Title

Development of a Database for Translational Spinal Cord Injury Research

Journal

Journal of Neurotrauma, 31(21)

ISSN

0897-7151

Authors

Nielson, Jessica L
Guandique, Cristian F
Liu, Aiwen W
et al.

Publication Date

2014-11-01

DOI

10.1089/neu.2014.3399

Peer reviewed

JOURNAL OF NEUROTRAUMA 31:1789–1799 (November 1, 2014)

DOI: 10.1089/neu.2014.3399

Development of a Database for Translational Spinal Cord Injury Research

Jessica L. Nielson,[1] Cristian F. Guandique,[1] Aiwen W. Liu,[1] Darlene A. Burke,[2] A. Todd Lash,[3] Rod Moseanko,[4] Stephanie Hawbecker,[4] Sarah C. Strand,[4] Sharon Zdunowski,[5] Karen-Amanda Irvine,[6] John H. Brock,[7] Yvette S. Nout-Lomas,[8] John C. Gensel,[9] Kim D. Anderson,[10] Mark R. Segal,[11] Ephron S. Rosenzweig,[7] David S.K. Magnuson,[2] Scott R. Whittemore,[2] Dana M. McTigue,[12] Phillip G. Popovich,[12] Alexander G. Rabchevsky,[9] Stephen W. Scheff,[9,13] Oswald Steward,[14] Grégoire Courtine,[15] V. Reggie Edgerton,[5] Mark H. Tuszynski,[7,16] Michael S. Beattie,[1] Jacqueline C. Bresnahan,[1] and Adam R. Ferguson[1]

Abstract

Efforts to understand spinal cord injury (SCI) and other complex neurotrauma disorders at the pre-clinical level have shown progress in recent years. However, successful translation of basic research into clinical practice has been slow, partly because of the large, heterogeneous data sets involved. In this sense, translational neurological research represents a ''big data'' problem. In an effort to expedite translation of pre-clinical knowledge into standards of patient care for SCI, we describe the development of a novel database for translational neurotrauma research known as Visualized Syndromic Information and Outcomes for Neurotrauma-SCI (VISION-SCI). We present demographics, descriptive statistics, and translational syndromic outcomes derived from our ongoing efforts to build a multi-center, multi-species pre-clinical database for SCI models. We leveraged archived surgical records, postoperative care logs, behavioral outcome measures, and histopathology from approximately 3000 mice, rats, and monkeys from pre-clinical SCI studies published between 1993 and 2013. The majority of animals in the database have measures collected for health monitoring, such as weight loss/gain, heart rate, blood pressure, postoperative monitoring of bladder function and drug/fluid administration, behavioral outcome measures of locomotion, and tissue sparing postmortem. Attempts to align these variables with currently accepted common data elements highlighted the need for more translational outcomes to be identified as clinical endpoints for therapeutic testing. Last, we use syndromic analysis to identify conserved biological mechanisms of recovery after cervical SCI between rats and monkeys that will allow for more-efficient testing of therapeutics that will need to be translated toward future clinical trials.

Key words: bioinformatics; monkeys; rodents; syndromics; translation

[1]Brain and Spinal Injury Center, Department of Neurological Surgery, University of California San Francisco, San Francisco, California.
[2]Kentucky Spinal Cord Injury Research Center, Department of Neurological Surgery, University of Louisville, Kentucky.
[3]Office of Research Office of Responsible Research Practices, Ohio State University, Columbus, Ohio.
[4]California National Primate Research Center, University of California Davis, Davis, California.
[5]Department of Integrative Biology and Physiology, University of California Los Angeles, Los Angeles, California.
[6]Department of Neurology, San Francisco VA Medical Center, University of California San Francisco, San Francisco, California.
[7]Center for Neural Repair, Department of Neurosciences, University of California San Diego, La Jolla, California.
[8]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado.
[9]Spinal Cord and Brain Injury Research Center, Chandler Medical Center, University of Kentucky, Lexington, Kentucky.
[10]Miami Project to Cure Paralysis, Department of Neurological Surgery, Miller School of Medicine, University of Miami, Miami, Florida.
[11]Center of Bioinformatics & Molecular Biostatistics, Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California.
[12]Center for Brain and Spinal Cord Repair, Department of Neuroscience, Ohio State University, Columbus, Ohio.
[13]Sanders-Brown Center on Aging, Department of Anatomy and Neurobiology, University of Kentucky, Lexington, Kentucky.
[14]Reeve-Irvine Research Center, Departments of Anatomy and Neurobiology, Neurobiology and Behavior, and Neurosurgery, University of California Irvine, Irvine, California.
[15]Center for Neuroprosthetics and Brain Mind Institute, Swiss Federal Institute of Technology, Lausanne, Switzerland.
[16]Veterans Administration Medical Center, La Jolla, California.

Introduction

Spinal cord injury (SCI) is a devastating syndrome, affecting approximately 1.3 million people in the United States and costing the nation almost $10 billion per year.[1] There has been significant progress over the past 20 years in our understanding of the pathophysiology and behavioral components of recovery after SCI using animal models[2] with the goal of providing therapies to improve the human condition. Nevertheless, few therapies have successfully made the transition into treatments for humans, and attempts to independently replicate published pre-clinical studies describing various treatment strategies have been mostly unsuccessful.[3] Similar problems have arisen in other neurotrauma fields, such as stroke[4] and traumatic brain injury (TBI),[5] suggesting that SCI is not alone in its translational challenges. As with other central nervous system diseases, SCI is complex not only in the nature of the histopathology, but also in the injury-induced changes observed in both the motor and sensory systems over the course of recovery. To understand this biobehavioral complexity, different laboratories have used various animal models (e.g., rodents, cats, dogs, pigs, and primates) and injury paradigms (e.g., transections and contusions) to mimic the deficits in human SCI. An important step forward that began around 25 years ago was the development of standardized, quantifiable, and validated measures of functional recovery, rather than the lab-specific and often nonquantitative measures used previously.[6–14] Nevertheless, a range of nonstandardized outcome measures are still used to address the full spectrum of behavioral recovery. Various histological assessments of postmortem tissue as well as *in vivo* imaging techniques have shed light on the biological mechanisms of these functional changes. However, the neurotrauma field has not yet come to grips with the way that these outcomes inter-relate to form a complete quantitative picture of the SCI syndrome.[15,16] The lack of quantitative statistical integration across pre-clinical research is a substantial barrier to translational therapeutic testing.

In this context, leveraging existing knowledge in the field offers the promise of improving computational sophistication in SCI and maximizing translational potential for both pre-clinical and clinical studies. A typical rodent SCI study produces a vast quantity of data in the form of primary endpoints (e.g., open-field locomotor scores, histopathological outcomes, and fine motor coordination) and ancillary outcomes (e.g., animal care records, bladder expression, antibiotic and pain medication history, and so on) that may be of equal importance for determining translational therapeutic potential. Each piece of data can be viewed as critical information that, when taken together, describe the full syndromic state of the experimental subject.[15,16] Here, we report on the development of the first data-rich, multi-center, translational database of SCI from large numbers of subjects to enable statistical integration of basic pre-clinical SCI data in a manner that is not possible within a single study.

Methods

Subjects

Subjects included rodents (mice and rats) and monkeys.

Raw data

Data donors offered raw data from published studies from the Ohio State University, University of Louisville, University of Kentucky, University of California Irvine, University of California San Francisco, and the California Spinal Cord Injury Consortium. Data donors provided our team with full access to raw data archives in various formats, including paper records, data flat files, analyzed images, and videos, with periodic interviews with the data donors for clarification regarding data integrity, content, and organization. Data were curated using a combination of hand data entry and data formatting before integration and analysis, organized initially into Microsoft Excel flat files and then uploaded into a MySQL database. Before integration into SQL, a star schema was created for accurate data integration based on hierarchical organization of the data. We received data from a total of 7 laboratories whose data was largely heterogeneous as a result of variability in hypotheses and outcomes tested between laboratories. Because of this heterogeneity, there is a considerable amount of potential data that can be considered ''missing.'' Complete data records in the database are from 102 separate studies, both published ($N=48$ studies; 69% of subjects) and unpublished ($N=38$ studies; 27% of subjects), and rigorous, systematic error checks are performed on the database to ensure quality control of the original data. There are 1124 variables in the database, both predictor and outcome measures that were collected between 1993 and 2013 in both cervical and thoracic injury models.

Database development

The error-checked database contains a completely annotated data dictionary for every variable that exists. A MySQL interface was developed for efficient parsing of data files after they have been formatted to the data dictionary. Python scripts are actively developed to do efficient extract/transform/load (ETL) jobs when loading data from flat files into MySQL. The scripts support exporting data files in various formats (.xls, .csv, .txt, and so on) to the MySQL database, as well as exporting those formats from MySQL for analysis in other programs. As the database grows, it will be maintained and updated, with secure backup and access.

Data set assembly

The first step in creating the database involved locating archived paper records (''file drawer'')[17] of SCI data. For ease of data entry and formatting, these archives are digitized using an automatic feed, high-speed scanner (Sharp AR-M355N) to convert paper records to PDFs that can be stored on hard drives that serve as the raw data repository. These files can then be further processed using optical character recognition software (Omnipage) to be formatted to the database. For handwritten records, manual data entry is performed through a Health Insurance Portability and Accountability Act (HIPAA)-compliant data entry portal (UCSF-REDCap) and error checked for accuracy. Additional archived records in digital formats (e.g., data disks and external hard drives) are copied into the raw data repository and formatted to be merged with the master database.

Data annotation

Each set of data has variables corresponding to both predictor (e.g., animal model and injury paradigm) and outcome measures (e.g., behavioral tests and histological confirmation of injury) that are not only unique to each animal, but also to each experiment. Therefore, an important aspect of the database curation is to annotate all the variables into a detailed data dictionary and ensure that it loads correctly into the database schema. This will facilitate parsing of variables and their corresponding data into their proper location in the MySQL database.

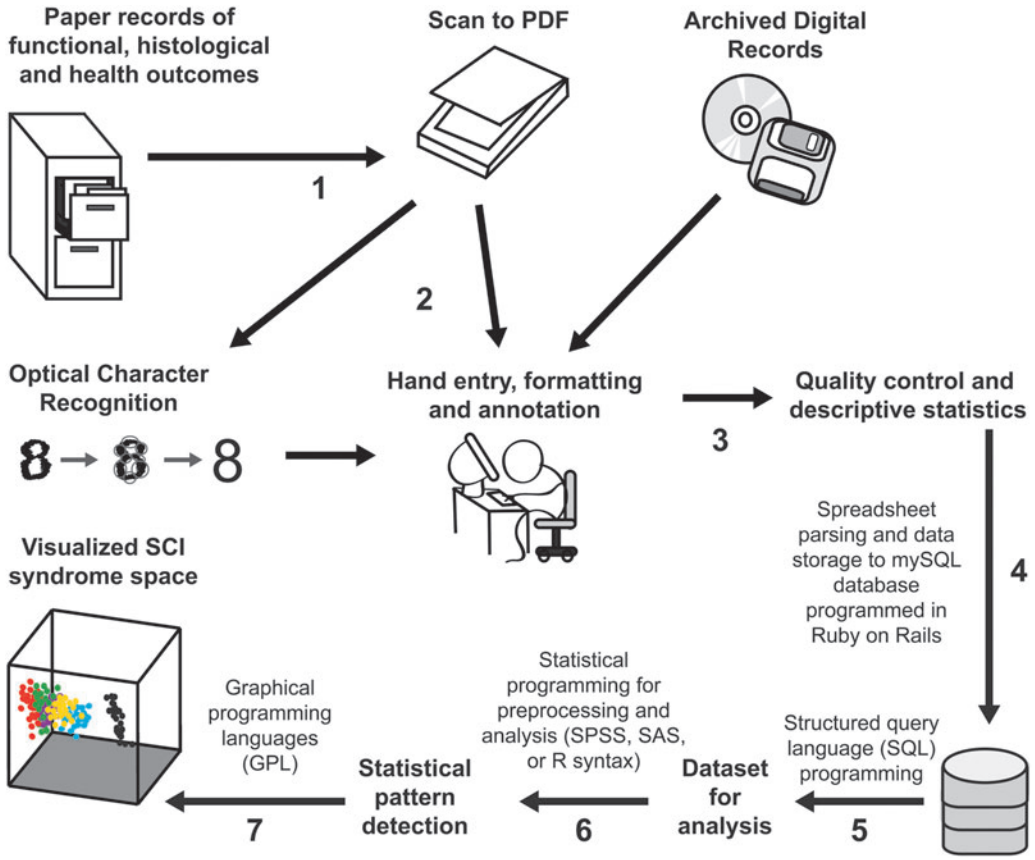

FIG. 1. Data entry, formatting, and analysis workflow. A workflow for collection, curation, formatting, and analysis of the data from our data donors is shown. We start by adding raw spinal cord injury (SCI) from the data sources using a combination of digital technologies and hand entry by data analysts with backgrounds in accounting and engineering (steps 1–3). We then use spreadsheet parsing scripts to upload data into a MySQL database running on a Linux server array programmed in Ruby on Rails by our database architect (step 4). Steps 4–7 will eventually be automated, thereby democratizing multi-variate analysis for use by a wide range of SCI researchers without needing to learn database parsing, SQL, statistical programming, or GPL. This will improve translation of diverse SCI findings from all over the world. Color image is available online at www.liebertpub.com/neu

Data quality assurance

According to the goals of our project, we have designed a series of check points in our data management process to ensure quality assurance of data entry, formatting, storage, and distribution. When new data are located, conversations and interviews with the data donors are conducted to determine the scope of each variable, as well as the completeness of the data set. Original data are never modified, but duplicated and converted into new (or existing) database variables that are coded according to the data dictionary. Data are stored in multiple secure locations, including encrypted hard drives and secure database systems, with periodic backup to off-site locations. Any distribution of the data is done so across a secure server, or locally between encrypted hard drives, to prevent unauthorized access of sensitive information.

Data quality control

Once data have been digitized and transferred from the original source to our raw data repository, the data are formatted and cross-checked with the source data to ensure no errors were introduced and that the full data set was entered. This is followed by quality control measures to ensure accuracy of the final data set. Systematic error checks are performed, where original records of the data are cross-referenced with what has been entered into the database. All errors are cataloged and analyzed to highlight problem areas with any point in the process of data management and to fine tune our methods and minimize errors with future data sets. Although the overall error in data entry and formatting was low ($<1.5\%$ of all data points), occasional data curation and entry errors were observed. Of this small percentage of errors, the most common was the classification of data as missing, when, in fact, it simply had not been formatted and entered into the master database (41%) for one reason or another (e.g., overlooked or skipped). The second-most common errors were repetitive entries of data points (39% of total errors), followed by data entry typos of either the wrong information (14% of total errors) or the entry of information that did not actually exist for that data point (5%). The remaining errors combined ($<1\%$) included issues with data curation and miscommunication about the definition of certain types of data.

Data visualization

Graphical representations of the database demographics were done in a combination of Microsoft Excel (2010), GraphPad Prism (v 5.04), the online word frequency tool, Wordle (http://www.wordle.net/), and Adobe Illustrator (CS5) and were assembled together using Adobe Photoshop (CS5).

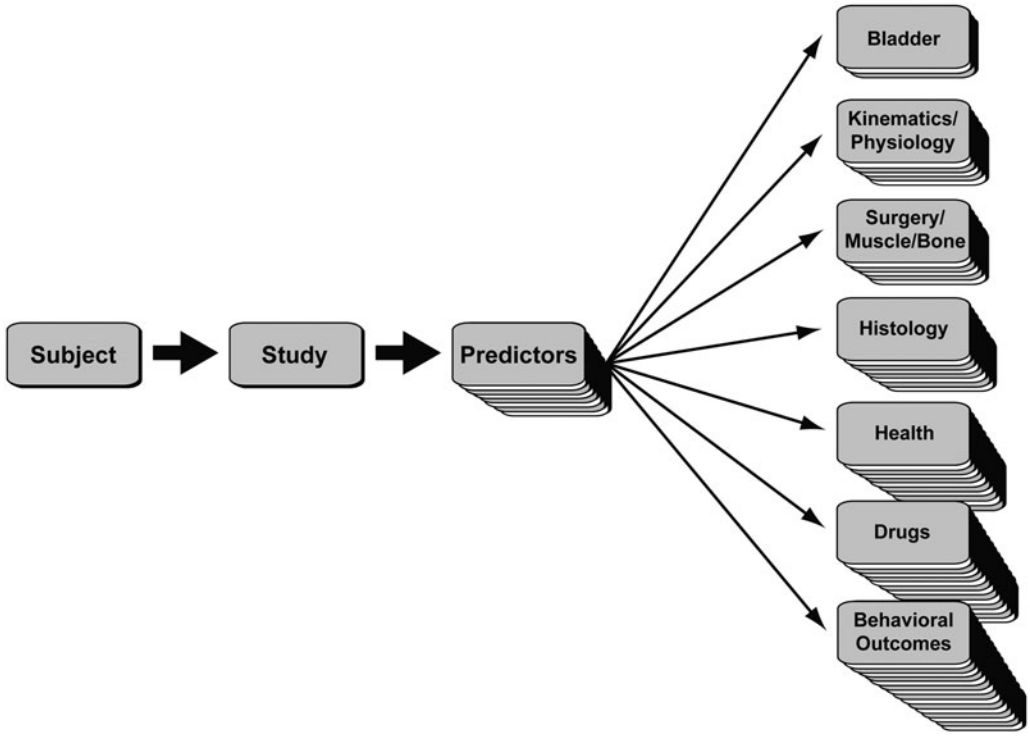

FIG. 2. Database star schema for parsing into online interface. Data in the database were organized hierarchically based on independent (predictor) and dependent (outcomes) variables within the data sets. Independent variables include data collected regarding subject identification, dates, experimental details, and injury biomechanics. Most, if not all, subjects have some degree of these independent variables that uniquely identify them during specific dates and times postinjury for a given laboratory and experimental paradigm. Dependent outcome measures vary between laboratories in this heterogeneous data set; however, they can be grouped into seven major categories based on similarities of measurements. These include measures of bladder function and urine content, kinematics and physiology, surgical details and measures of bone density and muscle mass, histopathology, health, experimental and therapeutic drugs, and various behavioral outcome measures. This is a simplified version of the variables in the database and their organization. Within each general measure, such as behavioral outcomes, there are subvariables for outcomes, including the BBB locomotor scale, Catwalk analysis, Exercise cage, and many others, that will not be discussed in detail here, and are difficult to represent visually in a two-dimensional space (see Supplementary Fig. 1 for variable details) (see online supplementary material at http://www.liebertpub.com). This organization is maintained for all data entered into the database for parsing scripts to be used for easy integration into the MySQL database as additional data continues to be added.

Prevalence of variables in the database

Quantitative word clouds were generated to show the distribution of either independent or dependent variables collected for all subjects from published studies. Word size reflects the prevalence of each variable in the database. By identifying common variables used across heterogeneous studies, we have the opportunity to identify consistent SCI metrics that may facilitate translation. Toward that end, we aligned prevalent pre-clinical variables with clinical SCI common data elements (CDEs) that have been published by the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS).[20] One of the figures highlights prevalent preclinical metrics in the database that, on face value, correspond to clinical CDEs. The NINDS SCI CDE working group has classified variables as core, supplemental, or emerging/exploratory. Core variables reflect critical information (e.g., gender, age, treatment site, and cause of injury), which all clinical trials should collect to maximize comparison across studies. Supplemental variables are those variables that provide important additional information that could be useful for describing patients (e.g., cardiovascular and bladder/bowel function). Emerging variables reflect novel metrics that are not fully standardized, but may provide important information about patient populations (e.g., GRASSP[18,19]). Analysis of the pre-clinical data suggests that most of the prevalent variables in the database correspond to supplemental and emerging clinical CDEs, with a small number of pre-clinical variables corresponding to core clinical CDEs. Additionally, there is a lack of clinical outcome measures that line up with measures collected in pre-clinical studies, for which potential translation from pre-clinical models would benefit. That is not to say that clinical outcome measures that could be potential endpoint metrics for clinical trials do not exist, but they have not been incorporated into the approved CDEs for SCI.[18–24]

Multi-variate analysis to test database functionality

To test the utility of the database for extracting translational features of SCI across heterogeneous studies, we performed unsupervised, data-driven multi-variate pattern detection on data from two previously published studies in the database for both rats[15] and monkeys.[9,25] To the extent that SCI reflects a syndrome, the large-scale and heterogeneous nature of the database should allow detection of coherent subfeatures that are reflected as patterns within sets of related variables. Once identified, such variable sets may be applied as outcome sets for experimental therapeutics at the syndrome level that are conserved between species.

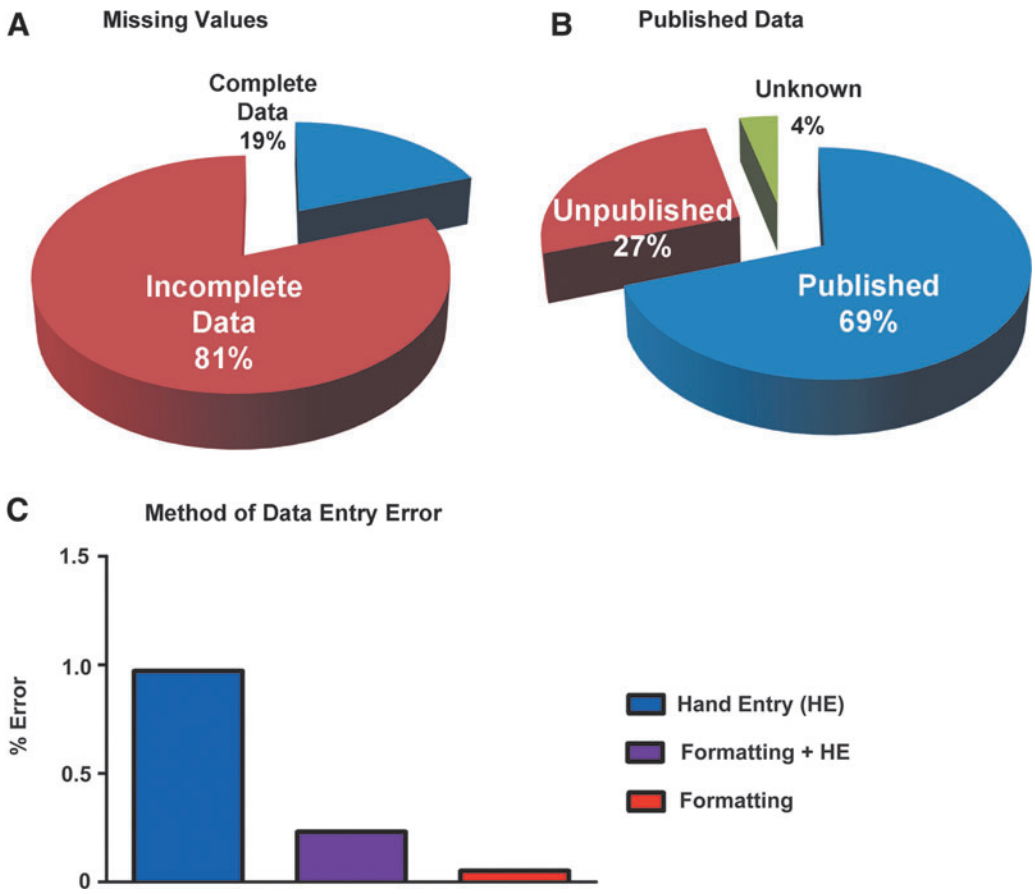

FIG. 3. Database quality control. Because of the heterogeneity and structure of the database, there are many variables that do not overlap between research centers and studies. Therefore, there are a lot of ''missing'' data in the database for measures that were either never collected or have been archived in paper records and not digitized and analyzed as a functional outcome measure (e.g., postoperative care sheets). There are methods, such as missing values analysis and detailed record archiving, that can be done to fill in these missing values. However, at the current stage of the database development, only 19% of these missing data have been entered (**A,** blue pie). Within these complete data points, data from 69% of the animal subjects ($n = 1870$) contributed data to studies that were published (**B,** blue pie; 47% of studies). Subjects (B, red pie; 27% of subjects) from unpublished studies (37% of studies) included either studies that did not work (e.g., file-drawer data[17]) or were collected during training or suboptimal conditions and not considered suitable for publication. Because of concerns with accuracy of data collection and experimental methods, only data from published studies were included in the demographics and multi-variate analyses for the remainder of present study. Additionally, in order to ensure that all data that are entered into the database are accurate and error free, periodic error checks are performed on the database in comparison to the original data to assess the data entry error rate (**C**). Various types of data entry methods were used to create the database, including hand entry or data formatting from flat files we received from the data donors. The least amount of errors were noted when only formatting the data was necessary (0.05%), with an increasing percentage of errors when combined with hand entry (0.23%) or with hand entry alone (0.97%). However, the overall error rate for data entry is very low for the nearly 60 million data points that have already been entered. Color image is available online at www.liebertpub.com/neu

A subselection of the database containing rat and monkey cervical SCI was created to run principal component analysis (PCA),[26] a type of exploratory factor analysis that allows for dimension reduction in large data sets to create new multi-variables (principal components; PCs) determined by the variance in the data set. In the context of SCI, PCs represent syndromic measures of outcome as detected by multiple outcome variables simultaneously (e.g., sensorimotor and autonomic function, histopathology, and so on). To evaluate translational potential of PCs, individual outcome measures were standardized using z-scores and combined into new translational variables (e.g., Object Manipulation). Data were binned across time for syndromic analysis. PCA was performed in SPSS (v.19) to extract a correlation matrix of the standardized variables, PC loadings for the outcomes onto each PC, and individual PC scores for post-hoc analysis of both species and injury predictors.

Bar graphs of the PC scores for each subject were plotted and analyzed to test the influence of predictor variables on these syndromic clusters and analyzed for significance with Student's t-tests ($p < 0.01$) or analysis of variance with Tukey's post-hoc correction (p, significant, at alpha < 0.05).

Results

We created a scalable, multi-species, multi-center database, currently populated with data from SCI models in rodents and monkeys, with plans to incorporate clinical data for SCI. The database was created by archiving data records and integrating them into a bioinformatics framework for statistical analysis (Fig. 1) and organized into a star schema for scalability (Fig. 2). Quality control of data entered into the database was maintained at a rate of less than 1% error (Fig. 3).

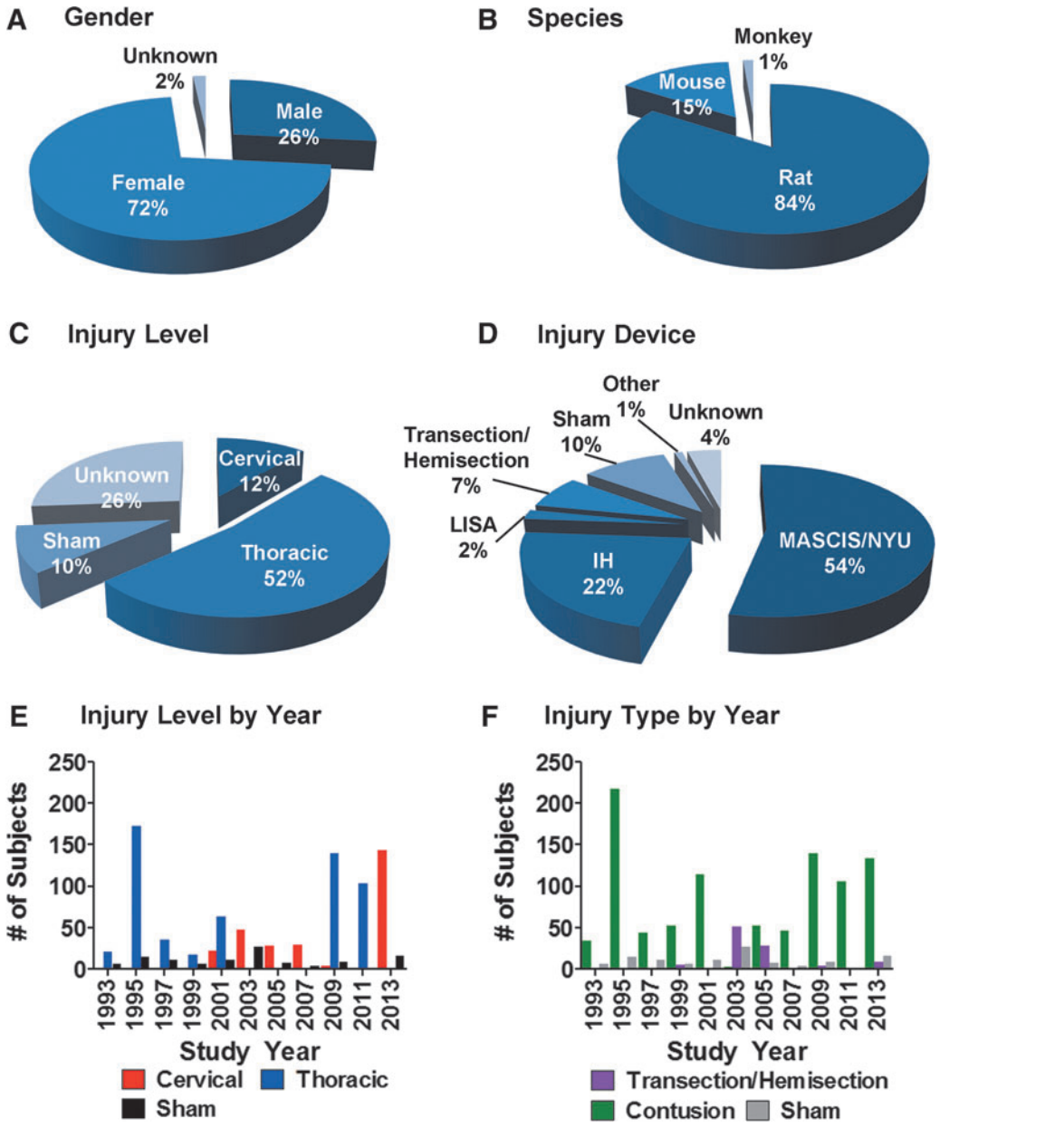

FIG. 4. Database demographics of published, pre-clinical spinal cord injury (SCI) models between 1993 and 2013. From the subjects that were involved in published studies, we have determined general demographics regarding the animal gender (**A**), species (**B**), and injury paradigms regarding spinal level (**C**) and injury device (**D**) and how these patterns have changed over time (**E** and **F**). These patterns do not necessarily reflect the status of the entire pre-clinical literature, but rather of the specific selection of investigators and laboratories that have donated their data to this database. From this, we have determined that most of the animals are female (72%; A) rats (84%; B) receiving thoracic-level injuries (52%; C) using the New York University/Multicenter Animal Spinal Cord Injury Study (NYU/MASCIS) contusion device (54%; D). There are a small number of male subjects in the database (26%; A), as well as other species, including mice (15%) and monkeys (1%; B). Additionally, there are cervical-level injuries in the data set (12%); however, a modest proportion of the subjects (26%) do not have specific details in their records as to their injury level (C). Further, various other injury devices are used, including Infinite Horizons (IH) contusions (22%), hemisection/transections (7%), and shams (10%; D). By looking at the study year in the database, we were able to show, based on the data we have collected thus far from the data donors, that the initial level of SCI in animal models was at the thoracic level (blue bars), with a wave of cervical injuries emerging in 2001 (red bars; E), and that the majority of the injuries over time have been contusions (green bars), with a modest amount of transection/hemisection injuries (purple bars) scattered throughout the timespan of the data collected (F). LISA, Louisville Injury System Apparatus. Color image is available online at www.liebertpub.com/neu

Database demographics

For the purposes of generating a snapshot of the database contents, we primarily assessed data from published studies (69% of the subjects; Fig. 3B). Descriptive statistics of the previously published studies were obtained by collapsing the database across time to assess which variables existed for each subject. Because of the large heterogeneity in the database regarding variables collected, variables were binned into broad categories based on conceptual similarities (Fig. 2 and Supplementary Fig. 1) (see online

FIG. 5. Variable distribution within the database based on word frequency. The word frequency website, Wordle, was used to generate word clouds of the quantified variable categories collected for each subject in the database (published studies only) for both the independent (predictor) variables (**A**) and the dependent (outcome) variables (**B**). Word height is a reflection of the number of subjects that have each variable collected, and the subject number scale bar in both (A) (I = 935 subjects) and (B) (I = 444 subjects) represents the height of the word to the respective number of subjects with that variable collected in the database. (A) Nearly all the subjects from published studies have information regarding subject identification, study details, laboratory information, time points of data collection, and injury paradigm details and biomechanics. (B) There is much more variability in word size for the outcome measures collected, with the most commonly collected outcomes being measurements taken during surgery (e.g., body temperature, heart rate, blood pressure, blood gases, and anesthetic given), postoperative care monitoring (e.g., weight, bladder function, and therapeutics), and functional outcome measures of locomotion (BBB) and histology (tissue sparing). A detailed list of each variable in the data set is outlined in the schema in Supplementary Figure 1.(see online supplementary material at http://www.liebertpub.com). BBB, Basso, Beattie, Bresnahan locomotor rating scale; BMS, Basso Mouse Scale. Color image is available online at www.liebertpub.com/neu

A Common Preclinical Variables

Preclinical Variable	% of Subjects	% of Labs
Subject	100	100
Laboratory	100	100
Study	100	100
Time	99.9	100
Injury	96.1	100
TissueSparing	23.4	85.7
Date	84.6	71.4
CellLabel	14.7	57.1
BladderFunction	47.2	42.9
BBB	38.1	42.9

B Matched Clinical Common Data Elements (CDE)

Clinical CDE Name	CDE Variable Name	Classification
Gender type	GenderTyp	Core
Subject identifier number	SubjectIDNum	Core
Hospital discharge destination type	HospDischrgDestTyp	Core
Site identifier number	SiteIDNum	Core
None	***None***	***None***
Data collected date and time	DataCollDateTime	Supplemental
Spinal Cord Injury Etiology Type	SpnalCrdInjEtlgyTyp	Core
SCI Classification sensory neurological level left result	SCIClssSensNeuroLvlLftReslt	Core
SCI Classification sensory neurological level right result	SCIClssSensNeuroLvlRtReslt	Core
SCI Classification motor neurological level left result	SCIClssMtrNeuroLvlLftReslt	Supplemental
SCI Classification motor neurological level right result	SCIClssMtrNeuroLvlRteReslt	Supplemental
None	***None***	***None***
Birth date	BirthDate	Core
Injury date time	InjDateTime	Core
None	***None***	***None***
Bladder function post void volume value	BldrFuncPostVoidVolVal	Supplemental
Bladder function detrusor leak point pressure value	BldrFuncDtrsrLekPntPressrVal	Supplemental
Urinary incontinence past three months frequency	UrinIncntPstThreeMoFreq	Supplemental
Bladder function bladder capacity value	BldrFuncBldrCapacityVal	Supplemental
None	***None***	***None***

FIG. 6. Candidate pre-clinical common data elements (CDEs) for translation to clinical CDEs. Frequency of each variable collected in the database is represented by % of subject or % of labs. By looking at the clinical CDEs that have been defined by the National Institutes of Health for spinal cord injury (SCI), we have lined up the top pre-clinical measures in the database with their clinical CDE counterpart that could potentially be a translational endpoint when considering moving forward with clinical trials. Although there is a moderate amount of top measures that overlap, quite a few preclinical metrics do not have a standardized CDE at the clinical level (right columns, none). See Supplementary Figure 2 for an extended list of matched pre-clinical and clinical variables. (See online supplementary material at http://www.liebertpub.com/neu).

supplementary material at http://www.liebertpub.com). The majority of the animals in the database are female (72%; Fig. 4A) rats (84%; Fig. 4B) with thoracic-level (52%; Fig. 4C) contusions (54% New York University/Multicenter Animal Spinal Cord Injury Study [NYU/MASCIS] and 22% Infinite Horizons [IH]; Fig. 4D). The database also contains mice (15%) and monkeys (1%; Fig. 4B) as pre-clinical models (Fig. 4A). Injury levels in the database include 52% thoracic, 12% cervical, 10% sham, and 26% unknown (Fig. 4C), induced by either contusions with an NYU/MASCIS (54%), IH (22%), or Louisville Injury System Apparatus (LISA; 2%) device, or transection/hemisection injuries (7%). Additionally, 10% of the subjects were sham controls, and 4% and 1% were unknown or other types of injuries, respectively (Fig. 4D). Plotting the number of subjects over time represented by each injury level (Fig. 4E) or type (Fig. 4F) reveals that before 2001, studies in the database were typically sham-controlled thoracic contusion studies, with an emergence of transection and cervical injuries starting at the turn of the 21st century.

Variable distribution

Word frequency clouds (Fig. 5) were created in Wordle™ to understand the most common data collected in the sample of studies in the current database. Word clouds are based on quantitative measurements of the distribution of each variable by subject, for both independent predictor variables (Fig. 5A) and dependent outcome measures (Fig. 5B). Word size is proportional to the number of subjects associated with each variable. For example, all animals have some information about the subject, whether it is identifying information, gender, or strain. Therefore, the word height in Figure 5A for ''subject'' represents all the animals from published studies in the database.

In order to determine outcomes and the predictor variables collected by each laboratory, data were sorted by variable frequency. Of over 1100 variables, only approximately 9% were collected by all laboratories (Fig. 6A). These common variables include descriptive data for experimental subjects, such as species and gender (100% of subjects), laboratory/research center (100% of subjects), study details (100% of subjects), measurements of time (99.9% of subjects), injury biomechanics and characteristics (96.1% of subjects), and measurements of weight (85.3% of subjects; Fig. 6A). These top pre-clinical variables match up with core and supplemental CDEs recommended by NIH/NINDS working groups for clinical SCI data collection (Fig. 6B).[16] Tissue-sparing measurements were collected by 6 of the 7 labs (85.7% and 23.4% of subjects) and 5 out of 7 labs (71.4% and 84.6% of subjects) have dates listed in their data sets. More than half of the labs (4 of 7; 57.1%) collected information about antibiotics (62.9% of subjects), cell labeling (14.7% of subjects), and lesion size (12.2% of subjects). Less than half of the labs (3 of 7; 42.9%) collected information about anesthetic given during surgery (68.4% of subjects), fluids given during postoperative care (49.3% of subjects), urine volume and quality (48.1% of subjects), bladder function (47.2% of subjects), Basso, Beattie, Bresnahan (BBB) locomotor scale (38.1%), and analgesics given postoperatively (12%). Data from surgical notes (28.6% of subjects), volumes of supplemental nutrients (15.5% of subjects), and Basso Mouse Scale (BMS) locomotor scale (11.1% of subjects) were collected by 2 the 7 labs (28.6%). There were many other variables that were only collected by 1 lab (14.3%), and for the purposes of presentation, we have only shown those variables that are represented by more than 10% of the subjects in the database and include body temperature (39.8% of subjects), blood gases (21% of subjects), blood pressure (20.1% of subjects), heart rate (19.1%), and grip strength (11.8%; Fig. 6A).

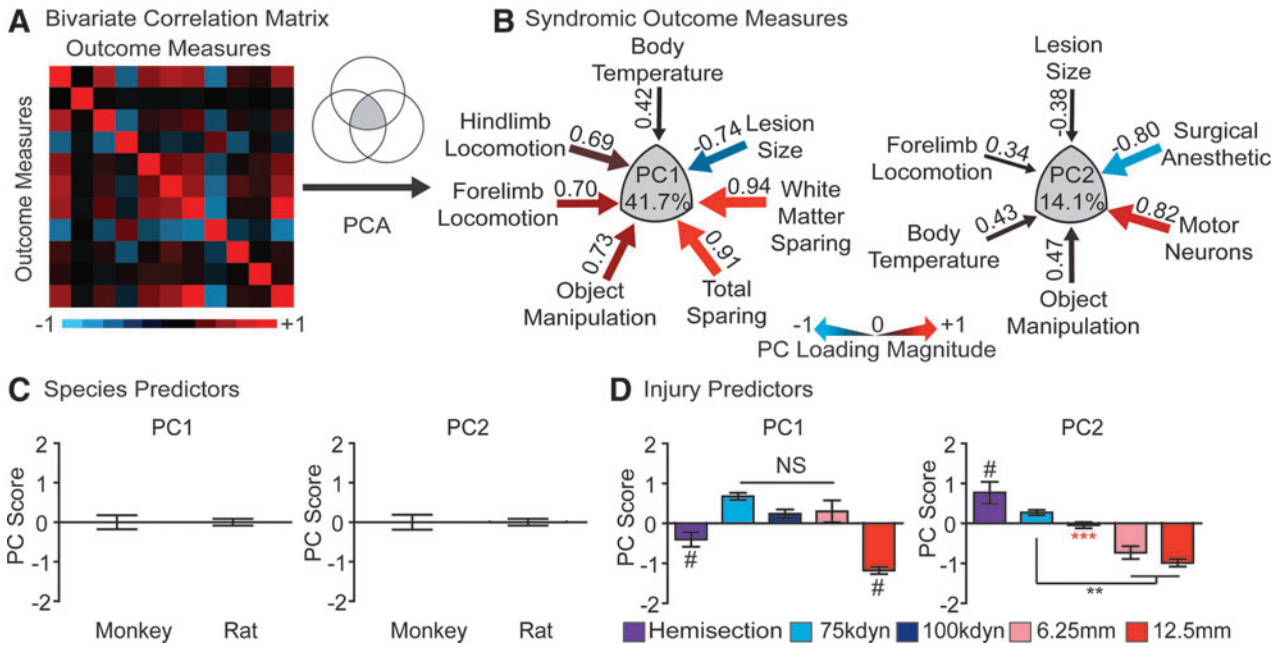

FIG. 7. Syndromic analysis of candidate translational metrics between rats and monkeys. In an attempt to identify outcome measures that reflect conserved biological measures of functional recovery between species, we performed a principal components analysis (PCA), a type of exploratory factor analysis, on a subselection of the database for rats and monkeys that received cervical spinal cord injury (SCI) and had similar outcome measures collected. Variables with similar outcome measurement properties (e.g., lesion size, object manipulation, and locomotion) were combined into a data set that was analyzed for syndromic patterns (principal components; PCs) for this multi-species data set. PCA organizes the data into a bivariate correlation matrix, which shows the direct correlation of all outcomes analyzed (**A**), where all outcomes are compared to all other outcomes, including themselves. These correlations range from negative (blue, -1) to positive (red, $+1$), where a positive correlation is always observed when an outcome is correlated to itself (red outlined diagonal). A linear transformation is performed to identify measures that covary together to give us a set of variables that make up the syndromic space of SCI (gray intersection of the variables analyzed; A). From this specific data set from rats and monkeys with cervical injuries, we identified two syndromic measures that accounted for over 50% of the total variance in the data set (**B**). PC1 accounts for 41.7% of the variance and is explained by measures of tissue sparing, lesion size, hindlimb and forelimb locomotion, object manipulation, and body temperature. PC2 accounts for 14.1% of the variance and is an orthogonal (independent) relationship mostly explained by the relationship between motor neuron survival, surgical anesthetic, forelimb function, and body temperature. After PCA, each subject is given a syndrome score (PC score) that can be plotted to test specific hypotheses regarding predictors of this newly identified translational syndromic space, where we can assess the effect of species (**C**) and injury severity (**D**) on the syndrome. We have shown that the translational syndrome measure we have identified is a result of injury severity, and not species, suggesting that these measures may be conserved between species and may be valuable candidate metrics to use to assess emerging therapies being translated between rats and monkeys. Data plotted as mean ± standard error of the mean (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$; $^{\#}$group $p < 0.05$, compared to all other groups; Student's *t*-test (C) and one-way analysis of variance (D).

A proof-of-concept test of database utility was performed using exploratory factor analysis (PCA) to reveal syndrome level patterns after cervical injuries in both rats and monkeys. Outcomes that shared functionality were grouped together into candidate translational outcomes, normalized for species difference in scalar properties, and tested for multi-variate syndromic patterns (Fig. 7).[15,16] There were two translational PCs for this combined model (Fig. 7B). PC1 accounts for 41.7% of the variance in the data set and is explained by the positive correlation of tissue sparing, object manipulation, locomotion, and body temperature during surgery, which are inversely correlated with lesion size. PC1 is not significantly predicted by species (Fig. 7C), however is predicted by gradations of spinal cord injury (Fig. 7D). Even though the monkeys only received hemisections, combined with rats with graded cervical SCI, hemisections and 12.5-mm New York University (NYU) injuries performed significantly worse on PC1, compared to the other injury severities. PC2 accounts for 14.1% of the variance in the data set and is explained by the positive correlation of spared motor neurons, object manipulation, body temperature, and forelimb locomotion, which are inversely correlated with both lesion size and the amount of anesthetic administered during surgery (Fig. 7B). This PC was also not significantly predicted by species (Fig. 7C), however was predicted by injury severity, with hemisections performing significantly better on this syndromic outcome (Fig. 7D), revealing a true set of multi-variate outcomes for cross-species translation.

In summary, multi-variate analysis identified nine candidate translational outcome measures that, when analyzed as a multi-dimensional set, reveal conserved biological mechanisms between rats and monkeys after cervical SCI. These conserved multi-variate biological features provide an outcome set for translational comparisons across models.

Discussion

The current article introduces VISION-SCI, a new pre-clinical database of raw multi-center data from pre-clinical spinal cord injury models. The creation of this database answers the recent call from the neurological disease research community to standardize

study design and create transparency of pre-clinical studies aimed to mirror clinical trials.[27] This transparency will help facilitate independent replications, which have been mostly unsuccessful with current methods,[3] and identify mitigating, personalized factors that dictate therapeutic success. Most important, this database provides a computational framework to improve translation of emerging therapeutic candidates from bench to bedside.[28]

From the creation of this database, we have been able to derive patterns in pre-clinical models of a subpopulation of the preclinical SCI research community over the past 20 years. We have identified that the prominent injury paradigms used during this time have mostly been thoracic-level contusive injuries in female rats. During this 20-year period, the field used predominantly thoracic-level injuries, with an emergence of cervical-level models at the turn of the 21st century, perhaps in response to recent calls from patients and advocacy groups for the SCI research community to better understand and treat injuries affecting hand and arm function.[29] Additionally, we have identified several measures that, at face value, align with measures being collected clinically, opening the possibility to standardize pre-clinical models toward the clinical standards set by the NINDS CDE working groups.[30] VISION-SCI also provides an opportunity to test emerging reporting standards, such as the Minimal Information About Spinal Cord Injury (MIASCI) standard[31] and the robustness of multiple pre-clinical trials being considered for translation to clinical trials.[3] Other complimentary efforts in the field are also attempting to increase the robustness of pre-clinical drug trials. The Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies performs meta-analyses of published animal studies to identify problem areas in the current publishing and reporting of study design and treatment efficacy.[34] Additionally, analysis of VISION-SCI provides data that supports earlier anecdotal arguments that SCI laboratories tend to use female rats, as opposed to male rats, suggesting a misalignment with the clinical population, which is predominately male.[1] This may be because of the fact that male animal models of thoracic-level SCI are significantly more difficult to care for postoperatively when it comes to bladder impairment than females (Supplementary Fig. 3) (see online supplementary material at http://www.liebertpub.com). Studies do exist in the database for both genders, which may help facilitate future analyses regarding metrics that may be gender specific. It is noteworthy that bladder issues and sex dependency seem less problematic for cervical injury models.[32] Finally, in an effort to promote translation between species, we have used the information in the current database to identify translational metrics between rats and monkeys in cervical SCI, with the goal of aligning outcomes with several metrics currently being used in humans.[18,19,22,24]

VISION-SCI is designed for consistency with the goals of the NINDS CDE working groups for neurological diseases.[30] To our knowledge, this represents the first pre-clinical study that has attempted to align pre-clinical and clinical CDE outcomes for neurotrauma, setting the stage for determining translational predictor and outcome variables as part of ongoing pre-clinical standardization efforts. VISION-SCI is a living repository of knowledge that can grow with additional data contributions from the field and can be queried for syndromic patterns to guide future studies. In time, our plan is to make the database openly available to the research and clinical community and provide a mechanism for outside contributions, similar to the IMPACT database for TBI.[33] We are currently working with experts in information technology and bioinformatics, including the Neuroscience Information Framework,[35] to make VISION-SCI available online. Our hope is for VISION-SCI to be a publically available database, both for contributions from the community, and data mining from interested researchers. Our goal is for this database to be a queriable, user-friendly, committee-regulated system, similar to standards set by other databases such as IMPACT (http://www.tbi-impact.org/?p=impact/db)[33] and FITBIR (https://fitbir.nih.gov/) that can be used not only to determine syndromic clusters of specific injury paradigms and their appropriate outcome measures, but also to help investigators fine tune future studies based on existing information. With the formation of a pre-clinical SCI committee, this will facilitate assessment of the integrity of new data coming into the database and provide a review process for research proposals for those wishing to query the database. With additional contributions from other groups, this database will help identify conserved syndrome clusters between species that can be used as a translational bridge to move promising therapies into standards of care for people living with neurotrauma.

Acknowledgments

The authors thank, in alphabetical order, Rochelle Deibert, Crystal Forrider, Jenny Haefeli, J. Russell Huie, Amity Lin, Brandon Miller, Vladimir Muraru, Ellen Stück, Amy Tovar, Montina J. Van Meter, and Sergio Veiga for their technical assistance and fruitful discussions regarding database development. This work was supported by NIH grants R01NS067092 (to A.R.F.) and F32NS079030 (to J.L.N.); Craig H. Neilsen Foundation 224308, and Wings for Life WFLUS008/12. Primary data collection was supported by NIH grants R01NS038079, R01NS042291, R01NS031193, and R01NS032000; NYS CoRE CO19772, R21 AG032518, R01 NS052292, P01 RR15576, P30 GM103507, R01 NS073584, R01 NS045734, R01 NS089324, R01 NS059776, P30-NS045758, P01NS010165, NIH-N01-NS-3-2353, and NIH-NO1-NS-3-2354 contract (Facilities of Research Excellence in Spinal Cord Injury), the Veterans Administration, the Kentucky Spinal Cord and Head Injury Research Trust, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, Research for Cure, the Roman Reed Spinal Cord Injury Research Fund of the State of California, the Craig H. Neilsen Foundation, the American Paralysis Association, Paralyzed Veterans of America, and the Christopher and Dana Reeve Foundation.

Author Disclosure Statement

No competing financial interests exist.

References

1. Christopher and Dana Reeve Foundation (CDRF-PRC). (2009). Paralysis Resource Center: paralysis facts & figures. Available at: http://www.christopherreeve.org/site/c.mtKZKgMWKwG/b.5184189/k.5587/Paralysis_Facts__Figures.htm. Accessed April 14, 2014.
2. Fouad, K., and Tetzlaff, W. (2012). Rehabilitative training and plasticity following spinal cord injury. Exp. Neurol. 235, 91–99.
3. Steward, O., Popovich, P.G., Dietrich, W.D., and Kleitman, N. (2012). Replication and reproducibility in spinal cord injury research. Exp. Neurol. 233, 597–605.
4. Cook, D.J., and Tymianski, M. (2011). Translating promising preclinical neuroprotective therapies to human stroke trials. Expert Rev. Cardiovasc. Ther. 9, 433–449.
5. Loane, D.J., and Faden, A.I. (2010). Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. Trends Pharmacol. Sci. 31, 596–604.
6. Basso, D.M., Beattie, M.S. and Bresnahan, J.C. (1995). A sensitive and reliable locomotor rating scale for open field testing in rats. J. Neurotrauma 12, 1–21.

7. Basso, D.M., Fisher, L.C., Anderson, A.J., Jakeman, L.B., McTigue, D.M., and Popovich, P.G. (2006). Basso Mouse Scale for locomotion detects differences in recovery after spinal cord injury in five common mouse strains. J. Neurotrauma 23, 635–659.
8. Irvine, K.A., Ferguson, A.R., Mitchell, K.D., Beattie, S.B., Beattie, M.S., and Bresnahan, J.C. (2010). A novel method for assessing proximal and distal forelimb function in the rat: the Irvine, Beatties and Bresnahan (IBB) forelimb scale. J. Vis. Exp. Dec 16;(46). pii: 2246. doi: 10.3791/2246.
9. Nout, Y.S., Ferguson, A.R., Strand, S.C., Moseanko, R., Hawbecker, S., Zdunowski, S., Nielson, J.L., Roy, R.R., Zhong, H., Rosenzweig, E.S., Brock, J.H., Courtine, G., Edgerton, V.R., Tuszynski, M.H., Beattie, M.S., and Bresnahan, J.C. (2012). Methods for functional assessment after C7 spinal cord hemisection in the rhesus monkey. Neurorehabil. Neural Repair 26, 556–569.
10. Rivlin, A.S. and Tator, C.H. (1977). Objective clinical assessment of motor function after experimental spinal cord injury in the rat. J. Neurosurg. 47, 577–581.
11. Tarlov, I.M. (1954). Spinal cord compression studies. III. Time limits for recovery after gradual compression in dogs. A. M. A. Arch. Neurol. Psychiatry 71, 588–597.
12. Tarlov, I.M., and Klinger, H. (1954). Spinal cord compression studies. II. Time limits for recovery after acute compression in dogs. A. M. A. Arch. Neurol. Psychiatry 71, 271–290.
13. Tator, C.H. (1998). Biology of neurological recovery and functional restoration after spinal cord injury. Neurosurgery 42, 696–707; discussion, 707–698.
14. Wrathall, J.R., Pettegrew, R.K., and Harvey, F. (1985). Spinal cord contusion in the rat: production of graded, reproducible, injury groups. Exp. Neurol. 88, 108–122.
15. Ferguson, A.R., Irvine, K.A., Gensel, J.C., Nielson, J.L., Lin, A., Ly, J., Segal, M.R., Ratan, R.R., Bresnahan, J.C., and Beattie, M.S. (2013). Derivation of multivariate syndromic outcome metrics for consistent testing across multiple models of cervical spinal cord injury in rats. PloS One 8, e59712.
16. Ferguson, A.R., Stuck, E.D., and Nielson, J.L. (2011). Syndromics: a bioinformatics approach for neurotrauma research. Transl. Stroke Res. 2, 438–454.
17. Scargle, J.D. (2000). Publication bias: the ''file-drawer'' problem in scientific inference. J. Sci. Explor. 14, 16.
18. Kalsi-Ryan, S., Beaton, D., Curt, A., Duff, S., Popovic, M., Rudhe, C., Fehlings, M., and Verrier, M. (2012). The Graded Redefined Assessment of Strength Sensibility and Prehension: reliability and validity. J. Neurotrauma 29, 905–914.
19. Kalsi-Ryan, S., Curt, A., Fehlings, M.G., and Verrier, M.C. (2009). Assessment of the hand in tetraplegia using the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): impairment versus function. Top Spinal Cord Inj. Rehabil. 14, 34–46.
20. Anderson, K.D., Acuff, M.E., Arp, B.G., Backus, D., Chun, S., Fisher, K., Fjerstad, J.E., Graves, D.E., Greenwald, K., Groah, S.L., Harkema, S.J., Horton, J.A., III, Huang, M.N., Jennings, M., Kelley, K.S., Kessler, S.M., Kirshblum, S., Koltenuk, S., Linke, M., Ljungberg, I., Nagy, J., Nicolini, L., Roach, M.J., Salles, S., Scelza, W.M., Read, M.S., Reeves, R.K., Scott, M.D., Tansey, K.E., Theis, J.L., Tolfo, C.Z., Whitney, M., Williams, C.D., Winter, C.M., and Zanca, J.M. (2011). United States (US) multi-center study to assess the validity and reliability of the Spinal Cord Independence Measure (SCIM III). Spinal Cord 49, 880–885.
21. Catz, A., Itzkovich, M., Agranov, E., Ring, H., and Tamir, A. (1997). SCIM–spinal cord independence measure: a new disability scale for patients with spinal cord lesions. Spinal Cord 35, 850–856.
22. Dittuno, P.L., and Ditunno, J.F., Jr. (2001). Walking index for spinal cord injury (WISCI II): scale revision. Spinal Cord 39, 654–656.
23. Ditunno, J.F., Jr., Barbeau, H., Dobkin, B.H., Elashoff, R., Harkema, S., Marino, R.J., Hauck, W.W., Apple, D., Basso, D.M., Behrman, A., Deforge, D., Fugate, L., Saulino, M., Scott, M., and Chung, J. (2007). Validity of the walking scale for spinal cord injury and other domains of function in a multicenter clinical trial. Neurorehabil. Neural Repair 21, 539–550.
24. Ditunno, J.F., Jr., Ditunno, P.L., Graziani, V., Scivoletto, G., Bernardi, M., Castellano, V., Marchetti, M., Barbeau, H., Frankel, H.L., D'Andrea Greve, J.M., Ko, H.Y., Marshall, R., and Nance, P. (2000). Walking index for spinal cord injury (WISCI): an international multicenter validity and reliability study. Spinal Cord 38, 234–243.
25. Nout, Y.S., Rosenzweig, E.S., Brock, J.H., Strand, S.C., Moseanko, R., Hawbecker, S., Zdunowski, S., Nielson, J.L., Roy, R.R., Courtine, G., Ferguson, A.R., Edgerton, V.R., Beattie, M.S., Bresnahan, J.C., and Tuszynski, M.H. (2012). Animal models of neurologic disorders: a nonhuman primate model of spinal cord injury. Neurotherapeutics 9, 380–392.
26. Pearson, K. (1901). On lines and planes of closest fit to systems of points in space. Philosoph. Mag. 2, 559–572.
27. Landis, S.C., Amara, S.G., Asadullah, K., Austin, C.P., Blumenstein, R., Bradley, E.W., Crystal, R.G., Darnell, R.B., Ferrante, R.J., Fillit, H., Finkelstein, R., Fisher, M., Gendelman, H.E., Golub, R.M., Goudreau, J.L., Gross, R.A., Gubitz, A.K., Hesterlee, S.E., Howells, D.W., Huguenard, J., Kelner, K., Koroshetz, W., Krainc, D., Lazic, S.E., Levine, M.S., Macleod, M.R., McCall, J.M., Moxley, R.T., III, Narasimhan, K., Noble, L.J., Perrin, S., Porter, J.D., Steward, O., Unger, E., Utz, U., and Silberberg, S.D. (2012). A call for transparent reporting to optimize the predictive value of preclinical research. Nature 490, 187–191.
28. Lammertse, D.P. (2013). Clinical trials in spinal cord injury: lessons learned on the path to translation. The 2011 International Spinal Cord Society Sir Ludwig Guttmann Lecture. Spinal Cord 51, 2–9.
29. Anderson, K.D. (2004). Targeting recovery: priorities of the spinal cord-injured population. J. Neurotrauma 21, 1371–1383.
30. National Institute of Neurological Disorders and Stroke (NINDS). (2014). NINDS common data elements: spinal cord injury CDE standards. Available at: http://www.commondataelements.ninds.nih.gov/SCI.aspx. Accessed April 14, 2014.
31. Lemmon, V.P., Ferguson, A.R., Poporich, P.G., Xu, X.M., Snow, D.S., Igarashi, M. Beattie, C.E., and Bixby, J.L. (2014). Minimum information about spinal cord injury experiments (MIASCI)—a proposed reporting standard for spinal cord injury experiments. J Neurotrauma 2014 Jul 11. [Epub ahead of print.]
32. Aguilar, R.M., and Steward, O. (2010). A bilateral cervical contusion injury model in mice: assessment of gripping strength as a measure of forelimb motor function. Exp. Neurol. 221, 38–53.
33. Marmarou, A., Lu, J., Butcher, I., McHugh, G.S., Mushkudiani, N.A., Murray, G.D., Steyerberg, E.W., and Maas, A.I. (2007). IMPACT database of traumatic brain injury: design and description. J. Neurotrauma 24, 239–250.
34. Watzlawick, R., Sena, E. S., Dirnagl, U., Brommer, B., Kopp, M. A., Macleod, M. R., Howells, D. W., Schwab, J. M. (2014). Effect and reporting bias of RhoA/ROCK-blockade intervention on locomotor recovery after spinal cord injury: a systematic review and meta-analysis. JAMA neurology 71, 91–99.
35. NIF (2014). Neuroscience Information Framework. *Developer Tools.* [Online]. Available: http://www.neuinfo.org/ [Accessed April 14, 2014].

Address correspondence to:
Adam R. Ferguson, PhD
Brain and Spinal Injury Center
Department of Neurological Surgery
University of California, San Francisco
1001 Potrero Avenue
Building 1
Room 101
San Francisco, CA 94110

E-mail: adam.ferguson@ucsf.edu