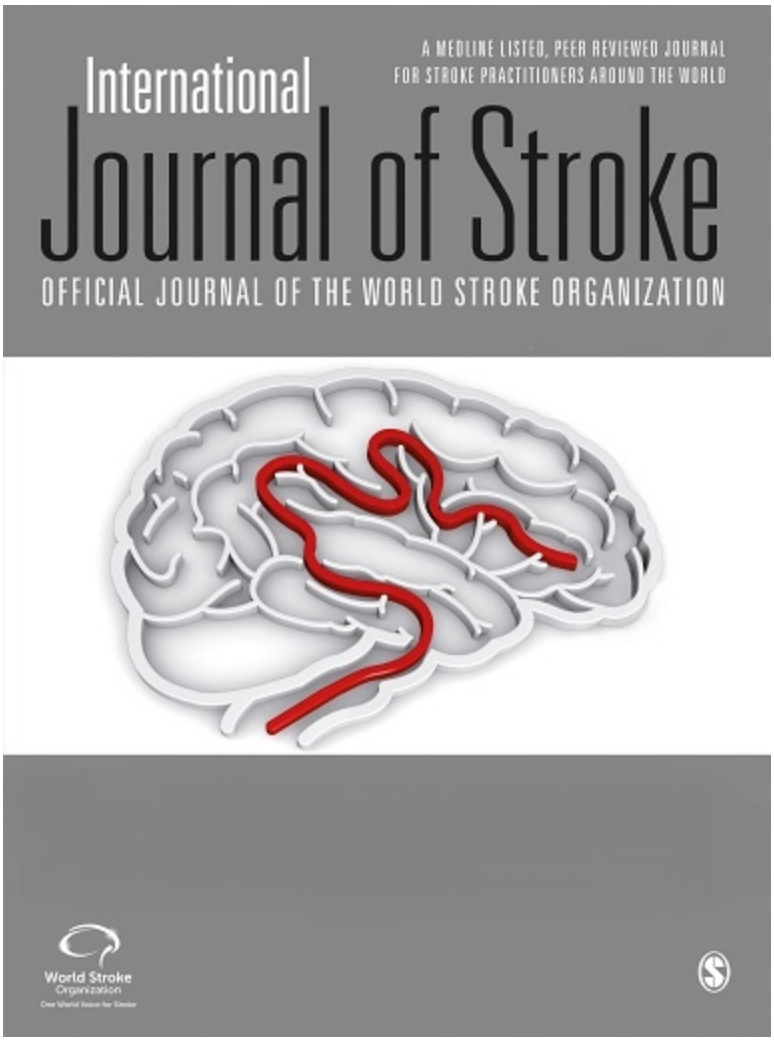

Setting the scene for the second Stroke Recovery and Rehabilitation Roundtable

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ABSTRACT

The Stroke Recovery and Rehabilitation Roundtable (SRRR) meetings bring together an international group of preclinical and clinical researchers along with statisticians, methodologists, funders and consumers, working to accelerate the development of effective treatments for stroke recovery and to support best-evidence uptake in rehabilitation practice. The first meeting (2016) focused on four recommendation areas: translation of preclinical evidence into human discovery trials; recovery biomarkers to provide knowledge of therapeutic targets and prognosis in human stroke; intervention development, monitoring, and reporting standards; and standardized measurement in motor recovery trials. The impact of SRRR is growing, with uptake of recommendations emerging, and funders exploring ways to incorporate research targets and recommendations. At our second meeting (SRRR2, 2018), we worked on new priority areas: 1) cognitive impairment, 2) standardising metrics for measuring quality of movement, 3) improving development of recovery trials, and 4) moving evidence-based treatments into practice. To accelerate progress towards breakthrough treatments, formation of an International Stroke Recovery and Rehabilitation Alliance (ISSRA) is our next step, where working groups will take recommendations and build partnerships needed to achieve our goals.

Introduction

The first Stroke Recovery and Rehabilitation Roundtable (SRRR1, 2016), was a major international collaborative effort that set the scene for a new direction in recovery research. This collaboration, and the consensus recommendations from the meeting,[1-6] have garnered tremendous interest from researchers and the broader stroke community. We are seeing uptake of recommendations from SRRR1 in research development. Funders of stroke research are interested in integrating recommendations and proposed strategic directions into calls that target stroke recovery research. Our goal is to complement, not replicate, the work of other collaborations. The breadth and ambition of stroke recovery and rehabilitation research requires synergistic collaborative work. The international community is aligned in the search for life-changing recovery treatments, beyond what is currently available during the hyperacute phase.

Leveraging current momentum, SRRR2 aimed to create the pathways to realise key objectives and targets identified in SRRR1 (*Figure*). Motor recovery, about which we know more than other domains, was a logical target for early consensus building. However, the need to further build consensus around definitions, measurement and research priorities in the cognitive domain was evident (Theme 1). After setting recommendations for core outcomes for motor recovery trials in SRRR1, improving our approach to measuring recovery and brain repair, not just functional change, was an important next step. This required recommendations for standardization of kinematics (i.e., metrics) to measure quality of upper limb movement that accompanies motor system changes (Theme 2). Theme 3 is focused on how we build better recovery trials in the future, while Theme 4 tackles the challenge of getting evidence-based treatments adopted into practice (delivering what we know works).

In this paper, we outline issues impeding progress in each theme, and the consensus targets for SRRR2. In keeping with our efforts to break down silos, we continue to include a broad mix of researchers with relevant expertise. Some are returning, while others are new to the SRRR collaboration. In this convening exercise, groups also extended their consultation to researchers beyond those who attended the face-to-face meeting, to capture a broader range of skills and perspectives.

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Theme 1: Cognitive impairment after stroke

Cognitive impairment, like motor impairments, can persist for years and has a major effect on quality of life. Over 40% of stroke survivors report cognitive difficulties.[7] One added complexity, in comparison with motor impairment, is individual variation in the timing and trajectory of cognitive impairment. Deficits can be progressive or take months to appear,[8, 9] with dementia developing in ~25% of all stroke survivors within 5 years of stroke onset.[10, 11] Conversely, up to one-third of stroke survivors demonstrate substantial improvement in cognition in the first two years. The underlying mechanisms associated with progression or recovery of post-stroke cognition are not understood. The cognitive working group includes preclinical and clinical researchers aiming to define recovery epochs for cognition, review alignment of assessments between rodents and humans, and make recommendations to improve translation.

Recovery is not a manifestation of a single biological process, so recognizing different phases or epochs of recovery is important. Heterogeneity of clinical symptoms and associated cognitive and behavioral deficits supports assessment of the neurobiological underpinnings of cognition across functional domains. For motor recovery, several phases have been conceptualized, which are likely to link with specific assessments and concepts of therapeutic windows.[2] While there may be common processes, motor and cognitive recovery are likely to share some, but not all, processes given the differences in neural systems involved. Lack of preclinical and clinical data linking biological or functional assessments to impaired cognitive function across time, makes it difficult to define recovery epochs (acute, early subacute, late subacute, etc.). Our group sees this as a major gap that needs urgent attention. Ideally, knowledge of recovery epochs should translate across species, to facilitate appropriate timing of therapy and translation in humans.

Cognition is multi-dimensional and hierarchical, creating difficulties in defining treatment targets and practical measurements of efficacy for interventional research. Some constructs have relatively well-developed definitions that can be used in intervention studies (e.g. aphasia or neglect), while others do not. There is overlap in existing constructs. For example, some scales to assay mood incorporate behavioral apathy and some apathy scales refer to cognitive symptoms. Consensus on the following questions would help move the field forward: 1) Should we adopt a form of international harmonization of valid and accepted constructs? A model for this might be the adoption of a set of diagnoses by diagnostic manuals, along with efforts to apply these in contexts related to stroke[12] and 2) Can we agree on a set of constructs that are i) already defined in a way that is applicable to recovery trials, by broadly accepted definitions; or ii) could be refined to this point in a short time.

One reason for the lack of preclinical translation into positive clinical trials is the limited translational efficacy of animal behavioral assessments.[13] Many preclinical assessments of drug treatments for cognition are undertaken using behavioral assessments that have little in common with clinical tests. To bridge this translational gap, we must align animal and human cognitive assessments and understand whether tests are assessing comparable cognitive

processes between species. Once we have parallel assessments with confirmed test validity, we will be better positioned to assess and translate therapeutic treatment options. We need to replicate in cognition, selection of tests well-suited to recovery studies, as was done in SRRR1.[4] One special consideration is the dependency of many cognitive testing approaches on language in humans. This creates difficulties in performing research across countries or ethnic groups. It also leads to people with aphasia being excluded from many recovery studies. Understanding causative events and mechanisms, both in animals and humans that underpin the pathogenesis of cognitive impairments are important factors to consider for translation. Greater efforts are necessary to fill gaps and overcome confounds in the generation, study design, testing, and evaluation of animal models and subsequent clinical testing of future treatments.

Theme 2: Standardized measurement of quality of upper limb movement after stroke.

Greater standardization in clinical outcome tools and protocols will facilitate communication, decision making, and understanding of stroke recovery. It will also inform trial design, understand treatment effects and consolidate research knowledge through meta-analyses.

Stroke recovery is a complex process occurring through a combination of spontaneous neurobiological recovery and learning-dependent brain plasticity, including reorganization of spared neuronal networks to regain lost neuronal function, and learning adaptive movement strategies.[14, 15] Our understanding of the processes and mechanisms that drive improvements in quality of movement of the paretic upper limb after stroke, i.e., restitution and substitution (adaptation or compensation) is still in its infancy. Clinical trials and observational studies have so far failed to distinguish behavioural restitution from behavioural substitution, leaving the association between quality of movement and recovery of upper limb capacity underexplored.[14] With the exception of the Reaching Performance Scale for Stroke,[16] no clinical assessment scale for the upper paretic limb is able to measure change in intra-limb coordination while addressing this concern.[17]

During SRRR1, we agreed a consensus is required for objective kinematic measures of quality of motor performance to help distinguish behavioural restitution from compensation post stroke.[5] Relating two classes of measurement, neuroimaging (fMRI, DTI, hdEEG) and motor performance, greater understanding of learning early post stroke would be enabled in trials evaluating interventions targeting brain repair.[18] While ideally we want consensus for upper limb recovery, balance and gait, all of which have been assessed using motion analysis systems to derive kinematics, the scope was considered too large. Instead, our group focused on reaching performance of the upper limb which will serve as a blueprint for achieving consensus-based recommendations for measuring kinetics and kinematics of other basic and extended mobility-related ADLs.

The past two decades has seen growth in using motion analysis systems, including wearables and robotic devices.[19] These systems measure end point movement in external space, quantifying variables such as trajectory, speed, precision, smoothness, and movement path

straightness (i.e., end point characteristics), as well as movements in body space, in which ranges of individual joints and segments (i.e., trunk), spatial and temporal intra-limb coordination, and muscle activation patterns can be measured (i.e., movement quality variables).[17] However, there is currently a lack of agreement on how to measure upper limb movement and what should comprise a core set of metrics in stroke recovery and rehabilitation trials after stroke.[17, 19, 20] For example, after reviewing the literature, Tran and colleagues[19] recently identified 49 kinematic parameters in studies of upper limb robotics involving 1750 stroke patients, whereas Alt Murphy and Hager[21] found 93 kinematic studies of the upper limb investigating different movements and tasks and measuring more than 20 different types of metrics. As the technology for measuring movement advances and becomes more widely used, there are likely to more methods and metrics, creating an urgent need for harmonization and standardization.

Our working group comprising experts in the field of biomechanical studies after stroke is addressing key questions important for future research, which will enable us to understand spontaneous neurobiological recovery and effect of therapy-induced improvements in terms of quality of movement of the paretic upper limb post stroke. We aim to agree upon a set of recommendations on the performance assays of the paretic upper limb that should be used in stroke recovery and rehabilitation trials to address questions about the quality of movement at the impairment level. Second, we aim to recommend the behavioural task(s) that should be applied for measuring quality of functional upper limb movement. Finally, we aim to reach consensus on the type of technological equipment *(e.g.,* optoelectronic and electromagnetic movement tracking systems) that should be used to measure performance assays and behavioural tasks in stroke recovery and rehabilitation trials. Recommendations will be independent of commercial entities.

Theme 3: Improving how we develop recovery trials

The SRRR1 group worked to develop a core set of outcomes, baseline variables, biomarkers and agreed time points recommended for motor recovery trials.[2, 3, 5] Further work to prioritize and recommend a broader set of outcomes is ongoing, and other groups are working to standardize outcomes in aphasia trials.[22] The trials group at SRRR2 aims to address the broader challenge of developing recovery trials of the future – aspiring to target true recovery rather than compensation.

Preclinical literature and our growing human trial experiences highlight several topics that are important for developing stroke recovery trials. Many stroke recovery treatment types are under consideration, including drugs, biological products (e.g. stem cells and growth factors), devices, and activity-based therapies. Patient selection is critical, as application of stroke recovery treatments does not benefit from a "one-size-fits-all" approach. Currently, patient selection often relies on outdated clinical assessments that do not take advantage of what can be gleaned from validated neuroimaging measures. Efforts to apply such measures, which might more accurately stratify participants, are vital. Further studies are needed; the biomarker working group in SRRR1 outlined the current state of the evidence and proposed a way

forward.[3] When designing stroke recovery treatment trials, whether translating from preclinical work[4] or progressing through the phases of human trials,[6] there are wide-ranging considerations. Selecting details of the treatment (including timing, dose, schedule, and content) requires careful planning. Stroke recovery treatments target the brain and so in addition to measuring effects on behavioural outcomes, trials need to understand how treatment impacts brain structure and function. A key message of our group is the critical need to integrate these points into the design of stroke recovery trials.

The field of rehabilitation and recovery has experienced unprecedented growth in the number of randomized controlled trials over recent years. Our research community has demonstrated the ability to effectively conduct trials, from smaller trials that include biomarkers to larger multi-site (even PhaseIII) clinical trials. Some smaller trials that have developed recovery treatments using a model-based strategy have experienced success, while large trials with broader eligibility criteria or pragmatic designs, generally have not. Identification of efficacious stroke recovery treatments may therefore be best pursued through stepwise research that identifies target subgroups most likely to derive benefit. Growing frustration with the lack of progress is prompting careful consideration of how stroke recovery treatment trials are designed and conducted.

In this context, the primary goal of our working group is to develop a framework for critically examining key steps in stroke recovery treatment trial development creating a 'go' or 'no-go' decision pathway for advancing a therapy through the phases of stroke recovery trials, incorporating preclinical knowledge and other scientific advances, as well as lessons learned from recent clinical trials.

Much of the current focus is on upper limb recovery, given the preponderance of data on motor system recovery, but the approach will become increasingly inclusive as evidence emerges for other neural systems. An additional goal is to outline alternative trial designs and methods that might be used to advance recovery therapeutics in the most efficient and effective manner to develop the knowledge we need to progress to the next stages in trial design. To meet our aims, our team includes methodologists, preclinical scientists, trialists, and clinical researchers. Through development of this decision pathway, we aim to challenge investigators to critically appraise whether a given stroke recovery treatment is ready to translate or move through the developmental pipeline, and whether evidence is sufficient to warrant an appropriate investment of time and money.

Theme 4: Moving knowledge into practice

Stroke survivors should receive rehabilitation treatment based on high quality evidence to optimize their health outcomes. However, there is increasing recognition that moving research evidence into practice can be challenging across all sectors of health care.[23, 24] Knowledge translation has been defined as a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically-sound application of knowledge to improve health and health services.[25] Of importance, the term "application" includes the process of putting knowledge into practice.[25] There are many barriers to moving interventions or processes supported by high-quality evidence into everyday practice, including limited time, expertise, administrative support and resources.[26] Furthermore, it can be difficult to replicate published interventions because knowledge translation was not considered in the design of trials, nor were the appropriate details reported in the publication to replicate findings, especially around intervention fidelity.[6] Successful examples of translating stroke rehabilitation research into practice have highlighted the need for stakeholders, including clinicians, researchers, patients, services and policymakers to collaborate throughout the entire research or implementation life cycle to bring about change.[6] When stakeholders have input into the design of research, the findings are more likely to be relevant and useful to stakeholders.[27] Low- and middle-income economy countries have additional challenges and may lack even basic stroke rehabilitation services.[28, 29] The World Health Organization Rehabilitation 2030 Call for Action stressed that rehabilitation is not a luxury, but should be an essential part of the continuum of care as it has important health, social and economic benefits.[30]

Ideally, all interventions that have high quality evidence should be moved to practice, however, reality is that health care systems have limited resources. Our group asked the question 'How do we determine what research or knowledge to move to practice to have the maximum impact for people after stroke?' The quality of the evidence is an important consideration prior to implementation as it assesses supporting research and considers aspects such as research design, size of effect, confidence intervals, sample sizes, and relevance of the evidence. Such evidence can inform the likelihood that treatment will work as expected. Perspectives from health care providers and service managers play a large role in what interventions are currently moved to practice. However, we also need to consider what stroke survivors and their caregivers feel are important. Furthermore, we should also weigh how the intervention might impact the health care system, e.g., does it reduce the length of hospital stay or costs? On the practical side, we need to ensure that interventions that we try to move to practice are feasible and consider the local context; e.g. a treatment requiring highly specialized skills, beyond those normally available, may not be sustainable if there is a high staff turnover.

While prioritizing research topics has been undertaken previously (e.g., Pollock et al. 2014[31]), how and what to prioritize to implement in stroke rehabilitation is a relatively new challenge that would move the field forward. Our working group will undertake a consensus exercise to prioritize what should be moved into practice based on international stakeholder input. Such information can be used at multiple levels within the health system by policy makers and funders to direct resources, and by hospitals and communities to prioritize and implement

activities that can have an immediate impact on the quality of lives of people living with stroke. Understanding priorities can lead to activities to develop resources on how to implement specific activities, as well as lead to national and international collaborations to address these gaps in practice. We anticipate that some of the priorities will have readily available resources that can inform health care providers how to harness the necessary means to implement existing knowledge and solutions into their practice.

Conclusion

SRRR participants are committed to progressing stroke recovery and rehabilitation science and practice, and building strong, international partnerships to accelerate change. We hope that researchers, clinicians and academics in the field of stroke recovery, together with funding bodies and journal editors, will join us in pursuing and promoting the goals outlined here and in our previous recommendation papers, supporting our vision for change.

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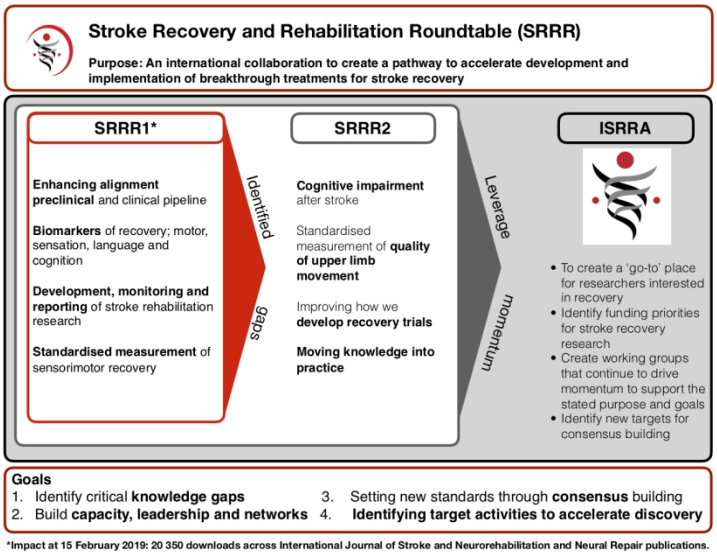

Development of Stroke Recovery and Rehabilitation Roundtables (SRRR I and II), and International Stroke Recovery and Rehabilitation Alliance (ISRRA)

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