Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce.

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Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce.

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Abstract

The first Stroke Recovery and Rehabilitation Roundtable (SRRR) established a game changing set of new standards for stroke recovery research. Common language and definitions were required to develop an agreed framework spanning the four working groups: translation of basic science, biomarkers of stroke recovery, measurement in clinical trials and intervention development and reporting. This paper outlines the working definitions established by our group and an agreed vision for accelerating progress in stroke recovery research.

Keywords: stroke, research standards, stroke recovery, rehabilitation, definitions, translation

Introduction

The Stroke Recovery and Rehabilitation Roundtable (SRRR) was convened with the aim to move rehabilitation research forward (1). Working collectively across four initial priority areas we reviewed, discussed, and attempted to achieve consensus on key recommendations in each of the areas of translation of basic science (2), biomarkers of stroke recovery (3), measurement in clinical trials (4) and intervention development and reporting (5). Agreed definitions were a priority. Definitions within stroke recovery research are particularly complex given both the extended time window over which research, clinical interventions and recovery take place; and the multi-disciplinary, multi-faceted nature of the field. This paper outlines the working definitions established by our group that underpinned the scope and methodologies of each of the four groups. Agreed priority areas for accelerating progress in stroke recovery research are highlighted as a way forward for the field. These were developed following comprehensive discussions at the first SRRR roundtable meeting convened in Philadelphia, 2016.

A major point of agreement of the SRRR expert group was to focus on progress of stroke recovery research in the next decade and beyond. 'Rehabilitation' as a blanket term for all therapy-based interventions post-stroke was considered problematic, vague and an impediment to progress. Rehabilitation reflects *a process* of care, while recovery reflects the extent to which body structure and functions, as well as activities, have returned to their pre-stroke state. With that, the term 'recovery' can be represented in two ways: (1) the change (mostly improvement) of a given outcome that is achieved by an individual between two (or more) timepoints, or (2) the mechanism underlying this improvement in terms of behavioural restitution or compensation strategies (6, 7). We used the definition of rehabilitation developed by the British Society of Rehabilitation Medicine (8), "a process of active change by which a person who has become disabled acquires the knowledge and skills needed for optimum physical, psychological and social function". Stroke rehabilitation is most often delivered by a multidisciplinary team, defined by the World Health Organisation (WHO) (9) to encompass the coordinated delivery of intervention(s) provided by two or more disciplines in conjunction with medical professionals. This team aims to improve patient symptoms and maximise functional independence and participation (social integration) using a holistic biopsychosocial model, as defined by the International Classification of Functioning Disability (ICF) (9).

Recovery

The motor system has been studied more than any other in stroke recovery research, as such this was the focus of most dialogue within the SRRR. While many of the principles of recovery emerging from research conducted on the motor system likely extend to non-motor systems, differences exist in the organisation of brain systems. In discussing stroke recovery, acknowledging that any improvement in any domain of the ICF can be viewed as a sign of ongoing recovery is important. For research, understanding the processes that underpin *how* recovery is achieved during stroke rehabilitation is of utmost value. An understanding that distinguishes between behavioural restitution and use of compensation strategies will further direct how we should train stroke patients to regain the ability to complete meaningful tasks and how we should design interventions, including technology applications for stroke such as rehabilitation robotics.

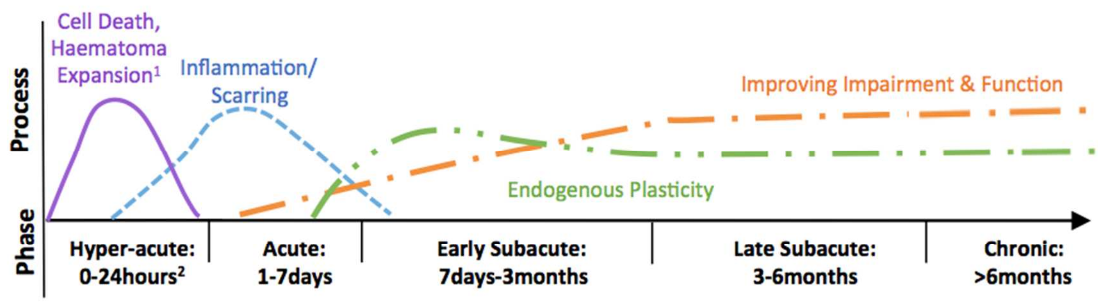
Behavioural restitution or true recovery: Behavioural restitution has been defined as a return towards more normal patterns of motor control with the impaired effector (a body part such as a hand or foot that interacts with an object or the environment) and reflects the process toward *'true recovery'* (10, 11). True recovery defines the return of some or all of the normal repertoire of behaviours that was available before injury. Neural repair is required for true recovery. Although rarely complete after stroke, some degree of true recovery is nearly always achieved (12). For the motor system, recovery is best measured with kinematics (4), and for the language system, a test of speech or language production may be the optimal measure (13). The development of stroke treatments administered after the hyperacute period of early damage and brain cell death that restore normal function, thereby promoting true recovery, remains an aspirational goal yet to be realised across functional domains.

Compensation: A patient's ability to accomplish a goal through substitution with a new approach rather than using their normal pre-stroke behavioural repertoire constitutes compensation. This behaviour does not require neural repair, but may require learning. Compensation may be seen in all functional domains. In the motor domain, compensation strategies employ the use of intact muscles, joints and effectors in the affected limb, to accomplish the desired task or goal (10, 11). In the language system, compensation may refer to the use of an augmentative and alternative communication device, including a communication board. At present, researchers commonly test interventions that allow or promote compensation, rather than behavioural restitution, in order to improve a patient's safety and quality of life. This approach is compounded by the choice of an outcome measure, which is unable to distinguish between the two, so that the potential mechanism of an intervention remains opaque.

Spontaneous biological recovery: In animals, this term refers to improvements in recovery of behaviour in the absence of a specific, targeted treatment and occurs during a time-sensitive window that begins early after stroke and slowly tapers off (6, 11, 14). In human stroke survivors, a similar period of heightened recovery of behaviours occur early post-stroke with little or no active treatment (15). The duration of the window varies across neural systems, e.g., weeks to months post stroke for arm movement (16), but longer (weeks to years) for other systems, such as language (13). There is literature pertaining to motor (17-20), visuospatial neglect (21) and language (22, 23) systems; data for other neural systems exist but are sparser, highlighting research priorities for the field. Most stroke survivors exhibit spontaneous recovery, progressing through characteristic stages (24). Proportional recovery rules suggesting that the degree and rate of recovery are strongly predictable post stroke have been proposed in a number of domains (e.g., in upper limb recovery (19, 20), visuospatial neglect (21) and language functions (22, 25)). However, a substantial group of patients do not fit such proportional recovery rules. Our challenge is to study spontaneous recovery, to understand its biological basis, to determine if we can identify recovery phenotypes in order to select patients for interventions (26), and to use this knowledge to guide the development of interventions that boost behavioural recovery beyond that which occurs spontaneously.

Timeline of stroke recovery

A further challenge for our field is determining the optimal timing to implement interventions focused on recovery and repair (1, 6, 27, 28). As a first step, we needed to agree on a common framework – underpinned by what we know about the biology of recovery - for defining what is meant by 'acute', sub-acute' and 'chronic' (6, 29). These terms are often used in recovery research without adequate definition. Building on previous work by Dobkin and Carmichael (28), we developed the framework shown in Figure 1. The framework is strongly informed by pre-clinical research in animal models of stroke (30-33), as well as individuals with stroke (18, 27, 34), particularly from studies of the motor system. This framework should be updated as more knowledge is acquired. Figure 1 outlines the **timing** (hours, days, months) of several important biological processes in ischaemic (35) and haemorrhagic (36) stroke, as well as the **temporal terms** (hyper-acute, acute, early and late sub-acute, chronic) across the first 6 months post-stroke and beyond. The possibility for behavioural changes even years post-stroke is recognised. However, the current understanding of brain repair processes suggests that the majority of behavioural recovery, and the rapid changes occur in the first weeks-to-months post stroke for most people. This time perspective represents an important treatment target to maximise the potential of restorative interventions.



[1] Haemorrhagic stroke specific. [2] Extends to 24 hours to accommodate options for anterior and posterior circulation, as well as basilar occlusion.

Figure 1: Framework that encapsulates definitions of critical timepoints post stroke that link to the currently known biology of recovery.

The convention proposed for recovery research is that treatments commenced within a week of stroke onset should be classed as 'acute'. Relatively few recovery trials have initiated restorative treatments within this post-stroke phase (for reviews see (37, 38)). The first week until the first month post-stroke (acute and early sub-acute) is a critical time for neural plasticity (6, 30, 39) and should be a target for recovery trials, with some uncertainty about how early and how intensively to start training (37, 40). Importantly, we strongly recommend that in all recovery and rehabilitation research, the *time from stroke onset* is gathered and reported. The start and end of any intervention(s), experimental or standard of care, as well as timing of outcome and follow-up assessment should also be reported. Using this framework the SRRR groups provide recommendations e.g., the measurement group recommend core measures to be included in every trial of stroke recovery and rehabilitation (4); the biomarker group provide recommendations about the timing and type of data acquisition (3).

The way forward

As the body of research in stroke recovery and rehabilitation continues to grow, we will increasingly see interventions specifically developed with the aspiration to target true recovery rather than compensation. Finding breakthrough treatments is critical and has the potential to set the stroke recovery research field on a radically new path. One only needs to look at the transformational effect of thrombolysis and endovascular thrombectomy on acute stroke outcomes, research funding in this area, and importantly, on health service delivery, to understand the importance of breakthrough treatments in recovery. A number of key themes for future research and collaboration emerged from the SRRR discussions and are briefly outlined below.

- **Improved understanding of the natural history of recovery and stratification in trials.** Applying repeated measurements at set time points (Figure 1) that start early and continue well into the chronic phase in larger cohorts of patients will help to establish the natural history of recovery in specific functional domains. We need better prognostic models of long-term outcome after stroke that are informed by behavioural, neurophysiological and neuroimaging data. Crucially, we need to better stratify patients in clinical trials that target restitution based on recovery potential (41). Most proof-of-concept trials to date that have started early after stroke are heavily underpowered by lack of proper stratification; leading often to prognostically unbalanced groups at baseline (42). Neurophysiology or neuroimaging approaches for stratification are only just emerging (43); areas where there is sufficient evidence to support their use in recovery research are outlined in our biomarkers paper (3). Informed by such data, trials of promising new treatments would have a higher likelihood of identifying a true treatment effect if there is one.

- **Better understanding of the neurobiology of spontaneous and treatment-induced recovery in human subjects.** Animal studies have provided insights into the cellular and molecular events that underlie stroke recovery; this must continue, however a pressing need exists to achieve this level of understanding in human subjects. Such an understanding will require an overhaul of many current approaches and the development of biomarkers that best reflect important stroke plasticity mechanisms. The resulting insights can be expected to identify a series of biological targets that could translate into improved application of post-stroke therapies in humans and provide a biological basis for testing novel stroke recovery interventions (44).
- **Characterising different stroke recovery phenotypes.** In clinical trials we consistently identify the presence of responder and non-responder groups to a given treatment, but little is known regarding the underlying biological group differences. We need pre-clinical and clinical researchers to consistently measure neural injury and function and apply outcome measures that can distinguish behavioural restitution from compensation. This distinction will help us characterise and ultimately predict those most likely from those least likely to respond to a given intervention. An effort to understand recovery phenotypes will help target

efficacious treatments towards responders and create renewed focus to develop better treatments for non-responders.

- **Training new researchers.** Given these priorities, an emphasis on cross-disciplinary training of new researchers will build capacity and linkages, while concurrently break down the silos that have historically divided basic and clinical researchers. This training should also include standardised training in core outcome assessment and biomarker acquisition for use in stroke recovery research in both animals and humans.
- **Development of a network of clinical Centres of Excellence in stroke recovery.** These centres would represent a place where clinicians understand, advocate and importantly, apply treatments at the right time and the right dose according to current best knowledge. Research would also be embedded in these centres.
- **A radical new aim.** We believe a new dialogue and a collective collaborative investment is needed to work towards a radical new goal of restitution and brain repair. Much of the thinking in this field is currently pragmatic, investigating interventions that could be delivered in existing health care settings. However, we urgently need to know what is possible in terms of recovery and restitution of function after stroke. This knowledge will only come about through aspirational research which seeks to achieve the largest effect size for the benefit of stroke survivors (45,46). We need look no further than the first thrombolysis trials for inspiration, as they had little or no chance of implementation on a wide scale within acute stroke services as they were then set up. The early thrombolysis trials drove changes in the way acute (and hyperacute) services were delivered around the world. The field of restorative therapy after stroke requires the same sense of purpose and resolve.

As a group the SRRR participants are committed to progressing these themes. We hope that researchers, clinicians and academics working or interested 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 recommendation papers (2-5).

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Appendix 1: Additional definitions that are key for the field of stroke rehabilitation and recovery.

Behavioural control is how the CNS creates behaviour. For example, in the motor system, motor control is the process by which motor commands produced by the CNS activate and coordinate muscles to generate joint torques to move effectors in goal-directed actions (47, 48).
Effector is defined as a body part, such as a hand or foot that interacts with an object and the environment (10).
Behavioural learning is a set of processes associated with practice or experience leading to relatively permanent changes in the capability for responding. In the motor system, for example, behavioural learning might arise as a result of the modification of the temporal and spatial organisation of muscle synergies, which result in smooth, accurate, and consistent movement sequences (47).
Skill is improved behavioural status acquired through practice. For example, in the motor system, skill is an all-encompassing term that includes action selection in particular contexts and the smooth, precise, and accurate execution of that selected movement (49).
Task-specific training in rehabilitation focuses on improvement of performance in tasks through goal-directed practice and repetition (50). In practice, the focus is often on training of functional tasks rather than impairment. Other terms used that reflect these elements are 'repetitive functional task practice', 'repetitive task practice' (51), 'task-related training' (52) and 'task-orientated therapy' (53).
Adaptation is the reduction of systematic errors in response to perturbation to maintain or improve performance (54-56).

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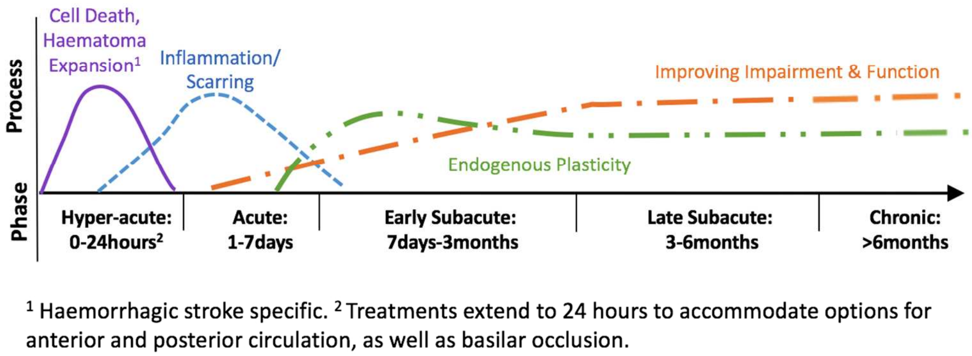

Figure 1: Framework that encapsulates definitions of critical timepoints post stroke that link to the currently known biology of recovery.

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