Explaining Plasticity after Stroke?

Floor Elske Buma

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Printed by: Ridderprint BV | www.ridderprint.nl

The studies described in this thesis were carried out at the department of Neurology and Neurosurgery of the UMC Utrecht, and the Centre of Excellence at the Rehabilitation center the Hoogstraat. These studies were part of the EXPLICIT-stroke research project which was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw; Grant No. 89000001; URLhttp://www.zonmw.nl/nl/). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Explaining Plasticity after stroke?

Het verklaren van plasticiteit na een beroerte
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Universiteit Utrecht
op gezag van rector magnificus,
prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen
op donderdag 3 mei 2018 des middags te 4.15 uur

door

Floor Elske Buma

geboren op 28 december 1982 te Duiven

Promotoren:
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General Introduction

Stroke is one of the leading causes of disability in adults around the world. Stroke treatment generally is twofold: 1) in the acute stages by preventing damage by reperfusion the ischemic area 2) in the subacute stage by therapeutic interventions aimed at regaining function and reducing impairment. The latter has not proven to be very effective above the rate of spontaneous recovery that signifies recovery of upper limb function after stroke in the first weeks after stroke (Kwakkel, 2004). Understanding mechanisms of recovery may result in new treatment strategies to improve motor outcome after stroke.

The studies described in this thesis are part of the EXPLICIT-stroke trial (Kwakkel et al., 2008). Aims for this trial were postulated as follows:

- Investigate the effects of early interventions for the upper paretic limb post stroke
- Exploring dynamics in cerebral plasticity during upper limb recovery after stroke
- Improving early prediction of outcome of the upper paretic limb after stroke
- Exploring what patients exactly learn when showing functional recovery in the upper paretic limb after stroke

For this thesis the overall aim was to investigate changes in brain function related to motor impairment as well as quality of motor function as measured with kinematics. The rationale behind this thesis is explained in the review papers in de first two chapters.

In the first chapter we systematically review the current state of longitudinal imaging in stroke until 2008 and assess all studies according to their methodology. In the second chapter we review literature on stroke recovery and plasticity from preclinical studies in rats to RCTs in humans. The focus lied specifically on the defining what upper limb recovery entails as well as exploring what is meant in literature when neural plasticity is referred to. A phenomenological model incorporating known factors involved in recovery after stroke is proposed. In the 3 experimental papers that follow upper-limb function and brain activity patterns are investigated.

The following research questions are underlying this thesis:

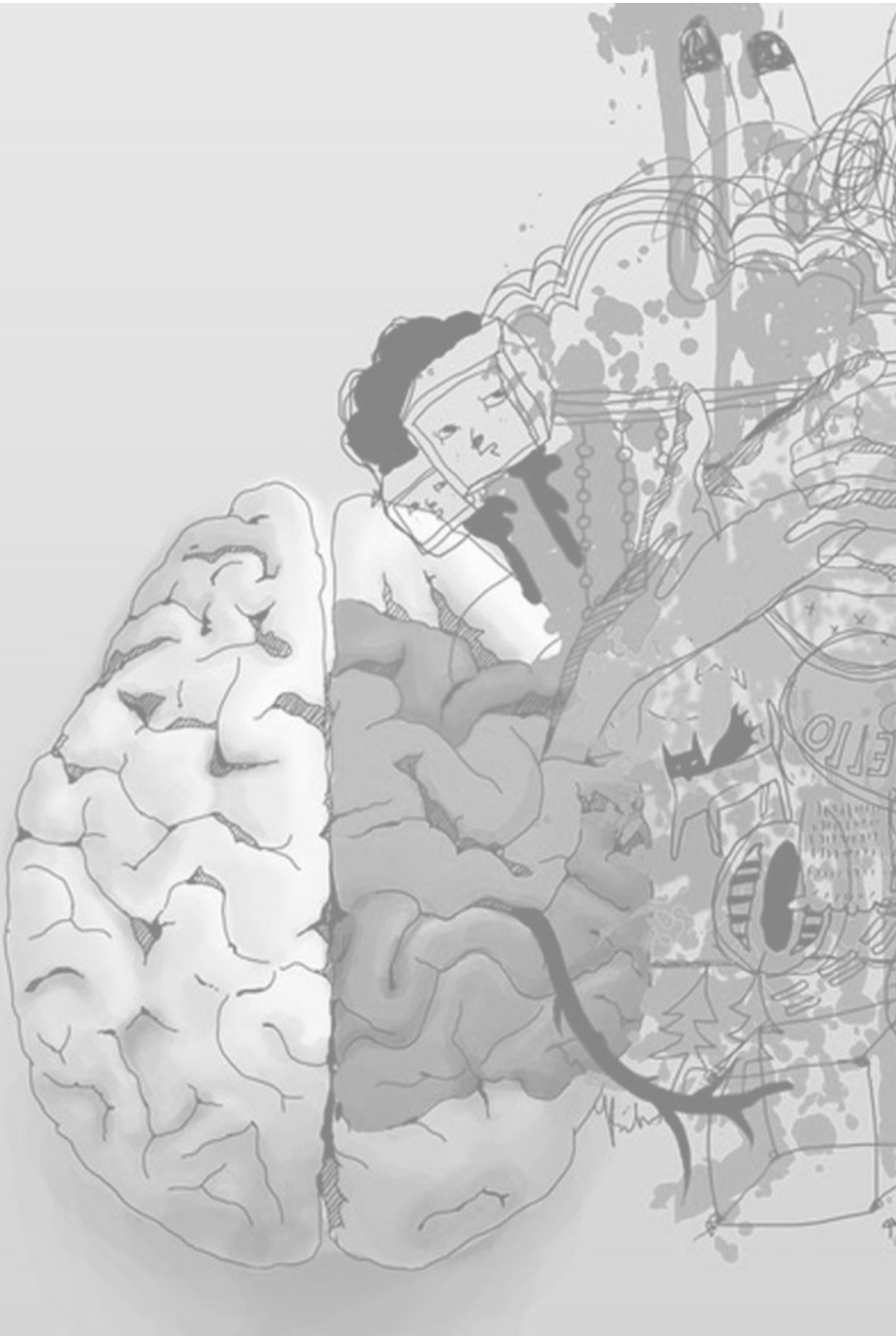
- Chapter 1: What is the current state of knowledge on the mechanisms underlying recovery in stroke?

- Chapter 2: What is the current state of knowledge on longitudinal imaging studies investigating recovery in stroke?

- Chapter 3: A cross-sectional study in well recovered patients compared to healthy controls
    - Is normal performance of a motor task in recovered stroke patients accompanied by an altered brain activation pattern compared to controls?

- Chapter 4: A longitudinal study in the first six months after stroke
    - How are changes in quality of movement related to changes in brain activation patterns in the first six months after stroke?

- Chapter 5: A longitudinal study, in the same population as chapter 5
    - How is recovery after stroke related to changes in functional connectivity?



Chapter 1

Understanding upper limb recovery after stroke.

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Abstract

This review addresses what is currently known about the time course of motor and functional recovery 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 functional 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 recovery, 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.

Key words: Neuroplasticity, Recovery, Stroke, Rehabilitation, Paresis, Hebbian learning

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 post 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 post 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, Wegen, & Wel, 2010; Stinear, Barber, Petoe, Anwar, & Byblow, 2012), and lower limb (Veerbeek, Van Wegen, Harmeling-Van der Wel, & Kwakkel, 2011) as well as basic activities of daily living (ADLs)in general (Kwakkel, Kollen, & Twisk, 2006; Prabhakaran et al., 2008). Almost all patients show a certain degree of spontaneous neurological recovery, following a natural logarithmic pattern (Langhorne, Bernhardt, & Kwakkel, 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. These mechanisms are the subject of the present Point of View article. We first introduce the theoretical phenomenological model shown in Figure 1 (Panel A), 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 (Figure 1, Panels B and C). 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.

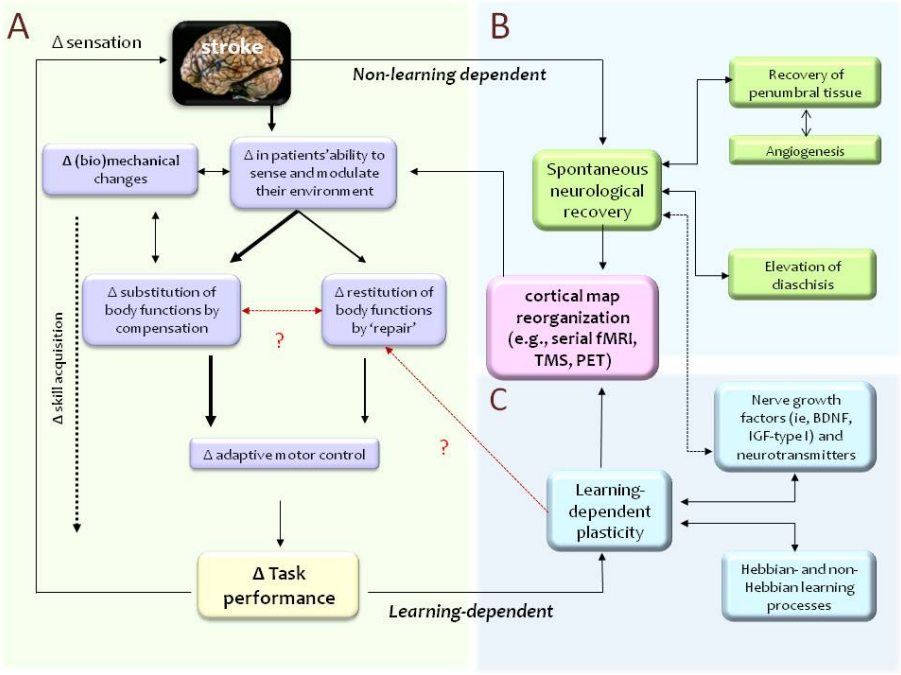

Figure1: . Proposed phenomenological model Panel A) shows the processes underlying skill reacquisition after stroke and emphasizes the fact that most evidence for skill improvement is due to compensatory mechanisms, partly driven by biomechanical changes and the interaction with spontaneous and learning-dependent reorganization. Panels B and C show the mechanisms underlying cortical map reorganization. Panel B shows the events of spontaneous recovery after stroke, while panel C shows the experience-dependent processes.
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. The 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 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).

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 of activities after stroke, such as dexterity (Cirstea & Levin, 2000) is mainly driven by learning compensation strategies rather than by neural repair (Kwakkel, Kollen, & Lindeman, 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, Kleim, & Wolf, 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 of activities such as dexterity and gait post 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).

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, Carmichael, Corbett, & Wittenberg, 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). Functional recovery through motor compensation at an activity level 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, recovery at 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; Stella Maris Michaelsen, Dannenbaum, & Levin, 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. 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). A number of studies in animals have suggested that substitution of the affected limb by the unaffected limb is a maladaptive compensatory strategy which impairs functional recovery of the paretic limb (Jones, 1994; Taub, Uswatte, Mark, & Morris, 2006). Unfortunately animal studies have usually not focused on whether recovery 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, Alaverdashvili, & Kolb, 2008; Whishaw, 2000). Moon and colleagues found that rats showed compensatory movement strategies during recovery after photothrombotic stroke (Moon, Alaverdashvili, Cross, & Whishaw, 2009). The occurrence of compensatory movement strategies in animal models after stroke suggests that this should not be overlooked when investigating the quality of motor performance in tasks such as reaching for food pellets (Metz, Antonow-Schlorke, & Witte, 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, Cheng, & Jones, 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 Peg-test (Chen, Chen, Hsueh, Huang, & Hsieh, 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, Santello, Gordon, & Krakauer, 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 by the affected arm itself is caused by true neurological repair or by learning compensation strategies.

Defining Neuroplasticity

There are several definitions of neuroplasticity in the literature. Murphy and 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 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 behavioral recovery after stroke. The precise way in which changes at a neuronal level influence neurological as well as functional recovery is still under investigation.

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., 2011, 2009). 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) (Steven L Wolf, Winstein, Miller, & Morris, 2006). Another way to assess improvement of body functions is by using kinematic analysis to establish whether therapeutic interventions have an effect at the impairment level. Recovery patterns 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 recovery 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, Van Peppen, et al., 2004). Such a design is, however, necessary to understand exactly what and how stroke patients learn during stroke recovery supported by rehabilitation interventions) (Kwakkel, Kollen, et al., 2004; Kwakkel et al., 2006; Kwakkel & Wagenaar, 1996; Sunderland & Tuke, 2006; S.L. Wolf, Butler, Alberts, & Kim, 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 post 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, Kollen, 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, Kollen, 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 &

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, Bidmon, Schiene, Redecker, & Hagemann, 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, Kollen, 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. This time window corresponds to enhanced gene-expression profiles in the post-ischemic brain in animals (Ge, Yang, Hsu, Ming, & Song, 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 post 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 post stroke do suggest that the final outcome of upper limb function at 6 months in terms of motor

synergies is mainly defined within the first 4 weeks post 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 post stroke, than when the upper limb training was delayed beyond 28 days (Jeff Biernaskie, Chernenko, & Corbett, 2004). In the latter case, training turned out to be ineffective in resolving the forelimb impairment as well as in promoting dendritic outgrowth (J 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 post stroke, either by targeting motor function at the impairment level as a reflection of neural repair and/or by directly targeting neurological repair itself.

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, Holubar, Acosta, Beer, & Dewald, 2005; Lang, Wagner, Edwards, Sahrmann, & Dromerick, 2006; Stella M Michaelsen, Jacobs, & Levin, 2004; Sukal, Ellis, & Dewald, 2007), also known as synergistic movement, is often seen during upper limb recovery. 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 (M. L. Latash, Scholz, & Schöner, 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 (M L Latash & Anson, 1996). Therefore, serial kinematic measurements in which the quality of motor performance is measured systematically in the first

months post stroke are vital in explaining the dynamics of neural recovery. Nevertheless, animal studies have usually not investigated whether recovery of activities (such as reaching for a food pellet) is due to compensatory mechanisms as opposed to restitution of function, since studies that measure kinematics in animals are scarce. A few studies using video analysis have shown that functional recovery in rats consists mostly of compensatory movements (Moon et al., 2009; Whishaw, 2000).

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 (M. L. 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 (M M Mirbagheri, Tsao, & Rymer, 2009; M.M. Mirbagheri, Tsao, Settle, Lilaonitkul, & Rymer, 2008). 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, Rymer, Harvey, & Mirbagheri, 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 (M M Mirbagheri et al., 2009; M.M. Mirbagheri et al., 2008). 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, Lindeman, Ramsey, & Kwakkel, 2010).

Understanding non-learning- and learning-dependent mechanisms of recovery

A number of mechanisms in the brain have been proposed to underlie sensorimotor recovery after stroke, as shown in Figure 1, panels B and C. 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, Simon, & Stenzel-poore, 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 (J Biernaskie & Corbett, 2001) or even months (R. J. J. 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 (J Biernaskie & Corbett, 2001). First, however, we need to define what is meant by neuroplasticity after stroke and what its relationship with recovery is (either restitution or compensation).

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.

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, Boyd, Delaney, & Murphy, 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, van Eijsden, de Graaf, & Dijkhuizen, 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.

Spontaneous neuroplasticity

After injury the area 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 (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 & Corbett, 2009; Overman et al., 2012). Homeostatic plasticity mechanisms might cause an initial

overproliferation of new connections 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).

Alleviation of diaschisis

Spontaneous recovery after stroke is not restricted to the first hours post 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 post 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; R. J. J. 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; R. J. J. 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 stroke recovery (Chu et al., 2002; R. J. J. 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).

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, Arboix, & Krupinski, 2010). Recent research demonstrated that angiogenesis and neurogenesis are coupled restorative mechanisms that contribute to functional recovery (Chopp, Zhang, & Jiang, 2007).

For example, metalloproteinase (MMP) released in the penumbral area after stroke causes breakdown of the blood–brain barrier (BBB) and is therefore associated with edema and neuronal loss. However, MMP has also been suggested to be involved in revascularization in the later stages after stroke (Zhao et al., 2006; Zhao, Tejima, & Lo, 2007). Thus, downregulation of MMP 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 (Michelle Ploughman et al., 2009).

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, Wu, Kaelin-Lang, & Cohen, 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 post stroke (J Biernaskie & Corbett, 2001; Michelle Ploughman et al., 2009). For example, moderate treadmill training in rats was found to increase levels of proteins such as BDNF, neurophisin-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 (M 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 (Michelle 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 functional recovery and to produce elevated levels of BDNF (MacLellan et al., 2011). There seems to be a critical time window when administering rehabilative therapy in animals after stroke. An important study showed that delaying rehabilative treatment in a rodent stroke model for 30 days after stroke, led to poor recovery of upper limb function as well a no change in dendritic outgrowth. Rehabilitation therapy administered in the first few weeks after stroke, however, enhanced recovery of function on a reaching task as well as increasing dendritic outgrowth (Jeff Biernaskie et al., 2004).

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, Isaacs, Anderson, Alcantara, & Greenough, 1990; Ding et al., 2004; Kleim, Cooper, & Vandenberg, 2002). In interaction with some of the above mentioned forms of cortical reorganization around the infarct rim, treadmill running therapy does indeed up-regulate 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.

***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 is plastic and changes in activity patterns have often been seen (Askim, Indredavik, & Vangberg, 2008; Calautti & Baron, 2003; Johansen-berg et al., 2002; Nelles, Jentzen, Jueptner, Müller, & Diener, 2001; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012; Ward, Brown, Thompson, & Frackowiak, 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 recovery compared to control subjects. These over-activations were predominantly seen in the bilateral premotor cortex (PM), supplementary motor area, as well as parietal regions (R. J. Seitz et al., 1998; Ward, Brown, Thompson, & Frackowiak, 2003b). Good recovery of motor performance 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, Hlustik, Noll, Genovese, & Solodkin, 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 motor recovery 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 poor motor recovery (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, Stinear, Barber, & Byblow, 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, Bauder, Miltner, Taub, & Weiller, 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 recovery 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 recovery 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).

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 post stroke (Figure 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 substitution of functions.

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 post 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 functional recovery 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, Van de Port, Lindeman, Twisk, & Kwakkel, 2005; Kwakkel et al., 2008; Wagner, Lang, Sahrmann, Edwards, & Dromerick, 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 3 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 and haptic robotics post 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 substitution (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 (M L Latash & Anson, 1996; M. L. 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, Sheshadri, Dawson, & Beer, 2001; M M 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 functional recovery resulting from neurological repair and from compensation strategies (Figure 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 post 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).

Limitations
The focus in the review has been on bridging the gap between preclinical and clinical research on recovery 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, Erickson, & Kramer, 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, Bruneau, VandenBerg, Goertzen, & Kleim, 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(Jeff Biernaskie et al., 2004) to a specific period in humans is difficult and deserves further investigation. 4) In animal studies the recovery that is aimed for is relearning a well-practiced task just before stroke, and is not focused on reduction of impairments in general.

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 post 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 recovery by restitution of body functions as a reflection of neural repair, and recovery 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 (M. L. 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, Dobkin, Cen, Wu, & Winstein, 2006).

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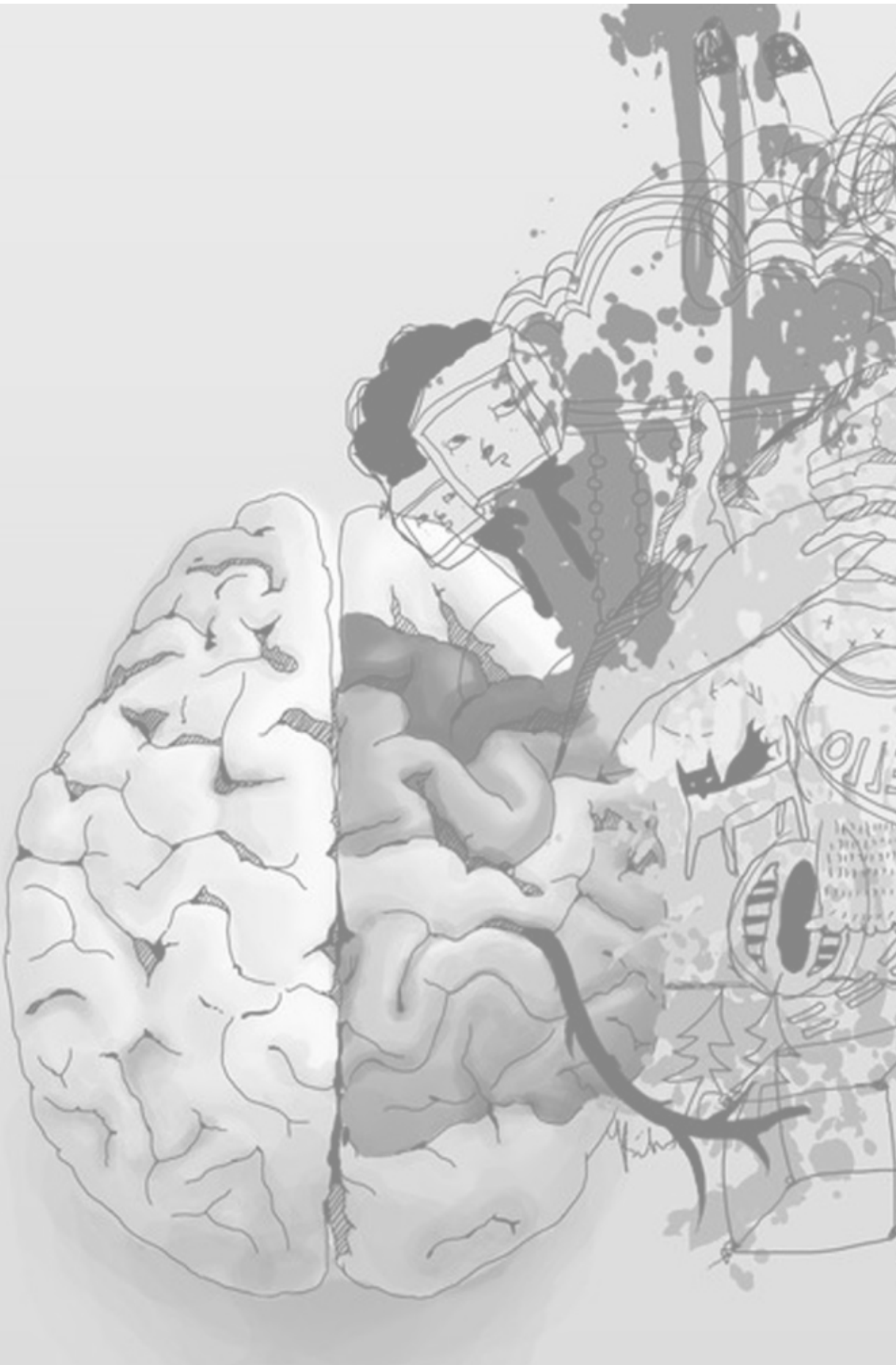

Chapter 2

Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review of the literature.

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Abstract

Background: Understanding mechanisms of recovery may result in new treatment strategies to improve motor outcome after stroke. Imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission topography (PET) allow changes in brain activity after stroke recovery to be identified.

Objective: To systematically review serial imaging studies on recovery within 6 months post stroke, assess their methodological quality and identify trends in association between task-related brain activation patterns and functional upper limb recovery. Methods: A literature search was performed using Medline, PICARTA and EMBASE. Studies were appraised using binary weighted methodological criteria for internal, statistical and external validity. Results: Twenty-two of 859 identified studies met our inclusion criteria. Studies showed methodological weaknesses with respect to controlling for task performance, selecting appropriate outcome measures, and adequate presentation and execution of statistical analysis. After stroke, motor task performance shows: unilateral overactivation of motor and non-motor areas, a posterior shift in activity in the primary motor cortex, and bilateral recruitment of associated motor and non-motor areas. Concomitant with neurological recovery, over-activation appears to diminish longitudinally, but not in all patients.

Conclusion: Despite methodological shortcomings and heterogeneity, trends can be discerned. However, statistically sound associations with recovery are not consistent. The challenges in future research will be controlling for confounding factors, find outcomes that specifically measure dexterity of the paretic limb, to control for the extent of white matter damage and changes in perfusion in order to establish the longitudinal construct validity of fMRI and PET with regard to upper limb recovery after stroke.

Introduction

Stroke has been described as the second cause of mortality, as well as a major cause of disability, in Western society (1). Upper limb paresis is found in more than 80% of all stroke patients, although 30% to 40% regain some dexterity after 6 months (2). A number of longitudinal studies have shown that the non-linear pattern of recovery of the upper paretic limb is highly predictable at an early stage after stroke onset (3;4). For example, early return of voluntary wrist and finger extension is a prerequisite for regaining dexterity after stroke, as was shown by a number of longitudinal studies (5-7). Promising results have been found for high-intensity, task-oriented intervention programs aimed at improving voluntary control of wrist and finger extension, such as constraint induced movement therapy (CIMT) (8). However, the interaction of such therapies with underlying learning-dependent and non-learning-dependent mechanisms of stroke recovery is poorly understood. For example, a recent longitudinal study with repeated measurements has shown that progress over time as a reflection of 'spontaneous neurological recovery' is found to be an independent covariate that significantly explains improvement in dexterity in the first 10 weeks post stroke (9;10).

A number of mechanisms are assumed to be involved in the non-linear recovery pattern of the upper paretic limb, such as salvation of the penumbral surrounding cerebral tissue and alleviation of diaschisis due to cerebral shock in areas anatomically related to the infarcted area (11;12). These mechanisms are accompanied by cortical reorganization, as revealed by functional magnetic resonance imaging (fMRI), positron emission topography PET, magneto-encephalography (MEG) and transcranial magnetic stimulation (TMS) (13-16). The main challenge for the future is to improve our understanding of the relation between the dynamics of observed activation patterns as revealed by fMRI and PET and the observed recovery in upper limb function after stroke. Moreover, time-dependent changes in motor activation patterns after stroke can be explained by changes in stroke-related brain circuitry as a reflection of 'take-over' or 'vicariation of functioning' (17), or may reflect changes in the adaptive motor control used to perform the requested motor paradigm in order to deal with existing sensorimotor deficits (18). In other words, understanding the meaning of these dynamics in cortical activation patterns during upper limb recovery requires knowledge about changes in motor control observed while the patient is executing a standardized well-controlled

motor paradigm. In this respect, the increased ipsilateral activation shown with fMRI or PET may reflect increased support in executing the requested motor paradigm, or it may reflect increased ipsilateral activity through mirror movements of the non-affected limb(19). Understanding the meaning of changes in fMRI and PET for the recovery of the upper paretic limb requires repeated measurements with brain imaging techniques as well as simultaneous measurement of motor performance. Such studies should also simultaneously control for quality of motor performance by distinguishing restitution of upper limb and/or hand function and the use of adaptive compensation strategies(18).

In the past two decades, various strategies have been used to uncover the nature of changes in post-stroke neural activity. Some imaging studies on this subject have compared fully recovered patients at an arbitrarily chosen time-point with healthy, age-matched controls to see how changes in the lesioned brain might account for their recovery (20), and have confirmed that most stroke patients do indeed show different patterns in task-related brain activity. Unfortunately, this approach does not clarify the possible non-linear, time-dependent dynamics during the process of recovery and does not account for learned adaptive compensation strategies to accomplish the requested motor paradigm. The present systematic review focused on studies that longitudinally investigated stroke patients still in the process of recovery during the first 6 months post stroke, to asses time-dependent changes in the brain measured with PET or fMRI. For this purpose, studies were assessed for their (1) appropriateness in terms of the control of requested motor paradigms (e.g. strength, range of motion, mirror movements) (21) and (2) methodological quality (i.e. internal and statistical validity). On the basis of these findings, we have identified possible trends in the literature and offer suggestions to improve future longitudinal fMRI and PET studies.

Materials and methods

Selection criteria

Serial fMRI or PET imaging studies (consisting of at least 2 measurements) of subjects with a clinical diagnosis of first-ever ischemic stroke were included, with first measurements within 6 months after stroke onset. These studies had to have used an active and/or passive motor paradigm of the paretic arm during imaging and measure recovery of the paretic limb

after stroke. We limited the review to articles written in English, Dutch, French, Spanish or German.

Search strategy

A literature search in the bibliographic databases MEDLINE (1949 to January 2009), PICARTA (1980 to January 2009) and EMBASE (1947 to January 2009) was undertaken by the first author and an independent researcher (HK). Combinations of the following search terms were used: cerebrovascular disorders OR cerebrovascular accident OR stroke, AND magnetic resonance imaging OR Positron-Emission Tomography, AND stroke recovery, stroke outcome, clinical outcome, functional outcome OR prognosis AND upper extremity OR arm OR hand. We collected articles featuring combinations of the following MeSH terms (Medical Subject Headings; the U.S. National Library of Medicine's controlled vocabulary thesaurus): (1) Stroke/epidemiology OR Stroke/mortality OR Stroke/pathology OR Stroke/radionuclide imaging OR Stroke/rehabilitation OR Stroke/complications; (2) Diagnostic Imaging/Magnetic Resonance Imaging; (3) Diagnostic Imaging /Positron-Emission Tomography; (4) Paresis; (5) Hand. The six categories were combined, and the MeSH terms were truncated to increase the sensitivity of the electronic search. References of selected articles were also examined. Requests for a detailed description of the search can be submitted to the second author. One author (FB) read the titles and abstracts (when available) of identified references and dismissed obviously irrelevant studies. Potentially relevant studies were then assessed independently by two researchers (FB, HK) using the aforementioned criteria.

Assessment of methodological quality

Two authors (FB, GK) evaluated the selected studies in terms of internal, statistical and external validity, using an adapted version of the methodological criteria of internal, statistical and external validity, which was adapted from Clinical Epidemiological Rounds (22) and has been used previously (23;24) (Table 1). Studies were critically appraised using the following binary weighted methodological criteria.

Table 1. Binary quality assessment of reviewed studies

Evaluation of:		Criterion
Internal Validity		
1. Measurements of the dependent variable reliable and valid?	Positive if the longitudinal study tests the reliability and validity of measurements used or referred to other studies that established reliability and validity	A
2. Measurements on hand function	Positive if primary outcome measure indeed measures dexterity of the affected upper limb	B
3. MRI/PET measurements clearly presented and consistent	Positive if calculation of coordinates, voxel count, voxel intensity, LI, and so on is clearly presented	C
4. Inception cohort during period of observation?	Positive if MRI/PET scan was obtained from sroke onset (ie, <2 weeks poststroke)	D
5. Appropriate number of observations?	Positive if number of imaging sessions is at least 3	E
6. Appropriate endpoints of measurements?	Positive if final measurement was obtained at least 6 months post stroke	F
7. Description of additional medical and paramedical interventions	Positive if information on medical or paramedical treatment is reported	G
8. Controlled for mirror movements?	Positive if mirror movements were assessed with EMG or kinematically *during* fMRI/PET sessions	H
9. Control of motor task performance?	Positive if performance on motor task was specified to the type of requested motor task as well as controlled for frequency, ROM, and force	I
Statistical Validity		
10. Corrected for multiple comparisons?	Positive if P values are controlled for multiple testing, for example, by applying a Bonferroni correction	J
11. Statistics on group differences valid?	Positive if applied statistics within and between subject analyses are appropriate	K
External Validity		
12. Specification of relevant patient characteristics	Positive if age, type, location, and number of strokes are specified.	L

Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; EMG, electromyography; LI, lateralization index; fMRI, functional
MRI; ROM, range of motion.

Internal Validity

A. Outcome measures had to assess dexterity of the paretic limb, rather than mere strength or spasticity of the paretic limb (25;26). Applying clinically used ADL scales that allow for compensation strategies, are not appropriate (27;28).

B. All outcome measures of recovery used by these studies had to be validated and reliable. Studies had to either test the reliability and validity of measurements used or refer to other studies that established reliability and validity (29).

C. A requirement regarding data analysis was a clear presentation of the MRI/PET system, fMRI/PET acquisition, pre-processing, statistical modelling, group modelling, reporting MNI or Talairach coordinates of activity and statistical inference (30).

D. The first imaging session preferably had to have taken place within 1-8 weeks after stroke (3).

E. Recovery after stroke is largely determined in the first 6 months after stroke. Measures of recovery remain relatively stable after this 6-months period, therefore the timing first measurements had to take place within this 6-month critical period (Figure 1) (3;31).

F. The variability in recovery rate between patients and the non-linear nature of recovery implies a minimum of 3 sessions to follow the dynamics of recovery in the post-stroke brain (3).

G. Studies using fMRI rely on a relationship between blood oxygen level-dependent (BOLD) signal and neural activity, which can be distorted by use of medication (32), and this had to be at least mentioned in the article. In the same way therapeutic interventions can confound the interpretation of results of fMRI or PET measurements (33), and therefore must be reported.

H. One of the main potential confounders in these studies are abnormal synergies in patients (34). Movements of various parts of the body not involved in the task (the contralateral non-paretic hand and ipsilateral, anatomically more proximally oriented muscles of elbow, shoulder and/or trunk) introduce a serious bias to reports of contralesional activity in fMRI and PET studies investigating stroke (31;35;36). Studies had to assess the occurrence of mirror movements by means of electromyography (EMG) during scanning.

I. Quality of motor performance should be specified to the type of requested motor task. In addition range of motion or amplitude of movement of the motor paradigm had to be controlled for, since with increasing amplitude of movement additional brain areas become activated

(37). A variable rate of movement causes variability in brain activation as revealed by PET (38) as well as fMRI (39). In addition, the force exerted (EMG) during a motor task correlates positively with fMRI and PET activations (40;41). Task difficulty and functional improvement also influence the activation of the motor system (42).

Statistical Validity

J. To reliably determine significant activation, a correction for multiple comparisons had to have been applied to p-values for activated brain areas (43).

K. Correct use of statistical instruments in accordance with the number of subjects had to have been applied (23).

External validity

L. Patient characteristics such as age had to be clearly presented, since they influence fMRI outcome(44). Furthermore, changes in activation in the post-stroke brain are affected by the location of the infarction with respect to the corticospinal tract, so information on location and type of stroke had to be specified(4;45;46).

Results

The searches resulted in 541 references retrieved from three searches in PubMed, 170 references in EMBASE and 158 in PICARTA (Flowchart, Appendix 1). After dismissing doubles, off-topic and non-longitudinal studies, 37 articles remained. After further inspection, 17 articles were excluded because they concerned chronic stroke patients and/or had not used fMRI/PET imaging, and another 2 articles were excluded based on language (Chinese), leaving 18 articles. These were supplemented with four studies found through reference search. The characteristics of these 22 studies are described in Appendix 1. We differentiated between MRI and PET studies (15 and 7, respectively). The results of the analyses of internal, statistical and external validity are summarized in Table 2. An overview of study results for PET and fMRI can be found in Table 3. A non-significant trend was found in the relationship between total score on the criteria and year of publication (Spearman's rho r= 0.41, p = 0,07).

Internal Validity

Studies used a variety of outcome measures, ranging from measures not specifically targeting recovery of the affected limb but rather at the activity level of the World Health Organization International Classification of Functioning (ICF): Barthel Index (BI) (13;16) and the Rankin score (16). On

the level of functioning, measures of gross motor function and muscle strength were used: the European Stroke Scale (ESS) (13), the National Institute of Health Stroke Scale (NIHSS) (47;48), the Orpington prognostic stroke scale (16), the Fugl-Meyer test (FM) (47;48), the Medical Research Council hand score (MRC) (49-52), the Motricity index (MI) (16;53;54), hand and pinch dynamometer scores (55), thumb to index tapping (31;47;52;56-58), tip pinch and palmar pinch (PI) (14;16;31;54-58), grip test (16;54;57-59) and finger tapping (FT) rate (47;52;57;58). Another type of measurements used to assess functioning of the affected limb are measures of dexterity: the Frenchay arm test (FAT) (14), the Box Block test (BBT) (14), the Action Research Arm test (ARAT) (54;60;61), the Perdue Pegboard test (PP) (51), the 9-Hole Peg-Test (9HPT) (14;16;54;55;58;59). Of the 22 longitudinal studies, 10 fMRI studies used measurements on at least 3 time points (14;16;21;47;49;54;55;57;58). Only one study reported the use of medication (16), 19 studies did not report any medical or paramedical intervention. Ten of the 22 studies did not control for mirror movement or synergies. In those studies where there was a form of control it usually consisted of visual observation of motor performance during the task (14;50-52;57;61;62). Some used the visual scale proposed by Woods and Teuber (1978) (43), a 5-level visual motor score which to our knowledge has never been validated. Others measured EMG during a practice session outside the scanner to control for the occurrence of mirror movements (16;53). EMG during scanning was used in one study (55).

The studies used either passive (48;53;54) or active (13;14;16;21;47;49-52;55;56;60-62) motor paradigms or both (52;57). These paradigms consisted of active (14;21;50;55;57;58;61) and passive (53;54;57) flexion extension, finger tapping (13;21;47;51;52;55;56;60;62), grasping (16;49) Most studies controlled for timing during the execution of the motor task, either directly with a metronome (13;16;50;51;53-56;58;62) or in hindsight by assessing movement rate visually (14;59-61) or mechanically (47;48). There was no control of or correction for range of movement during the task, except in the study by Ward et al. (2003) (16) who let their subjects perform the task at 20% of maximum voluntary contraction measured at each session and 40% max rate at each session, keeping relative force and rate constant throughout recovery.

External validity

Twelve studies involved patients with a subcortical lesion (13;16;48;50;52-59;62). Three studies included cortical infarcts (47;49;51) while other studies did not differentiate (21;60;61). Feydy et al. (14) divided their subjects into subgroups based on lesion location in their further analysis.

Longitudinal changes in location of brain activity within subjects

Subcortical stroke

Calautti et al. 2001 (13) found bilateral overactivation in the SMA, and a posterior shift in activity in the inferior parietal cortex (PC) and insula at the first session, while finding primary sensory motor cortex (SM1) activity in the lesioned hemisphere at the second session, using an active task. In the contralesional hemisphere, overactivations were seen in the SM1, inferior PC and SMA. At the second session, they only found premotor cortex (PMC) over activity. In their 2003 study, (62) peak activations in SM1 showed a significant posterior shift, while no difference between patients and controls was found in terms of SM1 peak activation at the second session. Small et al. (2002) (55) found that the difference between poor and good recovery groups was explained by ipsilesional SM1 and contralesional cerebellar activation, where the good recovery group showed more activation in the contralesional cerebellum. Jang et al. (2003) (50) found bilateral SM1 activation disappearing in 4 out of 8 patients at 14 months. Askim et al. (2008) (59) found more ipsilesional SM1 activation at 3 months after stroke as well as more contralesional cerebellar and bilateral thalamic activity.

Nelles et al. (1999) (48) used passive movements and found activity in the ipsilesional inferior PC and SM1 at their first measurement, and in the ipsilesional SM1 and inferior PC at their second measurement. In the contralesional hemisphere, they found activity in the inferior parietal cortex at the first measurement and in the inferior parietal cortex, pre-motor area and CG at the second measurement. Marshall et al. (2000) (52) found bilateral activity in PFC, and posterior PC region activation at the first measurement were some patients performed passive instead of active tasks, followed by a decrease in bilateral PFC activity at the second measurement, as well as more ipsilesional SM1 activity at the second measurement. Loubinoux et al. (2003) (53) found more bilateral inferior PC activity and SM1 activation in the ipsilesional hemisphere at the time of the second session and less activity in the superior parietal areas and the

			Internal Validity								Statistical Validity		External Validity	
Reference	***N***	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**score max 12**
MRI														
Nelles et al (1999)	6	+	-	+	-	-	-	-	-	+	+	-	+	5
Marshall et al (2000)	8	-	-	+	+	-	-	-	-	-	+	-	+	5
Calautti et al (2001)a[\]	5	+	-	+	-	-	+	-	-	-	+	-	+	5
Calautti et al (2001)b	5	-	-	+	-	-	+	-	-	-	-	+	+	4
Feydy et al (2002)	14	-	+	+	-	+	+	-	-	-	+	-	+	6
Small et al (2002)	12	+	+	+	-	+	+	-	-	-	-	-	+	6
Calautti et al (2003)	5	-	-	+	-	-	+	-	-	-	-	+	+	4
Jang et al (2003)	8	+	-	-	+	-	+	-	-	-	+	-	+	5
Loubinoux et al (2003)	9	+	+	+	+	-	-	-	-	+	+	+	+	8
Ward et al (2003)	8	+	+	+	+	+	+	-	-	+	+	-	+	9
Binkofski et al (2004)	8	+	-	+	+	+	-	-	-	-	+	-	+	6
Jang et al (2004)	6	+	+	+	-	+	+	-	-	-	+	-	+	7
Tombari et al (2004)	8	+	-	+	-	+	+	-	-	-	+	-	+	5
Carey et al (2005)	9	+	+	-	-	-	+	-	-	-	+	-	+	5
Jaillard et al(2005)	4	+	-	+	+	+	+	-	-	+	+	+	+	8
Carey et al (2006)	10	+	+	+	+	-	+	-	+	-	+	+	+	8
Ward et al (2006)	2	+	+	+	+	+	-	+	-	+	+	-	+	9
Loubinoux et al (2007)	8	+	+	-	+	+	+	-	-	-	+	-	+	6
Puh et al (2007)	7	-	-	-	+	+	-	-	-	-	-	-	+	4
Askim et al (2008)	12	+	+	+	+	-	-	-	-	-	-	+	+	6
Total Score Criteria		15	9	12	7	10	13	1	2	4	15	6	20	

dorsal posterior cingulate and ipsilesional superior supramarginal gyrus. Tombari et al. (2004) (57) found an increase in the ipsilesional SM1 activity, opercular to triangular area, insula, secondary sensory cortex (SII) and supramarginal gyrus between the first and second measurements, whereas between the second and third sessions they found a decrease in activity in the bilateral SMA, cerebellum and ipsilesional PMC.

Cortical stroke

Jang et al. (2004) (51) individually analyzed 6 subjects performing an active task and found bilateral SM1 activity in all subjects at the first measurement, which progressed to ipsilesional SM1 activity in 4 out of 6 patients at 6 months. Binkofski et al. (2004) (49) found perilesional SM1 activation, which became less pronounced in the second and third measurements. In the contralesional hemisphere they found SM1, SMA and PMC activity in most patients, which became more pronounced at the second measurement and had disappeared at the third session.

Jaillard et al. (2005) (47) used two tasks: FT and FE. The FT produced ipsilesional SMA activity at the first session, ipsilesional dorsolateral premotor cortex (PMd), primary motor cortex (M1) and PC activity at the second session and ipsilesional PMd and M1 activity at the third. The FT also produced contralesional PMd activity and bilateral S1 and cerebellar activation, decreasing at the second measurement to contralesional cerebellar activity. The FE produced ipsilesional PMd, M1, SMA and S1 activity at the first measurement, ipsilesional M1 and PMd activity at the second session, and ipsilesional M1, PMd and S1 activity at the third session. The FE produced bilateral cerebellar activity at the first and contralesional cerebellar activity at the second session.

Both cortical and subcortical stroke

Using an active task Feydy et al. (2002) (14) distinguished three patterns: (1) initial focusing, (2) progressive focusing and (3) persistent recruitment. In patients with initial focussing activity in ipsilesional SM1 did not change over time and was comparable to that in healthy controls. In patients with progressive focussing, the focus of activation shifted from bilateral SM1 and contralesional SMA, PMC and prefrontal cortex to SM1 activity on the ipsilesional side; 3) bilateral SM1 and contralesional SMA, PMC and PFC activity did not change over time. Carey et al. 2006 (61) found ipsilesional activity in the SM1 and cingulate gyrus (CG) of the good recovery group and stable activity in SM1 and SMA in the poor recovery group. Both groups

showed a posterior shift in the SM1. Contralesional activity was found in the good recoverers at the first session only. Puh et al. (2007) (21) found no clear pattern of activation in their regions of interest (ROI) and did not perform group analysis.

Association with Clinical Recovery

Subcortical stroke

Using an active task Calautti et al. (2001b) (56) found a significant correlation between increased lateralization index (LI) and changes in the maximum number of thumb to index tapping within 15s (r=0.975). In their other 2001 study, (13) however, they found no significant association for SM1 peak coordinate changes and thumb to index tapping or pinch scores from the first to second measurement. Small et al. (2002) (55) constructed a linear prediction model on the basis of exploratory data for the ipsilateral cerebellum. Jang et al. (2003) (50) found no significant correlations between changes in MRC and LI (SM1) and MRC and mirror movements and mirror movements and LI (SM1). Their 2007 study (58) found associations between FT and ipsilesional M1, ipsilesional S1 contralesional cerebellum and ipsilesional PMC at the first measurement. In addition, FT performance at the third session correlated with ipsilesional M1 and insula activity at the first session. Ward et al. (2003)(16) found a decrease in task related brain activity in bilateral M1, PMC, PC, ipsilesional SMA, cerebellum, cingulate sulcus and contralesional PFC significantly correlating with an increase in recovery. In addition, they found early outcome scores significantly correlating with first session task related activation. Askim et al. (2008) (59) found positive associations between UL-MAS scores and activity in the contralesional SII and cerebellum, as well as between 9HPT-speed and activity in the contralesional SM1, SII, bilateral SMA, and cerebellum, between transversal grip strength and activity in the contralesional SII and bilateral thalamus, and between key grip strength and activity in the bilateral M1 and SMA, based on a covariate analysis.

Using a passive task Loubinoux et al. (2003) (53) found significant relationships between MI and ipsilesional SMA, contralesional SII, contralesional PFC, contralesional angular cortex, contralesional caudate nucleus (CN), and dorsal posterior CG to superior PC at the first measurement. At the second measurement, they found relationships between MRC and contralesional cerebellum, ipsilesional M1 and contralesional PFC. In addition significant correlations were seen between M1 activity at the second session and activity in the SMA, ipsilesional SII,

contralesional PFC, superior parietal cortex to dorsal posterior cingulate cortex, contralesional CN and angular gyrus at the first session. In their 2006 (54) study Ward et al. found a positive correlation between size of activity in ipsilesional M1, S1 and recovery scores in the good recovering patient. In addition they showed a positive correlation with size of activity in the contralesional inferior PC in poorer recovering patient.

Cortical stroke

Using an active task Jang et al (2004), (51) they did find significant correlations between MRC scores and LI (SM1) and PP scores and LI (SM1) as well as mirror movements and LI (SM1).

Both cortical and subcortical stroke

Using an active task Feydy et al. (2002) (14) found no significant association between recovery (poor, moderate or good) and activation patterns. Carey et al. (2005) (60) found a significant correlation between ARAT score at first measurement and activity in the contralesional SMA, bilateral CG and contralesional insula as well as ipsilesional SM1 activity. At 6 months a correlation was found with rCBF in the ipsilesional SM1 and CG. Improvement on ARAT score correlated with a decrease in contralesional activity and an increase in the ipsilesional post central gyrus.

Measures of Laterality

Subcortical stroke

Using an active task Calautti et al. (2001b) (56) used the LI measure for whole hemisphere activation and found a non-significant decrease (more contralesional activation) from the first to the second measurement. Jang et al. (2003) (50) found that LI (SM1) increased between the first and second measurements.

Marshal et al. (2000)(52) found a significant increase in LI (SM1) at 3 months.

Cortical stroke

Jang et al. (2004) (51) found that LI (SM1) increased between the first and second measurements. Binkofski et al. (2004) (49) found a rise in SM1 LI between the first and second and between the second and third measurements.

Both cortical and subcortical stroke

Feydy et al. (2002) (14) found that LI scores (whole hemisphere and SM1) followed the recruitment patterns they found in three patients. No group analysis was performed. Askim et al. (2008)(59) found a rise in LI for the SM1 and cerebellum.

Discussion

Twenty-two studies met our inclusion criteria and 19 of them (6 PET and 13 fMRI studies) satisfied our methodological criteria for adequately reporting on imaging technique and analysis (13;14;16;21;47-55;57-61). However, some of them lacked statistical power (21;55;59;60;62) and their internal validity was poor with respect to control of motor performance (13;14;21;49-53;55-57;59-62), mirror movements (13;14;16;21;47-54;56-60;62) and reporting (co-)interventions received by patients (13;14;16;21;47-53;55-62), as well as with respect to selecting clinically meaningful outcome measures that reflect dexterity of the paretic limb (13;21;47-52;56;57;62). Even though the underlying relationship with upper limb recovery remains largely unclear, certain patterns of cortical activation can be identified, suggesting time-dependent reorganization in cerebral networks that accompany functional recovery after stroke.

Trends

In the first weeks post stroke, a profound cerebral reorganization was evident, showing (1) overactivation of primary and association motor areas (47;57-59;61), (2) perilesional overactivation around M1 and premotor areas (13;47;57;58;62), sometimes evident as a posterior shift in activity, (13;61;62) and (3) contralesional activation in M1 as well as in other motor areas (49-52;59).

In patients who showed a favorable recovery, these overactivations are transient and activity tends to return towards its original state in many, but not all stroke patients (13;47;49;57;59;61;62). In poorly recovering patients, however, there seems to be persistent recruitment of contralesional motor areas and areas frequently associated with motor learning in healthy subjects (14;16;54;55;59;61).

Explaining these findings in terms of functional significance is a challenge, and the ideas postulated in different studies are diverse and remain inconclusive. First, the excessive recruitment of the spared connections in the motor network that circumvent the lesion can be seen as a reflection of

neuroplasticity, in which secondary, function-related areas support the reduced cortical output of the primary motor areas affected. Secondly, the role of the posterior shift seen in and around the ipsilesional M1 has previously been explained in the literature as reflecting either 'unmasking' of pre-existent representations or alternatively reflecting recruitment of neurons not usually devoted to this type of function, so-called 'vicariation' of function (13;17;47;62). Thirdly, the functional significance of a more bilateral motor pattern has been extensively discussed in the literature. Some results suggest that the change in lateralization is not linear (14), and depends on recovery and the initial severity of the stroke. However, this observation was not statistically analysed. In addition, some studies obtained LI at different stages after stroke or measured LI only twice (50-52;56;59) obscuring the possible non-linear dynamic nature of time-dependent changes in laterality. The functional significance of activity in the contralesional hemisphere has been the subject of different theories. Interhemispheric GABA-ergic inhibition in the motor control of healthy subjects (63) could be affected in M1 lesioned patients, explaining increased contralesional M1 activation(14). A former theory proposed that uncrossed fibres from the contralesional cortex to the spinal cord substitute signalling trough the lesioned corticospinal tract (CST). However, bilateral activation could also be merely a reflection of the effort experienced by stroke patients in executing a formerly 'simple' motor task. When a task is more effortful either because it is to be learned of relearned in the case of recovering stroke patients, performance requires more executive control than an automated task. The increase in bilateral activation could therefore reflect an increase in executive control while performing a formerly simple automated movement paradigm. (42) The mechanism of action of bilateral cortical activation in potentially supporting recovered motor function remains to be explained in future studies.

The difficulty of explaining the functional significance of the activity patterns found becomes clear from the variation in the outcome of correlation analysis of regions of interest and outcome at a particular time point. Significant associations between recovery scores and activity in these regions, including the cerebellum, (55) have been found in some studies (16;50;51;53;54;56;58;59), although the results are not consistent across all studies (14;62). Activity returning to the original motor areas (56;57) seems to be the most consistent predictor of recovery.

Need for additional measures

Since fMRI and PET measurements cannot distinguish between inhibitory and excitatory activity, transcranial magnetic stimulation (TMS) might help to understand the functional significance of contralesional motor cortex activity by either silencing this activity or determining the origin of functional connections to the affected hand (64-66).

The time-dependent changes in cortical activation are obviously heterogeneous and should be reported depending on the location and extent of the infarction (4;45;46). Nevertheless, few studies have reported on the extent to which the CST was damaged (14;49;50;55). Alternatively, diffusion tensor imaging (DTI) can be used to map the white matter tract and assess white matter degeneration in both hemispheres, which can extend well beyond the original lesion and develop up to at least 14 weeks after stroke (67).

Even though the notion of reorganization of the cortical map in M1 is attractive, the activity could partly reflect a behavioural compensation technique used by patients while recovery is still in progress (18). A shift in the M1 area of activation may reflect shifts in activation of motor unit parts and/or recruitment of more proximal muscles in the affected arm. The issue of 'cause or consequence' may play a role in the altered neuromechanical properties of muscles, and, on the other hand, the altered cortical activity pattern (68). Measures of coordination dynamics should accompany serial imaging research relating to recovery and cortical activation patterns to separate behavioural compensation and co-contraction (18;67).

Changes in blood flow in the infarcted area after a stroke can influence cerebral blood flow (PET) as well as the BOLD fMRI signal (69;70). Arterial Spin Labelling MRI (ASL-MR) is a non-invasive method to quantify changes in cerebral perfusion after stroke and may provide a valuable tool in understanding changes in such vascular pathophysiological factors as salvation of the penumbra and alleviation of diaschisis, and perhaps also revascularization of the infarcted area (71;72). The recently started translational research program ‘EXPLICIT-stroke’ in the Netherlands aims to combine above mentioned measurements such as fMRI, TMS, neuromechanics, kinematics and dexterity within subjects to identify how dynamics in brain activity are longitudinally associated with changes in motor performance after stroke (73).

General methodological concerns

Assessment of upper limb outcome in the studies included in this review used a wide variety of outcome measures, ranging from general

neurological scales or disability scales such as NIHSS (74;75) or Barthel Index (76) to specific tests of dexterity of the paretic limb itself, such as the Action Research Arm Test (ARAT) (77). It should be noted that indexes such as BI do not measure upper limb function specifically, but rather assess how patients cope with daily activities such as eating, grooming and dressing (19). Differences in the underlying constructs of outcome measures may have caused the inconsistencies between studies in terms of associations between activity patterns and recovery.

Equally important, however, is careful consideration of the performance of the motor paradigm used during the fMRI sessions. Movement rate, range of motion and exerted force influence the intensity and range of activation of PET and fMRI images, as shown in healthy subjects (37-41). No consensus has yet been reached regarding the type, modality, cue and difficulty of the task as well as controlling for these factors. The system for motor learning of complex movements may be used to facilitate formerly automated tasks such as finger tapping in patients after stroke (78;79). Studies using a passive performance paradigm (48;53;54;57;61) found similar trends. However, active and passive paradigms are not equivalent. One paradigm considers an input rather than an output of the motor system and so meaningful comparisons cannot be made. Exploring different tasks ranging from simple finger tapping to elaborate paradigms that require more cognitive load, while controlling for speed, accuracy, force and amplitude, might shed some light on the role of over recruitment of motor and non-motor areas after stroke. When using a paradigm that consists of a different number of movements over sessions or subjects, a sparse event related design should be considered, since a blocked design does not account for number of movements within that block. This can lead to a wrongful interpretation of 'overactivations' measured within and between these subjects(80;81). A possible confounding factor in bilateral activation patterns is the occurrence of mirror movements during the performance of a unilateral motor task in stroke patients (36). Care should be given to ensure proper execution of the motor task. Careful preparation of the experimental set up to minimise confounding variables is essential, by ensuring sufficient task practice, proper placement of patients in the scanner to ensure maximum comfort, keeping scanning time down, as well as using a paradigm that is not to difficult. Whether mirror movements cause the bilateral activation pattern or are a consequence of this phenomenon remains to be elucidated.

Suggestions for further research

The challenge in this particular field of research lies in controlling for the many confounding factors. In addition, it is important to explore different motor task modalities during imaging and measure outcome accordingly to understand the functional role of the elaborate recruitment seen in stroke patients. Acknowledging that the recovery of upper limb function after stroke is non-linear, serial measurements of brain activation should be timed in the same critical window of recovery (10;23). Merely imaging the brain is insufficient to increase our understanding of the functional significance of changes observed in cortical activity. One should explore the attentional as well as behavioural and neuromechanical strategies used in the motor performance of the affected arm. In addition, promising techniques currently available in brain imaging research, such as TMS, ASL and DTI, should be combined to investigate changes in CST integrity as well as perfusion in the post-stroke brain, and its influence on the activation patterns seen previously with fMRI and PET.

Limitations

The present review was limited by the fact that we only searched for English, German, Spanish, Dutch and French articles, and only those which used PET and fMRI techniques, acknowledging that there is a broad range of other techniques available to measure functional activity such as SPECT, NIRS, MEG, and EEG. Unfortunately, pooling of studies was impossible due to lack of consensus on movement paradigms and outcome measures. While the criteria we used to assess the quality of included studies were based on existing knowledge about confounding factors in longitudinal imaging research (22-24), and the proposed criteria were derived from accepted criteria in the field of neurophysiology, epidemiology and biostatistics, they remain open to debate. Especially since solving confounding factors such as uncontrolled task parameters should be controlled for in an optimal way depending on the research question at hand. Encouragingly, a non-significant trend was found between, on the one hand, assessed methodological quality of the fMRI study and, on the other hand, year of publication, suggests increasing awareness of investigators of the factors that may confound findings in serial fMRI measurements after stroke.

Acknowledgements

We would like to thank Mr. H. Ket for his support in this critical review. The EXPLICIT-stroke research project is supported by a grant from the

Netherlands Organization for Health Research and Development (ZonMw; grant no. 89000001).

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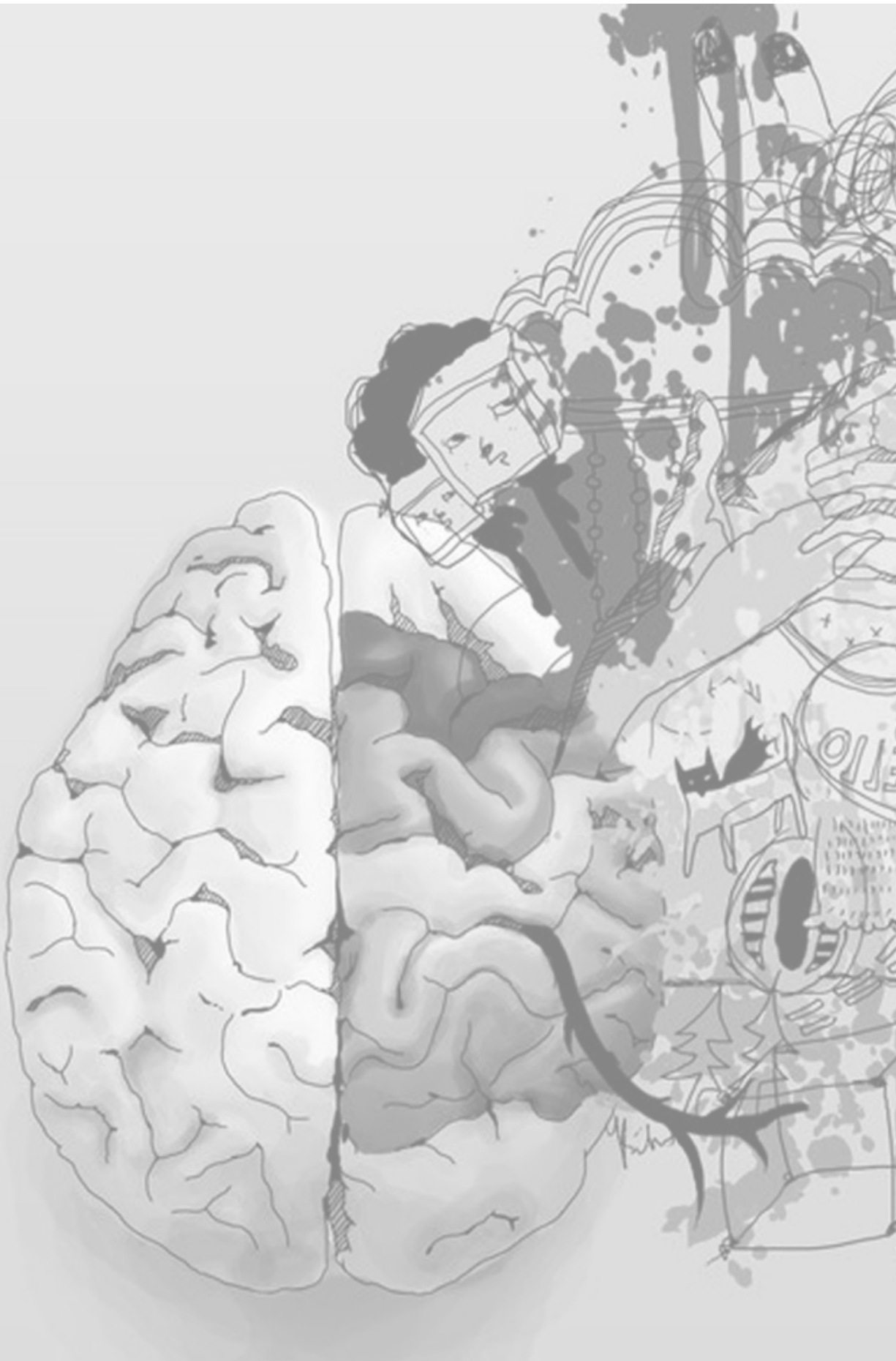

Chapter 3

Brain Function and Upper Limb Outcome in Stroke: A Cross-Sectional fMRI Study

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Abstract

Objective

The nature of changes in brain activation related to good recovery of arm function after stroke is still unclear. While the notion that this is a reflection of neuronal plasticity has gained much support, confounding by compensatory strategies cannot be ruled out. We address this issue by comparing brain activity in recovered patients 6 months after stroke with healthy controls.

Methods

We included 20 patients with upper limb paresis due to ischemic stroke and 15 controls. We measured brain activation during a finger flexion-extension task with functional MRI, and the relationship between brain activation and hand function. Patients exhibited various levels of recovery, but all were able to perform the task.

Results

Comparison between patients and controls with voxel-wise whole-brain analysis failed to reveal significant differences in brain activation. Equally, a region of interest analysis constrained to the motor network to optimize statistical power, failed to yield any differences. Finally, no significant relationship between brain activation and hand function was found in patients. Patients and controls performed scanner task equally well.

Conclusion

Brain activation and behavioral performance during finger flexion-extensions in (moderately) well recovered patients seems normal. The absence of significant differences in brain activity even in patients with a residual impairment may suggest that infarcts do not necessarily induce reorganization of motor function. While brain activity could be abnormal

with higher task demands, this may also introduce performance confounds. It is thus still uncertain to what extent capacity for true neuronal repair after stroke exists.

Introduction

Stroke is a leading cause of disability in western society (1). The European Registers of Stroke study (EROS) show that of 2000 patients with first-ever strokes, 40% had a poor outcome in terms of a Barthel Index (BI) below 12 points at 3 months post stroke (2). In the United States, 50% of stroke survivors suffer from hemiparesis (3,4). Physical therapy aimed at restoring activities of daily living (ADL) remains the gold standard of treatment but outcomes are variable (5). Recently, two independent studies have shown that an early return of some shoulder abduction and finger extension within 72 hours post stroke is highly predictive for outcome of upper limb function (6–8). The patients' ability to extend the paretic fingers voluntary is seen as an early sign of some intactness of corticospinal tract system (CST) after stroke (7,9). In addition, in rehabilitation medicine voluntary control of finger extension is judged as a key function for achieving of some dexterity with the paretic limb (6,8,10).

An approach to improve our understanding of the mechanisms underlying functional recovery is to investigate the neural correlates of movement of the affected hand. Many cross-sectional as well as longitudinal studies have previously demonstrated a relationship between various patterns of fMRI brain activation and post-stroke outcome in patients with infarcts that spare M1. Correlations have been found between outcome after stroke, and increased (but also decreased) activation in secondary motor areas (such as PM and SMA), ipsilesional M1 overactivation, contralesional M1 activity as well as more bilateral activation patterns within the motor network, including the cerebellum (11–13). While there is variation in results of these studies, a recent meta-analysis has shown a consistent pattern of higher contralesional M1 activity and generally more widespread activity in secondary motor areas in stroke patients (14).

The relationship between these changes in brain activation and recovery of motor function is however not necessarily straightforward. Task parameters defining quality of motor performance as well as the occurrence of mirror movements are often not monitored in fMRI and may confound the interpretation of fMRI (12). In addition, a number of recent longitudinal studies suggest that improvement of upper limb function after stroke is mainly driven by learning compensation strategies rather than by actual neuronal repair (15,16). In animal studies compensatory strategies as correlates of recovery have also been shown after photothrombotic stroke (17,18). Patients might learn to deal with impairments by using the affected limb to perform a task in a different way than before the stroke using alternative neuronal pathways, for example by reducing the number of

degrees of freedom during movement (16,19–21). While such strategies may underlie clinical improvement, they do not constitute true neuronal plasticity or repair.

In the present fMRI study brain activity during motor function while performing an isolated, voluntary finger extension motor paradigm, is compared between patients with damage to the corticospinal tract and healthy controls. The patients are measured >6 months after stroke, when most of the recovery would be expected to have taken place. In addition, the quality of task performance was closely monitored with kinematic measurements to detect potential performance confounds, so that observed differences in brain activation between patients and control subjects can potentially be directly linked to neuronal plasticity (12). We hypothesize that extent of functional recovery after stroke is associated with reorganization of brain function during a motor task, as proposed in literature (9,22). We expect task-related brain activation to differ between subjects that have shown some motor recovery of the upper paretic limb, and healthy, age-matched controls. Specifically, we expect to find in stroke patients 1) elevated activation of secondary motor areas, 2) a more bilateral activation pattern across the motor network, as well as 3) a correlation between brain activity and functional outcome. However, we observed that under these well controlled conditions, there were differences in brain activation between patients and control subjects.

Materials and Methods

Subjects

Twenty patients with chronic stroke and fifteen healthy, age matched controls were included. All patients were measured at least 5 months after a first-ever ischemic stroke, at which time point most of the functional recovery has already occurred (23). Patients had no previous history of other neurological conditions. Clinical characteristics of patients studied are described in Table 1. Patients had a mean age of 56 years and 5 months (SD 10 years 4 months) and control subjects mean age was 55 years 11 months (SD 9 years 1 month). Groups were matched on age, sex and dexterity. Patients were included if, in the first weeks after stroke they had suffered from hemiparesis or paralysis of the hand. Further patient inclusion criteria were: age between 18 and 80 years, ability to understand instructions (score above 22 on the mini mental state examination (MMSE)) (24). Exclusion criteria consisted of: orthopedic restrictions of the upper extremities; botulin toxin injections or other medication influencing the

function of the upper extremity. Subjects gave written informed consent. The protocol was approved by the ethical board of the University Medical Center Utrecht, and was in accordance with the Declaration of Helsinki (2008).

Patient Characteristics.

Clinical Assessments

Motor function of the affected arm of each patient was rated using the upper extremity motor part of the Fugl-Meyer (FM-arm) test, the Action Research Arm Test (ARAT) and the nine-hole peg test (NHPT) at the time of fMRI measurement. The FM-arm is a test based on the concept of sequential stages of return of motor function (25) and it tests reflexes, synergy of the upper extremities as well as hand function. The assessments are scored on an ordinal 3-point scale to express a maximum motor score for the affected side, with a total score ranging from 0 to 66. The ARAT is a quantitative test of arm motor function (26). Hand movements, including pinch, grasp, grip and gross, are performed and scored on a 4-point scale, with a total score ranging from 0 to 57. The ARAT score can be divided into 3 categories, poor, moderate or good recovery (i.e. <10 points, 10–56 points, or 57 points) (27). The NHPT measures dexterity of the hand, focusing on fine motor function. Pegs are inserted and removed from a nine-hole peg-board. Scores are based on the time (in seconds) taken to complete the test and are calculated as a percentage of a healthy sample norm adjusted for age, sex, and handedness (28,29).

Patient	Age(Years)	TPS(Months)	Gender	Hand	Hem	Location	FM	ARAT	%NHPT*
1	42	26	F	L	L	SC	66	57	86
2	52	24	M	R	R	P	61	57	80
3	53	46	F	R	L	C	61	57	76
4	47	45	M	R	R	SC	56	52	72
5	67	31	M	R	L	SC	63	57	62
6	67	33	M	R	R	SC	53	56	65
7	73	22	M	R	R	P	66	57	125
8	57	36	M	R	L	C	58	57	65
9	57	41	M	A	R	SC	65	57	84
10	60	14	M	NA	R	SC	66	57	67
11	50	5	M	R	R	SC	59	57	69
12	73	22	M	R	L	C	44	50	57
13	48	39	M	R	L	SC	57	53	18
14	73	113	M	R+	R	SC	66	57	100
15	49	26	M	R	L	SC	55	57	58
16	40	128	F	L	R	SC	64	57	46
17	64	20	M	R+	L	SC	61	57	82
18	59	21	F	R	L	SC	61	53	34
19	45	11	M	R	L	P	61	57	70
20	53	14	F	R	R	SC	66	57	65
Mean	56.5±10.3	35.9±31.0	5 F/15 M	2L/14R/2R+/1A	10L/10R	3P/3C/14SC	60.5±5.6	56.0±2.1	69.25±22.55
Mean controls	55.9±9.1		5F/10M	1L/13R/1A					

Abbreviations: TPS time post stroke, M Male, F Female, Hand Handedness (Dexterity was established by the Edinburgh Hand Inventory), R right, L left, R+ forced to write, A ambidextrous, Hem lesioned hemisphere, P pontine, C extending to cortex, SC subcortical.
*NHPT results are given as percentage of norm scores (corrected for age and handedness).

Data Acquisition

Images were acquired with a Philips Achieva 3.0 Tesla MR scanner (Philips Healthcare, Eindhoven, Netherlands). A 3D PRESTO sequence was used for functional scanning (FA = 10 degrees, FOV = 224 × 256 × 160 mm, voxel size 4 × 4 × 4 mm, TE/TR = 33/23 ms, time per 40-slice whole-brain volume 0.63 s) (30). High-resolution whole brain anatomical scans were acquired for all subjects as reference for functional activation maps (3D T1-weighted scan: TR = 9.717 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, 0.875 x 0.857 x 1.2 mm, FOV = 224 x168 x177 mm). Electromyography (EMG) was measured during scanning over the extensor digitorum communis of the hand contralateral to the moving hand with four scanner compatible surface electrodes. The EMG electrodes were attached to the connector on the scanner for physiological synchronization. The EMG was acquired to detect and control for isometric contractions of the hand contralateral to the hand that was instructed to move (31). In addition, two MR-compatible data gloves (5DT Inc.) were used to measure overt hand movements (32).

Motor Paradigm

Patients were asked to perform two different motor tasks in the MRI scanner, consisting of flexion and extension of the fingers of the hand (alternating 20 seconds of movement and 20 seconds of rest for a period of 6 minutes per task).

Before fMRI scanning, subjects were trained to perform active extension movements with the fingers, using a plastic wrist-hand orthosis. The orthosis guaranteed a correct movement in the flexion–extension direction. To maximize mental engagement during the task, the active extension of the fingers varied in amplitude of movement for the first task, and varied in exerted force during extension for the second task. The two tasks used similar visual stimuli. For the first task (AMP), subjects wore a data glove on each hand, and movement amplitude was varied by subjects themselves while they were guided by an online visual representation of their movement, as assessed with the data glove of the hand that was instructed to moves. Both arms rested comfortably in a supine position supported by cushions next to the patients hips, with the elbows slightly bent in a comfortable position for each patient. The average position of the fingers was calculated based on the average angle between the extended fingers and the hand. The signal was calibrated by asking the subject to bend the stretched fingers in a 90 degree angle, and then stretch the fingers in line with the hand. The calibration was visually inspected by a researcher who was present in the scanner room at all times. The task was presented on a

screen, with graphical instructions. On the left, the target cue moved vertically moving up (representing stretching of the fingers) and down (representing bending the fingers in 90 degrees flexion). On the right side of the screen feedback was given (as an object also moving up and down a vertical line) of the actual position of the hand through online processing of the signals from the data glove. Subjects were asked to make the feedback object follow the target cue to the best of their ability. A movement cycle of the cue lasted 1 second and changed color to inform the patient that a rest or a move block was indicated. The requested amplitude of finger extension was varied between blocks at 3 levels (low, medium and full extension). The height of the target cue indicated the level of finger extension.
For the second task (FORCE) the requested force for the movement was varied between blocks by attaching 0, 1 or 2 elastic bands to the orthosis. The requested amplitude of the movement during the force task was at maximum (between 0 and 90 degrees), as guided by the visual cue. The amount of required force was thus kept the same for all subjects. No data-glove measurements were obtained during the FORCE task, as the orthosis that was used introduced physical constraints so that it could not be combined with the data glove. All subjects performed both tasks with the affected as well as the unaffected hand or right and left hand in controls, making a total of four tasks per subject. Visual inspection by a researcher who was in the scanner room during scanning, confirmed that all patients extended their fingers maximally in response to the changing force.

Data Preprocessing fMRI

All spatial preprocessing and first level analyses were done with statistical Parametric Mapping (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB (Mathworks Inc, Massachusetts, USA). All functional images of each participant were realigned to the first scan of each session, using 5 mm FWHM spatial smoothing during parameter estimation. After realignment, all imaging data were coregistered to the T1-weighted anatomical scan using a mutual information cost-function with 7 x 7 pixels FWHM histogram smoothing. Subsequently, images were normalized to the Montreal Neurological Institute brain using the unified segmentation procedure of SPM, which can perform intersubject image registration based on tissue classification maps (33). To prevent incorrect warping near the lesions, the ischemic lesions were masked during the segmentation. The masks were generated by manually drawing borders around the lesion in MRIcro (http:/www.psychology.nottingham.ac.uk/staff/cr1/mricro.html), and subsequently inverted so that voxels in and around the area affected by

stroke could not contribute to the establishment of the normalization parameters. Motion-related and high frequency artifacts were removed from the normalized timeseries data using MELODIC of the FMRIB software library (34). in combination with a General Linear Model (GLM).
The resulting normalized images were spatially smoothed for voxelwise group comparisons using a Gaussian filter of 8-mm full width at half maximum. Unsmoothed data were kept for an ROI analysis. The design matrix for the first level analysis was generated, using a high-pass filter with a cutoff at 128 seconds to remove low-frequency artifacts and correction for serial correlations with an autoregressive model.
Contrast maps were calculated for the active periods versus rest for each subject and each session. Contrast images from ten patients with right-sided lesions were flipped over the mid-sagittal plane, so that the affected hemisphere corresponded to the left side of the brain for all patients. The same was done with 7 matched controls to match groups.

Groupwise Comparisons of fMRI Data
An ROI based comparison was performed using the unsmoothed fMRI data. ROI's were generated by an automatic segmentation that was applied to all subjects anatomical image to delineate the cortical areas using Freesurfer (35). This automatic delineation is performed on the basis of geometric information of individual cortical model as well as neuroanatomical convention, and does not require explicit back-projection from a template segmentation to generate ROI's. The motor segments were selected from the segmentation and ROI's were generated by taking the 15% most active voxels (i.e. highest beta values within a segment) during the motor task (task vs. rest) in each anatomical motor segment (Supplementary Motor Area (SMA), Premotor area (PM), precentral and postcentral gyrus, insula and cerebellum; see Fig 1 for an example).

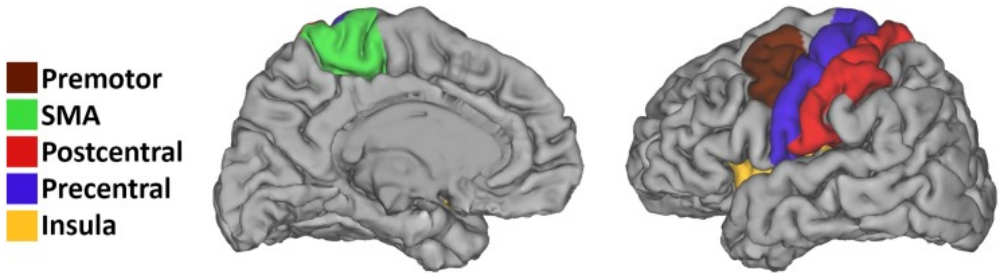

Fig 1

Surface reconstruction of a single subject with the anatomical motor segments depicted by different colors.

A proportional instead of absolute threshold was used in the ROI definition to account for global signal variations (36). The choice of 15% was based on a rough estimate of the mean volume of activation across the included ROI's, which was based on data of previous work of our group regarding reliability of fMRI motor activation (37). BOLD signal changes per ROI were represented by the mean beta value during each task. All the motor segments were then visually inspected to ensure correct segmentation for each subject. All selected motor segments were unaffected by the lesion, which were mainly subcortical or in some cases extending to other cortical areas (Fig 1). The segmentation maps were normalized to MNI space with the previously estimated normalization parameters. ROI's included bilateral precentral and postcentral gyrus, SMA, PM, and cerebellum.

In addition a laterality index (LI) was determined for the different motor areas by selecting the top 15% voxels in the bilateral anatomical motor segments (combined left and right), and counting the number of voxels selected in each segment. The laterality index was defined as $LI = (vox_i - vox_c)/ (vox_i + vox_c)$, where vox_c and vox_i denote the number of voxels of the hemisphere contralateral and ipsilateral to the lesion respectively (22). The LI ranges from 1 (all activated voxels are in the ipsilesional hemisphere) to -1 (all activated voxels are in the contralesional hemisphere). Differences in the activation in the ROI's between patients and controls were tested with a general linear model (repeated measures ANOVA) with ROI (6 levels), hemisphere (2 levels) and amount of force/amplitude (3 levels) as within-subjects factors. In addition to the ROI based analysis, a voxelwise group analysis was performed in MNI template space to test for possible differences outside the predefined ROIs. Voxelwise differences in the activation maps between groups were

estimated with an independent samples t-test in SPM5. The resulting statistical maps were thresholded at p <0.05 (corrected) (38).

Correlation with Outcome

To assess whether task related activity in the ROI's was predictive of outcome, a design matrix was constructed for each task, with each factor in the design matrix representing the activation in a single ROI for each patients. The three design matrices were applied to each of the behavioral measures (%NHPT, FM, and ARAT scores) in a stepwise regression procedure. The threshold for inclusion of factors in the model was set at p<0.05, and at p>0.10 for exclusion.

Data Glove and EMG Analysis

The signal of the data-glove and EMG data were analyzed offline with MATLAB. The signal from the data-glove was high-pass filtered to correct for drift in the signal and resampled to a 15 ms temporal resolution. Subsequently, the number of hand movements was derived by counting the number of maxima and minima of the movement signal and then dividing that number by two. The correlation coefficient of the envelope of the movement signal with the task boxcar was calculated to assess the adherence to the changing amplitude and timing of the task.

The EMG signal was analysed using a previous established approach (39,40). To remove fMRI artefacts induced by the gradient magnets, the EMG signal was notch filtered at 45 and 90 Hz. Second the signal was high pass filtered at 10 Hz to remove movement artefacts. Third the signal was rectified to regain low frequency components, the signal was rectified. Data were then band-pass filtered between 2 and 130 Hz and a correlation coefficient was calculated for the envelope of the signal time series and the task as a boxcar function.

Subjects were asked to perform a maximal voluntary extension (MVE) of the fingers before every task in the scanner. The corresponding EMG signal over that time was averaged and used as a norm value for average %MVE (%MVE) during movement blocks. %MVE was calculated by dividing the average EMG signal during the task by the average MVE and multiplying this by 100%.

$$\overline{\%MVE} = \frac{\overline{\mathrm{EMG}}}{\mathrm{MVE}} \cdot 100$$

This scaling was performed to account for intersubject variation in the amplitude of the signal as a result of factors such as conductivity of the skin,

amount of muscle tissue, and the exact locations of the electrodes on the hand. EMG Mirror Movements (MM_{EMG}) were represented by the correlation coefficient of the envelope of the EMG signal (E_{EMG}) and the task boxcar (T) multiplied with the %MVE.

$$MM_{EMG} = r_{T,E_{EMG}} \cdot \overline{\%MVE}$$

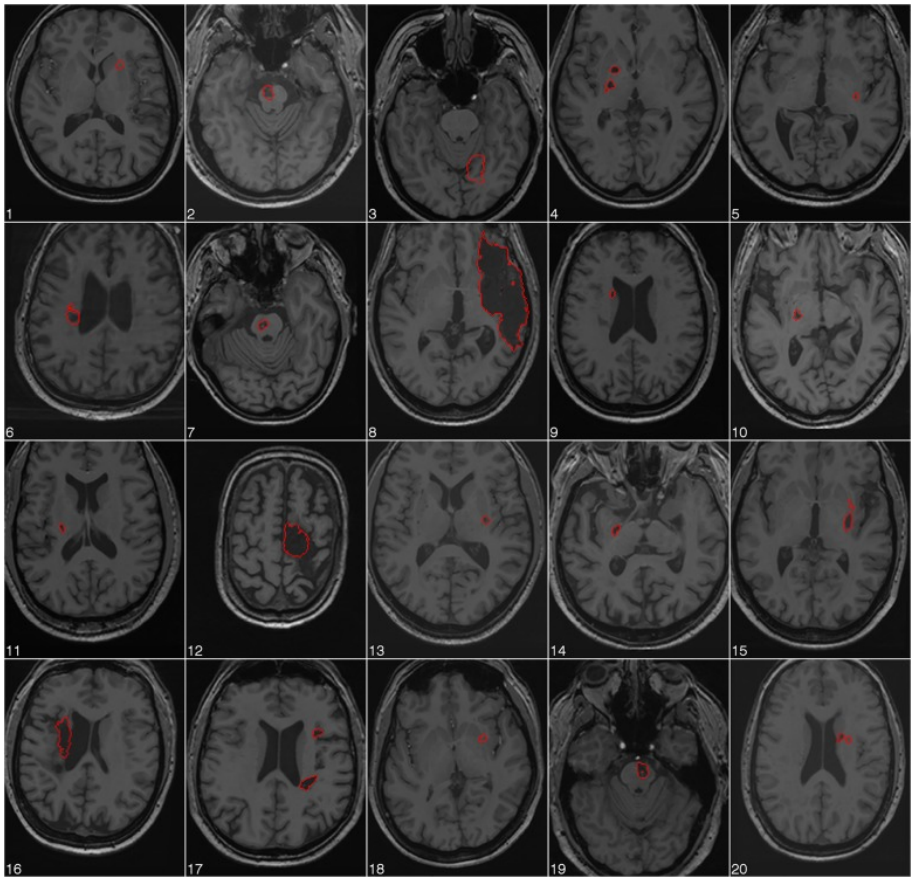

Fig 2

Axial structural T1-weighted MRI scans at the level of maximum infarct volume for each patient performed at the time of the fMRI session.

Results

Clinical Data

The site of cerebral infarction was determined from the structural MR images (Fig 2). Fourteen patients had subcortical infarctions in the capsular region, 3 patients had pontine infarctions, and 3 patients had infarctions extending into the cortex. No infarcts included motor cortex (Brodmann area 4). At the time of the measurement patients were on average at 36 months (SD = 31 months) post stroke.

On the ARAT test (Table 1) patients scored significantly less than the maximum score of 57 at an average of 56 (one-sample Wilcoxon rank test: $p = 0.042$). On the FM-arm test (Table 1) patients scores 60 points on average, which is significantly lower than the maximum score of 66 points (one-sample Wilcoxon rank test: $p<0.001$). On the NHPT patients scored a mean of 69.3% of norm values, which is significantly lower than %100 (one-sample T-test: $p<0.001$). Hence, as a group the patients were not fully recovered.

Glove Data

Problems with the acquisition hardware resulted in the absence of glove data for a total of 6 tasks in 5 subjects. All patients were able to perform the flexion/extension (AMP) task during scanning. A 2-sample t-test showed no difference for either amplitude or frequency of movements during the amplitude task between patients and controls for both hands ($t_{33}<1$; $p>0.4$ for all tests). In addition no actual mirror movements were seen in patients as well as controls during the amplitude task, as shown by a low correlation (MM_{glove}) of the inactive hand with the task (mean $r = -0.02$ for the unaffected arm; mean $r = 0.00$ for the affected arm). A paired t-test also showed no difference in amplitude or frequency of movements between the affected and unaffected hand movements in patients as well as right and left hand movements in controls($t_{18}<1$; $p>0.401$ for patients; $t_{13}<1.538$; $p>0.14$ for controls. For individual data, see Table 2.

Table 2

Results from analysis of data-glove data on task performance and mirror movements and scores on isometric contractions derived from EMG-data for patients.

P	MMEMG score				MMglove		Compliance Correlation		Number of movements (Hz)	
	UA	AA	UF	AF	UA	AA	UA	AA	UA	AA
1	0.43	0.08	0.07	0.59	-0.17	-0.16	0.77	0.78	92	89
2	0.64	0.77	0.22	0.01	-0.08	0.16	0.82	0.79	92	92
3	0.02	0.06	0.00	0.26	-0.12	-0.16	0.89	0.88	92	89
4	0.00	0.78	0.04	0.08	-0.03	-0.04	0.68	0.77	98	98
5	NA	0.60	0.02	0.02	-0.17	NA	0.96	NA	87	NA
6	0.07	1.13	0.01	0.01	0.33	-0.15	0.39	0.47	81	84
7	4.65	10.80	4.95	43.18	NA	NA	NA	NA	NA	NA
8	NA	NA	20.13	NA	0.06	-0.03	0.27	0.83	86	86
9	0.16	0.02	0.01	4.10	0.19	-0.01	0.71	0.6	75	64
10	0.07	0.00	0.19	0.44	0.15	-0.06	0.8	0.8	91	95
11	2.40	24.50	0.05	1.06	-0.09	-0.13	0.85	0.52	90	84
12	0.05	0.27	0.07	0.35	-0.12	-0.15	0.87	0.66	88	89
13	0.01	9.02	0.01	45.13	-0.18	0.38	0.86	0.85	97	92
14	0.01	1.38	0.02	0.15	0.01	NA	0.15	NA	85	NA
15	4.55	0.08	0.05	0.97	-0.07	0.01	0.61	0.78	86	93
16	1.48	0.77	0.00	0.61	0.08	-0.09	0.67	0.48	102	86
17	0.31	0.11	0.13	0.75	-0.03	-0.07	0.72	0.66	98	98
18	0.33	0.25	1.35	0.22	-0.04	0.05	0.77	0.68	95	93
19	0.08	0.21	0.05	0.30	-0.04	0.21	0.86	0.85	94	82
20	0.03	0.08	25.27	0.03	-0.03	0.16	0.72	0.55	90	94
Mean	0.85	2.68	2.63	5.17	-0.02	0.00	0.70	0.70	89.95	88.71
SD	1.50	6.09	7.00	13.77	0.13	0.15	0.22	0.14	5.83	7.96
Independent t-test, differences patients and controls										
t-test	.808	.912	.389	.861			-.291	.796	-.499	-1.14
P	.426	.545	.700	.401			.77	.62	.62	.26
Paired t-test, Affected vs. unaffected hand										
t-test	.712		.861				.390		1.538	
P	.488		.401				.70		.14	

Abbreviations: EMG Electromyography, MM mirror movements, SD standard deviation, t-test student's t test statistic, p p-value for student's t test statistic, UA unaffected amplitude, AA affected amplitude, UF unaffected force, AF affected force, NA Data unavailable (due to malfunction of equipment), %MVE % of EMG signal during maximum voluntary contraction.

EMG Data

Problems with the acquisition hardware resulted in the absence of EMG data for 3 tasks in 1 subject. No difference was found in EMG activity scores between patients and controls, or between affected and unaffected hand movements for patients, or between left and right hand movements for controls (Fig 3). A number of patients as well as controls had a high score (Score ≥5) for the EMG data during some sessions. The reason for these high scores remains elusive. However, a high EMG score during one session did not automatically mean a high score during other sessions, or during movements of the other hand, meaning that a relationship with stroke is unlikely (for individual data see Tables)

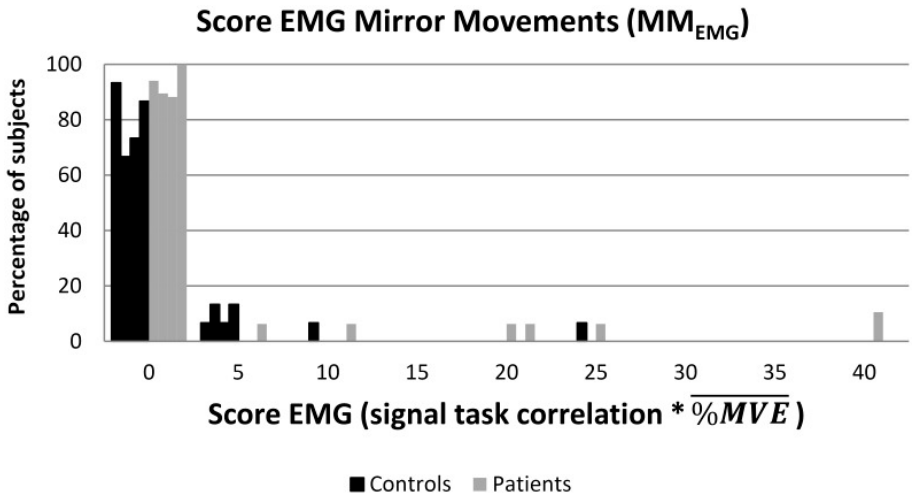

Fig 3

Histogram of incidence of isometric contractions (MM) in the contralateral hand defined by a score consisting of the correlation of the electromyography (EMG) signal measured at the extensor muscles of the contralateral hand during the task with the task ...

Table 3
Results from analysis of data-glove data on task performance and mirror movements and scores on isometric contractions derived from EMG-data for patients.

C	MMEMG score				MMglove		Compliance Correlation		Hz	
	UA	AA	UF	AF	UA	AA	UA	AA	UA	AA
1	0.18	0.16	0.36	0.20	0.02	0	0.71	0.71	89	89
2	4.47	2.09	0.39	0.33	0.01	-0.06	0.91	0.87	97	92
3	3.33	1.57	1.63	0.00	0.06	-0.27	0.19	0.27	81	96
4	0.39	0.86	0.02	0.01	0	-0.01	0.81	0.51	93	100
5	0.05	0.23	0.29	0.01	-0.15	NA	0.9	NA	90	NA
6	0.01	0.02	2.57	0.15	-0.11	-0.2	0.35	0.7	93	97
7	0.01	0.09	0.11	4.54	0.03	0.06	0.92	0.88	92	93
8	0.08	6.01	0.03	0.00	0.18	0.1	0.83	0.76	90	94
9	3.42	0.03	0.66	3.75	0.07	NA	0.86	NA	93	NA
10	0.23	0.54	2.87	4.64	0.11	-0.17	0.63	0.49	95	93
11	1.30	10.39	1.23	9.84	0.19	-0.2	0.56	0.81	82	88
12	7.89	0.46	1.17	1.06	-0.1	-0.32	0.72	0.62	94	93
13	0.08	0.99	5.96	0.00	0.36	0.01	0.74	0.43	105	80
14	0.03	0.00	0.04	0.26	-0.01	-0.07	0.88	0.82	91	85
15	0.34	29.91	0.02	7.36	-0.06	-0.06	0.87	0.66	88	91
Mean	1.45	3.56	1.16	2.14	0.04	-0.09	0.73	0.66	91.53	91.62
SD	2.32	7.83	1.62	3.16	0.13	0.13	0.22	0.19	5.74	5.24
Paired t-test. Affected vs. unaffected hand										
t-test	-.394		-.525				.858		-.030	
P	.699		.611				0.41		0.98	

Abbreviations: EMG Electromyography, MM mirror movements, SD standard deviation, t-test student's t test statistic, p p-value for student's t test statistic, UA unaffected amplitude, AA affected amplitude, UF unaffected force, AF affected force, NA Data unavailable (due to malfunction of equipment), %MVE % of EMG signal during maximum voluntary contraction.

Results from analysis of data-glove data on task performance and mirror movements and scores on isometric contractions derived from EMG-data for controls.

Since no actual movements were detected in the contralateral hand with the data-glove, a high score in EMG data seen in some subjects is more likely a representation of isometric contractions of the hand extensor muscles, and not a representation of EMG signal correlating with actual movement.

Imaging Results

The activation levels for all conditions in the different ROIs for each subject can be seen in the spreadsheet in S1 File. ROI analysis for Cerebellum, SMA, PM, precentral cortex, postcentral cortex and insula did not show differences between groups for affected amplitude, affected force, unaffected amplitude, or unaffected force (Table 4, Fig 4).

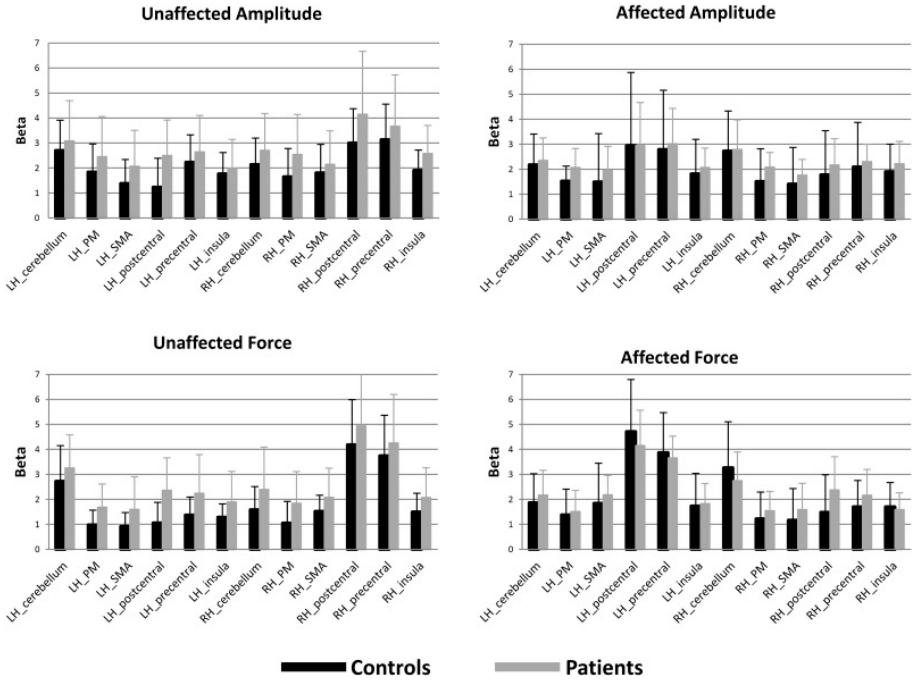

Fig 4

Mean results for Amplitude and Force tasks for the unaffected and affected hand for patients and controls.

Table 4

Results ANOVA Differences in brain activation between and within groups.

Contrast	Betas	LI
Patients vs. Controls		
Affected Amplitude	F = 0.333;p = 0.568 1	F = 0.439;p = 0.512 2
Affected Force	F = 2.422;p = 0.129 1	F = 0.225;p = 0.638 2
Unaffected Amplitude	F = 1.028;p = 0.318 1	F = 1.774;p = 0.192 2
Unaffected Force	F = 0.540;p = 0.468 1	F = 2.077;p = 0.159 2
Affected vs. Unaffected hand		
Force Patients	F = 0.733;p = 0.403 3	F = 0.422;p = 0.524 4
Force Controls	F = 0.397;p = 0.539 3	F = 1.066;p = 0.319 4
Amplitude Patients	F = 1.642;p = 0.215 3	F = 1.259;p = 0.276 4
Amplitude Controls	F = 0.916;p = 0.355 3	F = 0.600;p = 0.452 4

Abbreviations: F value for F-statistic, p p-value for f-statistic.
1 = group * ROI * hemisphere interaction
2 = group * ROI interaction
3 = condition * ROI * hemisphere interaction
4 = condition * ROI interaction

In addition, there was no difference in ipsi- or contralesional ROI activity between the affected and unaffected hand neither for patients nor for controls. The laterality index did not show a significant effect for group (Table 4, Fig 5), and did not show a difference between affected and unaffected hands for patients or for controls. There was no interaction effect for group with task, ROI, or hemisphere. To see if significant results were absent due to heterogeneity in lesion location, we repeated the ROI analysis with inclusion of only patients with lesions in the basal ganglia, the largest subgroup. However, still none of the tasks showed a significant effect regarding activity levels (betas) or laterality indices. In addition, we repeated the analysis within patients (affected vs. unaffected) while including time post stroke as covariate, to nullify potential within group

variance as a result of different levels of functional reorganization as a consequence of between subject differences in time post stroke. Again this did not produce significant effects for any of the tasks.

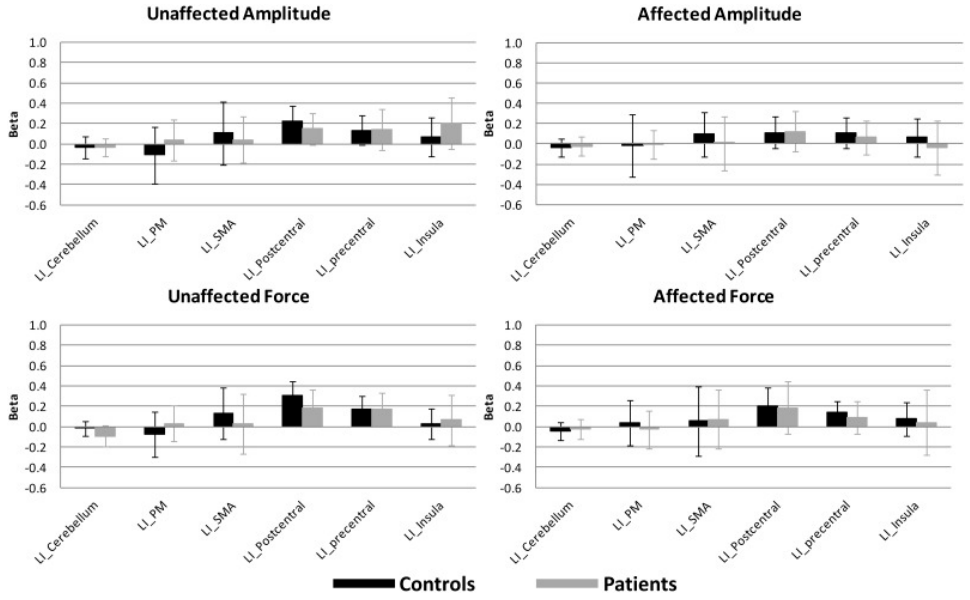

Fig 5

Mean results for Laterality Index for Amplitude and Force tasks for the unaffected and affected hand for patients and controls.

Voxelwise group comparisons were made with SPM for each task separately, for both groups separately and for the difference between patients and control subjects. The contrast maps in niftii format for each patient and control subject and for each condition can be found in a ZIP file archive in the supporting files (S2 Filefor patients and S3 File for control subjects). The analysis of the main effect (flexion-extension compared with rest) of the amplitude as well as the force task revealed activation in a broad network of brain regions (Fig 6). The most lateralized activation was in the sensorimotor cortex and superior cerebellum, with larger activation contralateral and ipsilateral to the moved hand respectively. Other activations were more bilateral, including the PM, SMA, inferior parietal cortex and, insular cortex, and bilateral cerebellum. Comparison between patients and controls did not reveal any significant increase or decrease in activation for the amplitude or force task and for either hand. Comparison

between affected and unaffected hand movements also did not reveal any difference in activation for patients, nor for controls.

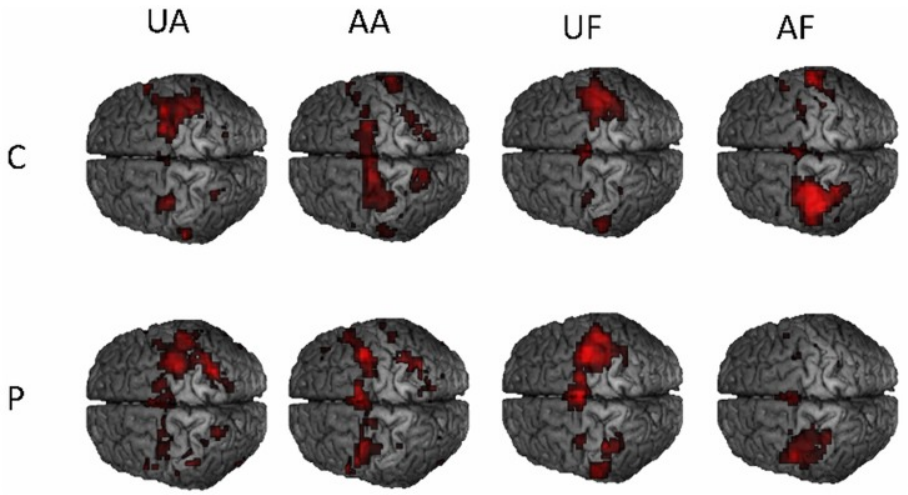

Fig 6

Group activation move vs. rest for 4 sessions, unaffected amplitude (UA), affected amplitude (AA), unaffected force (UF), and affected force (AF) between patients (P) and controls(C).

During stepwise regression none of the factors of the design matrices were included. This means that there was no significant correlation in any of the ROI's between task-related activity and %NHPT, ARAT or FM scores. In addition, LI scores did not correlate with clinical assessments for any of the sessions. There was no effect of mirror movements assessed with either EMG measures or data glove on brain activity. EMG and glove mirror movement scores did not correlate with task-related activity in any of the ROI's.

Discussion

Patients exhibited various degrees of recovery with mainly reduced scores on the NHPT and less so on the FM. While significantly lower than the maximum score, there was no clinically meaningful reduction (>6 points) in average scores for the ARAT, indicating good performance in general (41).

Brain activation during movement of the affected hand was not different for patients and controls with either a voxelwise whole brain analysis in MNI template space, or statistically more powerful ROI analyses including regions of the motor system. Moreover, the data showed no significant correlation between brain activation during any of the flexion-extension tasks, and functional outcome measures, in spite of the fairly wide range in outcome on the NHPT (%NHPT 18–125%). Detailed monitoring of movement extent and rate, and of mirror movements, indicated that patients and controls did not differ significantly with regard to any of these measures. We thus could not confirm an association between partial or complete recovery from stroke affecting the upper limbs and altered engagement of secondary or more bilateral motor areas, even when residual impairment is evident as demonstrated with the NHPT. The data thus do not provide evidence that in these patients the motor system adjusts to the CST damage in a way that could be detected with fMRI and a simple motor task.

Many studies have previously demonstrated a relationship between fMRI brain activation and post-stroke outcome in patients with infarcts that spare M1. While the outcome of these studies varies to some extent, good recovery of motor performance has generally been associated with a preservation or restoration of activity in the ipsilesional hemisphere (11–14,42–45). Sustained elevated task-related activity in the non-affected hemisphere has been associated with poor outcome (13,14,42–45). Elevated recruitment of secondary and bilateral motor areas has been interpreted as a reflection of a compensatory strategy in patients who show poor recovery after stroke (46,47). In accordance with previous research, longitudinal studies suggest that in the first weeks after stroke, movement of the affected hand is associated with overactivation within the bilateral sensorimotor network, and that this is more pronounced in patients with greater impairment (9,45,48).

The current results do not provide evidence for neuronal compensation beyond 6 months after stroke in patients with moderate (ARAT = < 57) to good (ARAT = 57) functional recovery. Even though multiple patients in the present study still showed significantly reduced speed of the upper paretic limb as reflected by reduced NHPT-scores, a more sensitive test of dexterity in our study, this did not induce detectable signs of neuronal plasticity. This is a negative finding which in principle places limits on the conclusions that can be drawn from this study. However, the comparatively large sample size in addition to the agreement with the observation that patients with

good outcome at >6 months after stroke showed 'normal' activation compared to healthy controls (17), suggest that any differences in brain activity during this task in this particular experimental group are small at best.
Putatively, during the relatively simple fMRI task minimal motor output is sufficient for performance. However, with higher demands on the sensorimotor network (e.g. during the NHPT), the brain may switch to a new strategy that includes compensatory mechanisms. This was previously shown in patients where a higher exerted force induced higher activation in secondary motor areas (9,47). Higher motor demands also might induce compensatory mechanisms in the musculoskeletal system by causing the intended action to be performed with different motor strategies (9,49). Interpretation of differences in brain activity between patients and controls is clearly affected by the exact features of movement, in that different motor strategies are likely to engage the motor system in different ways which give little information about reorganization of brain function per se.
In our opinion, understanding the changes in activation in the affected and the non affected hemispheres after stroke found in literature, require a more fine distininction in measuring the quality of motor control after stroke. Future research should address how neural correlates of multi-joint movements change with increasing complexity in well recovered patients, while simultaneously assessing compensatory mechanisms in the musculoskeletal system using kinematic analyses (16,50,51).

Analysis of the data-glove data did not show evidence for overt mirror movements in patients or controls. However, the EMG-data showed isometric contractions correlating with the task in some patients as well as some controls. Since there was no difference in EMG score between patients and controls we do not expect this variable to affect our results. Interestingly, the occurrence of mirror isometric contractions was variable within patients. Mirror movements were often not present during both tasks. Therefore a check for mirror movements performed during the actual task is warranted. In addition, since some patients showed substantial isometric contractions of the extensor muscle of the arm, the mere observation of movement in the contralateral arm does not seem sufficient in assessing mirror contractions. While we did not observe evidence that during scanning isometric contractions had an effect on brain activity in this study, it is important to eliminate these confounding factors.

A flexion/extension task of the fingers was applied in the present study because it can be performed and monitored relatively easy in a scanner environment, and performance on this task during the first weeks after stroke is a good predictor of upper limb function at 3 and 6 months post stroke (6–8). While our selected task was applicable in the scanner and clinically relevant, we did introduce a selection bias, by including only patients who showed some form of dexterity after stroke and in which the lesion might have spared some of the connections between the extensor muscle of the hand and M1 (6–8). Although all of our included stroke patients showed clear signs of brain damage, and all reported impaired motor function after stroke indicating an insult to the sensorimotor system, there is thus still the possibility that in more poorly recovered patients there are more compensatory mechanisms in the arm during task. We do not believe however that the observation of more compensatory activation in more poorly recovered patients would be a straightforward sign of neuronal reorganization. These patients would most likely perform the task less well or in a different way using alternative preserved neuronal pathways (16). Such a difference in performance could confound any evidence for neuronal plasticity. While the current patient group was only moderately impaired, we were able to perform an unbiased assessment of activity within the motor circuitry after stroke, and the absence of evidence for abnormalities in a relatively large sample may suggest that effects of true neuronal plasticity were small at best.

The current study contains several shortcomings that may have affected the sensitivity of our design. Most importantly, the patient population was quite heterogeneous regarding lesion location, which may have reduced statistical power by increasing variance within the patient group. While this issue is impossible to completely avert in stroke studies, we have attempted to lower its influence in a secondary analysis by including only patients of the largest subgroup (patients with lesions in the basal ganglia) and comparing them with control subjects. The overall pattern of results remained the same however. Secondly, for combining results of patients with left and right sided lesions, the fMRI results of some patients and controls were flipped across the interhemispheric fissure. While this procedure does not represent a confounding factor as it was done for both patients and controls, it can increase the variance within groups, and thus the sensitivity of the design. Finally, although the finger flexion/extension task we used is correlated to large muscle strength in the upper extremities,

this relationship is incomplete. Although we believe that the choice for a finger motor task is optimal considering that large arm movements cannot be performed in the scanner without introduction of serious motion artifacts, it may have affected sensitivity in detecting abnormalities in some of the patients.

In conclusion, we did not find differences in brain activity between patients and controls, nor did we observe significant correlations with measures of outcome in patients. The absence of differences may suggest that functional reorganization in the sensorimotor network is not present in patients with good outcome. However, NHPT scores of patients indicated the motor system was compromised. While these patients show normal brain activation during simple finger extensions, this may not so with more challenging motor paradigms. With increasing task difficulty and increased taxing of the motor system, we may observe changes in motor system activation to overcome for the impairment. The same may happen when the current finger extension task would be performed by poorly recovered patients. It is however uncertain if observations of altered brain activity in the presence of differences in task performance could be regarded as true signs of neuronal plasticity.

Supporting Information

We would like to thank Nayibe Statia and Ellen Jobse for helping with patient recruitment and assisting during scanning sessions.

Funding Statement

The authors have disclosed receipt of the following financial support for the research and/or authorship of this article: The EXPLICIT-stroke research project was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw; Grant No. 89000001; URLhttp://www.zonmw.nl/nl/). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Chapter 4

Brain activation is related to smoothness of upper limb movements after stroke

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Abstract

It is unclear whether additionally recruited sensorimotor areas in the ipsilesional and contralesional hemisphere and the cerebellum can compensate for lost neuronal functions after stroke. The objective of this study was to investigate how increased recruitment of secondary sensorimotor areas is associated with quality of motor control after stroke. In seventeen patients (three females, fourteen males; age: 59.9±12.6 years), cortical activation levels were determined with functional magnetic resonance imaging (fMRI) in 12 regions of interest during a finger flexion-extension task in week 6 and 29 after stroke. At the same time-points and by using 3D kinematics, the quality of motor control was assessed by smoothness of the grasp aperture during a reach-to-grasp task, quantified by normalized jerk. Ipsilesional premotor cortex, insula and cerebellum, as well as the contralesional supplementary motor area, insula and cerebellum, correlated significantly and positively with the normalized jerk of grasp aperture at week 6 after stroke. A positive trend towards this correlation was observed in week 29. This study suggests that recruitment of secondary motor areas at 6 weeks after stroke is highly associated with increased jerk during reaching and grasping. As jerk represents the change

in acceleration, the recruitment of additional sensorimotor areas seems to reflect a type of control in which deviations from an optimal movement pattern are continuously corrected. This relationship suggests that additional recruitment of sensorimotor areas after stroke may not correspond to restitution of motor function, but more likely to adaptive motor learning strategies to compensate for motor impairments.

Keywords: Stroke, Neuroplasticity, Recovery, Upper extremity, Brain activation, Motor Control

Introduction

Outcomes of neurorehabilitation after stroke are variable and depend largely on the intensity and task-specificity of the intervention applied as well as the severity of initial impairment at stroke onset (Langhorne et al., 2011). For the paretic upper limb in particular, treatment effects are mainly restricted to patients with some voluntary control of finger extension after stroke (Kwakkel and Kollen, 2013; Langhorne *et al.*, 2011). These findings suggest that there is a need for a better understanding of the neuronal mechanisms underlying functional recovery after stroke.

Task-related recruitment of secondary sensorimotor areas in the affected and non-affected hemisphere have been associated with poor motor recovery in terms of body functions and activities (Buma *et al.*, 2010; Ward *et al.*, 2004). It is therefore unlikely that secondary sensorimotor areas are able to take-over the functions of the primary injured motor areas (Buma *et al.*, 2010; Ward *et al.*, 2004). Recruitment of these additional areas may rather reflect support in the execution of compensatory motor control while performing a motor task with the paretic upper limb.

However, it is still unclear how brain activation patterns are associated to quality of upper limb control after stroke (Buma *et al.*, 2013). Most traditional clinical assessment scales are not suitable for capturing *how* patients perform functional tasks. By contrast, 3D kinematics can assess intra-limb coordination and smoothness of movement patterns, which are important characteristics of quality of motor control.

A recent study with intensive repeated 3D kinematic measurements in the first 6 months after stroke suggested that basic synergistic couplings between the shoulder and elbow during a functional reaching task diminished as a function of time after stroke (van Kordelaar *et al.*, 2013). This suggests that the ability to plan movements in advance (i.e. feedforward motor control) may improve, thereby decreasing the need for continuous online corrections based on proprioceptive feedback (van Kordelaar *et al.*, 2014; Meulenbroek *et al.*, 2001). Such corrections based on afferent information have been shown to negatively affect the smoothness of hand and finger movements (Merdler *et al.*, 2013).

An important measure to quantify smoothness is normalized jerk. Jerk is the third time derivative of the position of a particular body part. Normalized jerk is obtained by correcting for differences in movement duration and movement distance (Caimmi *et al,* 2008). As high smoothness is reflected by minimal changes in position, smoothness is inversely related to normalized jerk. We have recently shown that this jerk measure decreases (*i.e.* smoothness increases) substantially in the first 8 weeks after

stroke (van Kordelaar *et al.*, 2014) and levels off up to 26 weeks after stroke, suggesting that jerkiness is a sensitive measure to investigate time-dependent changes in quality of motor control, particularly early after stroke. However, due to a lack of studies combining imaging techniques with kinematic analyses, the neurological mechanisms underlying the recovery of smoothness of upper limb movements are still largely unknown. We hypothesized that elevated recruitment of secondary sensorimotor areas would be associated to jerky movements. This hypothesis was tested by investigating the association between smoothness of finger movements during a reach-to-grasp task, measured with 3D kinematics, and activation levels in sensorimotor networks of the brain during a finger flexion-extension task, measured with functional MRI (fMRI) (Buma *et al.*, 2010). There are strong indications that the potential for neural adaptation is mainly limited to a time-window of 10 weeks after stroke in which most spontaneous neurological recovery occurs (Murphy and Corbett, 2009; Langhorne *et al*., 2011). We tested the association between brain activation and smoothness of finger movements at 6 and 29 weeks after stroke, to assess whether this association changes with time after stroke (Buma *et al.*, 2010; van Kordelaar *et al.*, 2014).

Methods

Patients

Seventeen patients (three females and fourteen males) with stroke were included in this study. Patients had a mean age of 59.9 years (SD=12.6 years) and were included if they (1) had had their first ever ischemic stroke and had suffered from mono- or hemiparesis of the hand at the time of their stroke; (2) were between 18 and 80 years old; (3) were able to understand instructions as indicated by a Mini Mental State Examination (MMSE) score of 23 or higher (Folstein *et al.*, 1975) ;(4) gave written consent to participate in the study. Exclusion criteria were (1) not being able to make flexion-extension movements with the fingers or reach-to-grasp movements with the paretic upper limb in week 6 after stroke; (2) pacemakers or other metallic implants incompatible with the 3T MRI scanner; (3) orthopaedic impairments of the upper extremities; (4) communication restrictions as indicated by a score of 3 or less on the

Utrecht Communication Observation (UCO) (Schepers *et al.*, 2005); (5) botulinum toxin injections or other medication influencing the function of the upper limb.

The seventeen patients were recruited within the EXPLICIT-stroke programme and they were stratified according to the ability to perform some finger extension within 1 week after stroke (Kwakkel *et al.*, 2008). Patients with an unfavourable prognosis based on finger extension were randomly allocated to the experimental group that received electromyography-triggered neuro-muscular stimulation (EMG-NMS) or the control group that received usual care (N = 5). Patients with a favourable prognosis were randomly allocated to the experimental group that received modified constraint-induced movement therapy (mCIMT) or the control group that received usual care (N = 12) (Kwakkel *et al.*, 2008). EMG-NMS and mCIMT were applied from week 2 to week 5 after stroke. Handedness was established with the Edinburgh Handedness Inventory (Oldfield, 1971). After the experimental intervention period, all patients who participated in this study underwent two fMRI and two 3D kinematic measurements, performed at weeks 6 and 29 after stroke. To avoid effects of fatigue, measurements were performed on separate days. Informed consent was obtained according to the declaration of Helsinki and the study protocol was approved by the local ethics committee.

Clinical measurements

Motor function of the affected arm of each patient was assessed at 6 and 29 weeks after stroke using the upper extremity section of the Brunnstrom Fugl-Meyer Motor Assessment (FMA), the Action Research Arm Test (ARAT) and the nine hole peg test (NHPT). The FMA test is an assessment based on the concept of sequential stages of motor recovery (Fugl-Meyer *et al.*, 1975) and it tests reflexes, basic limb synergies of the paretic upper limb and hand function. Each item is scored on an ordinal 3-point scale to express a motor score for the affected side, with a total score ranging from 0 to 66. The ARAT is a clinical test of arm motor function (Lyle, 1981). Upper limb movements, in terms of pinch, grasp, grip and gross movements are performed and scored on a 4-point scale, with a total score ranging from 0 to 57. The NHPT measures dexterity of the hand, focusing on fine motor function. Pegs are inserted and removed from a nine hole peg-board, scores are based on the time (in seconds) taken to complete the test and were calculated as percentage of healthy sample norms (Oxford Grice *et al.*, 2003).

Functional MRI

Data acquisition

Images were acquired with two Philips Achieva 3.0 Tesla MR scanners (Philips, Eindhoven, Netherlands), located at UMCU and LUMC. Patients recruited from hospitals near Utrecht (N = 9) were measured with the scanner at UMCU, and patients recruited near Leiden were measured with the LUMC scanner (N = 8). High-resolution whole brain anatomical scans were acquired for all subjects for anatomical reference (3D T1-weighted scan: TR = 9.717 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, .875 × .857 × 1.2 mm, FOV = 224×168×177). During the motor task, 384 fMRI PRESTO scans were acquired (flip angle = 10 degrees, FOV = 224×256×160 mm, voxel size 4×4×4 mm, TE/TR = 33/23 ms, time per whole-brain volume 0.63 s) (Neggers *et al.*, 2008). To check for mirror movements, EMG was applied to the hand opposite the moving hand with four scanner-compatible surface electrodes (MR Physiology Logging, Philips Medical Systems B.V., Eindhoven, The Netherlands).

Motor paradigm

During the fMRI measurements, flexion-extension of the fingers of the affected hand was paced at 1 Hz (i.e. 1 movement / s) by means of an arrow on a computer screen (alternating 30 seconds of movement and 30 seconds of rest for a period of 4 minutes). In addition, patients wore headphones to minimize the level of perceived noise induced by the MRI scanner. Patients' hand and wrist were enclosed by a plastic orthosis only allowing simultaneous movement of 4 fingers of the hand flexing only at the MCP joints. Thumb and wrist were restrained as previous studies found extension of the fingers to be one of the most important predictors of functional outcome after stroke (Nijland et al., 2010; Stinear, 2010). In addition, the thumb has been shown to be mainly invariant during reach-to-grasp movements, whereas the fingers contributed most to the grasping movement (Galea et al, 2001). During the entire fMRI assessment, both arms rested comfortably alongside the patient's hips, with the elbows slightly bent in a comfortable position. Task performance was monitored visually by the researcher present during scanning.

Data pre-processing for fMRI

fMRI data were analysed with Statistical Parametric Mapping (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/) in Matlab (Matlab 11.1; The Mathworks Inc, MathWorks, Natick, Massachusetts). All functional images of each participant were realigned to the first functional scan of each session. After realignment, all images were co-registered to the T1-weighted anatomical scan. Subsequently, images were transformed to standard Montreal Neurologic Institute (MNI) space, and smoothed using a Gaussian kernel with a 8 mm full width at half maximum, while also keeping the non-smoothed data. The task box-car function was convolved with the canonical hemodynamic response function, and the resulting model was estimated in combination with a high-pass filter with a cut-off at 128 seconds to remove low-frequency artefacts. In the first-level analysis, contrast maps were calculated using a General Linear Model representing periods of motor activity versus rest for each patient and each session separately (Friston *et al.*, 1995; Worsley and Friston, 1995). Contrast images containing the regression coefficients, i.e. beta values, for each voxel from twelve patients with right-sided lesions were flipped across the mid-sagittal plane, so that the affected hemisphere corresponded to the left side of the brain for all patients.

ROI data analysis

A region of interest (ROI) based comparison was performed using the unsmoothed data. An automatic segmentation procedure (Freesurfer ASEG) (Fischl *et al.*, 2004) was applied using the individual anatomical images of each subject to delineate the cortical areas, including the bilateral precentral and postcentral gyrus, supplementary motor area, premotor cortex, cerebellum and insula. All motor segments were visually inspected to ensure correct segmentation for each subject. The volumes containing the motor segments were normalized to MNI space using the previously estimated normalization parameters. ROI activation levels were established by taking the 15% most active voxels during the motor task in each anatomical motor segment. A proportional rather than an absolute threshold was used in the ROI definition to account for between-subject differences in the volume of activation (Raemaekers *et al.*, 2012). Blood oxygen level dependent (BOLD) signal changes per ROI were represented by the mean beta value during each task.

Detection of potential mirror movements with EMG

The EMG data were analyzed as described by Van Rootselaar and colleagues (van Rootselaar *et al.*, 2008). During each fMRI session, the EMG signal was recorded using electrodes attached to the hand contralateral to the moving hand, over the musculus extensor digitorum communis and musculus abductor pollicis brevis. The EMG data were analysed in Matlab (2011a). First, the EMG signal was notch filtered at 45 and 90 Hz to remove fMRI artefacts induced by the gradient magnets, and high-pass filtered at 10 Hz to remove movement artefacts. The signal was rectified to regain low-frequency components. Data were then band-pass filtered between 2 and 130 Hz and a correlation coefficient was calculated for the envelope of the signal time series and the task as a boxcar function. Subjects were asked to extend their hand maximally as a measure of maximal voluntary extension (MVE) before every task in the scanner. The corresponding EMG signal over that time was averaged and used as a norm value for average %MVE during movement blocks. Average %MVE was calculated by dividing the average EMG signal during the task by the average MVE and multiplying this by 100%. A score for the presence of mirror movements was calculated from the correlation coefficient of the envelope of the EMG signal and the task boxcar, multiplied by the value for %MVE. This score was correlated with the average beta for each contralesional ROI.

3D Kinematics

Data acquisition

3D kinematic data were collected using a portable electromagnetic motion tracking device (Polhemus Liberty, Polhemus, Vermont). Motion sensors were attached to the trunk, scapula, upper arm, forearm, hand, thumb and index finger of the paretic upper limb. This study focused on the data obtained from the thumb and index finger sensors. The sampling frequency was 240 Hz. Before each measurement, a pointer device (ST8, Polhemus Liberty, Polhemus, Vermont) was used to locate the tips of the thumb and index finger relative to their associated finger sensors.

Measurements were conducted at the site where patients resided. A previous study showed that data could be accurately and reliably recorded within a distance of 60 cm from the magnetic source and in a wide range of measurement environments, including a motion laboratory, treatment room or home situation (van Kordelaar *et al.*, 2012).

Paradigm and data analysis

One table with a height of 76 cm was used for all 3D-kinematic measurements. While seated at this table participants performed a functional reaching task. During this task patients had to reach forward with the paretic arm to grasp a block (5 × 5 × 5 cm and 150 g) at maximum reaching distance. After picking up the block they had to transport it to a target location, which was located at the contralateral side at a distance equal to the reaching distance. Patients were instructed not to slide their hand over the table and to perform the task at a comfortable pace. Seven trials were performed in each measurement. Details of the kinematic data acquisition and reach-to-grasp paradigm have been published elsewhere (van Kordelaar *et al.*, 2012).

The start of reach-to-grasp was defined as the moment at which the forearm sensor exceeded 5% of the maximum speed during the forward reach. The end of reach-to-grasp was defined as the moment at which the transportation of the block started and the block lost contact with the table. This moment was identified as the moment at which the forearm sensor exceeded 5% of the maximum speed during the transportation of the block towards the target location. The time-series for grip aperture were calculated from the start to the moment the block lost contact with the table, and were filtered with a second-order Butterworth low-pass filter with a cut-off frequency of 20 Hz. All kinematic data processing was performed using custom-made programs in Matlab version R2006a.

Movement duration was defined as the time between the start and end of reach to grasp. The smoothness of the grasp movement was quantified by the normalized jerk of the grasp aperture between the thumb and index finger (NJ_{grasp}). NJ_{grasp} was calculated for each trial. NJ_{grasp} represents the smoothness of the grasp aperture signal and is defined as the amount of jerk (*i.e.* third derivative) in the grasp aperture signal, normalized for movement duration and net change in grasp aperture during the reach-to-grasp movement (Hogan and Sternad, 2009). Specifically, normalized jerk was calculated as follows:

$$NJ_{grasp} = \sqrt{\frac{1}{2}\int_{t_{start}}^{t_{end}} jerk_{grasp}^{2}(t)dt * MD^{5} / L_{grasp}^{2}} \quad , \tag{1}$$

Where NJ_{grasp} represents the normalized jerk of the grasp aperture; t_{start} represents the time the reach-to-grasp movement started; t_{end} represents the time at which the reach-to-grasp movement ended; $jerk_{grasp}$ represents the third time derivative of the grasp aperture; MD represents the movement duration and L_{grasp} represents the difference in grasp aperture between the start and end of reach-to-grasp. NJ is mathematically independent of movement duration and the net change in grasp aperture, as a result of the normalisation of MD^5/L^2 (Hogan and Sternad, 2009)
Details of the kinematic data analysis have been published elsewhere (van Kordelaar *et al.*, 2014).

Statistics
The change in the ARAT, FMA and %NHPT between week 6 and week 29 was assessed using two-sided paired-samples t-tests ($p < 0.05$).
Differences in ROI activation levels between weeks 6 and 29 were tested with repeated measures analysis of variance (ANOVA), with ROI (12 levels) and time of measurement (2 levels) as within-subject factors. Furthermore, a voxelwise analysis was performed to test for possible differences outside the predefined ROIs. Voxelwise differences in the activation maps between weeks 6 and 29 were estimated with a paired samples t-test in SPM5. The resulting statistical maps were thresholded at $p < 0.05$ (family-wise error (FWE)-corrected).
We plotted the frequency distribution of the clinical data and NJ_{grasp} to check whether NJ_{grasp} was normally distributed. The change in MD and NJ_{grasp} between weeks 6 and 29 after stroke was assessed using paired t-tests (two-sided, $p < 0.05$).
Repeated measures ANOVAs in SPSS (version 20.0, IBM Corporation, New York) were conducted to investigate the interaction between activation levels in the 12 ROIs and NJ_{grasp} at weeks 6 and 29 after stroke. In each ANOVA, activation levels in the 12 ROIs at week 6 or 29 were used as the within-subject factor, whereas NJ_{grasp} at week 6 or 29 was taken as a between-subject covariate. The interaction between activation in the ROIs and NJ_{grasp} specified whether activation in the ROIs was related to NJ_{grasp}. The significance of the interaction was assessed using a Bonferroni correction to correct for multiple testing resulting in a significance level of $p < 0.05/4 = 0.01$. In case of a significant interaction between activation levels and NJ_{grasp}, separate Pearson correlation coefficients were calculated between each ROI and NJ_{grasp}. In addition, Pearson correlation coefficients were used to assess whether there was a mutual relationship between

NJ_{grasp} and basic 3D kinematic and clinical measures including MD, ARAT, FMA and NHPT. The significance level for these post-hoc correlation tests was set conservatively at $p < 0.01$ (two-sided) in order to avoid a type I error as a result of multiple testing.

Results

Table 1 shows the characteristics of the patients included in this study. The patients improved significantly from week 6 to week 29 as assessed with the FMA ($t = -2.911$, $p = 0.010$), ARAT ($t = -2.748$, $p = 0.014$) and %NHPT ($t = -6.044$, $p = 0.000$).

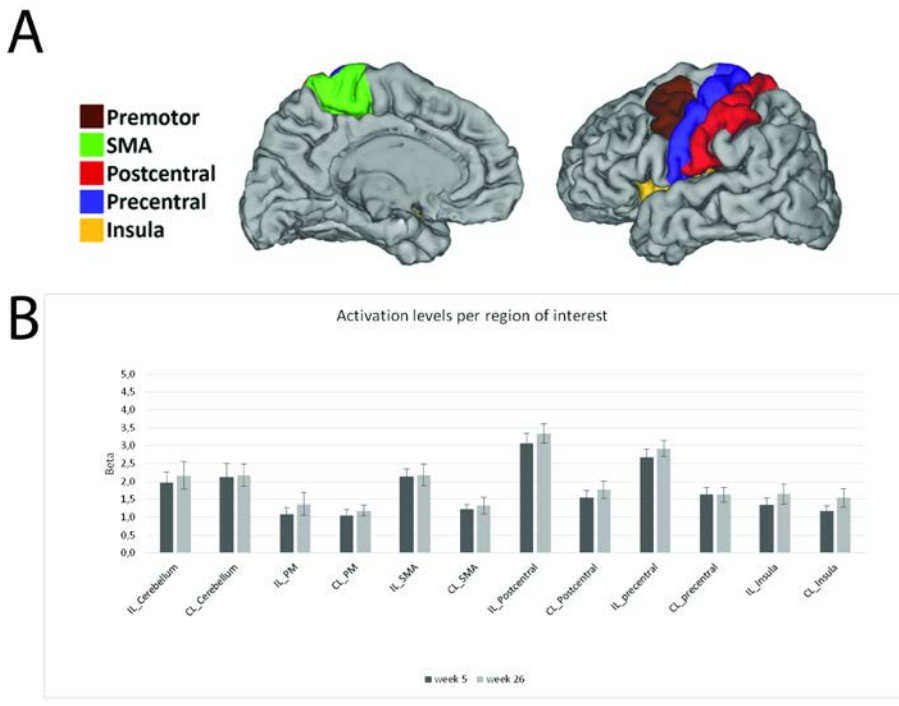

Figure 1 A
Example of definition of cortical ROI's for one example patient.
Figure 1B
Mean results for task-related activity for the affected hand at weeks 6 and 29 after stroke. Mean beta values (±1 SE) in the cerebellum, premotor area (PM), supplementary motor area (SMA), postcentral gyrus, precentral gyrus and insula for the left (affected) and right (unaffected) hemispheres (LH and RH, respectively). Patients' T-maps were flipped so the affected hand corresponded to the right hand.

The Appendix shows that thirteen patients had subcortical infarctions in the capsular region, whereas in two patients the infarction extended into the cortex. Two patients had pontine ischemic infarctions. No infarcts included the primary motor cortex (Brodmann area 4).
The average (±SD) time post stroke at which the first fMRI measurement took place was 6.4±2.1 weeks, and 5.9±1.1 weeks for the kinematic assessment. The second session took place at 29.4±4.7 weeks after stroke for fMRI and 28.8±1.2 weeks for kinematic assessment.

Activation in all ROIs was not significantly different between week 6 and week 29 ($F=0.699$, $p=0.415$) (Figure 1). We checked if this lack in significant results could be caused by variations in the quantity of mirror movements between sessions. However, all correlations between EMG score and ROI activation were not significant (all correlations had $p > 0.085$) for subjects with successful EMG measurements (week 6, N=13 and week 29, N=9). Problems with the acquisition hardware resulted in the absence of EMG data for 4 subjects at week 6 and 7 subjects at week 29).
Table 2 F-values and significance levels for each combination of activation levels (within subject factor) and NJ_{grasp} (between subject covariate) at weeks 6 and 29 after stroke.

	Beta week 6	Beta week 29
NJ_{grasp}, week 6	$F = 5.287$, $p = 0.002$ *	$F = 1.914$, $p = 0.099$
NJ_{grasp}, week 29	$F = 3.209$, $p = 0.021$	$F = 2.669$, $p = 0.029$

* $p < 0.01$, NJ_{grasp} Normalized Jerk of Grasp Aperture

Table 1 Patient characteristics at 6 and 29 weeks after stroke

Patient	Age (Y)	Gender	Hand	Hem	Location	FMA W6	FMA W29	ARAT W6	ARAT W29	%NHPT W6	%NHPT W29	MD W6	MD W29	NJ_{grasp} W6	NJ_{grasp} W29
1	73	M	R	R	C	63	60	32	34	6	14	1.35	1.11	5.37	4.23
2	63	M	R	R	SC	51	65	39	57	21	66	5.08	1.34	3.70	3.45
3	60	M	R	R	C	57	60	36	40	7	43	2.68	1.83	4.21	3.66
4	66	M	R	R	SC	63	61	57	57	48	51	1.07	0.99	3.82	3.46
5	45	M	R	R	P	14	58	4	56	0	58	1.12	1.01	5.08	3.63
6	32	M	R	R	SC	44	57	47	55	0	46	1.14	1.11	3.49	3.37
7	71	M	R	L	P	65	66	57	57	101	103	1.29	1.41	3.65	3.60
8	64	M	L	R	SC	62	63	52	57	58	72	2.79	1.54	3.41	3.51
9	37	F	R	R	SC	59	63	47	57	40	67	2.33	1.09	4.06	3.77
10	65	M	R	R	SC	63	63	57	57	55	54	1.61	1.23	4.31	3.68
11	65	M	R	L	SC	46	54	31	37	28	72	1.07	0.81	3.48	3.36
12	54	M	R	R	SC	44	57	31	38	0	46	1.45	1.37	4.57	4.03
13	79	F	R	L	SC	66	66	57	57	80	96	1.60	0.95	3.43	3.89
14	73	M	R	L	SC	46	61	22	57	0	59	1.96	1.35	4.26	3.65
15	56	M	R	R	SC	56	66	36	57	26	82	1.28	0.97	3.96	3.79
16	57	F	R	R	SC	54	56	48	44	36	57	1.47	1.32	3.68	3.55
17	59	M	R	L	SC	62	65	48	57	48	82	1.07	0.79	3.66	3.41
Mean	59.9					55.0	61.6	41.20	51.4	32.5	62.8	1.79	1.19	4.00	3.65
SD	12.6					12.7	3.7	14.5	8.7	30.0	21.3				
Total		3 F/ 14 M	1L/ 16R	5L/ 12R	2P/ 2C/ 13SC										

Abbreviations: M Male, F Female, Hand Handedness, R right, L left, Hem lesional hemisphere, FMA Upper limb section of the Fugl Meyer Motor Assessment, ARAT Action Research Arm Test, NHPT Nine-hole Peg Test, MD Movement Duration in seconds, P pontine, C extending to cortex, SC subcortical, Y years. *NHPT results are given as a percentage of norm scores (corrected for age and handedness).

The analysis of the main effect of the flexion-extension task vs rest revealed activation in a broad network of motor areas during both sessions at week 6 and week 29. Voxelwise comparisons between the sessions at 6 and 29 weeks did not reveal any significant change in activation.
NJ_{grasp} values were log-transformed, to meet assumptions of normality. The mean $log(NJ_{grasp})$ values were 4.00 (SD=0.57) and 3.65 (SD=0.24) in week 6 and week 29, respectively. The hand aperture traces of a patient that showed $log(NJ_{grasp})$ values close to the group mean values are shown in Figure 2. A paired t-test showed a significant decrease in $log(NJ_{grasp})$ (t=3.3, p=0.004) and MD (t = 2.72, p=0.015) between weeks 6 and 29.

Table 2 shows that task-related activation in the various ROIs at week 6 after stroke interacted significantly with $log(NJ_{grasp})$ at week 6 after stroke. Results from the other three ANOVAs were not significant after Bonferroni correction. However, a positive trend toward an interaction between activation in various ROIs and $log(NJ_{grasp})$ was observed at week 29. Pearson correlations showed that increased activation in the ipsilesional premotor cortex, insula and cerebellum and the contralesional supplementary motor area, insula and cerebellum was significantly ($p<0.01$) and positively associated with $log(NJ_{grasp})$ at week 6 (Table 3). The significant correlations between activation in ROIs and NJ_{grasp} are also shown by the scatterplots in Figure 3. Almost all ROIs that showed significant correlation with NJ_{grasp} also showed a significant correlation with MD, except for the contralesional cerebellum. The activation level in the contralesional precentral gyrus was significantly correlated to MD but not to NJ_{grasp}. In addition, one negative correlation was found between ARAT scores and brain activation in the ipsilesional premotor cortex at week 6, indicating that poor upper limb capacity was correlated to increased activation this ROI. No significant correlations were found between the ROI activation levels and the FMA scores at week 6. Lastly, $log(NJ_{grasp})$ was significantly related to ARAT (R = -0.635, $p < 0.001$) and MD (0.828, $p<0.001$) at week 6. No significant relation was found between $Log(NJ_{grasp})$ and FMA (R = -0.381, p = 0.131) and NHPT (R = -0.542, p = 0.025).

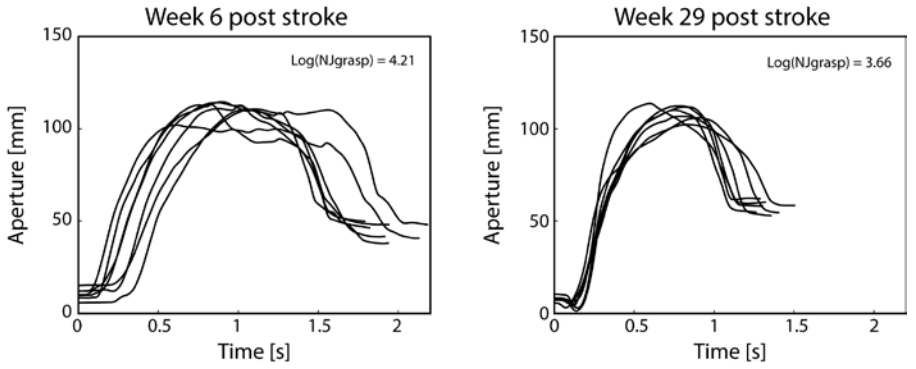

Figure 2

Grasp aperture between the thumb and index finger during the reach-to-grasp movement for one patient with stroke at weeks 6 and 29 after stroke. Each line represents one repetition of the task. Log(NJ_{grasp}) values for this patient are provided for week 6 and 29 after stroke.

Discussion

The key finding of the present study was that jerkiness correlated highly and positively with levels of brain activity in the ipsilesional premotor cortex, insula and cerebellum and the contralesional supplementary motor area, insula and cerebellum at week 6 after stroke. This finding confirms part of our hypothesis that elevated recruitment of secondary sensorimotor areas would be associated to jerky movements.

Regarding effects of time, patients improved significantly on the clinical assessment scales including the ARAT (~10 points), FMA (~7 points) and %NHPT (~30 percentage points) from week 6 to week 29. The improvements exceeded the minimal clinically important differences of 5.7 points, 6.6 points and 10% reported for the ARAT, FMA and %NHPT, respectively (Van der Lee et al. 1999), reflecting clinically relevant improvements between the two sessions. The reduction in movement duration between sessions was not significant although a trend was visible. In line with a previous longitudinal study, the quality of grasping control improved as reflected by a significant decrease of jerkiness of grasp aperture between weeks 6 and 29 after stroke (van Kordelaar *et al.*, 2014).

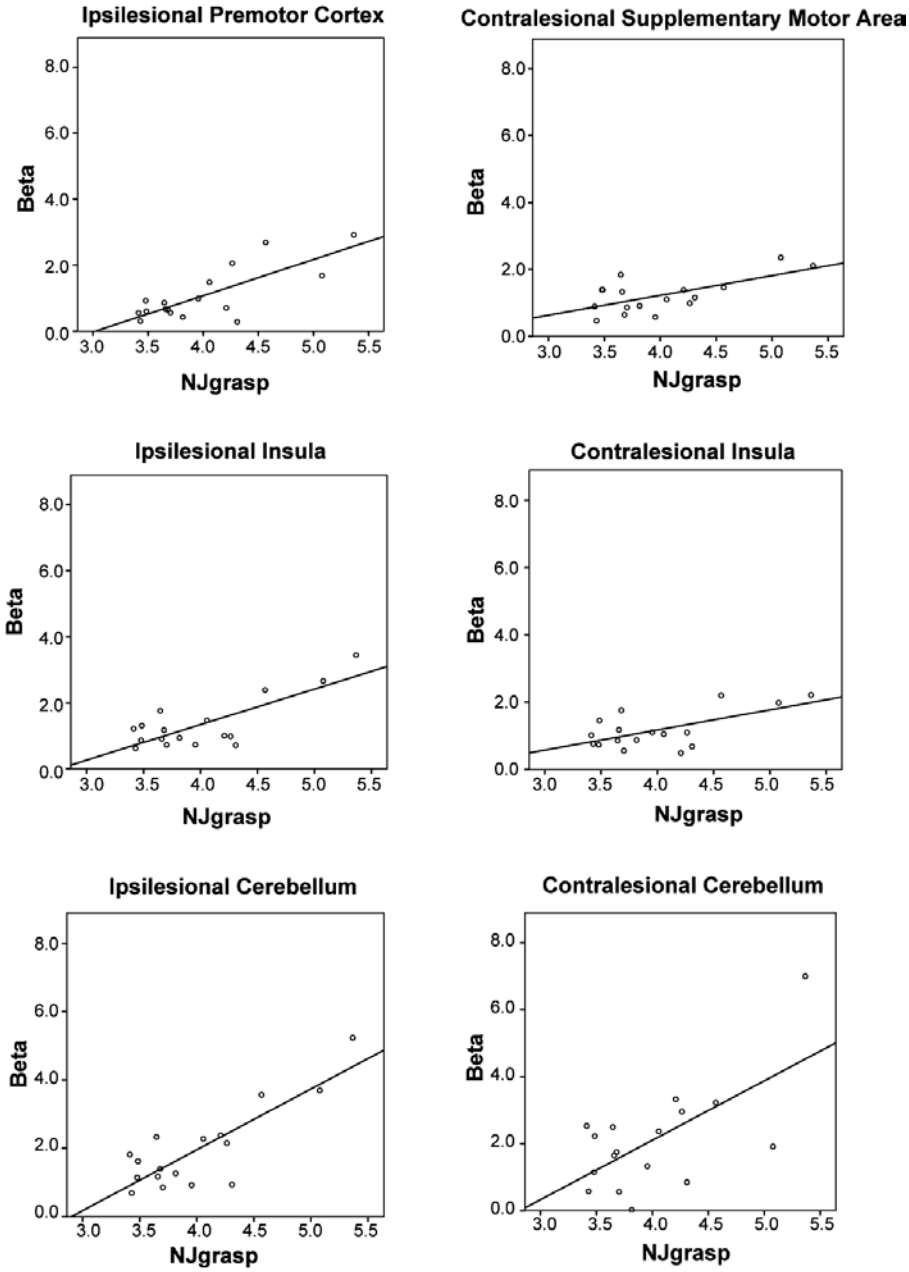

Figure 3

Scatterplots with regression line of significant correlations between beta values of individual ROIs and NJ_{grasp}.

In this previous study the greatest improvement occurred during the first 5 weeks after stroke and only a relatively small amount of improvement may have occurred between week 6 and week 29. This relatively minor improvement in motor control may explain why in the present study no significant change in brain activation patterns was observed between week 6 and 29 after stroke, neither with whole-brain analyses nor with ROI analysis.

In addition, the significant association between brain activation levels and smoothness was absent in week 29 after stroke. However, even after the Bonferroni correction a positive trend towards an association between brain activation and jerk was still present at 29 weeks, suggesting that a significant association might be observed when sample size is increased.

Previous studies have already shown that activity in the contralesional hemisphere early after stroke is associated with reduced functional capacity as indicated by poor performance on clinical assessment scales (Buma *et al.*, 2010; Ward *et al.*, 2004). Moreover, focal activation in the ipsilesional hemisphere, contralateral to the moving hand as observed in healthy controls (Ward *et al.*, 2003), is related to a favorable prognosis after stroke (Stinear, 2010). The present study extends on this finding showing that additionally recruited secondary sensorimotor areas are highly associated with jerky grasping movements in the subacute phase at 6 weeks after stroke.

The mechanisms underlying disruptions of smoothness are, however, poorly understood. After stroke, cortico-spinal pathways required for selective motor control are interrupted as shown with TMS (Stinear et al., 2007). This disrupted cortico-spinal control after stroke affects the execution of pre-planned movements (Daly et al., 2006) and selecting the optimal ballistic movement strategy during functional tasks (Meulenbroek et al., 2001). As a consequence, patients must adapt their motor behavior in order to compensate for these motor impairments. Given that jerk represents the change in acceleration (Rohrer et al., 2002), an increase in this metric may reflect the extent to which patients with stroke adjust their coordination patterns during a movement to correct for deviations from the intended movement pattern. This suggests that an increase in this metric reflects a type of control in which deviations from an optimal movement pattern are continuously corrected, possibly based on proprioceptive and visual feedback information. Therefore, the observed relationship between brain activation and smoothness, as quantified by jerk, suggests that secondary sensorimotor areas may be specifically involved in this error-correction process.

In particular the cerebellum is believed to play an important role in feedback driven motor control and motor learning (Ramnani *et al.*, 2001). In healthy subjects, ipsilateral and contralateral cerebellar activity have been found to be involved in closed-loop control during goal-directed upper limb movements using proprioceptive input and an internal copy of outgoing motor commands, *i.e.* efference-copy (Ramnani *et al.*, 2001). In stroke patients the sensory motor representation of movements is likely disturbed and this representation must be relearned. The potential involvement of the cerebellum may highlight the interconnectedness between the cortex and cerebellum—a phenomenon yet to be fully understood. One would expect a higher demand on the cerebellum in relearning grasping or flexion-extension movements with the fingers in stroke (Hubbard et al, 2014). There is growing evidence that transfer of motor learning is accompanied with an increased reliance on the cerebellum (Seidler et al, 2010; Dyan et al, 2011).

In addition, previous studies have shown that during finger movements the premotor cortex seems to be more involved in patients with stroke as compared to healthy subjects (Johansen-Berg et al., 2002) and is associated with a higher cognitive demand (Dennis et al., 2011). The present study suggests that this increased contribution of the premotor cortex does not necessarily improve quality of motor control. More generally, the present study suggests that a wide network of secondary sensorimotor areas may be involved in an adaptive relearning process in which stroke patients gradually regain the ability to reach for and grasp objects. Indeed, in a recent study Kantak and colleagues showed changes in the motor network after robotic reach training in healthy adults (Kantak et al., 2013).

Scientific and clinical implications

The size and significance of the correlations between brain activation and normalized jerk were similar to the correlations between brain activation and movement duration. In addition, movement duration and normalized jerk were also strongly and negatively correlated, indicating that patients

Table 3 Post-hoc Pearson correlation coefficients (R) and significance levels (P) between each ROI and NJ_{grasp} at week 6 after stroke. For illustration purposes, the bivariate correlation coefficients between activation levels in each ROI, Movement Duration, the upper limb section of the Fugl-Meyer Motor Assessment and the Action Research Arm Test.

	NJ_{grasp}		MD		FMA		ARAT	
	R	P*	R	P*	R	P*	R	P*
I premotor cortex	0.776	< 0.001	0.639	0.006	-0.336	0.188	-0.637	0.006
I supplementary motor area	0.316	0.216	0.359	0.157	-0.290	0.259	-0.397	0.115
I postcentral gyrus	-0.106	0.685	-0.049	0.851	0.069	0.793	0.187	0.473
I precentral gyrus	-0.019	0.943	0.057	0.829	-0.125	0.634	-0.100	0.703
I insula	0.778	< 0.001	0.691	0.002	-0.340	0.182	-0.474	0.055
I cerebellum	0.832	< 0.001	0.709	< 0.001	-0.310	0.225	-0.538	0.026
C premotor cortex	0.380	0.133	0.374	0.139	-0.275	0.285	-0.313	0.221
C supplementary motor area	0.665	0.005	0.642	0.005	-0.458	0.065	-0.507	0.038
C postcentral gyrus	0.373	0.140	0.515	0.034	-0.468	0.058	-0.331	0.195
C precentral gyrus	0.486	0.048	0.608	0.010	-0.513	0.035	-0.450	0.070
C insula	0.617	0.008	0.621	0.008	-0.439	0.078	-0.463	0.061
C cerebellum	0.639	0.006	0.373	0.140	0.013	0.962	-0.336	0.187

Abbreviations: I Ipsilesional, C Contralesional, NJ_{grasp} Log-transformed values of Normalized Jerk of the grasp movement, MD Movement Duration, FMA Upper limb section of the Fugl-Meyer Motor Assessment, ARAT Action Research Arm Test, R Pearson Correlation Coefficient, P significance value, * Significant correlations are underlined

with jerkier movements took longer to complete the reach-to-grasp task. A mathematical relation between normalized jerk and movement duration can be ruled out as an explanation for this correlation as these variables are mathematically independent (Hogan and Sternad, 2009). This findings therefore suggests that movement duration may directly depend on the brains capacity to control the quality of movement. This implication is supported by a previous study in which movement duration and normalized jerk showed the same longitudinal recovery pattern after stroke (Van Kordelaar et al., 2014).

Normalized jerk was also significantly and negatively correlated with the ARAT, suggesting that patients with jerkier grasping movements also had a reduced capacity to perform functional activities with the paretic upper limb. However, the positive correlation between brain activation and jerk as obtained with 3D kinematics was stronger compared to the negative correlation between brain activation and the FMA as well as with the ARAT. Together these findings imply that the measure of jerk captured with 3D kinematics has an added value next to ordinal clinical scales which measure improvement at an activities level and do not take quality of movement into account (Alt Murphy et al, 2012; Levin et al., 2009). To investigate neural dynamics underlying stroke recovery, jerk may add to our understanding of the changes in brain activation dynamics when patients are relearning skills and improving motor control.

The relationship between brain activation and normalized jerk further suggests that additional recruitment of sensorimotor areas after stroke may not correspond to restitution of motor function, but more likely to adaptive motor learning strategies to compensate for motor impairments as reflected by an increase of jerk. Translational research programs, such as EXPLICIT-stroke, should therefore establish whether therapies focusing on improving body functions, while avoiding compensation strategies, are able to promote restoration of neural networks in the cortex which may lead to improvements in quality of motor control (Kwakkel *et al.*, 2008; van Vliet *et al.*, 2013; Dobkin *et al.,* 2015).

To optimally benefit from this apparent added value of 3D kinematics, we argue that the development of motion trackers should be oriented to facilitating the use of 3D kinematics in clinical research. We have previously shown that we were able to use a mobile 3D kinematic set-up in order to realize an intensive follow-up of patients in the first 6 weeks and up to 6

months after stroke (Van Kordelaar *et al,* 2012). The advantage of the jerk measure as used in this study is that it can be obtained with only two kinematic sensors on the fingers and does not require full arm kinematics, which reduces donning time and hence improves clinical applicability of this measure. Moreover, low cost cameras in combination with innovative motion tracker software can register 3D kinematics even without the need to attach markers or sensors to the body (Brokaw *et al,* 2013; Kurillo *et al,* 2013). These recent developments are highly promising with regard to the use of 3D kinematics in clinical research and clinical practice. We favor the implementation of these kind of mobile motion trackers as well as easy to measure kinematic variables such as jerk to investigate quality of motor control after stroke.

Limitations

Our findings should be considered in the context of the following limitations. First, as the included patients were generally mildly affected the present results cannot be generalized to patients with a severe paresis of the upper limb, since severely affected patients were not able to perform the motor paradigms during the fMRI and 3D kinematic assessments. Second, the flexion-extension task that was administered in the scanner differed from the reaching task during the 3D kinematic measurements. Therefore, control strategies may have differed between the fMRI and 3D kinematic measurements. For instance, patients were able to rely on visual feedback during the 3D kinematic measurements, whereas this was not possible during fMRI scanning.

Furthermore, we used a continuous and rhythmic task during fMRI scanning whereas we used a discrete reaching task during 3D kinematic measurements. However, we argue that there is sufficient overlap, since the motor tasks during fMRI scanning and the reach-to-grasp task during the 3D kinematic assessments required flexion-extension of the fingers, which is considered an improvement with respect to the often used comparisons between fMRI and clinical tests. Third, given the large number of patients with a right hemispheric lesion (N=12) compared to patients with a left-sided lesion (N=5), possible effects of lesion side could not be investigated. Fourth, the measurements were performed at week 6 and 29 after stroke. Earlier fMRI scanning was impossible since patients were required to show sufficient finger extension to perform the motor paradigm. However, the moment of 6 weeks after stroke was well within the critical time window of 10 weeks after stroke in which most spontaneous neurological recovery is observed (Buma *et al.*, 2013).

Lastly, the fact that we found a relation between jerk and neural activation at week 6 but not at week 29 might be due to a lack of power, as we included a relatively small sample of 17 patients and variation in BOLD signal appeared to be considerable between and within subjects. In part, this variation between subjects may have been caused by differences in therapy as patients were allocated to different intervention groups within the EXPLICIT-stroke trial (Kwakkel et al, 2015). However, as severity of the initial motor impairment determines most of the variance in motor outcome between patients (Langhorne et al., 2011), we argue that differences in intervention would only have a minor effect on the variance between patients and the found correlations between smoothness and brain activation.

Future studies should therefore investigate correlations between brain activation patterns and quality of motor control, using large sample sizes, starting at an earlier time point after stroke and following up with intensively repeated measurements to capture the changes in these correlations over time after stroke. This relationship should preferably be measured directly in real time, with for example EEG or TMS coupled with kinematic measurement.

Acknowledgements

The authors would like to thank Dr. Dietsje D. Jolles for her cooperation during the fMRI scans in this study.

Funding

This study was part of the EXPLICIT-stroke programme (www.explicit-stroke.nl), which is registered with the Netherlands National Trial Register (Trialnumber: NTR1424); the work was supported by 'Het Revalidatiefonds', 'Revalidatie Nederland' and 'De Nederlandse Vereniging van Revalidatieartsen (VRA)' and was funded by the Netherlands Organization for Health Research and Development (grant #89000001).

Conflict of Interest

None

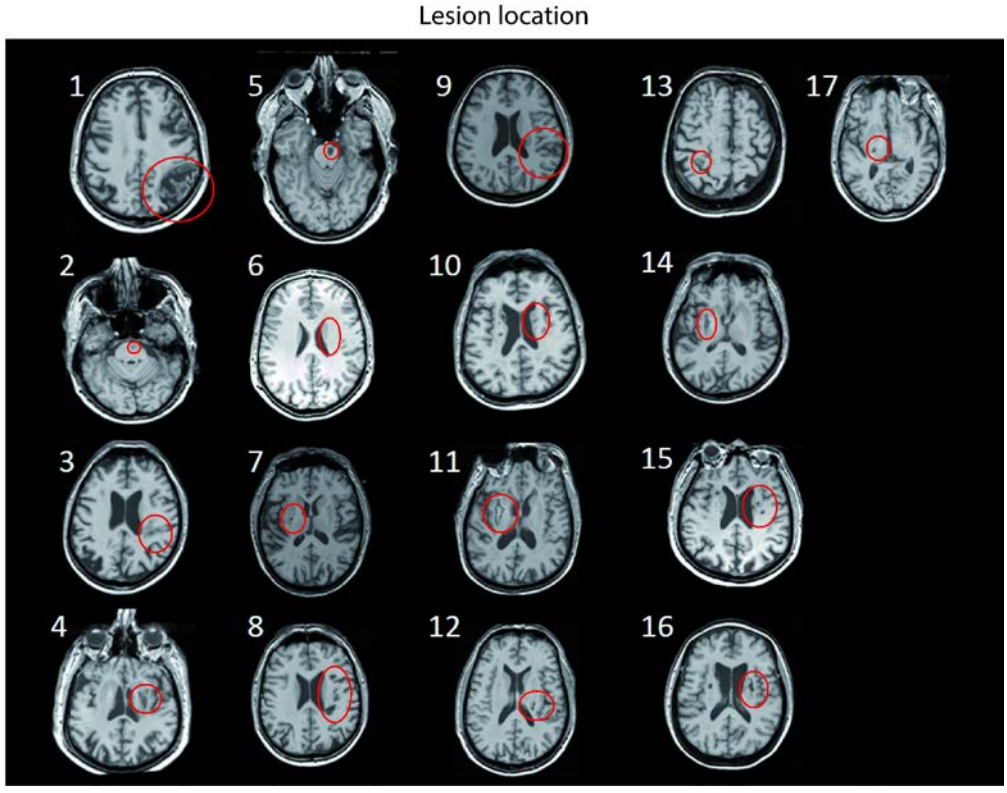

Fig 1 Appendix

Axial structural T1-weighted MRI scans at the level of maximum infarct volume for each patient, obtained at the time of the second fMRI session at 6 months after stroke.

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Chapter 5

No changes in functional connectivity during motor recovery beyond 5 weeks after stroke; a longitudinal resting-state fMRI study

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Abstract

Spontaneous motor recovery after stroke appears to be associated with structural and functional changes in the motor network. The aim of the current study was to explore time-dependent changes in resting-state (rs) functional connectivity in motor-impaired stroke patients, using rs-functional MRI at 5 weeks and 26 weeks post-stroke onset. For this aim, 13 stroke patients from the EXPLICIT-stroke Trial and age and gender-matched healthy control subjects were included. Patients' synergistic motor control of the paretic upper-limb was assessed with the upper extremity section of the Fugl-Meyer Assessment (FMA-UE) within 2 weeks, and at 5 and 26 weeks post-stroke onset. Results showed that the ipsilesional rs-functional connectivity between motor areas was lower compared to the contralesional rs-functional connectivity, but this difference did not change significantly over time. No relations were observed between changes in rs-functional connectivity and upper-limb motor recovery, despite changes in upper-limb function as measured with the FMA-UE. Last, overall rs-functional connectivity was comparable for patients and healthy control subjects. To conclude, the current findings did not provide evidence that in moderately impaired stroke patients the lower rs-functional connectivity of the ipsilesional hemisphere changed over time.

Keywords: stroke, recovery, motor impairment, resting-state, functional connectivity, fMRI

Introduction

Motor impairment is one of the most frequently occurring consequences of stroke (Langhorne et al. 2009). Even though post-stroke recovery varies across patients and over time, prospective cohort studies have indicated that functional motor recovery at 6 months post-stroke onset is highly predictable within the first few days (Nijland et al. 2010; Winters et al. 2015). The underlying mechanisms responsible for recovery, however, are not well understood. One mechanism that has been proposed to underlie functional recovery of upper limb paralysis is neuroplasticity. Spontaneous motor recovery appears to be associated with structural and functional changes in the motor network. Initial suppression of activation within the ipsilesional motor networks is gradually replaced by unilateral over-activation of the motor areas (as well as adjacent areas), during the initial stages of recovery (Nudo 2006; Cramer 2008). Optimal motor recovery coincides with patterns of activation comparable to those seen in healthy subjects (Ward et al. 2003a), as well as with an overall normalised activity in secondary ipsilesional and contralesional sensorimotor areas post-stroke (Ward et al. 2003b)for a review see (Buma et al. 2010). These longitudinal changes in patterns of fMRI activity have also been reported during recovery of other modalities such as language (Saur et al. 2006), attention (Corbetta et al. 2005) and somatosensory impairments (Rossini et al. 2007; Carey et al. 2011).

The aim of the current study was to explore the time-dependent changes in resting-state (rs) functional connectivity in motor-impaired stroke patients, using rs-functional MRI. Rs-fMRI reflects the temporal synchrony of fMRI signals between remote regions, without the confounds associated with task-compliance or performance that can occur when using task-based fMRI. Previous studies indicated that rs-functional connectivity within either the ipsilesional primary sensorimotor cortex (Wang et al. 2010; Park et al. 2011; Golestani et al. 2013) or contralesional primary sensorimotor cortex (Xu et al. 2014) was decreased early after stroke, followed by a gradual increase during recovery up to near normal levels in those patients who also showed improvement in motor impairment. Here, we investigated in stroke patients: (1) overall time-dependent changes in rs-functional connectivity of motor networks; (2) the relation between magnitude of time-dependent changes in rs-functional connectivity and time-dependent changes in motor impairment as measured with the upper extremity section of the Fugl-Meyer Assessment (FMA-UE; (Fugl-Meyer et al. 1975); (3) potential differences in rs-functional connectivity (at 5 weeks post-

stroke onset) with healthy control subjects; and (4) potential changes in connectivity outside the motor system.

Methods

Participants

Thirteen stroke patients (eleven males) were included from the EXPLICIT-stroke Trial (Kwakkel et al. 2008; Kwakkel et al. 2016), from August 2008 up to February 2013. Patients were included for this trial when they (1) had a first-ever ischemic stroke within the previous 2 weeks, verified by CT or MRI scan; (2) suffered from hemi- or monoparesis of the arm at baseline, determined by a National Institute of Health Stroke Score (NIHSS) item 5 of 4 point or less; (3) were able to make flexion-extension movements with the fingers or reach-to-grasp movements with the paretic upper-limb at 5 weeks post-stroke onset; (4) were aged between 18 and 80 years old; (5) were able to understand instructions as indicated by a Mini Mental State Examination score of 23 or higher (MMSE; (Folstein et al. 1975)); (6) were able to sit for 30 secs without support; (7) demonstrated sufficient motivation to participate in an intensive rehabilitation treatment programme for at least 3 weeks; and (8) gave written informed consent to participate in the study. Exclusion criteria for this trial were (1) orthopaedic impairments of the upper extremities; (2) communication restrictions as indicated by a score of < 3 on the Utrecht Communication Observation (UCO; (Schepers et al. 2005)); (3) botulinum toxin injections or other medication influencing the function of the upper-limb; and/or pacemakers or other metallic implants incompatible with the 3T MRI scanner.

Age and gender-matched healthy control subjects were included when they (1) did not have a history of neurological and/or psychiatric disorders; (2) were aged between 18 and 80 years old; and (3) did not have metallic implants incompatible with the 3T MRI scanner. Informed consent for the trial was obtained in accordance with the declaration of Helsinki (2013) and the study protocol was approved of by the local ethics committee (Medical Ethics Review Committees of Leiden University Medical Center (No. P08.035) and Dutch Central Committee on Research Involving Human Subjects (CCMO: No. NL21396.058.08)). The EXPLICIT-stroke Trial was registered in the Dutch Trial Registry (NTR, www.trialregister.nl, TC1424;

see Figure 1). The authors confirm that all related trials for this intervention were registered.

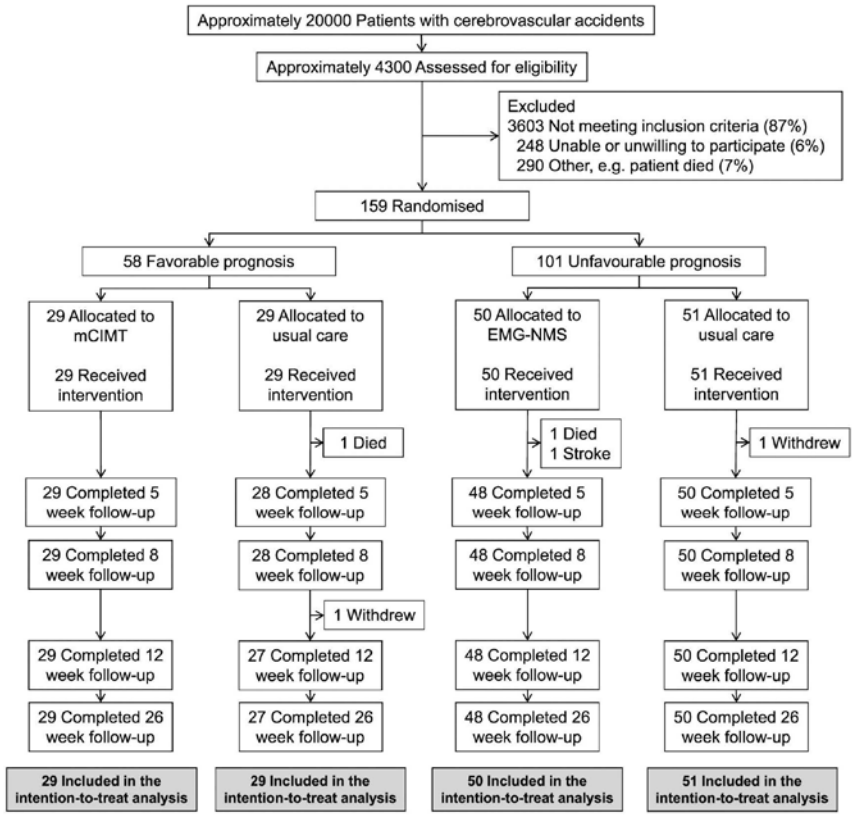

Figure 1. Flowchart of EXPLICIT-stroke Trial.

Clinical assessments

Patients' baseline characteristics and neurological function were assessed within 2 weeks post-stroke onset, and included: age, gender, Bamford classification (Bamford et al. 1991), Mini Mental State Examination (Folstein et al. 1975), Cumulative Illness Rating Scale (de Groot et al. 2003) and the modified Ranking Scale (Banks and Moratta 2007). Overall neurological impairment was measured with the National Institutes of Health Stroke Scale (Brott et al. 1989), the degree of disability during activities of daily

living with the Barthel Index (Collin et al. 1988) and motor strength of the upper-limb with the Motricity Index (Collin and Wade 1990). Patients' synergistic motor control of the paretic arm was assessed at baseline (within 2 weeks post-stroke onset), 5 and 26 weeks post-stroke onset with the upper extremity section of the Fugl-Meyer Assessment (FMA-UE)(Fugl-Meyer et al. 1975).

Scanning Protocol

Of the 13 included patients, rs-fMRI data was collected at weeks 5 and 26 post-stroke onset. Images were acquired with two Philips Achieva 3.0 Tesla MR scanners (Philips, Eindhoven, the Netherlands), located at the University Medical Center Utrecht and Leiden University Medical Center.

For functional scanning, an EPI-pulse sequence was used with the following parameters: TR=2200 ms, TE = 30 ms, flip angle = 80°, transverse orientation, FOV (AP, FH, LR) = 220 x 113 x 220 mm, slice gap = 0.272 mm. Slices were acquired in descending order. The acquired matrix had the following dimensions: 38 x 80 x 80, voxel size: 2.72 x 2.75 x 2.75 mm. The functional images where positioned to cover the entire cortex. 160 images were acquired during rs for a total duration of approximately 6 minutes. During scanning, patients were instructed to keep their eyes open and think of nothing in particular without falling asleep. The screen was blackened to keep visual input to a minimum.

High-resolution whole brain anatomical scans were acquired for all subjects as reference for functional activation maps (3D T1-weighted scan: TR=9.717 ms; TE=4.59 ms, flip angle=8 degrees, 140 slices, 0.875 x 0.857 x 1.2 mm, FOV=224 x168 x177 mm).

Data pre-processing

Data were spatially pre-processed using Parametric Mapping (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm/) in Matlab (Matlab 12; The Mathworks Inc, MathWorks, Natick, Massachusetts). The pre-processing entailed the realignment of all functional scans to the mean functional scan, slice time correction, and co-registration to the T1-weighted image. Normalisation to MNI (Montreal Neurological Institute) space was performed using SPM 12. Multimodal connectivity-based parcellation was included using the Brainnetome Atlas (Fan et al. 2016).

All subsequent analyses were performed using custom built routines in the Interactive Data Language (David Stern & ITT Visual Information Solutions, Boulder, Colorado, USA). For patients with lesions in the right hemisphere (n=7), left and right ROI definitions were interchanged. Interchanging of left and right ROI definition was also done for an equal number of randomly picked control subjects to avoid a bias introduced by hemispheric asymmetries. Low frequencies were removed from the functional time series using a high-pass filter with a cut-off at 0.01 Hz. For each ROI the average time series was calculated and subsequently correlated with all other ROIs. The correlation coefficients (R) within the matrices were Fisher Z transformed for second level analysis, using $z' = \left(\frac{1}{2}\right) \times ln\left(\frac{1+R}{1-R}\right)$..

Statistical analysis

To evaluate time-dependent changes in rs-functional connectivity of motor networks, we calculated the mean connectivity between the ROIs comprising the motor system (average Z-score for all pairs of Caudal Middle Frontal, Paracentral, Postcentral, Precentral) within the ipsilesional and contralesional hemisphere, for the first and second session (week 5 and 26 post-stroke onset). This resulted in two connectivity values for each session, one for the ipsilesional, and one for the contralesional hemisphere. The same connectivity values were calculated for the single session of the healthy control subjects.

To evaluate time-dependent changes in the motor network of patient, we performed a 2 x 2 repeated measures ANOVA with session (week 5 versus 26) and hemisphere (affected versus non-affected) as within subject factors. In addition, we investigated the relation between magnitude of time-dependent changes in rs-functional connectivity and time-dependent changes in motor impairment as measured with the FMA-UE. The change in FMA-UE between week 5 and week 26 was tested using a paired-samples t-test (two-sided). To investigate rs-functional connectivity differences per hemisphere between patients and control subjects, we compared rs-functional connectivity of the patients at week 5 with the rs-functional connectivity of control subjects using a repeated measures ANOVA, with hemisphere (ipsilesional/contralesional) as within subjects-factor, and group (patient/control) as between subjects-factor.

To further investigate potential changes in connectivity beyond the hypothesized areas, we performed an additional analysis. We tested

differences in the connections between all ROI pairs between week 5 and week 26 using a paired-sample t-tests, and between patients week 5 and control subjects using paired samples t-tests ($p<.05$ with Bonferroni corrections for the number of tests, n=29890: $p<.00000167$). Additionally, to measure overall effects instead of focusing on every corrected significant ROI, we also observed the actual proportion of significant tests while keeping the threshold at $p<.05$.

Results

The characteristics of the patients included in this study are presented in Table 1. The average time post-stroke onset at which the first and second rs-fMRI took place was 35.6 days (SD=4.4) and 187.0 days (SD=6.4) respectively. From 35.6 days (week 5) to 187.0 days (week 26), patients showed an average improvement in upper-limb function of 4 points (FMA-UE; $Z = -2.32$, $p=.020$ (two-tailed).

Table 1. Demographic and stroke characteristics measured at 8 days, 35.6 days, and 187 days post-stroke.

	Patients (n=13)	Healthy Controls (n=13)
Baseline		
Age (years (SD))	63.6 (9.0)	55.1 (9.0)
Gender (% male)	84.6	76.9
Bamford (LACI/PACI/TACI; %)	69.2/15.4/15.4	NA
MMSE (0-30)	27.2 (SD: 3.1; IQR: 25.3-30.0)	30
CIRS (0-52)	2.3 (SD: 1.5; IQR: 2.0-3.0)	0
NIHSS Total (0-42)	5.8 (SD: 2.6; IQR: 4.0-7.5)	0
Modified Ranking Scale (0-5)	3.9 (SD: 0.7; IQR: 3.0-4.0)	0
Barthel Index (0-20)	10.1 (SD: 5.1; IQR: 7.5-14.5)	20
Motricity Index arm (0-100)	50.3 (SD: 28.9; IQR: 34.0-74.0)	100
FMA-UE (0-66)	29.6 (SD: 18.5; IQR: 11.0-46.0)	66
Time post-stroke onset (days)	7.2 (2.5)	NA
Week 5		
Time post-stroke onset (days)	35.6 (4.4)	NA
Barthel Index (0-20)	18.2 (SD: 2.7; IQR: 17.5-20.0)	20
Motricity Index arm (0-100)	81.5 (SD: 16.3; IQR: 76.0-96.0)	100
FMA-UE (0-66)	53.5 (SD:14.1; IQR: 47.0-63.0)	66
Week 26		
Time post-stroke onset (days)	187.0 (6.4)	NA
Barthel Index (0-20)	19.9 (SD: 0.3; IQR: 20.0-20.0)	20
Motricity Index arm (0-100)	88.1 (SD: 10.6; IQR: 84.0-100.0)	100
FMA-UE (0-66)	60.9 (SD: 3.95; IQR: 57.5-65.0)	66

F: female; M: male; MMSE: Mini Mental State Examination; CIRS: Cumulative Illness Rating Scale; NIHSS: National Institutes of Health Stroke Scale; FMA-UE: Fugl-Meyer Assessment of the Upper Extremity; IQR: Inter Quartile Range; NA: Not Applicable, i.e. healthy control subjects did not have neurological or upper-limb impairments.

Three patients had infarctions extending to cortical areas, whereas 10 patients had subcortical infarctions (Table 2). In more detail, 9 lesions were located in the basal ganglia, 2 in the pons, and 1 of the patients had an infarction involving the primary motor cortex (Brodmann area 4).

Table 2. Subcortical and cortical areas (including hemisphere of stroke) containing the lesion for individual patients.

Patient	Subcortical area (hemisphere)	Cortical area (hemisphere)
1	Putamen (left)	NA
2	Putamen (left)	NA
3	Caudate (left)	NA
4	Caudate (left), Putamen (left)	NA
5	Brainstem	NA
6	Putamen (right)	NA
7	Thalamus (left), Putamen (left)	NA
8	NA	Postcentral (right), Supramarginal (right), Parsopercularis (right), Inferior parietal (right)
9	NA	Postcentral (right), Supramarginal (right)
10	Caudate (right)	NA
11	Caudate (right)	Precentral (right)
12	Putamen (right)	NA
13	Brainstem	NA

NA: Not Applicable

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Time-dependent differences in rs-functional connectivity of motor networks in the contralesional and ipsilesional hemisphere

A main effect of hemisphere (affected versus non-affected) was observed ($F(1,12) = 4.838$, $p = .048$), indicating that the rs-functional connectivity of the ipsilesional hemisphere (average = .465, SD = .056) was lower than the rs-functional connectivity of the contralesional hemisphere (average = .511, SD .049). No main effect of session (week 5 versus week 26) was observed ($F(1,12) = .667$, $p = .430$), indicating that rs-functional connectivity in week 5 (average = .474, SD = .053) was comparable to week 26 (average = .502, SD = .055). Additionally, no interaction between hemisphere and session was

found (F(1,12) = .618, p = .447), indicating that hemisphere differences in rs-functional connectivity were comparable over time (Table 3).

Table 3. Rs-functional connectivity scores of the affected and non-affected hemisphere, split for time post-stroke onset (weeks 5 and 26).

Patient	Affected hemisphere week 5	Unaffected hemisphere week 5	Affected hemisphere week 26	Unaffected hemisphere week 26
1	.93	.92	.97	.98
2	.41	.52	.55	.69
3	.74	.66	.62	.61
4	.27	.61	.29	.60
5	.23	.33	.41	.37
6	.48	.55	.64	.43
7	.53	.50	.50	.52
8	.14	.13	.23	.21
9	.31	.26	.50	.41
10	.40	.58	.45	.61
11	.36	.29	.36	.48
12	.41	.58	.54	.61
13	.56	.58	.50	.57

Potential changes in rs-functional connectivity within the motor networks in stroke patients

When testing for additional effects beyond the hypothesized connection, we observed no differences in connectivity between week 5 and week 26, regarding all 29890 ROI-pairs (t_{crit}=8.11; t_{max}=4.97 and t_{min}=-5.83). In other words, this analysis revealed no changes in rs-functional connectivity from 5 to 26 weeks post-stroke onset (Figure 2, 3, 4A).

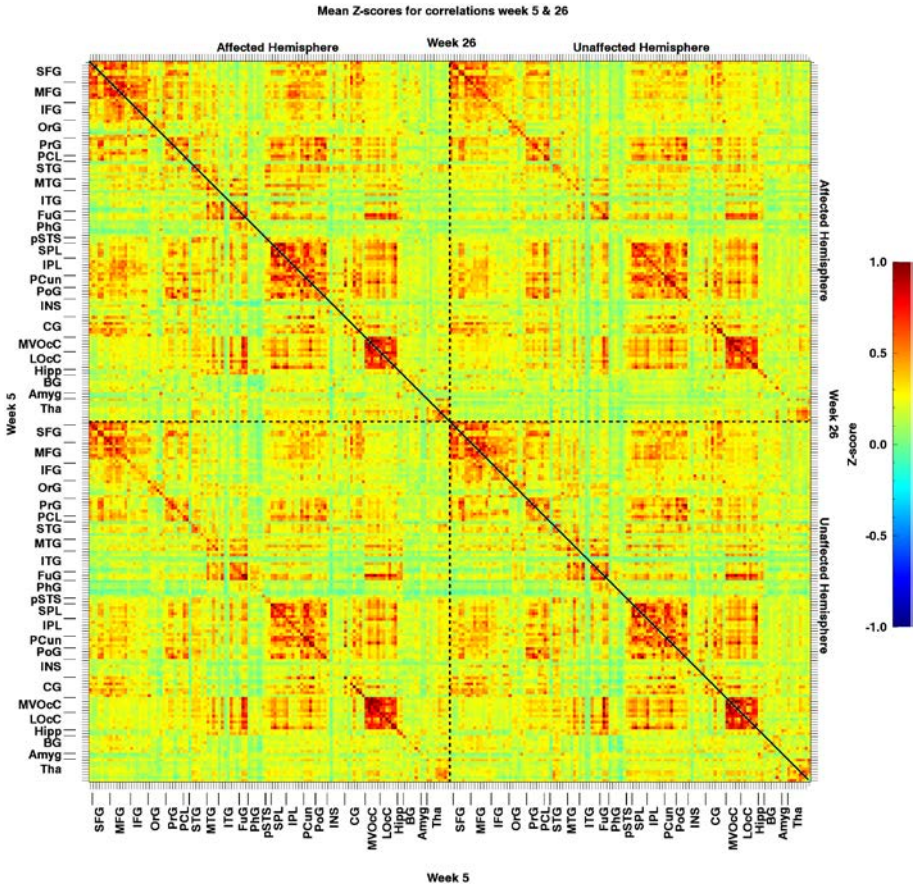

Figure 2. Mean resting-state Z-transformed correlations of the patients (n=13) between all regions of interest. The matrix area on the bottom left of the diagonal represents the correlations for week 5, while the area on the top right represents the correlations for week 26. Note that the colour representation of the values was clipped beyond -1 and 1, although due to the Fisher transformation values can actually exceed the [-1,1] interval. AH: Affected Hemisphere; UA: Unaffected Hemisphere; lesion location = left hemisphere.

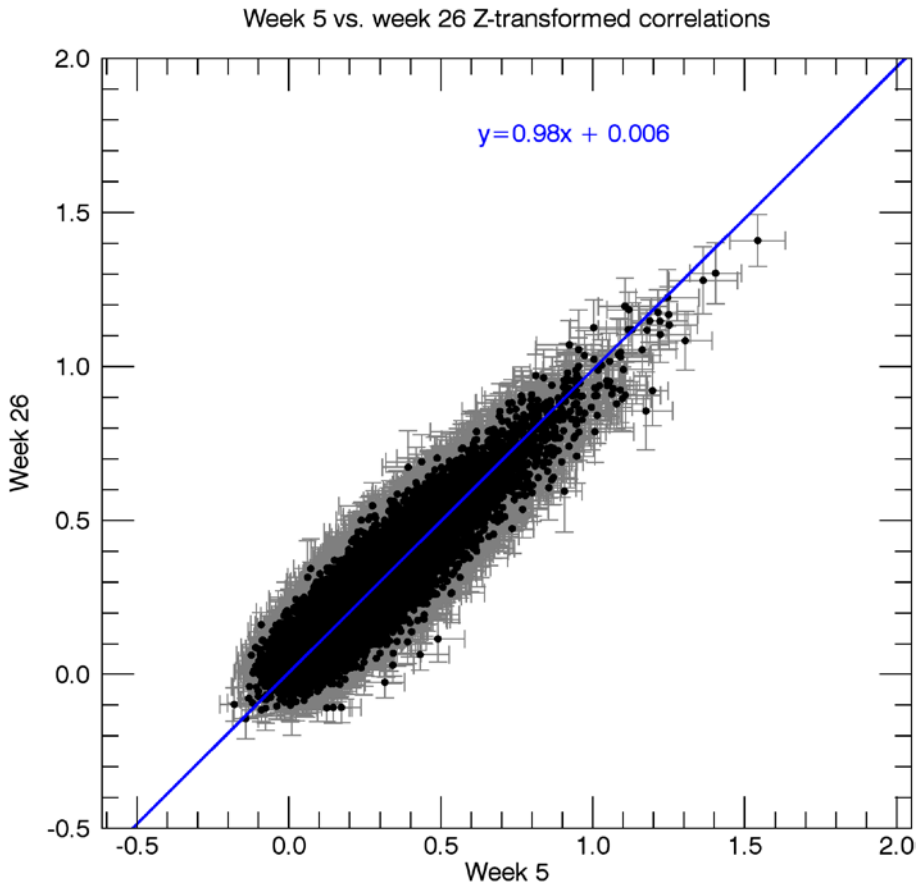

Figure 3. Scatterplot of the resting-state correlations in the patients for week 5 vs. week 26. Every data point in the graph represents an ROI pair, with the x-coordinate indicating the mean Z-score (n=13) for the correlation between the two ROIs at week 5, and the y-coordinate indicating the mean Z-score between the two ROIs at week 26. Grey bars indicate the standard error of the mean for week 5 (horizontal bar) and week 26 (vertical bar). The blue line depicts a straight line fit through the data points (Press and Teukolsky 1992).

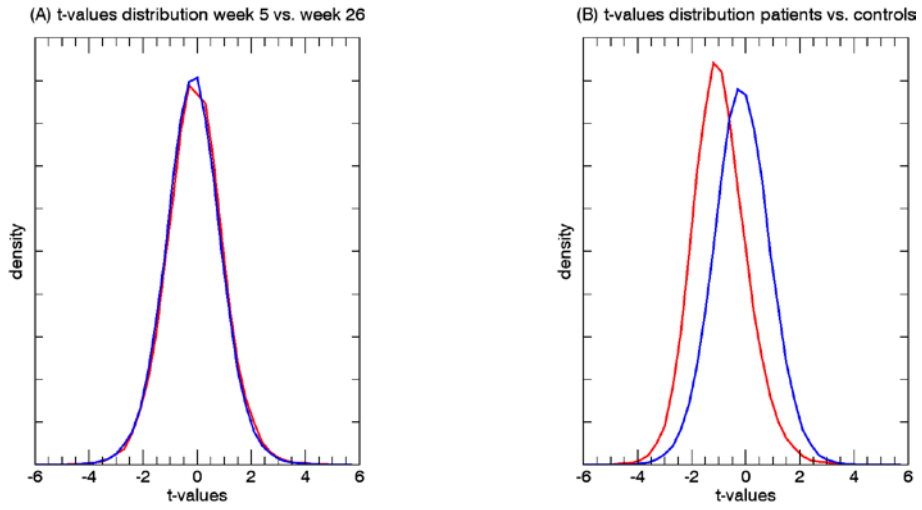

Figure 4. A. Density of t-value distributions for the patients for week 5 versus week 6. B. Density of t-value distributions for the patients versus healthy controls. For both comparisons, the distributions are largely comparable.

When comparing all connections between patients (week 5 post-stroke) and healthy controls, we found that a total of 4 out of the 29890 connections were significantly decreased in patients. None of the 29890 connections showed a significant increase compared to healthy controls (Figures 4B, 5 and 6).

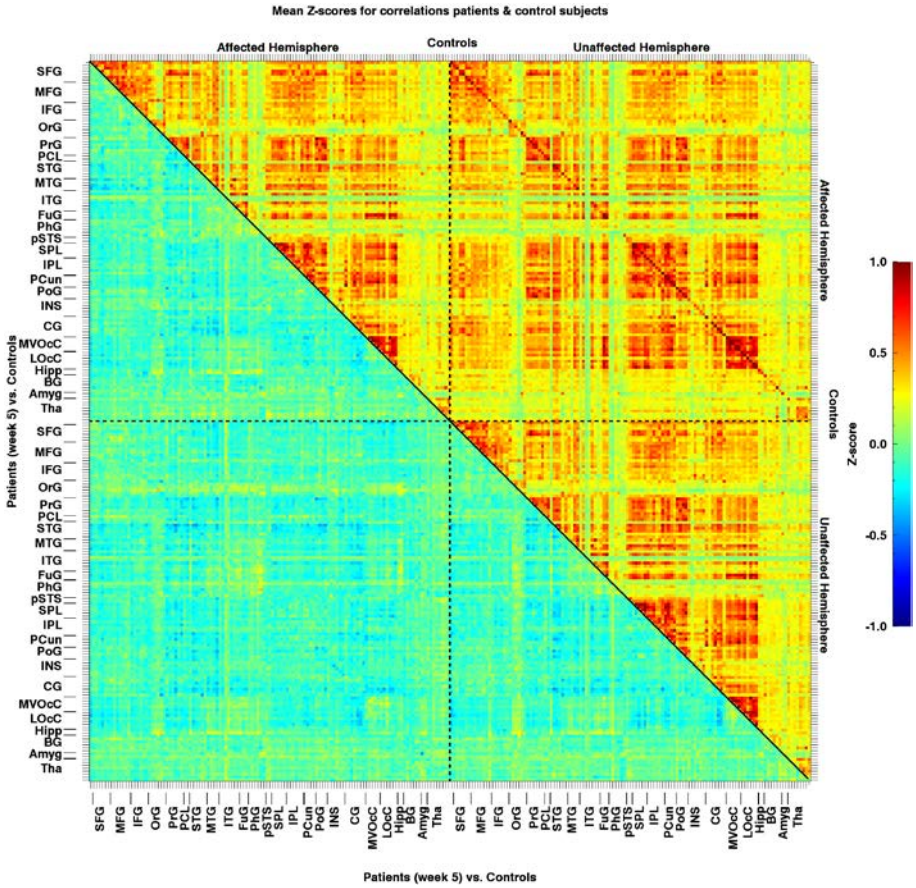

Figure 5. Mean resting-state Z-transformed correlations for patients at week 5 (n=13) vs. control subjects (n=13) between all regions of interest. The matrix area on the top right of the diagonal represents the correlations for control subjects, while the area on bottom left represents the difference in correlations between patients at week 5 and healthy controls. The colour representation of the values was clipped beyond -1 and 1.

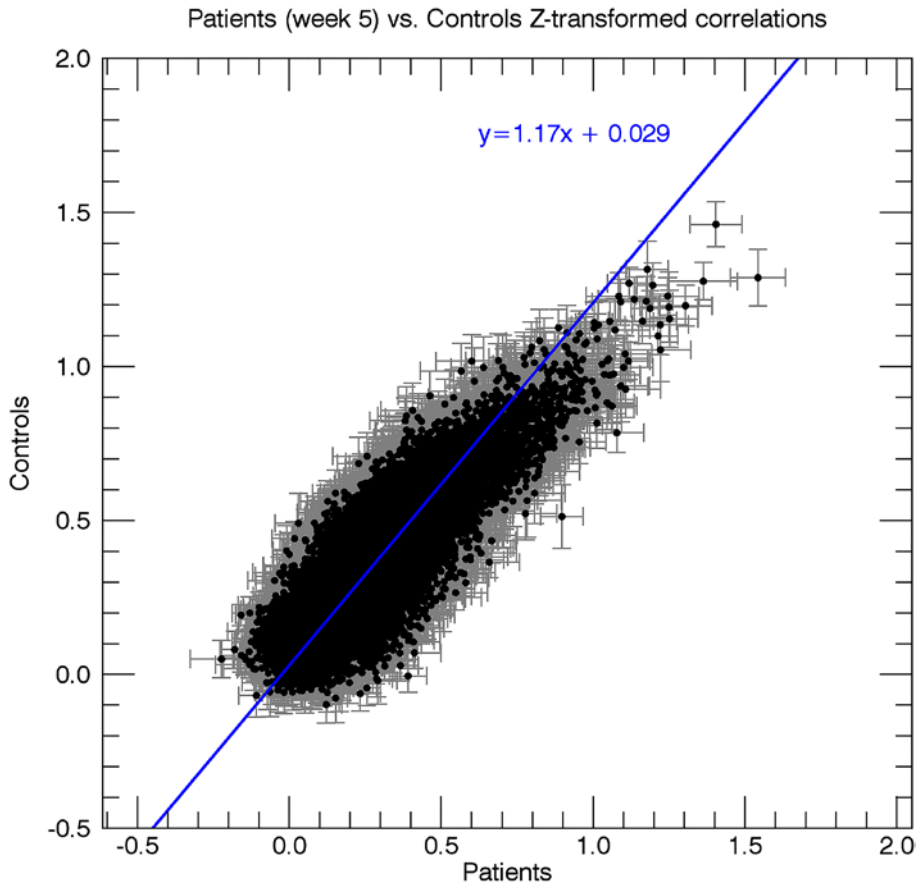

Figure 6. Scatterplot of the resting-state correlations in the patients at week 5 vs. healthy controls. Every data point in the graph represents an ROI pair, with the x-coordinate indicating the mean Z-score (n=12) for the correlation between the two ROIs for patients at week 5, and the y-coordinate indicating the mean Z-score between the two ROIs for control subjects. Grey bars indicate the standard error of the mean for patients at week 5 (horizontal bar) and healthy controls (vertical bar). The blue line depicts a straight line fit through the data points.

Discussion

The aims of the present study were fourfold: to investigate (1) time-dependent changes in rs-functional connectivity of motor networks in stroke patients; (2) the relation between magnitude of time-dependent changes in rs-functional connectivity and time-dependent changes in motor impairment as measured with the FMA-UE in stroke patients; (3) potential differences in rs-functional connectivity between stroke patients (at 5 weeks post-stroke onset) and healthy control subjects; and (4) potential changes in connectivity outside the motor system in stroke patients.

In stroke patients, the ipsilesional rs-functional connectivity between motor areas was lower compared to the contralesional rs-functional connectivity, but this difference did not change over time. No relations were observed between individual changes in rs-functional connectivity and upper-limb motor recovery, despite changes in upper-limb function as measured with the FMA-UE. Last, overall rs-functional connectivity was comparable for patients and age- and gender matched healthy control subjects.

There are a few possibilities for the observed discrepancy between changes in upper-limb motor recovery and the lack of significant changes in rs-functional connectivity. First, the improvement over time was 4 points on the FMA-UE, which is a 6% change of the maximum possible score of 66 points over time. Such a percentage is often considered not to be clinically relevant (Duncan et al. 1983; Sanford et al. 1993; Gladstone et al. 2002), stressing the importance of caution on interpreting these effects at the behavioural level. Second, spontaneous neurobiological recovery as reflected by improvements in FM-arm motor scores (Buma et al. 2013), is mainly restricted to the first 5 weeks post stroke in patients with moderate to mildly paresis (Kwakkel et al. 2006). We assume that structural changes leading to improvements in rs-functional connectivity occur in the same time window, prior to the first rs-fMRI measurement at 5 weeks post-stroke. (Wang et al. 2010; Park et al. 2011; Golestani et al. 2013; Xu et al. 2014). The lack of significant changes in rs-functional connectivity is also in line with our longitudinal kinematic studies in which we found that improvements in intra-limb coordination dynamics are mainly restricted to the first 5 weeks post-stroke, whereas minor improvements are found beyond this time window of spontaneous neurobiological recovery (van Kordelaar et al. 2013; van Kordelaar et al. 2014).

For further interpretation of our results, it is important to realise that previous studies that showed large significant changes in functional connectivity were mainly based on populations of severely affected patients (Xu, Qin, Chen, Jiang, Li, Yu, 2014). Our patient population presented with mild upper-limb impairments and could therefore only show a limited amount of improvement (i.e. ceiling effect). The changes in brain activation patterns (i.e. cerebral reorganization) may therefore have been smaller in our patient population in comparison to a population of severely impaired patients. Furthermore, most studies reporting significant correlations between cortical reorganization and functional upper-limb recovery used task-related brain activation during active motor tasks (Ward Brain 2013). One might argue that task-related activity represents a more direct measure for identifying changes in brain activity patters in relation to upper-limb recovery in mild to moderately impaired patients. However, as task performance is more difficult to control for as compared to compliance with rs longitudinal changes can be confounded by differences in quality of motor performance while executing a task. Another study in this cohort indeed demonstrated that motor abnormalities during grasping are subtle, with patients compensating for the deficit instead of actually showing true neurological recovery of neurological impairments (Buma et al., 2016). In other words, changes in motor task fMRI might thus reflect behavioural compensatory mechanisms rather than behavioural restitution of neuronal deficits.

We found hemisphere specific abnormalities; the connectivity within the affected hemisphere was lower when compared to the unaffected homologue at 5 weeks post-stroke. This difference between the affected area and the unaffected homologue did not change over time. Additionally, comparing patients at 5 weeks post-stroke with age and gender-matched healthy control subjects revealed only 4 significantly decreased correlations in the patient group out of the 29890 correlations.

The present study had some limitations. First, the sample of stroke patients was relatively small. This most likely has had an effect on the power needed to find potential differences. Second, our moderately impaired stroke patients were required to have some remaining hand function (i.e. still be able to perform voluntary flexion and extension of the fingers of the paretic upper-limb) for the task-fMRI subproject of the EXPLICIT-stroke trial, so current results may not be generalizable to patients with more severe stroke (Kwakkel et al. 2008). Despite these relatively mild impairments, the abnormality in ipsilesional connectivity was significant. Third, the

cerebellum has been found to play an important role in the compensation of motor impairment. In our sample of patients, however, the cerebellum was not included in the MRI scans in all patients. Therefore, we were unable to include the cerebellum in our analyses. An additional shortcoming is the relatively small magnitude of upper-limb recovery between week 5 and week 26. The changes in FMA-UE was largest in between week 1 and 5 (28 points on average), but no rs-fMRI data were collected at week 1. The observed changes in fMRI connectivity may thus not represent the full range of post-stroke changes. Importantly, although the improvement between week 5 and 26 was mathematically significant, it was not regarded as clinically significant. Last, the disturbance in rs-activity early after stroke may reflect functional dysfunction caused by interhemispheric diaschisis (Feeney and Baron 1986; Andrews 1991) Xu and co-workers (2014) found a decreased interhemispheric functional connectivity between the ipsilesional and contralesional primary sensorimotor cortex early after stroke onset which increased to near normal levels after 3 months post-stroke onset. In our sample, potential large scale disturbances in rs-activity after stroke were not present at 5 weeks after stroke. We did not, however, measure rs-activity earlier than 5 weeks post-stroke onset.

To investigate the differences in cerebral reorganization between subgroups, future studies should include a larger population of stroke patients with various degrees of functional motor impairment. As most spontaneous neurobiological recovery occurs within the first 8-10 weeks post-stroke (Kwakkel 2006), and is assumed to be the main driver for recovery of structural connectivity early post stroke, we recommend rs-fMRI measurements preferably should start within the first weeks post stroke with frequent follow-up measurements at fixed time-points, at least up to 3 months after stroke onset.

To conclude, the current findings did not provide evidence that in moderately impaired stroke patients the lower rs-functional connectivity of the ipsilesional hemisphere changes over time.

Acknowlegdements: The EXPLICIT-stroke research project is supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw; Grant No. 89000001).

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Chapter 6

Summary, General Discussion, Future perspectives

Scope of this thesis

Stroke is the leading cause of disability. However, patients may show excellent functional recovery despite severe initial impairment in the first days post stroke (Krakauer, 2015; Winters et al., 2015). In the past few years there has been an upsurge of studies across neurological disorders that have tried to find indications of beneficial neuronal plasticity, i.e. changes in brain function related to improved neurological functioning, in an attempt to identify new therapeutic targets. In stroke literature, such a beneficial reorganization of brain activity and connectivity has indeed been a hot topic. Unfortunately, the functional significance of many of the brain changes observed on MRI remains unclear; it has been difficult to relate some of those changes to functional preservation and recovery. Therefore, the first main question remains: How does brain plasticity interact with spontaneous neurobiological recovery and contribute to functional improvement post stroke. The second key question is, Can these natural processes of neurobiological recovery influenced by neurorehabilitation?

The studies described in this thesis are part of the multicenter EXPLICIT-stroke program conducted from 2008 (Kwakkel et al., 2008) to 2016 (Kwakkel et al, 2016), which comprised five parallel running sub-studies investigating: longitudinal brain changes related to spontaneous recovery early after stroke, recovery of upper limb coordination, the added value of transcranial magnetic stimulation, recovery of muscle stiffness and the effect of intervention with physical therapy. The projects described in this thesis were centered on the first two parts of the trial only. As such, the overall aim of this thesis was to investigate changes in brain function related to motor impairment as well as functional recovery in stroke patients (measured with clinical measures and kinematics).

After introducing the topic, Chapters 1 to 5 describe the results of two (systematic) reviews and three experimental studies in patients with stroke. These are discussed in this Chapter, as well as methodological considerations and the concept of neuroplasticity. The Chapter ends with general conclusions and new research questions following from this thesis.

Outline Chapter 6 and research questions

- 6.1 Chapter 1 and 2: Reviews of literature
  - What is the current state of knowledge on the mechanisms underlying recovery in stroke? A narrative review
  - What is the current state of knowledge on longitudinal studies investigating recovery in stroke? A systematic review

- 6.2 Chapter 3: A cross-sectional study in well recovered patients compared to healthy controls
  - Is normal performance of a motor task in recovered stroke patients accompanied by an altered brain activation pattern compared to controls?

- 6.3 Chapter 4: A longitudinal study in the first six months after stroke
  - How are changes in quality of movement related to changes in brain activation patterns in the first six months after stroke?

- 6.4 Chapter 5: A longitudinal study, in the same population as Chapter 5
  - How is impairment after stroke related to difference in functional connectivity?

- 6.5 Future perspectives

- 6.6 Conclusions and new research questions

6.1 Why study brain function in stroke?

What is the current state of knowledge on the mechanisms underlying recovery in stroke? A narrative review

As reviewed in Chapter 1, functional recovery through motor compensation at an activity level 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, recovery at 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, Jacobs, Roby-Brami, & Levin, 2004) .
Obviously, both situations, i.e. behavioral 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. This also indicates that without quantifying the quality of task performance, it is not possible to delineate 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, Kleim, & Wolf, 2009). It is unclear from the literature, both on animals and humans, to what extent the improvement in motor performance by the affected arm itself is caused by true neurological repair or by learning compensation strategies. While much can be learned from animal studies caution must be taken in translating these results to humans. Animal stroke models are mostly based on cortical stroke, whereas subcortical stroke is much more common in humans. Exercise therapy used in animal studies does not easily translate to human studies on task specificity as well as dose which is much higher in the animals than feasible for humans (Krakauer et al., 2012; Lang et al., 2009; Remple, Bruneau, VandenBerg, Goertzen, & Kleim, 2001)

What is the current state of knowledge on longitudinal studies investigating recovery in stroke? A systematic review

The field of neuroimaging in stroke has grown exponentially over the years. In a systematic review described in Chapter 2, generally most papers aim to find changes in task-related brain activation that are related to recovery after stroke. Many studies have previously demonstrated a relationship between fMRI brain activation and post-stroke outcome in patients with infarcts that spare M1. While the outcome of these studies varies, good recovery of motor performance has generally been associated with a preservation or restoration of activity in the ipsilesional hemisphere (Buma, Lindeman, Ramsey, & Kwakkel, 2010; Calautti & Baron, 2003; Ward, 2005; Ward, Brown, Thompson, & Frackowiak, 2003b). Sustained elevated task-related activity in the non-affected hemisphere has been associated with poor outcome (Buma et al., 2010; Carey, Abbott, Egan, Bernhardt, & Donnan, 2005; Dong, Winstein, Albistegui-DuBois, & Dobkin, 2007; Ward, 2005; Ward, Brown, Thompson, & Frackowiak, 2003a). Elevated recruitment of secondary and bilateral motor areas has been interpreted as

a reflection of compensatory strategies of motor control in patients who show poor recovery after stroke (Maier et al., 2002; Ward, 2007).

Conclusion

In humans there is no evidence that neural tissue that has degenerated by the infarct is regenerated during recovery. Therefore any plasticity-related neural mechanisms found must be compensatory by default.

It is therefore vital that the performance quality of movement is taken into account (by kinematic assessment) for correct interpretation of imaging studies. And since these adaptive strategies will be dependent on the site and extent of the damage in the brain, these measurements should be serial to be able to interpret changes in quality of movement in relation to brain activation patterns.

6.2 Brain activation patterns in stroke patients compared to controls

Is normal performance of a motor task in recovered stroke patients accompanied by an altered brain activation pattern compared to controls?

While there is the impression that changes in task-related brain activation are related to recovery after stroke, it was our feeling that these could also be caused or at least majorly confounded by compensatory strategies and mirror movements exerted during measurements in the scanner. As such in Chapter 3, we measured 20 chronic stroke patients (>6 months after stroke) and 15 healthy aged-matched controls. These patients exhibited various degrees of post-stroke outcomes with reduced scores on upper limb function, mainly on NHPT, and mildly so on the FM and ARAT. All subjects underwent functional imaging during a finger extension and flexion task, after which we compared activation patterns to controls. Our results showed no difference in brain activation between patients and healthy controls, and both groups performed comparably (measured with EMG and movement tracking in the scanner). This was the case for a voxel-wise whole-brain analysis as well as a region of interest analysis constrained to the motor network. In addition, the level of brain activity and functional impairment of the upper limb were not related, in spite of the fairly wide range in outcome on the nine-hole-peg-test NHPT (%NHPT 18–125%).

In summary, even though multiple patients in the present study still showed significantly reduced speed of the upper paretic limb as reflected by reduced NHPT-scores, however, none were abnormal compared to

controls on the task performed during MRI, measured with EMG and a kinematic glove. This task also did not induce detectable signs of altered activation in primary or secondary sensorimotor areas or elsewhere in the brain. These results therefore indicate that patients with good outcomes at >6 months after stroke do not show increased brain activation in secondary sensorimotor brain areas that were found patients in earlier stages after stroke, suggesting that any differences in brain activity are temporary at best in patients who recover well.

Methodological considerations

It is possible during the relatively simple fMRI task, that minimal motor output is sufficient for performance in stroke patients with residual impairment in motor function. However, with higher demands on the sensorimotor network (e.g. during the NHPT), the brain may switch to a new strategy that includes compensatory mechanisms. This was previously shown in patients where a higher exerted force induced higher activation in secondary motor areas (Ward, 2007; Ward et al., 2003b). Higher motor demands however, also might induce compensatory mechanisms in the musculoskeletal system by causing the intended action to be performed with different motor strategies (van Kordelaar et al., 2012; Ward et al., 2003b). These patients would most likely perform the task less well or in a different way using alternative strategies (Kwakkel, Kollen, & Lindeman, 2004). Additionally, putting more strain on the motor system would reveal more about the function of the damaged brain, but simultaneously insert more chance of confounding factors such as mirror movements and differences in task compliance.

Conclusion

To understand more about how activation in the brain is related to learning of compensation mechanisms in motor performance stroke patients, measuring the quality of movement in addition to task-related activity would be valuable. What we have learned from this study is that patients who perform well on a single motor task and show no concurrent deviating brain activity as measured with fMRI, may still show inaccuracies in motor control as revealed by the reduced speed scores following the NHPT as well as visible lesions in the T1-weighted images in MRI-scans. Although these deficits in sensorimotor control are subtle, it would be interesting to investigate further how the brain adapts to damage over time and how this affects quality of movement.

6.3 Brain activation changes in more disabled patients, measured over time

How are changes in quality of movement related to changes in brain activation patterns in the first six months after stroke?

Based on the results of Chapter 3, we had clear indications that we needed to measure sooner after stroke, preferably when patients are within the window of spontaneous processes of neuronal recovery. Additionally, we wanted to evaluate whether measuring the quality of movement would be of added value for understanding brain plasticity. The main objective of this study was to investigate how recruitment of sensorimotor areas is associated with quality of motor control after stroke.

We applied a comparable fMRI task for the previous study, focusing on finger extension, but also measured kinematics during hand reaching tasks outside of the scanner, in 17 mildly disabled patients at 6 and 28 weeks after stroke. Using 3D kinematics, the quality of motor control was assessed by smoothness of the grasp aperture during a reach-to-grasp task. Results showed no changes in brain activation over time, although deficits in the smoothness of movement improved significantly. At baseline, a higher recruitment of secondary motor areas was associated with a reduced smoothness of movement. A reduced smoothness is represented by change in acceleration during the performance of the task.

We interpreted the recruitment of additional sensorimotor areas during the motor task in the scanner as a type of control in which deviations from an optimal movement pattern are continuously corrected. This interpretation suggests that additional recruitment of sensorimotor areas after stroke is likely to represent adaptive motor learning strategies in order to compensate for motor impairments. Especially since studies have also shown that the level of activity in the contralesional hemisphere early after stroke is associated with reduced functional capacity as indicated by poor performance on clinical assessment scales, which could be interpreted in a similar way (Buma et al., 2010; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012; Ward, Brown, Thompson, & Frackowiak, 2004). In addition, previous studies have shown that during finger movements the premotor cortex seems to be more involved in patients with stroke as compared to healthy subjects (Johansen-Berg et al., 2002) and is associated with a higher cognitive demand (Dennis et al., 2011)

A limitation of this study was that the flexion-extension task that was administered in the scanner in the study described in Chapter 5 differed from the reaching task during the 3D kinematic measurements. Therefore, control strategies may have differed between the fMRI and 3D kinematic measurements. For instance, patients were able to rely on visual feedback during the kinematic measurements, whereas this was not possible during fMRI scanning.

Conclusion

The present study suggests that the observed increased contribution of the premotor cortex is not related to improved quality of motor control. What remains unclear however, is whether the altered smoothness is due to activation related to increased reliance on enhanced visual and proprioceptive feedback mechanisms instead of feedforward mechanisms seen in healthy subjects, to perform the requested movement. Obviously, additional recruitment of associated motor areas such as premotor and cerebellum are needed to optimize the requested task. It is tempting to think that the brain is able to compensate for damage (and being 'plastic' in that sense). Alternatively, one may also hypothesize that this relation could be a sign of maladaptive activity or an epiphenomenon caused by reduced inhibitory (GABAergic) pathways causing release and unwanted jerky movements.

Interestingly, several other kinematic studies have shown that the ipsilesional upper limb is also impaired in function especially when it comes to quality of movement. The ipsilesional hand moves less smooth than controls (Metrot et al., 2013; Noskin et al., 2008). This would indicate that impairment after stroke is dependent on the state of the whole brain and not only a focal issue due to the lesion.

6.4 Brain connectivity after stroke

In this study, we investigated spontaneous motor recovery by looking at functional connectivity changes in the whole brain and in the motor network specifically. The aims of the study were to map network changes at baseline and over time in stroke patients, and to relate these to changes in motor impairment in a subset of the study mentioned above.

In the ipsilesional hemisphere rs-functional connectivity between motor areas was significantly lower when compared to contralesional rs-functional connectivity, however, this difference did not change significantly over time

from 5 weeks onwards post stroke. No relationship was observed between altered connectivity and upper-limb motor recovery, despite significant within-subject changes in upper-limb function as measured with the FMA-UE, which showed an average improvement in upper-limb function of 4 points (FMA-UE; Z = -2.32, p =.020 (two-tailed). However this difference is not large enough to be a clinically meaningful difference at impairment level.

The hemispheric difference that we observed was from 5 weeks onwards after stroke, and showed no detectable change up till 6 months post-stroke. No difference had been found between controls and patients in overall RS connectivity however. This might be due to the small sample size and the fact that variation between subjects is possibly too high to detect a subtle difference. It would be interesting to see whether this difference in connectivity between hemispheres was present or even more pronounced before 5 weeks after stroke and how these dynamics may parallel spontaneous neurobiological recovery.

Patients in our resting state study described in Chapter 5 were required to have some remaining hand function at 1 week after stroke (i.e. still be able to perform voluntary flexion and extension of the fingers of the paretic upper-limb) for the task-fMRI subproject of the EXPLICIT-stroke trial, which may have limited the chance to observe change as well as excluding more severe upper-limb impairments in the first week after stroke (Kwakkel et al., 2008).

6.5 Future perspectives

Literature on longitudinal fMRI in stroke patients within the first 6 months after stroke has shown dynamic changes in brain activation over time in response to motor recovery (Buma et al., 2010). However, while subtle changes as a reflection of learning might happen in response to training, in my point of view these changes are always a reflection of compensatory or learning behavior.
We have found this in our subset of patients in relation to smoothness of movement (Chapter 4). Patients that are well recovered and only show little residual impairment do not show any differences in brain activation patterns when asked to perform a simple motor task (Chapter 3). Finally there seems to be a global signal difference in the motor network between

the ipsi- en contralesional hemisphere in well recovered patients, where the ipsilesional hemisphere shows lower connectivity (Chapter 5).

If the imaging field keeps measuring well recovered patients using simple tasks, we are only scraping the surface of what might be driving recovery after stroke, and of what residual impairment looks like after stroke. In the following paragraphs I will explain the rationale behind this notion and give direction for future research.

New insights into: what drives spontaneous neurobiological recovery in which patients?

Prevention of damage by reperfusion of the ischemic brain is still the best treatment for stroke (Wardlaw, Murray, Berge, & del Zoppo, 2014). However, most patients still end up with disabilities following stroke. With intensive physical therapy treatment recovery after stroke can be accelerated but not improved beyond spontaneous neurological recovery (Kwakkel et al., 2016). The main driver of observed recovery of neurological impairments after stroke is spontaneous neurobiological recovery (Kwakkel et al, 2004). As a consequence, progress of time as a reflection of spontaneous neurobiogical recovery explains about 80 to 90% of sensorimotor recovery (Kwakkel et al, Stroke 2006; Buma et al, 2013) and cognitive impairments (Nijboer et al, Cortex 2013). Unfortunately, no interaction effects are found with impairment focused therapies till so far (Buma et al, 2013; Byblow Ann Neurology 2015; Kwakkel et al, Lancet Neurol 2015) Also the EXPICIT-trial failed to show significant effects of early started therapies such as EMG-NMS and mCIMT in terms of neurological impairments. In addition, recent prospective cohort studies showed that this spontaneous neurobiological recovery of motor impairment (Prabhakaran et al, 2008; Winters et al, 2015), aphasia (Lazar et al, 2010) and neglect (Winters et al, 2017) is highly predictable following the 70% recovery rule (Ward et al, 2017) Therefore, the holy grail of further stroke research in animal studies (Corbett et al, 2017) and humans (Boyd et al, 2017) is to find the biomarkers that drive spontaneous neurobiological recovery after stroke (Ward et al, 2017). In particular the 20 to 30% of patients with an initially more severe paresis (i.e., FM-UE scores < 18 points within first 72 hours) or neglect (i.e., 16 missing O's out of 20 within the first week post stroke) who fail to show spontaneous neurobiological recovery (Kwakkel et al., 2016; Winters, van Wegen, Daffertshofer, & Kwakkel, 2015; Winters et al, 2017; Winters et al, 2017). Recently, it has

been shown that patients who do not follow the proportional recovery rule for motor impairment (i..e, non-fitters) after a first-ever hemispheric stroke are the same patients who also fail to recovery for other modalities such as neglect (Winters et al, 2017) This finding suggests that spontaneous neurobiological recovery is irrespective of modalities involved and already defined within the first days after stroke onset. More importantly, due to the lack of prospective valid biomarkers of spontaneous neurobiological recovery, the (non-)fitters can be identified only retrospectively. This is something that hinders stratification for designing adequate phase II trials in stroke rehabilitation (Winters et al, Trials 2016) and may explain the many neutral trial published recent years that were often designed to find small treatment effects in neurorehabilitation.

The questions that arise from these insights in terms of designing new imaging studies are twofold 1) Can we use structural and functional imaging techniques to identify neurological biomarkers that explain the difference between the fitters and non-fitters? These biomarkers could for example be identified as a specific lesion location and difference between cortical and subcortical or pontine strokes. The network dynamics of the recovery in brain in rest and its relation with structural damage could be an equally importer biomarker. 2) Why is the brain only able to recover up to a proportion of initial impairment and when challenged what are the characteristic of that residual impairment exactly?

Can we use structural and functional imaging techniques to identify neurological biomarkers that explain the difference between the fitters and non-fitters?

Structure

What is the relationship between structural white matter damage and function en how does this interact with network dynamics in the first days and weeks after stroke? CST integrity, measured with MEPS, after stroke has shown to predict which patients will show proportional recovery (Byblow et al., 2015) independent of upper limb therapy dose. Patients who do not show functional intactness of CST are not likely to regain any function in the upper limb (Nijland, van Wegen, Harmeling-van der Wel, Kwakkel, & Investigators, 2010). This suggests that the brain is not able to overcome severe damage to specific areas in the brain, areas that are

widely connected to other parts of the motor network. Apparently there is a 'tipping point', or a point of no return, where damage in the brain cannot be compensated by the motor network and function collapses. However early after stroke MEPs or the inability to provoke MEPs should be interpreted with caution. The influence of edema and area of the penumbra may either increase or block the conduction of the CST or excitability of the cortex (Escudero 1998; Piron 2005). How structural damage changes over time is still unclear and the interaction between structural integrity and function is interesting to explore further by using T1 scans and DTI to assess the structural integrity of the white matter tracts as well as studying network behavior throughout the whole brain (Silasi & Murphy, 2014).

Function

One explanation of spontaneous neurobiological recovery could be alleviation of cerebral 'shock' or suppression. In particular taking into account that penumbral tissue is already defined as infarcted or non-infarcted brain areas within the first 6 hours post stroke as revealed by rTPA and thrombectomy. Diaschisis is a term devised by Von Monakow over a hundred years ago and was described as a state of shock in areas anatomically connected to a focal lesion. Diaschisis can be seen as metabolic as well as functional de-afferentiation of connected areas after stroke, which causes an initial massive collapse of neural output, which is reversible (Rehme G2012). Connectional diaschisis (Carrera Brain, 2016) is a term that is gaining more attention in literature (Fornito, Zalesky, & Breakspear, 2015). It entails functional changes in connecting brain areas or networks (either hyperactivity or decreased activity) to the ischemic area in the brain. Network measures and the notion network collapse especially, are gaining interests in others fields such as MS and tumor research (Fornito 2016). The disturbance in resting state activity early after stroke may reflect functional dysfunction caused by interhemispheric diaschisis (Andrews, 1991; Feeney & Baron, 1986). For instance, Xu and co-workers (Xu et al., 2014) found a decreased interhemispheric functional connectivity between the ipsilesional and contralesional primary sensorimotor cortex early after stroke onset which increased to near normal levels after 3 months. What is interesting and has been mentioned earlier in this discussion is that the ipsilesional upper limb moves less smooth than

controls (Bustren, Sunnerhagen, & Alt Murphy, 2017; Metrot et al., 2013; Noskin et al., 2008). This would indicate that the behavior of the brain after stroke seems to be dependent on the state of brain beyond the areas around the lesion itself. Task related activation is sometimes hard to measure in poorly recovering patients, and higher task demands will induce compensatory behavior especially in patients that are severely impaired.
The lack of a longitudinal change in Chapter 4 is an indication that measuring even earlier after stroke onset is necessary, as most improvements in motor function often occur very early after stroke onset (Golestani, Tymchuk, Demchuk, Goodyear, & Group, 2013; Park et al., 2011; Wang et al., 2010; Xu et al., 2014). However, fMRI scanning is often too much of a burden for patients especially in the early days after stroke. After a few days patients are transferred to the rehabilitation facility after which transporting them to and from the hospital to receive fMRI scanning is very burdensome. Early monitoring of recovery (< 7 days) by task independent measures of the brain might shed a light on the dynamics of intracortical connectivity (Xu et al., 2014) as compared to healthy controls. This should be done serially in time with the first measurements in the first days post stroke preferably at the bedside by for example portable EEG. It might then even be possible to find differences between stratified patient groups that predict outcome after stroke and look at the difference between recovery and non-recovery patients. Since a lesion disrupts not only activity in the ischemic area and surrounding penumbra but also all communication to and from the lesion, connectivity analysis is a nice way to investigate the following research question: what are the dynamics of network changes in response to an ischemic lesion and is there a relationship with recovery profiles?
Several interesting subquestions can proposed in understanding the concept of alleviation of diaschisis after stroke: 1) Is this the main driver of spontaneous recovery beyond the first days after stroke? 2) Why would recovery of these suppressed networks take several weeks, if neuronal impairment is just a 'shock' reaction to a sudden damage? 3) Is there any interaction in humans between spontaneous biological recovery and early started intensive impairment-focused stroke rehabilitation?

Why is the brain only able to recover up to a proportion of initial impairment and when challenged what are the characteristic of that residual impairment exactly?

As mentioned earlier in this discussion as well as following from the results in chapter 3, over-activation of brain areas seems to be related to lower

quality of movement. However there is no direct relationship found yet, nor has it given insight into the mechanism of regaining brain function after stroke. The relationship between brain activation and motor function should preferably be measured directly in real time, with for example EEG or TMS coupled with a difficult task with simultaneous kinematic measurements of the system to investigate the influence of compensatory behavior on brain activation in stroke patients as well as controls (Casellato et al., 2010; Kwakkel et al., 2004; Kwakkel et al., 2008). Furthermore, if we want to know what is the effect of residual impairment in the brain, we need to know how the injured brain handles a more challenging motor task compared to controls. There is evidence that patients have trouble performing two tasks at the same time (Yang, Chen, Lee, Cheng, & Wang, 2007). Understanding how the system reacts to greater strain in patients that obey the proportional recovery rule, will give insight in how isolated clinical measures of upper extremity function might overestimate recovery of the brain. Patients often report not being able to walk and talk at the same time (Al-Yahya et al., 2016). Measuring upper-limb function in an isolated way will reveal the intactness of the CST in performing such a task, however does not reveal the attention and reliance on other brain networks needed to perform well. Quality of motor control is hypothesized to be reduced by dividing attention in a dual task paradigm, i.e. by adding increased strain using additional cognitive load to a task while still controlling movement in the scanner.

Future studies in imaging the brain after stroke should focus on finding out 1) what happens to brain function and structure in response to ischemic damage in the first few days to weeks after stroke irrespective of task performance, and what is the difference between fitters and non-fitters of the proportional recovery rule, and 2) what is the nature of residual impairment and which subtle changes in the brain are visible when we challenge the well recovering brain across modalities as well as controls while still monitoring quality of movement in both groups.

6.6 Conclusion

In general the brain seems to be quite invariant in response to initial damage beyond 5 weeks after stroke and is nicely able to substitute for residual damage either by a different use of end effector or by more subtle compensation (top down control, using more feedback, more attention). However the massive reduction in function that is seen hours after stroke is more likely not to be a result of actual neuronal damage but to be a result of functional deafferentation of all connected areas to the infarcted area as well as the consequences of reversible mechanism such as disruption in the blood brain barrier, edema, inflammation in the surrounding penumbra (chapter 1).

Unfortunately at this moment there is no evidence that rehabilitative interventions including exercise therapy are able to promote behavioral restitution and true neurological repair beyond still poorly understood mechanisms of spontaneous neurobiological recovery (Kwakkel, 2016).
The goal of future imaging studies should be indeed clearly oriented towards understanding the difference between adaptive processes due to residual damage in the brain as well understanding spontaneous neurological recovery how much of this is alleviation of diaschisis, or some form of repair of neuronal function. What factors define what patients show recovery and what patients will not.

In general stratifying patients based on their potential for recovery rather than severity of damage will be beneficial in finding appropriate therapies for these groups of patients and eliminate recovery potential as confounding factor in trials. What mechanisms underlie potential for recovery and in the same vein what defines damage after stroke should be the main questions.
The proportional rule of 70% recovery shows that most patients learn within the constraints of damage and there is no known way to influence beneficial brain plasticity in a way that it can rise above damage that has been done (Prabhakaran et al., 2008). At the moment it is not clear who we need to treat and at what time (Langhorne, 2012). In designing new trials it is therefore certainly important to be aware of the different recovery profiles that patients show (Winters, Heymans, van Wegen, & Kwakkel, 2016). These future studies can only be successful if there is intensive collaboration by setting up a worldwide network of stroke research so larger cohorts can be measured. Combining imaging data by collectively using standard protocols will improve the sample sizes needed for

statistically well powered studies especially in imaging research. Patients show a wide range of recovery profiles (some proportional some not) and at the moment it is unclear how these profiles are specifically related to actual brain function (Bernardt, 2016).

Researchers should be aware when, which, and how patients are measured to identify biomarkers for future stroke research.

Point by point summary of most important conclusions and suggestions for future research:

Chapter 3. Correlations of functional neuroimaging and outcome

- no difference in brain activation was found between patients with moderate residual motor impairment after stroke and healthy controls during a simple task
- task performance in the scanner was equal for patients and controls in rate of movement as well as presence of mirror movements

Chapter 4. Correlations of functional neuroimaging and recovery

- patients' grasping movements became smoother over time after stroke, rate of recovery was highest between 1-6 weeks, lower between 6 and 26 weeks
- no significant change in task related brain activation was found between 6 and 26 weeks
- a smoother hand-opening during a reaching task (more automated movement) was associated with less activity in bilateral cerebellum, and accessory motor areas

Chapter 5. Functional connectivity during motor recovery

- connectivity in the lesioned hemisphere was lower in patients than in the non-lesioned hemisphere
- no change in functional connectivity was found
- no difference in whole brain connectivity between patients and controls was found

Future research:

- Identify biological and neurobehavioral markers that define spontaneous neurobiological recovery. in more recovered stroke patients try to be more demanding on the network and offer dual task for example to see how the motor network reacts to residual damage
- the relationship between brain activation and motor function should preferably be measured directly in real time, with for example EEG or TMS coupled with kinematic measurements or robotics perturbations of the system to investigate the influence of compensatory behavior on brain activation (compensation and behavioral restitution)
- early monitoring of recovery < 7 days by task independent measures of the brain preferably noninvasive and bedside (like EEG)(Xu et al., 2014) to investigate the nature of spontaneous

recovery by assessing network characteristics in controls, and stratified patient groups

Methodological Recommendations

- Due to the high variability and noise in brain imaging data, a control group should be included for all longitudinal data, also since motor learning and plasticity (in sense of recovery) are so closely related.
- Task-related imaging based on performance of a precisely defined voluntary motor paradigm will always exclude patients that show more severe impairment. As a consequence, fMRI findings lack generalizability to more severely affected stroke patients.
- In addition, motor paradigms used for fMRI in a selected group of stroke patients may not distinguish sufficiently between full recovered stroke patients and those with minimal impairments. In addition, the interpretation of fMRI findings post stroke is dependent on time post stroke.
- Use large international cohorts of patients to be able to stratify patients based on observed outcome and predicted outcome.

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Chapter 7

Appendix

Nederlandse Samenvatting
Dankwoord
List of Publications
Curriculum Vitae

Nederlandse Samenvatting

Een beroerte is een van de belangrijkste oorzaken van invaliditeit in de westerse samenleving. Ongeveer 40 procent van de mensen dat een ischemisch infarct krijgt, heeft blijvende schade aan de functie van de aangedane arm. Toch treedt bij de meeste patiënten rond de 70% van hun maximale mogelijkheid tot herstel op in de eerste weken na een cerebrovasculair accident (CVA). In die eerste weken na zo'n CVA proberen de hersenen de schade te beperken en wellicht zelfs te herstellen. Er vindt een cascade aan processen plaats, geleid door verschillende eiwitten die effect hebben op het gebied direct rond het infarct en daarbuiten (penumbra). Deze processen zijn van invloed op de uitgroei van dendrieten, maar ook op de bloed-hersenbarrière en aanmaak van bloedvaten. De term plasticiteit wordt vaak gebruikt als parapluterm voor deze processen. Echter, de relatie tussen veranderingen in het brein en de verbetering in het aanturen van beweging is niet duidelijk. Daarnaast is veel van dit onderzoek gedaan bij muizen en ratten, waardoor dit niet direct vertaald kan worden naar mensen. Wat wel zeker is, is dat er spontaan herstel plaatsvindt van functies in de eerste 8 weken na een CVA. Dit herstel lijkt niet beïnvloed te worden door therapie. De grote vraag is natuurlijk: wat is de oorzaak van dit herstel na een CVA en is het mogelijk dit proces op een of andere manier te beïnvloeden?

Om antwoord te krijgen op deze vragen, startte 10 jaar geleden het onderzoek EXplaining PLastICITy after Stroke (EXPLICIT-stroke) (Kwakkel et al. 2008). Door in een vroege fase van herstel te meten en in te grijpen, hoopten wij dit spontane herstel te bevorderen en daarnaast te meten wat er precies via kinematica aan bewegingssturing herstelt. Hierbij waren we geïnteresseerd in het effect van het CVA op spierstijfheid via de haptic robot, en het effect op hersenactivatie (via fMRI en TMS).

De laatstgenoemde vraag wordt in dit proefschrift behandeld. Hoofdstukken 1 tot 5 van dit proefschrift beschrijven de resultaten van 2 reviews (1 systematisch) en 3 experimentele studies. Deze worden in de komende paragrafen besproken. Deze samenvatting eindigt met de belangrijkste conclusies van dit proefschrift en aanwijzingen voor verder onderzoek.

Inhoud Proefschrift en onderzoeksvragen

- Hoofdstuk 1 en 2: Literatuur reviews
  - Wat is de huidige staat van kennis over de mechanismen die ten grondslag liggen aan herstel na een CVA: een narrative review
  - Wat is de huidige staat van kennis over longitudinale beeldvormende studies over veranderingen in het brein na herstel van een CVA? Een systematische review.

- Hoofdstuk 3: Een cross-sectionele studie bij goed herstelde patiënten om te kijken of daar verschillen in taakactivatie zichtbaar zijn als de condities goed en streng gecontroleerd worden
  - Is normale uitvoering van een motortaak in herstelde CVA-patiënten gerelateerd aan een veranderd activatiepatroon in de hersenen, vergeleken met controles?

- Hoofdstuk 4: Gelijktijdig longitudinaal meten van herstel van coördinatie en hersenactivatie bij CVA-patiënten in de eerste 9 maanden na een CVA.
  - Hoe zijn veranderingen in de kwaliteit van het bewegen gerelateerd aan verandering in hersenactivatie in de eerste 6 maanden na een CVA?

- Hoofdstuk 5: Zijn er bij CVA-patiënten veranderingen te zien in connectiviteit tijdens het herstel in de eerste maanden, en is er sprake van een verschil in connectiviteit tussen gezonde mensen en CVA-patiënten
  - Hoe is verminderde handvaardigheid gerelateerd aan een verschil in functionele connectiviteit?

- Aanbevelingen voor toekomstig onderzoek, conclusies en nieuwe onderzoeksvragen

Hersenfunctie na een CVA

Literatuur reviews

Hoofdstuk 1: Wat is de huidige staat van kennis over de mechanismen die ten grondslag liggen aan herstel na een CVA: een narrative review

In dit hoofdstuk wordt beschreven dat herstel na een CVA moet worden onderverdeeld in restitutie van functies en compensatiemechanismen. Zonder het meten van kwaliteit van bewegen kan niets worden gezegd over de aard van het herstel na een CVA. Voorlopig is het nog onduidelijk of er neurobiologisch gezien echt restitutie plaatsvindt, of dat herstel altijd een uiting is van compensatiemechanismen in het brein. De vraag wat hersenplasticiteit is, en wat de functionele betekenis hiervan is in mensen, is nog niet beantwoord.

Hoofdstuk 2: Wat is de huidige staat van kennis over longitudinale beeldvormende studies over veranderingen in het brein na herstel van een CVA? Een systematische review.

In een systematisch review hebben we gekeken naar studies die longitudinaal de veranderingen in de hersenen over tijd gemeten hebben in de eerste 6 maanden na een CVA. Over het algemeen is te zeggen dat een goede uitkomst na een CVA gerelateerd is aan een zo normaal mogelijk activatiepatroon, terwijl slecht herstel gerelateerd is aan overactiviteit in secundaire en ipsilaterale motorgebieden. De functionele betekenis van deze resultaten is echter nog steeds onduidelijk. We weten niet of die reorganisatie, of veranderde activiteit, ook echt zorgt voor herstel of dat het compensatoir gedrag is. Daarnaast zijn het vaak kleine studies waarbij herstel niet op het niveau van impairment wordt gemeten en taken, uitgevoerd in de scanner, niet gecontroleerd worden.

Hoofdstuk 3: Een cross-sectionele studie bij goed herstelde patiënten om te kijken of daar verschillen in taakactivatie zichtbaar zijn als de condities goed en streng gecontroleerd worden.

Is normale uitvoering van een motortaak bij herstelde CVA-patiënten gerelateerd aan een veranderd activatiepatroon in de hersenen vergeleken met controles?

In deze studie hebben wij 20 CVA-patiënten in de chronische fase (>6 maanden) en 15 gezonde controles gemeten. De patiënten waren over het algemeen goed hersteld (FM 60.5±5.6, ARAT 56.0±2.1). We vonden geen verschil in hersenactivatiepatronen (zowel over het hele brein als in specifieke motorgebieden) tussen patiënten en controle proefpersonen en

geen relatie tussen activatiepatronen en uitkomst na een CVA, ondanks het feit dat de e nine-hole-peg-test NHPT scores een grote spreiding lieten zien (%NHPT 18-125%). We kunnen hieruit concluderen dat patiënten die goed hersteld zijn na 6 maanden na een CVA geen veranderde hersenactivatie laten zien die kan worden opgepikt met functionele MRI. De uitvoering van de taak in de scanner was goed gecontroleerd (met EMG en tracking van bewegen) en was niet verschillend tussen patiënten en controles. Het zou kunnen dat als er een meer uitdagende motortaak gebruikt wordt de subtiele verschillen in strategie tussen patiënten en controles duidelijker wordt. Hierna wilden we graag kijken naar de dynamiek van hersenactiviteit in patiënten in de vroege fase na een CVA, waarbij we ook naar de kwaliteit van bewegen hebben gekeken.

Hoofdstuk 4: Gelijktijdig longitudinaal meten van herstel van coördinatie en hersenactivatie bij CVA-patiënten in de eerste negen maanden na een CVA

Hoe zijn veranderingen in de kwaliteit van het bewegen gerelateerd aan verandering in hersenactivatie in de eerste 6 maanden na een CVA?

In deze studie hebben we 17 patiënten gemeten in week 6 en week 28 na een CVA. Met 3D-kinematica hebben we de veranderingen in kwaliteit van bewegen gemeten door de schokkerigheid van het openen van de hand tijdens een reik- en grijptaak te kwantificeren. Tijdens het scannen voerden de patiënten een flexie-extensie taak met de vingers uit. Na 6 weken vonden we een relatie tussen schokkerigheid van bewegen en activatie in secondaire motorgebieden, zoals het cerebellum en ipsilaterale premotor cortex. Deze resultaten leiden tot de voorzichtige conclusie dat patiënten die kwalitatief minder goed en schokkerig bewegen waarschijnlijk meer vertrouwen op proprioceptische feedback en continue de beweging bijsturen. Dit in tegenstelling tot patiënten die heel vloeiend bewegen en meer op feedforward mechanismen vertrouwen. Het is ook mogelijk dat de relatie die wij vonden, zijn verklaring vindt in maladaptieve activatie, die wordt veroorzaakt door reductie van GABA erge activatie (disinhibitie) die voor de schokkerigheid zorgt. Interessant genoeg zijn er studies die laten zien dat ook de gezonde arm deze schokkerigheid laat zien bij CVA-patiënten. Dit zou indiceren dat activatie in het brein na een CVA niet alleen een focaal issue is door de laesie zelf, maar ook afhangt van de staat van het gehele brein en alle gebieden die direct of indirect in verbinding staan met de laesie.

Hoofdstuk 5: Bij dezelfde groep kijken of er veranderingen te zien zijn in connectiviteit tijdens herstel in de eerste maanden, en of connectiviteit verschilt tussen gezonde controles en CVA-patiënten

Hoe is verminderde handvaardigheid gerelateerd aan een verschil in functionele connectiviteit?

In deze studie keken we naar taak onafhankelijke 'rust' activiteit van het brein in een subgroep van dezelfde groep patiënten als in de vorige studie. Deze werden vergeleken met een controlegroep. We vonden dat de connectiviteit binnen het motornetwerk aan de laesiezijde van het brein lager was dan aan de niet laesiezijde van het brein binnen de patiëntengroep. Er was geen verandering over tijd en we vonden ook geen verschillen tussen controles en patiënten in connectiviteit. Dit laatste is te verklaren door de kleine groepen en de variatie tussen personen in fMRI signaal. De patiënten veranderden niet over tijd. Het is voor vervolgonderzoek belangrijk dat de patiënten niet geselecteerd worden voor beeldvorming van activiteit van het brein zodra ze een bepaalde taak kunnen uitvoeren, maar dat zij juist in de eerste dagen tot weken na het CVA worden gemeten in rust en gevolgd over tijd. Op deze manier kunnen de processen die leiden tot herstel makkelijker geïdentificeerd worden.

Aanbevelingen voor toekomstig onderzoek

Het is belangrijk om ons te realiseren dat wij door alleen naar hersenactivatie te kijken van patiënten die een bepaalde taak aankunnen, we alleen het topje va ijsberg zien. We komen zo niet dichterbij wat nou de drijvende factor is van het spontane neurobiologische herstel in de hersenen en wat de reden is dat sommige mensen juist niet herstellen.

Nieuwe inzichten: wat drijft spontaan neurobiologisch herstel en bij welke patiënten?

Uit recente literatuur en de resultaten van patiënten van het EXPLICIT onderzoek blijkt dat het spontane motorische herstel van de arm proportioneel een vast percentage laat zien van ongeveer 70% van de maximaal haalbare verbetering op de Fugl-Meyer schaal ten opzichte van initieel functieverlies. Van de patiënten blijkt 20 tot 30% zich niet te houden aan deze regel (non-fitters). Deze patiënten blijken ook vaker niet te herstellen van neglect. Het proportionele herstel lijkt dus een proces te zijn dat zich over meerdere modaliteiten uit, en al vaststaat in de eerste dagen na een CVA.

De vragen die uit deze inzichten opkomen zijn: kunnen wij de fitters (70% herstel) en non-fitters (niet proportioneel herstel) van elkaar onderscheiden (dmv. het meten van biomarkers) door hun breinen structureel en functioneel te onderzoeken en hen over te tijd te volgen? ; en kunnen wij dan wellicht verklaren waarom het brein alleen tot een bepaalde proportie van de initiële schade kan herstellen en begrijpen wat dan de eigenschappen van die functionele stoornis die overblijft dan precies zijn?

Conclusies:

Het is in de toekomst belangrijk dat alle patiënten zo vroeg mogelijk na het CVA worden gemeten, waarbij er gekeken wordt naar de structuur en dynamiek van het systeem, vergeleken met controles. Als het brein wordt onderzocht terwijl patiënten een taak uitvoeren, zal die taak uitdagend genoeg moeten zijn om in kaart te kunnen brengen wat de resterende schade is en welke strategieën het brein gebruikt om dit defect het hoofd te bieden.

Al dit type onderzoek is alleen zinvol als landelijk of zelfs Europees wordt samengewerkt met gebruik van standaard scans, zoals bij het EXPLICIT-stroke-onderzoek, zodat een zo groot mogelijke groep patiënten gevolgd kan worden.

Puntsgewijze samenvatting belangrijkste resultaten

Hoofstuk 3. Relatie tussen hersenactivatie en uitkomst na een CVA

- Er is geen verschil gevonden in hersenactivatie tussen patiënten met weinig functieverlies en gezonde proefpersoenen tijdens een simpele motortaak.
- Patiënten en controles voerden de taak op dezelfde manier uit. Er was geen verschil in spiegelbewegingen met de andere hand.

Hoofdstuk 4. Relatie tussen hersenactivatie en herstel van kwaliteit van bewegen

- Grijpbewegingen van patiënten werden minder schokkerig na een CVA en de snelheid waarop dit gebeurde was het hoogst tijdens de eerste 5 weken na een CVA.
- Er is geen verschil gevonden tussen hersenactivatie tussen week 6 en week 26.
- De schokkerigheid van bewegen is gerelateerd aan activatie in gebieden van het brein die verantwoordelijk zij voor leren en het corrigeren van bewegingen.

Hoofdstuk 5. Functionele connectiviteit tijdens herstel

- Connectiviteit in de gezonde hemisfeer is hoger dan in de niet gezonde hemisfeer
- Er is geen verandering in functionele connectiviteit na een CVA gevonden en geen verschil met gezonde mensen

Vervolgonderzoek

- Identificeren van biomarkers die spontaan neurobiologisch herstel definiëren. Bij meer herstelde CVA-patiënten proberen het netwerk meer uit te dagen door bijvoorbeeld een dubbeltaak aan te bieden om te zien hoe het motornetwerk reageert op resterende schade.
- De relatie tussen hersenactivatie en motorfunctie moet bij voorkeur direct in realtime worden gemeten, bijvoorbeeld met EEG of TMS gekoppeld aan kinematische metingen of robotische storingen van het systeem om de invloed van compenserend gedrag op de hersenactivatie te onderzoeken (compensatie en restitutie).
- Vroeger monitoren van herstel (<7 dagen) door taakonafhankelijke metingen van de hersenen, bij voorkeur non-invasief en bedside (zoals EEG) om de aard van spontaan neurobiologisch herstel te onderzoeken door netwerkeigenschappen te onderzoeken in (achteraf) gestratificeerde patiëntengroepen.

Methodologische aanbevelingen

- Vanwege de hoge variabiliteit en voorkomen van ruis in beeldvormende hersentechnieken, moet een controlegroep worden opgenomen voor alle longitudinale data, ook omdat motorisch leren en plasticiteit (in termen van herstel) zo nauw verwant zijn.
- Taakgerelateerde beeldvorming op basis van uitvoering van een precies gedefinieerd vrijwillig motorparadigma zal altijd patiënten uitsluiten die ernstiger aangedaan zijn. Als gevolg daarvan zijn deze taakgerelateerde fMRI onderzoeken minder generaliseerbaar voor alle patiënten met een CVA.
- Bovendien kunnen motorparadigma's die worden gebruikt voor fMRI in een geselecteerde groep patiënten met een beroerte, niet voldoende onderscheiden tussen volledig herstelde beroertepatiënten en die met minimale beperkingen. Bovendien is de interpretatie van fMRI-bevindingen na beroerte afhankelijk van tijd na beroerte.
- Gebruik grote internationale patiënte cohorten om patiënten te kunnen stratificeren op basis van het waargenomen en voorspelde herstel na een CVA.

Dankwoord

Hierbij wil ik graag iedereen bedanken die op enige manier in de afgelopen 10 jaar heeft bijgedragen aan mijn proefschrift, zowel op inhoudelijk als op persoonlijk vlak. Daarbij gaat mijn bijzondere dank uit naar de patiënten die geheel belangeloos hebben meegewerkt aan mijn onderzoek.

In dit dankwoord wil ik graag een aantal mensen persoonlijk bedanken. Allereerst mijn promotoren prof.dr. N.F. Ramsey, Prof.dr. G. Kwakkel en prof.dr. E. Lindeman en natuurlijk mijn copromotor dr. M. Raemaekers.

Beste Nick, ik wil je graag bedanken voor je begeleiding tijdens mijn promotietraject. Je bleef altijd optimistisch als we een keer geen significante resultaten vonden en zorgde ervoor dat we de data aan alle kanten bekeken hadden zodat we zeker wisten dat we niets over het hoofd zagen. Ik heb veel van je geleerd over imaging van het brein. Toen ik het moeilijk had heb je dat heel begripvol opgepakt waardoor ik ook snel weer door kon. Dank daarvoor.

Beste Gert, na 10 jaar had je de moed nog niet opgegeven, mede daardoor bleef ik er zelf ook in geloven. Het is af! Ik heb altijd genoten van onze discussies over herstel na een CVA en welke veranderingen in het brein daarvoor wel of juist niet verantwoordelijk zouden kunnen zijn. We zaten altijd op een lijn wat betreft onze ideeën over plasticiteit en compensatie. Ik heb veel van je geleerd. Ik begon als student en liep daarna stage bij Erwin en bij jou, waarna jij me vroeg of ik wilde solliciteren voor deze promotie plek. Ik ben er trots op dat ik onderdeel uitmaakte van het EXPLICIT team.

Beste Mathijs, wat fijn dat je zo onverstoorbaar bent, en dank voor je geduld met mij als ik weer eens ontzettend gefrustreerd was wanneer iets niet lukte of onduidelijk was, of wanneer ik precies wilde weten waarom je iets gedaan had en of het niet anders kon. Zonder jouw ervaring met imaging was het mij allemaal niet gelukt.

Beste Eline, mijn derde promotor, helaas hebben wij maar kort mogen samenwerken. Jouw overlijden was niet onverwacht, maar toch een schok voor iedereen. Ik had nog veel van je kunnen en willen leren.

Mijn paranimfen: Menno Schoonheim, Lori Buma. Menno zonder jou en Noordwijk was het noooit gelukt, pink fluffy unicorns for life! Lori, zusje! Jij hebt de hele totstandkoming van dit proefschrift van dichtbij meegemaakt de afgelopen 10 jaar het zou gek voelen als je bij het einde niet naast me zou staan. En als er statistiek vragen komen gaan ze naar jou ;)

EXPRO - de EXplicit PROmovendi, verspreid over het hele land. We hebben samen een heleboel metingen gedaan, patiënten geïncludeerd, vergaderd op Utrecht Centraal, gediscussieerd, nieuwsbrieven gemaakt, maar daarnaast zijn we ook samen volwassen geworden. Er zijn meer EXPLICIT-baby's dan proefschriften inmiddels, er zijn mensen verliefd geworden, verloofd, getrouwd en van studentenwoningen naar 'echte' grote mensen huizen verhuisd. Rinske: jij was de spil van het onderzoek en van onze groep. Degene die alle patiënten heeft gemeten, altijd opgewekt en als eerste klaar! Joost: ons gezamenlijke paper kwam uit onze tenen maar het is gelukt, bedankt voor de samenwerking en dat je bleef pushen om het af te krijgen. Hanneke: helaas geen papers samen, maar genoeg beleefd. Ik kon in Leiden altijd even bij je op de afdeling buurten, hopelijk ben jij ook snel klaar. Asbjorn: jij was altijd de vreemde eend in de bijt qua onderwerp, jouw boekje heb ik in de kast (maar ik begrijp er niets van). Toch was je altijd volwaardig onderdeel van de groep en altijd geïnteresseerd in wat wij met de patiënten aan het doen waren. Chantal: naast collega ben je ook een vriendin geworden, we hebben ontzettend veel lol gehad tijdens de metingen en ontzettend leuke ideeën voor onderzoek besproken, wie weet schrijven we nog eens een paper met die resultaten. Caroline: jij kwam er later bij, en wordt veelvuldig geciteerd in dit proefschrift. Jij pakte over wat Rinske na haar promotie achterliet en we komen uiteindelijk vlak na elkaar over de eindstreep.

Ook dank aan de rest van het EXPLICIT consortium: dr. Erwin van Wegen, Prof.dr. Hans Arendzen, Prof.dr. Frans van der Helm, Prof.dr Sander Geurts, Prof.dr. Carel Meskers en Prf.dr. Anne Visser-Meily, Dr. Annette van Kuijk.

Mijn dank gaat ook uit naar de leden van de leescommissie (Prof.dr. R.M. Dijkhuizen, Prof.dr. J.M.A. Visser-Meily, Prof.dr. L.J. Kappelle, Prof.dr. G. Ribbers, Prof.dr. S.A.R.B. Rombouts), die de moeite hebben genomen mijn proefschrift te lezen en te beoordelen.

Dietsje, bedankt voor het helpen met de metingen in het LUMC ☺ hij is eindelijk af!

Collega's in het UMCU, de RIBS groep: Erika, ik heb genoten van onze discussies over het leven. Matthijs, wij bleken een zelfde interesse te hebben in wetenschapsvertaling. Gert, Wouter, Gerry, Zac, Mariska, Elmar, Dora en Erik: wie weet weer tot bij de Griek. Annemiek, door jouw warmte heb ik mij ondanks de lastige nul uren constructie erg welkom gevoeld in de groep bij het UMCU. Dit is erg waardevol voor mij geweest. Ben, ontzettend bedankt voor je hulp bij de inclusie en het wegwijs maken op de afdeling revalidatie in het UMCU, zonder jou hadden we veel patiënten gemist.

Graag wil ik ook alle patiënten (en hun echtgenoten) bedanken die hebben meegewerkt aan het EXPLICIT onderzoek en in het bijzonder aan de metingen die in mijn papers beschreven zijn. Het was vaak een zware belasting en het feit dat mensen na zo'n heftige gebeurtenis toch graag meededen om kennis over CVA voor andere patiënten te vergroten heeft me altijd ontroerd.

Inmiddels werk ik alweer 5 jaar bij het VUmc op de afdeling Anatomie en Neurowetenschappen. Ook daar wil ik graag wat mensen bedanken.

Prof. Geurts, Jeroen, zonder jou was dit proefschrift niet afgekomen. Ik ben ontzettend blij dat wij elkaar zowel op werkgebied als privé gevonden hebben. Ik leerde je kennen als promotor van Menno en Hanneke tijdens een etentje in San Francisco tijdens HBM in 2008. Daarna ben ik bij jouw stichting Brein in Beeld vrijwilliger geworden en daardoor dacht je aan mij toen jij afdelingshoofd werd van ANW in 2013. Ik heb me ontzettend ontwikkeld in de afgelopen paar jaar. Jij hebt me altijd gepusht en in de gelegenheid gesteld om dit proefschrift (ook onder werktijd) af te maken en daar ben ik je bijzonder dankbaar voor. Just keep swimming!

Collega's van ANW, bedankt dat jullie mij zo welkom hebben laten voelen, een warm bad waar het voelt alsof ik er al tien jaar zit. Ik heb met ieder van jullie weleens gepraat over dit proefschrift en al die gesprekken samen zorgen er toch voor dat het er nu echt is. Meiling en Sandra bedankt voor al jullie hulp (ook bij het versturen van dit proefschrift).

Hanneke bedankt dat je mij de kans gaf aan wetenschapscommunicatie te snuffelen bij Brein in Beeld, en het lesgeven aan HAVO 4 op vrijdag middag heeft mijn didactische vaardigheden zeker versterkt!

KNWers jullie zijn allemaal een beetje van mij, bedankt voor alle borrel gezelligheid! Chris, Geert, Linda, Hanneke en Laura zie jullie in de Mahler!

Michael! Nog eentje dan! I'll snap you like a twig! Jij bent mijn grote voorbeeld :P Ik leer ontzettend veel van jou in mijn rol als docent. En gelukkig kan ik je nu af en toe ook helpen met jouw onderzoek.

In dit laatste deel van het dankwoord graag mijn vrienden en familie bedanken.

Mama en Papa bedankt voor alles. Jullie hebben mij altijd gestimuleerd, en liggen aan de basis van dit proefschrift (en natuurlijk van mij).

Lori en Jordi bedankt voor alle wijntjes en gezelligheid en dat ik altijd bij jullie mocht komen uithuilen. Yvon, bedankt voor je ontnuchterende opmerkingen: misschien weten we nu eindelijk hoeveel engelen er op de punt van een naald dansen.

Familie Kloos, naast het afronden van dit proefschrift ben ik afgelopen jaar ook met jullie zoon getrouwd, en dus ook een beetje met jullie en daar ben ik ontzettend blij mee.

Lieve vrienden ik ga jullie niet allemaal noemen, en dus ook niemand in het bijzonder. Jullie weten wie jullie zijn en zijn me allemaal even lief. Vanaf nu mogen jullie mij eindelijk allemaal Doctor Floor noemen.

Rein, mijn liefste! Jij bent er het aller dichtste bij geweest, hebt alle tranen meegemaakt en gezien hoe ik uiteindelijk op mijn plek terecht gekomen ben. Zonder jou had ik daar een stuk minder vertrouwen in gehad. Bedankt voor je optimisme en je steun de afgelopen 12,5 jaar, en voor je DNA, want onze zoon is toch wel het mooiste wat we afgelopen jaren voor elkaar gekregen hebben.

Lieve Willem, deze is voor jou!

List of publications

Buma FE, Lindeman E, Ramsey NF, Kwakkel G. 2010 Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review of the literature. Neurorehabil Neural Repair. Sep;24(7):589-608.

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Buma FE*, Kordelaar J*, Raemaekers M, van Wegen E., Ramsey N.F. Kwakkel, G. 2016 Brain activation is related to smoothness of upper limb movements after stroke Exp Brain Res

Nijboer T, **Buma FE,** Raemaekers M, Kwakkel G, Ramsey NF. 2017 No changes in functional connectivity during motor recovery beyond 5 weeks after stroke; A longitudinal resting-state fMRI study PloS One

Bookchapter:
Kwakkel, G**., Buma, F. E.,** Selzer, M. E., Selzer, M. E., Clarke, S., Cohen, L. G., ... & Miller, R. H. (2014). Understanding the mechanisms underlying recovery after stroke. Textbook of neural repair and Rehabilitation 2e, eds. Selzer Michael E., Clarke Stephanie, Cohen Leonardo G., Kwakkel Gert, and Miller Robert H.

Curriculum Vitae

Floor Buma was born in Duiven in 1982. After moving from Duiven to Nijmegen, Amsterdam and Abcoude, she attended secondary education at the Vossius Gymnasium in Amsterdam.

In 2001 she started Communication science at the University of Amsterdam. After finding out this was not her true calling, she switched to Human Movement Sciences at the VU University in 2002. Especially the Anatomy and Neuroscience courses spiked her interest during the bachelor.

After the bachelor she joined the Master of Neuroscience research program at the VU (focusing on clinical neuroscience) and completed the Master of Human Movement sciences (focusing on rehabilitation) at the same time.

She started her PhD in Utrecht in 2008. The first years were focused on setting up the clinical trial for the EXPLICIT stroke study. 182 patients were included in total, of which 17 patients in Utrecht and Leiden were eligible for longitudinal task related fMRI. The final patient for the MRI follow-up study was measured in December 2012. From 2012 Floor volunteered with the Brein in Beeld foundation and further developed her interest in teaching and science communication.

In April 2013 she left science and started as a an assistant professor in Anatomy at the department of Anatomy and Neurosciences at the VU medical centre in Amsterdam. Currently she holds a permanent position at the dept. teaching general Anatomy to (bio)medical students, operating theatre assistants, physical therapists etc. and as a member of the management team (holding the portfolio for finance and HR)

Floor lives in Haarlem and is married to Rein Kloos. They have a 3 year old son together named Willem.