Moving rehabilitation research forward: Developing consensus statements for rehabilitation and recovery research

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Abstract
Stroke recovery is the next frontier in stroke medicine. While growth in rehabilitation and recovery research is exponential, a number of barriers hamper our ability to rapidly progress the field. Standardized terminology is absent in both animal and human research, methods are poorly described, recovery biomarkers are not well defined, and we lack consistent timeframes or measures to examine outcomes. Agreed methods and conventions for developing, monitoring, evaluating and reporting interventions directed at improving recovery are lacking, and current approaches are often not underpinned by biology. We urgently need to better understand the biology of recovery and its time course in both animals and humans to translate evidence from basic science into clinical trials. A new international partnership of stroke recovery and rehabilitation experts has committed to advancing the research agenda. In May 2016, the first Stroke Recovery and Rehabilitation Roundtable will be held, with the aim of achieving an agreed approach to the development, conduct and reporting of research. A range of methods will be used to achieve consensus in four priority areas: preclinical recovery research; biomarkers of recovery; intervention development, monitoring and reporting; and measurement in clinical trials. We hope to foster a global network of researchers committed to advancing this exciting field. Recovery from stroke is challenging for many survivors. They deserve effective treatments underpinned by our evolving understanding of brain recovery and human behaviour. Working together, we can develop game-changing interventions to improve recovery and quality of life in those living with stroke.

Keywords
Consensus, neurobiology, recovery, rehabilitation, recommendations, stroke

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Introduction: The problem and solution
The explosion of knowledge about the stroke-damaged brain must be incorporated into our collective thinking about the nature and delivery of rehabilitation and restorative therapies. Variable methodological quality of animal studies, poorly defined interventions, and lack of agreed methods for developing, monitoring, evaluating and reporting interventions limit translation of research into evidence-based therapies. Furthermore, patient descriptions are not standardized, recovery biomarkers are not well defined, and we lack agreed time-points or measures to examine outcomes in rehabilitation and recovery trials.

By creating an international partnership of experts from a broad range of scientific and clinical disciplines, we aim to achieve consensus on developing, conducting and reporting rehabilitation and recovery research, and create a new community of practice. In this first roundtable, four areas that we will examine represent...
important roadblocks to current research efforts. The aim of this paper is to summarize priorities for each theme.

**Theme 1: Pre-clinical recovery research: “Addressing the first translational gap”**
To address the first gap in translation, we need to better translate pre-clinical evidence into human discovery trials in a bidirectional and iterative manner. The goal is to develop a deeper understanding of the neurobiology of recovery in human stroke survivors. Basic scientists need to understand the most pressing issues in stroke recovery and rehabilitation and work closely with their clinical counterparts in designing studies, taking a “Bedside to Bench” approach instead of the conventional “Bench to Bedside” approach. Understanding the biology and timing of recovery in animals and in humans requires knowledge of underlying molecular mechanisms that may be influenced by different therapies, such as rehabilitation and stem cells, with the potential to augment post-stroke plasticity and brain repair. Methods for enhancing the potential for functional and structural plasticity in surviving brain and spinal cord are needed. However, their value via the generation of recovery biomarker use may foster developments in new therapies and improve clinical trial efficiency through better patient selection or stratification. Tailoring of therapies for individual patients based on their capacity for neural reorganization and recovery will facilitate personalized interventions, guiding the delivery of effective treatment to the right people, at the right time. Once identified, we must define the psychometric qualities and performance of proposed biomarkers at different time-points of recovery. Prediction models for...
Theme 3: Intervention development, monitoring and reporting
Sequential development, testing, and refining of interventions through trial phasing are less common in stroke rehabilitation than other areas of stroke medicine. Furthermore, the description of interventions in stroke rehabilitation studies is typically incomplete and monitoring of interventions poorly described and reported, leading to significant research waste.

The need for systematic development of complex interventions has been highlighted for some time and useful frameworks exist. To date, researchers employ various methods to develop interventions intended for evaluation, and many fail to describe the underpinning theoretical framework or intended biological mechanisms to improve recovery or outcomes. Dosing studies in the trial development phase are rare and insufficient attention has been paid to how much training is needed, and when it should be applied to drive neurological recovery. Too often, our choice of intervention type, dose, or scheduling is arbitrarily assigned (as reflected in many meta-analyses of stroke rehabilitation interventions), with a “more is better” mantra that is likely too simplistic and may even be harmful at certain points in the recovery pathway. In complex behaviour change research, we see increased attention on codesign of interventions with the health consumer; turning these types of interventions into standardized protocols for delivery in trials is not simple.

Intervention fidelity is also poorly addressed in most rehabilitation trials, with few reporting the methods used to monitor the delivery of interventions. While interest in the area is growing, establishing agreed standards for monitoring and reporting of fidelity would significantly improve our research. When evidence of intervention efficacy exists, insufficient reporting of intervention protocol is a substantial barrier to reliable implementation or replication of research findings; yet this has received little attention. The Template for Intervention Description and Replication, which provides authors with guidance about how to structure accounts of their interventions, is a step in the right direction. But we must improve how we develop, monitor and report interventions. This will reduce research waste and, when interventions are effective, hasten translation into clinical practice.

Theme 4: Measurement in clinical trials
The number of rehabilitation trials is growing exponentially; however, many (98% of physical therapy trials in one recent review) are underpowered, single site, testing feasibility of an intervention or are proof-of-concept trials. Systematic reviews of rehabilitation trials are challenging given the high variability in outcomes used, the timing of intervention delivery, and outcome assessment. These problems are further compounded by poor reporting of interventions raised in Theme 3. If researchers used a core set of trial measures, gathered at agreed time-points after stroke, our ability to compare results across trials, pool data for meta-analyses or undertake individual patient meta-analyses would be vastly improved. Large pooled data sets from rehabilitation trials could be used to develop hypotheses about stroke recovery or help validate prognostic tools. We also need to consider how we stratify patients in trials and whether recovery biomarkers are robust enough for that purpose (Theme 2). When recruitment occurs later after stroke, some measure of stroke severity at time of onset is critical to developing our understanding of recovery. We may need to consider new recruitment models that track patients from stroke onset or retrospectively acquiring reliable and simple proxy measures of baseline severity. Insufficient attention has also been paid to systematic acquisition of pre-stroke lifestyle and other variables that are likely to inform stroke recovery phenotypes.

Limitations of many measurement tools are well known, and a number of frameworks exist to support selection of core measurements, for example the international classification of functioning, disability and health model, and COSMIN (www.cosmin.nl) which provides criteria for evaluating psychometric properties of tools. Importantly, we need to ensure that tools we adopt can measure meaningful change and can distinguish true neurological repair from use of adaptation strategies to achieve a goal. Important achievements would be to standardize definitions for common terms (e.g. recovery), time-points of measurement, and distinguish between different types of outcomes. Simply stated, our challenge is not just to agree on a core set of measurements but to consider what we need to measure and why, to improve rehabilitation and recovery trial methods.

Conclusion
A new partnership of around 60 leading stroke experts has committed to advancing stroke recovery and rehabilitation, by achieving an agreed approach on how to develop, conduct, and report research across the...
four reported themes. A key issue to address is defining important time-points in stroke recovery, underpinned by our best understanding of biological processes. The next step towards developing consensus is the inaugural Stroke Recovery and Rehabilitation Roundtable meeting, to be held in Philadelphia, USA, in May 2016. Recommendations from this meeting will be pivotal for progressing stroke recovery and rehabilitation research, and provide impetus for development of strong international partnerships to tackle the challenge of improving stroke recovery.

Declaration of Conflicting Interests
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