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RESEARCH ARTICLE

RETHINKING STROKE RECOVERY RESEARCH: A REVIEW OF KNOWLEDGE USE AND THE NEED FOR TEAM SCIENCE

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ABSTRACT

Stroke recovery research on living humans has made recent strides toward a consensus in support of new knowledge-to-action interventions. This venue could become fertile ground for future milestones, driven by the conceptualization and dissemination of standards that can aid the aggregation of large datasets for further interpretation in the stroke recovery science. For example, a meta-analysis could identify biomarkers that predict recovery, or outcome measures that detect neurological recovery. Nevertheless, the current breadth of research requires a systematic framework to enable the transfer of this powerful knowledge to the end users (e.g., clinicians and decision-makers). Team Science (TS) and the Science of Team Science (SciTS) are two emerging concepts that could foster an approach of inter professional collaboration on specific research inquiries between scientists in different fields. Presently, however, the stroke recovery literature favours parallel but separate research interventions in the areas of sensor motor, cognitive and speech-language problems. TS and the SciTS together hold the potential to navigate the interference between these three problem categories, avoid unnecessary overlapping efforts and facilitate the broad translation of the findings.

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INTRODUCTION

In its most recent ten-year public health report, the World Health Organization (WHO) estimates that between 2007 and 2017, 17.5 million people died annually from cardiovascular disease, with heart attacks and strokes causing approximately 80% of these deaths (WHO, 2017). Stroke treatment has always been challenging, and an evolving consensus among the research community advocates for a focus on preclinical studies, acute stroke care and rehabilitation in stroke units. Within the past two years alone, many scholars have scrutinized stroke recovery and agreed that we need more advanced stroke research to achieve a breakthrough (Bernhard *et al.*, 2016; Hayward *et al.*, 2017; Jolkkonen and Kwakkel, 2016; Stinear, 2016; Zerna, Hill, and Boltze, 2017). Though there are plenty of knowledge gaps to be addressed (Bosettiet *et al.*, 2017; Langhorne, Coupar, and Pollock, 2009; Sacco *et al.*, 2015), this is not the only barrier to a breakthrough. Generally speaking, setbacks in stroke recovery research stem not from a lack of knowledge, but rather from inadequate translation and transference of that knowledge. Stroke recovery is one of the most sophisticated and challenging topics in the health sciences, and the extent of our

knowledge use is potentially much less than what we expect and desire to uptake (Graham *et al.*, 2006). As a result, most stroke recovery research remains trapped within processes that require constant reassessments to resolve the complicated matrix of factors. Because there are many overlapping subcategories of research, useful knowledge may get lost between teams—inter professional collaboration is not yet the norm. Stroke recovery factors can be clearly identified and described, however, when the research community prioritizes efficient dynamics of knowledge use. Unfortunately, the majority of current models do not demonstrate proper interactions between knowledge use components—namely, "knowledge translation" and "knowledge transfer"—to find advanced solutions for stroke questions. Even these terms themselves often are misused, making it challenging for the existing models to trace their dynamics and monitor the process of interaction. Here, we argue that the underlying problem is the unidimensional feature of the current research projects, which force these projects to move knowledge within only one portion of one topic, rather than across a wide range of topics or sciences. Accordingly, this review argues for a broader scope of stroke recovery research to advance the field and facilitate a breakthrough. We first present current conflicts in the components of knowledge use, and then advocate for the

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adoption of systematic inter professional collaboration to support large-scale research projects in the field of stroke recovery.

First Theme: Knowledge Use: To use current and future knowledge about stroke recovery efficiently, researchers should first translate that knowledge and then transfer it to the clinicians, decision-makers, clients and other stakeholders. The distinction between "knowledge translation" and "knowledge transfer" is key to establishing evidence-based practice founded on clear reasoning and accurate transformation of knowledge into actions (Graham *et al.*, 2006). Unfortunately, "translation" and "transfer" have been, and continue to be, misused as interchangeable terms, perhaps due to their relative novelty in the literature. The Canadian Institutes of Health Research (2016) defines "knowledge translation" as the "dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system," while "knowledge transfer" describes "the one-way flow of knowledge from researchers to potential users" (Johnson, 2005).

Once research creates knowledge about a certain problem, systematic models must facilitate knowledge dissemination and implementation. For some topics, it can be challenging to select appropriate models; for stroke recovery, however, the literature has explored and categorized many models to assist future researchers with model selection. Still, of the many research products, only a few are converted into practices and policies that can improve public health (Tabak, Khoong, Chambers, and Brownson, 2012). This is evident in the many stroke recovery studies that create ostensibly useful knowledge but are found to be low in effect size and compromised by methodological flaws, and therefore are criticized for poor translational value (Jolkonen and Kwakkel, 2016). The following paragraphs present a sampling of studies in stroke recovery research that are limited by translational issues which, if solved, could lead us into a new era of stroke science.

The misuse of terminologies: Inconsistent and overlapping terminologies impede the dissemination and use of stroke recovery research. For example, the literature often interchanges the following terms: "motor recovery", "motor compensation", and "functional recovery". Even the word "recovery" is sometimes misleading, especially when presented within the context of improving stroke science. The simplifications have been discussed in the literature within the scope of the International Classification of Functioning (ICF) model (Levin, Kleim, and Wolf, 2009), which categorizes recovery under the three levels: impairment, activity and participation (WHO, 2001). "Recovery" or "stroke recovery" also are interchanged sometimes with "rehabilitation" and "stroke rehabilitation," all with the intention of referencing the process of care rather than the change in the physical status of a patient. Thus, systematic collaboration, expanded consensus and language monitoring are required across the researchers and knowledge users (e.g., therapists and decision-makers). Researchers and scholars must not only agree on definitions, but also ensure that this updated foundational knowledge is sustained, appropriately transferred and used by other stakeholders as illustrated in the of knowledge-to-action cycle (Figure 1).

Using biomarkers to detect recovery: Biomarkers of stroke recovery, as described by Marie-Hélène and Cramer (2008), are measures or indicators that result from molecular or cellular events in the recovery process and are good proxies for a patient's clinical progress. Unfortunately, the current science is yet unable to measure or detect the molecular or cellular events themselves in living humans. Bernhardt *et al.* (2016) suggest three types of biomarkers in research: 1) measures of biological state, 2) measures that predict future clinical events and 3) measures that parallel behavioural changes. Biomarkers may represent direct or surrogate changes in body status, arising from any level of recovery and reflecting the results of the applied interventions (e.g., physical exercises or drugs). It is important to note that biomarkers apply not only to motor changes, as is widely discussed and explored in most of the stroke recovery research, but also to status changes in soma to sensation, cognition and speech-language. An understanding of biomarkers can help the whole team, including the rehabilitation staff and the patient—biomarkers are not merely for researchers or the medical team. The current evidence in stroke recovery science suggests that biomarkers are woefully underused as predictors for recovery (Kim and Winstein, 2017). Major gaps exist in the knowledge-to-action cycle, from identifying practices that could be informed by biomarkers to using knowledge sustainably. Therefore, there is an urgent need to evaluate and synthesize the massive volume of emergent biomarker research to enable the implementation of evidence-based interventions. This process commenced recently in stroke recovery research—Boyd *et al.* (2017) describe a consensus on biomarkers that distinguish stroke subgroups and can be included in clinical trials. The consensus identifies some biomarkers of brain structure and function that are approved for use in clinical trials, but only to evaluate the motor and language domains (Table 1). This newfound use of biomarkers must be extended from the research context to the clinical and educational contexts to facilitate a successful uptake of practical guidelines (Stone, 2012). Though the recommendations unfortunately do not approve any biomarkers for the cognitive and soma to sensory domains, some existing biomarkers hold promise for the future.

Using outcome measures in stroke recovery research: The use of non-standard outcome measures to collect data in stroke recovery trials is another main hurdle opposing a breakthrough. Many researchers agree on the importance of 1) standardizing on core variables from existing outcome measures, 2) harmonizing measurements at specific point-time and 3) implementing large multi-centre trials (Ali, English, Bernhardt, Sunnerhagen, and Brady, 2013; Bernhardt *et al.*, 2016; Stinear, 2016). With these three components, researchers will be able to pool data for systematic review, conduct meta-analysis on the effects of interventions and confidently inform therapeutic guidelines. Once we select core variables represented by certain outcome measures, do we no longer need to develop other outcome measures? The answer lies in the question: core variables are, by definition, the minimum data sets needed to form an essential framework (Boers *et al.*, 2014; Dworkin *et al.*, 2005; Grieve *et al.*, 2017). We will always need outcome measures for focused and nuanced treatment targets. For example, we still need outcome measures for a sensitive differentiation between true neurological recovery and compensatory strategies (Bernhardt *et al.*, 2017). At the same time, we need to follow consensus-based criteria to steer the research toward consistent interventions.

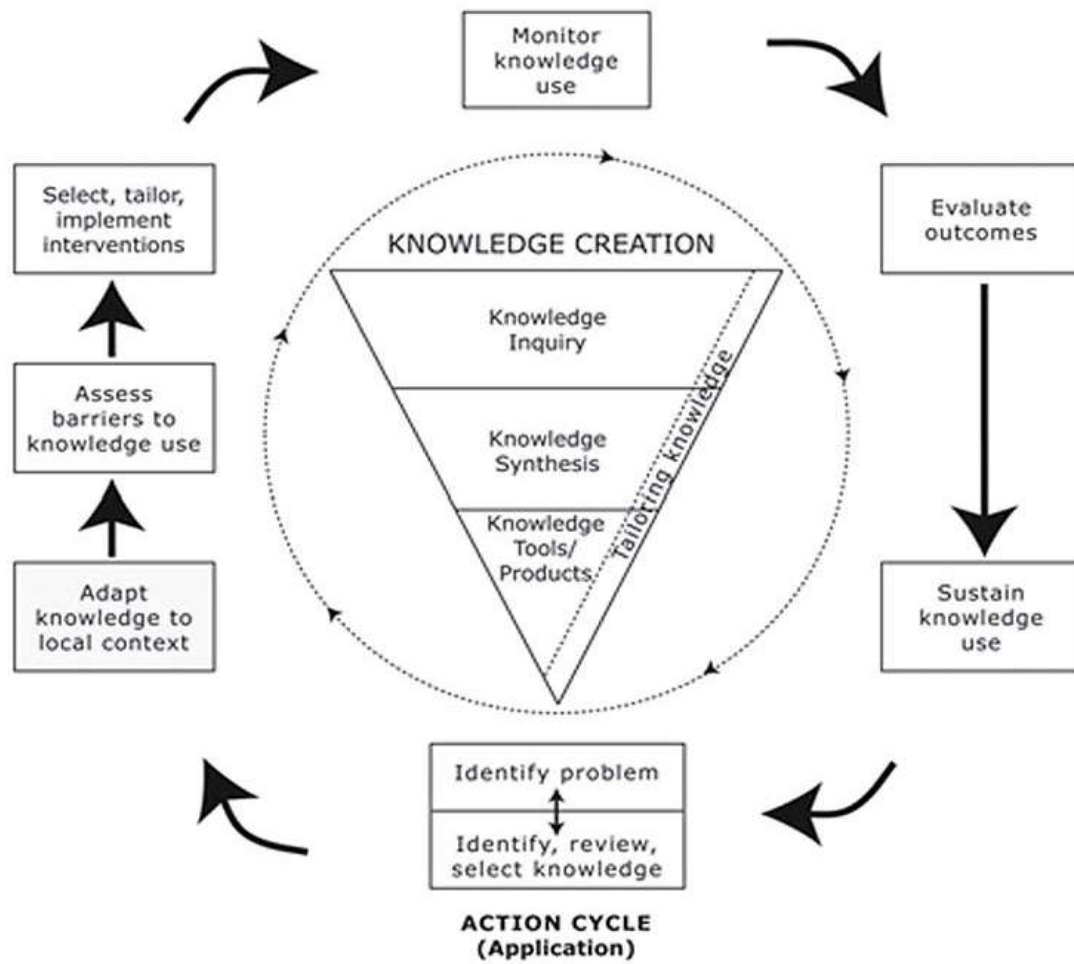


Figure 1. The knowledge-to-action process (Graham *et al.* 2006)

Table 1. Consensus-based biomarkers recommended for use in stroke recovery clinical trials (Boyd *et al.*, 2017).

Motor	Language
<p>CST indexed by DTI or by lesion overlap in the hyperacute, acute, early subacute, late subacute and chronic phases: This has demonstrated a moderate to strong relationship with impairment (outcome and recovery).</p> <p>TMS measure of MEP+ or MEP- of the upper limb: This tracks motor recovery up to the late subacute phase and monitors the effects of rehabilitation interventions up to the chronic phase. There is evidence of a strong relationship between impairment (outcome and recovery) and MEP status. We recommend that future studies of upper limb interventions determine whether patients are MEP+ or MEP- for the purposes of stratification.</p>	<p>Index structural damage as per the PLORAS imaging protocol: This predicts recovery from the chronic phase. The PLORAS database allows for an interpretation of an individual's lesion information, combined with time post-stroke and speech behaviour, to predict longitudinal aphasia recovery.</p>

Note. CST: corticospinal tract; DTI: diffusion tensor imaging; MEP+: motor evoked potential present; MEP-: motor evoked potential absent; PLORAS: predicting language recovery and outcome after stroke; TMS: transcranial magnetic stimulation.

In general, stroke recovery research lacks a standardized approach to measurement, which usually is taken at arbitrary time points after the injury. Instead, certain measures should be assessed at agreed-upon points after stroke onset, and for agreed-upon impairment constructs, to standardize the dataset for meta-analysis and identification of therapeutic interventions (Kwakkel *et al.*, 2017). Researchers also may need to develop new tools, such as kinematic and kinetic measures, and to improve participation measures as suggested by Kwakkel. Given the time and resources required to develop a rigorous instrument, however, it is paramount to conceptualize and agree on the essential constructs first (Dijkers, 2010). While there is a clear need to advance the science of outcome measurement in stroke recovery, it is important to recognize the existing foundations (Jolkonen and Kwakkel, 2016).

By recognizing that the current heterogeneity in outcome measures is a barrier to the uptake of new recommendations or guidelines, we may shift toward consensus-based outcome measures in stroke trials. The adoption of such measures may be inhibited by 1) insular environments and systems that lack international collaboration, 2) lack of opportunity to obtain and try new measurement tools (MacDermid, Law, and Michlovitz, 2014), 3) individual or institutional bias toward a particular measure, 4) misunderstanding of contextual relevance (Dunckley, Aspinall, Addington-Hall, Hughes, and Higginson, 2005), 5) new operational costs at clinical and research sites for tools and training (MacDermid, Law and Michlovitz, 2014) and 6) lack of culturally-validated translations to support consistent implementation and international collaboration (Dunckley, Hughes, Addington-Hall, and Higginson, 2003; Beaton, Bombardier, Guillemin, and Bosi Ferraz, 2000).

Second Theme: Improving Stroke Recovery as a Science

This theme argues that researchers need to adopt a systematic approach to address the gross human effort directed at answering stroke-related questions and building a cohesive foundation for scientific advancements across the continuum of care, from prevention to community reintegration. Therefore, it is useful at this juncture to think backward, examining the two concepts of "stroke rehabilitation" and "stroke recovery" and asking, are these two concepts different? "Stroke rehabilitation" implies a process of care that may or may not contribute to the resolution of stroke symptoms (Maulden, Gassaway, Horn, Smout, and DeJong, 2005); the resolution process is called "stroke recovery" (Young and Forster, 2007). The distinction between these two terms underscores the need to differentiate between specific phenomena, their interactions in our research programs and targeted outcomes. At the same time, we need a systematic approach to synergize the parallel efforts presently addressing these topics. This should lead us to ask, what does the emerging evidence suggest in the next breakthrough? Is this a breakthrough in stroke rehabilitation, stroke recovery or both? From the answers, researchers can build general working frameworks or models. Here, too, we face a decision: should the models focus on improving the healthcare system, such as the Model of Improvement developed by Associates in Process Improvement (Kilo, 1998), or focus on improving the healthcare research system's ability to solve scientific problems, such as the Team Science (TS) and Science of Team Science (SciTS) approaches (Stokols, Hall, Taylor, and Moser, 2008)? The two focuses could complement each other, but the current best practice models in both stroke research and stroke service delivery are still underdeveloped and struggling, mainly because of the lack of resources (Kuntz *et al.*, 2013; Stinear, 2016). Kuntz's (2013) paper reveals that this struggle includes many operational issues within and between the models and users on both sides. Therefore, there is a pressing need to develop not only models that improve stroke research and service delivery, but also frameworks that improve the dynamics between the two. The following paragraphs present high-level discussions from the current literature about the establishment of more powerful and specialized scientific teams and processes in research.

Team Science (TS) vs. the Science of Team Science (SciTS):

There are few publications on TS and SciTS in the health literature; though most were reproduced in the last decade, the topics themselves are not necessarily new (Baker, 2015; Hall, Feng, Moser, Stokols, and Taylor, 2008; Little *et al.*, 2016; Stokols, Hall, Taylor, and Moser, 2008). The lack of literature in this field may reflect the high level of specialization it requires, as TS/SciTS is considered one of the most complicated issues in the field of health policy and management (Glasgow, 2012). Also, there has been a recent increase in acknowledgment of the power of multiple disciplines, instead of a lone science, to solve complex questions in research (Fiore, 2008). While it is beyond the scope of this paper to review the dynamics and mechanisms of both topics fully, we will consider their potential to inform practical solutions for stroke recovery. Generally, the shared purpose of TS and SciTS is to address the most

challenging research demands by strengthening highly specialized collaborations between different sciences and across organizations (Koch and Jones, 2016; Stokols, Hall, Taylor, and Moser, 2008). The SciTS emerged to "understand, manage, and evaluate team science conditions, collaborative processes, and outcomes to enable translation of research findings into new scientific knowledge, advances, clinical practices, and policies" (Little *et al.*, 2017). Stokols highlights that SciTS must be distinguished from TS itself, which deals with training initiatives that are conducted by scholars or scientists working together to integrate their knowledge into one research project. TS may deal with high-scale trials in which the organizational context extends beyond one location or beyond the boundaries of any research setting (National Research Council, 2015). The National Research Council's 2015 book, "Enhancing the Effectiveness of Team Science," presents specific examples as well as models and frameworks of collaboration for building teams. These models and other emerging projects could inform our approaches to topics, like stroke recovery, with many potential challenges and mutual resources. For example, some advocates are calling for the adoption of TS to fill knowledge gaps, such as treatment evidence for sleep-disordered breathing (Drager, McEvoy, Barbe, Lorenzi-Filho, and Redline, 2017). The Allen Brain Observatory project is one example of a large project that has actually applied the TS approach (Koch and Jones, 2016), providing a potential roadmap for the use of TS in stroke recovery research. Despite the relative scarcity of literature about the SciTS, the impact of the TS inter professional collaboration in large research projects has established TS as an essential methodology (Little *et al.*, 2016). By integrating new TS initiatives, stroke recovery research may both benefit from its inter professional collaborative feature and nourish the SciTS literature. Researchers and decision-makers should anticipate challenges and barriers for any new initiative, and should be prepared to assess creatively and develop flexible and diverse mechanisms across scientific teams. Users of TS also are encouraged to design and implement rigorous roadmaps for knowledge translation and dissemination (Hall, Feng, Moser, Stokols, and Taylor, 2008) within and beyond their teams.

A Call for Parallel Research among Sensorimotor, Cognitive and Speech-Language Problems:

A quick review of the literature reveals that the majority of clinical trials have focused on motor recovery through interventions that target leg and hand movement. However, we now know that it is inadequate to promote motor recovery without considering other aspects, like sensation, cognition, speech and language (Levin, Kleim, and Wolf, 2009). The clinical and practical evidence has emerged gradually: Haggard *et al.* (2000) suggest, and Sagnier *et al.* (2017) confirm, that significant motor-cognitive interference exists when rehabilitation interventions focus on motor recovery in isolation. These studies identify a strong association between a participant's gait and cognitive performance, implying that motor assessments should always consider cognitive context during implementation. These two studies also include speech and language functions in the cognitive assessments. The stroke rehabilitation research has only a

tentative understanding about the interference and association between sensor motor, cognitive and speech-language recoveries. Larger longitudinal studies for stroke subgroups may clarify these relationships and enable researchers to transfer a prioritized list of evidence-based rehabilitation interventions to clinicians. The current evidence also recommends that these studies be conducted with strict adherence to a framework, such as the ICF, and that unified terminologies be established between the sensor motor, cognitive and speech-language themes. This standardization will enable researchers to use a transferrable language and, accordingly, ensure the parallel improvement of sensorimotor, cognitive and speech-language research. Additionally, the assessment of one theme within the context of the other themes may improve the quality of the current outcome measures within the primary theme, or may lead to the development of more valid and reliable instruments in research and practice. Finally, the parallel movement of somatosensory, cognitive and speech-language research alongside motor research is essential to overcoming translational hurdles. Challenges are expected in any complex pursuit, including stroke recovery research, but these can be minimized with systematic interprofessional collaboration that builds large-scale alliances under the umbrella of TS, and manages these teams by building intervention models based on the SciTS.

Conclusion

This paper illuminates two themes within stroke recovery research: 1) current problems in knowledge use and 2) the potential for a broad systematic approach to promote operational research and eliminate hurdles. The SciTS warrants further research to evaluate its efficiency with big data and its ability to facilitate top-tier international collaboration between scientific and clinical institutions. We also recommend further research and translational work in the soma to sensory, cognitive and speech-language domains, as these not only are integral to motor recovery research but also will tangibly benefit many patients who receive stroke rehabilitation.

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