Restorative Neurology and Neuroscience 31 (2013) 707–722
DOI 10.3233/RNN-130332
IOS Press

Review

Understanding upper limb recovery after stroke

Floor Buma[a], Gert Kwakkel[a,b,*] and Nick Ramsey[c]
[a]*Rudolph Magnus Institute of Neuroscience and Center of Excellence for Rehabilitation Medicine, University Medical Center Utrecht and Rehabilitation Center de Hoogstraat, Utrecht, The Netherlands*
[b]*Department of Rehabilitation Medicine, VU University Medical Center, Amsterdam, The Netherlands*
[c]*Department of Neurology and Neurosurgery, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands*

Abstract. This review addresses what is currently known about the time course of skill reacquisition after stroke. There is growing evidence that the natural logarithmic pattern of functional recovery can be modified by intensive task-oriented practice preferably initiated within 6 months after stroke. However, the impact of practice on the learning-dependent and intrinsic spontaneous mechanisms of neurological recovery is poorly understood. At least four probably interrelated mechanisms have been identified that drive motor and recovery after stroke: (1) salvation of penumbral tissue in the first days to weeks after stroke; (2) alleviation of diaschisis; (3) homeostatic and learning-dependent (Hebbian) neuroplasticity; (4) behavioral compensation strategies. These mechanisms underlying recovery are highly interactive, and operate in different, sometimes limited, time-windows after stroke onset. In line with these mechanisms of improvement after stroke, we present a hypothetical phenomenological model for understanding skill reacquisition after stroke. Translational research is important at this point to improve our knowledge about the neural correlates of *what* and *how* patients learn when they show functional improvement after stroke. This knowledge should serve as a basis to optimize the timing, focus and intensity of evidence-based rehabilitation interventions and to design innovative strategies to enhance motor recovery after stroke.

Keywords: Neuroplasticity, recovery, stroke, rehabilitation, paresis, hebbian learning

1. Introduction

Stroke is the leading cause of disability in western society (Wardlaw, Sandercock, & Murray, 2009). The European Registers of Stroke (EROS) show that in a sample of 2,034 first-ever strokes, about 40% had a poor outcome in terms of death, institutionalization or a Barthel Index (BI) below 12 points at 3 months after after stroke (Heuschmann et al., 2011). In the United States, stroke has a mortality rate of 15%, and 26% of stroke survivors aged 65 years and older are institutionalized at 6 months after stroke, while 50% suffer from hemiparesis and 30% cannot walk without assistance (Kelly-Hayes et al., 2003; Lloyd-Jones et al., 2009). Although individual recovery patterns and outcome differ between patients, several prognostic studies have shown that outcome at 3 or 6 months is highly predictable for upper (Nijland et al., 2010; Stinear et al., 2012), and lower limb (Veerbeek et al., 2011) as well as basic activities of daily living (ADLs) in general (Kwakkel et al., 2006; Prabhakaran et al., 2008). Almost all patients show a certain

*Corresponding author: prof. Gert Kwakkel (PhD), Department of Rehabilitation Medicine, VU University Medical Centre, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel.: +31 204 440460; Fax: +31 204 44; E-mail: g.kwakkel@vumc.nl.

0922-6028/13/$27.50 © 2013 – IOS Press and the authors. All rights reserved
This article is published online with Open Access and distributed under the terms of the Creative Commons Attribution Non-Commercial License.

degree of spontaneous neurological recovery, following a natural logarithmic pattern (Langhorne et al., 2011). The recovery rate is highest in the first months after stroke, after which recovery levels of and reaches a plateau (Kwakkel et al., 2006; Langhorne et al, 2009; Ng et al., 2007). Unfortunately, the underlying mechanisms responsible for these spontaneous, natural logarithmic changes in impairment in the first months after stroke are poorly understood and the subject of the present review. We first introduce the theoretical phenomenological model shown in Fig. 1 (Panel A), and to explain processes involved in skill reacquisition. This model summarizes the present body of knowledge relating to the empirical observations of motor recovery after stroke in a way that is consistent with the more fundamental knowledge about underlying mechanisms of brain plasticity after stroke. Subsequently, we discuss the various underlying mechanisms that may explain the natural logarithmic time course of recovery, and briefly discuss the specific timeframes in which these mechanisms may play a role after stroke. We then focus on the sizeable contribution of non-learning–dependent, spontaneous neurological mechanisms and the possible influence of learning-dependent mechanisms in the brain that might underlie the processes of skill reacquisition after stroke (Fig. 1, Panel B). Finally, we define targets for translational research with respect to motor recovery and neuroplasticity mechanisms and discuss new opportunities for rehabilitation interventions to enhance motor recovery in patients after stroke.

2. Defining stroke recovery

To understand recovery from stroke, it is important to define what we mean by the terms recovery, restitution, compensation and substitution, and their relation to neuroplasticity and changes in the role of specific brain regions (cortical map reorganization) (Dobkin, 2009; Rothi & Horner, 1983). A number of recent longitudinal studies show that improvement at the level of activities after stroke, such as dexterity (Cirstea & Levin, 2000) is mainly driven by learning compensation strategies rather than by neural repair (Kwakkel et al., 2004) where patients learn to re-use the same body segments in the same way as they did before their stroke. It is therefore essential to be explicit when talking about recovery, and to refer to the different levels of the International Classification of Functioning, Disability and Health (ICF) as suggested by Levin and colleagues (Levin et al., 2009). The ICF defines three levels of recovery: body structure and functions, activities and participation (Levin et al., 2009). In this Point of View article we will focus on recovery of body functions and activities. We will distinguish neurological recovery at the level of body functions such as strength, synergism and sensation, from improvement at the level of activities such as dexterity and gait after stroke. Although some impairments such as synergies are poorly defined in the literature we prefer to define synergies according to Thomas Twitchell's work as "increased co-activation between muscles in the paretic limb that can be elicited voluntarily or as a reflexive reaction" (Twitchell, 1951). As a consequence, the joints that are coupled within a synergy cannot be mastered in isolation (Twitchell, 1951).

Skill reacquisition is defined as improvement on an outcome measure either at the level of functions or at the level of activities. Improvement after stroke encompasses two distinct types of improvement: 1) True (neurological) recovery reflects the return or restitution (or repair) of body functions (or reduction of impairments), which results in the reappearance of the same end effectors during task performance (Krakauer et al., 2012). In this context, an end effector is defined as a body part, such as a hand or foot, that interacts with an object or the environment (Levin et al., 2009). And 2) Skill reacquisition through motor compensation at an activity level which can be defined as the appearance of 'new' motor patterns resulting from compensation by the remaining intact motor elements at the level of body function. However, skill reacquisition at an activity level can also entail "take-over", or substitution of function by entirely different end effectors or body segments that accomplish the task (Cirstea & Levin, 2000; Michaelsen et al., 2006).

Obviously, both situations i.e., restitution and compensation (or substitution) mean that patients are able to accomplish the task, but they differ greatly in the way the task is performed, in terms of quality of motor performance. An improvement in quality of movement after stroke in for example a reach to grasp task can be defined as approaching 'normal performance' when compared to healthy individuals. Recent, intensive repeated kinematic measurements early after stroke have shown that the normalization of movement performance in stroke recovery is accompanied with a gradual increments in the number of degrees of freedom (DoF) to control for, as observed in healthy

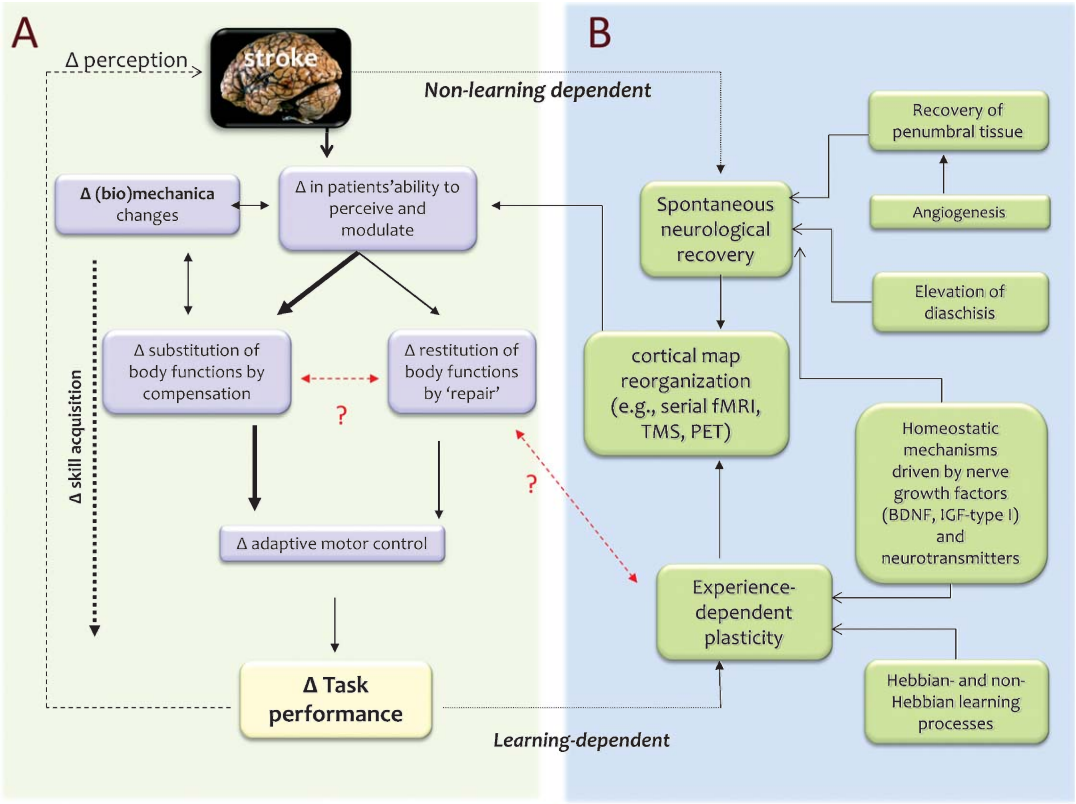

Fig. 1. Proposed phenomenological model. Panel A) shows the processes underlying skill reacquisition after stroke and emphasizes the fact that most evidence for skill improvement is due to compensatory mechanisms, partly driven by biomechanical changes and the interaction with spontaneous and learning-dependent reorganization. Panel B refers to the underlying neuronal mechanisms influencing the process of skill acquisition after stroke. Dashed lines represent connections for which there is as yet no direct evidence to be found in the literature, while bold lines represent connections for which there is considerable evidence. These lines represent the existence of a relationship between two mechanisms, and do not necessarily refer to a causal relationship. The challenge in this field of research is represented by the red dashed lines and question marks: can we modulate restitution of function after stroke? And can we understand the interaction between compensatory mechanisms and true restitution of body functions after stroke. (The symbol Δ represents change in this model).

age-matched subjects (van Kordelaar, 2013). In the same vein, Duff and colleagues showed that normalization of motor control of the upper paretic limb is significantly accompanied with improvement in peak speed, smoothness of movement, efficiency and consistency of the trajectory of the hand to the target, reduced errors in placing the hand on the target as well as minimizing compensation by shoulder and torso movements and minimizing coupling in elbow and shoulder and wrist in completing the reaching task (Duff, 2013).

This also indicates that without quantifying the quality of task performance, it is not possible to distinguish restitution of function as a result of neurological repair from compensation strategies, especially when patients are using the same end effectors to accomplish the specific task (Levin et al., 2009). Unfortunately animal studies have usually not focused on whether improvement of a particular activity with the affected limb such as reaching for a food pellet is due to adaptive compensatory mechanisms or to restitution of function. Some of the studies that did address this issue are those by Whishaw and colleagues who demonstrated by video analysis that functional recovery after stroke in rats involves mostly compensatory movements (Whishaw et al., 2000; Whishaw, 2008). Moon and colleagues found that rats showed compensatory movement strategies during recovery after photothrombotic stroke (Moon et al., 2009). The occurrence of compensatory mechanisms in animal

models after stroke suggests that this should not be overlooked when investigating the outcome in tasks such as reaching for food pellets (Metz et al., 2005). These findings are in line with a recent review by Kerr and colleagues who concluded that experience and behavioral interventions such as rehabilitative training can drive functionally beneficial neural reorganization in the injured adult hemisphere, but may also have detrimental effects on neuroplasticity (Kerr et al., 2011).

In the same vein, clinical outcome measures that are used to assess activities in humans are not suitable to assess the quality of motor performance and, with that, to distinguish between restitution and compensation. For example, most disability scales for activities of daily living, such as the BI (Mahony & Barthel, 1965) and modified Rankin Scale (Banks & Marotta, 2007), allow the use of the non-paretic hand to accomplish tasks such as dressing, making the outcome of such scales almost independent of the amount of neurological "repair" of the paretic limb. In a less marked way, most clinical outcome measures of the upper paretic limb do not account for trunk involvement in their final scoring system. An example is the Nine Hole Pegtest (Chen et al., 2009), where the final score is based only on the accomplishment of the task. Some studies have shown that even in grasping an object a number of compensatory mechanisms might play a role in shaping the hand around the object (Raghavan et al., 2010). Therefore, the mere accomplishment of grasping such as used in the Nine Hole Peg-test might not be sufficient to reveal the use of these subtle compensatory strategies. Hence, it remains unclear from the literature, both on animals and humans, to what extent the improvement in motor performance at an activity level by the affected arm itself is caused by true neurological repair or by learning compensation strategies.

3. Defining neuroplasticity

There are several definitions of neuroplasticity in the literature. Murphy & Corbett (2009) defined neuroplasticity as "Changes in the strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network" (Murphy & Corbett, 2009). True neurological recovery at the level of the brain may be defined as restitution of the function of the neurons that have escaped infarction but have been functionally impaired trough changes in metabolic activity. However, since true repair in the brain might only be possible by replacing lost neurons in the brain, neuroplasticity mechanisms in the brain itself may always be viewed as compensatory (Levin et al., 2009). The functioning of these neurons will always be in response to tissue loss and might interact with changes in synaptic activity in the motor network. Compensatory mechanisms at a behavioral level are thought to involve neuroplasticity mechanisms in the brain itself in order to develop and sustain these compensatory strategies. Changes at the neural level (neuroplasticity) can be either adaptive or maladaptive to recovery and not all changes in the brain will have functional significance for skill reacquisition after stroke. The precise way in which changes at a neuronal level influence restitution as well as compensation is still under investigation.

4. True neurological recovery in skill reacquisition after stroke

Apart from saving neural tissue by thrombolysis, there is insufficient evidence that it is possible to modulate true recovery (i.e. restitution of function or reduction of impairment) by specific rehabilitation interventions that start in the first weeks after stroke beyond spontaneous neurological recovery after stroke (Langhorne et al., 2009, 2011). Only a few randomized controlled trials have been designed to specifically study the restoration of body functions by measuring motor impairment directly such as the motor part of the Fugl-Meyer arm test (FM-arm) (Wolf et al., 2006). Another way to assess improvement at the level of body functions is by using kinematic analysis to establish whether therapeutic interventions have an effect at the impairment level. Patterns of improvement are often characterized by movements in synergistic patterns (Cirstea & Levin, 2000). Synergistic movement patterns have been described as pathological couplings between, for example, shoulder and elbow movements by either voluntary of reflexive co-contraction of muscles before isolated movement of the end-effectors is possible (Brunnström, 1970). However, most RCT's have focused on improvement at the level of activities after stroke and were therefore not designed to measure the quality of motor performance and to distinguish between restitution and compensation strategies after stroke (Kwakkel et al., 2004). Such a design is, however, necessary to understand

exactly what and how stroke patients learn during skill reacquisition after stroke supported by rehabilitation interventions (Kwakkel & Wagenaar, 1996; Kwakkel et al., 2004; Kwakkel et al., 2006; Sunderland & Tuke, 2006; Wolf et al., 2005). Longitudinal regression analysis of change scores suggests that progress of time as a reflection of spontaneous neurological recovery, rather than rehabilitative therapeutic interventions, account for the majority of improvements contributing to restitution of function in the first weeks after stroke (Kwakkel et al., 2006). As a consequence, mere progress of time in the first three months after stroke is a major confounder in understanding the effects of rehabilitation interventions, which further underlines the need for large, well-designed randomized controlled clinical trials. Such trials should preferably adhere to the CONSORT statement, an evidence-based set of minimum recommendations for reporting randomized trials. It provides a tool to standardize reports and minimize bias in trial results, by clear and transparent reporting of findings (Kwakkel et al., 2004).

The time window of neural mechanisms assumed to play a role in the natural logarithmic pattern of recovery of body functions (or reduction of impairments) (Kwakkel et al., 2004; Levin et al., 2009) may further underline the need for RCTs starting in the first weeks after stroke. As suggested by Murphy and Corbett after stroke a number of neural mechanisms are operating in different, partly overlapping time frames (Murphy & Corbett, 2009). In the first hours to days, the brain is trying to limit tissue damage in the penumbra (the brain region that suffers from ischemia but in which the ischemic damage is potentially or at least partially reversible) (Witte et al., 2000) and is thought to promote useful neuroplasticity by upregulating a number of proteins (such as inflammatory cytokines, nerve growth factors, and neurotransmitters) in the ischemic core as well as the penumbra (Murphy & Corbett, 2009). In addition, alleviation of diaschisis (Feeney & Baron, 1986) and Hebbian as well as non-Hebbian learning mechanisms are thought to drive cortical map reorganization in the first weeks after stroke (Witte et al., 2000).

Longitudinal studies in humans with repeated measurements over time show that the pattern of restitution of impairments is mainly seen within the first 10 weeks after stroke (Kwakkel et al., 2004). After this time window, improvement of the outcome in terms of activities is thought to be mainly defined by adaptation or compensatory motor strategies. Furthermore, since the outcome in terms of body functions as well as activities in humans can be predicted with a very high degree of certainty in the first few weeks after stroke (Kwakkel et al., 2006; Prabhakaran et al., 2008; Stinear et al., 2012), we hypothesize that true neurological recovery is mainly defined by spontaneous, non-learning-dependent mechanisms in the first weeks after stroke, such as salvation of penumbral tissue and alleviation of diaschisis or shock. The first evidence that both processes (compensation and restitution) emerge simultaneously early post stroke is shown by van Kordelaar et al. (2013) in which the number of degrees of freedom to control as reflected by synergism is almost completed within the first 3 months post stroke (van Kordelaar, 2013). This time window corresponds to enhanced gene-expression profiles in the post-ischemic brain in animals (Ge et al., 2007), and this might be true for human stroke as well. These findings have important implications for the treatment of motor impairments after stroke. If there is a limited time window for plasticity mechanisms, this suggests that it is critical to start rehabilitative interventions in the first weeks after stroke (Carmichael, 2006). Although this assumption is not directly supported by evidence found in trials started in the first weeks after stroke in humans, several prognostic models for regaining dexterity after stroke do suggest that the final outcome of upper limb function at 6 months in terms of motor synergies can be maximally predicted within the first 4 weeks after stroke (Kwakkel et al., 2006; Prabhakaran et al., 2008; Stinear et al., 2012). In animal research, rats showed better outcomes in terms of upper limb reaching tasks, with more dendritic outgrowth, when they received upper limb training in combination with an enriched environment within the first 28 days after stroke, than when the upper limb training was delayed beyond 28 days (Biernaskie et al., 2004). In the latter case, training turned out to be ineffective in resolving the forelimb impairment as well as in promoting dendritic outgrowth (Biernaskie & Corbett, 2001). The challenge in this field thus lies in trying to influence the mechanisms that are active during neurological recovery in the first weeks after stroke, either by targeting motor function at the impairment level as a reflection of neural repair and/or by directly targeting neurological repair itself. The question is, however, does allowing patients to use compensation strategies within the first 12 weeks prevent true neurological repair? This latter question is unsolved by lack of trials in this field.

5. Compensation strategies in skill reacquisition after stroke

In humans, increased coupling between shoulder abduction and elbow flexion of the paretic limb, as well as increased trunk involvement to improve accuracy of reaching with the affected hand (Cirstea & Levin, 2000; Ellis et al., 2005; Lang et al., 2006; Michaelsen et al., 2004; Sukal et al., 2007), also known as synergistic movement, is often seen during skill reacquisition after stroke. This suggests that functional improvement is achieved by compensatory mechanisms using preserved descending motor pathways to compensate for distal impairment through better trunk control, as opposed to restitution of function (Lang et al., 2006). For instance, improvement after constraint induced movement therapy (CIMT), where the unaffected limb is being constrained to enforce the use of the affected limb, is not merely based on overcoming learned non-use, but also on adopting alternative movement strategies to accomplish upper limb tasks (Kitago et al., 2012). Poor selectivity of motor control, defined as the impaired ability to isolate activation of muscles in a selected pattern, is characterized by a reduced number of degrees of freedom, reduced speed and a more proximal control of the affected arm and hand (Latash et al., 2007). One may argue that, from the perspective of controlling degrees of freedom, proximal control through the trunk and shoulder while fixating the elbow is easier than controlling all joints simultaneously while performing a functional task (Latash & Anson, 1996). Therefore, serial kinematic measurements in which the quality of motor performance is measured systematically in the first months after stroke are vital in explaining the dynamics of neural recovery.

The occurrence of compensatory movement strategies suggests that this should be seen as an important confounder in understanding true motor recovery. This finding underlines that limitations in terms of body functions and restrictions of activities are not the only parameters that should be measured to understand changes in motor performance. Moreover, one may hypothesize that biomechanical changes in the musculoskeletal system itself may contribute to a gradually changing preferred performance during the execution of tasks (Latash et al., 2007). For example, recent studies using electromyography (EMG) of the arm muscles found that mechanical perturbations of the elbow angle resulted in two different temporal change patterns (Mirbagheri et al., 2008, 2009). In some patients, intrinsic and reflex stiffness increases continuously after stroke, while in other patients, intrinsic stiffness decreases continuously over a 12-month interval. The mere existence of these different and potentially opposing processes suggests that global joint-stiffness measures may be misleading (Alibiglou et al., 2008). It therefore seems worthwhile for future studies to distinguish between neural resistance induced by reflex activity and the increased non-neural passive resistance by changes in muscle and connective tissue (Mirbagheri et al., 2008, 2009). A longitudinal study suggested that muscle stiffness at 5 weeks is a better predictor of arm function measured with the Fugl Meyer arm test (FMA) at 6 months, than FMA score itself at 5 weeks (Mirbagheri et al., 2012). These results suggest that muscle stiffness affects upper limb recovery These peripheral biomechanical changes within the neuromuscular system itself (i.e., neuromechanics) are an important, but so far neglected component in the study of skill reacquisition after stroke, and will allow better interpretation of neural dynamics in longitudinal fMRI and TMS studies (Buma et al., 2010).

6. Understanding non-learning- and learning-dependent mechanisms of skill reacquisition

A number of mechanisms in the brain have been proposed to underlie sensorimotor recovery after stroke, as shown in Fig. 1, panel B. The following sections first explain the spontaneous mechanisms shown in panel B. Starting from the ischemic cascade in the first minutes after stroke, there are mechanisms protecting neurons on the one hand, and mechanisms accommodating and driving spontaneous peri-infarct neuroplasticity (Brouns & Deyn, 2009; Doyle et al., 2008) on the other. In addition, metabolic changes (including diaschisis) take place around and distal to the lesion site, which can last up to several weeks (Biernaskie & Corbett, 2001) or even months (Seitz et al., 1999). Subsequent sections then present the evidence for the learning-dependent mechanisms in panel C, introducing evidence to suggest that these spontaneous mechanisms can be influenced by experience (Biernaskie & Corbett, 2001). First, however, we need to define what is meant by neuroplasticity after stroke and what its relationship with skill reacquisition is (through restitution or compensation).

7. Spontaneous (non-learning-dependent) mechanisms of recovery

In the first weeks after stroke, a number of mechanisms are hypothesized to be involved in spontaneous neurological recovery such as: (1) salvation of the penumbra, (2) physiological and neuroanatomical reorganization, (3) alleviation of diaschisis, (4) and reperfusion enhanced by post-stroke angiogenesis.

7.1. Salvation of the penumbra

Neurological recovery is assumed to be linearly correlated with the volume of at-risk tissue in the penumbra that escapes infarction, whether this is spontaneous or enhanced by recombinant Tissue Plasminogen Activator (rTPA) (Baron, 2005). Two mechanisms underlie this correlation: (1) return of neural function (probably due to blood flow being reduced but not below a certain threshold), within hours or days, and (2) gradual recovery over weeks through structural and functional plasticity in the infarct rim. Reperfusion after stroke can greatly reduce injury after ischemia and can improve neurological outcome after stroke. Structural damage to the dendrites can even be reversed during reperfusion (Zhang et al., 2005). However, reperfused tissue might still be at risk for inflammation and selective neuronal death up to several days to weeks after stroke (Guadagno et al., 2008). Cellular events related to tissue inflammation and selective cell death during salvation of the penumbra are assumed to interact with plasticity mechanisms in the infarct rim, which are therefore important when trying to model the mechanisms involved in recovery after stroke (Baron, 2005; van der Zijden et al., 2008). Subsequently the amount of recovery that a patient shows in this period might well be influenced by these mechanisms related to the survival of the penumbra.

7.2. Spontaneous neuroplasticity

After injury, the areas around the lesion as well as anatomically connected areas further away from the lesion undergo substantial spontaneous physiological and neuroanatomical changes. Homeostatic mechanisms ensure that activity in the surviving neurons is scaled to previous input, meaning that high levels of activation favor synaptic depression while low levels of activation (for example deafferentiation due to the lesion) induce facilitation (Turrigiano, 2008). Under influence of an upregulation of a number of growth promoting genes connectivity in surviving neurons is restored. For example, in the first weeks after focal stroke in rats, growth promoting factors (such as brain-derived neurotrophic factor, BDNF and nerve growth factor, NGF) are expressed in waves by neurons in the peri-infarct area, creating a favorable environment for dendritic outgrowth and synaptogenesis (Carmichael, 2006). Evidence for the involvement of these factors in recovery after stroke has been found in studies on BDNF, where administering BDNF in rats promoted the improvement of skilled reaching after stroke, as well as dendritic outgrowth (Schäbitz et al., 2004). There seems to be a change in the balance between the excitation and inhibition of neurons, and this hyperexcitability can be a signal of the resetting of neuronal activity in the infarcted area due to homeostatic mechanisms (Murphy & Corbett, 2009). This could provide a favorable environment for the presence of waves of depolarization in the infarct area, which are thought to be a signal of axonal sprouting (Carmichael, 2006). At a later time point after upregulation of growth factors, outgrowth is modulated by inhibitory factors (such as NOGO, chondroitin sulphate proteoglycan64, eprhin A5, semaphoring 3A and neuropilin 1). These factors are expressed in a later stage after stroke in rats, probably to control axonal outgrowth and prevent overconnectivity (Murphy and Corbett, 2009; Overman et al., 2012). Homeostatic plasticity mechanisms might cause an initial overproliferation of new connections through axonal sprouting due to disinhibition in the areas connected to the injury (Winship & Murphy, 2009). These overconnections might be pruned by Hebbian- and non-Hebbian like learning mechanisms in optimizing these adapted neural circuits in response to relearning skills. Interestingly, both Hebbian-like mechanisms in the peri-infarct area and homeostatic synaptic neuroplasticity could be coordinated by upregulation of factors such as BDNF (Pozo & Goda, 2010).

7.3. Alleviation of diaschisis

Spontaneous recovery after stroke is not restricted to the first hours after stroke, but may happen during a longer period, even up to 10 weeks (Kwakkel et al., 2006). The limited therapeutic window for rTPA, three to four hours after stroke, suggests that other mechanisms, such as recovery from “cerebral shock” or alleviation of diaschisis, may explain the

spontaneous neurological recovery that may continue for several weeks. Monakov first described the phenomenon of diaschisis in 1914, and proposed that areas distant from the lesion could be functionally affected by neuronal damage. The term diaschisis is used today for any "remote" effect initiated by a focal lesion or ischemic event to the brain (Andrews, 1991; Seitz et al., 1999; Witte et al., 2000). Diaschisis is accompanied by depression of regional cerebral blood flow extending beyond the anatomical lesion, as demonstrated by a perfusion deficit in the region of cortical diaschisis measured with rCBF-SPECT (Chu et al., 2002; Komaba et al., 2004). Alleviation of the suppression of brain areas anatomically related to the lesion (i.e. reversal of diaschisis) is thought to contribute to motor recovery of neurological function and motor control in the first months after stroke (Feeney & Baron, 1986; Seitz et al., 1999). While serial assessments of diaschisis have been scarce, the topographical overlap between lesion-affected and recovery-related brain networks supports the idea that reversal of the suppressed areas may play a significant role in skill reacquisition after stroke (Chu et al., 2002; Seitz et al., 1999). However, its physiological aspects, as well as its time window, are still largely unknown, and persistent remote effects of cortical injury are more complex than previously thought (Gold & Lauritzen, 2002). For example, diaschisis involves disinhibition of anatomically related brain areas as well as hyperexcitability, in addition to the well-known hypometabolism and inhibition of these areas (Andrews, 1991).

7.4. Non-neural forms of plasticity after stroke

New blood vessels are formed in the peri-infarct zone in the first days to weeks after stroke (Font et al., 2010). Recent research demonstrated that angiogenesis and neurogenesis are coupled restorative mechanisms that contribute to neurological recovery (Chopp et al., 2007).

For example, metalloproteinases (MMPs) released in the penumbral area after stroke causes breakdown of the blood–brain barrier (BBB) and are therefore associated with edema and neuronal loss. However, MMP-9 has also been suggested to be involved in revascularization in the later stages after stroke (Zhao et al., 2006, 2007). Thus, downregulation of MMPs over a longer period might protect neurons in the first few hours but might subsequently be detrimental to neuroplasticity. It seems that timing is important in finding an appropriate therapeutic target in the penumbral area in the first hours after stroke. Proteins associated with neuroplasticity and dendritic outgrowth in stroke, such as BDNF and transforming growth factor alpha (TGFa), have also been associated with angiogenesis and are therefore referred to as angioneurins (Font et al., 2010). Interestingly, these proteins are involved in learning-dependent neuroplasticity as well (Ploughman et al., 2009).

7.5. Learning-dependent mechanisms of neuroplasticity

The synaptic scaling caused by homeostatic neuroplasticity seems to create a favorable environment in which other forms of learning-dependent plasticity (Hebbian-type synaptic strengthening and pruning) can take place, and ensures that neurons in the peri-infarct area continue to receive sufficient input. The brain quickly adapts in response to a lack of input by remapping the somatosensory cortex, as was shown in monkeys following deafferentiation (Clifford, 1998; Nudo & Milliken, 1996). If a single digit is removed from an adult animal (a form of deafferentiation) the cortical area connected to that digit rapidly remaps to represent the remaining intact digits that project to the adjacent cortex (Nudo & Milliken, 1996). The formation of new cortical connections occurs in areas that are not involved in the infarct itself and that start to receive input of information from the nearby cortex (Dancause et al., 2005). Strong excitatory or inhibitory NMDA receptor-dependent postsynaptic changes may lead to long-term potentiation (LTP) or long-term depression (LTD), respectively (Cooke & Bliss, 2006). Further enhancement of the production of proteins involved in synaptic neuroplasticity can be obtained through experience, including training and afferent stimulation (Sawaki et al., 2006; Winship & Murphy, 2009).

Animal studies have revealed a complex interplay between mechanisms of homeostatic and Hebbian- and non-Hebbian forms of plasticity, in which mechanisms of neuroplasticity are not only dependent on the amount of practice, but also on the type of training as well as its timing after stroke (Biernaskie & Corbett, 2001; Ploughman et al., 2009). For example, moderate treadmill training in rats was found to increase levels of proteins such as BDNF, neurophysin-I and insulin-like growth factor (IGF) type I. However, when these rats engaged in an intensive (60 minutes, forced) motorized running training, the elevation of growth factors was

more short-lived than after voluntary running initiated by the rats themselves (Ploughman et al., 2005). This finding suggests that frequent but low-intensity exercise episodes (voluntary running over a 12 h period) has a delayed but sustained effect on BDNF production (Ploughman et al., 2007). The importance of therapy dosage is shown by MacLellan and colleagues who found that voluntary reaching in rats needed to rise above a certain threshold to cause improvement of motor function at an activity level and to produce elevated levels of BDNF (MacLellan et al., 2011). There seems to be a critical time window when administering rehabilitative therapy in animals after stroke. An important study showed that delaying rehabilitative treatment in a rodent stroke model for 30 days after stroke, led to poor improvement of upper limb function as well a no change in dendritic outgrowth. Rehabilitation therapy administered in the first few weeks after stroke, however, enhanced improvement on a reaching task as well as increasing dendritic outgrowth (Biernaskie et al., 2004).

7.6. Other forms of brainplasticity

Animal studies have shown that treadmill running may also enhance the blood-vessel density in the motor cortex, cerebellum and striatum thereby allowing increased metabolism in poorly perfused areas (Black et al., 1990; Ding et al., 2004; Kleim et al., 2002). In interaction with some of the above mentioned forms of cortical reorganization around the infarct rim, treadmill running therapy does indeed upregulate endothelial nitric oxide synthase (Endres et al., 2003), as well as reducing pro-coagulation factors and increasing factors associated with anticoagulation (Wittenberg et al., 2003). Nevertheless, the exact role of angiogenesis evoked by training in the human brain is an unexplored area.

8. *In vivo* imaging of cortical map reorganization in humans

Cross-sectional and longitudinal fMRI, PET and TMS studies suggest that the damaged adult human brain shows changes in activity patterns (Askim et al., 2008; Calautti & Baron, 2003; Johansen-Berg et al., 2002; Nelles et al., 2001; Rehme et al., 2012; Ward et al., 2003a). These changes are thought to represent remapping and vicarious functions of areas in the motor network (Dancause, 2006). In the early days most fMRI studies were performed on patients in the chronic stage (>6 months) after stroke. These studies found overactivations in a number of motor areas in patients who showed poor skill reacquisition compared to control subjects. These over-activations were predominantly seen in the bilateral premotor cortex (PM), supplementary motor area, as well as parietal regions (Seitz et al., 1998; Ward, Brown et al., 2003b). High scores on outcome measures in terms of body functions and activities is associated with preservation or restoration of activity in the ipsilesional hemisphere, rather than task-related recruitment of activity in the non-affected hemisphere (Small et al., 2002; Ward et al., 2003a). Recent serial fMRI and PET studies have suggested that cortical reorganization over time (i.e. the amount of recruitment and activation of task-specific areas in the unaffected and affected hemispheres) is largely dependent on the intactness of the corticospinal tract, which can be measured with TMS (Ward et al., 2003a, 2003b), or diffusion-tensor imaging (DTI) (Newton et al., 2006).

It is unlikely (from the perspective of regaining dexterity) that secondary motor areas are able to take over the actions of the primary motor system (Maier et al., 2002; Ward, 2007). Indeed, ipsilateral increments in cortical activation are correlated with poor skill reacquisition in terms of body functions and activities (Buma et al., 2010). An increase in axial muscle control has recently been suggested to be accompanied by an increase in ipsilateral cortical activity, whereas for distal arm muscles, ipsilateral increases are correlated with moderate to severe impairment (Schwerin et al., 2010). These findings might suggest that an increase in the excitability of ipsilateral pathways projecting to the proximal upper arm may contribute to the control of arm extension following stroke (Bradnam et al., 2012). Apparently, it is much more difficult to restore the affected primary motor networks responsible for distal multi-joint coordination than to use more proximal motor control in a sequential, fragmented type of movement (Cirstea & Levin, 2000).

The mechanisms of cortical reorganization are probably stimulated by task-specific therapy. For example, repeated TMS (Liepert et al., 2000), PET (Nelles et al., 2001) or fMRI (Johansen-Berg et al., 2002) measurements show that therapy-mediated improvements by CIMT result in increased activity in the affected hemisphere and decreased activity in the unaffected hemisphere while a motor task is being

performed with the affected hand. However, these macroscopic changes in cortical activation after arm training or CIMT may reflect compensatory motor skill learning rather than restoration of lost representations (Sunderland & Tuke, 2006). As mentioned above, it is of paramount importance to kinematically assess whether synergistic compensatory movement patterns (such as trunk involvement) might be responsible for the improved task performance and whether these compensatory mechanisms are confounding the relationship between skill reacquisition and brain activation as measured with fMRI.

Since improvement after stroke is time-dependent, results of imaging studies are heavily influenced by the moment of scanning after stroke, at least when measuring during the first 6 months after stroke (Kwakkel, 2006). The great complexity of assessing neural correlates of skill reacquisition after stroke demands an appropriate study design taking account of the confounders often encountered in stroke imaging research. Statistical, anatomical, experimental and task-dependent factors may confound results, leading to interpretation problems in serial fMRI studies (Buma et al., 2010, for a systematic review). Examples are: (1) using appropriate measures of functional improvement of the upper paretic limb, which measure improvement of body functions; (2) using quantitative measures of the quality of performance in executing a motor paradigm (e.g. strength, ROM, speed, attention and sensation), so that performance of the task can be accounted for; (3) controlling for "mirror movements" of the non-paretic limb to ensure proper interpretation of activity in the unaffected hemisphere (Kim et al., 2003). In addition it might be relevant to assess the influence of time-dependent neuromechanical changes in the arm itself in terms of increased stiffness and spasticity, to be able to understand the relationship between task dependent changes in the brain and the possibly increased non-neural passive resistance by changes in muscle and connective tissue (for critical comments see Dobkin, 2003).

9. Connecting the dots and targets for future research

The likelihood of regaining skills after stroke is complex and determined by a number of learning- and non-learning-dependent mechanisms. These are brought together and summarized in context in our proposed phenomenological model for understanding skill reacquisition after stroke (Fig. 1). As discussed, panel A illustrates that skill reacquisition through motor learning may take place in a number of steps. At first, most patients suffer from a reduced ability to modulate their movement apparatus due to loss of somatosensory sensation, muscle strength and selectivity in muscle recruitment. At the same time, biomechanical changes occur as a result of loss of muscle fibers by orthograde degeneration, increased stiffness and velocity-dependent changes in myotatic stretch reflexes (spasticity). Patients with a poor prognosis will use compensatory movement strategies to recover motor control, whereas patients with a favorable prognosis will be able to restore impaired functions. Ultimately, the actual motor performance, and consequently the ability to accomplish a particular task, will depend on the equilibrium between the capacity for restitution versus compensation.

In the early stages after stroke, non-learning-dependent mechanisms such as spontaneous motor recovery (panel B) as well as learning-dependent mechanisms (panel C) are responsible for changes in cortical reorganization. The process of spontaneous recovery is defined by salvation of penumbral tissue by reperfusion, angiogenesis and "spontaneous" alleviation of diaschisis or cerebral shock (panel B). Mechanisms related to spontaneous neurological recovery are mainly defined by progress of time and restricted to the first 10 weeks after stroke (Dobkin, 2005; Kwakkel et al., 2006). Simultaneously, and in interaction with spontaneous neurological recovery, experience through practice will also lead to cortical reorganization, starting within minutes from stroke onset (Panel C). Hebbian and non-Hebbian learning mechanisms lead to LTP and LTD. Both mechanisms result in a change in interneuronal connectivity and efficiency in the communication along existing neuronal networks (Cooke & Bliss, 2006).

We argue that understanding skill reacquisition after stroke requires a translational, multidisciplinary approach, with intensive measurements repeated over time. In these time-series both motor performance and changes in brain activity need to be measured simultaneously during identical time frames after stroke. The first measurements should preferably start in the first days after stroke, and they should be repeated until skill reacquisition has reached a plateau. In order to improve our understanding of skill reacquisition after stroke, serial assessments should investigate the relationships

between observed improvements in clinical measures, kinematics, biomechanics and cortical map reorganization (Kollen et al., 2005; Kwakkel et al., 2008; Wagner et al., 2007). Such serial measurements may enable us to distinguish "true" neurological repair from learning to use compensation strategies. This goal does not seem to be sufficiently served merely by studying the changes in cortical map reorganization by fMRI or PET in relation to the intactness of the corticospinal tract system assessed by TMS or fiber tracking. Understanding the meaning of changes in cortical activity as a function of time requires simultaneous measurements of changes in motor performance, including kinematics (Goodwin & Sunderland, 2003; Kwakkel & Wagenaar, 1996; Wagner et al., 2007).

The above phenomenological model currently serves as a template for the EXPLICIT-stroke program in the Netherlands (Kwakkel et al., 2008). EXPLICIT-stroke is an acronym for 'EXplaining PLastICIiTy after stroke'. The EXPLICIT-stroke program is a 6-year translational research program supported by the The Netherlands Organisation for Health Research and Development (ZonMw). The main aim of EXPLICIT-stroke is to investigate the effects of intensive intervention to regain dexterity starting within 2 weeks after stroke, and to explore the underlying mechanisms involved in regaining upper limb function in the first 6 months after stroke. For this purpose stroke patients are longitudinally investigated by applying a multimodal approach in which clinical outcomes are related to observed changes measured with fMRI, TMS, DTI, kinematic assessments and haptic robotics after stroke. The EXPLICIT-stroke program is expected to provide an answer to the key question how much of therapy-induced improvement is due to restitution of function and how much to compensatory mechanisms (Kwakkel et al., 2008).

In addition, future studies, including those conducted in animals should measure the quality of motor performance, by including kinematic analysis, in addition to outcome measures in terms of body functions and activities. With that, research relating the principles of cortical map reorganization to a better understanding of *what and how* patients learn, instead of relating it to *whether* they learn, is expected to further enhance our understanding of the meaning of the neural dynamics in activation patterns after stroke. Acknowledging that patients' motor performance is also determined by changes in the structure of the movement apparatus itself (Latash & Anson, 1996; Latash et al., 2007), phenomena such as increased intrinsic stiffness and reflex stiffness need to be measured to understand the observed changes in motor performance (Dewald et al., 2001; Mirbagheri et al., 2009).

As a consequence, our model of the processes and mechanisms of skill reacquisition after stroke may be helpful in designing trials and selecting therapy. First, our model recommends that clinicians and researchers should distinguish between skill reacquisition resulting from neurological repair and from compensation strategies (Fig. 1) (Levin et al., 2009). Second, the contribution of non-learning-dependent mechanisms such as spontaneous neurological recovery suggests that trials should use appropriate randomization procedures when studying the impact of therapeutic interventions on skill reacquisition in the early stages after stroke (Kwakkel et al., 2006). This confirms the general rule that stroke outcome data should only be reported when the observations of experimental and control groups are made during the same time interval after stroke onset. Third, our model supports the general conviction that the selection of a type of therapy in the early stages after stroke, matters for the final outcome. For example, there is a longstanding debate in rehabilitation medicine whether specialists should aim for restitution of body functions or should allow patients to adopt compensation strategies (Kollen et al., 2005; Krakauer et al., 2012). The current view is an extension of reports from longitudinal studies that suggest that restitution and compensation complement each other in the process of skill acquisition that starts immediately after stroke onset. The question whether we should prevent patients from adaptive motor learning in the first weeks after stroke to optimize normal movement remains unsolved, through lack of proper randomized clinical trials (Kollen et al., 2005).

10. Limitations

The focus in the present review has been on bridging the gap between preclinical and clinical research on skill reacquisition after stroke. We have attempted to show where there are gaps in our knowledge and have focused on constructing a phenomenological model for understanding stroke recovery. While much can be learned from animal studies some caution must be taken in translating these results to humans. We suggest there are a number of issues (1) Animal stroke

models are mostly based on cortical stroke, whereas subcortical stroke is much more common in humans (Carmichael, 2005) (2) The exercise therapy used in animal studies does not easily translate to human studies since (a) treadmill running does not translate to task specific training used in rehabilitative setting in humans (Hillman et al., 2008) (b) the threshold dose for treatment of task-specific training in animal studies is found to be around a factor of 10 higher than that observed in humans in a rehabilitative setting (Krakauer et al., 2012; Lang et al., 2009; Remple et al., 2001) (3) The timeframe of recovery studied in animals is different from that for humans, so translating the critical time window for some plasticity mechanisms in animals (Biernaskie et al., 2004) to a specific period in humans is difficult and deserves further investigation (4) In animal studies applied interventions are aimed at relearning a well practiced task and not at reducing impairments in general.

11. Conclusion

Several longitudinal studies have provided strong evidence that neural repair in which the quality of motor control is restored is mainly confined to a limited time window of spontaneous neurological recovery in the first 3 months after stroke (Kwakkel et al., 2006). So far, large, well-designed randomized clinical trials starting within this time window have been scarce, while the clinical outcome measures used were unable to distinguish between skill reacquisition by restitution of body functions as a reflection of neural repair, and skill reacquisition by learning to compensate while performing meaningful tasks. In view of this, the ICF framework is essential for interpreting motor recovery and neural dynamics after stroke (Levin et al., 2009). Unfortunately, neither animal nor human studies have shown that restitution of impaired body functions by certain rehabilitation interventions can restore the quality of normal motor performance. A better understanding of the underlying mechanisms that drive "spontaneous" recovery after stroke and restitution of body functions may lead to the development of interventions starting within days after stroke and aimed specifically at restoring functions to a level as close to normal as possible (Latash et al., 2007). For this purpose, translational research should be guided by the ICF framework and be built around solid hypotheses derived from and founded on knowledge of basic and preclinical science (Cheeran et al., 2009). The research questions addressed will then lead to answers to clinically relevant problems that are perceived as critical for improving care for one of the most common disabling diseases, stroke (Dong et al., 2006).

References

Alibiglou, L., Rymer, W.Z., Harvey, R.L. & Mirbagheri, M.M. (2008). The relation between Ashworth scores and neuromechanical measurements of spasticity following stroke. *J Neuroeng Rehabil*, *5*, 18.

Andrews, R. (1991). Transhemispheric diaschisis. A review and comment. *Stroke*, *22*, 943-949.

Askim, T., Indredavik, B. & Vangberg, T. (2008). Motor skill relearning after acute ischemic stroke. *NeuroRehabilitation*, *1*, 1-10.

Banks, J.L. & Marotta, C.A. (2007). Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials: A literature review and synthesis. *Stroke*, *38*, 1091-1096.

Baron, J. (2005). How healthy is the acutely reperfused ischemic penumbra? *Cerebrovasc Dis*, *20*(suppl 2), 25-31.

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

Biernaskie, J., Chernenko, G. & Corbett, D. (2004). Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *Neuroscience*, *24*(5), 1245-1254.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A. & Greenough, W.T. (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc. *Nati Acad Sci*, *87*, 5568-5572.

Bradnam, L.V., Stinear, C.M., Barber, P.A. & Byblow, W.D. (2012). Contralesional hemisphere control of the proximal paretic upper limb following stroke. *Cereb Cortex*, *22*(11), 2662-2671.

Brouns, R. & Deyn, P.P., De (2009). The complexity of neurobiological processes in acute ischemic stroke. *Clin Neurol and Neurosur*, *111*, 483-495.

Brunnström, S. (1970). Movement therapy in hemiplegia. New York: Harper and Row.

Buma, F.E., Lindeman, E., Ramsey, N.F. & Kwakkel, G. (2010). Functional neuroimaging studies of early upper limb recovery after stroke: A systematic review of the literature. *Neurorehab Neural Re*, *24*(7), 589-608.

Calautti, C. & Baron, J.C. (2003). Functional neuroimaging studies of motor recovery after stroke in adults: A review. *Stroke*, *34*(6), 1553.

Carmichael, S.T. (2005). Rodent models of focal stroke : Size. *mechanism, and purpose. NeuroRx*, *2*(July), 396-409.

Carmichael, S.T. (2006). Cellular and Molecular Mechanisms of Neural Repair after Stroke: Making Waves. *Ann of Neurol*, *59*, 735-742.

Cheeran, B., Cohen, L., Dobkin, B., Ford, G., Greenwood, R., Howard, D. & Wolf, S. (2009). The future of restorative neurosciences in stroke: Driving the translational research pipeline from basic science to rehabilitation of people after stroke. *Neurorehab Neural Re*, *23*(2), 97-107.

Chen, H.-M., Chen, C.C., Hsueh, I.-P., Huang, S.-L. & Hsieh, C.-L. (2009). Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehab Neural Re*, *23*(5), 435-440.

Chopp, M., Zhang, Z.G. & Jiang, Q. (2007). Neurogenesis, angiogenesis, and MRI indices of functional recovery from stroke. *Stroke*, *38*(2 Suppl), 827-831.

Chu, W.-J. W, Mason, G.F., Pan, J.W., Hetherington, H.P., Pedro, E.C.S. & Mountz, J.M. (2002). Regional cerebral blood flow and magnetic resonance spectroscopic imaging findings in diaschisis from stroke. *Stroke*, *33*(5), 1243-1248.

Cirstea, M.C. & Levin, M.F. (2000). Compensatory strategies for reaching in stroke. *Brain*, *123*, 940-953.

Clifford, E. (1998). Neural Plasticity: Merzenich, Taub, and Greenough. *Harvard Brain*, 16-20.

Cooke, S.F. & Bliss, T.V.P. (2006). Plasticity in the human central nervous system. *Brain*, *129*, 1659-1673.

Dancause, N. (2006). Vicarious function of remote cortex following stroke : Recent evidence from human and animal studies. *Neuroscientist*, *12*, 489.

Dancause, N., Barbay, S., Frost, S.B., Plautz, E.J., Chen, D., Zoubina, E. & Nudo, V., R.J. (2005). Extensive cortical rewiring after brain injury. *Neuroscience*, *25*(44), 10167-10179.

Dewald, J.P.A., Sheshadri, V., Dawson, M.L. & Beer, R.F. (2001). Upper-limb discoordination in hemiparetic stroke: Implications for neurorehabilitation. *Top Stroke Rehab*, *8*(1), 1-12.

Ding, Y., Li, J., Luan, X., Ding, Y.H., Lai, Q., Rafols, J. & Diaz, F.G. (2004). Exercise pre-conditioning reduces brain damage in ischemic rats that may be associated with regional angiogenesis and cellular overexpression of neurotrophin. *Neuroscience*, *124*(3), 583-591.

Dobkin, B.H. (2003). Functional MRI: A potential physiologic indicator for stroke rehabilitation interventions. *Stroke*, *23*, 23-28.

Dobkin, B.H. (2005). Rehabilitation and functional neuroimaging dose-response trajectories for clinical trials. *Neurorehab and Neural Re*, *19*, 276-283.

Dobkin, B.H. (2009). Collaborative models for translational neuroscience and rehabilitation research. *Neurorehab and Neural Re*, *23*(7), 633-640.

Dong, Y., Dobkin, B.H., Cen, S.Y., Wu, A.D. & Winstein, C.J. (2006). Motor cortex activation during treatment may predict therapeutic gains in paretic hand function after stroke. *Stroke*, 1552-1555.

Doyle, K.P., Simon, R.P. & Stenzel-poore, M.P. (2008). Mechanisms of ischemic brain damage. *Neuropharmacology*, *55*, 310-318.

Duff, M., Chen, Y., Cheng, L., Liu, S.M., Blake, P., Wolf, S.L. & Rikakis, T. (2013). Adaptive mixed reality rehabilitation improves quality of reaching movements more than traditional reaching therapy following stroke. *Neurorehab neural re*, *27*(4), 306-315.

Ellis, M.D., Holubar, B.G., Acosta, A.M., Beer, R.F. & Dewald, J.P. (2005). Modifiability of abnormal isometric elbow and shoulder joint torque coupling after stroke. *Muscle Nerve*, *32*(August), 170-178.

Endres, M., Gertz, K., Lindauer, U., Katchanov, J., Schultze, J., Schröck, H. & Laufs, U. (2003). Mechanisms of stroke protection by physical activity. *Ann Neurol*, *54*(5), 582-590.

Feeney, D.M. & Baron, J.C. (1986). Diaschisis. *Stroke*, *17*(5), 817-830.

Font, M.A., Arboix, A. & Krupinski, J. (2010). Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Curr Cardiol Rev*, *6*(3), 238-244.

Ge, S., Yang, C., Hsu, K., Ming, G. & Song, H. (2007). A Critical Period for Enhanced Synaptic Plasticity in Newly Generated Neurons of the Adult Brain. *Neuron*, 559-566.

Gold, L. & Lauritzen, M. (2002). Neuronal deactivation explains decreased cerebellar blood flow in response to focal cerebral ischemia or suppressed neocortical function. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(11), 7699-7704.

Goodwin, N. & Sunderland, A. (2003). Intensive, time-series measurement of upper limb recovery in the subacute phase following stroke. *Clin Rehabil*, *17*(1), 69-82.

Guadagno, J.V., Jones, P.S., Aigbirhio, F.I., Wang, D., Fryer, T.D., Day, D.J. & Baron, J.C. (2008). Selective neuronal loss in rescued penumbra relates to initial hypoperfusion. *Brain*, *131*(Pt 10), 2666-2678.

Heuschmann, P., Wiedmann, S., Wellwood, I., Rudd, A., Di Carlo, A., Beyot, Y. & Wolfe, C. (2011). Three- Month stroke outcome: The European Registers of Stroke (EROS) investigators. *Neurology*, *28*(8), 884-892.

Hillman, C.H., Erickson, K.I. & Kramer, A.F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature*, *9*, 58-65.

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S.M., Wade, D.T. & Matthews, P.M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, *125*, 2731-2742.

Johansen-Berg, H., Rushworth, M.F.S., Bogdanovic, M.D., Kischka, U., Wimalaratna, S. & Matthews, P.M. (2002). The role of ipsilateral premotor cortex in hand movement after stroke. *Stroke*, *99*(22), 14518-14523.

Kelly-Hayes, M., Beiser, A., Kase, C., Scaramucci, A., D'Agostino, R. & Wolf, P. (2003). The influence of gender and age on disability following ischemic stroke: The Framingham study. *J Stroke Cerebrovasc*, *12*(3), 119-126.

Kerr, A.L., Cheng, S.-Y. & Jones, T.A. (2011). Experience-dependent neural plasticity in the adult damaged brain. *J Commun Disord*, *44*(5), 538-548.

Kim, Y., Jang, S.H., Chang, Y., Byun, W.M., Son, S. & Ahn, S.H. (2003). Bilateral primary sensori-motor cortex activation of post-stroke mirror movements: An fMRI study. *Neuroreport*, *14*(10), 1329-1332.

Kitago, T., Liang, J., Huang, V.S., Hayes, S., Simon, P., Tenteromano, L. & Krakauer, J.W. (2012). Improvement After Constraint-Induced Movement Therapy: Recovery of Normal

Motor Control or Task-Specific Compensation? *Neurorehab Neural Re*, *27*(2), 99-109.

Kleim, J.A., Cooper, N.R. & Vandenberg, P.M. (2002). Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Res*, *934*, 1-6.

Kollen, B., Van de Port, I., Lindeman, E., Twisk, J. & Kwakkel, G. (2005). Predicting improvement in gait after stroke: A longitudinal prospective study. *Stroke*, *36*(12), 2676-2680.

Komaba, Y., Mishina, M., Utsumi, K., Katayama, Y., Kobayashi, S. & Mori, O. (2004). Crossed cerebellar diaschisis in patients with cortical infarction: Logistic regression analysis to control for confounding effects. *Stroke*, *35*(2), 472-476.

Krakauer, J.W., Carmichael, S.T., Corbett, D. & Wittenberg, G.F. (2012). Getting neurorehabilitation right: What can be learned from animal models? *Neurorehab Neural Re*, *26*(8), 923-931.

Kwakkel, G., Kollen, B. & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke : Facts and theories. *Restor Neurol Neuros*, *22*, 281-299.

Kwakkel, G., Kollen, B. & Twisk, J. (2006). Impact of time on improvement of outcome after stroke. *Stroke*, *37*, 2348-2353.

Kwakkel, G., Meskers, C.G.M., Van Wegen, E.E., Lankhorst, G.J., Geurts, A.C.H., Van Kuijk, A.A. & Arendzen, J.H. (2008). Impact of early applied upper limb stimulation: The EXPLICIT-stroke programme design. *BMC Neurol*, *8*, 49.

Kwakkel, G., Van Peppen, R., Wagenaar, R.C., Wood Dauphinee, S., Richards, C., Ashburn, A. & Langhorne, P. (2004). Effects of augmented exercise therapy time after stroke: A meta-analysis. *Stroke*, *35*(11), 2529-2539.

Kwakkel, G. & Wagenaar, R.C. (1996). Predicting Disability in Stroke — A Critical Review of the Literature. *Age Ageing*, (25), 479-489.

Lang, C.E., Macdonald, J.R., Reisman, D.S., Boyd, L., Jacobson Kimberley, T., Schindler-Ivens, S.M. & Scheets, P.L. (2009). Observation of amounts of movement practice provided during stroke rehabilitation. *Arch Physical Med Rehab*, *90*(10), 1692-1698.

Lang, C.E., Wagner, J.M., Edwards, D.F., Sahrmann, S.A. & Dromerick, A.W. (2006). Recovery of grasp versus reach in people with hemiparesis poststroke. *Neurorehab Neural Re*, *20*(4), 444-454.

Langhorne, P., Bernhardt, J. & Kwakkel, G. (2011). Stroke Rehabilitation. *Lancet*, *377*, 1693-1702.

Langhorne, P., Coupar, F. & Pollock, A. (2009). Motor recovery after stroke: A systematic review. *Lancet Neurol*, *8*(8), 741-754.

Latash, M.L. & Anson, J.G. (1996). What are "normal movements" in atypical populations? *Behav Brain Sci*, *19*(1), 55-106.

Latash, M.L., Scholz, J.P. & Schöner, G. (2007). Toward a New Theory of Motor Synergies. *Motor Control*, *11*, 276-308.

Levin, M.F., Kleim, J.A. & Wolf, S.L. (2009). What Do Motor "Recovery" and "Compensation" Mean in Patients Following Stroke? *Neurorehab Neural Re*, *23*(4), 313.

Liepert, J., Bauder, H., Miltner, W.H.R., Taub, E. & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke*, *31*(6), 1210-1216.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T.B., Flegal, K. & Hong, Y. (2009). Heart disease and stroke statistics 2009 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, *119*(3), e21-181.

MacLellan, C.L., Keough, M.B., Granter-Button, S., Chernenko, G.A., 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.

Mahony, F.I. & Barthel, D.W. (1965). Functional evaluation: The Barthel Index. *Maryland State Med J*, *14*, 61-65.

Maier, M.A., Armand, J., Kirkwood, P.A., Yang, H., Davis, J.N. & Lemon, R.N. (2002). Differences in the Corticospinal Projection from Primary Motor Cortex and Supplementary Motor Area to Macaque Upper Limb Motoneurons : An Anatomical and Electrophysiological Study. *Cereb Cortex*, *12*, 281-296.

Metz, G.A., Antonow-Schlorke, I. & Witte, O.W. (2005). Motor improvements after focal cortical ischemia in adult rats are mediated by compensatory mechanisms. *Behav Brain Res*, *162*(1), 71-82.

Michaelsen, Stella, M., Jacobs, S. & Levin, A.R.M.F. (2004). Compensation for distal impairments of grasping in adults with hemiparesis. *Exp Brain Res*, 162-173.

Michaelsen, Stella, M., Dannenbaum, R. & Levin, M.F. (2006). Task-specific training with trunk restraint on arm recovery in stroke: Randomized control trial. *Stroke*, *37*(1), 186-192.

Mirbagheri, M.M., Tsao, C. & Rymer, W.Z. (2009). Natural history of neuromuscular properties after stroke: A longitudinal study. *J Neurol Neurosur Ps*, *80*(11), 1212-1217.

Mirbagheri, M.M., Tsao, C., Settle, K., Lilaonitkul, T. & Rymer, W.Z. (2008). *Time course of changes in neuromuscular properties following stroke*. *Conf Proc IEEE Eng Med Biol Soc*, *1*, 5097-5100.

Moon, S.K., Alaverdashvili, M., Cross, A.R. & Whishaw, I.Q. (2009). Both compensation and recovery of skilled reaching following small photothrombotic stroke to motor cortex in the rat. *Exp Neurol*, *218*(1), 145-153.

Murphy, T.H.T.H. & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. *Nat Rev Neurosc*, *10*(12), 861-872.

Nelles, G., Jentzen, W., Jueptner, M., Müller, S. & Diener, H. (2001). Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *Neuroimage*, *13*(6), 1146-1154.

Newton, J.M., Ward, N.S., Parker, G.J.M., Deichmann, R., Alexander, D.C., Friston, K.J. & Frackowiak, R.S.J. (2006). Non-invasive mapping of corticofugal fibres from multiple motor areas–relevance to stroke recovery. *Brain*, *129*(7), 1844-1858.

Ng, Y.S., Stein, J., Ning, M. & Black-Schaffer, R.M. (2007). Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke*, *38*(8), 2309-2314.

Nijland, R.H.M., Wegen, E.E.H., Van, & Wel, B.C.H., Der (2010). presence of finger extension and shoulder abduction within

72 hours after stroke predicts functional recovery early prediction of functional outcome after stroke: The EPOS cohort study. *Stroke*, *45*, 745-750.

Nudo, R.J.J. & Milliken, G.W.W. (1996). Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J Neurophysiol*, *75*(5), 2144-2149.

Overman, J.J., Clarkson, A.N., Wanner, I.B., Overman, W.T., Eckstein, I., Maguire, J.L. & Carmichael, S.T. (2012). A role for ephrin-A5 in axonal sprouting, recovery, and activity-dependent plasticity after stroke. *P Natl Acad Sci USA*, *109*(33), 1-10.

Ploughman, M., Granter-Button, S., Chernenko, G., Tucker, B.A., Mearow, K.M. & Corbett, D. (2005). Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin-like growth factor I after focal ischemia. *Neuroscience*, *136*(4), 991-1001.

Ploughman, M., Granter-Button, S., Chernenko, G., Attwood, Z., Tucker, B., a, Mearow, K.M. & Corbett, D. (2007). Exercise intensity influences the temporal profile of growth factors involved in neuronal plasticity following focal ischemia. *Brain Res*, *1150*, 207-216.

Ploughman, M., Windle, V., MacLellan, C.L., White, N., Dore, J.J. & Corbett, D. (2009). Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke*, *40*(4), 1490.

Pozo, K. & Goda, Y. (2010). Review Unraveling Mechanisms of Plasticity. *Neuron*, *66*(3), 337-351.

Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J.Y., Lazar, R.M. & Krakauer, J.W. (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehab Neural Re*, *22*(1), 64-71.

Raghavan, P., Santello, M., Gordon, A.M. & Krakauer, J.W. (2010). Compensatory motor control after stroke: An alternative joint strategy for object-dependent shaping of hand posture. *Journal of Neurophysiol*, *103*(6), 3034-3043.

Rehme, A.K., Eickhoff, S.B., Rottschy, C., Fink, G.R. & Grefkes, C. (2012). Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *Neuroimage*, *59*(3), 2771-2782.

Remple, M.S., Bruneau, R.M., VandenBerg, P.M., Goertzen, C. & Kleim, J.A. (2001). Sensitivity of cortical movement representations to motor experience: Evidence that skill learning but not strength training induces cortical reorganization. *Behav Brain Res*, *123*(2), 133-141.

Rothi, L. & Horner, J. (1983). Restitution and substitution: Two theories of recovery with application to neurobehavioral treatment. *J Clin Neuropsychol*, *5*(1), 73-81.

Sawaki, L., Wu, C.W.H., Kaelin-Lang, A. & Cohen, L.G. (2006). Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. *Stroke*, *37*(1), 246.

Schäbitz, W.-R., Berger, C., Kollmar, R., Seitz, M., Tanay, E., Kiessling, M. & Sommer, C. (2004). Effect of brain-derived neurotrophic factor treatment and forced arm use on functional motor recovery after small cortical ischemia. *Stroke*, *35*(4), 992-997.

Schwerin, S., Dewald, J.P.A., Haztl, M., Jovanovich, S., Nickeas, M. & MacKinnon, C. (2010). Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: Implications for the expression of arm synergies. *Exp Brain Res*, *185*(3), 509-519.

Seitz, R.J., Hoflich, P., Binkofski, F., Tellmann, L., Herzog, H. & Freund, H.J. (1998). Role of the Premotor Cortex in Recovery From Middle Cerebral Artery Infarction. *Arch Neurol*, *55*, 1081-1088.

Seitz, R.J.J., Azari, N.P.P., Knorr, U., Binkofski, F., Herzog, H. & Freund, H.J.J. (1999). The role of diaschisis in stroke recovery. *Stroke*, *30*(9), 1844-1850.

Small, S.L., Hlustik, P., Noll, D.C., Genovese, C. & Solodkin, A. (2002). Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. *Brain*, *125*, 1544-1557.

Stinear, C.M., Barber, P.A., Petoe, M., Anwar, S. & Byblow, W.D. (2012). The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*, *135*(8), 2527-2535.

Sukal, T.M., Ellis, M.D. & Dewald, J.P.A. (2007). Shoulder abduction-induced reductions in reaching work areas following hemiparetic stroke: Neuroscientific implications. *Exp Brain Res*, *183*(2), 215-223.

Sunderland, A. & Tuke, A. (2006). Neuroplasticity, learning and recovery after stroke : A critical evaluation of constraint-induced therapy. *Neuropsychol Rehabil*, *15*(2), 81-96.

Turrigiano, G.G. (2008). The self-tuning neuron: Synaptic scaling of excitatory synapses. *Cell*, *135*(3), 422-435.

Twitchell, T. (1951). The restoration of motor function following hemiplegia in man. *Brain*, *74*, 443-480.

van der Zijden, J.P., Van Eijsden, P., De Graaf, R., a, & Dijkhuizen, R.M. (2008). 1H/13C MR spectroscopic imaging of regionally specific metabolic alterations after experimental stroke. *Brain*, *131*(Pt 8), 2209-2219.

van Kordelaar, J., van Wegen, E.E., Nijland, R.H., Daffertshofer, A. & Kwakkel, G. (2013) Understanding Adaptive Motor Control of the Paretic Upper Limb Early Poststroke: The EXPLICIT-stroke Program. *Neurorehab Neural Re*, 2013 Jul 24. [Epub ahead of print] PubMed PMID: 23884015.

Veerbeek, J.M., Van Wegen, E.E.H., Harmeling-Van der Wel, B.C. & Kwakkel, G. (2011). Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. *Neurorehab Neural Re*, *25*(3), 268-274.

Wagner, J.M., Lang, C.E., Sahrmann, S., a, Edwards, D.F. & Dromerick, A.W. (2007). Sensorimotor impairments and reaching performance in subjects with poststroke hemiparesis during the first few months of recovery. *Phys Ther*, *87*(6), 751-765.

Ward, N. (2007). Future perspectives in functional neuroimaging in stroke recovery. *Eura Medicophys*, *43*(2), 285-294.

Ward, N., Brown, M., Thompson, A. & Frackowiak, R. (2003a). Neural correlates of motor recovery after stroke: A longitudinal fMRI study. *Brain*, *126*(11), 2476-2496.

Ward, N., Brown, M., Thompson, A. & Frackowiak, R. (2003b). Neural correlates of outcome after stroke: A cross-sectional fMRI study. *Brain*, *126*(6), 1430-1448.

Wardlaw, J.M., Sandercock, P.A.G. & Murray, V. (2009). Should more patients with acute ischaemic stroke receive thrombolytic treatment? *BMJ*, *339*, 1251-1254.

Whishaw, I.Q. (2000). Loss of the innate cortical engram for action patterns used in skilled reaching and the development of behavioral compensation following motor cortex lesions in the rat. *Neuropharmacology*, *39*, 788-805.

Whishaw, I.Q., Alaverdashvili, M. & Kolb, B. (2008). The problem of relating plasticity and skilled reaching after motor cortex stroke in the rat. *Behav Brain Res*, *192*, 124-136.

Winship, I.R. & Murphy, T.H. (2009). Remapping the somatosensory cortex after stroke: Insight from imaging the synapse to network. *Neuroscientist*, *15*, 507-524.

Witte, O.W., Bidmon, H.J., Schiene, K., Redecker, C. & Hagemann, G. (2000). Functional differentiation of multiple perilesional zones after focal cerebral ischemia. *J Cerebr Blood F Met*, *20*, 1149-1165.

Wittenberg, G.F., Chen, R., Ishii, K., Bushara, K.O., Taub, E., Gerber, L.H. & Cohen, L.G. (2003). Constraint-Induced Therapy in Stroke: Magnetic-Stimulation Motor Maps and Cerebral Activation. *Neurorehab Neural Re*, *17*(1), 48-57.

Wolf, S.L., Butler, A.J., Alberts, J.L. & Kim, M.W. (2005). Contemporary linkages between EMG, kinetics and stroke rehabilitation. *J Electromyogr Kines*, *15*(3), 229-239.

Wolf, Steven, L., Winstein, C.J., Miller, J.P. & Morris, D. (2006). Effect of Constraint-Induced Movement Therapy on upper extremity function 3 to 9 Months After Stroke. *J Am Med Assoc*, *296*(17), 2095-2104.

Zhang, S., Boyd, J., Delaney, K. & Murphy, T.H. (2005). Rapid reversible changes in dendritic spine structure *in vivo* gated by the degree of ischemia. *Neuroscience*, *25*(22), 5333-5338.

Zhao, B.-Q., Tejima, E. & Lo, E.H. (2007). Neurovascular proteases in brain injury, hemorrhage and remodeling after stroke. *Stroke*, *38*, 748-752.

Zhao, B.-Q., Wang, S., Kim, H.-Y., Storrie, H., Rosen, B.R., Mooney, D.J. & Lo, E.H. (2006). Role of matrix metalloproteinases in delayed cortical responses after stroke. *Nat Med*, *12*(4), 441-445.