Title
Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce*

Journal
Neurorehabilitation and Neural Repair, 31(9)

ISSN
1545-9683

Authors
Bernhardt, Julie
Hayward, Kathryn S
Kwakkel, Gert
et al.

Publication Date
2017-09-01

DOI
10.1177/1545968317732668

ASNR AMERICAN SOCIETY OF NEUROREHABILITATION

Neurorehabilitation and Neural Repair
2017, Vol. 31(9) 793–799
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1545968317732668
journals.sagepub.com/home/nnr
SAGE

Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce*

Julie Bernhardt, PhD[1,2], Kathryn S. Hayward, PhD[1,2,3], Gert Kwakkel, PhD[4,5], Nick S. Ward, MD[6,7], Steven L. Wolf, PhD[8,9], Karen Borschmann, PhD[1,2], John W. Krakauer, MD[10], Lara A. Boyd, PhD[3,11], S. Thomas Carmichael, MD, PhD[12], Dale Corbett, PhD[13,14], and Steven C. Cramer, MD[15]

Abstract

The first Stroke Recovery and Rehabilitation Roundtable 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 first 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

[1]Stroke Division, The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Australia
[2]NHMRC Centre of Research Excellence Stroke Rehabilitation and Brain Recovery, Melbourne, Australia
[3]Department of Physical Therapy, University of British Columbia, Vancouver, Canada
[4]Department Rehabilitation Medicine, MOVE Research Institute, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, the Netherlands
[5]Department of Physical Therapy and Human Movement Sciences, Feinberg School of Medicine, Northwestern University Chicago, Evanston, IL, USA
[6]Sobell Department of Motor Neuroscience, UCL Institute of Neurology, Queen Square, London, UK
[7]The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
[8]Department of Rehabilitation Medicine, Department of Medicine, and Department of Cell Biology, Division of Physical Therapy, Emory University School of Medicine, Atlanta, GA, USA
[9]Atlanta VA Center for Visual and Neurocognitive Rehabilitation, Atlanta, GA, USA
[10]Departments of Neurology, Neuroscience, and Physical Medicine & Rehabilitation, Johns Hopkins University, Baltimore, MD, USA
[11]The Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver Canada
[12]Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[13]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Canada
[14]Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Ottawa, Canada
[15]Departments of Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation, University of California, Irvine, CA, USA

*This article was first published in *International Journal of Stroke* 2017, Volume 12, Issue 5, pages 444–450. To request permission to re-use any part of this article, please contact SAGE Publishing: https://uk.sagepub.com/en-gb/eur/journals-permissions.

Corresponding Author:
Julie Bernhardt, PhD, The Florey Institute of Neuroscience and Mental Health, University of Melbourne, 245 Burgundy St, Heidelberg, Victoria 3084, Australia.
Email: Julie.Bernhardt@florey.edu.au

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.

Behavioral restitution or true recovery

Behavioral 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 behaviors 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 realized 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 behavioral repertoire constitutes compensation. This behavior 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 behavioral 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 behavior 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 behaviors occur early post-stroke with little or no active treatment.[15]

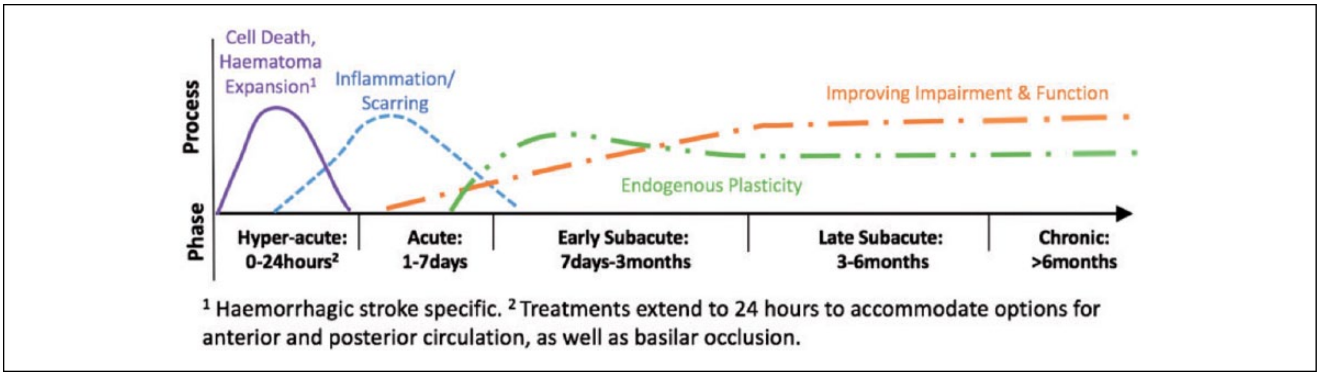

Figure 1. Framework that encapsulates definitions of critical timepoints post stroke that link to the currently known biology of recovery.

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 behavioral recovery beyond that which occurs spontaneously. Additional definitions that are key for the field of stroke rehabilitation and recovery are contained throughout this document and in Appendix 1.

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 six months post-stroke and beyond. The possibility for behavioral changes even years post-stroke is recognized. However, the current understanding of brain repair processes suggests that the majority of behavioral 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 maximize the potential of restorative interventions.

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 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 behavioral, 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]
- **Characterizing 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 behavioral restitution from compensation. This distinction will help us characterize 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 breaking down the silos that have historically divided basic and clinical researchers. This training should also include standardized 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 centers of excellence in stroke recovery.** These centers 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 centers.
- **A radical new aim.** We believe a new dialogue and a collective collaborative investment are 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 to 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]

Appendix 1. Additional Definitions That Are Key for the Field of Stroke Rehabilitation and Recovery.

Behavioral control is how the CNS creates behavior. 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]

Behavioral 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, behavioral learning might arise as a result of the modification of the temporal and spatial organization of muscle synergies, which result in smooth, accurate, and consistent movement sequences.[47]

Skill is improved behavioral 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-oriented therapy."[53]

Adaptation is the reduction of systematic errors in response to perturbation to maintain or improve performance.[54–56]

Acknowledgments

We would like to acknowledge Professor Julie Bernhardt for convening this first Stroke Recovery and Rehabilitation Roundtable (SRRR), Ms Katie Lafferty for moderating discussions at SRRR and Dr Karen Borschmann for project management. We thank everyone who contributed to the SRRR meeting: Myzoon Ali, Jovita Balcaitiene, Michele Basso, Francesca Bosetti, Marian C. Brady, Leeanne M. Carey, Alexandre R. Carter, Daofen Chen, Leonid Churilov, Andrew N. Clarkson, Leonardo G. Cohen, David A. Copland, Numa Dancause, Catherine M. Dean, Janice J. Eng, Coralie English, Amanda J. Farrin, Cynthia Felix, Rebecca J. Fisher, Anne Forster, Mary Elizabeth Harriman, Tammy C. Hoffman, Heidi Johansen-Berg, Jukka Jolkkonen, Theresa A. Jones, Mary Teena Joy, Katie Lafferty, Peter Langhorne, Natasha A. Lannin, Alex P. Leff, Elizabeth A. Lynch, Jane M. Maguire, Louise D. McCullough, Timothy H. Murphy, Michael Nilsson, Kathryn A. Radford, Charlotte Rosso, Gustavo Saposnik, Martin E. Schwab, Cathy M. Stinear, Katharina S. Sunnerhagen, Erwin E. H. van Wegen, Marion F. Walker, Caroline L. Watkins, Tadeusz Wieloch, Carolee Winstein.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: JB was supported by NHMRC (1058635); KSH was supported by NHMRC (1088449) and Micheal Smith Foundation for Health Research (MSFHR) (15980); SLW was supported by National Institutes of Health (NIH) (1U10NS086607); LAB was supported by the Canada Research Chairs and MSFHR (CI-SCH-01796); DC was supported by the HSF of Canada and CPSR; SCC was supported by a grant from NIH (K24 HD074722). We acknowledge the following organisations for their financial support of the meeting: National Health and Medical Research Centre (NHMRC) Centre of Research Excellence in Stroke Rehabilitation & Brain Recovery (Australia), Heart and Stroke Foundation (HSF) of Canada, Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (CPSR). An unrestricted educational grant was provided by Ipsen Pharma. The Florey Institute of Neuroscience and Mental Health acknowledges support from the Victorian Government, in particular funding from the Operational Infrastructure Support Grant.

References

1. Bernhardt J, Borschmann K, Boyd L, et al. Moving rehabilitation research forward: developing consensus statements for rehabilitation and recovery research. *Int J Stroke* 2016; 11: 454–458.
2. Corbett D, Carmichael ST, Murphy ST, et al. Enhancing the alignment of the preclinical and clinical stroke recovery research pipeline: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR) translational working group. *Int J Stroke* 2017. DOI: 10.1177/1747493017711814.
3. Boyd LA, Hayward KS, Ward NS, et al. Biomarkers of stroke recovery: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). *Int J Stroke* (under review).
4. Kwakkel G, Lannin N, Borschmann K, et al. Standardised measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). *Int J Stroke* 2017. DOI: 10.1177/1747493017711813.
5. Walker MF, Hoffmann TC, Brady MC, et al. Improving the development, monitoring and reporting of stroke rehabilitation research: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). *Int J Stroke* 2017. DOI: 10.1177/1747493017711815.
6. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehab Neural Repair* 2012; 26: 923–931.
7. Kwakkel G, Veerbeek JM, van Wegen EEH, Wolf SL. Constraint-induced movement therapy after stroke. *Lancet Neurol* 2015; 14: 224–234.
8. British Society of Rehabilitation Medicine. *Rehabilitation following acquired brain injury: National Clinical Guidelines*. London, UK: Physicians RCo, 2003.

9. World Health Organisation. *International classification of functioning, disability and health*. Geneva: World Health Organisation, 2001.
10. Levin MF, Kleim JA, Wolf SL. What do motor 'recovery' and 'compensation' mean in patients following stroke? *Neurorehab Neural Repair* 2009; 23: 313–319.
11. Zeiler SR, Krakauer JW. The interaction between training and plasticity in the post-stroke brain. *Curr Opin Neurol* 2013; 26: 609–616.
12. Duff M, Chen Y, Cheng L, et al. Adaptive mixed reality rehabilitation improves quality of reaching movements more than traditional reaching therapy following stroke. *Neurorehab Neural Repair* 2013; 27: 3016–315.
13. Hope TM, Seghier ML, Leff AP, Price CJ. Predicting outcome and recovery after stroke with lesions extracted from MRI images. *Neuroimage Clin* 2013; 2: 424–433.
14. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. *Ann Neurol* 2006; 59: 735–742.
15. Cramer SC, Koroshetz WJ, Finklestein SP. The case for modality-specific outcome measures in clinical trials of stroke recovery-promoting agents. *Stroke* 2007; 38: 1393–1395.
16. Nakayama H, Jorgensen H, Raaschou H, Olsen T. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1994; 75: 394–398.
17. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol* 2015; 78: 848–859.
18. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke:outcome assessment and sample size requirements. *Stroke* 1992; 23: 1084–1089.
19. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehab Neural Repair* 2008; 22: 64–71.
20. Winters C, van Wegen EEH, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehab Neural Repair* 2015; 29: 614–622.
21. Winters C, van Wegen EEH, Daffershofer A, Kwakkel G. Generalizability of the maximum proportional recovery rule to visuospatial neglect early poststroke. *Neurorehab Neural Repair* 2017; 31: 334–342.
22. Lendrem W, Lincoln NB. Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks after stroke. *J Neurol Neurosurg Psychiatr* 1985; 48: 743–748.
23. Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995; 38: 659–666.
24. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain* 1951; 74: 443–480.
25 Lazar RM, Minzer B, Antoniello D, Festa JR, Krakauer JW, Marshall RS. Improvement in aphasia scores after stroke is well predicted by initial severity. *Stroke* 2010; 41: 1485–1488.
26. Burke E, Cramer SC. Biomarkers and predictors of restorative therapy effects after stroke. *Curr Neurol Neurosci Rep* 2013; 13: 329.
27. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. *Restor Neurol Neurosci* 2013; 31: 707–722.
28. Dobkin BH, Carmichael ST. The specific requirements of neural repair trials for stroke. *Neurorehab Neural Repair* 2016; 30: 470–478.
29. Bernhardt J, English C, Johnson L, Cumming TB. Early mobilization after stroke: early adoption but limited evidence. *Stroke* 2015; 46: 1141–1146.
30. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci* 2004; 24: 1245–1254.
31. Caliaperumal J, Colbourne F. Rehabilitation improves behavioral recovery and lessens cell death without affecting iron, ferritin, transferrin, or inflammation after intracerebral hemorrhage in rats. *Neurorehab Neural Repair* 2014; 28: 395–404.
32. Clarkson A, Overman J, Zhong S, Mueller R, Lynch G, Carmichael ST. AMPA receptor-induced local brain-derived neurotrophic factor signaling mediates motor recovery after stroke. *J Neurosci* 2011; 31: 3766–3775.
33. Carmichael ST. The 3 Rs of stroke biology: radial, relayed, and regenerative. *Neurotherapeutics* 2016; 13: 348–359.
34. Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci* 2004; 22: 281–299.
35. Hankey GJ. Stroke. *Lancet* 2016; 389: 641–654.
36. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; 5: 53–63.
37. Bernhardt J, Godecke E, Johnson L, Langhorne P. Early rehabilitation after stroke. *Curr Opin Neurol* 2017; 30: 48–54.
38. Stinear C, Ackerley S, Byblow W. Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. *Stroke* 2013; 44: 2039–2045.
39. Birkenmeier RL, Prager EM, Lang CE. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehab Neural Repair* 2010; 24: 620–635.
40. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT. *Neurology* 2009; 73: 195–201.
41. Kwakkel G, Winters C, van Wegen EEH, et al. Effects of unilateral upper limb training in two distinct prognostic groups early after stroke: the EXPLICIT-stroke randomized clinical trial. *Neurorehab Neural Repair* 2016; 30: 804–816.
42. Winters C, Heymans MW, van Wegen EEH, Kwakkel G. How to design clinical rehabilitation trials for the upper paretic limb early post stroke? *Trials* 2016; 17: 468.
43. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain* 2012; 135: 2527–2535.
44. Cortes JC, Goldsmith J, Harran MD, et al. A short and distinct time window for recovery of arm motor control early after stroke revealed with a global measure of trajectory kinematics. *Neurorehab Neural Repair*. Published online March 16, 2017: 1545968317697034.

45. Ward NS. Restoring brain function after stroke – bridging the gap between animals and humans. *Nat Rev Neurol* 2017; 13: 244–255.
46. Cramer SC, Wolf SL, Adams HP Jr., et al. Stroke recovery and rehabilitation research: issues, opportunities, and the national institutes of health StrokeNet. *Stroke* 2017; 48: 813–819.
47. Schmidt RA, Lee TM. *Motor control and learning: a behavioural emphasis*. 4th ed. Champaign, IL: Human Kinetics, 2005.
48. Haith AM, Krakauer JW. Theoretical models of motor control and motor learning. In: Gollhofer I, Taube W, Nielsen JB (eds) *Handbook of motor control and motor learning*. Abingdon, Oxon, UK: Routledge, 2012, pp. 7–28.
49. Shmuelof L, Krakauer JW, Mazzoni PJ. How is a motor skill learned? Change and invariance at the levels of task success and trajectory control. *J Neurophysiol* 2012; 108: 578–594.
50. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation into clinical practice. *OccupTher Int* 2009; 16: 175–189.
51. French B, Thomas LH, Leathley MJ, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev* 2007; 4: CD006073.
52. Carr J, Shepherd R. *Movement science: foundations for physical therapy in rehabilitation*. Maryland, USA: Aspen Publishers, 2000.
53. Bayona NA, Bitensky J, Salter K, Teasell RW. The role of task-specific training in rehabilitation therapies. *Topics Stroke Rehab* 2005; 12: 58–65.
54. Fasotti L, van Kessel M. Novel insights in the rehabilitation of neglect. *Front Hum Neurosci* 2013; 7: 780.
55. Richards L, Hanson C, Wellborn M, Sethi A. Driving motor recovery after stroke. *Top Stroke Rehabil* 2008; 15: 397–411.
56. Dobkin BH, Dorsch A. New evidence for therapies in stroke rehabilitation. *Curr Atheroscler Rep* 2013; 15: 331.