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The Effects of Stroke and Stroke Gait Rehabilitation on Behavioral and Neurophysiological Outcomes:

Challenges and Opportunities for Future Research

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Abstract

Stroke continues to be a leading cause of adult disability, contributing to immense healthcare costs. Even after discharge from rehabilitation, post-stroke individuals continue to have persistent gait impairments, which in turn adversely affect functional mobility and quality of life. Multiple factors, including biomechanics, energy cost, psychosocial variables, as well as the physiological function of corticospinal neural pathways influence stroke gait function and training-induced gait improvements. As a step toward addressing this challenge, the objective of the current perspective paper is to outline knowledge gaps pertinent to the measurement and retraining of stroke gait dysfunction. The paper also has recommendations for future research directions to address important knowledge gaps, especially related to the measurement and rehabilitation-induced modulation of biomechanical and neural processes underlying stroke gait dysfunction. We posit that there is a need for leveraging emerging technologies to develop innovative, comprehensive, methods to measure gait patterns quantitatively, to provide clinicians with objective measure of gait quality that can supplement conventional clinical outcomes of walking function. Additionally, we posit that there is a need for more research on how the stroke lesion affects multiple parts of the nervous system, and to understand the neuroplasticity correlates of gait training and gait recovery. Multi-modal clinical research studies that can combine clinical, biomechanical, neural, and computational modeling data provide promise for gaining new information about stroke gait dysfunction as well as the multitude of factors affecting recovery and treatment response in people with post-stroke hemiparesis.

Introduction

Stroke is a leading cause of adult disability in the United States,[1] with stroke prevalence, stroke-related healthcare costs, and public health burden expected to increase in the next 20 years.[2] Gait dysfunction persists at discharge from rehabilitation in over 2/3rd stroke survivors, adversely affecting community participation and quality of life.[3–6] Due to the importance of walking in daily activities, restoration of gait function is a major goal of rehabilitation.[4,7] However, stroke gait deficits are complex and multi-factorial. Stroke gait impairments adversely affect kinematics and kinetics in all paretic lower limb joints, disrupt stance and swing phases, and are marked by inter-limb asymmetry.[3,8,9] making the diagnosis and identification of targets for treatment challenging. Several gait training interventions have been shown to improve walking function, and there is consensus that stroke survivors benefit from gait rehabilitation.[10–15] However, agreement in literature is lacking on how to maximize treatment rehabilitation efficacy.[16,17] Also, for a majority of gait interventions, irrespective of whether the intervention is proven to be statistically superior, there is high inter-individual variability in treatment effects.[16,18,19] While a subset of stroke participants show large or meaningful improvements (responders), others do not (non-responders). The challenge is that multiple factors, including biomechanics, energy cost, psychosocial factors, as well as the physiological function of corticospinal neural pathways influence stroke gait function and training-induced gait improvements. As a step toward addressing this challenge, the objective of the current perspective paper is to outline knowledge gaps and future research opportunities pertinent to the measurement and retraining of gait after stroke.

Recommendations for future research related to measuring the effects of stroke on gait performance and walking function using behavioral data

Clinical outcomes commonly used to assess sensorimotor impairment (e.g. Fugl-Meyer score) and gait function (e.g. gait speed)[20] are an indispensable part of clinical rehabilitation, but they fail to capture gait quality and spatio-temporal *movement patterns* (*how* a person is moving). With respect to gait biomechanics outcomes, comprehensively mapping the effects of stroke is challenging because stroke gait impairments adversely affect kinematics (the description of motion) and kinetics (description of forces causing motion) in all paretic lower limb joints, disrupting all phases of gait.[8,9] Our laboratory has published several studies that measured post-stroke gait patterns via biomechanical evaluation (gait kinematics and kinetics). There is high variability in gait biomechanics metrics over the gait cycle between the paretic and nonparetic leg of stroke survivors, compared to an able-bodied individual. These effects of stroke on multiple gait variables across different stroke survivors are often poorly characterized using current approaches. Even with laboratory instrumentation, typically, in biomechanics and rehabilitation research, our lab[21–29] and others[30–39] use discrete metrics derived from complex gait data (e.g. peak ankle angle, peak anterior ground reaction force (AGRF)) to answer scientific questions about effects of interventions[18,22,40–43] However, such univariate analysis of discrete variables fails to capture the multivariate nature of gait deficits. Discrete variables that represent one sub-phase or singular point in the gait cycle may fail to capture the time courses and continuous nature of gait throughout the walking cycle and across multiple cycles. Even the time histories of continuous kinematics and kinetics may fail to capture the inter-dependences between the variables and inter-limb coordination over time. There is a need for more research incorporating computational methods to capture multivariate effects of stroke on gait, while accounting for different phases of gait, to derive comprehensive, holistic metrics of gait quality.

Furthermore, two stroke survivors with the same gait speed or Fugl-Meyer score can have very different impairments in their gait biomechanics or coordination patterns. Due to lack of access to expensive laboratory equipment and limited treatment time, clinicians commonly also subjectively observe and their patient's walking patterns without using quantitative data, limiting the objectivity and reproducibility of clinical decision-making. With emerging technologies, wearable sensors and smart phone videos can enable gait to be measured quantitatively in clinical settings. However, these systems still generate a lot of data, subject to interpretation, including multiple joint angles, and over 20-50 spatiotemporal gait metrics.[44,45] Thus, another avenue for future research is the development and clinical validation of gait analysis methods that can be applied to clinical settings, while being rapid, objective, intuitive, interpretable, and user-friendly to supplement clinical outcomes.

Biomechanical metrics or computational analysis have strong potential for enhancing our understanding of the biomechanical mechanism underlying rehabilitation response, because they can provide valuable insights about restitution versus compensation as well as underlying changes in motor control. Gait treatments may allow compensation, rather than true restitution, to improve gait speed and endurance. Outcomes of gait function (e.g. gait speed or endurance) lack the specificity to differentiate behavioral restitution from compensation, and fail to elucidate mechanisms. In a 2018 study, three categories of stroke survivors who walked at similar self-selected speeds demonstrated high variability in pelvic excursion deviation and inter-limb asymmetry in gait biomechanics,[9] supporting the sensitivity and advantage of biomechanical measures over speed-based outcomes. Use of gait speed and endurance to assess treatment-related improvements, without regard to biomechanical patterns or neuropathological responses is a limitation in gait rehabilitation research. For example, training-induced improvements in speed may be accompanied by improved propulsive symmetry, greater reliance on the nonparetic leg (e.g. for forward propulsion), or energy-inefficient compensations from proximal joints (e.g. circumduction, increased pelvic excursion[9]). Similarly, improvements in paretic peak AGRF can be accompanied by worsening of other metrics, including inter-limb propulsion or step length asymmetry, or inefficient compensations in other gait variables at different points in the gait cycle. Previous studies have also suggested that gait rehabilitation efficacy may depend on individual differences in muscle coordination[28,46,47] that generate spatiotemporal gait coordination patterns. Individual-specific biophysical modeling methods can also help predict and interpret mechanisms of treatment-induced changes in stroke gait,[28,46] and merit more investigation in future research. Finally, multi-modal clinical research studies with inter-disciplinary study teams can combine clinical, biomechanical, and modeling data to gain new information about stroke gait dysfunction as well as factors affecting recovery and treatment response.

Recommendations for future research related to measuring the effects of stroke on neural circuits using non-invasive human neurophysiology data

Stroke induces a cascade of changes in cortical and spinal circuits involved in locomotor control.[48–50] The stroke-lesion induces structural and functional changes in cortical, brain stem, and spinal circuitry controlling locomotion.[48] Effects of stroke on different neural circuits are complex, with potential disparities at different sites of the neuraxis, necessitating the use of multimodal approaches for in-depth assessment. There is a gap in our understanding of neurobiological processes underlying gait recovery and rehabilitation. The international Stroke Recovery and Rehabilitation Roundtable convened to “move rehabilitation research forward,” listed “*identifying neurobiological mechanisms* of treatment” and “*sequential* development, testing, and *refining* of interventions” as important research goals.[51,52]

While increasing gait speed, understandably, is a major focus of gait rehabilitation, increases in gait speed may occur via diverse biomechanical and neural mechanisms. Although gait treatments may increase speed by making a compensatory strategy more effective, current neurorehabilitation philosophies based on neuroplasticity principles strive for restitution of deficits. In a 2017 review, Bowden et. al. concluded that “because rehabilitation literature is yet to support a causal, mechanistic link for functional gains post-stroke, a multimodal approach to stroke rehabilitation is necessary.”[53] We posit that lack of inclusion of neuroplasticity outcomes is a major limitation in gait rehabilitation research.[16,17,51,52,54–59]

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Neuroplasticity, the capacity of the nervous system to demonstrate structural and functional change in response to experience, is a fundamental yet under-investigated mechanism of stroke gait rehabilitation.[48,49,60–64] Neuroplasticity research has helped develop consensus that to induce lasting improvements in gait function, training must incorporate repetitive, intense, and challenging practice,[65] and informed innovative clinical algorithms to predict upper limb recovery post-stroke.[61,66] Several non-invasive neuromodulation interventions have also been tested to enhance post-stroke recovery.[67–69] However, current neuroplasticity principles are still derived largely from upper limb studies, leaving a gap regarding neural substrates of *gait* treatments. While randomized controlled trials may show that an intervention is efficacious, they often fail to inform us whether the intervention modified the stroke-related neurophysiological sequelae, and *why* or *for whom* the intervention is effective.[70] Thus, there is a need for a shift toward *mechanism-focused* clinical trials.[52,70]

The importance of corticospinal tract and motor cortex (M1) excitability in human locomotor control and stroke recovery is well studied. Transcranial magnetic stimulation-derived outcomes such as motor evoked potential amplitude and motor threshold can supplement clinical and biomechanical measures to evaluate overall corticospinal tract excitability or output in the lesioned hemisphere post-stroke. Paired pulse transcranial magnetic stimulation methods can probe intracortical circuitry, which also plays a role in gait, and can influence training-induced plasticity.[55,71–73] Hoffman's or H-reflexes and related non-invasive measures (e.g. reciprocal inhibition) can provide valuable measures of spinal circuit physiology, which in turn may be associated with spasticity and coactivation during gait.[55,74] In addition to cortical and spinal circuits, the effects of stroke and training-induced neuroplasticity on brain stem, propriospinal, and other circuitry can provide important information to guide future clinical research and practice. Related, measures of brain structure derived using neuro-imaging can supplement neurophysiology, as well as behavioral gait outcomes.

As an example to illustrate research on gait rehabilitation-induced neuroplasticity, high-intensity treadmill training is an evidence-supported treatment that provides practice of thousands of steps and aerobic exercise within a safe, predictable environment. However, depending on the type and content of adjunctive feedback or cues (verbal, biofeedback, stimulation), the effects of the treatment on paretic leg biomechanical deficits may vary. Importantly, neural correlates underlying high-intensity training need more study. A single session of high-intensity interval treadmill walking exacerbated already suppressed ankle muscle corticospinal excitability in the paretic leg post-stroke.[75] Four weeks of treadmill training in chronic stroke improved gait speed compared to control treatment, but increased cortical excitability in the *non-lesioned* hemisphere.[76] Similarly, the 'FastFES' intervention combines fast treadmill training with functional electrical stimulation (FES) to ankle dorsi- and plantar-flexor muscles timed with the appropriate phase of gait. FastFES is designed to improve paretic leg AGRF by synergistically facilitating more posterior positioning of paretic trailing limb relative to the body's center of mass and use FES to augment activation of the paretic plantarflexors during late stance—key parameters underlying forward propulsion (L. N. Awad et al., 2016a; Hsiao, Knarr, Higginson, & Binder-Macleod, 2015a).[18,77] FastFES forms a valuable gait treatment paradigm because it uses a hypothesis-based biomechanical approach to improve gait function by targeting specific impairments in the paretic leg; has been shown to improve gait speed, endurance, and energy efficiency; and should facilitate motor learning and neuroplasticity.[18,22,30] However, similar to most gait interventions, with high-intensity fast treadmill training and FastFES, not all participants improve gait function, with training-induced change in gait speed showing high inter-individual variability.[18,37] We posit that inclusion of neurophysiology measures in clinical trials is important to understand *how* and *why* an intervention improves gait function, especially with regards to neural mechanisms. Another related limitation in current gait rehabilitation is that intervention-prescription is not determined based on baseline impairments or neurobiological characteristics.

Summary

Stroke continues to be a leading cause of adult disability, contributing to immense healthcare costs. Even after discharge from rehabilitation, post-stroke individuals continue to have persistent gait impairments, which in turn adversely affect functional mobility and quality of life. This perspective paper provides an overview of current research, and recommendations for future research directions to address important knowledge gaps. We posit that there is a need for leveraging emerging technologies to develop innovative, comprehensive, methods to measure gait patterns quantitatively, to provide clinicians with objective measure of gait quality that can supplement conventional clinical outcomes of walking function. Additionally, we posit that there is a need for more research on how the stroke lesion affects multiple part of the nervous system, and to understand the neuroplasticity correlates of gait training and gait recovery.

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