# Plasticity and motor recovery after stroke: Implications for physiotherapy

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## ABSTRACT

Despite advances in prevention and acute management of stroke and a proliferation of motor rehabilitation trials over the last decade, disability rates after stroke remain high. This commentary considers recent evidence, which suggests that it is time to extend our thinking beyond the model of cortical use-dependent plasticity that has underpinned much of physiotherapy stroke rehabilitation for the last 20 years. The discovery of a fixed, proportional recovery of impairment has led to a renewed focus on how rehabilitation may interact with spontaneous biological recovery. There is also increasing interest in use-dependent plasticity in the *white matter* as a possible mechanism for improving motor recovery after stroke. These emerging areas in stroke rehabilitation research have yet to be fully investigated, but provide some promise for future trials. In the interim, becoming familiar with all aspects of neural plasticity after stroke may help to equip physiotherapists with greater understanding of the mechanisms of stroke recovery and enable critical decision-making around the selection and timing of interventions after stroke.

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## INTRODUCTION

Stroke is a leading cause of disability, with up to 50% of stroke survivors experiencing ongoing disability and 30% requiring assistance for activities of daily living (Roger et al 2012). Despite advances in the prevention and acute management of stroke, the prevalence of stroke survivors living with disability is increasing worldwide (Feigin et al 2014).

The number of randomised controlled trials (RCTs) in motor rehabilitation after stroke has increased three-fold in the last 10 years (Veerbeek et al 2014). These RCTs have investigated a variety of physiotherapy interventions after stroke, with around half aimed at arm and hand recovery and a third aimed at gait and mobility (Veerbeek et al 2014). The strength of evidence supporting physiotherapy interventions after stroke has increased since a systematic review in 2004 (Van Peppen et al 2004). However positive effect sizes are small (5-15%) and a disappointingly large proportion of studies indicate that the experimental interventions produce equal, rather than better, results when compared with conventional physiotherapy (Veerbeek et al 2014). What is contributing to the small effect sizes in stroke rehabilitation research? Is it a lack of efficacy of the intervention, when the research is conducted during recovery, how the effects of the intervention are measured, or a combination of all of these factors?

One possible explanation is that the research is conducted primarily in the chronic stage after stroke, which means the intervention has no chance to interact with spontaneous biological recovery. Spontaneous biological recovery occurs during the first three months when the brain is in a state of heightened neuroplasticity (Krakauer et al 2012). This is not only the time when most recovery occurs (Jorgensen et al 1995, Kwakkel et al 2006) but also when most rehabilitation takes place. A systematic review by Stinear and colleagues (2013) found only 6% of good quality RCTs in motor rehabilitation enrolled all participants within the first 30 days of stroke. Therefore, the evidence base for therapies aimed at improving voluntary movement during this sub-acute stage is quite small. The mechanisms underlying therapy effects are likely to be quite different at the chronic stage to those during the sub-acute stage (Raghavan et al 2010, Stinear et al 2013). This limits the generalisability of trials conducted in chronic stroke to clinical practice, as most therapy is delivered in the sub-acute stage.

Small effect sizes may also reflect selection of outcome measures that are not sensitive to the proposed mechanisms of the intervention (Jolkkonen and Kwakkel 2016, Veerbeek et al 2014). Clarity about what the intervention is targeting (such as movement quality, speed, the ability to complete a task or return to functional activities) is critical both in choosing a sensitive outcome measure and understanding the biological rationale for the intervention (Bernhardt et al 2016, Buma et al 2013).

Trial design issues aside, the hunt is still on for an intervention that is able to increase stroke recovery above what is currently possible with conventional physiotherapy. New insights into neural plasticity early after stroke may provide some direction.

The purpose of this commentary is two-fold. Firstly, to consider recent developments in the study of spontaneous biological recovery and use-dependent plasticity after stroke, and secondly, to discuss how motor training interacts with recovery mechanisms. We then consider what this means for the practising physiotherapist.

## DISTINCTION BETWEEN IMPAIRMENT AND FUNCTION

One challenge in reviewing the literature in stroke rehabilitation is the interchangeable use of terms such as functional recovery, motor recovery, motor impairment and compensation (Levin et al 2009). Defining these terms clearly will reduce confusion. For the purposes of this commentary, motor impairment refers to the ability to perform a *movement* and can be evaluated with measures of strength and motor control. Function refers to the ability to perform a *task* and can be measured as task completion or time taken to complete the task.

True neurological recovery requires resolution of *impairment*, which allows movements and activities to be performed in the *same* way as before the stroke (using the same neural connections and motor patterns). Functional recovery, however, can still occur without full resolution of impairment. Compensation for residual impairment enables the recovery of function by using alternative neural connections and/or different patterns of muscle activity. For example, during a reaching task, the patient may compensate by: accessing different neural connections; altering the timing of muscle activation resulting in an altered movement pattern; using a combination of shoulder abduction and flexion instead of pure flexion; using an alternate grip; and/or they may lean forward with the trunk. These compensations allow the patient to achieve a functional reach, despite their residual impairment.

Improvement in function can occur without any change in impairment, and recovery of impairment does not always lead to functional improvement (Buma et al 2013, Kitago et al 2013, Kwakkel et al 2015). As the use of task-specific training has become established in stroke rehabilitation (Winstein and Kay 2015), most motor outcome measures assess functional recovery. These measures assess whether a task is completed or not, or how fast it is completed, rather than how *well* it is completed. They are unable to distinguish between an improvement in function due to a reduction in impairment, or an improvement in function due to compensation (Kitago and Krakauer 2013). Yet, this distinction is critical in understanding the biological mechanisms of recovery and therefore in understanding the role of physiotherapy in this process (Zeiler and Krakauer 2013).

## SPONTANEOUS BIOLOGICAL RECOVERY AND PROPORTIONAL RESOLUTION OF IMPAIRMENT

Spontaneous biological recovery is motor recovery that occurs in the absence of motor training after ischaemic injury to the brain (Cramer 2008, Nudo 2011, Zeiler and Krakauer 2013) and has been reported in both animals and humans after stroke (Carmichael 2010, Krakauer et al 2012, Nudo 2011). Ischaemia in the peri-infarct area triggers a cascade of effects (Xing et al 2012) ultimately resulting in upregulation of genes responsible for neuronal growth (heightened neuroplasticity), increases in long term potentiation (enabling strengthening of synapses and improved neurotransmission), alterations in excitation and inhibition via neurotransmitters in the lesioned cortex and axonal sprouting around the infarct site (Brown et al 2007, Carmichael 2006, Hagemann et al 1998, Zeiler and Krakauer 2013). This period of heightened sensitivity in the brain begins within hours of stroke onset and lasts up to one month in animals and around three months in humans, although the time frame may vary with individuals or stroke severity (Carmichael 2006, Cramer 2008, Krakauer et al 2012). Rapid improvements occur in both impairment and function during this sensitive period.

The importance of spontaneous biological recovery in the resolution of *impairment* after stroke has been established by the discovery of the Proportional Recovery Rule. Prabhakaran et al (2008) investigated the resolution of impairment in the upper limb using the Fugl-Meyer scale (FM) in 41 patients with stroke. The FM scale is used to measure strength and motor control in the affected limb (Fugl-Meyer 1980). Patients were assessed within 72 hours of stroke and again three and six months after stroke. The degree of initial impairment was defined as the maximum FM score possible minus the baseline FM score. For example, if a patient scores 26 / 66 on baseline FM, their initial impairment is 66 – 26 = 40 points. Prabhakaran et al (2008) discovered that by three months after stroke, patients reduced their impairment by an almost fixed amount of 70%. In other words, patients recovered 70% of the movement (at an impairment level) that they lost due to the stroke. Using the example above, this means that although the maximum improvement available was 40, the actual increase in FM score was only 0.7 x 40 = 28, making the final FM score 26 + 28 = 54.

This phenomenon of proportional resolution of impairment in the upper limb after stroke has since been replicated in several other studies (Byblow et al 2015, Feng et al 2015, Marshall et al 2009, Winters et al 2015, Zarahn et al 2011). A study by Lazar et al (2010) examined resolution of impairment in aphasia after stroke and reported that it also follows proportional recovery between baseline and 90 days. This finding supports the theory that proportional recovery may be generalisable across other functional domains (Winters et al 2015). The proportional resolution of impairment is consistent across patient samples from four different countries, with different rehabilitation services and for patients of both genders, all ages and ethnicities. This indicates that it is likely to reflect a fundamental spontaneous biological recovery mechanism, about which we currently know very little (Byblow et al 2015, Krakauer and Marshall 2015, Prabhakaran et al 2008).

Another interesting finding is the lack of influence of physiotherapy and occupational therapy on proportional resolution of impairment. Byblow et al (2015) measured impairment using the FM at 2, 6, 12 and 26 weeks after stroke in 93 patients. Patients were separated into: 1) a standardised therapy cohort who received 30 minutes of upper limb therapy five days a week for four weeks in addition to standard care, and 2) a variable therapy cohort who received standard care with therapy dose determined by the treating therapist based on clinical judgement (ranging from 0 to 803 minutes of total upper limb therapy time). Participants with functionally intact corticospinal tracts (CST) followed the proportional recovery rule regardless of their initial impairment, the group they were in or their therapy dose, indicating that therapy did not have an influence on resolution of impairment (Byblow et al 2015, Krakauer and Marshall 2015). These results indicate that current physiotherapy practice has not yet found a way to enhance spontaneous biological recovery (resolution of impairment) early after stroke.

Some patients with severe initial impairment exhibit proportional recovery, while others do not and recover by less than 70%, or not at all. Unfortunately, there is no clinical assessment that can identify which patients will follow the 70% rule and which ones will not. A recent study showed that a functional CST is required to achieve proportional resolution of impairment. Patients whose CST is no longer able to transmit descending motor commands do not exhibit proportional resolution of impairment (Byblow et al 2015), and these patients also achieve a poor functional recovery of the upper limb (Stinear 2010, Stinear et al 2012). These findings demonstrate that without a viable connection between the brain and the muscles, any neuroplastic reorganisation occurring in the cortex, whether due to spontaneous biological processes or use-dependent plasticity, is largely redundant.

It is not clear why proportional resolution of impairment sits at 70%, and not some other number. This threshold may reflect inefficient and incomplete re-myelination of damaged axons in the descending motor pathways (Byblow et al 2015, El Waly et al 2014). This possibility, and other potential mechanisms, remain to be explored.

To date, there have been no published studies investigating proportional recovery in the lower limb. For the lower limb, there are more projections to the corticospinal pathway from the contralesional (unaffected) cortex than for the upper limb (Dawes et al 2008, Jang et al 2005). There are also several alternative pathways involved in generating movement in the legs and trunk such as the vestibulospinal and reticulospinal tracts which receive bilateral inputs (Jang et al 2013, Matsuyama and Drew 2000, Nathan et al 1996). This means the damage from the stroke may be compensated for by other existing motor pathways and descending control from the contralesional cortex. For these reasons, it is possible that if proportional recovery of the lower limb does occur, it may differ from the upper limb.

The proportional recovery rule enables clinicians and researchers alike, for the first time, to quantify spontaneous biological recovery after stroke in humans. While using functional outcome measures remains an essential part of research into interventions aimed at improving function, the inclusion of impairment-based measures may assist in understanding the neurobiological mechanisms underpinning the recovery process, ultimately targeting future therapies more effectively.

To summarise these findings, return of movement at an *impairment* level after stroke is a spontaneous process controlled by biological mechanisms, which occurs in the first three months after stroke and is not influenced by current therapy practices. This does not mean that rehabilitation early after stroke is ineffective but rather that it promotes neurological compensation (such as cortical reorganisation) in order to improve function rather than restoring damaged neural networks.

## USE-DEPENDENT PLASTICITY

Neuroplasticity can be defined as "the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganising its structure, function and connections" (Cramer et al 2011).

The discovery that the brain has the capacity to change in response to both experience and injury transformed our understanding of mechanisms underlying training effects and learning both in the healthy and injured brain (Nudo 2006, Winstein and Kay 2015).

Use-dependent or experience-dependent plasticity was originally discovered in animal models. Motor training was found to increase synaptic efficacy and long term potentiation (strengthening of synapses), and induce synaptogenesis, axonal sprouting and formation of dendritic spines (Brown et al 2009, Carmichael 2006, Jones et al 1999, Krakauer et al 2012). These cellular effects are accompanied by enlargement of the cortical motor map specific to the limb involved in the training (Nudo 2006, Nudo et al 1996a).

The concept of plasticity has driven our rationale for rehabilitation, however there are some challenges inherent in applying research in animal models to stroke recovery in humans. Firstly, the rodent brain is structurally quite different from the human brain with much less white matter relative to grey matter (Wang et al 2016). Secondly, in animals, a stroke is artificially induced in a specific and localised area (usually the motor cortex). This creates a pure cortical infarct which spares adjacent cortical areas and white matter pathways (Wang et al 2016). In contrast, in humans, the majority of stroke damage is likely to be in *subcortical* regions (Bogousslavsky et al 1988, Corbetta et al 2015, Kang et al 2003, Wessels et al 2006), with damage not only to grey matter but also to ascending and descending white matter tracts and white matter connections between cortical and subcortical structures (Corbetta et al 2015, Wang et al 2016). This results in a disruption in the brain's ability to transmit a message not only via descending pathways to the muscles, but also between cortical regions.

In other words, our understanding of neuroplasticity comes from examining pure cortical infarcts in animals with great capacity for reorganisation within surrounding grey matter, and is being applied to stroke in humans, which is predominantly a white matter disconnection problem (Corbetta et al 2015).

The distinction between pure cortical damage and subcortical damage is important when considering the effects of stroke and how neuroplasticity shapes stroke recovery. Stinear and colleagues (2012) reported that recovery of upper limb function after stroke requires a functional CST. No amount of training-induced cortical plasticity will enable motor function to improve if the white matter motor pathways are irreparably damaged, as there is very little capacity within the human motor system to use alternative pathways (Krakauer and Marshall 2015).

### Synaptic (grey matter) plasticity

Synaptic plasticity occurs in the cortical grey matter through mechanisms such as synaptogenesis, increased synaptic efficacy and altered neurotransmitter levels. Animal research forms the basis of our understanding of synaptic plasticity in the human brain, and provides some fundamental concepts of motor learning and plasticity such as the importance of therapy intensity (MacLellan et al 2011), time-sensitivity (Biernaskie et al 2004, Biernaskie and Corbett 2001, Carmichael 2006) and the effect of environmental enrichment (Biernaskie and Corbett 2001, Johansson and Ohlsson 1996, Krakauer et al 2012).

Synaptic plasticity is sensitive to many inputs from other regions of the cortex (Murphy and Corbett 2009), which is why reward, motivation, attention, the environment, task variation and challenge are important (Biernaskie and Corbett 2001, Winstein and Kay 2015, Wulf et al 2012). A study in squirrel monkeys compared the effects of simple task repetition (practice) with learning a new task and reported that changes in cortical motor map representation only occurred after training on the new task, not with simple high repetition practice (Plautz et al 2000). This means that synaptic plasticity occurs with motor *learning* not with repetitive practice alone (Remple et al 2001).

Further research in motor learning in both healthy adults and adults with stroke has highlighted three main principles for motor learning. In order for learning to occur, the motor training must be challenging (both in intensity and difficulty), it must be progressive and adapted over the practice period (variability and novelty are important), and the patient must be motivated (the task must be meaningful). These principles have led to the development of task-oriented training as the recommended rehabilitation focus for motor skill learning after stroke (Cramer et al 2011, Winstein and Kay 2015).

Synaptic plasticity drives functional recovery after stroke, and large gains may be made early after stroke, often in the face of residual impairment. This is achieved through the use of neurological compensation (cortical reorganisation and increasing efficiency of surrounding synapses) (Buma et al 2013, Kitago and Krakauer 2013, Moon et al 2009, Whishaw et al 2008). There are two important points to remember when embarking on a rehabilitation programme aimed at improving synaptic plasticity. Firstly, time frame is critical. Once outside the sensitive period of the first three months after stroke, the capacity for neuroplasticity in the stroke brain returns to that of the non-injured brain (Biernaskie et al 2004, Carmichael 2006, Krakauer et al 2012). Harnessing the heightened plasticity in the first three months is essential.

Secondly, although functional recovery occurs largely through synaptic plasticity, it is still reliant on intact white matter (Borich et al 2014, Corbetta et al 2015, Jang et al 2010). Irreparably damaged motor tracts prevent the message from being sent to the muscles. For the upper limb, it is possible to identify which patients have sustained severe damage to the white matter pathways and which patients have spared white matter pathways using a combination of clinical assessments, transcranial magnetic stimulation and magnetic resonance imaging (Stinear et al 2012). Unfortunately, this type of prediction algorithm has not yet been established in the lower limb.

### White matter plasticity

White matter plasticity occurs in the white matter tracts through mechanisms which promote structural changes such as remyelination of axons and axonal sprouting (Brown et al 2007, Clarkson et al 2013, Fields 2005, McIver et al 2010, Wang et al 2016, Zheng and Schlaug 2015). These changes may contribute to recovery of transmission in the motor pathways. White matter plasticity may contribute to spontaneous biological recovery (Carmichael 2006, Dancause et al 2005, Zeiler and Krakauer 2013) and research in animal models has shown that it is also use-dependent (Clarkson et al 2013, Fang et al 2010, Sanchez et al 1998). Increased axonal firing in response to activity stimulates the proliferation of oligodendrocytes which are responsible for remyelination of the axons and may also provide the stimulus for axonal sprouting, and synaptogenesis (Carmichael and Chesselet 2002, Juraska and Kopcik 1988, McIver et al 2010, Simon et al 2011).

We do not know yet how to promote white matter plasticity after stroke, but the hypothesis is that there is a training response that is dose-dependent (Bengtsson et al 2005, Fields 2005, Kwon et al 2012, Nudo 2011). Exactly how many repetitions are required to generate a change in white matter has not been investigated in humans, but it is expected to be very high (Krakauer et al 2012). One study in humans has attempted to look at the effects of training on white matter (Scholz et al 2009). Twenty-four healthy adults underwent a six-week training programme for a juggling task. The authors concluded that training improved the structural organisation of the axonal bundles, possibly due to increased myelination and/or axon calibre. They hypothesised that this may lead to increased conduction velocity and better synchronisation of descending motor commands (Scholz et al 2009). This preliminary work in healthy adults provides some direction for future research into promoting white matter plasticity in humans. Other potential avenues for investigating white matter plasticity interventions after stroke are pharmacological interventions such as medications that interact with myelin formation, neurophysiological interventions, such as non-invasive brain stimulation, or robotics to support high-repetition practice.

## MOTOR TRAINING AND USE-DEPENDENT PLASTICITY

Motor training makes up the bulk of physiotherapy rehabilitation after stroke and aims to improve function through skill learning and adaptation. The highly neuroplastic state that exists in the first months after stroke means that the brain is primed for growth and change. However this plasticity is not targeted, but occurs indiscriminately throughout the cortex (Zeiler and Krakauer 2013). This means the plasticity can be either adaptive, leading to an improvement in function (Cohen et al 1997, Dancause and Nudo 2011), or maladaptive, leading to loss of function or other negative consequences such as seizures or pain disorders (Karl et al 2001, Nudo 2006, Prince et al 2009).

Examples of maladaptive motor plasticity after stroke are the development of compensatory movement patterns out of proportion to the level of impairment and cortical reorganisation due to learned non-use (Krakauer 2006, Sunderland and Tuke 2005, Whishaw et al 2008, Winstein and Kay 2015, Wolf et al 2006). Motor training may facilitate adaptation and prevent maladaptation by directing and shaping the cortical reorganisation as it occurs (Carmichael 2010, Huang et al 2008, Kitago and Krakauer 2013, Nudo et al 1996b). A useful analogy for this is to imagine a tree planted in exceptionally fertile ground. Rapid growth occurs randomly in all directions and requires pruning to shape and increase the efficiency of the growth, analogous to the role of the physiotherapist in rehabilitation after stroke.

One reason that task specific functional training may primarily promote compensatory reorganisation is that there is usually an incentive and a requirement for the task to be completed immediately. This means that the brain may choose to bypass the damaged networks in favour of compensation in order to achieve the goal. This form of reinforcement learning may lead to preferential selection of these alternative motor strategies in the future and establishing a new motor pattern to complete the task (Huang et al 2011, Kitago and Krakauer 2013).

There have been suggestions that early motor training should only include very high intensity impairment training in the absence of functional training, in order to reduce early compensation and to promote attempts to access the damaged neural pathways (Krakauer et al 2012). However, this approach is highly impractical in a setting where health resources are limited and patients are intent on getting home as soon as possible. Returning *some* focus to impairment training and increasing focus on quality of movement rather than task completion may start to lead us in the right direction.

Gains in function produced by motor training carried out six months or more after stroke are almost certainly due to compensatory mechanisms, and for this reason, improvements will be relatively small (Lefebvre et al 2015, Raghavan et al 2010, Zeiler and Krakauer 2013). By this time, the impairment resolution process is complete. Training in the chronic stage teaches the patient how to use the movement that they already have in a more effective way (Kwakkel et al 2015). There is evidence that improving function occurs in the absence of further impairment resolution, however, the effects of the residual impairment do contribute to the poor quality and increased energy expenditure of the movement (Massie et al 2009, Page et al 2008).

A small study recently investigated the neurological basis for constraint-induced movement therapy (CIMT) in patients with chronic stroke (Kitago et al 2013). They demonstrated that a two-week programme of CIMT improved functional use of the arm as assessed with the action research arm test (ARAT). However, joint kinematic data and upper limb motor impairment (FM) showed no improvement after CIMT (Kitago et al 2013). In other words, CIMT did not improve their movement patterns or underlying impairment. This is an example of using an impairment assessment alongside a functional one to establish that functional improvements were a result of neurological compensation rather than restoring damaged networks.

## WHAT DOES THIS MEAN FOR PHYSIOTHERAPY AFTER STROKE?

Spontaneous biological recovery and use-dependent plasticity are powerful drivers towards recovery early after stroke. Understanding the difference between neurological recovery in the first 12 weeks after stroke and in the chronic stage will help direct the physiotherapist in decision making about a particular treatment modality in both stages of stroke recovery.

The discovery of proportional resolution of impairment, for the first time, provides insight into the ceiling effect on stroke recovery we so often see in our patients. This research necessitates a shift in thinking away from the classic neuroplasticity model which has long suggested that the brain has unlimited capacity to keep remodelling and changing with skill learning throughout adulthood. Although the capacity of the cortex to undergo synaptic plasticity after stroke is the same as in a healthy adult, damage to white matter structures places some definite limitations on the beneficial effects of this reorganisation. Quite simply, if there is no way to communicate between the brain and the body, there is no capacity for motor recovery no matter how much cortical reorganisation occurs. Fortunately, in most patients with stroke, damage to the white matter connections is not complete, providing a substrate for communication between the reorganised cortex and body.

There is an abundance of research attempting to improve stroke outcomes through variations on current therapy (all based on task-dependent training to promote synaptic plasticity), yet results are unimpressive. An important new question for the field is how can we improve the resolution of impairment? Can we find an intervention that raises the ceiling above 70%? It is time to try to find a way to work with and enhance spontaneous biological recovery. This may be an opportunity for physiotherapists to align themselves closely with neuroscience researchers in order to find an answer that is applicable in a clinical setting.

In the interim, the role of physiotherapy after stroke has not changed. It is still to teach patients how to move in the most efficient way possible and to live their lives to the best of their ability with the impairments that they have. Our new understanding that the neural mechanisms underlying functional recovery are largely compensatory provides a stronger rationale for a treatment approach focused on retraining movement patterns that minimise unnecessary compensation.

And finally, the analogy of a kayak in a white water rapid may be useful to describe the recovery journey after stroke. Imagine the stroke survivor in the kayak. The force of the river is the powerful drive that the brain has towards recovery after stroke. The patient can either choose to let the flow of the river dictate their recovery or they can take up the paddle and move forward more quickly with some control of their direction. Ultimately, the river widens, the flow lessens, and the person ends up in a calm lake as the spontaneous recovery period finishes. At this point, every move forward is unassisted by flow, and relies solely on the efforts of the paddler. Progress is slow and much more difficult. Our role as physiotherapists is to teach the patients how to use the paddle to shape the direction and speed the trajectory of their recovery, so that when they reach the "lake" they are able to continue making their own gains over time.

## KEY POINTS

1. Spontaneous biological recovery of the upper limb results in fixed proportional resolution of impairment.
2. Task specific motor training promotes use-dependent plasticity through neurological compensation rather than restoring damaged neural networks.
3. Both spontaneous biological recovery and use-dependent plasticity rely on a functioning corticospinal tract to relay the message from the brain to the body.

4. As impairment does not continue to resolve at the chronic stage, the time post stroke is an important clinical consideration when delivering upper limb therapy after stroke.

## DISCLOSURES

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## REFERENCES

Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F (2005) Extensive piano practicing has regionally specific effects on white matter development. *Nature Neuroscience* 8(9): 1148-1150. doi:10.1038/nn1516.

Bernhardt J, Borschmann K, Boyd L, Carmichael ST, Corbett D, Cramer SC, Hoffmann T, Kwakkel G, Savitz SI, Saposnik G, Walker M, Ward N (2016) Moving rehabilitation research forward: Developing consensus statements for rehabilitation and recovery research. *International Journal of Stroke* 11(4): 454-458. doi:10.1177/1747493016643851.

Biernaskie J, Chernenko G, Corbett D (2004) Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *Journal of Neuroscience* 24(5): 1245-1254. doi:10.1523/JNEUROSCI.3834-03.2004.

Biernaskie J, Corbett D (2001) Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *Journal of Neuroscience* 21(14): 5272-5280.

Bogousslavsky J, Van Melle G, Regli F (1988) The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke* 19(9): 1083-1092. doi:10.1161/01.STR.19.9.1083.

Borich MR, Brown KE, Boyd LA (2014) Motor skill learning is associated with diffusion characteristics of white matter in individuals with chronic stroke. *Journal of Neurologic Physical Therapy* 38(3): 151-160. doi:10.1097/NPT.0b013e3182a3d353.

Brown CE, Aminoltejari K, Erb H, Winship IR, Murphy TH (2009) In vivo voltage-sensitive dye imaging in adult mice reveals that somatosensory maps lost to stroke are replaced over weeks by new structural and functional circuits with prolonged modes of activation within both the peri-infarct zone and distant sites. *Journal of Neuroscience* 29(6): 1719-1734. doi:10.1523/JNEUROSCI.4249-08.2009.

Brown CE, Li P, Boyd JD, Delaney KR, Murphy TH (2007) Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. *Journal of Neuroscience* 27(15): 4101-4109. doi:10.1523/JNEUROSCI.4295-06.2007.

Buma F, Kwakkel G, Ramsey N (2013) Understanding upper limb recovery after stroke. *Restorative Neurology and Neuroscience* 31(6): 707-722. doi:10.3233/RNN-130332.

Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ (2015) Proportional recovery after stroke depends on corticomotor integrity. *Annals of Neurology* 78(6):848-59. doi:10.1002/ana.24472.

Carmichael ST (2006) Cellular and molecular mechanisms of neural repair after stroke: making waves. *Annals of Neurology* 59(5):735-42. doi:10.1002/ana.20845.

Carmichael ST (2010) Translating the frontiers of brain repair to treatments: starting not to break the rules. *Neurobiology of Disease* 37(2): 237-242. doi:10.1016/j.nbd.2009.09.005.

Carmichael ST, Chesselet MF (2002) Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *Journal of Neuroscience* 22(14): 6062-6070. doi:20026605.

Clarkson AN, Lopez-Valdes HE, Overman JJ, Charles AC, Brennan KC, Carmichael ST (2013) Multimodal examination of structural and functional remapping in the mouse photothrombotic stroke model. *Journal of Cerebral Blood Flow and Metabolism* 33(5): 716-723. doi:10.1038/jcbfm.2013.7.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catala MD, Hallett M (1997) Functional relevance of cross-modal plasticity in blind humans. *Nature* 389(6647): 180-183. doi:10.1038/38278.

Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS, Astafiev SV, Rengachary J, Zinn K, Lang CE, Connor LT, Fucetola R, Strube M, Carter AR, Shulman GL (2015) Common behavioral clusters and subcortical anatomy in stroke. *Neuron* 85(5): 927-941. doi:10.1016/j.neuron.2015.02.027.

Cramer SC (2008) Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology* 63(3): 272-287. doi:10.1002/ana.21393.

Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, Rumsey JM, Hicks R, Cameron J, Chen D, Chen WG, Cohen LG, deCharms C, Duffy CJ, Eden GF, Fetz EE, Filart R, Freund M, Grant SJ, Haber S, Kalivas PW, Kolb B, Kramer AF, Lynch M, Mayberg HS, McQuillen PS, Nitkin R, Pascual-Leone A, Reuter-Lorenz P, Schiff N, Sharma A, Shekim L, Stryker M, Sullivan EV, Vinogradov S (2011) Harnessing neuroplasticity for clinical applications. *Brain* 134(Pt 6):1591-609. doi:10.1093/brain/awr039.

Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, Stowe AM, Nudo RJ (2005) Extensive cortical rewiring after brain injury. Journal of Neuroscience 25(44):10167-79. doi:10.1523/JNEUROSCI.3256-05.2005.

Dancause N, Nudo RJ (2011) Shaping plasticity to enhance recovery after injury. *Progress in Brain Research* 192: 273-295. doi:10.1016/B978-0-444-53355-5.00015-4.

Dawes H, Enzinger C, Johansen-Berg H, Bogdanovic M, Guy C, Collett J, Izadi H, Stagg C, Wade D, Matthews PM (2008) Walking performance and its recovery in chronic stroke in relation to extent of lesion overlap with the descending motor tract. *Experimental Brain Research* 186(2): 325-333. doi:10.1007/s00221-007-1237-0.

El Waly B, Macchi M, Cayre M, Durbec P (2014) Oligodendrogenesis in the normal and pathological central nervous system. *Frontiers in Neuroscience* 8: 145. doi:10.3389/fnins.2014.00145.

Fang PC, Barbay S, Plautz EJ, Hoover E, Strittmatter SM, Nudo RJ (2010) Combination of NEP 1-40 treatment and motor training enhances behavioral recovery after a focal cortical infarct in rats. *Stroke* 41(3): 544-549. doi:10.1161/STROKEAHA.109.572073.

Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C, Global Burden of Diseases I, Risk Factors S, the GBDSEG (2014) Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *The Lancet* 383(9913): 245-254. doi:10.1016/S0140-6736(13)61953-4.

Feng W, Wang J, Chhatbar PY, Doughty C, Landsittel D, Lioutas VA, Kautz S, Schlaug G (2015) Corticospinal tract lesion load - An imaging biomarker for stroke motor outcomes. *Annals of Neurology* 78(6):860-70. doi:10.1002/ana.24510.

Fields RD (2005) Myelination: an overlooked mechanism of synaptic plasticity? *Neuroscientist* 11(6): 528-531. doi:10.1177/1073858405282304.

Fugl-Meyer AR (1980) Post-stroke hemiplegia assessment of physical properties. *Scandinavian Journal of Rehabilitation Medicine* 7: 85-93.

Hagemann G, Redecker C, Neumann-Haefelin T, Freund HJ, Witte OW (1998) Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. *Annals of Neurology* 44(2): 255-258. doi:10.1002/ana.410440217.

Huang VS, Haith A, Mazzoni P, Krakauer JW (2011) Rethinking motor learning and savings in adaptation paradigms: model-free memory for successful actions combines with internal models. *Neuron* 70(4): 787-801. doi:10.1016/j.neuron.2011.04.012.

Huang VS, Shadmehr R, Diedrichsen J (2008) Active learning: learning a motor skill without a coach. *Journal of Neurophysiology* 100(2): 879-887. doi:10.1152/jn.01095.2007.

Jang SH, Ahn SH, Sakong J, Byun WM, Choi BY, Chang CH, Bai D, Son SM (2010) Comparison of TMS and DTT for predicting motor outcome in intracerebral hemorrhage. *Journal of the Neurological Sciences* 290(1-2): 107-111. doi:10.1016/j.jns.2009.10.019.

Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS (2013) Functional role of the corticoreticular pathway in chronic stroke patients. *Stroke* 44(4): 1099-1104. doi:10.1161/strokeaha.111.000269.

Jang SH, You SH, Kwon YH, Hallett M, Lee MY, Ahn SH (2005) Cortical reorganization associated lower extremity motor recovery as evidenced by functional MRI and diffusion tensor tractography in a stroke patient. *Restorative Neurology and Neuroscience* 23(5-6): 325-329.

Johansson BB, Ohlsson AL (1996) Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Experimental Neurology* 139(2): 322-327. doi:10.1006/exnr.1996.0106.

Jolkkonen J, Kwakkel G (2016) Translational hurdles in stroke recovery studies. *Translational Stroke Research* 7(4):331-42. doi:10.1007/s12975-016-0461-y.

Jones TA, Chu CJ, Grande LA, Gregory AD (1999) Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. *Journal of Neuroscience* 19(22): 10153-10163.

Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS (1995) Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Archives of Physical Medicine and Rehabilitation* 76(5): 406-412. doi:10.1016/S0003-9993(95)80568-0.

Juraska JM, Kopcik JR (1988) Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. *Brain Research* 450(1-2): 1-8. doi:10.1016/0006-8993(88)91538-7.

Kang DW, Chalela JA, Ezzeddine MA, Warach S (2003) Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. *Archives of Neurology* 60(12): 1730-1734. doi:10.1001/archneur.60.12.1730.

Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H (2001) Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *Journal of Neuroscience* 21(10): 3609-3618.

Kitago T, Krakauer JW (2013) Motor learning principles for neurorehabilitation. *Handbook of Clinical Neurology* 110: 93-103. doi:10.1016/B978-0-444-52901-5.00008-3.

Kitago T, Liang J, Huang VS, Hayes S, Simon P, Tenteromano L, Lazar RM, Marshall RS, Mazzoni P, Lennihan L, Krakauer JW (2013) Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation? *Neurorehabilitation and Neural Repair* 27(2): 99-109. doi:10.1177/1545968312452631.

Krakauer JW (2006) Motor learning: its relevance to stroke recovery and neurorehabilitation. *Current Opinion in Neurology* 19(1): 84-90.

Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF (2012) Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabilitation and Neural Repair* 26(8): 923-931. doi:10.1177/1545968312440745.

Krakauer JW, Marshall RS (2015) The proportional recovery rule for stroke revisited. *Annals of Neurology* 78(6): 845-847. doi:10.1002/ana.24537.

Kwakkel G, Kollen B, Twisk J (2006) Impact of time on improvement of outcome after stroke. *Stroke* 37(9): 2348-2353. doi:10.1161/01.STR.0000238594.91938.1e.

Kwakkel G, Veerbeek JM, van Wegen EE, Wolf SL (2015) Constraint-induced movement therapy after stroke. *Lancet Neurology* 14(2): 224-234. doi:10.1016/S1474-4422(14)70160-7.

Kwon YH, Nam KS, Park JW (2012) Identification of cortical activation and white matter architecture according to short-term motor learning in the human brain: functional MRI and diffusion tensor tractography study. *Neuroscience Letters* 520(1): 11-15. doi:10.1016/j.neulet.2012.05.005.

Lazar RM, Minzer B, Antoniello D, Festa JR, Krakauer JW, Marshall RS (2010) Improvement in aphasia scores after stroke is well predicted by initial severity. *Stroke* 41(7): 1485-1488. doi:10.1161/STROKEAHA.109.577338.

Lefebvre S, Dricot L, Laloux P, Gradkowski W, Desfontaines P, Evrard F, Peeters A, Jamart J, Vandermeeren Y (2015) Neural substrates underlying motor skill learning in chronic hemiparetic stroke patients. *Frontiers in Human Neuroscience* 9: 320. doi:10.3389/fnhum.2015.00320.

Levin MF, Kleim JA, Wolf SL (2009) What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabilitation and Neural Repair* 23(4): 313-319. doi:10.1177/1545968308328727.

MacLellan CL, Keough MB, Granter-Button S, Chernenko GA, Butt S, Corbett D (2011) A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. *Neurorehabilitation and Neural Repair* 25(8): 740-748. doi:10.1177/1545968311407517.

Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW (2009) Early imaging correlates of subsequent motor recovery after stroke. *Annals of Neurology* 65: 596-602. doi:10.1002/ana.21636.

Massie C, Malcolm MP, Greene D, Thaut M (2009) The effects of constraint-induced therapy on kinematic outcomes and compensatory movement patterns: an exploratory study. *Archives of Physical Medicine and Rehabilitation* 90: 571-579. doi:10.1016/j.apmr.2008.09.574.

Matsuyama K, Drew T (2000) Vestibulospinal and reticulospinal neuronal activity during locomotion in the intact cat. II. Walking on an inclined plane. *Journal of Neurophysiology* 84(5): 2257-2276.

McIver SR, Muccigrosso M, Gonzales ER, Lee JM, Roberts MS, Sands MS, Goldberg MP (2010) Oligodendrocyte degeneration and recovery after focal cerebral ischemia. *Neuroscience* 169(3): 1364-1375. doi:10.1016/j.neuroscience.2010.04.070.

Moon SK, Alaverdashvili M, Cross AR, Whishaw IQ (2009) Both compensation and recovery of skilled reaching following small photothrombotic stroke to motor cortex in the rat. *Experimental Neurology* 218(1): 145-153. doi:10.1016/j.expneurol.2009.04.021.

Murphy TH, Corbett D (2009) Plasticity during stroke recovery: from synapse to behaviour. *Nature Reviews Neuroscience* 10(12): 861-872. doi:10.1038/nrn2735.

Nathan PW, Smith M, Deacon P (1996) Vestibulospinal, reticulospinal and descending propriospinal nerve fibres in man. *Brain* 119 ( Pt 6): 1809-1833. doi:10.1093/brain/119.6.1809

Nudo RJ (2006) Plasticity. *NeuroRx* 3(4): 420-427.doi: 10.1016/j.nurx.2006.07.006

Nudo RJ (2011) Neural bases of recovery after brain injury. *Journal of Communication Disorders* 44(5): 515-520. doi:10.1016/j.jcomdis.2011.04.004.

Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM (1996a) Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience* 16(2): 785-807.

Nudo RJ, Wise BM, SiFuentes F, Milliken GW (1996b) Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 272(5269): 1791-1794. doi:10.1126/science.272.5269.1791.

Page SJ, Levine P, Leonard A, Szaflarski JP, Kissela BM (2008) Modified constraint-induced therapy in chronic stroke: results of a single-blinded randomized controlled trial. *Physical Therapy* 88(3): 333-340. doi:10.2522/ptj.20060029.

Plautz EJ, Milliken GW, Nudo RJ (2000) Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiology of Learning and Memory* 74(1): 27-55. doi:10.1006/nlme.1999.3934.

Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong JY, Lazar RM, Marshall RS, Krakauer JW (2008) Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabilitation and Neural Repair* 22(1): 64-71. doi:10.1177/1545968307305302.

Prince DA, Parada I, Scalise K, Graber K, Jin X, Shen F (2009) Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. *Epilepsia* 50 Suppl 2: 30-40. doi:10.1111/j.1528-1167.2008.02008.x.

Raghavan P, Santello M, Gordon AM, Krakauer JW (2010) Compensatory motor control after stroke: an alternative joint strategy for object-dependent shaping of hand posture. *Journal of Neurophysiology* 103(6): 3034-3043. doi:10.1152/jn.00936.2009.

Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA (2001) Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behavioural Brain Research* 123(2): 133-141. doi:10.1016/S0166-4328(01)00199-1.

Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C, Stroke Statistics S (2012) Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 125(1): e2-e220. doi:10.1161/CIR.0b013e31823ac046.

Sanchez MM, Hearn EF, Do D, Rilling JK, Herndon JG (1998) Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research* 812(1-2): 38-49. doi:10.1016/S0006-8993(98)00857-9.

Scholz J, Klein MC, Behrens TE, Johansen-Berg H (2009) Training induces changes in white-matter architecture. *Nature Neuroscience* 12(11): 1370-1371. doi:10.1038/nn.2412.

Simon C, Gotz M, Dimou L (2011) Progenitors in the adult cerebral cortex: cell cycle properties and regulation by physiological stimuli and injury. *Glia* 59(6): 869-881. doi:10.1002/glia.21156.

Stinear C (2010) Prediction of recovery of motor function after stroke. *Lancet Neurology* 9(12): 1228-1232. doi:10.1016/S1474-4422(10)70247-7.

Stinear C, Ackerley S, Byblow W (2013) Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. *Stroke* 44(7): 2039-2045. doi:10.1161/STROKEAHA.113.000968.

Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD (2012) The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain* 135(pt8): 2527-2535. doi:10.1093/brain/aws146.

Sunderland A, Tuke A (2005) Neuroplasticity, learning and recovery after stroke: a critical evaluation of constraint-induced therapy. *Neuropsychological Rehabilitation* 15(2): 81-96. doi:10.1080/09602010443000047

Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J (2004) The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clinical Rehabilitation* 18(8): 833-862. doi:10.1191/0269215504cr843oa

Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G (2014) What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PloS one* 9(2): e87987. doi:10.1371/journal.pone.0087987.

Wang Y, Liu G, Hong D, Chen F, Ji X, Cao G (2016) White matter injury in ischemic stroke. *Progress in Neurobiology* 141: 45-60. doi:10.1016/j.pneurobio.2016.04.005

Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, Jauss M (2006) Contribution of diffusion-weighted imaging in determination of stroke etiology. *American Journal of Neuroradiology* 27(1): 35-39.

Whishaw IQ, Alaverdashvili M, Kolb B (2008) The problem of relating plasticity and skilled reaching after motor cortex stroke in the rat. *Behavioural Brain Research* 192(1): 124-136. doi:10.1016/j.bbr.2007.12.026.

Winstein CJ, Kay DB (2015) Translating the science into practice: shaping rehabilitation practice to enhance recovery after brain damage. *Progress in Brain Research* 218: 331-360. doi:10.1016/bs.pbr.2015.01.004.

Winters C, van Wegen EE, Daffertshofer A, Kwakkel G (2015) Generalizability of the Proportional Recovery Model for the Upper Extremity After an Ischemic Stroke. *Neurorehabilitation and Neural Repair* 29(7): 614-622. doi:10.1177/1545968314562115.

Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D, Investigators E (2006) Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *Journal of the American Medical Association* 296(17): 2095-2104. doi:10.1001/jama.296.17.2095.

Wulf G, Chiviacowsky S, Lewthwaite R (2012) Altering mindset can enhance motor learning in older adults. *Psychology and Aging* 27(1): 14-21. doi:10.1037/a0025718

Xing C, Arai K, Lo EH, Hommel M (2012) Pathophysiologic cascades in ischemic stroke. *International Journal of Stroke* 7(5): 378-385. doi:10.1111/j.1747-4949.2012.00839.x.

Zarahn E, Alon L, Ryan SL, Lazar RM, Vry MS, Weiller C, Marshall RS, Krakauer JW (2011) Prediction of motor recovery using initial impairment and fMRI 48 h poststroke. *Cerebral Cortex* 21(12): 2712-2721. doi:10.1093/cercor/bhr047.

Zeiler SR, Krakauer JW (2013) The interaction between training and plasticity in the poststroke brain. *Current Opinion in Neurology* 26(6): 609-616. doi:10.1097/WCO.0000000000000025.

Zheng X, Schlaug G (2015) Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS and physical therapy. *Frontiers in Human Neuroscience* 9: 229. doi:10.3389/fnhum.2015.00229.