Recovery of the paretic upper limb early after stroke

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CHAPTER 1

General introduction

INTRODUCTION

Six months after his stroke a patient told me: “As a patient with a stroke you do not recover, but instead, you become more skilled”. Apparently, this patient felt that he could not use his body like he could before his stroke. However, despite the perceived absence of improvements in body functions, he acquired the skills to perform activities of daily living and, eventually, he was able to live independently.

This example perfectly illustrates that motor recovery after stroke is a complex process that involves the reacquisition of motor skills.[1,2] However, the mechanisms underlying skill acquisition after stroke are still largely unclear.[1,3,4] The greatest improvements in upper limb function occur generally in the first 10 weeks and taper off over the first 6 months after stroke.[5] In addition, the functional outcome of the paretic upper limb at 6 months can already be predicted within the first days and weeks after stroke.[6,7] It is assumed that these predictable and time-dependent improvements in upper limb function are mainly the result of ‘spontaneous neurological recovery’, which is, unfortunately, still poorly understood.[1,5,8]

Next to spontaneous neurological recovery, adaptive motor learning, i.e. the ability to improve motor performance by practice, may also be an important mechanism underlying upper limb motor recovery after stroke.[1,9] For instance, during reaching and grasping, patients with stroke often show qualitatively different coordination patterns compared to healthy adults.[10–12] These different coordination patterns are assumed to reflect adaptive motor learning strategies whereby patients learn to compensate for existing motor deficits.[1,2,9]

However, it is unclear how these adaptive strategies emerge as a function of time poststroke and how these strategies interact with spontaneous neurological recovery. Therefore, it is necessary to investigate the impact of time poststroke on quality of motor control in order to understand *what* and *how* patients exactly learn when they recover from a stroke.[1,8,9] Importantly, intensively repeated 3D kinematic measurements, conducted at fixed time-points starting in the first weeks and continued up to 6 months after stroke, are required to establish the time-dependent changes in quality of motor control.[13,14]

The aim of the current thesis was to improve our understanding of the time-dependent and learning-dependent mechanisms underlying motor recovery of the paretic upper limb after stroke. Improved understanding of these mechanisms may ultimately provide insight to the question whether therapeutic strategies in neurorehabilitation should be aimed at restoring quality of motor control or whether compensation strategies should be promoted.[4] Moreover, recommendations concerning the timing of such intervention strategies may be provided.[4,15]

The next section of this general introduction provides the definition and incidence of stroke. Subsequently, it is explained how the International Classification of Functioning, Disability and Health (ICF) was used in this thesis to define the term "recovery" and how it is related to "true motor recovery" (i.e. "restitution") versus "compensation" (i.e. "substitution"). Furthermore, the relevance of measuring quality of motor control for neurorehabilitation is explained and a description of the hypothetical pattern of upper limb motor recovery and the assumed adaptation strategies are provided. This general introduction ends with the outline of this thesis.

This thesis was part of the translational research programme called EXplaining PLastICITy after stroke (acronym: EXPLICIT-stroke, www.explicit-stroke.nl).[16] EXPLICIT-stroke (trial registration number: NTR1424) was funded by ZonMw (grant no: 89000001) and aimed to (1) assess the effects of early applied upper limb therapy in patients with stroke and (2) improve our understanding of the mechanisms underlying motor recovery after stroke.[16]

Definition and incidence of stroke

A stroke is defined as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause than that of vascular origin".[17] According to the World Health Organization (WHO) there are, worldwide, 16.3 million incidences of stroke each year of whom 3 out of 4 survive beyond the acute phase.[18] With that, stroke is the second leading cause of death worldwide and a leading cause of disability among adults.[18] Eighty percent of all patients with a stroke is confronted with impaired arm and/or hand function.[19] Depending on initial severity of stroke, 30 to 66 % of all patients never achieve any arm and hand function,[20,21] whereas only 5 to 20 % fully recovers from a stroke.[20,22]

To understand the impact of a stroke on human functioning, consistent terminology to describe human functioning is necessary. The next section explains how the framework of the ICF can be applied to recovery after a stroke with respect to body functions, activities and participation in society.

International Classification of Functioning

Traditional models of illness, like the biomedical model, which dominated healthcare during the 20th century, assume that illness is caused by disease or pathology alone.[23–26] Based on this view, health was simply defined as "the absence of disease".[27] However, this reductionistic approach was not able to explain many aspects of human functioning in healthy and disabled individuals.[25] Since the 1970s, a series of new models were developed under the auspices of the WHO, eventually leading to the International Classification of Functioning, Disability and Health (ICF), which was first published in 2001.[28]

In the ICF it is recognized that a person's functioning can be described at the levels of body structures and functions, activities and participation in society. The ICF further recognizes that a person's functioning depends not only on his or her health condition (i.e. disorder or disease) but also on personal and environmental factors.

According to the ICF, (quality of) motor control is defined at the body functions level whereas performance of functional activities is defined at the activity level. To understand how recovery of quality of motor control is related to recovery of performance we first need to define what we actually mean with "recovery" after stroke.

How to define "motor recovery" after stroke?

Several studies have shown that upper limb function improves as a function of time poststroke.[5,29,30] These improvements, typically assessed using the upper limb section of the Fugl-Meyer Motor Assessment (FMA), are often interpreted as reflections of true neurological recovery.[31] By contrast, 3D kinematic studies have shown that patients with stroke exhibit coordination patterns which are substantially different compared to aged matched, healthy subjects.[10,11] For instance, patients with stroke often show increased elbow flexion and increased forward trunk displacement

and axial trunk rotation during forward reaching tasks.[10,11] In addition, different patterns of joint couplings, i.e. synergies, were found between the shoulder, elbow and wrist as compared to healthy subjects.[32,33] This adaptive recruitment of the mechanical degrees of freedom (i.e. muscles and joints) is hypothesized to serve as a compensation strategy allowing performance of functional tasks despite the presence of motor deficits in the paretic upper limb.[3,9] Therefore, it is unclear to what extent motor recovery after stroke is really a process of true neurological recovery (i.e. restitution) or should rather be considered as a process of adaptive motor learning by which patients learn to master the degrees of freedom of the paretic upper limb in a different way in order to compensate for existing motor impairments (i.e. substitution). To investigate this question, a clear framework of definitions on the various levels of the ICF is necessary. Table 1.1 provides the definitions of recovery, restitution, substitution and compensation at the levels of Body Structures, Body Functions and Activities of the ICF, as used in this thesis.[34]

Table 1.1 Defining "Recovery", "Restitution", "Substitution" and "Compensation"

	Body Structures	Body Functions	Activities
Recovery	Any change in the structure that leads to improved function. (includes restitution and substitution)	Improvement of the ability to perform a movement. (includes restitution and compensation)	Improvement of the ability to perform a functional task. (includes restitution and compensation)
→ **Restitution**	True neurological recovery: change toward the original state	True motor recovery: identical employment of body components* as before the injury	Identical task performance as before the injury
Substitution/ Compensation	Alternative employment of body structures.	Alternative employment of the same body components as before injury.*	Task performance, using alternative limbs and / or environmental adaptations

See text for explanation. *Body components are defined as a collection of body structures that contribute to a specific body function.

According to our definition, recovery at each level of the ICF can theoretically be achieved by means of restitution and substitution.[34] At the neuronal level, there is probably some degree of restitution early after stroke that is referred to as spontaneous neurological recovery. Several mechanisms are assumed to

contribute to spontaneous neurological recovery, including salvation of penumbral tissue,[35] alleviation of diaschisis,[36,37] angiogenesis [38] as well as an upregulation of growth promoting factors.[39] However, it is still poorly understood how these non-learning-dependent mechanisms interact with learning-dependent neuronal reorganization driven by, for instance, Hebbian and non-Hebbian learning processes.[40,41] Hypothetically, motor learning may lead to substitution of neuronal function by which lost neuronal functions after stroke are compensated or "taken-over" by the contralesional hemisphere or adjacent brain areas.[3] Indeed, changes in the recruitment of cortical brain areas have been observed with for example fMRI.[42–44] However, it is still largely unclear whether this learning-induced cortical reorganization reflects true motor recovery or compensatory motor control.[45] Moreover, this insufficient distinction between restitution by true motor recovery and substitution by motor compensation severely compromises the optimization of therapeutic strategies within neurorehabilitation.[3,4,9]

How can therapeutic strategies optimally assist upper limb motor recovery after stroke?

Due to our insufficient understanding of learning-induced neuronal reorganizations after stroke it is unclear whether patients can learn to regain or improve quality of motor control. For instance, the Bobath concept is targeted at improving quality of motor control by normalizing movement patterns and avoiding compensatory movements.[46] However, there is still no evidence that the Bobath concept is superior to other approaches that allow compensatory strategies.[47] By contrast, there is growing evidence that intensive and task-oriented training can improve motor performance, without meaningful reductions of motor impairments.[2,4,48] This finding suggests that therapy induced improvements in motor performance are mainly achieved by adaptive strategies by which patients learn to compensate for existing deficits.[4]

To date, robotic devices are often used in order to further enhance the effects of exercise therapy.[49,50] Robot-assisted treatment programmes enable patients to practice independent of their therapist, whereas the intensity and complexity can be specifically tailored to the patient's capabilities.[51] However, there are many

robotic devices commercially available with a wide variety in the mechanical degrees of freedom that they control.[51] For instance, exoskeletons such as the Armin and L-Exos, encapsulate the arm and actively guide the proximal motions of the shoulder and elbow, whereas end-effector systems, such as the MIT-MANUS and Bi-Manu-Track, interact with the patient by a distal attachment point at the forearm or hand.[52] There is still a debate regarding how robots should be designed to optimally promote motor recovery of the paretic upper limb after stroke.[51] More generally, it is unclear if and how the focus on restitution of motor control or the allowance of compensatory movements during robot-assisted or human administered therapy should change depending on time poststroke. Therefore, it is important to measure quality of motor control, rather than motor impairments alone, in order to distinguish between restitution and substitution. Based on this distinction and dependent on time poststroke, improved therapeutic strategies may be targeted at either restitution of motor control or at using compensatory strategies in order to assist the natural pattern of upper limb motor recovery after stroke.

The hypothetical pattern of motor recovery after stroke

Thomas Twitchell was one of the first scientists to notice that, in patients with stroke, recovery of motor function emerges in a specific pattern during which basic limb synergies or couplings diminish as a function of time poststroke. These basic limb synergies involve (1) the flexion synergy, which is defined as a simultaneous abduction and external rotation of the shoulder, flexion of the elbow and supination of the forearm, when elevating the arm, and (2) the extension synergy, defined as an adduction and internal rotation of the shoulder, extension of the elbow and a pronation of the forearm when stretching the elbow.[53,54] Twitchell described that the emergence of these synergies follows a rather predictable pattern during motor recovery after stroke.[54] According to his observations, muscle weakness dominates during the first hours after stroke, whereas after 24 hours, the first signs of voluntary motor control may be observed as small upper limb movements within the basic limb synergies. When patients further recover, dissociations from these basic limb synergies may become possible.

The exact neuronal mechanisms underlying these basic limb synergies are unknown. It is assumed that these synergies are a reflection of motor control mediated by hierarchically lower motor systems, such as the formatio reticularis, when cortical and cortico-spinal control is disrupted after stroke.[55] There are indications that these lower motor networks have more diffuse projections onto alpha motor neurons at the spinal level, which most likely explains the less selective activation of muscle groups and the resulting coupled joint movements within the basic limb synergies.[56]

Based on the predictable pattern in which movement synergies emerge after stroke several clinical tests have been developed in order to determine the stage of recovery.[53,57,58] The most prominent is the Fugl-Meyer Motor Assessment (FMA), which distinguishes 5 stages of motor recovery. The FMA score is generally assumed to reflect the amount of true neurological recovery after stroke.[57] Several longitudinal studies with intensively repeated measurements of the upper limb section of the FMA have shown that most recovery emerges in the first 3 months after stroke, whereas after 3 months FMA recovery patterns level off.[5,30,54]

Unfortunately, this spontaneous pattern of recovery is still one of the most neglected features of motor recovery after stroke.[5,8,13] As a consequence, it is unclear how the emergence of dissociated movements between the shoulder and elbow (i.e. true motor recovery or restitution) complements adaptive motor learning by which patients gradually adopt an alternative employment of the various degrees of freedom of the paretic upper limb (i.e. compensation or substitution). This distinction between true motor recovery and compensation requires insight into the 3-dimensional movements of all individual joints and body segments during functional tasks, such as reaching and grasping. Since traditional clinical assessment scales cannot capture all these individual joint movements, intensively repeated 3D kinematic measurements, particularly in the first weeks after stroke, are necessary to understand the changes in adaptive motor control as a function of time poststroke.

Adaptive motor control after stroke

Studies investigating quality of upper limb motor control after stroke are mainly limited to cross-sectional studies in the chronic phase (i.e. > 6 months after stroke) that compare 3D kinematic outcomes in patients with stroke with healthy subjects.[1]

In addition, studies investigating quality of motor control in animal models are almost missing in the literature.[59]

Cross-sectional 3D kinematic studies performed in the chronic phase after stroke suggest that patients exploit the flexion synergy to fixate the joints in the paretic upper limb [32,33], whereas they recruit the trunk as an additional proximal degree of freedom to move the arm and hand towards a target location.[10,60] According to Bernstein,[61] fixating distal degrees of freedom (i.e. 'freezing') and coordinated coupling of joint movements within movement synergies are two fundamental principles of the central nervous system to reduce the number of degrees of freedom to be controlled.[61,62] In addition, studies in healthy subjects have shown that skill acquisition is characterized by the gradual release of these distal degrees of freedom (i.e. 'freeing').[63,64] These findings suggest that freezing and coupling joints within basic limb synergies as observed in patients with stroke may be seen as a functional strategy to reduce the number of degrees of freedom that are involved in a particular reaching task. Hence, despite the pathological origin of the basic limb synergies, they should be considered optimal given the motor impairments, such as weakness and spasticity, that patients have to deal with.[65] However, due to the lack of studies with intensively repeated 3D kinematic measurements it is unclear whether freeing of degrees of freedom occurs during reaching tasks as a function of time poststroke. As a consequence, it is not known to what extent patients regain the capability to control the joints of the paretic upper limb independently in a functional and task-specific context.

Next to the alternative employment of degrees of freedom within basic limb synergies, movement patterns in patients with stroke are often accompanied by reduced smoothness of hand trajectories.[11,66,67] Smooth movements are a characteristic of skilled motor behavior,[68] which suggests that smoothness can be used as a measure of quality of motor control. Unfortunately, the mechanisms underlying smoothness of upper limb movements are unknown. It is assumed that a lack of smoothness reflects the inability of patients to pre-plan reaching movements accurately in advance, which leads to movement errors that have to be corrected based on visual and proprioceptive feedback.[69–72] In this thesis it is hypothesized that smoothness increases as patients regain control over the degrees of freedom of the

paretic upper limb. As a result of this improved control patients may be able to plan movements more accurately in advance, and on-line corrections based on visual and proprioceptive feedback during goal-directed movements become unnecessary.[73] Previous studies have suggested that feedback controlled motor behaviour is associated with increased activity levels in secondary sensorimotor areas[74] and the cerebellum,[75] whereas feedforward control is mainly associated with activation in the primary motor area.[76] Based on this finding we hypothesize that smoothness is negatively correlated with activation in the secondary sensorimotor areas and the cerebellum, whereas it is positively related with activation in the primary motor area. However, longitudinal studies that combine brain imaging techniques with 3D kinematic measurements in patients with stroke are currently lacking and as a consequence, it is unclear how changes in brain activation patterns are associated with improvements in smoothness of movement patterns after stroke. In addition, it is unclear how interventions within neurorehabilitation may influence brain activation patterns and quality of motor control. This paucity of knowledge illustrates the need for translational research programmes that incorporate preclinical techniques within clinical studies to investigate the mechanisms underlying motor recovery after stroke as well as the effects of specific interventions on motor function.

The need for translational research

Motor recovery of the paretic upper limb after stroke involves a complex interaction between the neurological processes in the brain,[45] the neuromechanical changes including muscle stiffness and spasticity in the paretic upper limb,[77] as well as motor learning processes by which patients learn to adapt coordination of the paretic upper limb.[1,9] An improved understanding of motor recovery after stroke requires intensive measurement designs with multiple measurement techniques to capture the relevant changes at the various levels of the motor system.[16] In addition, these measurements need to be incorporated in randomized controlled trials in order to investigate whether therapeutic strategies in neurorehabilitation targeted at true motor recovery are able to further enhance quality of motor control. The translational multi-center research programme EXPLICIT-stroke, which is currently running in the Netherlands, is one of the first research programmes in which functional magnetic

resonance imaging (fMRI), transcranial magnetic stimulation (TMS), 3D kinematics, and haptic robotics (HR) are conducted next to more common clinical assessment tools in the same cohort of patients with stroke. In addition, within two randomized controlled trials, the effects of early applied modified constraint-induced movement therapy (mCIMT) and EMG-triggered neuromuscular stimulation (EMG-NMS) are evaluated in patients with a favourable or unfavourable prognosis for recovery of upper limb function, respectively.[16] With that EXPLICIT-stroke aims to contribute to an improved understanding of the interaction between the different mechanisms underlying motor recovery after stroke.

Outline of this thesis

The aim of the current thesis was to establish whether motor recovery after stroke is principally a process of true motor recovery whereby coordination patterns change towards pre-existing coordination patterns (i.e. restitution). Alternatively motor recovery might rather be considered as a process of adaptive motor learning whereby patients learn to compensate for existing motor impairments in the paretic upper limb by employing alternative movement strategies (i.e. substitution).

Since patients are often transferred from the stroke unit, to rehabilitation centers, nursing homes and eventually their home environment, intensively repeated follow up would be cumbersome with 3D kinematic measurements in clinical motion laboratories. In **chapter 2**, it is explained how on-site 3D kinematic measurements can be conducted accurately and reliably in various environments. Furthermore, a case report illustrates how to interpret the longitudinal 3D kinematic data that are obtained from these measurements. By using principal component analysis (PCA) and a cross-sectional measurement design, in **chapter 3** we investigate how compensating trunk movements complement synergistic upper limb movements in a group of patients at 6 months after stroke. In **chapter 4** we investigate in a longitudinal measurement design with intensively repeated 3D kinematic measurements when and how patients regain control over the degrees of freedom of the paretic upper limb in the first 26 weeks after stroke. In **chapter 5** we investigate whether the changes in upper limb synergies observed early after stroke are accompanied by improvements in quality of motor control, quantified by normalized jerk, a measure of smoothness.

In **chapter 6** we investigate the hypothesis that reductions in the smoothness of upper limb movements, reflecting the amount of feedback control, are associated to increased activation levels in secondary sensorimotor areas and the cerebellum. Finally, this thesis ends with a general discussion in **chapter 7** with the interpretation of the findings from the above mentioned studies and the consequences of this thesis for further research and treatment of patients with stroke.

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