuszynski et al., 2014), brain-machine interfaces (Carmel et al., 2010; Carmel et al., 2013), and selective deletion of genes responsible for promoting axon regeneration of the corticospinal tract (CST; (Liu et al., 2010)). However, due to recent replication failures plaguing the field of SCI research in the rodent model (Steward et al., 2012), and the implications that this has for inefficient translation, it is crucial that we ensure this problem is not present when attempting to test therapeutic efficacy in the non-human primate model. Therefore the development and refinement of not only this important translational model, but also the biomedical informatics framework presented here are both necessary to maximize efficacy, interpretation and ultimately translation into standards of patient care.

One of the benefits of building a large-scale data commons is that it will allow data to be repurposed and reanalyzed as the role of biomedical informatics in research continues to expand in the coming years. It is likely that we will see the emergence of novel computational tools for assessing treatment efficacy and charting multidimensional recovery. The challenges of data collection, entry, curation, and visualization highlighted in the present review remain a significant bottleneck for bringing information science into the SCI field. However, technological advances are now being implemented into our search for a better, simpler way to organize, maintain and stream information into data repositories such as VISION-SCI (Nielson et al., 2014). At the moment, the non-human primate data in our database only consists of studies from the CSCC, but we are developing the infrastructure to add more primate data from other researchers in the community who are willing to share their data.

By leveraging the full biomedical information from these preclinical trials, not just for functional and anatomical recovery, but also from detailed clinical information about health and physiology during surgery and recovery from injury, we can ultimately reduce the total amount of time, money and effort it will take to push promising therapies from bench-to-bedside. This is important, especially considering recent advances in the field in human patients showing remarkable recovery following complete SCI (Angeli et al., 2014). The SCI field will greatly benefit translational application medical informatics to understand the complex relationships driving recovery in patients, and reverse-translating these into mechanistic therapeutic targets using rodents to non-human primate models in an enhanced discovery pipeline for SCI and related neurological diseases.

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- A review of a biomedical informatics framework for non-human primate SCI.
- Examples of data mined from electronic medical records during peri-operative care.
- Recovery and range of function on multiple measures currently used in primate SCI models.
- Multivariate analysis reveals the relationship between CST plasticity and recovery of function.
- Biomedical informatics can be fruitfully applied to improve translational SCI research.

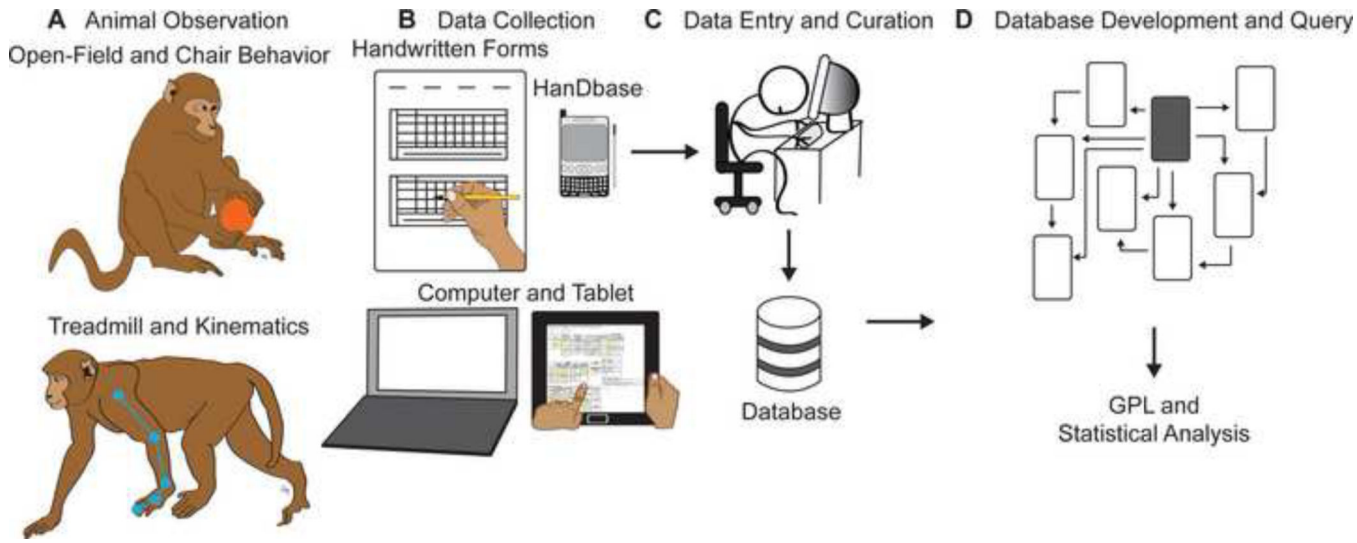


Figure 1. Biomedical informatics workflow for non-human primate SCI

During every experiment, subjects are monitored in either the primate chair or exercise cage to assess functional recovery of skilled reaching tasks and general daily behavior, as well as locomotion and muscle activity (EMG) while walking on a treadmill (A). Data is collected in various formats with either handwritten forms, or various electronic methods of data capture including hand held devices (e.g. PDAs or tablets), or collected onto a computer interface (B). Data from the various formats then are entered by hand and/or formatted by data entry technicians and SCI domain experts for curation and accuracy prior to being incorporated into our database (C). Data are parsed into a structured database that can be queried for further analyses using graphical programming languages (GPL) such as R, Python, and structured query language (SQL) for statistical analysis (D).

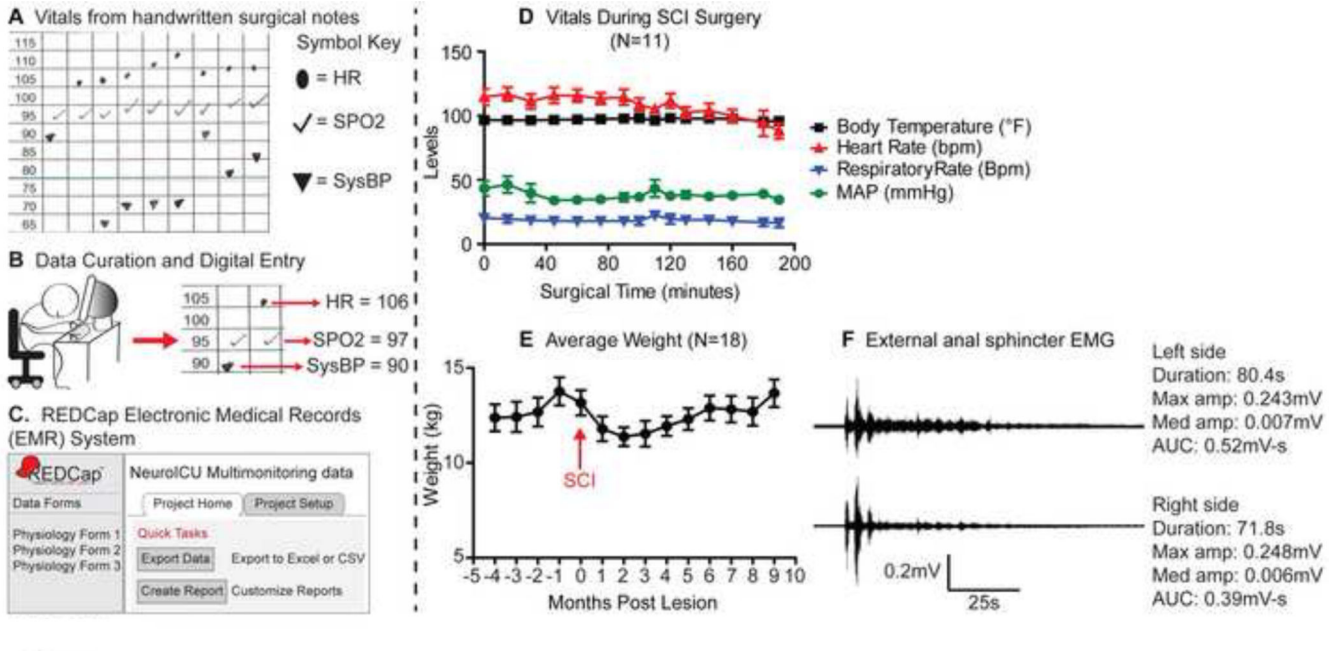


Figure 2. Leveraging medical records and electronic data capture for physiology and health monitoring

Detailed medical records are maintained for every subject in the CSCC studies. Most records are in the form of handwritten notes before, during and after the SCI surgery, from the birth of the animal until termination of the study. Surgical monitoring of physiology vitals, including heart rate, blood pressure, respiratory rate and blood oxygenation are hand written into the record book (A). Data entry technicians scan these de-ID records to PDF, check values for errors (B), and hand enter them into the Research Electronic Data Capture (REDCap) electronic medical records system (C). Data are stored in a HIPAA-compliant, secured, cloud storage system at UCSF where subsections of the records can be extracted for analysis of the results. Vital signs during SCI surgery from 11 subjects were plotted for the duration of their time under anesthesia during surgery, recorded every 15 minutes to show group averages of body temperature (°F), heart rate (bpm = beats per minute), respiratory rate (Bpm = breaths per minute) and mean arterial pressure (MAP, mmHg = millimeters of Mercury) (D). Weight (kg = kilograms) was plotted for 18 subjects spanning from 5 months before to 10 months after SCI (red arrow). Approximately 1 month before SCI surgery, animals were enrolled in training programs to acclimate them to the behavioral testing methods. The rapid increase in weight prior to SCI was due to extra food given to subjects to assist in their motivation and training on the behavioral tasks. Most animals lost a few kg of weight after injury, but then began to return to their pre-training weight about 4 months after injury (E). Data are plotted as mean ± standard error. Electromyography of the external anal sphincter (EAS) muscle is measured as a surrogate marker for autonomic bowel function (F). A glass probe, 10 mm in diameter, was inserted into the rectum of a male rhesus macaque for 5 seconds while under ketamine anesthesia. Evoked EAS EMG responses were obtained from electrodes placed in the left and right sides of the EAS muscle. Note quiescent baseline recordings followed by the symmetric evoked responses. The first two high amplitude bursts of EMG activity at the beginning of the evoked response represent the

insertion and removal of the glass probe. Quantitative analysis may be obtained from each evoked response and include, for instance maximum and median amplitudes, duration, and area under the curve (AUC) as a function of amplitude and time.

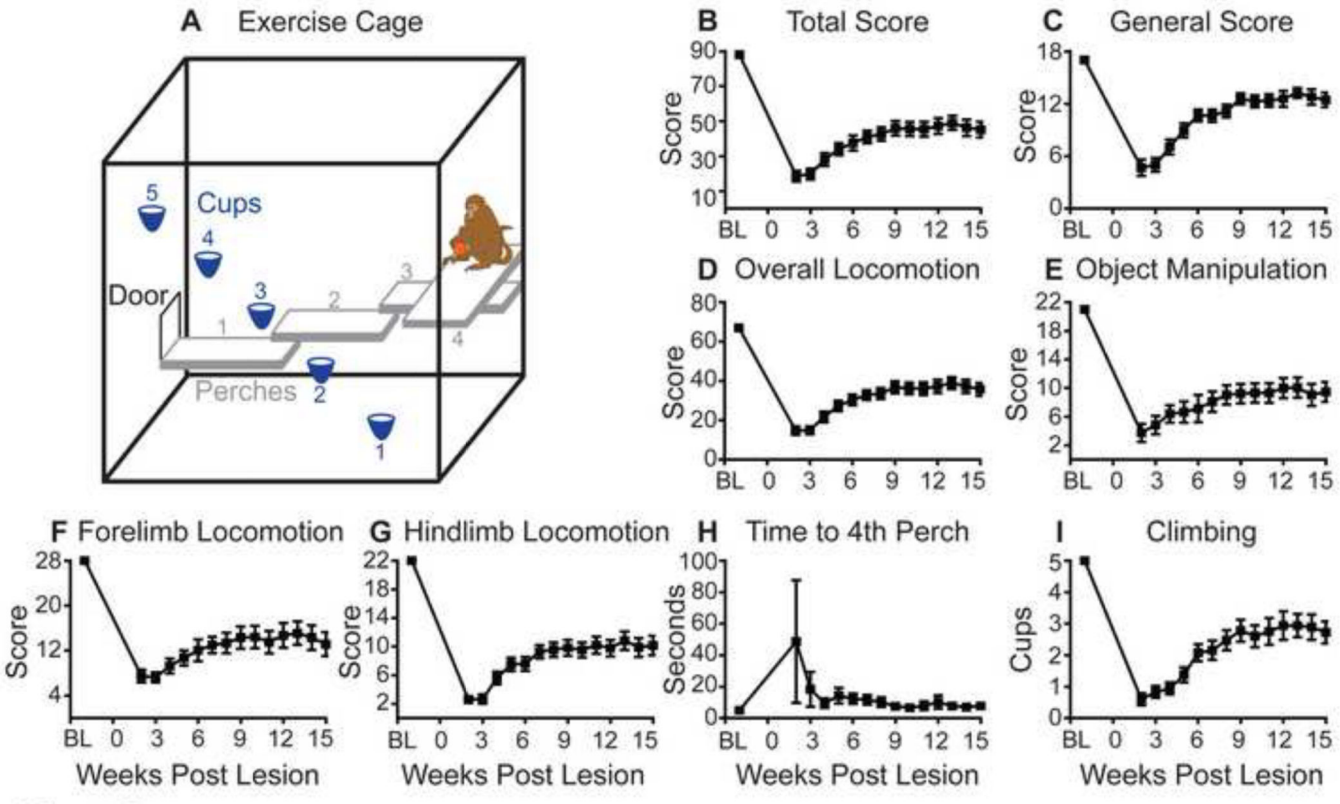


Figure 3. Recovery of gross motor skills measured in the open field exercise cage

Subjects are monitored in a large exercise cage to assess general open field locomotion, climbing, and object manipulation. Animals enter the cage through a door and they can climb up 4 perches where food is waiting for them on the 4th platform, as well as in each of 5 cups placed as different heights along the front of the cage to measure climbing ability (A). Details of the scoring of this measure have been described previously (Nout et al., 2012a). Group recovery curves were plotted from data extracted from the VISION-SCI database (Nielson et al., 2014) for 20 animals, and monitored for several weeks before injury to obtain baseline (BL) values, and weekly after injury. Scores were recorded as an overall total open field score (B), as well as various sub-scores, including general (C), locomotion (D), object manipulation (E), forelimb (F) and hindlimb locomotion (G), time it took to reach the 4th perch (H), and how many cups they were able access by climbing the fence to retrieve the food (I). Data are plotted as mean ± standard error.

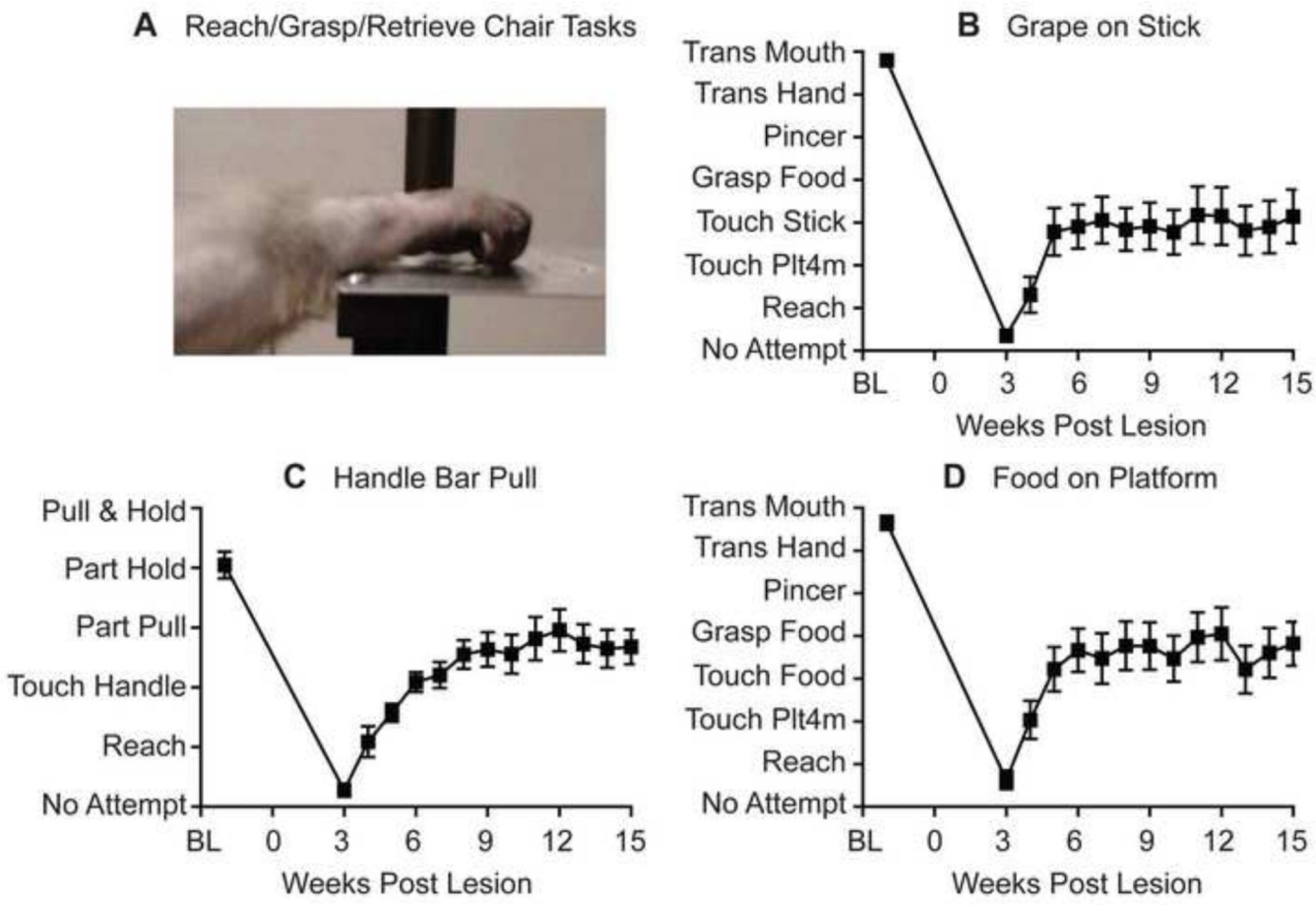


Figure 4. Partial recovery of fine motor skills in a reach/grasp/retrieve task performed while in a behavioral chair

Subjects were trained in a chair to reach out, grasp a piece of food, and retrieve it to their mouth. Subjects (N = 20) were trained and monitored for several weeks before injury to obtain baseline (BL) values, and weekly after injury to assess functional recovery. The picture of the monkey arm/hand reaching out is reprinted from Rosenzweig et al. (Rosenzweig et al., 2010) (A). Three separate tasks were tested for each subject to assess hand and arm function, with specific monitoring of the ability to perform a pincer grasp to retrieve the food item (opposing the index finger and thumb to pick up the food item). A grape was placed on a vertical stick at a reachable distance from the subject, and the method they used to perform the task was recorded and plotted as an ordinal scale ranging from no attempt, reaching, touching the platform (Plt4m), touching the stick, grasping the food, grasping the food with a pincer, successfully grasping the food and transferring it to their uninjured hand, or successfully grasping the food and transferring it to their mouth (B). A second task was used to assess grip strength using a handle bar attached to a spring with varying tensions. Animals also were rated on an ordinal scale ranging from no attempt, reach, touching the handle, partially pulling the handle, partially holding the handle, and being able to successfully pull and hold the handle (C). The third task was a simple retrieval of food items lying flat on the platform in front of the chair. The ordinal responses recorded were the same as for the grape on stick task; however touch food replaced the touch stick

response (D). On all tasks, the majority of subjects were able to reach out and either touch the test object or grasp the food item, with very few subjects able to perform the task to completion (i.e. transfer to mouth). Data are plotted as mean ± standard error.

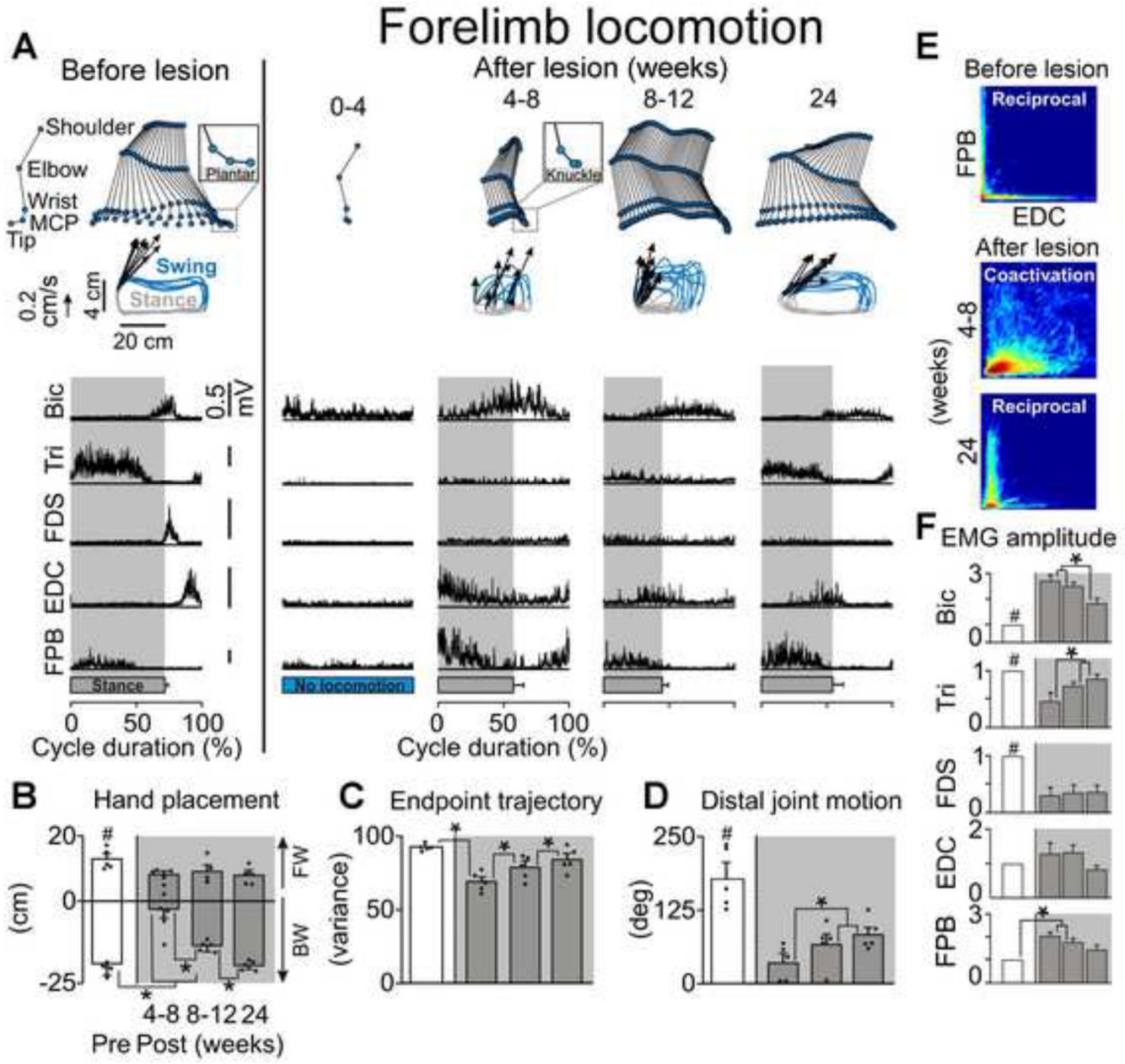
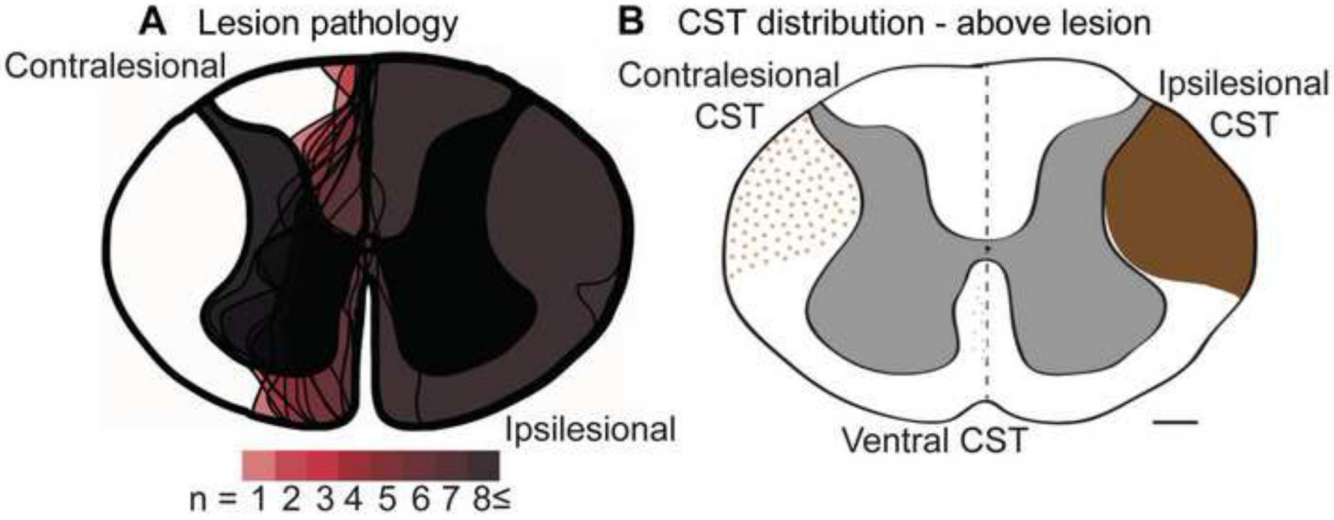


Figure 5. Partial recovery of forelimb use during locomotion after a C7 hemisection (reprinted from Rosenzweig et al., 2010)

(A) Representative stick diagram decompositions (30 msec between frames) of the right (lesioned) forelimb motion during the swing phase while stepping quadrupedally on the treadmill at 0.45 meters per second (m/s) before and at different time points post-injury. The successive (N = 10 steps), color-coded trajectories of the forelimb endpoint (metacarpo-phalangeal joint, MCP) are shown together with the intensity and direction of the forelimb endpoint velocity (arrows) at swing onset. Mean (N = 10 steps) integrated EMG activity of selected forelimb muscles is represented for the different time points. The shaded area indicates the duration of the stance phase. (B) Mean + standard error of mean (s.e.m.) values for the posterior (negative direction) and anterior (positive direction) positions reached by

the forelimb endpoint (MCP) with respect to the shoulder (horizontal distance) during each gait cycle are shown. Dots represent individual values (N = 5 monkeys). (C) Consistency of forelimb endpoint trajectory measured by principal component analysis (PCA). Mean (+s.e.m.) values of the amount of variance explained by the first principal component are reported. (D) Mean (+s.e.m.) values for the amplitude of distal joint motion measured during each gait cycle are shown. (E) Probability density distributions of normalized EMG amplitudes for the flexor pollicis brevis (FPB) and extensor digitorum communis (EDC) during treadmill stepping are shown. The L-shape pattern observed during stepping pre-lesion indicates reciprocal activation between the antagonist FPB and EDC motor pools. A D-shape pattern during stepping at 4–8 weeks post-lesion indicates increased coactivation between the FPB and EDC. (F) Mean EMG amplitudes (+s.e.m.) for forelimb EMG bursts during locomotion (N = 3 monkeys) are shown. # indicates significantly different from all other time points at $P < 0.05$; * indicates significantly different from indicated time points at $P < 0.05$.



C. Histopathology measures collected

Histology measure	Stain and/or label
Lesion	Lesion size, tissue sparing (H&E, Nissl)
Motor Neurons	Cell counts, cell size, cell type (NeuN, ChAT)
CST Axons	Anterograde labeling in cortex (BDA, 488)
Neuroinflammation	MHC II, Iba1, CD8

Figure 6. Average lesion size, corticospinal tract distribution, and histopathology measures collected in non-human primate SCI

Lesion reconstructions from 20 subjects were overlapped to highlight the average lesion distribution for unilateral cervical hemisections at spinal level 6/vertebral level 7 (C6/C7). Darker lesion areas represent lesion areas of the spinal cord observed in the largest number of subjects, with increasing color towards pink representing the variability between animals whose lesions cross the midline (A). Corticospinal tract (CST) axons were labeled in the primary motor cortex contralateral to the spinal cord injury, due to the majority of axons crossing the midline in the medullary pyramid (pyramidal decussation). Most of the labeled axons originating in the contralateral cortex are disrupted by the unilateral hemisection, disconnecting the ipsilesional CST fibers (right side) from their synaptic targets in the gray matter. A small portion of fibers do not cross the midline at the medulla and are located in either the contralesional white matter in the dorsolateral funiculus opposite from the lesion (left side; these axons are never disrupted by these unilateral hemisection), or in the left ventral funiculus (some or all of these axons are disrupted by the lesion) (B). Various measures of histopathology are collected postmortem to assess lesion pathology and tissue sparing (H&E = hematoxylin and eosin) by looking for pathological cells around the lesion epicenter, staining of motor neurons in the gray matter (NeuN = neuron-specific nuclear protein; ChAT = choline acetyltransferase) to assess neuron survival and atrophy, CST labeling in the white matter, and markers of neuroinflammation in the lesion epicenter, including infiltration of various antigen presenting cells (MHC II = major histocompatibility

complex class II), macrophages and microglia (Iba 1 = ionized calcium-binding adapter molecule 1), and CD8+ T-cells (C).

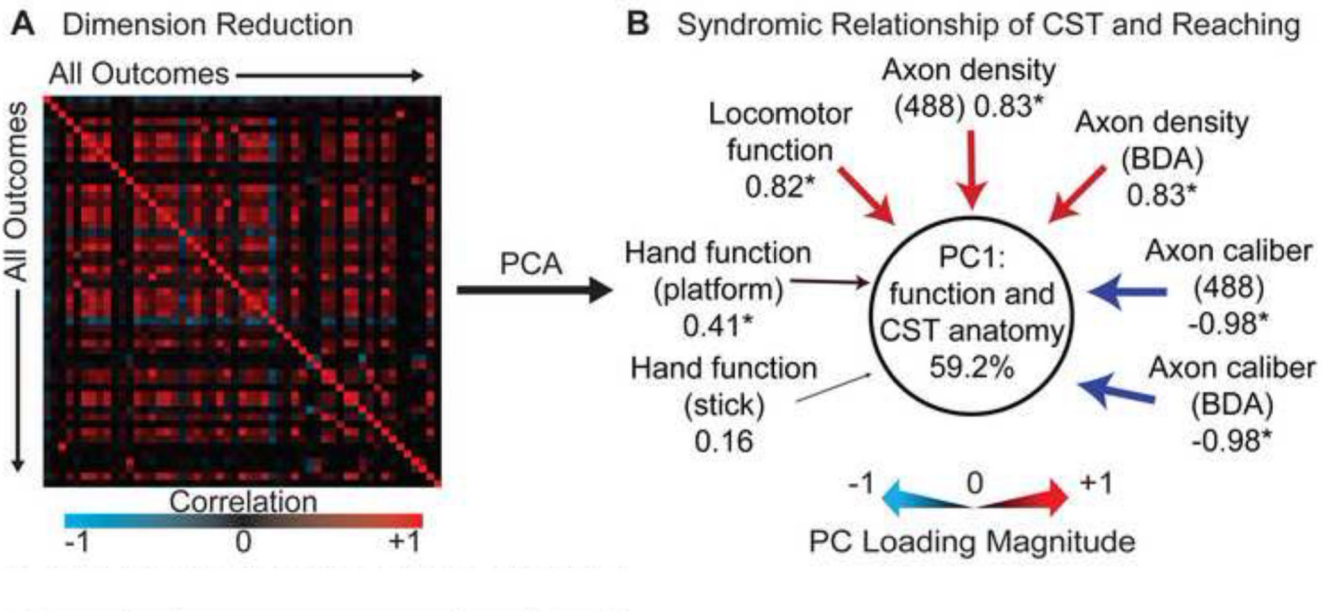


Figure 7. Relationship between anatomical plasticity and functional recovery (reprinted from Rosenzweig et al., 2010)

Functional and anatomical data were assessed using principal component analysis (PCA) following extraction from a bivariate correlation matrix of all outcomes (A). PCA revealed a multivariate relationship between CST sprouting density and functional recovery (B). The first principal component (PC1, circle) reflects a data-driven statistical clustering of the histological and functional outcome variables. Positive loading (analogous to a positive Pearson correlation) of variables onto PC1 is indicated in shades of red and negative loading (analogous to an inverse Pearson correlation) is indicated in shades of blue. The magnitude of the loading is indicated by arrow thickness and below each variable; asterisks indicate statistical significance (|loading| > 0.40). Note that axon density co-loads on PC1 with both locomotor function on a treadmill and success in recovering food rewards from a platform. PC1 accounts for 59.2% of the variability in the total outcome data used in Rosensweig et al. (2010). Work is ongoing to apply similar multivariate, data-driven approaches to the full set of outcomes collected in the CSCC database for improved precision translation of therapeutic effects.

Table 1
Overview of outcome measures collected in non-human primate SCI

Multiple high resolution measures of functional recovery are collected for every subject assessed in the California Spinal Cord Consortium (CSCC) before, during and after SCI surgery, as well as histology post-mortem. Measures collected include intra-operative physiology during SCI surgery, health monitoring, gross and fine motor skills in the exercise cage and primate chair, locomotion and kinematics on the treadmill, electrophysiological recordings from hand and arm muscles, sensorSy function, autonomic function and histopathology.

Function/Modality	Task	Variables/Regions	Comments	Reference
Physiology	Surgical Transcript Synthesis	Heart rate, blood pressure, respiratory rate	During surgery	Figure 2
Health	EMR Query	Weight	Pre and post injury	Figure 2
Bowel	EMG	External anal sphincter	Measured at baseline and 2–3 months post injury	Figure 2
Motor Assessment	Exercise Cage (gross motor skills)	General locomotion, climbing, object manipulation	Scored at baseline and 1x/weekpost injury	Figure 3
Motor Assessment	Chair (fine motor skills)	Stick, platform, handle pull	Scored at baseline and 1x/weekpost injury	Figure 4
Kinematics	Treadmill	Joints, placement, trajectory	Recorded at baseline and every 3 weeks post injury	Figure 5
Electrophysiology	EMG	Biceps, triceps, pronator. FDS, EDC. FPB	Recorded at baseline and every 3 weeks post injury	Figure 5
Histology	—	Lesion pathology, CST axonal distribution, neuroinflammation	Terminal	Figure 6
Motor Assessment	Brinkman Board	—	Scored at baseline and 1x/week post injury	Data not shown
Sensory Assessment	von Frey (electronic anesthesiometer)	Shoulder, hand, thorax, knee, foot	Scored at baseline and 2x/week post injury	Data not shown

Abbreviations: EMR = Electronic Medical Record, EMG = Electromyogram, FDS = Flexor Digitorum Superficialis, EDC = Extensor Digitorum Communis, FPB = Flexor Pollicis Brevis, CST = CorticoSpinal Tract, EAS = External Anal Sphincter.