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.[1] Variable methodological quality of animal studies,[2] poorly defined interventions,[3] and lack of agreed methods for developing, monitoring, evaluating and reporting interventions limit translation of research into evidence-based therapies.[4] Furthermore, patient descriptions are not standardized, recovery biomarkers are not well defined,[5] and we lack agreed time-points or measures to examine outcomes in rehabilitation and recovery trials.[6]

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,[5] 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.[7–9] Translation will improve by defining inter-species differences, developing robust, pre-clinical animal models that better represent clinical stroke populations (older, with co-morbidities)[10] who do not recover within a few weeks post-stroke,[11] and identifying more reliable, valid, and sensitive histological and behavioural outcomes. [7] Another important issue is to hold pre-clinical studies to the same quality standards and rigor as clinical research.[12] Sample size, age groups, and gender differences are not often considered in pre-clinical studies, ultimately limiting their clinical translation.[2,13,14] Thus, a main point of pre-clinical studies of stroke repair is to model human recovery.

Theme 2: Recovery biomarkers

A key impediment to the development of new therapies for promoting recovery after stroke is not knowing who or when best to treat. One of the most important findings to emerge from decades of work in rodents was the identification of a period of spontaneous biological recovery during which the effect of training is heightened. [15] Investigating the mechanisms involved in humans would reveal exciting therapeutic targets. A different type of problem, specific to human studies, is heterogeneity in the residual structural and functional post-stroke brain architecture and the impact this has on potential interventions.[16,17] The answer to ''who and when'' is the development of biomarkers to provide knowledge of both therapeutic targets and prognosis in human stroke. There are limited validated biological markers of stroke recovery, but promising potential targets exist.[5] We define stroke recovery biomarkers as ''indicators of disease state that can be used clinically as a measure reflecting underlying molecular/ cellular processes that may be difficult to measure directly in humans, and could be used to predict recovery/ treatment response,'' which may include markers of biology (blood, genetics), imaging (structural, functional, chemical), neurophysiology (patterns of brain excitability or electrical activity), or combinations of such.[1,18,19] While most research has explored relationships between late biomarkers[3–6] months post-stroke) and final stages of recovery,[19,20] investigation of early biomarkers (<7 days), reflecting the mechanisms of spontaneous biological recovery, is an urgent priority. Furthermore, distinction is required between cross-sectional measures that capture biological state, measures that predict future clinical events, and measures that change in parallel with behavioural change; each of these has value in stroke research.

Blood biomarker analysis is viable because many brain-derived molecules cross the blood–brain barrier, including micro-RNAs, lipids, short peptide chains, and exosomes. Based on similar analyses from traumatic brain injury[21] and Alzheimer's disease,[22] there is an expectation of identifying molecular signatures of recovery post-stroke in humans.[23] Individuals' genetic profiles may also influence recovery.[24–26] While interest has centred on genes known to contribute to neuroplasticity,[27] there are a number of candidate biomarkers to consider as well as gene–gene interactions and epigenetics.

Considerable attention has focused on brain imaging to define post-stroke patterns of recovery. Imaging is non-invasive and easily accessible, enabling categorization of brain anatomy, function, chemistry, and connectivity.[28–31] Another potential recovery biomarker is neurophysiological status mapped using noninvasive brain stimulation (i.e. transcranial magnetic stimulation (TMS)).[19,30] TMS-based neurophysiological measures of the electrophysiological relationship(s) between the cortical hemispheres[32] and corticospinal tract integrity via the generation of motor evoked potentials relate to motor outcome in chronic[19,33] and acute stroke.[34] However, their value in predicting recovery is not well understood.

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

patient subgroups would need to be validated; this would require large cohorts and the development of a worldwide network.[35]

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,[36] leading to significant research waste.[3]

The need for systematic development of complex interventions has been highlighted for some time and useful frameworks exist.[37] 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[38] 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.[39] In complex behaviour change research, we see increased attention on codesign of interventions with the health consumer[40]; 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,[41–43] 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.[3] The Template for Intervention Description and Replication, which provides authors with guidance about how to structure accounts of their interventions, [44] 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)[45] 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.[6] 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.[46] Important achievements would be to standardize definitions for common terms (e.g. recovery), time-points of measurement, and distinguish between different types of outcomes.[47] 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.[48,49]

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.

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