Reactive neurobiological recovery after ischaemic stroke?

PROGNOSIS & INTERVENTION

Caroline Winters
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General introduction
THE ISCHAEMIC CASCADE IN STROKE

The World Health Organisation (WHO) defines stroke as “rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.”1,2 Strokes can be generally classified as haemorrhagic or ischaemic and lead to hypoperfusion of a part of the brain tissue. Haemorrhagic strokes occur when a vessel ruptures and blood flows into or around the brain tissue. In ischaemic strokes, hypoperfusion is caused by a blood clot which blocks a vessel in or leading to the brain. In this thesis, the focus will be on patients with ischaemic strokes, accounting for 80% of all stroke victims.3-5 The reduced cerebral blood flow (i.e. hypoperfusion) to a brain area will trigger an ischaemic cascade involving a series of neurochemical processes.6,7 The ischaemic cascade starts with the failure of the energy (adenosine triphosphate) production, subsequently causing dysfunction of depolarisation of neurons, dysfunction of energy-dependent ion transport pumps and inflammation.8,9 Cell death through necrosis will occur in the ischaemic core where cerebral blood flow decreases to less than about 8 ml per 100 g brain tissue per minute.6,10,11 The degree and the duration of the oxygen deprivation are important variables for the amount of permanent damage to the brain tissue.12 The area of permanently damaged tissue will expand when energy failure and ion transport pump failure occur within the brain cells surrounding the core.10,13 This area is often called the perilesional region or penumbra. Initially, the cells in the penumbra are only dysfunctional (i.e. electrical failure) due to the decrease of cerebral blood flow below 20 ml per 100 g per min, however, cell death will occur through delayed apoptosis when the hypoperfusion maintains.10,14 The penumbra is the main focus of early treatment within approximately the first 4.5 hours after stroke onset.15,16 However, a large number of patients is not eligible for this early treatment, because they do not reach the hospital in time.

THE EPIDEMIOLOGY OF STROKE

According to the WHO, the worldwide incidence and prevalence of stroke was respectively 10.3 million and 25.7 million in 2013.5 Stroke is the second-leading cause of disease burden.5 The disease burden, expressed in the absolute number of Disability-Adjusted Life Years (DALYs), was 47.4 million and approximately 3.3 million people died from a stroke.5 The global burden of stroke will continue to increase, mainly due to the ageing population and the increase in DALYs in developing countries.5,17
Stroke survivors present a wide range of clinical symptoms, including cognitive and motor impairments. Motor impairment is one of the most common impairments after stroke and occurs in up to 80% of all stroke survivors.18,19 The face, upper and lower limb on one side of the body are typically affected. The severity of upper limb impairment early after stroke is strongly related to the ability to perform Activities of Daily Living (ADL).20 In addition, upper limb impairment is related to low subjective well-being in stroke survivors.21 Because up to 80% of the individuals with initial severe upper limb motor impairment is still disabled at 3 or 6 months after stroke onset,22,23 upper limb training is an important element of post stroke rehabilitative therapy.

**STROKE REHABILITATION**

Getting out of bed, going to the toilet, taking a shower, grooming, getting dressed, eating breakfast and drinking a cup of coffee; a list of basic ADLs that many people consider as normal and easy. The complexity of these activities becomes clear when motor function and/or cognition are affected by a stroke. Stroke remains a leading cause of long-term disability, despite the continuously advancing emergency medicine, acute and inpatient care.5,24 Hence, there is a need for more efficient stroke prevention and management.5 Stroke rehabilitation involves different steps which are part of a cyclic process, including: identifying and quantifying patients’ needs, setting realistic and attainable goals, supporting to attain those goals (i.e. intervention) and evaluating the process.25 The main goal of stroke rehabilitation is to reduce individuals’ disability and improve health-related quality of life.25

It is evident that knowledge about prognostic variables and time dynamics for predicting neurobiological recovery after stroke is paramount to: (1) make clinical decisions; (2) optimize (early supported) discharge planning; (3) allow patients to receive the most appropriate rehabilitation intervention, dependent on individual abilities; (4) correctly inform patients and relatives about their future perspectives regarding ADLs; and (5) design future Randomised Controlled Trials (RCTs) to investigate the effectiveness of interventions.20,25

In order to optimize therapeutic care within the field of stroke rehabilitation, there is need to increase knowledge about early prediction of outcome after stroke. This is in line with the quickly evolving research field of precision medicine. According to the National Research Council, precision medicine is “the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices
that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Before we can discuss early prediction and intervention after stroke, we first need to define the term ‘recovery’.

**WHAT IS RECOVERY?**

In this thesis, ‘recovery’ is defined as (1) patients’ overall improvement over time or (2) change over time in the underlying mechanisms of neurobiological recovery. We can further specify ‘recovery’ as improvements of body functions and structures (impairments), activities (disability), and participation (handicap), using the International Classification of Functioning, disability and health (ICF) framework. Generally, mechanisms of skill reacquisition after stroke are classified into behavioural restitution (i.e. true repair) and behavioural compensation of functions. Behavioural restitution is related to the reduction of impairment, for example, return of muscle strength or arm movements outside of the synergistic movement pattern (i.e. normalisation of the coupling between joints toward the level prior to stroke). Behavioural compensation consists of the alternative employment of the same structures, for example, a change in timing and/or increase in co-activation of the antagonist muscles, or even use of the non-affected bodyparts. A key question in neurorehabilitation is whether we can modulate behavioural restitution through therapy (i.e. experience-dependent plasticity). One of the primary mechanisms underlying patients’ recovery is spontaneous neurobiological recovery. Not yet fully unravelled mechanisms that have been suggested to contribute to spontaneous neurobiological recovery are: recovery of the penumbra, alleviation of diaschisis and homeostatic mechanisms. Unfortunately, spontaneous neurobiological recovery remains a neglected area of research in neurorehabilitation.

A number of longitudinal studies with intensive repeated measurements in time show that most improvements in neurological impairments such as motor function, neglect, aphasia and somatosensory function occur in the first 3 months post stroke. Serial measurements of change scores by intensive repeated measurements suggested that progress of time alone explained 80 to 90% of the neurological improvements observed in the first 8 to 10 weeks after onset, suggesting that spontaneous neurobiological recovery is
largely responsible for the improvements of impairments in the first 3 months after stroke, independent of variables like type of stroke, affected hemisphere, age and gender. Moreover, the recovery of neurological impairments is a time-dependent, non-linear process. Figure 1.1 shows the suggested timing of neural mechanisms, which are related to the progression of stroke damage. Various phases post stroke have been distinguished in the literature. In the current thesis the time line of neurobiological recovery is divided into the following 5 phases: (1) hyper-acute: 0–24 hours; (2) acute: 1–7 days; (3) early subacute: 7 days to 3 months; (4) late subacute: 3 to 6 months; and (5) chronic: 6 months or more. Insight into the timing of underlying mechanisms of neurobiological recovery is important for early prediction of outcome after stroke, which allows improved clinical decision making and optimisation of discharge planning.

A number of prospective cohort studies showed that the initial severity of neurologic impairments within the first days after stroke onset is an important predictor for functional outcome at 3 or 6 months after stroke. For example, strength of the hemiparetic lower extremity and sitting balance, measured within 72 hours after stroke onset, were strong predictors for regaining independent gait at 6 months. In addition, the National Institutes of Health Stroke Scale (NIHSS), a measure for overall neurological impairment, was found to be highly associated with final outcome in terms of ADL at 6 months after stroke onset when measured within approximately 1 week post stroke. In terms of upper limb motor

![Figure 1.1 Progression of stroke damage and tissue reorganisation.](image-url)

**Figure 1.1 Progression of stroke damage and tissue reorganisation.**
Adapted from Bernhardt and co-workers (2017); previous work of Dobkin and Carmichael (2016).
function, early presence of some Voluntary Finger Extension (VFE) is a strong predictor for recovery of upper limb capacity.\textsuperscript{54,57-59}

Recently, two independently conducted prospective cohort studies showed that early presence of some VFE, combined with presence of some Shoulder Abduction (SA), is a key variable in predicting a favourable outcome of upper limb capacity at 3 and 6 months post stroke.\textsuperscript{54,58} This clinical model known as the SAFE-model showed a high Positive Predictive Value (PPV) when applied within 72 hours to predict outcome at 6 months post stroke (PPV = 0.93, 95% CI = 0.88–0.96).\textsuperscript{54} However, prediction of upper limb recovery in patients who were not likely to regain some upper limb capacity at 6 months (i.e. based on absence of VFE and SA) was much less accurate (Negative Predictive Value, NPV = 0.76, 95% CI = 0.67–0.83).\textsuperscript{54} Retesting the SAFE-model at day 5 and 9 post stroke did show an increase of NPV (0.86, 95% CI = 0.77–0.93) while preserving the high PPV (0.93, 95% CI = 0.89–0.95), suggesting that the accuracy of early prediction of upper limb capacity in patients without initial voluntary SAFE improves during the time course post stroke.\textsuperscript{51} The relationship between the severity of initial impairment and long-term outcome after stroke may not be unexpected, however, it is remarkable that we can accurately predict outcome within 72 hours post stroke. This finding suggests that the amount of neurobiological recovery is already defined within this early time window and that therapy most likely does not have a major contribution to the recovery of neurological impairments.\textsuperscript{60,61} Moreover, spontaneous neurobiological recovery is estimated to explain up to 70% of the variance in neurobiological recovery in the first 3 to 6 months after stroke.\textsuperscript{53} Although the majority of patients show improvement of their neurological impairments to some extent, the amount of spontaneous neurobiological recovery after stroke differs greatly between patients.\textsuperscript{53}

In 2008, the maximum proportional recovery rule was introduced by Prabhakaran and colleagues to describe a general principle behind the large heterogeneity in patients’ recovery patterns of upper extremity motor function.\textsuperscript{53} They measured Upper Extremity (UE) motor function with the Fugl-Meyer Assessment (FMA) in a group of 41 first-ever ischaemic stroke patients.\textsuperscript{53} The motor section of the FMA is suggested to reflect behavioural restitution as it assesses patients’ ability to move outside of patterns of abnormal joint coupling.\textsuperscript{32,62,63} Prabhakaran and colleagues (2008) used linear regression analysis to model the change in FMA-UE scores with clinical predictors. Baseline FMA-UE score (FMA-UE\textsubscript{initial}), subcortical lesion volume, age and time to reassessment were predictors included in the model. They thereafter evaluated the regression model at average subcortical lesion volume, age and time to reassessment, reducing the model to ΔFMA-UE = 0.70 \cdot (66 - FMA-UE\textsubscript{initial}).
Moreover, their proportional recovery rule stated that patients would recover to a level that is 70% of their maximum possible improvement measured with the FMA-UE within 72 hours after stroke onset. However, 7 patients (17%) were characterized as ‘outliers’ and excluded from applied linear regression analysis. These patients failed to follow the rule regarding predicted amount of upper extremity motor recovery. As a consequence of the small sample investigated, Prabhakaran and colleagues (2008) were unable to investigate differences between patient who did and did not follow the proportional prediction rule. Advanced knowledge of patients’ potential for neurobiological recovery and understanding how outliers (i.e. non-fitters) differ from other patients (i.e. fitters) with stroke can help optimize early prediction of outcome. In addition, the identification of non-fitters of spontaneous neurobiological recovery will have a huge impact on designing stroke recovery trials, acknowledging that heterogeneity in patients’ recovery is one of the key problems that lead to failure to underpin evidence-based therapies in stroke rehabilitation. Therefore, identification of fitters and non-fitters on this assumed proportional recovery rule should be seen as a major target for moving stroke rehabilitation forward. Additionally, the maximum proportional recovery rule has been found to be also applicable to the recovery of aphasia. The generalisability of the proportional recovery rule to different neurological impairments may reflect common underlying mechanisms of spontaneous neurobiological recovery and needs to be further investigated.

CAN WE INFLUENCE NEUROBIOLOGICAL RECOVERY WITH EARLY APPLIED INTERVENTIONS?

At this moment, the most effective curative interventions after ischaemic stroke are early reperfusion of the penumbra using recombinant tissue Plasmogen Activator (rt-PA) and endovascular thrombectomy. Both interventions aim to minimize the final size of the ischaemic core by breakdown or removal of the blood clot within the first 4.5 and 6 hours in the hyper-acute phase, respectively. A smaller time window between onset of stroke and intervention is associated with better long term functional outcome in terms of the modified Rankin Scale (mRS) score. About 70% of all stroke patients are not eligible for intravenous or intra-arterial treatment, primarily due to this small time window. Resulting in a number needed to treat (NNT) of 1:4 for intravenous rt-PA and 1:3 for intra-arterial treatment (e.g. mechanical trombectomy and/or intra-arterial thrombolysis) in the Netherlands. To elucidate, the results from the MR CLEAN trial suggest that for every
4 patients with ischaemic stroke treated with rt-PA, 1 patient will be saved from death or dependency following the modified Rankin Scale (mRS, 0–2 points), whereas for intra-arterial treatment this will be the case in 1 out of 3 admitted stroke patients.\textsuperscript{66} However, in middle and low income countries the NNT will be larger mostly due to lower income levels, less high quality stroke-units and limited urbanisation, which results in increased time from stroke onset to hospital admission.\textsuperscript{74} Fortunately, in the Netherlands and in other countries in Europe, the health system is well organized and the distance from patients’ home to a specialized hospital is relatively short.\textsuperscript{74}

Stroke rehabilitation starts early after the hyper-acute phase, as soon as patients are medically stable.\textsuperscript{25} Evidence-based guidelines may help physiotherapists and occupational therapists to choose the most appropriate treatment for each individual patient.\textsuperscript{52} A large number of RCTs focus on testing the effect of new or enhanced therapies to improve self-care, mobility, communication and cognition after stroke. Naturally, the type of treatment is dependent on patients’ level of impairment, time after stroke onset and treatment goals.\textsuperscript{25} It is unclear if and how early applied therapies can influence spontaneous neurobiological recovery. In terms of upper limb function, exercise therapy for those patients with no initial voluntary hand function may focus on compensatory techniques and supportive devices. There are currently no effective evidence-based interventions that improve upper limb function in severely impaired patients.\textsuperscript{19} There is however evidence that ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) may improve motor function of the arm in patients with some VFE, measured in the early subacute, late subacute and chronic phase post stroke.\textsuperscript{75-78} Meta-analyses showed significant positive summary effect sizes of EMG-NMS on motor function of the paretic upper limb (3 RCTs, \( N = 49 \)) and upper limb capacity (14 RCTs, \( N = 162 \)), respectively.\textsuperscript{52} With this, somatosensory stimulation via EMG-NMS may cause changes in neural networks, specifically changes in cortical activation patterns and excitability.\textsuperscript{79,80} Therefore, the value of EMG-NMS in patients without VFE early after stroke should be investigated by applying EMG-NMS in the acute and early subacute phase post stroke to try to influence spontaneous neurobiological recovery and facilitate return of VFE.

Therapies are available for those patients with voluntary movement of the paretic upper limb, including task-specific training and strength training.\textsuperscript{19,25,52} Constraint-Induced Movement Therapy (CIMT) and its modified versions (mCIMT) have shown to be effective interventions.\textsuperscript{52,81-87} For example, Wolf and colleagues (2006) investigated the effect of CIMT in a group of 222 patients in the late subacute and chronic phase post stroke.\textsuperscript{86} Within the 2 week intervention period, patients in the CIMT group received 6 hours of task-specific
upper limb training per day, on weekdays, and were instrumented to wear a padded safety mitt on their less impaired hand to encourage use of the impaired upper limb in ADLs, daily, during 90% of their waking hours. The results showed that patients displayed significant more improvement of upper limb capacity and performance, in terms of Wolf Motor Function Test performance time and Motor Activity Log (amount of use), when administered 2 weeks of CIMT in comparison to usual care. In contrast, a proof-of-concept trial of Dromerick and colleagues suggested that a higher dose of mCIMT of 2 hours per day may harm upper limb recovery ($N_{\text{experimental}} = 16$), in terms of Action Research Arm Test (ARAT) scores, early post stroke when compared to 1 or 2 hours of mCIMT per day ($N_{\text{experimental}} = 19$) and control treatment ($N_{\text{control}} = 17$). Unfortunately, like other previous RCTs, this VECTORS trial only included a small number of patients with stroke ($N = 52$) and did not include measures like the FMA-UE to investigate the impact of mCIMT on the recovery of neurological impairment. Although above proof-of-concept trials were underpowered, meta-analysis of Nijland and co-workers (2011) showed that low-intensity mCIMT of less than 3 hours of shaping procedures of the affected upper limb per working day (3 RCTs, $N_{\text{experimental}} = 32$) was more beneficial than high-intensity mCIMT applied for more than 3 hours (3 RCTs, $N_{\text{experimental}} = 32$) per day, after pooling the results of 5 trials ($N = 106$) that started within the first 3 months post stroke. However, due to the small number of phase II trials of poor to moderate quality, one may conclude that additional high quality trials are needed to underpin the value of low-intensity mCIMT on upper limb recovery in terms of body functions and structure, activities and participation, following the ICF framework. Finally, a meta-analysis of the efficacy of limb constraint in animals showed conflicting results, and suggests a significantly better cognitive function (12 RCTs, $N = 173$) and trend for worse behavioural scores after constraining (2 RCTs, $N = 28$), whereas no significant group differences were found for infarct volume (13 RCTs, $N = 194$).

At this moment, there are no trials on rehabilitation interventions in humans that show large differential effects of more than 15% on top of the within group changes due to spontaneous neurobiological recovery. Taking a more optimistic point of view of early started stroke rehabilitation, a number of animal studies showed that the first weeks post stroke are characterized by increased levels of brain plasticity. Nonetheless, most of the RCTs investigating the effects of (m)CIMT in humans started in the late subacute or chronic phase after stroke and it remains difficult to translate the results from animal to human trials. The variation between animals can easily be reduced by controlling the experimental environment with measurements at fixed time points post stroke and by
controlling animal characteristics (e.g. same genes, lesion location and size). Unfortunately, this is more difficult in human trials. Although the variation between patients will remain, it is possible to reduce the heterogeneity in patients’ recovery within studies by paying more attention to trial design and patient selection in human studies. A more selected, homogeneous, study population will most likely increase the chance of finding clinically meaningful intervention effects in human stroke rehabilitation trials. In addition, the differences in intervention effects between animal and human trials may be partly explained by the higher treatment intensity in animal studies resulting in sufficient treatment contrast. Therefore, acknowledging the importance of tailored interventions and precision medicine in stroke rehabilitation, it is important to conduct stratified trials to address heterogeneity in subjects’ recovery (see also recommendations Langhorne and co-workers, 2011).

**OUTLINE OF THIS THESIS**

The main aims of this thesis are to gain insight into early prediction of neurobiological outcome after stroke and investigate whether we can influence neurobiological recovery with early applied interventions. Therefore, the time window for return of VFE within the first 6 months post stroke onset and the clinical baseline characteristics of those patients who, despite initial absence of VFE, do show some return of upper limb capacity is examined in chapter 2. Next, in chapter 3, early prediction of upper limb motor function in terms of spontaneous neurobiological recovery is investigated. Patients’ upper limb motor function is assessed within 72 hours and 6 months after stroke onset to investigate the generalisability of the ‘maximum proportional recovery rule’, developed in 2008. Thereafter, the generalisability of this rule to the recovery of lower limb motor function and visuospatial neglect is examined in chapters 4 and 5. In addition, differences in patients’ baseline characteristics are investigated to discriminate between patients who follow the rule (i.e. fitters) and patients who do not (i.e. non-fitters). The main results of the EXPPLICIT-stroke trial are described in chapter 6. In EXPPLICIT-stroke, the effects of upper limb training, in comparison to usual care, are investigated in two distinct prognostic patient groups with a first-ever ischaemic stroke. In chapter 7, the effects of various time intervals for patient randomisation and prognostic stratification on the required sample size to find significant and clinically relevant intervention effects in upper limb trials are investigated. Finally, the thesis concludes with a general discussion (chapter 8), reflecting on the main findings of this thesis and discussing directions for future research.
This thesis was part of the prospective cohort study 4D-EEG which runs from 2012 till 2017 in the Netherlands and is funded by the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013; grant number 291339-4D-EEG). The chapters of this thesis are based on the data of the prospective cohort study ‘Early Prediction of Outcome after Stroke’ (acronym: EPOS) funded by the Royal Dutch Society for Physical Therapy (KNGF, grant number 33368),\textsuperscript{20,54} the ‘Stroke Intensity’ trial funded by the Netherlands Heart Foundation (grant number 93.134)\textsuperscript{96} and the ‘EXplaining PLastICITy after stroke’ clinical trial (acronym: EXPLICIT-stroke) funded by the Dutch Organisation for Health Research and Development (ZonMw, grant number 89000001; www.explicit-stroke.nl).\textsuperscript{97}

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When does return of voluntary finger extension occur post stroke?
A prospective cohort study

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ABSTRACT

Background and objective Patients without Voluntary Finger Extension (VFE) early post stroke are suggested to have a poor prognosis for regaining upper limb capacity at 6 months. Despite this poor prognosis, a number of patients do regain upper limb capacity. We aimed to determine the time window for return of VFE during motor recovery and identify clinical characteristics of patients who, despite an initially poor prognosis, show upper limb capacity at 6 months post stroke.

Methods Survival analysis was used to assess the time window for return of VFE (Fugl-Meyer Assessment hand sub question finger extension ≥ 1). A cut-off of ≥ 10 points on the Action Research Arm Test was used to define return of some upper limb capacity (i.e. ability to pick up a small object). Probabilities for regaining upper limb capacity at 6 months post stroke were determined with multivariable logistic regression analysis using patient characteristics.

Results 45 of the 100 patients without VFE at 8 ± 4 days post stroke achieved an Action Research Arm Test score of ≥ 10 points at 6 months. The median time for regaining VFE for these recoverers was 4 weeks (lower and upper percentile respectively 2 and 8 weeks). The median time to return of VFE was not reached for the whole group (N = 100). Patients who had moderate to good lower limb function (Motricity Index leg ≥ 35 points), no visuospatial neglect (single-letter cancellation test asymmetry between the contralesional and ipsilesional sides of < 2 omissions) and sufficient somatosensory function (Erasmus MC modified Nottingham Sensory Assessment ≥ 33 points) had a 0.94 probability of regaining upper limb capacity at 6 months post stroke.

Conclusions Patients with paresis mainly restricted to the upper limb, no visuospatial neglect and sufficient somatosensory function are likely to show at least some return of upper limb capacity at 6 months post stroke. We recommend weekly monitoring of VFE within the first 4 weeks post stroke and preferably up to 8 weeks.
INTRODUCTION

Voluntary Finger Extension (VFE) early after stroke is an important predictor of recovery of upper limb capacity at 6 months post stroke.\textsuperscript{1,2} Patients without VFE within the first days post stroke have been suggested to have a poor prognosis for regaining some upper limb capacity at 6 months.\textsuperscript{1-3} Absence of VFE likely reflects the loss of functional corticospinal tract integrity, acknowledging that the hand muscles are almost solely innervated by contralateral corticospinal pathways.\textsuperscript{4} Indirect bilateral innervation of the hand muscles by the reticulospinal tract may also contribute to hand motor control after stroke.\textsuperscript{5} However, it remains unclear if the reticulospinal system can influence the digital extensor muscles of the paretic hand.\textsuperscript{6}

Despite an initially poor prognosis, some patients without VFE within the first days after stroke do regain upper limb capacity at 6 months.\textsuperscript{2} In view of the lack of evidence-based therapies for patients without VFE,\textsuperscript{7,8} this return of VFE seems most likely to be driven by spontaneous neurobiological mechanisms such as alleviation of diaschisis.\textsuperscript{9} Unfortunately, the clinical characteristics as well as the optimal time window for recovery of VFE are unknown, due to lack of prospective cohort studies in which patients are assessed serially at fixed times post stroke.\textsuperscript{10,11} More knowledge regarding this time window is important for future prognostic algorithm development. Up till now, the most optimal timing and added value of neurophysiological and neuroimaging measurements with respect to clinical measurements like VFE are unclear.

The aims of the present study were therefore (1) to determine the clinical time window for return of VFE in ischaemic stroke patients without VFE in the first days post stroke, and (2) to identify clinical characteristics for the return of some upper limb capacity in these patients within the first 6 months after stroke. We hypothesized that return of VFE would occur within the purported time window of spontaneous neurobiological recovery between 0 and 10 weeks after stroke onset.\textsuperscript{10,12} We also hypothesized that patients with lesions affecting upper limb function who exhibit no other neurological impairments such as visuospatial neglect and somatosensory dysfunction would have a high probability of regaining some upper limb capacity at 6 months.\textsuperscript{13-15}
MATERIALS AND METHODS

Recruitment

Data from the EXPLICIT-stroke program was used.\textsuperscript{16,17} EXPLICIT-stroke was a Dutch translational research program including two multi-centre single blinded randomised controlled trials and an intensive repeated measurements design up to 6 months post stroke. Between October 2008 and November 2013 a total number of 159 patients were included. For the present study only patients in the ElectroMyoGraphy-triggered neuromuscular stimulation (EMG-NMS) trial were selected ($N = 101$). Patients were recruited within the first 2 weeks post stroke and allocated to control treatment (usual care) or experimental treatment focused on regaining VFE (EMG-NMS). Details of the EMG-NMS treatment protocol have been described elsewhere.\textsuperscript{16,17} EXPLICIT-stroke was approved by the ethics committee of Leiden University Medical Center and local feasibility was approved by the institutional review boards of the participating centres (Leiden University Medical Center: No. P08.035; Dutch Central Committee on Research Involving Human Subjects, CCMO: No. NL21396.058.08) and was registered at the Netherlands Trial Registry (NTR1424).

Subjects

Patients were included when they met the following criteria upon screening: (1) first-ever ischaemic middle cerebral artery stroke verified by CT and/or MRI scan; (2) upper limb paresis according to National Institutes of Health Stroke Scale item 5 (score > 0); (3) no VFE at baseline according to Fugl-Meyer Assessment hand sub question FE (score = 0); (4) mini mental state examination $\geq 23$; (5) 18–80 years of age; (6) no upper limb musculoskeletal impairments; (7) no botulinum toxin treatment, as this may distort the measurement of upper limb capacity; (8) able to sit independently for 30 seconds, i.e. sufficient sitting balance to facilitate clinical measurements; (9) written informed consent.

Serial assessments

Eight repeated assessments were performed using the Fugl-Meyer Assessment hand sub question FE to monitor return of VFE (0 = no movement, 1 = partial movement, 2 = full movement).\textsuperscript{18} Assessments were performed weekly in the first 5 weeks post stroke and at 8, 12 and 26 weeks.
**Dependent variable**

The Action Research Arm Test (ARAT) served as outcome measure at 6 months post stroke. The ARAT is a capacity test in the activities domain of the International Classification of Function, Disability and Health framework\(^\text{19}\) and includes 19 tasks divided into 4 subdomains: grasp, grip, pinch and gross movement (maximum = 57 points). The ARAT has a maximal score of 57 points and good clinimetric properties.\(^\text{20,21}\)

**Independent variables**

The following independent baseline variables were identified based on previous literature:\(^\text{22}\)

1. sex;
2. age;
3. hemisphere of stroke;
4. Bamford classification;\(^\text{23}\)
5. time between stroke and baseline assessment;
6. hemianopia and facial palsy (National Institutes of Health Stroke Scale);\(^\text{24}\)
7. visuospatial neglect (letter cancellation test);\(^\text{25}\)
8. somatosensory function of the upper limb (touch, sharp-blunt discrimination and proprioception of the Erasmus MC modified Nottingham Sensory Assessment);\(^\text{26}\)
9. range of motion and strength of the elbow, shoulder, and lower limb (Motricity Index).\(^\text{27}\)

In addition, we added the EXPLICIT-stroke randomisation group as independent variable: experimental (EMG-NMS) versus control group.

**Data analyses**

We used survival analysis on the repeated assessments to determine the time until patients regained VFE for the first time (i.e. partial or full movement according to the Fugl-Meyer Assessment hand sub question FE). For those patients with missing data we took the first assessment where VFE was measured as ‘time to return of VFE’. Possibly, these patients could have regained VFE earlier in time. Recovery was defined as an ARAT score of ≥ 10 points, representing at least some upper limb capacity, i.e. patients should at least be able to pick up a small object against gravity (dichotomisation: 0 = ARAT < 10 and 1 = ARAT ≥ 10).\(^\text{2,28}\)

A Kaplan-Meier\(^\text{29}\) cumulative ‘event’ curve was constructed for the whole group and for the patients with 10 or more points on the ARAT at 6 months post stroke.

For our second objective, statistical analyses were performed on subjects with complete baseline and 6-month assessments. Dichotomisation of independent variables was preferably based on clinical reasoning or previous literature.\(^\text{2}\) Otherwise, we used the Youden index to
determine the cut-off point with the highest sensitivity and specificity.\textsuperscript{30} Bivariable logistic regression analysis was used to preselect independent variables when the Wald statistic had a p-value of < .05. Subsequently, collinearity diagnostics between preselected variables was applied using two-way contingency tables. If the Phi correlation coefficient between two variables was ≥ .80, the variable with the lowest Wald statistic was excluded from further analysis. Thereafter, we used a backward stepwise multivariable logistic regression analysis on the selected variables to form the prediction model (removal criterion = $p \geq .10$). In view of the large number of preselected variables relative to the number of patients included in the study, we applied a forward stepwise approach to test model stability (entry criterion = $p < .05$). In view of the large number of preselected variables relative to the number of patients included in the study, we applied a forward stepwise approach to test model stability. The Hosmer-Lemeshow test and the $c$-statistic (i.e. area under the receiver-operating characteristic curve) were used to quantify the goodness-of-fit of the logistic regression model, and two-way contingency tables to calculate sensitivity, specificity, positive predictive value, and negative predictive value, including the corresponding 95% confidence intervals (95% CI). Statistical analyses were two-tailed with an alpha of .05 (SPSS version 20).

RESULTS

One hundred one first-ever ischaemic stroke patients were recruited for the EXPLICIT-stroke EMG-NMS trial. In the present study, 1 patient was excluded for further analyses due to presence of some VFE. Patient characteristics of the 100 patients eligible for further analysis are shown in Table 2.1. At 6 months post stroke, 45 of the 100 patients achieved an ARAT score of ≥ 10 points. This group of patients had a baseline ARAT score ranging from 0 points to 7 points, with 30 patients scoring 0 points, 11 patients scoring between 1 and 5 points, and 4 patients scoring 6 or 7 points. At 6 months post stroke, this group had a median ARAT score of 34 points (interquartile range, IQR = 20–45; range = 10–57); 4 patients scored 10 points, and 5 of them attained the maximum score of 57 points. In comparison, the median 6-month ARAT score for the other group was 0 (IQR = 0–3; range = 0–4).

Approximately 7% of the repeated assessments of VFE were missing. The Kaplan-Meier curve for the whole group of 100 patients is shown in Figure 2.1. Three patients were lost to follow-up due to death, recurrent stroke and withdrawal. The median time to return of VFE was not reached within the first 26 weeks post stroke. Visually, we do see that return of VFE occurs primarily within the first 8 weeks. Note that the cumulative ‘event’ curve is 1 minus
Table 2.1  Patient characteristics

<table>
<thead>
<tr>
<th>Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female, % male</td>
<td>64/36, 64%</td>
</tr>
<tr>
<td>Age, years\textsuperscript{1}</td>
<td>58.67 (11.72)</td>
</tr>
<tr>
<td>Hemisphere of stroke, right/left, % right</td>
<td>69/31, 69%</td>
</tr>
<tr>
<td>Bamford classification, LACI/PACI/TACI</td>
<td>55/39/6</td>
</tr>
<tr>
<td>Global disability (NIHSS, range: 0–40) (&lt;i&gt;N&lt;/i&gt; = 99)\textsuperscript{*}</td>
<td>9 (7–11)</td>
</tr>
<tr>
<td>Hemianopia (NIHSS item 3): yes/no, % yes</td>
<td>8/92, 8%</td>
</tr>
<tr>
<td>Facial palsy (NIHSS item 4): yes/no, % yes</td>
<td>85/15, 85%</td>
</tr>
<tr>
<td>Extinction and inattention (NIHSS item 11): yes/no, % yes</td>
<td>32/68, 32%</td>
</tr>
<tr>
<td>Sensation (NIHSS item 8): yes/no, % yes</td>
<td>48/52, 48%</td>
</tr>
<tr>
<td>Visuospatial neglect (LCT): yes/no, % yes (&lt;i&gt;N&lt;/i&gt; = 94)</td>
<td>58/36, 58%</td>
</tr>
<tr>
<td>Somatosensory function (EmNSA): good/poor, % poor (&lt;i&gt;N&lt;/i&gt; = 99)</td>
<td>57/42, 42%</td>
</tr>
<tr>
<td>Upper limb function (MI, range: 0–100)\textsuperscript{*}</td>
<td>0 (0–23)</td>
</tr>
<tr>
<td>Upper limb function (FMA, range: 0–66)\textsuperscript{*}</td>
<td>5 (4–8)</td>
</tr>
<tr>
<td>Lower limb function (MI, range: 0–100) (&lt;i&gt;N&lt;/i&gt; = 99)\textsuperscript{*}</td>
<td>32 (9–47)</td>
</tr>
<tr>
<td>Upper limb capacity (ARAT, range: 0–57)\textsuperscript{*}</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Time between stroke and baseline assessment, days\textsuperscript{1}</td>
<td>8.26 (4.10)</td>
</tr>
</tbody>
</table>

6 months post stroke

| Upper limb capacity (ARAT, range: 0–57, <i>N</i> = 97)\textsuperscript{*} | 4 (0–30.5) |
| Time between stroke and 6-month assessment, days\textsuperscript{1} | 189.90 (14.10) |

Data from all 100 subjects, unless otherwise indicated. EmNSA: Erasmus MC modified Nottingham Sensory Assessment; FMA: Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; LCT: Letter Cancelation Test; MI: Motricity Index; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; TACI: Total Anterior Cerebral Infarction. Data presents number of patients (<i>N</i>); * Median (IQR); \textsuperscript{1} Mean (SD).

Figure 2.1  Kaplan-Meier cumulative ‘event’ curve for return of voluntary finger extension (<i>N</i> = 100). Three patients were lost to follow-up.
survival, and resembles the probability of an event. In other words, a high and/or rapidly rising curve is a favourable outcome (i.e. return of VFE). An additional analysis was performed on the group of patients who did regain some upper limb capacity (i.e. ARAT ≥ 10 points) at 6 months post stroke (N = 45, Figure 2.2). The Kaplan-Meier curve in Figure 2.2 shows an initial sharp rise and reaches a median time to return of VFE at 4 weeks post stroke (SE = 0.52; 95% CI = 2.99–5.01). The lower (25th) and upper (75th) percentiles were respectively 2 weeks and 8 weeks post stroke. Twenty-three patients (51%) of the recoverers had regained VFE at 4 weeks after stroke, and at 8 weeks this number had increased to 38 patients (84%).

![Kaplan-Meier cumulative ‘event’ curve for return of voluntary finger extension in the group of patients who regain some upper limb capacity at 6 months post stroke (N = 45).](image)

Logistic regression analyses were only performed on patients with complete baseline and 6-month assessments (N = 91); we excluded 3 drop-outs as described before and another 6 patients due to missing baseline data. Bivariable logistic regression analysis showed that 7 of the 13 baseline variables were significantly related to recovery of upper limb capacity (ARAT ≥ 10 points) at 6 months post stroke (p < .05, Table 2.2). Collinearity diagnostics between independent variables showed no correlation coefficients ≥ .80. The subsequent backward multivariable logistic regression analysis, performed on the 7 preselected baseline variables, yielded a prediction model for return of upper limb capacity despite initial lack of VFE consisting of 3 variables: (1) moderate to good lower limb motor function, i.e. Motricity Index-
leg ≥ 35 points; (2) absence of visuospatial neglect, i.e. a letter cancellation test asymmetry between the contralesional and ipsilesional sides of < 2 omissions; and (3) sufficient somatosensory function, i.e. Erasmus MC modified Nottingham Sensory Assessment ≥ 33 points.

Table 2.2  Candidate baseline variables associated with regaining some upper limb capacity at 6 months post stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (0 = female; 1 = male)†</td>
<td>0.79</td>
<td>0.33–1.91</td>
<td>.606</td>
</tr>
<tr>
<td>Age (years)‡</td>
<td>1.00</td>
<td>0.97–1.04</td>
<td>.950</td>
</tr>
<tr>
<td>Hemisphere of stroke (0 = right; 1 = left)†</td>
<td>2.40</td>
<td>0.94–6.10</td>
<td>.066</td>
</tr>
<tr>
<td>Type of stroke (Bamford classification: 0 = PACI/TACI; 1 = LACI)†</td>
<td>3.33</td>
<td>1.39–8.01</td>
<td>.007*</td>
</tr>
<tr>
<td>Time between stroke and baseline (days)‡</td>
<td>1.07</td>
<td>0.96–1.18</td>
<td>.222</td>
</tr>
<tr>
<td>Hemianopia (NIHSS item 3: 0 = yes; 1 = no)†</td>
<td>0.85</td>
<td>0.16–4.44</td>
<td>.845</td>
</tr>
<tr>
<td>Facial palsy (NIHSS item 4: 0 = yes; 1 = no)†</td>
<td>3.99</td>
<td>1.16–13.69</td>
<td>.028*</td>
</tr>
<tr>
<td>Visuospatial neglect (LCT asymmetry: 0 ≥ 2; 1 &lt; 2)§</td>
<td>6.54</td>
<td>2.53–16.90</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Somatosensory function (EmNSA: 0 &lt; 33; 1 ≥ 33)</td>
<td></td>
<td></td>
<td>4.06</td>
</tr>
<tr>
<td>Shoulder abduction (MI: 0 &lt; 9; 1 ≥ 9)†</td>
<td>3.68</td>
<td>1.54–8.79</td>
<td>.003*</td>
</tr>
<tr>
<td>Elbow flexion (MI: 0 &lt; 9; 1 ≥ 9)‡</td>
<td>8.00</td>
<td>2.65–24.17</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Lower limb function (MI-leg: 0 &lt; 35; 1 ≥ 35)</td>
<td></td>
<td></td>
<td>12.67</td>
</tr>
<tr>
<td>Randomisation (0 = control group; 1 = experimental group)†</td>
<td>0.80</td>
<td>0.35–1.84</td>
<td>.605</td>
</tr>
</tbody>
</table>

EmNSA: Erasmus modified Nottingham Sensory Assessment; LACI: Lacunar Anterior Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; LCT: Letter Cancellation Test; MI: Motricity Index; PACI: Partial Anterior Cerebral Infarction; TACI: Total Anterior Cerebral Infarction; * Wald statistic with p < .05; † Based on clinical grounds; ‡ Not dichotomised; § Dichotomisation based on previous literature;¶ Based on area under the receiver-operating characteristic curve.

Table 2.3  Probabilities of regaining some upper limb capacity at 6 months post stroke in patients who initially did not show finger extension

<table>
<thead>
<tr>
<th>LL</th>
<th>VSN</th>
<th>SSF</th>
<th>True negatives (N)</th>
<th>False negatives (N)</th>
<th>False positives (N)</th>
<th>True positives (N)</th>
<th>Predicted probability (0–1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>No</td>
<td>Good</td>
<td>36</td>
<td>5</td>
<td>13</td>
<td>37</td>
<td>0.94</td>
</tr>
<tr>
<td>Good</td>
<td>No</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Good</td>
<td>Yes</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Poor</td>
<td>No</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Good</td>
<td>Yes</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Poor</td>
<td>No</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Poor</td>
<td>Yes</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Poor</td>
<td>Yes</td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

Model: P (upper limb capacity) = 1/1+e (-3.24+2.80xLL+1.91xVSN+1.36xSSF). LL: Lower Limb function (Motricity Index leg); SSF: SomatoSensory Function (Erasmus MC modified Nottingham Sensory Assessment); VSN: VisuoSpatial Neglect (Letter Cancellation Test asymmetry).
Forward stepwise analysis confirmed these results. Table 2.3 displays all predicted probabilities of the model, ranging from 0.04–0.94, with a Hosmer-Lemeshow chi-square of 3.41 ($p = .637$) and a c-statistic of 0.89. Two-way contingency tables showed a sensitivity of 0.88 (95% CI = 0.74–0.96), specificity of 0.73 (95% CI = 0.60–0.85), positive predictive value of 0.74 (95% CI = 0.60–0.85) and negative predictive value of 0.88 (95% CI = 0.74–0.96) for the final model.

**DISCUSSION**

To our knowledge, this is the first study to prospectively investigate the clinical time window for spontaneous return of VFE in ischaemic stroke patients who showed no VFE within the first days post stroke. The present study shows that if patients do regain VFE, this will most likely occur within the first 8 weeks after stroke onset. However, more than half of the patients who regained some upper limb capacity at 6 months post stroke already showed this return of VFE within the first 4 weeks post stroke. In view of the absence of evidence-based therapies for this specific group of patients, as well as our neutral trial showing no effects of early-start EMG-NMS intervention, we believe this return of VFE is most likely driven by spontaneous mechanisms of neurobiological recovery.

Acknowledging that most evidence-based therapies for the upper limb depend on selecting patients for their ability to voluntarily extend their fingers, we recommend that clinicians monitor these stroke patients for return of VFE weekly, at least up to 8 weeks post stroke. This recommendation is in line with the recently developed *Post Stroke Arm Algorithm* application (“app”) which offers clinicians an online tool to select the most appropriate evidence-based upper limb therapy for an individual patient, with an emphasis on the regular monitoring of VFE. If VFE returns within the time window for neurobiological recovery, the prognosis changes in favour of regaining upper limb capacity, and therapy may focus on improving motor function through high-intensity repetitive exercise to prevent learned non-use of the paretic arm, for example with (modified) constraint-induced movement therapy.

Importantly, we do not claim that return of VFE always occurs within the first 8 weeks, as there may be exceptions due to neglect, acknowledging the suppressive effects of neglect on motor recovery. However, the present study suggests that the likelihood of recovery after this time period is small. Future studies should further investigate those cases that constitute an exception to the rule, that is, focus on patients who show return of VFE beyond the first 8 weeks post stroke.
Concerning our second objective, we found that patients with no initial VFE who showed moderate to good lower limb motor function, no visuospatial neglect, and sufficient somatosensory function have a high probability (0.94) of regaining at least some upper limb capacity at 6 months post stroke (i.e. ability to pick up a small object). The model presented here may be seen as an important contribution to the prediction of upper limb capacity in patients with an initial poor prognosis early post stroke.

Severity of lower limb paresis was previously suggested to be an important predictor of regaining upper limb function and may reflect the extent of the lesion and as such the severity of initial neurological damage. The substantial negative impact of visuospatial neglect on upper extremity motor recovery which was found in other studies may reflect the suppressive effects of the dysfunctional site of injury on anatomically and functionally related brain areas at remote distance from the location of the infarct. Our model also suggests that somatosensory dysfunction is a crucial factor that prevents upper limb recovery. Repeated, systematic monitoring of neurological impairments within the first 8 weeks after stroke onset may give more insight in the underlying logistic pattern of spontaneous neurobiological recovery.

**Study limitations & future research**

It should be noted that half of the patients in the current study received 3 weeks of additional therapy with EMG-NMS focused at regaining VFE, in comparison to the other group that solely received usual care according to evidence-based guidelines. We postulate that this did not affect our results, as the EXPLICIT-stroke trial did not show any significant interaction effects of time with EMG-NMS on the likelihood of return of upper limb capacity within this time window. High quality randomised controlled trials are needed to determine if the likelihood and timing of this return of VFE can be improved and accelerated by innovative therapies that may enhance neuronal activity and restore activity homeostasis, such as transcranial direct-current stimulation, repetitive transcranial magnetic stimulation or pharmaceuticals combined with exercise therapy.

Second, the present study shows that in particular patients with a paresis of the arm without somatosensory dysfunction and neglect are more likely to have some return of upper limb capacity. The sensitivity of the current model was quite good (0.88, 95% CI = 0.74–0.96), however, the specificity was somewhat lower (0.73, 95% CI = 0.60–0.85). This misclassification of patients as recoverers was also observed in previous studies using
Transcranial Magnetic Stimulation (TMS).\textsuperscript{38,39} Moreover, the presence of a motor evoked potential does not necessarily mean that patients will show recovery of hand function.\textsuperscript{38,39} Preliminary results from the Prediction REcovery Potential (PREP)-algorithm, which sequentially combines clinical measurements of shoulder abduction and finger extension (SAFE) with TMS and Diffusion Tensor Imaging (DTI), showed a specificity and sensitivity of respectively 0.88 and 0.73.\textsuperscript{40} However, these values were for the ‘complete recovery’ subcategory (i.e. ARAT score of 50 points or higher). Sensitivity and specificity values for the other categories (i.e. notable, limited and no recovery) were not provided. We therefore cannot directly compare the preliminary results from the PREP-algorithm with our results as the cut-off values are different. The current results emphasize the importance of repeated clinical assessment of VFE in the first weeks post stroke for clinical decision making. Within the PREP-algorithm, SAFE was however not reassessed when TMS and DTI were performed at about 2 weeks post stroke.\textsuperscript{40} Determination of confidence intervals reflecting precision of this algorithm, as well as cross-validation are needed to underpin the robustness of propagated models. Future cohort studies are needed to refine our clinical prediction model by exploring the added value of neuroimaging, such as stroke volume or localisation (e.g. cortical or subcortical)\textsuperscript{41,42} and DTI,\textsuperscript{43} TMS\textsuperscript{39} and other biomarkers associated with the recovery of upper limb capacity after stroke.\textsuperscript{11}

Third, the sample size of the present study was relatively small in relation to the number of variables. However, model stability and robustness was confirmed with an additional forward stepwise logistic regression analysis.

Fourth, although models with dichotomised outcomes are often used within clinical practice, they do limit the understanding of individual recovery profiles. Moreover, with the current model we cannot differentiate between patients who regain some upper limb capacity (ARAT = 10 points) and those who regain full upper limb capacity (ARAT = 57 points). The cut-off value of 10 or more points on the ARAT was used in previous literature as it represents the recovery of some dexterity.\textsuperscript{2,28} Future studies are needed to identify subgroups of patients achieving notable or limited dexterity at 3 and 6 months post stroke. To achieve this goal, larger prospective cohorts are needed to test the precision and with that the robustness of current models for identifying these subgroups with limited and notable recovery.

Finally, the present study was restricted to patients with a first-ever ischaemic middle cerebral artery stroke and did not include cross-validation of the logistic regression model.
Acknowledgements

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REFERENCES


Generalisability of the proportional recovery model for the upper extremity after an ischaemic stroke

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ABSTRACT

Background and objective  Spontaneous neurobiological recovery after stroke is a poorly understood process. The aim of the present paper was to test the proportional recovery rule for the upper extremity post stroke, and to identify clinical characteristics of patients who do not fit this rule.

Methods  A change in the Fugl-Meyer Assessment Upper Extremity score (FMA-UE) measured within 72 hours and at 6 months post stroke served to define motor recovery. Recovery on FMA-UE was predicted using the proportional recovery rule: \( \Delta \text{FMA-UE}_{\text{predicted}} = 0.7 \cdot (66 - \text{FMA-UE}_{\text{initial}}) + 0.4 \). Hierarchical cluster analysis on 211 patients was used to separate non-fitters (outliers) from fitters, and differences between these groups were studied using clinical variables measured within 72 hours post stroke. Subsequent logistic regression analysis served to predict patients who may not fit the rule.

Results  The majority of patients (~70%; \( N = 146 \)) showed a fixed proportional upper extremity motor recovery of about 78%. Sixty-five patients had substantially less improvement than predicted. These non-fitters had more severe neurological impairments within 72 hours post stroke (\( p \)-values < .01). Logistic regression analysis revealed that absence of finger extension, presence of facial palsy, more severe lower extremity paresis, and more severe type of stroke as defined by the Bamford classification were significant predictors of not fitting the proportional recovery rule.

Conclusions  These results confirm in an independent sample that stroke patients with mild to moderate initial impairments show an almost fixed proportional upper extremity motor recovery. Patients who will most likely not achieve the predicted amount of recovery were identified using clinical variables measured within 72 hours post stroke.
INTRODUCTION

Spontaneous neurobiological recovery is a central, yet neglected topic in stroke rehabilitation. It is a prime confounder in understanding the real impact of new early applied rehabilitative interventions in addition to usual care. Longitudinal regression analysis of change scores suggests that most of the improvements in motor function are predominantly defined in the first 10 to 12 weeks post stroke. Recovery in terms of Fugl-Meyer Assessment (FMA) scores reflecting movement synergies is often considered indicative of “behavioural restitution" or “true neurological recovery” in the first months post stroke.

Prabhakaran and co-workers (2008) suggested that the amount of spontaneous motor recovery of the paretic upper extremity is relatively fixed and accounts for approximately 70% of patients’ maximum potential recovery. Accordingly, patients with severe initial upper extremity impairment may have greater change scores on the FMA than patients with mild initial upper extremity impairment. Detailed analysis revealed that 7 out of 41 patients displayed significantly less motor recovery after 3 or 6 months than predicted. Unfortunately, this small sample did not allow for identifying clinical factors characterizing these poor recoverers. These factors would be useful within clinical practice to improve prediction and provide focused and personalized rehabilitation.

The first objective of the present study was, therefore, to test the rule for proportional motor recovery of the paretic upper extremity in an independent sample of patients after a first-ever ischaemic stroke when measured within 72 hours post stroke. The second objective was to identify the clinical characteristics of those patients who do not show the predicted amount of motor recovery.

MATERIALS AND METHODS

Recruitment

From March 2007 till July 2010, patients were recruited for the prospective cohort study entitled Early Prediction of functional Outcome after Stroke (acronym: EPOS). All patients received solely usual care according to evidence-based stroke guidelines for physiotherapists. The ethics committees of all participating hospitals approved the study. Patients were included when they met the following criteria: (1) first-ever ischaemic anterior circulation stroke, including anterior or middle cerebral artery stroke; (2) premorbid Barthel
Index of ≥ 19; (3) at least 18 years of age; (4) no severe deficits of communication or memory; (5) hemiparesis within 72 hours after stroke onset; and (6) written informed consent. Additionally, for the present study only patients with a FMA Upper Extremity (FMA-UE) score < 66 points within 72 hours post stroke were eligible for analysis.

**Measurements**

Patients’ baseline characteristics were assessed within 72 hours post stroke. This included age, sex, treatment with recombinant tissue plasminogen activator (rt-PA), hemisphere of stroke, time between stroke and first assessment, co-morbidities (Cumulative Illness Rating Scale, CIRS),13 severity of stroke (Bamford Classification),14 neurological examination (National Institutes of Health Stroke Scale, NIHSS),15 upper and lower extremity motor function using the Motricity Index (MI)16 and FMA.17

Initial upper extremity impairment (within 72 hours after stroke) and motor function at six months post stroke were assessed by the FMA-UE,17 a sensitive, reliable, and valid measure of recovery at the impairment level.18-20 The difference between the initial and six months FMA-UE scores (\( \Delta \text{FMA-UE}_{\text{observed}} = \text{FMA-UE}_{\text{6months}} - \text{FMA-UE}_{\text{initial}} \)) was used to estimate motor recovery. In the proportional recovery rule (Equation 3.1) developed by Prabhakaran and co-workers8 to predict recovery, stroke patients are expected to achieve approximately 70% of the difference between their initial FMA-UE score and the maximum attainable score at 6 months post stroke, according to:

\[
\Delta \text{FMA-UE}_{\text{predicted}} = 0.7 \cdot (66 - \text{FMA-UE}_{\text{initial}}) + 0.4
\]

\[
\approx 0.7 \cdot \text{(maximum potential recovery)}
\]

**Data analyses**

Groups were classified using a hierarchical clustering21 based on average pairwise Mahalanobis distances (Matlab’s Statistics toolbox, Version 8.1, Matlab version 2013a, Mathworks Inc., Natwick, MA). Note that the Mahalanobis distance is closely related to Pearson’s correlation measure, rendering its use for the current data set justifiable. A fixed cut-off served to separate clusters. The resulting goodness-of-fit was determined via the cophenetic correlation coefficient between the cophenetic distance obtained from the dendrogram and the Euclidean distance within the original (unmodeled) data, and the Spearman correlation coefficient between Mahalanobis and cophenetic distances.
Comparisons between the fitters and non-fitters were made using baseline characteristics measured within 72 hours post stroke. The assumption of normality was tested by visual inspection of the histogram and box plot, and by the Kolmogorov-Smirnoff test to confirm visual plot analysis. The Levene's test was used to test for homogeneity of variance. Thereafter, categorical data were assessed using Pearson's chi-square test, parametric data using the independent $t$-test, and non-parametric data using the Mann-Whitney U test (two-tailed significance level of .05).

Bivariable logistic regression analysis was used as preselection for the multivariable logistic regression analysis with a dichotome outcome ($0 = \text{fitters}$ and $1 = \text{non-fitters}$). Candidate variables were selected on the basis of previous studies.\textsuperscript{10,22} Subsequent dichotomisation into 0 or 1 was based on clinical grounds and/or previous literature, with 1 indicating a poor score on the test, i.e. more severe neurological deficit or greater motor impairment. Odds ratios and confidence intervals (95\% CI) were calculated and candidate variables were selected when $p < .10$ (Wald test). Consecutive collinearity diagnostics using two-way contingency tables was applied between candidate variables. If the Phi correlation coefficient was $\geq 0.8$, we chose to exclude the variable with the lower Wald statistic from further analysis.

The probabilities of not fitting the recovery rule were derived from multivariable logistic regression analysis using a backward stepwise approach (entry criteria: $p \leq .05$; removal criteria: $p \geq .10$). A forward stepwise approach was used to test the stability of the model because of the large number of variables relative to the number of patients within the study. The Hosmer-Lemeshow test and the $c$-statistic (i.e. area under the receiver operating characteristic curve) were used to quantify the goodness-of-fit of the logistic regression model. Finally, sensitivity, specificity, Positive Predictive Value (PVV), and Negative Predictive Value (NPV), including the corresponding 95\% CIs, were calculated using two-way contingency tables. All statistical assessments were performed using SPSS (version 20).

**RESULTS**

A group of 211 patients with a first-ever ischaemic hemispheric stroke were eligible for analysis, out of a total of 275 patients in the EPOS study (see flow chart in Figure 3.1). Figure 3.2A shows the predicted versus the observed ΔFMA-UE scores. Hierarchical clustering yielded two clusters containing $N_1 = 146$ and $N_2 = 65$ samples, respectively, using $c = 2.194$.
as cut-off. The cophenetic correlation coefficient\(^{23}\) and the Spearman correlation coefficient between the Mahalanobis and cophenetic distances were 0.95 and 0.76, respectively. The resulting dendrogram is depicted in Figure 3.2B.

Within the subgroup of non-fitters (\(N = 65\)), the baseline FMA-UE ranged from 0–17 points and the observed median \(\Delta\)FMA-UE (7.00 (interquartile range, IQR = 2.00–15.00)) was approximately 84% lower than the predicted \(\Delta\)FMA-UE (43.80 (IQR = 42.40–45.20); \(p < .001\)). The fitters, on the other hand, had a 3 points higher observed median \(\Delta\)FMA-UE than predicted (observed: 20.50 (IQR = 7.00–39.25); predicted: 17.55 (IQR = 7.40–34.00); \(p < .001\)). Baseline FMA-UE of the fitters ranged from 0–65 points. The proportional motor recovery of the paretic upper extremity was 78.2% ± 31.6% in the group of fitters (\(\Delta\)FMA-UE\(_{\text{observed}} = 78\% \cdot (66 - \text{FMA-UE}_{\text{initial}})\)).

Figure 3.1 Patient exclusion flow chart.

From March 2007 to July 2010
4082 patients were submitted to the participating centres following a stroke

275 patients were included for the EPOS study

42 patients did not have the 6 month follow-up assessment:
- 3 refused follow-up
- 5 had a recurrent stroke
- 9 were not able to undergo the assessment
- 24 died before end of the survey
- 1 was lost to follow-up

5 patients had an initial FMA-UE score of 66 points

17 patients’ initial assessment was not performed within 72 hours post stroke

Total of 211 patients available for further analysis

3807 patients were excluded:
- 702 haemorrhagic stroke
- 456 posterior circulation stroke
- 591 recurrent stroke
- 207 premorbid Barthel Index <19
- 400 insufficient in communication and understanding
- 1451 other, e.g. patient died, unwilling to participate, transfer to other centre

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Figure 3.1 Patient exclusion flow chart.
Within 72 hours post stroke, the non-fitters had significantly lower upper and lower extremity motor function scores, displayed more neurological deficits as measured with the NIHSS, were more often treated with rt-PA, and had more often a total or partial anterior cerebral infarctions (TACI, PACI) than lacunar anterior cerebral infarction (LACI), in comparison to the fitters (p-values < .01; Table 3.1). No statistically significant differences at baseline were found between the non-fitters and fitters regarding age, sex, hemisphere of stroke, time between stroke and initial assessment, or co-morbidities. At 6 months post stroke, non-fitters had significantly
lower upper extremity motor function scores ($p < .01$) in comparison to the fitters. The time between stroke onset and the follow-up assessment did not differ significantly between groups.

Table 3.2 summarizes the results of the bivariable logistic regression analyses. Strong collinearity was found between elbow flexion and shoulder abduction ($\Phi = 0.89, p < .001$),

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fitters</th>
<th>Non-fitters</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 72 hours post stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>66.10 ± 14.10</td>
<td>67.26 ± 14.05</td>
<td>.714$^*$</td>
</tr>
<tr>
<td>Sex, male/female, % male</td>
<td>71/75, 48.6%</td>
<td>27/38, 41.5%</td>
<td>.340$^†$</td>
</tr>
<tr>
<td>rt-PA, yes/no, % yes</td>
<td>31/115, 21.2%</td>
<td>25/40, 38.5%</td>
<td>.009$^{**}$</td>
</tr>
<tr>
<td>Hemisphere of stroke, right/left, % right</td>
<td>77/69, 52.7%</td>
<td>41/24, 63.1%</td>
<td>.163$^†$</td>
</tr>
<tr>
<td>Time between stroke and initial assessment, days$^b$</td>
<td>2.09 ± 0.80</td>
<td>1.94 ± 0.92</td>
<td>.341$^*$</td>
</tr>
<tr>
<td>CIRS$^a$</td>
<td>3 (1–4)</td>
<td>2 (1–4)</td>
<td>.234$^‡$</td>
</tr>
<tr>
<td>Bamford classification, LACI/PACI/TACI</td>
<td>89/38/19</td>
<td>11/29/25</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS$^a$</td>
<td>5 (3–9)</td>
<td>16 (9.50–18)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS hemianopia$^a$</td>
<td>0 (0–0)</td>
<td>1 (0–2)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS facial palsy$^a$</td>
<td>1 (0–2)</td>
<td>2 (1–2)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS paretic upper extremity$^a$</td>
<td>1 (0–2)</td>
<td>4 (3–4)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS sensory loss$^a$</td>
<td>1 (0–1)</td>
<td>1 (1–1)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>NIHSS inattention$^a$</td>
<td>0 (0–1)</td>
<td>1 (0–2)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI arm$^a$</td>
<td>65 (38.75–76)</td>
<td>0 (0–10)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI pinch grip$^a$</td>
<td>22 (11–26)</td>
<td>0 (0–0)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI elbow flexion$^a$</td>
<td>25 (14–25)</td>
<td>0 (0–0)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI shoulder abduction$^a$</td>
<td>19 (14–25)</td>
<td>0 (0–9)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI leg$^a$</td>
<td>69 (47–83)</td>
<td>9 (0–39.50)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI dorsal flexion$^a$</td>
<td>25 (14–25)</td>
<td>0 (0–14)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI knee extension$^a$</td>
<td>25 (19–33)</td>
<td>9 (0–14)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>MI hip flexion$^a$</td>
<td>25 (14–25)</td>
<td>9 (0–14)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>FMA-UE$^a$</td>
<td>41.5 (18–56)</td>
<td>4 (2–6)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>FMA-UE shoulder elevation$^a$</td>
<td>2 (1–2)</td>
<td>0 (0–1)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>FMA-UE shoulder retraction$^a$</td>
<td>2 (1–2)</td>
<td>0 (0–0)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>FMA-UE finger extension$^a$</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>&lt; .001$^{**}$</td>
</tr>
<tr>
<td>FMA-LE$^a$</td>
<td>25 (18–30)</td>
<td>7 (3–13)</td>
<td>&lt; .001$^{**}$</td>
</tr>
</tbody>
</table>

| Follow-up assessment | | | |
| FMA-UE score at 6 months$^a$ | 63 (59–65) | 11 (6–21.5) | < .001$^{**}$ |
| Time between stroke and 6-month assessment, days$^b$ | 188.48±12.96 | 188.06±14.56 | .288$^‡$ |

CIRS: Cumulative Illness Rating Scale; FMA: Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; LE: Lower Extremity; MI: Motricity Index; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; rt-PA: recombinant tissue Plasminogen Activator; TACI: Total Anterior Cerebral Infarction; UE: Upper Extremity. Data is presented as number of patients (N); $^*$ Represents median (interquartile range); $^b$ Represents mean ± standard deviation; $^p < .05$; $^†$ Pearson’s chi-square test; $^‡$ Mann-Whitney U test.
Consequently, shoulder abduction was excluded from further analysis. Backward stepwise logistic regression analysis showed that patients who displayed (1) no finger extension (FMA-UE), (2) presence of facial palsy (NIHSS), (3) severe impairment of lower extremity motor function (FMA Lower Extremity), and (4) total or partial anterior cerebral infarction (Bamford classification) within 72 hours post stroke, were likely not to show the predicted proportional motor recovery (Tables 3.3 and 3.4). The sensitivity of the model was 0.80 (95% CI = 0.68–0.89) and the specificity was 0.89 (95% CI = 0.83–0.94), whereas the PPV and NPV were respectively 0.76 (95% CI = 0.65–0.86) and 0.91 (95% CI = 0.85–0.95). These results were confirmed by forward stepwise analysis.

| Table 3.2  Candidate variables measured within 72 hours post stroke associated with not fitting the proportional recovery rule |
|-----------------|-----------------|-----------------|-----------------|
| Variable        | Odds ratio      | 95% CI          | p               |
| rt-PA (0 = yes; 1 = no) | 0.43            | 0.23–0.82       | .010*           |
| Bamford (0 = LACI; 1 = TACI/PACI) | 7.67            | 3.70–15.88      | < .001*         |
| NIHSS (0 < 8; 1 ≥ 8) | 24.50          | 9.24–64.98      | < .001*         |
| NIHSS hemianopia (0 = 0; 1 ≥ 1) | 6.50           | 3.39–12.45      | < .001*         |
| NIHSS facial palsy (0 = 0; 1 ≥ 1) | 32.33          | 4.35–240.05     | < .001*         |
| NIHSS sensory loss (0 = 0; 1 ≥ 1) | 4.40           | 2.13–9.09       | < .001*         |
| NIHSS inattention (0 = 0; 1 ≥ 1) | 4.56           | 2.44–8.52       | < .001*         |
| FMA-UE finger extension (0 ≥ 1; 1 = 0) | 54.78          | 16.26–184.47    | < .001*         |
| FMA-UE shoulder elevation (0 ≥ 1; 1 = 0) | 16.45          | 8.01–33.78      | < .001*         |
| MI shoulder abduction (0 ≥ 9; 1 = 0) | 20.08          | 9.57–42.14      | < .001*         |
| MI elbow flexion (0 ≥ 9; 1 = 0) | 23.70         | 11.10–50.64     | < .001*         |
| FMA-LE (0 ≥ 18; 1 < 18) | 17.44           | 8.05–37.81      | < .001*         |

The cut-off scores for variables are shown in brackets; 1 indicates a poor score on the test, i.e. more severe neurological deficit or greater motor impairment. In detail, 1 indicates: no treatment with rt-PA; more severe type of stroke (TACI/PACI, Bamford classification); more impairment (NIHSS total score ≥ 8); impairment present (NIHSS subscores ≥ 1); no movement (FMA-UE subscores = 0); no random muscle activity palpable (MI-UE subscores = 0); and lower extremity motor function within the basic synergistic pattern (FMA Lower Extremity score < 18). FMA: Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; LE: Lower Extremity; MI: Motricity Index; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; rt-PA: recombinant tissue Plasminogen Activator; TACI: Total Anterior Cerebral Infarction; UE: Upper Extremity. Wald test: * p < .10.
Table 3.3  Predictor variables included in the final logistic prediction model

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>B</th>
<th>Odds ratio</th>
<th>95% CI odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger extension</td>
<td>3.084</td>
<td>21.840</td>
<td>5.859−81.414</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>2.477</td>
<td>11.906</td>
<td>1.204−117.718</td>
<td>.034</td>
</tr>
<tr>
<td>Lower extremity motor function</td>
<td>1.933</td>
<td>6.909</td>
<td>2.657−17.963</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Bamford classification</td>
<td>1.695</td>
<td>5.446</td>
<td>2.072−14.317</td>
<td>.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-7.435</td>
<td>0.001</td>
<td>&lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

Note: results from backward multivariable logistic regression analysis in the prediction of not fitting the proportional recovery rule.

Table 3.4  Probabilities of not fitting the proportional recovery rule

Non-fitter at 6 months post stroke

$$P = \frac{1}{1 + \exp(-(-7.44 + 3.08 \cdot FE + 2.48 \cdot FPa + 1.93 \cdot LE + 1.70 \cdot B)))$$

<table>
<thead>
<tr>
<th>Finger extension</th>
<th>Facial palsy</th>
<th>Lower extremity motor function</th>
<th>Bamford</th>
<th>TN (N)</th>
<th>FN (N)</th>
<th>FP (N)</th>
<th>TP (N)</th>
<th>Prob (0–1)</th>
<th>Freq (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>yes</td>
<td>poor</td>
<td>P/TACI</td>
<td>130</td>
<td>13</td>
<td>16</td>
<td>52</td>
<td>0.85</td>
<td>51</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>poor</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>17</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>good</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
<td>16</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>poor</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
<td>2</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>poor</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
<td>8</td>
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<tr>
<td>no</td>
<td>yes</td>
<td>good</td>
<td>LACI</td>
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<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>12</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>poor</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td>2</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>good</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
<td>1</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>poor</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
<td>5</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>good</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td>21</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>poor</td>
<td>P/TACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
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<td>no</td>
<td>good</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>good</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>31</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>poor</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
<td>3</td>
</tr>
<tr>
<td>yes</td>
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<td>P/TACI</td>
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<td></td>
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<td></td>
<td>&lt; 0.01</td>
<td>10</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>good</td>
<td>LACI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
<td>29</td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow: $$X^2 = 4.75, p = .576; c$$-statistic = 0.932. B: Bamford classification; FE: Finger Extension (Fugl-Meyer Assessment); FP: False Positives; FPa: Facial Palsy (National Institutes of Health Stroke Scale); Freq: frequency, i.e. number of patients with the observed pattern of variables at initial assessment within 72 hours post stroke; LACI: Lacunar Anterior Cerebral Infarction; LE: Lower Extremity motor function (Fugl-Meyer Assessment); Prob: Probability; P/TACI: Partial- or Total Anterior Cerebral Infarction; TN: True Negatives; FN: False Negatives; TP: True Positives.

**DISCUSSION**

The present study investigated the predictability of spontaneous motor recovery (i.e. proportional recovery) in a group of first-ever ischaemic hemispheric stroke patients by testing the maximum proportional recovery rule of Prabhakaran and co-workers and
aimed to identify the clinical characteristics of those patients who do not show the expected amount of motor recovery.

We found that the amount of upper extremity motor recovery was an almost fixed proportion, accounting for approximately 78% of the total possible change. This fixed proportion of spontaneous neurobiological change was particularly observed in those patients with a mild to moderate neurological deficit within 72 hours after stroke, which was the majority of patients in our population \( N = 146; \sim 70\% \). Our findings confirm the results of Prabhakaran and co-workers considering the majority of their mild to moderately impaired stroke patients showed a fixed amount of about 70% spontaneous motor recovery after stroke.\(^8\) The presence of a fixed proportional recovery after stroke is not unique to synergistic motor recovery but has also been found for speech. Lazar and co-workers reported that the improvement in aphasia scores following ischaemic stroke was also fixed, the change in the Western Aphasia Battery score achieved at 3 months post stroke was 73% of patients’ maximum potential recovery.\(^{24}\) Although their study was performed in a small sample of 21 stroke patients, this proportional recovery may be generic and could be applicable to other impairments.\(^{24}\)

The patients who did not follow the proportional recovery rule in the present study (i.e. non-fitters; \( \sim 30\% \) of the total group) had an initial low FMA-UE score ranging from 0 to 17 points and were characterized by larger strokes according the Bamford classification, and more motor impairment in terms of absence of finger extension, presence of facial palsy and more impaired lower extremity motor function (FMA-LE < 18) within 72 hours post stroke. The reasons why these patients show less spontaneous neurobiological improvement than predicted, remains unknown. One hypothesis is that changes in the integrity of the corticospinal tract due to ischaemia are associated with the size of the lesion and with processes involving recovery of neuronal networks in salvaged penumbral tissue after reperfusion,\(^{25}\) or with alleviation of diaschisis\(^{26}\) and homeostatic neuroplasticity in the first weeks post stroke.\(^{5,27}\) Zarahn and co-workers\(^{38}\) further investigated those patients who showed limited proportional change in upper extremity motor function measured with the FMA (i.e. non-fitters). Note that part of their patient population consisted of patients from the study of Prabhakaran and co-workers.\(^8\) Zarahn and co-workers reported that adding fMRI task-related brain activation patterns (during hand closure task) to the prediction did not significantly improve the accuracy of prediction of recovery. This latter finding might suggest that early assessment of brain activation patterns detected by associated changes in blood flow within 48 hours has limited value in predicting the reversibility of hypoperfused penumbral brain areas after acute stroke.\(^{25}\)
We note that the current study was subject to limitations. First, all patients received usual care according to evidence-based guidelines, however, the exact type and intensity of upper extremity therapy was not reported. Our patient population followed the proportional recovery rule very well despite differences between rehabilitation services Worldwide. The added value of other factors including rehabilitative therapy that may contribute to underlying spontaneous mechanisms of neurobiological recovery should be investigated. Second, although the present study investigated proportional recovery of the upper extremity in the largest sample of stroke patients to date, the sample is still relatively small as the non-fitter group consisted of 65 patients. The confidence intervals tend to give a less precise estimate of effects in smaller samples, which could explain the larger 95% CI around the odds ratios. Third, future studies should confirm the merits of the selected predictor variables in the logistic regression model for the prediction of non-fitters before it could be useful within clinical practice. Fourth, we did not include direct measurements of lesion volume but used the Bamford classification as an indication of stroke severity. Infarct size alone and concomitant injury to cortical and/or subcortical structures involved in recovery may offer further explanation of the divergent pattern in the non-fitter group. Further work should therefore try to include these imaging co-variates. Fifth, the proportional motor recovery rule may not be suitable for mildly affected patients with high baseline FMA scores due to the known ceiling effect of the FMA. Also, results cannot be readily generalised to the wide-ranging stroke population because our study sample included only patients with a first-ever ischaemic stroke, who were oriented and able to communicate.

The current study does underpin the importance of previous ideas regarding (proportional) motor recovery and provides clinical markers to identify those patients who are likely not to achieve the predicted amount of spontaneous neurobiological recovery in the first 6 months after stroke. Clinically, the proportional motor recovery rule may be used as a tool to guide the choice for therapy. The non-fitters have low potential to recover at the impairment level (FMA) and may be provided with arm-hand therapy focused on compensation strategies (i.e. using alternative limbs and/or environmental adaptation). Alternatively, therapy for fitters may initially focus on improving function by reducing the impairment. While model testing is an important step forward, it remains essential to investigate spontaneous neurobiological recovery from a neurophysiological perspective, including the regional disruption of blood-brain barrier, which leads to vasogenic oedema and hinders the reperfusion of non-infarcted oligemic and penumbral brain areas in the first days post stroke. In addition, the added predictive value of transcranial magnetic
stimulation for patients that do not show the expected proportional motor recovery requires further investigation.33 Future studies should also further investigate this proportional recovery for visuospatial inattention and somatosensory deficits, in order to gain insight into a possible common, yet poorly understood, mechanisms for spontaneous neurobiological recovery after stroke.

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REFERENCES


Is the proportional recovery rule applicable to the lower limb after a first-ever ischaemic stroke?

Janne M. Veerbeek
Caroline Winters
Erwin E.H. van Wegen
Gert Kwakkel
ABSTRACT

Background and objective To investigate (a) the applicability of the proportional recovery rule of spontaneous neurobiological recovery to motor function of the paretic Lower Extremity (LE); and (b) the presence of fitters and non-fitters of this prognostic rule post stroke. When present, the clinical threshold for fitting nor non-fitting would be determined, as well as within-subject generalisability to the paretic Upper Extremity (UE).

Methods Prospective cohort study in which the Fugl-Meyer Assessment (FMA)-LE and FMA-UE were measured < 72 hours and 6 months post stroke. Predicted maximum potential recovery was defined as \([\text{FMA-LE}_{\text{max}} - \text{FMA-LE}_{\text{initial}} = 34 - \text{FMA-LE}_{\text{initial}}]\). Hierarchical clustering in 202 first-ever ischaemic stroke patients distinguished between fitting and not fitting the rule. Descriptive statistics determined whether fitters and non-fitters for LE were the same persons as for UE.

Results 175 (87%) patients fitted the FMA-LE recovery rule. The observed average improvement of the fitters was ~64% of the predicted maximum potential recovery. In the non-fitter group, the maximum initial FMA-LE score was 13 points. Fifty-one out of 78 patients (~65%) who scored below the identified 14-point threshold at baseline fitted the FMA-LE rule. Non-fitters were more severely affected than fitters. All non-fitters of the FMA-LE rule did also not fit the proportional recovery rule for FMA-UE.

Conclusions Proportional recovery seems to be consistent within subjects across LE and UE motor impairment at the hemiplegic side in first-ever hemispheric ischaemic stroke subjects. Future studies should prospectively distinguish between fitters and non-fitters within the subgroup of patients who have initial low FMA-LE scores. Subsequently, patients could be stratified based on fitting or not fitting the recovery rule, as this would impact rehabilitation management and trial design.
INTRODUCTION

It is suggested that about 90% of all neurological improvement during the first 6 months after stroke is defined by progress of time alone.\(^1\) However, the neurophysiological mechanisms driving neurobiological recovery are poorly understood.\(^2\) Prospective studies showed that the amount of neurobiological recovery of the paretic Upper Extremity (UE),\(^3\)–\(^6\) VisuoSpatial Neglect (VSN),\(^7\) and speech\(^8\) is relatively fixed – ranging from 60 to 97% – and highly predictable. Proportional recovery is the percentage that a patient improves over time for a specific measure, such as the Fugl-Meyer Assessment (FMA) motor score, in relation to his or her theoretical maximum improvement on that specific measure. Patients with first-ever right hemispheric lesions who do not follow the proportional recovery rule (i.e. ‘non-fitters’, patients who improve to a lesser extent on a specific measure than would have been expected based on the proportional recovery rule) for one modality such as motor recovery of the upper limb are also likely not to follow the rule on other modalities such as VSN.\(^7\) This suggests that mechanisms driving spontaneous neurobiological recovery post stroke generalise across neurological impairments. Recently, in a small cohort of 32 patients, it was shown that the maximum proportional recovery rule is also applicable to motor function of the paretic Lower Extremity (LE).\(^9\) However, the lack of a non-fitter group in this cohort was an unsuspected finding, as all previous studies regarding proportional recovery identified such a cluster.

The present study therefore aimed to investigate the generalisability of the ‘proportional recovery rule’ for motor function of the paretic UE, measured with the Fugl-Meyer Assessment (FMA) UE subscale, to motor function of the paretic LE, measured with the FMA-LE subscale within 72 hours and at 6 months post stroke in a considerably larger cohort of first-ever ischaemic hemispheric stroke patients. This included investigating the presence of both fitters and non-fitters of the proportional recovery rule. When present, the secondary aims were to determine whether (a) there was a clinical threshold for the FMA-LE within 72 hours, separating non-fitters from fitters; (b) fitters and non-fitters could be distinguished based on demographic and clinical characteristics at baseline; and (c) fitters or non-fitters of the proportional recovery rule for the LE were the same patients who do or do not show proportional recovery for the paretic UE.
MATERIALS AND METHODS

Data from the prospective cohort of the Early Prediction of functional Outcome after Stroke (EPOS) study were used. Details of this study have been published elsewhere. Stroke patients were included when they met the following criteria: (1) first-ever ischaemic anterior circulation stroke in one hemisphere; (2) mono- or hemiparesis < 72 hours after onset; (3) premorbid Barthel Index score ≥ 19 out of 20; (4) aged ≥ 18; (5) no severe deficits of communication, memory, or understanding; and (6) written informed consent. For this study, only patients were included who had a FMA-LE motor score of less than 34 (i.e. a lower limb paresis), a FMA-UE motor score of less than 66 (i.e. an upper limb paresis) within 72 hours post stroke, and with available FMA-LE and UE scores at 6 months post stroke.

Ethical approval was obtained before start of participant recruitment from the nationally certified Ethical Committee of the VU University Medical Center, Amsterdam, the Netherlands (https://www.vumc.nl/afdelingen/METc/METc/). Local feasibility was approved by the institutional review boards of the participating hospitals (AMC, Amsterdam; Erasmus MC, Rotterdam; LUMC, Leiden; UMC Sint Radboud, Nijmegen; UMC Utrecht; Amphia Hospital Breda; Diaconessen Hospital, Leiden; Franciscus Hospital, Roosendaal) and nursing homes (Sint Jacob, Amsterdam; Zonnehuis, Amsterdam; Cordaan/Berkenstede, Amsterdam; Laurens Antonius Binnenweg, Rotterdam; Reumaverpleeghuis, Rotterdam; Albert van Koningsbruggen, Utrecht; Wiekendaal, Roosendaal). The capacity to consent was determined during the screening and consent visits. This was based on the patients’ ability to (1) understand the participant information (oral and written); (2) explain why they were admitted to the hospital; and (3) follow two-staged commands as requested in the Mini-Mental State Examination.

The FMA-LE (score range 0–34) and FMA-UE (score range 0–66) subscales were measured within 72 hours and at 6 months after onset. The FMA quantifies limb impairment in terms of synergistic (in)dependent motor control. Observed motor recovery of the lower extremity was defined as \[ \Delta \text{FMA-LE} = \text{FMA-LE}_{\text{6 months}} - \text{FMA-LE}_{\text{initial}} \] and predicted maximum potential recovery as \[ \text{FMA-LE}_{\text{max}} - \text{FMA-LE}_{\text{initial}} = 34 - \text{FMA-LE}_{\text{initial}}. \]

Hierarchical clustering analysis based on the average pairwise Mahalanobis distances method was used to classify patients into fitters and non-fitters of the proportional recovery rule (Matlab’s Statistic toolbox, version 8.1, Matlab version 2013a, Mathwords Inc, Natwick, MA). We selected the Mahalanobis distance method and not the more common used Euclidian
distance with circular boundaries, as it also takes co-variances into account and leads to elliptic decision boundaries. Fitters were defined as patients who showed a comparable amount of predicted maximum potential and observed improvement on the FMA-LE. Patients who did not show this comparable amount of predicted maximum potential and observed improvement were considered non-fitters. Goodness-of-fit was assessed by the cophenetic correlation and the Spearman correlation between the Mahalanobis and cophenetic distances obtained from the dendrogram. Linear regression was applied to determine the percentage of the predicted maximum potential recovery ($R^2$) that explained the observed change of the LE in the fitter subgroup. Normality of data was checked by visual inspection of histograms. Patient characteristics were analysed by descriptive statistics. Differences between fitters and non-fitters by the independent $t$-test for parametric data, Pearson's $X^2$ test for categorical data, and the Mann-Whitney U test for nonparametric data.

To assess the threshold value on the initial FMA-LE for not fitting the proportional recovery rule, the highest score of the initial FMA-LE in the non-fitter subgroup was taken. The sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of this threshold were determined. In a next step, characteristics were compared between patients who scored below this threshold value but still fitted the rule and those who did not. SPSS (version 22) was used unless indicated otherwise and a 2-tailed $p$-value < .05 was considered statistically significant.

Predicted maximum potential recovery and observed change for the upper extremity were defined as \[ \text{FMA-UE}_{\text{max}} - \text{FMA-UE}_{\text{initial}} = 66 - \text{FMA-UE}_{\text{initial}} \] and \[ \triangle \text{FMA-UE} = \text{FMA-UE}_{\text{6 months}} - \text{FMA-UE}_{\text{initial}} \]. Subsequently, $\triangle \text{FMA-LE}$ and $\triangle \text{FMA-UE}$ were expressed as percentages of their maximum possible scores in order to compare the distribution of maximum potential and observed recovery. Descriptive statistics were used to determine whether fitters and non-fitters were the same persons for both outcomes.

**RESULTS**

A total of 202 patients met the present inclusion criteria (Figure 4.1). The mean age of the total sample was 66.62 ± 13.97 years, 106 (52.5%) subjects were male, and the mean National Institutes of Health Stroke Scale (NIHSS) score within 72 hours was 9.27 ± 5.78 points. Hierarchical clustering analysis showed that 175 patients (86.6%) fitted the FMA-LE proportional recovery rule (Figure 4.2). The goodness-of-fit was $c = 0.73$ (i.e. cophenetic
correlation coefficient) and $r_s = 0.80$ (Spearman correlation). Two patients had high predicted maximum potential recovery and observed recovery (data points at the top right corner of Figure 4.2). These patients were also characterized as ‘outliers’ in the hierarchical cluster analysis. However, as their predicted and observed recovery matched, they were added to the ‘fitters’ group. Note that there were patients who had lower scores at follow-up, in comparison to their initial FMA-LE score, which resulted in a negative $\Delta$FMA-LE (see Figure 4.2). As these patients were part of the groups based on the hierarchical clustering analysis and the decline in FMA-LE score was within the measurement error of the FMA-LE, we did not exclude these patients from analyses.
For the fitters, the median FMA-LE maximum potential recovery was 12 (interquartile range, IQR = 6–22) points and ΔFMA-LE was 8 (IQR = 3–14). For the non-fitters, these were 30 (IQR = 25–32) and 3 (IQR = 0–6), respectively. The observed improvement of the fitters was ~64% (95% confidence interval, CI = 59–69%) of the predicted maximum potential recovery (i.e. proportional recovery). At baseline, fitters had significantly lower neurological impairments and less motor impairment when compared to non-fitters (p < .001; Table 4.1). In addition, predicted maximum potential recovery of both FMA-LE and FMA-UE was significantly higher in fitters (p < .001).
The maximum initial FMA-LE score within the non-fitter group \((N = 27)\) was 13 points (38% of the total score). Overall, 78 patients had a FMA-LE score of 13 points or lower at baseline. In this subgroup, 51 patients (~65%) fitted the rule for the lower extremity and 27 (~35%) did not.

The sensitivity was 0.71 (95% CI = 0.63–0.77), the specificity 1.00 (95% CI = 0.84–1.00), the positive predictive value 1.00 (95% CI = 0.96–1.00), and the negative predictive value 0.34 (95% CI = 0.24–0.46). The non-fitters were more severely affected than the fitters, as

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**Table 4.1  Group comparison regarding patient characteristics \((N = 202)\)**

<table>
<thead>
<tr>
<th>Determinant (&lt; 72 hours post stroke)</th>
<th>Fitters ((N = 175))</th>
<th>Non-fitters ((N = 27))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>65.71 (14.15)</td>
<td>72.56 (11.15)</td>
<td>.160</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>85/90</td>
<td>11/16</td>
<td>.448</td>
</tr>
<tr>
<td>Hemisphere of stroke, right/left</td>
<td>97/78</td>
<td>18/7</td>
<td>.372</td>
</tr>
<tr>
<td>Recombinant tissue plasminogen activator, yes/no</td>
<td>42/133</td>
<td>11/16</td>
<td>.066</td>
</tr>
<tr>
<td>Time between stroke onset and initial assessment, days*</td>
<td>2.06 (0.81)</td>
<td>1.85 (1.03)</td>
<td>.061</td>
</tr>
<tr>
<td>6-month assessment, days*</td>
<td>188.87 (12.75)</td>
<td>184.59 (17.70)</td>
<td>.603</td>
</tr>
<tr>
<td>Bamford classification, LACI/PACI/TACI</td>
<td>91/53/31</td>
<td>1/13/13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CIRS initial†</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
<td>.769</td>
</tr>
<tr>
<td>Cardiac disorders, yes/no</td>
<td>55/120</td>
<td>11/16</td>
<td>.337</td>
</tr>
<tr>
<td>Vascular disorders, yes/no</td>
<td>51/124</td>
<td>9/18</td>
<td>.657</td>
</tr>
<tr>
<td>Endocrine and metabolic disorders, yes/no</td>
<td>43/132</td>
<td>4/23</td>
<td>.264</td>
</tr>
<tr>
<td>NIHSS initial†</td>
<td>7 (4–12)</td>
<td>17 (15–20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemianopia, yes/no</td>
<td>43/132</td>
<td>20/7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sensory loss, yes/no</td>
<td>101/74</td>
<td>26/1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inattention, yes/no</td>
<td>68/107</td>
<td>21/6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FMA-LE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 72 hours†</td>
<td>22 (12–28)</td>
<td>4 (2–9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 months†</td>
<td>30 (26–33)</td>
<td>8 (4–12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum potential recovery†</td>
<td>12 (6–22)</td>
<td>30 (25–32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔFMA-LE†</td>
<td>8 (3–14)</td>
<td>3 (0–6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FMA-UE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 72 hours†</td>
<td>23 (7–52)</td>
<td>4 (2–5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 months†</td>
<td>60 (48–65)</td>
<td>7 (4–9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum potential recovery†</td>
<td>43 (14–59)</td>
<td>62 (61–64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔFMA-UE†</td>
<td>17 (7–37)</td>
<td>2 (0–5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CIRS: Cumulative Illness Rating Scale; FMA: Fugl-Meyer Assessment; LACI: Lacunar Anterior Circulation Infarcts; LE: Lower Extremity; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Circulation Infarcts; TACI: Total Anterior Circulation Infarcts; UE: Upper Extremity; Δ: change. * mean (standard deviation); † median (interquartile range).
indicated by the initial NIHSS (17 (IQR = 15–20) and 13 (IQR = 9–17), respectively; \( p = .001 \)) and Bamford classification (LACI = 1, PACI = 13, TACI = 13 vs. LACI = 20, PACI = 15, TACI = 16, respectively; \( p = .008 \)).

Comparing fitters and non-fitters for both the predicted maximum potential and observed \( \triangle \)FMA-LE showed the same pattern as for the maximum potential and observed \( \triangle \)FMA-UE (Figure 4.3). All non-fitters of FMA-LE \(( N = 27 \) also did not fit the rule for FMA-UE. Thirty-eight (21.7\%) of the FMA-LE fitters did not fit the rule for FMA-UE. Conversely, none of the patients that were non-fitters on FMA-UE fitted the rule for FMA-LE.

**DISCUSSION**

The present prospective cohort study confirmed that the proportional recovery rule is generalisable to motor function of the paretic lower extremity in patients with a first-ever ischaemic hemispheric stroke. Patients who fitted this rule improved on average 64\% (95\% CI = 59–69\%) of their predicted maximum potential recovery. In addition, the present study

![Figure 4.3](image-url)
shows that also for motor function of the LE, there seems to be a subgroup of patients who did not fit the proportional recovery rule (i.e. non-fitters). These non-fitters are characterized by having more neurological impairments such as hemianopia, VSN, and sensory loss, when compared to patients who did follow the rule (i.e. fitters). Importantly, *all* patients who had an initial FMA-LE score of 14 points or higher within 72 hours post stroke did follow the proportional recovery rule, whereas only 35% of the patients with scores below this critical threshold failed to follow the expected amount of spontaneous neurobiological recovery. This finding also suggests that even stroke patients with a very severe lower extremity deficit (i.e. below 14 points on a FMA-LE) at stroke onset may show a tremendous amount of spontaneous neurobiological improvement of up to 20 out of 34 points on the FMA-LE. This proportion of non-fitters was about 13% (N = 27) of our total cohort. This critical threshold of 14 points is in line with the threshold found for non-fitters of the FMA-UE (i.e. < 17 points)⁵ and suggests that there are common threshold-dependent mechanisms which define proportional recovery within the first days after a first-ever ischaemic stroke. Moreover, hemiplegic patients who were non-fitters of motor function of the paretic LE (N = 27) were also non-fitters on the proportional recovery rule of the paretic UE.

Our findings are in line with previous studies about the proportional recovery rule of motor function of the upper³-⁶ and lower extremity,⁹ speech,⁸ and VSN.⁷ However, in contrast to the recent published study of Smith and co-workers,⁹ the present larger cohort did include also some more severely affected hemiplegic stroke patients with an unfavourable prognosis for recovery of gait.¹⁰ Obviously, a number of these patients with a poor prognosis for gait did not follow the proportional recovery rule (i.e. non-fitters) of spontaneous neurobiological recovery after stroke. With that, we suggest that spontaneous neurobiological recovery is a consistent intra-hemispheric phenomenon that seems to occur irrespective of affected neurological impairments post stroke. In addition, this ‘70% recovery rule’ is not fixed, but may show variance ranging from 64% for motor recovery of the paretic LE (95% CI = 59–69%) in the present study to 97% (95% CI = 82–112) for VSN.⁷ At least, the result from the current and previous cohort studies in this field further confirm that proportional recovery is inherent to acute stroke and reflects common underlying mechanisms of spontaneous neurobiological recovery.

The key challenge is to disentangle the underlying causes that define the 10 to 30% of the stroke patients that did not follow the proportional recovery rule, irrespective of initial lower or upper extremity motor deficit and irrespective of the involved neurological modality opposite of the hemispheric lesion."
be thought of as an important cause of not showing proportional recovery, Prabhakaran and colleagues showed that subcortical infarct volume was significantly related to change in FMA-UE scores in both fitters and non-fitters. Other studies showed that there is no significant relation between lesion volume and proportional recovery of UE motor function and language. It is suggested that the metabolic cascade (initially starting with energy failure due to hypoperfusion) that causes the intrinsic degeneration of distal axons, known as Wallerian degeneration, is fundamental to absence of spontaneous neurobiological recovery, as mechanisms that suppress spontaneous neurobiological recovery early after stroke are highly associated with disruption of the corticospinal tract. However, one may also suggest that ‘abnormal network interactions’ suppress spontaneous neurobiological recovery, such as a deactivation to an anatomically related intact area or the changes in connectivity with this remote brain area (i.e. diaschisis). It could be hypothesized that, for example, when the connectivity in the brain network is not normalized, motor recovery is negatively influenced and patients do not show proportional recovery. In addition, potential factors that may limit neurobiological recovery are polymorphisms of the Brain-Derived Neurotrophic Factor (BDNF) gene, as well as blood-brain barrier dysfunction that is associated with vasogenic oedema. We therefore advocate that the focus of future research should not only be on validating the proportional recovery rule and its intra-hemispheric generalisability for other affected modalities, but also on understanding underlying mechanisms of spontaneous neurobiological recovery. The ability of innovative pharmacological interventions to influence the proportion of non-fitters should be investigated as well. Examples are immunotherapy targeting the neurite growth-inhibitory protein Nogo-A, therapies enhancing phasic GABA inhibition, and neural network modulating therapies. Specifically, GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that contributes to cortical functions, including motor control. Pharmacological agents may modulate phasic (synaptic) GABA signaling, which is suggested to enhance brain repair and plasticity related recovery after stroke. In addition, pharmacological agents are also suggested to modulate non-invasive brain stimulation-induced network reorganization. However, at this moment, we do not know which of these interventions are effective. Keeping in mind the suggested critical time window of recovery, these interventions should preferably be initiated within the first days post stroke. Furthermore, research is needed to identify factors that hamper neurobiological recovery and which may lead to a relatively higher proportion of patients who do not follow the expected proportional recovery after stroke. For example, one may assume that high doses of early mobilisation enhances orthostatic variation in penumbral and oligemic brain
areas early post stroke, and with that, may increase neurological damage early after stroke onset. Therefore, neuro-imaging and neurophysiological determinants such as the quality of collateral blood flow defining early regional perfusion within the first 24 hours post stroke, the integrity of the affected corticospinal tract and its (a)symmetry index, stroke location (grey matter versus white matter), and dynamics in brain connectivity should be taken into account when investigating neurobiological markers of proportional recovery. However, a recent systematic review showed that studies that use neurological biomarkers of brain impairment for prediction of motor recovery post stroke such as diffusion tensor imaging, structural MRI, and transcranial magnetic stimulation need to improve their methodological quality in terms of cross-validation, considering the minimally clinical important difference of motor recovery, and recruitment of a large enough sample to provide sufficient statistical power. In light of these recent findings, there is a need to underpin the added value of these neurological biomarkers next to behavioural markers in improving the predictive accuracy (i.e. true and false negatives) of fitters and non-fitters of the proportional recovery rule.

The first and main limitation of the present study is the exclusive use of clinical measures. Combining clinical with neuropsychological markers may improve prediction of neurobiological outcome, but further research needs to assess the cost-benefits of neuro-imaging measures in addition to clinical measures in predicting functional outcomes post stroke. Second, prediction of LE recovery following the FMA is less precise than for the UE. Although the reliability of the FMA has been described as excellent, the measurement error for the LE subscale is 6.4 points, resulting in a reliability change index of about 19% of the maximum score. In contrast, the measurement error for the UE is 7.2 points, which is about 11% of the maximum score. Consequently, this lack of precision makes the distribution of fitters and non-fitters along the estimated regression line in Figure 4.2 wider and more scattered when compared to the one for the paretic UE. In addition, due to the more scattered data points, using a different method to differentiate between fitters and non-fitters may have resulted in slightly different groups. Third, we included only patients with a first-ever ischaemic hemispheric stroke resulting in mild to moderate/severe neurological impairments at stroke onset. These patients may differ in the amount of pre-stroke comorbidities, as comorbidity is suggested to negatively influence outcome. In addition, research by Ng and colleagues found that patients with multiple infarcts show spontaneous neurobiological recovery to a lesser extent than patients with a first-ever stroke, suggesting that quality of vascularisation is an important issue for recovery. Contrary, a recent prospective cohort study did show that patients with previous or haemorrhagic strokes may also show proportional
recovery of the UE.\textsuperscript{38} Fourth, although our patients received usual care according to prevailing guidelines, rehabilitation may have differed in intensity and type of therapy.\textsuperscript{39} However, till so far, a number of studies failed to find evidence that type of therapy or intensity of practice interacts with spontaneous mechanisms of recovery.\textsuperscript{1,6,40} Being more positive, high quality trials are needed to investigate if very early applied intensive therapies are able to affect the proportion of fitters and non-fitters of the proportional recovery rule.

Prospectively being able to identify patients who will fit or not fit the proportional recovery rule would influence both trial design and rehabilitation management dedicated to investigate the impact of services for the LE.\textsuperscript{38,41} We already showed that stratifying patients based on expected spontaneous neurobiological recovery would have large consequences for the statistical power in stroke upper extremity trials as well as the choice for rehabilitation interventions.\textsuperscript{41} For the LE, we showed that all patients who scored 14 points or more on the FMA-LE at baseline followed the proportional recovery rule. However, also 51 out of the 78 patients who scored less than 14 points showed proportional recovery for the LE. Consequently, this cut-off cannot simply be used to stratify patients. Due to the lack of statistical power for a multivariable regression analysis, we were not able to develop a clinical prognostic model within this subgroup of patients with an initial FMA-LE score below 14 points. Therefore, we recommend to further investigate this subgroup of patients with initially severe strokes and pool the current data with other (sub)cohorts with FMA-LE baseline scores below 14 points. Subsequently, factors could be identified that are able to distinguish between fitters and non-fitters. This will enable stratification of patients based on proportional recovery and with that, investigating the impact of stratification in trials on LE outcomes post stroke. Ideally, the 70\% proportional recovery rule should be used in intervention trials by investigating interaction effects; aiming to increase the slope of the regression line (i.e. a higher percentage of proportional recovery) or to decrease the proportion of non-fitters. Above aims are in line with the recently published recommendations for improving stroke recovery and rehabilitation trials.\textsuperscript{42} In parallel, our understanding of underlying mechanisms of spontaneous neurobiological recovery should be increased. Therefore, we need more translational research in which clinical, neuroimaging, molecular, and neurophysiological biomarkers of spontaneous neurobiological recovery are combined.\textsuperscript{42}
**Acknowledgements**

The authors thank all EPOS assessors in the stroke units of the participating university centres and local hospitals (AMC Amsterdam; Erasmus MC Rotterdam; LUMC Leiden; UMC Sint Radboud; UMC Utrecht; VUmc Amsterdam; Amphia Hospital Breda; Diaconessen Hospital Leiden; Franciscus Hospital Roosendaal) and in the affiliated nursing homes (i.e. St. Jacob, Zonnehuis and Cordaan/ Berkenstede in Amsterdam, Laurens Antonius Binnenweg and Reumaverpleeghuis in Rotterdam, Albert van Koningsbruggen in Utrecht and Wiekendaal in Roosendaal) for performing the measurements. The authors also thank the patients who participated in the study.

**REFERENCES**


Generalisability of the maximum proportional recovery rule to visuospatial neglect early post stroke

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ABSTRACT

Background and objective  Proportional recovery of upper extremity motor function and aphasia after stroke may suggest common mechanisms for spontaneous neurobiological recovery. This study aimed to investigate if the proportional recovery rule also applies to VisuoSpatial Neglect (VSN) in right-hemispheric first-ever ischaemic stroke patients, and explored the possible common underlying mechanisms.

Methods  Patients with upper limb paresis and VSN were included. Recovery defined as the change in Letter Cancellation Test (LCT) score between ~8 days and 6 months post stroke. Potential recovery defined as $LCT_{\text{max}} - LCT_{\text{initial}} = 20 - LCT_{\text{initial}}$. Hierarchical clustering separated fitters and non-fitters of the prediction rule. A cut-off value on $LCT_{\text{max}} - LCT_{\text{initial}}$ was determined. The change in LCT and Fugl-Meyer Assessment Upper Extremity was expressed as a percentage of the total possible score to investigate the communality of proportional recovery.

Results  Eighty out of ninety patients displayed proportional recovery of VSN (i.e. ‘fitters’, 0.97 (95% CI = 0.82–1.12). All patients who did not follow the prediction rule for VSN (i.e. ‘non-fitters’) had ≥ 15 missing O’s at baseline and failed to show proportional recovery of the upper limb.

Conclusions  This study shows that the proportional recovery rule also applies to patients with VSN post stroke. Patients who fail to show proportional recovery of VSN are the same patients who fail to show proportional recovery of the upper limb. These findings support the idea of common intra-hemispheric mechanisms underlying spontaneous neurobiological recovery in the first months post stroke. Future studies should investigate the prognostic clinical and neurobiological markers of these subgroups.
INTRODUCTION

Early prediction of outcome after stroke is a major challenge in neurorehabilitation. Dependent on stroke severity, there is strong evidence that the logistic pattern of improvement during the first 10 weeks after stroke is mainly driven by the progress of time. In 2008, Prabhakaran and co-workers suggested that the amount of motor recovery in the first 6 months after stroke is proportionally fixed at 70% of the patients' maximum possible improvement on the Upper Extremity motor section of the Fugl-Meyer Assessment (FMA-UE). This ‘70% prediction rule’ of upper extremity motor recovery was confirmed in a number of prognostic studies. Recently, studies showed that functional intactness of the corticospinal pathway is essential to recover to a level of 70% of the maximum possible change.

The amount of spontaneous neurobiological recovery early post stroke, and with that, the maximum proportional recovery rule seems not to be related to age, gender and intensity of exercise therapy. This latter finding suggests that the improvement in motor impairment is mainly spontaneous by nature, whereas evidence that interventions are able to influence this spontaneous return is still lacking. Krakauer and co-workers showed that the maximum proportional recovery rule was not unique for motor recovery but also applies to aphasia in patients with a first-ever left-hemispheric stroke.

In line with these findings one may question if this maximum proportional recovery rule of spontaneous neurobiological recovery is also applicable to other neurological (cognitive) impairments such as VisuoSpatial Neglect (VSN) in patients with a right-hemispheric stroke. In order to investigate the commonality of the underlying mechanisms of spontaneous neurobiological recovery, one may ask indeed whether patients that fail to follow the maximum proportional recovery rule in VSN also fail to show spontaneous motor recovery early post stroke.

The first aim of the present study was to investigate whether the maximum proportional recovery rule also applies to VSN in patients with a first-ever ischaemic right-hemispheric stroke. Subsequently, we sought to identify the clinical characteristics of these hemiplegic patients with VSN who failed to show proportional recovery. We hypothesized that the proportional recovery rule is generalisable to VSN, i.e. that the majority of patients recover to a level of 70% of the maximum possible improvement. Further, we anticipated that those patients who did not show the expected recovery of VSN would clinically present more neurological deficits and more severe strokes according to the Bamford classification early
post stroke. To unravel whether the proportional prediction rule of spontaneous recovery reflects common underlying mechanisms, we explored if patients who fail to show the expected amount of proportional recovery for VSN would also fail to show proportional motor recovery of the upper paretic limb post stroke.

**MATERIALS AND METHODS**

**Participants**

The present study included two samples of patients from the Stroke Intensity trial and the EXPLICIT-stroke trial. The ethics committees of the participating hospitals approved both trials. Patients were included within 14 days after stroke onset.

Within the Stroke Intensity trial, patients were tested weekly during the first 10 weeks post stroke, biweekly until 20 weeks, and at the 26 weeks follow-up assessment. For the first 20 weeks after stroke onset all patients received 15 min of leg rehabilitation, 15 min of arm rehabilitation and 90 min of Activities of Daily Living (ADL) training per day. In addition, the different treatment groups received the following interventions for the first 20 weeks after stroke: (1) control treatment: immobilisation of the paretic arm and leg using an inflatable pressure splint (30 min on weekdays); (2) arm training: functional exercises with the arm and hand including grasping, moving objects and punching a ball (30 min on weekdays); and (3) leg training: sitting, standing, weigh-bearing exercises, with emphasis on stability and improving walking velocity (30 min on weekdays). After the 20-week intervention period the treatment was not controlled for; on average patients received treatment on 3 days, 30 min per week.

Patients participating in the EXPLICIT-stroke trial were assessed weekly during the first 5 weeks, and at 8, 12, and 26 weeks after stroke. Patients were stratified based on the presence or absence of voluntary finger extension prior to the randomisation procedure. Patients who presented voluntary finger extension were placed in the modified Constraint Induced Movement Therapy (mCIMT) trial, the other patients in the ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) trial. The interventions were provided on weekdays for 3 consecutive weeks starting within 2 weeks after stroke onset. The different groups received: (1) mCIMT experimental group: 60 min of upper extremity task-oriented training with increasing task difficulty, and 3 hours of wearing a padded safety mitt on the
non-paretic arm;\textsuperscript{17} (2) mCIMT control group: 30 min of conventional care based principles of the Neuro Development Treatment, including facilitation movements and training of mobility, strength and coordination; (3) EMG-NMS experimental group: 60 min of stimulation of the finger extensors, requiring active participation of the patient; and (4) EMG-NMS control group: 30 min of passive range-of-motion exercise and facilitation of voluntary movements. After the 3 week intervention period all patients received a maximum of 30 min of upper limb exercise therapy per day.\textsuperscript{9,16}

In both trials, no specific intervention was provided for VSN.

For the present study, patients were included when they: (1) had a first-ever ischaemic stroke in the territory of the anterior or middle cerebral artery; (2) were adults up to 80 years of age; (3) did not have severe co-morbidities, such as other neurological disorders; (4) did not have severe deficits in communication, memory, or understanding (mini mental state examination of at least 23 points); (5) had upper limb paresis (FMA-UE < 66 points); (6) gave written informed consent; (7) had a lesion in the right hemisphere; and (8) presented with VSN.

\textbf{Outcome measures}

A single-target Letter Cancellation Test (LCT) served as main outcome measure to assess VSN.\textsuperscript{18,19} Patients were requested to cross all O’s on an A4 paper taped on the table and aligned to their sagittal midline. Each paper contained 40 O’s (20 in the contralesional and 20 in the ipsilesional visual field, respectively left and right), and 425 distractor letters. We defined VSN as an asymmetry between the LCT omissions in the contralesional (left) and ipsilesional (right) visual field of at least two.\textsuperscript{20}

Baseline characteristics of the patients with a first-ever ischaemic right-hemispheric stroke included: time between stroke onset and baseline assessment, gender, age, clinical severity of stroke using the Bamford classification,\textsuperscript{13} and hemianopia and conjugate deviation of the eyes measured with the NIHSS.\textsuperscript{21} Upper extremity motor function was measured with the FMA-UE\textsuperscript{22} and the Motricity Index (MI).\textsuperscript{23} The MI was also used to assess lower extremity motor function. At 6 months, the LCT and the FMA-UE were again determined. Three trained researchers performed all assessments.
Data analyses

The effect of the type of intervention on the recovery of VSN (i.e. LCT score contralesional visual field) was tested with Generalised Estimating Equations for both trials separately. All the available longitudinal data was used for this analysis. The model included an exchangeable working correlation matrix, LCT baseline score, intervention group, time (continuous) and the interaction between intervention group and time.

Maximum potential recovery \((LCT_{\text{max}} - LCT_{\text{initial}})\) was calculated by subtracting the baseline LCT score from the maximum possible score of 20 O's in the contralesional (left) visual field. The observed change in LCT score was calculated as follows: \(\Delta LCT = LCT_{6\text{months}} - LCT_{\text{initial}}\). To investigate the relationship between \(\Delta LCT\) and \(LCT_{\text{max}} - LCT_{\text{initial}}\), we applied linear regression analysis to all available data. Hierarchical clustering based on average pairwise Mahalanobis distance (Matlab’s Statistics toolbox, version 8.1, Matlab version 2012a, Mathworks Inc, Natwick, MA) was used to identify two groups (i.e. fitters and non-fitters). This analysis was based on the \(\Delta LCT\) versus \(LCT_{\text{max}} - LCT_{\text{initial}}\) scatterplot. We determined the robustness of that clustering by computing the cophenetic correlation coefficient and the Spearman correlation coefficient between the Mahalanobis and cophenetic distances obtained from the dendrogram. In the group of fitters, we further investigated the relationship between \(\Delta LCT\) and \(LCT_{\text{max}} - LCT_{\text{initial}}\) and the impact of possible confounding factors. Thereafter, we determined a cut-off value on \(LCT_{\text{max}} - LCT_{\text{initial}}\) to separate fitters from non-fitters of the VSN prediction rule.

Baseline variables were compared between fitters and non-fitters, and tested for normality by visual inspection of histograms and Q-Q plots. The Levene’s test served to evaluate the assumption of homogeneity of variance. Group comparisons for categorical variables were realized using Fisher’s exact test, normally distributed data with equal variances using the independent t-test, and non-normally distributed data using the Mann-Whitney U test.

Observed and predicted maximum potential change in upper extremity motor function were determined similar to LCT using the FMA-UE with a maximum score of 66 points \((\Delta \text{FMA-UE} = \text{FMA-UE}_{6\text{months}} - \text{FMA-UE}_{\text{initial}}, \text{and FMA-UE}_{\text{max}} - \text{FMA-UE}_{\text{initial}} = 66 - \text{FMA-UE}_{\text{initial}})\). In addition, \(\Delta LCT\), \(LCT_{\text{max}} - LCT_{\text{initial}}\), \(\Delta \text{FMA-UE}\) and \(\text{FMA-UE}_{\text{max}} - \text{FMA-UE}_{\text{initial}}\) were expressed as percentage of the total possible score (20 and 66 points, respectively) to visually compare the distribution of in observed recovery and maximum potential recovery on both measures. Analyses were performed with SPSS version 20 using a 2-tailed significance level of .05, unless indicated otherwise.
RESULTS

A total of 90 patients with a first-ever ischaemic right-hemispheric stroke was eligible for analysis (Figure 5.1) and assessed at 7.6 ± 2.9 days and 189.6 ± 2.9 days after stroke onset. Patients’ baseline characteristics are shown in Table 5.1. For both trials, the type of intervention did not significantly affect the recovery of VSN in terms of LCT score for the contralesional (left) visual field. No significant interaction effects between type of intervention and time were found (p = .473 and p = .978 for respectively the Intensity Stroke trial and EXPLICIT-stroke trial).

Figure 5.2 shows the ΔLCT versus the $LCT_{\text{max}} - LCT_{\text{initial}}$ scatterplot for all 90 patients. The relationship between $LCT_{\text{max}} - LCT_{\text{initial}}$ and ΔLCT for the whole group was: ΔLCT = 0.73 (95% CI = 0.570.89) · $LCT_{\text{max}} - LCT_{\text{initial}}$ + 0.21 (95% CI = -2.24−2.67), with $R^2 = 0.48$. Using the hierarchical cluster analysis we identified two groups: $N_1 = 80$ and $N_2 = 10$ (clustering cut-off = 2.07). The cluster analysis had a goodness-of-fit of 0.86 and 0.87, for the cophenetic

![Patient exclusion flowchart to select patients with first-ever ischaemic right-hemispheric stroke.](image)

LCT: Letter Cancellation Test.
Table 5.1 Characteristics of the patients with first-ever ischaemic right-hemispheric strokes

<table>
<thead>
<tr>
<th>Variables</th>
<th>N = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline measurement</strong></td>
<td></td>
</tr>
<tr>
<td>Time between stroke and baseline assessment, days(^a)</td>
<td>7.62 ± 2.88</td>
</tr>
<tr>
<td>Gender, female/male(^b)</td>
<td>37 / 53</td>
</tr>
<tr>
<td>Age, years(^c)</td>
<td>60.41 ± 12.70</td>
</tr>
<tr>
<td>Bamford classification (dichotomised), LACI/ TACI+PACI(^b)</td>
<td>22 / 68</td>
</tr>
<tr>
<td>Hemianopia (NIHSS), no/yes(^b)</td>
<td>68 / 22</td>
</tr>
<tr>
<td>Déviation conjugée (NIHSS), no/yes(^b)</td>
<td>68 / 22</td>
</tr>
<tr>
<td>LCT contralesional (left) visual field (maximum score = 20)(^a)</td>
<td>6.08 ± 6.34</td>
</tr>
<tr>
<td>LCT ipsilesional (right) visual field (maximum score = 20)(^a)</td>
<td>14.38 ± 5.89</td>
</tr>
<tr>
<td>Upper limb function (MI-arm, maximum score = 100)(^c)</td>
<td>0 (0–15)</td>
</tr>
<tr>
<td>Lower limb function (MI-leg, maximum score = 100)(^c)</td>
<td>23 (0–48.25)</td>
</tr>
<tr>
<td>Upper limb function (FMA-UE, maximum score = 66)(^c)</td>
<td>5 (4–8.25)</td>
</tr>
<tr>
<td><strong>Follow-up measurement</strong></td>
<td></td>
</tr>
<tr>
<td>Time between stroke and 6 month assessment, days(^a)</td>
<td>189.56 ± 2.92</td>
</tr>
<tr>
<td>LCT contralesional (left) visual field (maximum score = 20)(^a)</td>
<td>16.48 ± 5.10</td>
</tr>
<tr>
<td>LCT ipsilesional (right) visual field (maximum score = 20)(^a)</td>
<td>19.23 ± 2.06</td>
</tr>
</tbody>
</table>

FMA-UE: Upper Extremity motor section of the Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; LCT: Letter Cancellation Test; MI: Motricity Index; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; TACI: Total Anterior Cerebral Infarction; VSN: VisuoSpatial Neglect. \(^a\) Mean ± standard deviation; \(^b\) Number of patients; \(^c\) Median (interquartile range).

and Spearman correlation coefficient, respectively. For the fitters (N = 80), the relationship between $LCT_{\text{max}} - LCT_{\text{initial}}$ and $\Delta LCT$ was: $\Delta LCT = 0.97 \ (95\% \ CI = 0.82–1.12) \cdot LCT_{\text{max}} - LCT_{\text{initial}} - 1.41 \ (95\% \ CI = -2.85–0.03)$, with $R^2 = 0.78$. This relationship was not influenced by age, stroke severity, hemianopia, or upper limb motor impairment (Table 5.2).

The patients in the “non-fitter group” (N = 10) all had 15 or more missing O’s (80%) at baseline assessment (Figure 5.2). This cut-off was used to separate patients into Group 1 ($LCT_{\text{max}} - LCT_{\text{initial}} \leq 15$ O’s; N = 45) with solely “fitters” and Group 2 ($LCT_{\text{max}} - LCT_{\text{initial}} > 15$ O’s; N = 45) with both “fitters” and “non-fitters”. Table 5.3 shows the comparison between a subgroup of fitters (N = 35) and non-fitters (N = 10) with a $LCT_{\text{max}} - LCT_{\text{initial}}$ of more than 15 O’s. At baseline assessment, fitters were 11 years younger than the non-fitters ($p = .007$) and presented with significant higher LCT scores for the ipsilesional (right) visual field (fitters: 11.3 ± 5.5; non-fitters: 7.2 ± 5.6; $p = .044$). Gender, severity of stroke according to the Bamford classification, hemianopia, déviation conjugée, upper and lower extremity motor function, and time between stroke and baseline assessment, were not significantly different between these two subgroups with 15 or more missing O’s at baseline.
Proportional recovery of visuospatial neglect: observed change on the Letter Cancellation Test ($\Delta LCT$) in the contralesional (left) visual field versus predicted maximum potential recovery ($LCT_{\text{max}} - LCT_{\text{initial}}$).

The circles and squares represent respectively the non-fitters and fitters according to the hierarchical cluster analysis. The dashed line represents the regression line of the whole group ($N = 90$): $\Delta LCT = 0.73$ (95% CI = 0.57–0.89) · $LCT_{\text{max}} - LCT_{\text{initial}} + 0.21$ (95% CI = -2.24–2.67); $R^2 = 0.48$. The solid line represents the regression line for the fitters ($N = 80$): $\Delta LCT = 0.97$ (95% CI = 0.82–1.12) · $LCT_{\text{max}} - LCT_{\text{initial}} - 1.41$ (95% CI = -2.85–0.03); $R^2 = 0.78$. LCT contralesional (left) visual field score, score ranging from 0 to 20 O’s. Not all data points are visible due to overlap. The numbers within the bold symbols indicate the number of subjects having the same score.

Table 5.2 Relationship between the observed change on the Letter Cancellation Test ($\Delta LCT$) and predicted maximum potential recovery ($LCT_{\text{max}} - LCT_{\text{initial}}$) for the group of fitters ($N = 80$)

<table>
<thead>
<tr>
<th>Model</th>
<th>Beta</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$LCT_{\text{max}} - LCT_{\text{initial}}$</td>
<td>0.95</td>
<td>0.87–1.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$LCT_{\text{max}} - LCT_{\text{initial}}$ corrected for age</td>
<td>0.94</td>
<td>0.86–1.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$LCT_{\text{max}} - LCT_{\text{initial}}$ corrected for stroke severity</td>
<td>1.00</td>
<td>0.91–1.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$LCT_{\text{max}} - LCT_{\text{initial}}$ corrected for hemianopia</td>
<td>0.97</td>
<td>0.89–1.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$LCT_{\text{max}} - LCT_{\text{initial}}$ corrected for FMA-UE_{initial}</td>
<td>0.96</td>
<td>0.88–1.04</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Beta $LCT_{\text{max}} - LCT_{\text{initial}}$ did not change more than 10% when potential confounding variables were added to the linear regression analysis. Stroke severity was determined with the Bamford classification (0: Lacunar Anterior Cerebral Infarction; 1: Partial/Total Anterior Cerebral Infarction). Hemianopia was measured with the National Institutes of Health Stroke Scale (0: no; 1: yes). FMA-UE_{initial}: baseline score on the Upper Extremity motor section of the Fugl-Meyer Assessment; $LCT_{\text{max}} - LCT_{\text{initial}}$: 20 minus the baseline LCT score.
Table 5.3 Comparison of baseline variables of fitters and non-fitters with a predicted maximum potential recovery score (LCT\textsubscript{max} - LCT\textsubscript{initial}) of more than 15 O’s

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fitters VSN (N = 35)</th>
<th>Non-fitters VSN (N = 10)</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female/male\textsuperscript{b}</td>
<td>14 / 21</td>
<td>3 / 7</td>
<td>.719\textsuperscript{d}</td>
</tr>
<tr>
<td>Age, years\textsuperscript{a}</td>
<td>56.63 ± 12.88</td>
<td>68.10 ± 6.97</td>
<td>.007\textsuperscript{e}</td>
</tr>
<tr>
<td>Bamford classification (dichotomised), LACI/ TACI+PACI\textsuperscript{b}</td>
<td>3 / 32</td>
<td>0 / 10</td>
<td>1.00\textsuperscript{d}</td>
</tr>
<tr>
<td>Hemianopia (NIHSS), no/yes\textsuperscript{b}</td>
<td>22 / 13</td>
<td>7 / 3</td>
<td>1.00\textsuperscript{d}</td>
</tr>
<tr>
<td>Déviation conjugée (NIHSS), no/yes\textsuperscript{b}</td>
<td>20 / 15</td>
<td>6 / 4</td>
<td>1.00\textsuperscript{d}</td>
</tr>
<tr>
<td>LCT contralesional (left) visual field (maximum score = 20)\textsuperscript{a}</td>
<td>0.63 ± 1.09</td>
<td>0.70 ± 1.49</td>
<td>.757\textsuperscript{a}</td>
</tr>
<tr>
<td>LCT ipsilesional (right) visual field (maximum score = 20)\textsuperscript{a}</td>
<td>11.26 ± 5.54</td>
<td>7.20 ± 5.63</td>
<td>.044\textsuperscript{e}</td>
</tr>
<tr>
<td>Upper limb function (MI-arm, maximum score = 100)\textsuperscript{c}</td>
<td>0 (0−9)</td>
<td>0 (0−0)</td>
<td>.262\textsuperscript{a}</td>
</tr>
<tr>
<td>Lower limb function (MI-leg, maximum score = 100)\textsuperscript{c}</td>
<td>9 (0−42)</td>
<td>9 (0−11.25)</td>
<td>.527\textsuperscript{a}</td>
</tr>
<tr>
<td>Upper limb function (FMA-UE, maximum score = 66)\textsuperscript{c}</td>
<td>4 (2−6)</td>
<td>4 (2−4.25)</td>
<td>.475\textsuperscript{a}</td>
</tr>
<tr>
<td>Time between stroke and baseline assessment, days\textsuperscript{a}</td>
<td>6.94 ± 2.70</td>
<td>8.00 ± 2.31</td>
<td>.228\textsuperscript{a}</td>
</tr>
</tbody>
</table>

FMA-UE: Upper Extremity motor section of the Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; LCT: Letter Cancellation Test; MI: Motricity Index; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; TACI: Total Anterior Cerebral Infarction; VSN: VisuoSpatial Neglect. \textsuperscript{a} Mean ± standard deviation; \textsuperscript{b} Number of patients; \textsuperscript{c} Median (interquartile range); \textsuperscript{d} Fisher exact; \textsuperscript{e} Mann-Whitney U; \textsuperscript{*} p < .05.

Observed change and predicted maximum potential recovery on the LCT and FMA-UE showed a similar pattern when expressed as percentage of the total possible score on each test, although more patients showed proportional recovery in VSN than in FMA-UE (Figure 5.3). All VSN non-fitters (N = 10) lacked proportional recovery for upper limb motor function. Cluster analysis on the FMA-UE scores yielded two groups: N\textsubscript{1} = 66 and N\textsubscript{2} = 24. The relationship between ΔFMA-UE and FMA-UE\textsubscript{max} - FMA-UE\textsubscript{initial} for the fitters (N = 24) was: ΔFMA-UE = 0.81 (95% CI = 0.66−0.96) · FMA-UE\textsubscript{max} - FMA-UE\textsubscript{initial} - 2.29 (95% CI = -8.74−4.17) with R\textsuperscript{2} = 0.85. This relationship was not influenced by age, stroke severity according to the Bamford classification, homonymous hemianopia or LCT\textsubscript{initial}.

DISCUSSION

The first aim of the present study was to probe the generalisability of the fixed proportional recovery rule, i.e. to determine if the 70% rule for upper extremity motor recovery also applies to VSN in first-ever ischaemic stroke patients with a lesion in the right hemisphere. We also sought to identify clinical characteristics of patients who failed to follow the proposed
maximum proportional recovery rule. Subsequently, we investigated whether there are common biological mechanisms underlying this prediction rule by identifying VSN patients who lacked both the predicted amount of proportional recovery for VSN as well as recovery of upper extremity motor function following the FMA-UE score.

To the best of our knowledge this is the first study showing that the majority of first-ever ischaemic right-hemispheric stroke patients (89%) follow a proportionally fixed amount of recovery of approximately 97% in VSN. The amount of proportional recovery seen in this cohort is higher when compared to the percentages previously found for upper extremity motor function (means ranging from 64% to 83%)\textsuperscript{2,5,11} and aphasia (means ranging from 68% to 78%).\textsuperscript{12} Patients who had 15 or less missing O’s on the LCT at baseline assessment showed an improvement on the LCT that was similar to their maximum potential recovery

Figure 5.3  Proportional recovery of upper extremity motor function and visuospatial neglect in the contralesional (left) visual field.
The circles and squares represent respectively the results for the Letter Cancellation Test (LCT; contralesional visual field, score: 0–20) and Upper Extremity motor section of the Fugl-Meyer Assessment (FMA-UE; score: 0–66). The closed circles and squares represent the group of VSN ‘non-fitters’ (see text for details). Δ Observed: observed change on the LCT; Max - Initial: predicted maximum potential recovery. Not all data points are visible due to overlap. The numbers within or beside the bold symbols indicate the number of subjects having the same score.
score at baseline, whereas non-fitters were only found at thresholds above 15 missing O’s in the first days post stroke. Most (78%) patients who had severe VSN impairment (more than 15 missing O’s at baseline) did follow the proportional recovery rule.

Our results suggest that in the subgroup of patients with severe VSN, older patients with seemingly bilateral VSN (represented by lower LCT scores for the ipsilesional visual field) were more likely to not show proportional recovery. We did not expect age to be a potential predictor for proportional recovery of VSN, as it did not appear a strong predictor in previous studies investigating proportional recovery.2-5,12 Neglect, however, was suggested to be more common and severe in older stroke survivors, which may be related to the larger amount of pre-stroke brain atrophy.27,28 The seemingly more bilateral impairment in the group of non-fitters in comparison to the fitters with severe VSN (15 or more missing O’s) may reflect a process of remote suppression of the non-affected hemisphere by transhemispheric diaschisis as hypothesized by Von Monakow more than a century ago.29-31

More importantly, patients who fail to show the proportional amount of spontaneous neurobiological recovery in VSN also fail to follow the proportional recovery rule in UE motor function. The latter lends further support to the idea that the processes that drive spontaneous neurobiological recovery are part of common biological mechanisms which are irrespective of the type of neurological impairment involved. As a consequence, a minority of all first-ever, ischaemic stroke patients fail to show the expected amount of spontaneous neurobiological recovery of impairments.3

Our findings are in line with previous prospective cohort studies showing that the time course of VSN parallels spontaneous neurobiological recovery in motor function such as synergistic movements measured with the FMA-UE and strength of the upper and lower paretic limb.1,20,32 A number of prospective cohort studies demonstrated that VSN may have a suppressive effect on the recovery patterns of upper extremity function via dysfunction of cortical networks.32,33 We believe that one needs to be careful in using strict cut-off points below which patients are expected to lack proportional recovery. Even very severely affected patients with scores below the threshold of 4 points (6% of maximum score) on the FMA-UE and 18 missing O’s (10% of maximum score) on the LCT within the first week may still follow the proportional recovery rule.

Unfortunately, we cannot explain why 10 to 30% of the first-ever ischaemic stroke patients fail to follow the proportional recovery rule. Previous studies showed that intactness of the corticomotor pathways, measured with transcranial magnetic stimulation and diffusion
Proportional recovery of neglect post stroke

tensor imaging, is an important predictor for discriminating between patients with or without proportional recovery of upper limb motor function.\textsuperscript{4,5,7} Other key white matter pathways may also be essential for spontaneous neurobiological recovery in the context of VSN. For example, Corbetta and co-workers showed that attention deficits in VSN are mediated by dysfunction of the frontoparietal attention networks.\textsuperscript{33}

Some limitations should be considered when interpreting the present results. First, only patients with a first-ever ischaemic right-hemispheric stroke were investigated. Our findings suggest, however, that there are unknown mechanisms driving spontaneous neurobiological recovery, irrespective of the type of neurological impairment involved. Hence, it appears obvious to investigate whether left-hemispheric stroke patients that lack proportional recovery of speech\textsuperscript{34} also fail to show proportional improvement of sensory-motor impairments. Second, we did not present direct measures for lesion size and location. However, the large array of clinical outcome measures suggest that the non-fitters had not only larger but also more cortical involvement of their strokes when compared to the fitters who presented with impairments related to smaller subcortical strokes in the white matter. Third, due to the relatively late initial assessment of on average 8 days (compared to within 72 hours after onset in other studies), we might have missed some cases of very early recovery of VSN. Fourth, we assessed VSN with a paper-and-pen single-letter cancellation test and used the asymmetry between the left and right side as a measure for neglect.\textsuperscript{32} We used an asymmetry cutoff point of 2 to include a range of patients with mild to severe neglect. Future studies may use a variety of tests to assess the different aspects of neglect and use other measurements and/or cut-off scores to determine neglect severity.\textsuperscript{35} Fifth, we only reported the LCT score for the contralesional (left) visual field. However, the recovery of VSN in terms of LCT score for the ipsilesional (right) visual field also followed the proportional recovery rule. Beyond a critical threshold of 15 missing O’s at baseline, the non-fitters did show more ‘bilateral impairment’ in comparison to those severely affected patients who did follow the recovery rule. Sixth, although the present study reflects one of the largest cohorts suffering from neglect post stroke, the relative small sample size and lack of neurobiological markers did not allow for further investigating the clinical differences between fitters and non-fitters using multivariate regression analysis.

In conclusion, the current findings provide further support for the conceptual notion that the amount of recovery is proportional to the initial impairment. There may be common biological mechanisms underlying spontaneous neurobiological recovery in the first months after stroke onset. To substantiate this premise, future studies should investigate
the proportional recovery for other neurological impairments in larger stroke populations. These studies should combine early clinical and neurophysiological, primarily to identify fitters and non-fitters of the maximum proportional recovery rule in order to optimize early stroke triage, better inform patient and caregivers, and most importantly, stratify patients for neurorehabilitation in early started intervention trials.

**Acknowledgements**

The authors thank the Stroke Intensity trial and EXPLICIT-stroke trial physicians, therapist and nurses at the stroke units of the participating university centers, local hospitals and in the associated rehabilitation centers and nursing homes, and the patients who participated in the study.

**REFERENCES**


Effects of unilateral upper limb training in two distinct prognostic groups early after stroke: the EXPLICIT-stroke randomised clinical trial

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ABSTRACT

Background and objective  Favourable prognosis of the upper limb is dependent on preservation or return of Voluntary Finger Extension (VFE) early after stroke. The present study aimed to determine the effects of modified Constraint-Induced Movement Therapy (mCIMT) and ElectroMyoGraphy (EMG)-triggered NeuroMuscular Stimulation (EMG-NMS) on upper limb capacity early post stroke.

Methods 159 ischaemic stroke patients were included: 58 patients with a favourable prognosis (> 10 degrees of VFE) were randomly allocated to 3-weeks mCIMT or usual care only; 101 patients with an unfavourable prognosis were allocated to 3-weeks EMG-NMS or usual care only. Both interventions started within 14 days post stroke, lasted up until 5 weeks, focused at preservation or return of VFE.

Results Upper limb capacity was measured with the Action Research Arm Test (ARAT), assessed weekly within the first 5 weeks post stroke and at post-assessments at 8, 12, and 26 weeks. Clinically relevant differences in ARAT in favour of mCIMT were found after 5, 8, and 12 weeks post stroke (respectively, 6, 7 and 7 points; \( p < .05 \)), but not after 26 weeks. We did not find statistically significant differences between mCIMT and usual care on impairment measures, such as the Fugl-Meyer assessment Upper Extremity. EMG-NMS did not result in significant differences.

Conclusions Three weeks of early mCIMT is superior to usual care in terms of regaining upper limb capacity in patients with a favourable prognosis; 3 weeks of EMG-NMS in patients with an unfavourable prognosis is not beneficial. Despite meaningful improvements in upper limb capacity, no evidence was found that the time-dependent neurological improvements early post stroke are significantly influenced by either mCIMT or EMG-NMS.
INTRODUCTION

Several prospective cohort studies among stroke patients have shown that the functional outcome of the upper limb is largely defined within the first 5 weeks post stroke and is mainly driven by (yet poorly understood) mechanisms of spontaneous neurobiological recovery.\textsuperscript{1,2} Observational studies showed that the presence of some Voluntary Finger Extension (VFE) within 72 hours is a favourable indicator for the return of dexterity post stroke.\textsuperscript{3,4} This suggests that early control of FE is an important prognostic factor in stratifying patients for upper limb intervention trials early post stroke.\textsuperscript{2}

For those with a favourable prognosis, indicated by some VFE early post stroke, Constraint-Induced Movement Therapy (CIMT) or a modified version (mCIMT) may benefit arm-hand activities and self-reported hand function in daily life.\textsuperscript{5} The number of phase II trials on mCIMT within the first days or weeks post stroke is however small and findings are rather inconclusive. For example, Dromerick and co-workers showed in a proof of concept trial that 1 or 2 hours mCIMT per working day for 2 weeks was not superior to an equal dosage of usual care, whereas a high dose of 3 hours mCIMT per working day resulted in less improvement on functional outcome measured with the Action Research Arm Test (ARAT) at 3 months post stroke.\textsuperscript{6}

For those with an unfavourable prognosis for functional outcome at 6 months, i.e. patients without VFE,\textsuperscript{1,3,4} no evidence-based therapies have been reported so far. In subacute and chronic stroke, innovative therapies such as ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) of the finger extensors to improve voluntary control have shown promise in terms of increasing active range of motion.\textsuperscript{7-11} Furthermore, several studies suggest that EMG-NMS may produce changes in cortical activation patterns and excitability in chronic stroke.\textsuperscript{12,13} For example, Shin and co-workers showed in a small proof of concept trial ($N = 14$) that a daily 30-minute program for 10 weeks shifted cortical activation patterns as seen in functional Magnetic Resonance Imaging (fMRI) from the ipsilateral SensoriMotor Cortex (SMC) to the contralateral SMC in chronic stroke.\textsuperscript{13} Despite the growing evidence for enhanced levels of homeostatic neuroplasticity in the first weeks post stroke,\textsuperscript{14} it is still unclear whether EMG-NMS can enhance this spontaneous neurological process of recovery as early started EMG-NMS trials for patients without VFE are lacking in this restricted time window.

The first objective of the present study was to investigate the effects of an early mCIMT program on recovery of upper limb capacity during the first 6 months, starting within 14 days post stroke in patients with some VFE. Our second objective was to investigate the
effects of early EMG-NMS on the recovery of VFE and upper limb capacity during the first 6 months, starting within 14 days post stroke in patients with no voluntary control of the finger extensors. We hypothesized that an intensive 3-week mCIMT program would result in a clinically meaningful improvement in ARAT scores compared to usual care alone. For the patients with an unfavourable prognosis we hypothesized that a higher percentage of patients (10% or more) would regain some dexterity (ARAT score > 9 points on a maximum of 57 points) if they received intensive daily EMG-NMS for 3 weeks, compared to usual care alone.

MATERIALS AND METHODS

Details of the present study regarding research questions, hypotheses, design, patient selection and stratification, interventions, primary and secondary outcomes, and power and statistical analyses were reported in a design article in 2008.15

Design

We conducted a stratified, multicentre, observer-blinded randomised controlled trial with eight repeated measurements within the first 26 weeks post stroke. After stratifying patients within the first 14 days after stroke to either the mCIMT trial (if they had VFE of 10 degrees or more) or the EMG-NMS trial (no VFE), randomisation to the experimental treatment or usual care was performed online by a restricted minimisation randomisation procedure. Randomisation was executed by two staff members not involved in the treatment protocol (GK and HA).

Two trained observers (RN and CW) who were blinded to the treatment allocation performed all clinical measurements at baseline (before randomisation), and at 2, 3, and 4 weeks follow-up during face-to-face sessions at the location of initial admission and at the location of subsequent rehabilitation. Post-intervention assessments were performed at 5, 8, 12, and 26 weeks after stroke. The same assessor performed the serial assessments for an individual subject in both trials. Patients were not blinded to the intervention, however, they remained naïve as to the supposed efficacy of the two intervention conditions.

Both clinical trials were part of the EXPLICIT-stroke program. EXPLICIT-stroke is an acronym for EXplaining PLastICITy after stroke and was funded for 5 years by the Netherlands Organisation for Health Research and Development (ZonMw no. 890000001).
The study was approved by the Medical Ethics Review Committees of Leiden University Medical Center (no. P08.035) and the Dutch Central Committee on Research Involving Human Subjects (CCMO: no. NL21396.058.08), and was registered in the Netherlands Trial Registry (NTR, www.trialregister.nl, no. NTR1424).

**Patient selection**

For both trials, we selected patients with: (1) first-ever ischaemic stroke in one of the cerebral hemispheres; (2) upper limb paresis according to national institutes of health stroke scale (NIHSS) item 5; (3) baseline ARAT score of ≤ 53 on a maximum of 57 points; (4) ability to communicate and comprehend (mini mental state examination ≥ 23 points on a maximum of 30 points); (5) ability to sit independently for at least 30 seconds; (6) 18–80 years of age; (7) no successful thrombolysis therapy resulting in upper limb motor recovery and attaining 0 points on NIHSS item 5 of the paretic arm; (8) no musculoskeletal impairments of the upper paretic limb; (9) no additional therapies such as botulinum toxin injections or medication intake that may influence upper limb function in the previous 3 months; (10) willing to participate in an intensive rehabilitation treatment program; and (11) written informed consent. At intake, patients were stratified to either the mCIMT trial if able to voluntarily extend the thumb and/or two or more fingers of the affected hand (10 degrees or more), or to the EMG-NMS trial if they could not.

**Interventions**

Patients allocated to the mCIMT group daily received 60 minutes of supervised intensive graded practice focused on improving task-specific use of the paretic arm and hand, including enhancing VFE. Therapy was delivered in either one session or split into two sessions of 30 minutes, depending on the available time and patients’ tolerance. Time between sessions per day was not controlled for. One hour of mCIMT therapy was chosen to not overload patients in the early phase post stroke.16;17 Patients were instructed to wear a padded safety mitt (Sammons Preston® #6727; Sammons Preston, Inc, Bolingbrook, IL, USA) for 3 hours per working day, during 3 consecutive weeks and lasting up until 5 weeks post stroke. Details of the mCIMT treatment protocol have been described previously.17

Patients allocated to the EMG-NMS group received two sessions of 30 minutes stimulation of the finger extensors each working day, for 3 weeks, using the Stiwell-Med4-system
(Ottobock Healthcare Products GmbH, Vienna, Austria). Active participation of the patient was required to reach an EMG threshold during the dorsiflexion movement of fingers and wrist in order to trigger the NMS. When triggered, the Stiwell-Med4-system stimulated for 5 seconds, followed by 25 seconds of rest. In case of absent EMG-activity, patients learned to facilitate extensor activity of wrist and fingers by simultaneously abducting their paretic arm (often described as Soques’ phenomenon) or by simultaneously EMG-triggering of the extensors of the non-paretic arm. EMG-NMS therapy was augmented by offering patients visual feedback presented in front of the patient on a computer screen. For this purpose, the amount of voluntary EMG-activity of FE was visualized in a computer game in which patients had to raise a hot air balloon above a mountain.

Usual upper limb therapy in both strata consisted of exercise therapy based on recommendations from current Dutch guidelines applied face-to-face by a physiotherapist or occupational therapist for 30 minutes per working day executed for 3 consecutive weeks. Patients in the control group with an unfavourable prognosis engaged in passive range-of-motion exercises and facilitation of voluntary movements, whereas those with a favourable prognostic group received exercise therapy, both according to Dutch guidelines.

All therapy sessions were performed in each participating centre by two to three trained physiotherapists and/or occupational therapists. The content and duration of therapy was recorded by the therapist in patient diaries. After the 3-week intervention phase, all patients received usual care (i.e. about 30 minutes arm-hand treatment per working day) during their stay in the rehabilitation centre or nursing home for on average 2 months. The exact duration and type of post-intervention usual care was not controlled for, and based on individual needs.

Outcomes

The primary outcome variable for both trials was the ARAT score. The ARAT is a performance test that assesses the ability to perform gross movements and the ability to grasp, move, and release objects of various sizes, weights, and shapes. The original test consists of 19 items rated on 4-point ordinal scales. Removing 4 items enabled the construction of a hierarchical 1-dimensional scale. The ARAT has been shown to be valid, reliable, and responsive. It was applied according to the guidelines developed by Yozbatiran and co-workers. The Minimal Clinically Important Difference (MCID) was set at 10% of the range of the scale, i.e. 6 points.
Secondary outcome variables in both trials were: Upper Extremity motor function section of the Fugl-Meyer Assessment (FMA-UE), Wolf Motor Function Test (WMFT), Motricity Index of the Upper Extremity (MI-UE), Erasmus MC modification of the Nottingham Sensory Assessment of the Upper Extremity (EmNSA-UE), Nine Hole Peg Test (NHPT), Frenchay Arm Test (FAT), Motor Activity Log (MAL), and the hand domain of the Stroke Impact Scale (SIS-hand, version 3.0).

The FMA-UE is a reliable and valid motor function test evaluating the ability to make arm movements outside the synergistic pattern. The WMFT is reliable and valid and consists of two strength items, six timed and nine integrative functional tasks. Assessment involves performance time with a maximum of 120 seconds and a 6-point Functional Ability Scale (FAS). The MI reliably and validly assesses upper limb strength by testing functions with the total score ranging from 0 to 100 points. The EmNSA is a three-point ordinal scale measuring sharp-blunt discrimination, two-point discrimination, and proprioception. Except for the two-point discrimination, intra- and inter-rater reliability are good to excellent (Kappa = 0.58–1.00). The NHPT is a reliable and valid test assessing manual dexterity by measuring the speed with which a patient grasps, inserts and removes nine pegs into a grid of vertical holes. The test was discontinued after 50 seconds if the patient was still unable to insert any pegs. Reliability and validity have been assessed and norms are available. The reliable and valid FAT measures dexterity using five functional tasks, scoring on a binominal scale (fail/pass). We used a translated and adapted version of the MAL comprising the 14 original activities. It was used to independently rate how well (6-point Quality of Movement scale, QOM) and how much (6-point amount-of-use scale, AOU) the paretic arm was used spontaneously to accomplish the activities of daily living outside the laboratory. Reliability and validity of the MAL have been proved in a number of studies. The SIS-hand was used to evaluate patient-perceived outcome for the paretic upper limb. Each item was scored on a 5-point rating scale from ‘not difficult at all’ to ‘cannot do at all’. The SIS has shown excellent psychometric properties in terms of concurrent and construct validity, test-retest reliability and responsiveness.

**Sample size estimation**

Power analysis showed that a sample size of 60 patients (including 10% dropout) was estimated to be sufficient for the mCIMT trial, and 120 (including 10% dropouts) for the EMG-NMS trial. Details are described elsewhere.
Data analyses

Successful blinding of the assessors for treatment allocation was tested by comparing assessors’ guesses with actual treatment assignment in both trials using a Cohen’s Kappa statistic. In both trials, we tested for differences in baseline values with Fisher’s exact test or the χ²-test for nominal outcomes, the Mann-Whitney U test for ordinal outcomes, and Student’s t-test for independent groups for other outcomes, assuming equal variances for interval or ratio scales. The assumption of normality was tested with Z-scores for skewness and kurtosis, and by visual inspection. To analyse time series of continuous outcomes, the Generalised Estimating Equations (GEE) model with a compound symmetry as a covariance structure was used to evaluate differences in overall effects in the experimental and control groups within each trial over the time course of 5, 8, 12, and 26 weeks post stroke. This model included time post stroke onset, group and the interaction between group and time post stroke onset in the regression model. We added the baseline value of the dependent variable to the regression model. The proportional difference in the number of stroke patients showing some return of VFE and dexterity in the EMG-NMS trial was assessed using a dichotomous GEE model. Intention-to-treat analyses were performed on all patients, including those with incomplete sets of data. Missing values were not imputed. We calculated β-values and standard errors for the time × group interaction effects and, subsequently, used the Wald test to obtain p-values. All hypotheses were tested two-tailed, with an alpha of .05. All analyses were carried out in SPSS, version 20.

RESULTS

Between October 2008 and November 2013, approximately 4300 patients were assessed for eligibility, and 159 were selected (Figure 6.1). No adverse effects were reported and none of the dropouts were related to type of therapy in either trial. Forty-one of the 464 (8.8%) measurements in the mCIMT trial and 63 of the 808 (7.8%) measurements in the EMG-NMS trial were missing. Comparing observers’ guesses about treatment allocation and actual allocation showed 89 matches for the 159 patients, which was not statistically significant (p = .132).

Table 6.1 shows patients’ baseline characteristics of each trial. Mean start of both trials was at 8 (standard deviation = 4; interquartile range = 5–10) days post stroke. No significant differences were found with respect to demographic, primary, or secondary outcomes at
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Table 6.2 shows the absolute values at 5, 8, 12 and 26 weeks, and the \( \beta \) (standard error) and \( p \)-values for the time \( x \) group interaction effects over the time course of 5, 8, 12 and 26 weeks post stroke, corrected for baseline. A mean significant time \( x \) group interaction effect was found in favour of mCIMT compared to usual care after 5 (\( p = .011 \)), 8 (\( p = .002 \)) and 12 weeks (\( p = .023 \)) post stroke, with respectively 6, 7 and 7 points difference on the primary outcome measure ARAT (Figure 6.2). In addition, a significant time \( x \) group interaction effect was found for SIS-hand after 8 weeks post stroke in favour of mCIMT in comparison to usual care (\( p = .038 \)).

The total amount of patients with cerebrovascular accidents was estimated using the number of admitted patients in each participating centre. EMG-NMS: Electromyography-triggered NeuroMuscular Stimulation. mCIMT: modified Constraint-Induced Movement Therapy.

Figure 6.1 Inclusion flow diagram.
The total amount of patients with cerebrovascular accidents was estimated using the number of admitted patients in each participating centre. EMG-NMS: Electromyography-triggered NeuroMuscular Stimulation. mCIMT: modified Constraint-Induced Movement Therapy.
Table 6.1  Baseline characteristics of first-ever ischaemic stroke patients allocated to mCIMT, EMG-NMS, or usual care

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>mCIMT TRIAL (N = 58)</th>
<th>EMG-NMS TRIAL (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mCIMT (N = 29)</td>
<td>Usual care (N = 29)</td>
</tr>
<tr>
<td>Gender, male/female, % male</td>
<td>14/15, 48%</td>
<td>17/12, 59%</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>58.97 (14.05)</td>
<td>65.34 (11.36)</td>
</tr>
<tr>
<td>Affected hemisphere, right/left, % right</td>
<td>18/11, 62%</td>
<td>18/11, 62%</td>
</tr>
<tr>
<td>Paresis of pre stroke dominant side, yes/no, % yes</td>
<td>10/19, 35%</td>
<td>12/17, 41%</td>
</tr>
<tr>
<td>Bamford classification, LACI/PACI/TACI</td>
<td>21/6/2</td>
<td>21/7/1</td>
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<tr>
<td>MMSE (range: 0–30)*</td>
<td>27.50 (2.32)</td>
<td>27.00 (2.86)</td>
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<tr>
<td>Urinary incontinence (Barthel Index), yes/no, % yes</td>
<td>5/24, 17%</td>
<td>8/20, 28%</td>
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<td>NIHSS (range: 0–42)*</td>
<td>4.17 (2.04)</td>
<td>4.75 (2.14)</td>
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<td>Visual gaze deficit (NIHSS subscale), yes/no, % yes</td>
<td>0/29, 0%</td>
<td>0/29, 0%</td>
</tr>
<tr>
<td>Hemianopia (NIHSS subscale), yes/no, % yes</td>
<td>1/28, 3%</td>
<td>2/27, 7%</td>
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<td>Somatosensory deficit (NIHSS subscale), yes/no, % yes</td>
<td>10/19, 34%</td>
<td>11/18, 38%</td>
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<tr>
<td>Extinction and inattention (NIHSS subscale), yes/no, % yes</td>
<td>3/26, 10%</td>
<td>4/25, 14%</td>
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<tr>
<td>Time between baseline assessment and stroke onset (days)*</td>
<td>8.17 (4.28)</td>
<td>8.79 (4.13)</td>
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<td>Primary outcome</td>
<td></td>
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<td>ARAT (range: 0–57)</td>
<td>23.93 (13.90)</td>
<td>20.97 (15.87)</td>
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Table 6.1  Continued

<table>
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<th>Secondary outcomes</th>
<th>mCIMT TRIAL (N = 58)</th>
<th>EMG-NMS TRIAL (N = 101)</th>
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<td>mCIMT (N = 29)</td>
<td>Usual care (N = 29)</td>
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<tr>
<td>FMA-UE (range: 0–66)*</td>
<td>42.93 (14.60)</td>
<td>35.64 (15.03)</td>
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<tr>
<td>MI-UE (range: 0–100)*</td>
<td>66.21 (17.55)</td>
<td>60.21 (18.17)</td>
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<td>EmNSA-UE (range: 0–40)*</td>
<td>33.00 (13.26)</td>
<td>32.75 (12.36)</td>
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<td>SIS-hand (range: 5–25)*, %</td>
<td>8.83 (5.17), 19.2%</td>
<td>7.35 (3.86), 11.8%</td>
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<tr>
<td>WMFT Median Time (sec, range: 0–120)*</td>
<td>54.57 (58.69)</td>
<td>57.66 (57.46)</td>
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<td>WMFT FAS (range: 0–5)*</td>
<td>2.38 (1.39)</td>
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<td>FAT (range: 0–5)*</td>
<td>2.15 (2.01)</td>
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<td>Average patient MAL-QOM (range: 0–5)*</td>
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<td>0.54 (0.65)</td>
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<tr>
<td>Average patient MAL-AOU (range: 0–5)*</td>
<td>0.96 (0.76)</td>
<td>0.74 (0.81)</td>
</tr>
<tr>
<td>NHPT (pegs/sec)*</td>
<td>0.10 (0.16)</td>
<td>0.05 (0.11)</td>
</tr>
</tbody>
</table>

Values are presented as number of patients; * Mean (standard deviation); † Not applicable.
AOU: Amount Of Use; ARAT: Action Research Arm Test; EMG-NMS: ElectroMyoGraphy-triggered NeuroMuscular Stimulation; EmNSA-UE: Erasmus MC modified (revised) Nottingham Sensory Assessment of the upper extremity; FAS: Functional Ability Scale; FAT: Frenchay Arm Test; FMA-UE: upper extremity motor function section of the Fugl-Meyer Assessment; LACI: Lacunar Anterior Cerebral Infarction; MAL: Motor Activity Log; mCIMT: modified Constraint-Induced Movement Therapy; MI-UE: Motricity Index of the upper extremity; MMSE: Mini Mental State Examination; NHPT: Nine Hole Peg Test; NIHSS: National Institutes of Health Stroke Scale; PACI: Partial Anterior Cerebral Infarction; QOM: Quality Of Movement; SIS-hand: hand function domain of the Stroke Impact Scale version 3.0; TACI: Total Anterior Cerebral Infarction; WMFT: Wolf Motor Function Test.
### Table 6.2 Effects of early mCIMT and EMG-NMS on the primary and secondary outcome measures

<table>
<thead>
<tr>
<th></th>
<th>mCIMT (N = 29)</th>
<th>Usual care (N = 29)</th>
<th>Generalised Estimating Equations: $\beta$ (SE), $p$ Group x time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT (range: 0–57)</td>
<td>45.21 (9.94)</td>
<td>49.46 (7.46)</td>
<td>49.74 (7.68)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMA-UE (range: 0–66)</td>
<td>58.79 (7.17)</td>
<td>60.00 (7.21)</td>
<td>60.63 (6.64)</td>
</tr>
<tr>
<td>MI-UE (range: 0–100)</td>
<td>86.30 (12.09)</td>
<td>86.70 (12.45)</td>
<td>88.50 (12.37)</td>
</tr>
<tr>
<td>EmNSA-UE (range: 0–40)</td>
<td>37.89 (6.88)</td>
<td>37.33 (7.47)</td>
<td>37.96 (6.91)</td>
</tr>
<tr>
<td>SIS-hand (range: 5–25), %</td>
<td>18.44 (5.92), 67.2%</td>
<td>21.11 (3.41), 80.6%</td>
<td>21.65 (2.98), 83.3%</td>
</tr>
<tr>
<td>WMFT Median Time (sec, range: 0–120)</td>
<td>2.63 (1.46), 80.6%</td>
<td>2.15 (0.94), 83.3%</td>
<td>1.93 (0.91), 87.3%</td>
</tr>
<tr>
<td>WMFT FAS (range: 0–5)</td>
<td>4.25 (0.75)</td>
<td>4.39 (0.78)</td>
<td>4.54 (0.59)</td>
</tr>
<tr>
<td>FAT (range: 0–5)</td>
<td>4.74 (0.45)</td>
<td>4.88 (0.34)</td>
<td>4.92 (0.27)</td>
</tr>
<tr>
<td>Average patient MAL-QOM (range: 0–5)</td>
<td>2.19 (1.05)</td>
<td>2.54 (1.03)</td>
<td>2.72 (1.25)</td>
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Table 6.2  Continued

<table>
<thead>
<tr>
<th></th>
<th>mCIMT (N = 29)</th>
<th>Usual care (N = 29)</th>
<th>Generalised Estimating Equations: β (SE), p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average patient MAL-AOU (range: 0–70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.52 (1.15)</td>
<td>2.86 (1.17)</td>
<td>2.97 (1.27)</td>
</tr>
<tr>
<td>NHPT (pegs/sec)</td>
<td>0.36 (0.24)</td>
<td>0.42 (0.20)</td>
<td>0.50 (0.21)</td>
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</tbody>
</table>

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<tbody>
<tr>
<td></td>
<td>5 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT (range: 0–57)</td>
<td>5.54 (11.58)</td>
<td>8.18 (12.77)</td>
<td>11.22 (14.99)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMA-UE (range: 0–66)</td>
<td>14.98 (14.29)</td>
<td>18.98 (16.05)</td>
<td>21.00 (17.80)</td>
</tr>
<tr>
<td>MI-UE (range: 0–100)</td>
<td>29.96 (23.07)</td>
<td>36.60 (23.43)</td>
<td>38.74 (24.86)</td>
</tr>
<tr>
<td>EmNSA-UE (range: 0–40)</td>
<td>31.58 (13.78)</td>
<td>33.09 (12.69)</td>
<td>34.07 (12.16)</td>
</tr>
<tr>
<td>SIS-hand (range: 5–25), %</td>
<td>5.77 (2.06)</td>
<td>6.80 (4.84)</td>
<td>8.03 (5.75)</td>
</tr>
</tbody>
</table>

Table 6.2 continues on next page
Table 6.2  Continued

<table>
<thead>
<tr>
<th></th>
<th>EMG-NMS (N = 50)</th>
<th>Usual care (N = 51)</th>
<th>Generalised Estimating Equations: $\beta$ (SE), $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>WMFT Median Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(sec, range: 0–120)</td>
<td>110.13 (32.74)</td>
<td>99.52 (44.42)</td>
<td>88.87 (52.09)</td>
</tr>
<tr>
<td>WMFT FAS (range: 0–5)</td>
<td>0.61 (1.05)</td>
<td>0.81 (1.22)</td>
<td>1.03 (1.46)</td>
</tr>
<tr>
<td>FAT (range: 0–5)</td>
<td>0.50 (1.35)</td>
<td>0.73 (1.44)</td>
<td>1.24 (1.83)</td>
</tr>
<tr>
<td>Average patient MAL-QOM (range: 0–5)</td>
<td>0.14 (0.34)</td>
<td>0.25 (0.49)</td>
<td>0.40 (0.65)</td>
</tr>
<tr>
<td>Average patient MAL-AOU (range: 0–5)</td>
<td>0.21 (0.45)</td>
<td>0.36 (0.60)</td>
<td>0.50 (0.75)</td>
</tr>
<tr>
<td>NHPT (pegs/sec)</td>
<td>0.02 (0.08)</td>
<td>0.02 (0.10)</td>
<td>0.06 (0.14)</td>
</tr>
<tr>
<td>Finger Extension (N)$^\text{‡}$</td>
<td>14</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Dexterity: ARAT &gt; 9 points (N)$^\text{‡}$</td>
<td>8</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

Values are presented as absolute numbers at 5, 8, 12 and 26 weeks after stroke, mean (standard deviation); baseline values are presented in Table 6.1; * $p < .05$; † Not applicable, assessment only performed at baseline, 5, 8, 12 and 26 weeks; $^\text{‡}$ Number of people with partial-full finger extension (minimally 10 degrees) / dexterity, analysis from generalised estimating equations using a binomial distribution. AOU: Amount Of Use; ARAT: Action Research Arm Test; EMG-NMS: ElectroMyoGraphy-triggered NeuroMuscular Stimulation; EmNSA-UE: Erasmus MC modified (revised) Nottingham Sensory Assessment of the Upper Extremity; FAS: Functional Ability Scale; FAT: Frenchay Arm Test; FMA-UE: Upper Extremity motor function section of the Fugl-Meyer Assessment; MAL: Motor Activity Log; mCIMT: modified Constraint-Induced Movement Therapy; MI-UE: Motricity Index of the Upper Extremity; NHPT: Nine Hole Peg Test; QOM: Quality Of Movement; SE: Standard Error; SIS-hand: hand function domain of the Stroke Impact Scale version 3.0; WMFT: Wolf Motor Function Test.
We found no significant time \( \times \) group interaction effects on the ARAT in favour of EMG-NMS compared to usual care. As shown in Figure 6.3 and Table 6.2, in the EMG-NMS trial, the proportion of patients showing some return of VFE and dexterity (i.e. ARAT > 9 points) did not differ significantly between groups. No significant time \( \times \) group interaction effects were found for motor impairment such as FMA-UE, MI-UE, and for other secondary outcomes favouring or disfavouring mCIMT or EMG-NMS therapy.
DISCUSSION

The present study showed that an early start of a 3-week mCIMT program in ischaemic stroke patients with some voluntary control of FE at stroke onset (minimally 10 degrees of VFE) was more effective in improving upper limb capacity as assessed by the ARAT in comparison to solely usual care. However, these clinically meaningful effects did not sustain up to 26 weeks after stroke, which was mainly due to delayed functional improvement of the usual care group with a favourable prognosis. mCIMT also benefitted the self-reported outcome of hand function according to the SIS. Unlike these favourable effects, no superiority of mCIMT was found in terms of motor impairment including the motor part of the FMA-UE. Finally, no added value of a 3-week EMG-NMS program in patients without initial VFE was found with respect to regaining upper limb capacity compared to usual care.

To our knowledge, this is the first trial in which patients were stratified on the basis of the powerful prognostic factor ‘VFE’ to type of therapy within the first 2 weeks post stroke. Our finding of significant and meaningful changes in upper limb capacity for mCIMT in comparison to the usual care without any significant therapy-induced improvements in neurological impairments, such as synergism, is in line with a recent randomised controlled...
Effects of upper limb training post stroke

as well as longitudinal kinematic studies showing that the observed meaningful improvements in upper limb capacity are predominantly driven by learning adaptive motor strategies. The lack of significant differences on the WMFT, measuring upper extremity motor ability, may be associated with the presence of impairment-related items in this test such as extending the elbow against resistance. True neurobiological recovery, in terms of regaining degrees of freedom in motor control as expressed by motor synergism and smoothness in reaching tasks, seems to be determined in the same time-window of spontaneous neurobiological recovery restricted to the first 8 to 10 weeks post stroke. Our findings are supported by a recent proof-of-concept study of Kitago and co-workers who found no significant changes in kinematic measures of movement coordination after mCIMT despite clinically meaningful improvements of upper limb capacity measured with the ARAT in the chronic phase. In addition, a treatment effect of constraint-induced therapy on the ARAT was found in the chronic phase after stroke, but this effect was not found for the FMA-UE. This suggests that the effects of mCIMT are mainly the result of learning to use preserved end-effectors in a different, more optimal way to accomplish meaningful tasks (i.e. adaptation strategies) and not of actual improvement of neurological impairments. In addition, the follow-up measures beyond 5 weeks showed that the significant effects on the ARAT were restricted to the first 3 months post stroke. A key question that remained unaddressed in the present study is whether a higher dose of mCIMT or continuation of therapy for more than 3 weeks post stroke would have resulted in effects that sustain beyond 3 months post stroke, assuming that higher doses of task-specific training may result in better outcomes.

Strengths and limitations

First, patient selection limits the generalisability to other stroke populations. Recruitment of patients with the same stroke type and no limiting co-morbidities early post stroke is difficult as is illustrated by the proportion of patients eventually included: 3.7%. The proportion of included patients was comparable to for example the 2.9% in the VECTORS-trial. Despite this low recruitment rate restricted to patients with a first-ever ischaemic hemispheric stroke, this study is the largest and earliest started upper extremity intervention trial conducted thus far. Fewer stroke patients were recruited for the EMG-NMS trial (N = 101) than originally planned (N = 120). However, increasing the number of patients in this trial and, hence, its statistical power for the probability of regaining some upper limb capacity would most likely not have changed our conclusion because the current results do not show any trend towards
positive, clinically significant effects of EMG-NMS in comparison to usual care. Omission of the stratification, by allocating all patients to one experimental ($N = 79$) and one control group ($N = 80$), would most likely have resulted in a neutral trial due to lack of homogeneity between subjects. We believe this prognostic stratification is essential when performing rehabilitation trials, and may be a powerful tool to prevent type-II-errors.\textsuperscript{2,43} Furthermore, in line with previous experience in rehabilitation trials\textsuperscript{4,28} we applied a repeated measurements design to create individual time series in order to reduce the unexplained variance due to within-subject measurement error and to enhance the precision of estimating the added value of therapy relative to the underlying logistic pattern of spontaneous neurobiological recovery. Unfortunately, most rehabilitation trials so far did include patients at arbitrary time points in the first 3 months post stroke,\textsuperscript{43} whereas time-dependent spontaneous neurobiological recovery explains almost 70\% of recovery.\textsuperscript{45,46} Not stratifying patients according to the expected proportional recovery, as well as starting recruitment of subjects in trials at non-fixed moments post stroke, such as moment of admission in a rehabilitation centre, will increase the variation in spontaneously driven gains between subjects.\textsuperscript{44} Patients recruited during the first days post stroke will show on average more change than those recruited after a number of weeks. We are of the opinion that differences in starting times post stroke and lack of stratification increases the within-group variance for measured improvement in trials, and that this will be at the expense of identifying therapy-induced effects between-groups in randomised clinical trials. An important next step is to figure out how differences in timing of recruiting patients for trials in the subacute phase post stroke will affect random as well as systematic error in parallel group designs by using simulation models.

Second, both the mCIMT and the EMG-NMS group received more therapy in comparison to the usual care groups, i.e. the amount of therapy was not dose-matched. We therefore cannot answer the question whether the beneficial treatment effect of mCIMT was completely due to the content of the therapy itself or partly by the higher dose of therapy applied. Another limitation may be the choice of EMG-NMS as an intervention for patients with no voluntary control of finger extensors at baseline. Thirty-two patients with an unfavourable prognosis showed return of VFE due to spontaneous neurobiological recovery within the first 5 weeks. Moreover, these patients showed more improvement in motor function than expected following the Shoulder Abduction Finger Extension (SAFE) model.\textsuperscript{4,47} Further research should try to identify these ‘false negatives’ in order to improve stratification for intervention. Despite return of some VFE, evidence based therapies for this patient group with an unfavourable prognosis are lacking at this moment. From our data it cannot be
determined if a longer intervention phase, or applying EMG-NMS solely with task specific movements would have changed the current findings. There is some evidence that the sensory-motor integration during EMG-NMS of the paretic arm may activate neuronal networks13,48 and increases the cortical perfusion of the ipsilesional SMC in chronic stroke.49 Our findings stress the need to explore the meaning of changes in neural networks, as revealed by imaging techniques such as fMRI and electroencephalography, regarding the impact of improved motor performance early post stroke.41 Furthermore, the added value of combining task specific practice with interventions directly focused at the damaged brain should be investigated (e.g. non-invasive brain stimulation and neuropharmacological therapies).

**Interpretation**

This is the first stratified randomised controlled trial of post stroke upper extremity rehabilitation based on functional prognosis using repeated measurements. Our results suggest that 1 hour daily supervised mCIMT for 3 weeks in those with some VFE early post stroke is more effective than usual care alone leading to clinically meaningful effects on arm-hand capacity up to 3 months post stroke. We found no evidence that 1 hour daily EMG-NMS for 3 weeks in those without VFE influences the likelihood of return of any VFE within the first 6 months after stroke. The present study therefore supports the clinical point of view that effects of upper limb training are restricted to patients with some voluntary motor control of finger extensors at baseline.2,43 The literature indeed offers no examples of evidence-based therapies resulting in significant improvements in patients with an initial flaccid hand.1,2,42,43,50 The preservation or return of VFE early post stroke is assumed to reflect the integrity of the corticospinal tract.3 Moreover, some innervation of end-effectors is needed to induce improvements by exercise therapy early post stroke. At the same time, we found no evidence that we were able to influence spontaneous neurobiological recovery of underlying impairments based on clinical scales, suggesting that functional improvements of the mCIMT group were based on adaptation strategies to use intact end-effectors in a more optimal way.38,42

**Acknowledgements**

The authors thank the EXPLICIT-stroke physicians, therapist and nurses at the stroke units of the participating university centres and local hospitals (VU University Medical Center Amsterdam; Leiden University Medical Center; University Medical Center Utrecht;
Radboud University Medical Center Nijmegen; and Sint Lucas Andreas hospital Amsterdam; Amstelland hospital Amstelveen; Rijnland hospital Leiderdorp; Diaconessen hospital Leiden; Sint Maartens hospital Nijmegen; Meander Medical Center Amersfoort; Diakonessen hospital Utrecht and Zeist) and in the associated rehabilitation centres and nursing homes (Reade rehabilitation centre, Slotervaart nursing home, Sint Jacob nursing home, and De Driehoven nursing home in Amsterdam; Zonnehuis nursing home in Amstelveen; Rijnlands rehabilitation centre in Leiden; Groot Klimmendaal rehabilitation centre in Arnhem; Tolbrug rehabilitation centre in ‘s-Hertogenbosch; Trappenberg rehabilitation centre in Huizen; De Hoogstraat rehabilitation centre and Albert van Koningsbruggen nursing home in Utrecht; Birkhoven nursing home in Amersfoort; Nassau Odijckhof nursing home in Driebergen-Rijsenburg; Warande nursing home in Zeist; Quarijn nursing home and Military Rehabilitation Center Aardenburg in Doorn) for providing the intervention and monitoring rehabilitation, and the patients who participated in the study.

REFERENCES


How to design clinical rehabilitation trials for the upper paretic limb early post stroke?

Caroline Winters
Martijn W. Heymans
Erwin E.H. van Wegen
Gert Kwakkel

Trials. 2016;17:468
ABSTRACT

Background and objective  The impact of spontaneous neurobiological recovery is still neglected in designing rehabilitation trials early post stroke. We aimed to investigate the impact of timing of randomisation and prognostic stratification on the required sample sizes to reveal significant intervention effects on upper limb function at 26 weeks after first-ever ischaemic stroke.

Methods  Sample size calculations were based on a cohort study of 159 patients, using the Fugl-Meyer Assessment Upper Extremity and Action Research Arm Test as outcome measures (power = 80%; two-tailed alpha = .05). We investigated different scenarios: random sampling of patients within 5 time intervals (stroke onset to 1, 3, 5, 8, and 12 weeks post stroke), and within stratified groups according to presence or absence of voluntary extension of the thumb and/or 2 or more fingers at intake.

Results  The heterogeneity between outcome scores of patients, and subsequently the required sample sizes, increased from the first to the fifth time interval. Compared to the whole group, the sample sizes for both stratified groups (i.e. patients with and without voluntary finger extension) were lower. The required sample sizes for the patient group without voluntary finger extension markedly increased when the time interval was broadened from 1 to 12 weeks post stroke, as opposed to the decrease seen for the group of patients with voluntary finger extension.

Conclusions  These results are fundamental for designing upper limb trials early post stroke. To prevent type II error, future upper limb trials should randomise patients at a fixed moment early post stroke and stratify patients according to their potential neurobiological recovery.
INTRODUCTION

Recent systematic reviews and meta-analyses of early started stroke rehabilitation trials that are started early after stroke show that the effect sizes of interventions are small to moderate and account for 5 to 10% of the differences in outcome.1,2 Approximately 98% of all Randomised Controlled Trials (RCTs) are proof-of-concept trials and often heavily underpowered.1 At this moment, there is no evidence that stroke rehabilitation programs started within the first 3 months post stroke are more effective than programs initiated beyond this time period, despite the growing evidence of heightened brain plasticity early post stroke.3-5

Only about 7% ($N = 18$) of the clinical stroke trials that focus on upper limb recovery performed the randomisation procedure within the first 2 weeks after stroke onset (i.e. hospital based trials).1 The majority of RCTs start their randomisation procedure when patients are discharged from the hospital and admitted in a rehabilitation ward or nursing home.1 As a consequence, inclusion of subjects in most phase II trials ranges from a few days up to several months post stroke. Such pragmatic design of RCTs ignores the impact of spontaneous neurobiological recovery during the first 5 to 10 weeks post stroke which accounts for about 80% of all neurological improvement clinically observed in longitudinal cohort studies of the upper limb, lower limb and cognitive impairments.6-9 One may therefore raise the fundamental question whether the timing of randomisation in the first 12 weeks post stroke is an important factor for designing phase II trials in stroke rehabilitation. One may hypothesize that the arbitrary timing of randomisation post stroke causes type II errors in small RCTs through the additional variance that is introduced by still poorly understood, time-dependent, mechanisms of spontaneous neurobiological recovery early post stroke.

Furthermore, several systematic reviews and meta-analyses suggest that evidence based therapies for the upper paretic limb are strongly dependent on an appropriate selection of patients at baseline.10,11 Several prospective cohort studies showed that the ability to voluntarily extend one or more fingers against gravity within the first 3 days is a robust clinical marker for upper limb recovery after 3 or 6 months post stroke,12,13 reflecting the intactness of the corticospinal tract.14 Unfortunately, only one clinical trial out of the 266 upper limb trials published1 stratified patients on the basis of their initial impairment prior to the randomisation procedure.15 At this moment, evidence-based interventions seem to be restricted to those patients with some Voluntary Finger Extension (VFE).1,16,17 One may hypothesize that the choice of whether or not to stratify patients prior to randomisation
based on early prognosis, for example using VFE, influences the heterogeneity in upper limb function between patients and consequently the probability of finding differential effects post intervention.6;10;18

The aims of the present study were to investigate the impact of (1) different time intervals that vary in length between stroke onset and randomisation and (2) prognostic stratification based on the presence or absence of VFE on the required sample size to reveal significant and clinically important intervention effects on the Action Research Arm Test (ARAT) and Upper Extremity motor section of the Fugl-Meyer Assessment (FMA-UE) at 26 weeks after stroke.

MATERIALS AND METHODS

Study population and procedure

Data from the EXPLCIT-stroke trial were used.16 Details of this RCT can be found elsewhere.16;19 The inclusion criteria were: (1) first-ever ischaemic middle cerebral artery stroke; (2) upper limb paresis according to item 5 of the National Institutes of Health Stroke Scale (NIHSS item 5 ≥ 1 point); (3) mini mental state examination ≥ 23 points; (4) age between 18 and 80 years; (5) no upper limb musculoskeletal impairments; (6) no botulinum toxin treatment in the previous 3 months; (7) able to sit independently for 30 seconds; and (8) written informed consent.

At intake within 2 weeks post stroke, patients were stratified to (1) group of patients with VFE (N = 58) and randomly assigned to either modified Constraint-Induced Movement Therapy (mCIMT) or usual care, or (2) group of patients without VFE (N = 101) and randomly assigned to ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) or usual care. The patients with VFE had the ability to voluntarily extend the thumb and/or 2 or more fingers of the affected hand (10° or more). The functional assessments were repeated weekly up to 5 weeks after stroke, and at 8, 12 and 26 weeks follow-up.16;19

Outcome measurements

In the present study we used the ARAT and FMA-UE as primary outcome measures. The ARAT is an upper limb capacity test which assesses the ability to grasp, move and release
How to design clinical rehabilitation trials

objects of various sizes, weights and shapes. It has 19 sub questions scored on a 4-point ordinal scale, added up to a total score between 0 and 57 points (57 = normal capacity).\textsuperscript{20,21} The Minimal Clinically Important Difference (MCID) was set at 5.7 points, i.e. 10% of the range.\textsuperscript{22} The FMA-UE assesses upper limb impairment in terms of synergistic motor control. It has 22 sub questions scored on a 3-point ordinal scale, added up to a total score between 0 and 66 points (66 = normal function).\textsuperscript{23,24} The MCID was set at 6.6 points.\textsuperscript{25,26}

**Data analyses**

Approximately 8% of the 1272 assessments in the EXPLICIT-stroke trial were missing due to various reasons (e.g. recurrent stroke, sickness).\textsuperscript{16} We estimated these missing data points using individual curve fitting for subjects with 2 or more available assessments by estimating the ARAT and FMA-UE recovery curves using a linear mixed model (linear and quadratic component) that best described the individual recovery pattern, and that accounted for the repeated measures. The estimated data was merged with the original data to create a new complete dataset and checked by visual inspection. All further analyses were performed on this new (modelled) dataset. A total of 157 out of the 159 patients were eligible for further analysis: 1 patient had only 1 available assessment and another patient’s recovery was negatively influenced by an open heart surgery 4 months after stroke.

For the first aim we randomly varied the length of the time interval from stroke onset to randomisation for each patient. Five different time intervals were evaluated: stroke onset ($T_0$) to 1 week post stroke, $T_0$ to 3 weeks, $T_0$ to 5 weeks, $T_0$ to 8 weeks, and $T_0$ to 12 weeks. Within each time interval patients ($N = 157$) were randomly selected. Resulting in a dataset in which some patients were included with a follow-up measurement at 1 week, others at 2, 3, 4, or 5 weeks when the time interval of 5 weeks after stroke onset was used. In this way heterogeneity in recruitment period post stroke onset was guaranteed.

For the second aim we adopted the EXPLICIT-stroke patient allocation to either the group of patients with or without VFE at intake. Fifty-seven patients with VFE at intake were available for analysis (1 drop-out as described above). To obtain equal groups, we randomly selected 57 out of the 100 patients without VFE at intake using random sampling in SPSS (version 22), taking into account the distribution of randomisation.

The minimum number of subjects in each group that is needed to find a differential effect at 26 weeks follow-up was calculated with equation 1. This number per group was multiplied
by 2 to obtain the total number of subjects where after 10% was added to account for dropouts. We used a standard t-test sample size calculation to assess group differences at 26 weeks follow-up, assuming a normally distributed outcome. The power was set at 80% and two-tailed alpha at .05. The Standard Deviation (SD) was determined using randomly selected patients for each different post stroke time interval as explained above. Different scenarios were used, selecting: (1) all patients (N = 157), (2) subgroup of 114 patients including 57 patients with VFE and 57 patients without VFE, (3) patients with VFE at intake (N = 57), and (4) patients without VFE at intake (N = 57), within the 5 different time intervals. The average of the SD of the 2 groups (equation 3) was used to calculate the Cohen’s d effect size (equation 2).

\[ N_{\text{group}} = 2 \times \frac{(Z_{\alpha} + Z_{\beta})^2}{d^2} \]  
(1)

\[ d = \frac{\bar{x}_1 - \bar{x}_2}{SD_{\text{pooled}}} \]  
(2)

\[ SD_{\text{pooled}} = \sqrt{SD_1^2 + SD_0^2} \]  
(3)

Where \( N_{\text{group}} \) is the number of subjects per group; \( Z_{\beta} = 0.842; Z_{\alpha} = 1.96; d = \) Cohen’s effect size; \( \bar{x}_1 - \bar{x}_2 = \) group mean difference at 26-weeks follow-up. This difference was set at the MCID of the ARAT and FMA-UE, respectively 5.7 and 6.6 points; \( SD_{\text{pooled}} = \) the average of the standard deviation of the sample (full dataset, after individual curve fitting); and \( SD_1 \) and \( SD_0 = \) standard deviation for respectively the intervention and control group (full dataset, after individual curve fitting).

The SD pooled values are presented as variances. Patients received an intervention after randomisation. We therefore recalculated the sample size estimations by taking account of this intervention effect by deriving the SD pooled from a linear regression model that included the intervention group variable, with as outcome the FMA-UE and ARAT score. The (square root of the) unexplained variances from this model were used as the SD pooled “controlled for” the intervention effect. As these were the same as the raw SD pooled values, we will present sample size estimations using the raw SD pooled values. Analyses were performed with R (version 3.1.1), unless otherwise indicated.
RESULTS

Table 7.1 shows the characteristics of the 157 patients included in the present study. The ‘individual curve fitting’ method was found successful after visual inspection of the individual recovery curves on the FMA-UE and ARAT. The FMA-UE and ARAT recovery curves are presented in Figure 7.1.

Table 7.1 Patient characteristics

<table>
<thead>
<tr>
<th>Determinants</th>
<th>N = 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female (N)</td>
<td>94/63</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>59.9 ± 9.3</td>
</tr>
<tr>
<td>Affected hemisphere, right/left (N)</td>
<td>104/53</td>
</tr>
<tr>
<td>Bamford classification, LACI/PACI/TACI (N)</td>
<td>96/52/9</td>
</tr>
<tr>
<td>Barthel Index (0–20 points, median (interquartile range))</td>
<td>9 (5–13)</td>
</tr>
</tbody>
</table>

LACI: Lacunar Anterior Cerebral Infarction; PACI: Partial Anterior Cerebral Infarction; TACI: Total Anterior Cerebral Infarction; SD: Standard Deviation.

Figure 7.1 Individual FMA-UE and ARAT recovery curves for patients with and without Voluntary Finger Extension (VFE).

The top 2 graphs represent patients with VFE at about 1 week after stroke and the lower 2 graphs the patients without VFE. The left 2 graphs and right 2 graphs represent respectively the Upper Extremity motor scores of the Fugl-Meyer Assessment (FMA-UE, score = 0–66, 66 = normal function) and the Action Research Arm Test (ARAT, score = 0–57, 57 = normal capacity).
Changing the time interval between stroke onset and randomisation showed an increase in required sample size to obtain an effect beyond MCID from the first to fifth time interval of 148 subjects for the FMA-UE and 228 subjects for the ARAT (Table 7.2 and Figure 7.2). The largest increase was visible between the first 2 time intervals for both outcome measures ($\Delta FMA-UE_{T1-T2} = 77$ subjects and $\Delta ARAT_{T1-T2} = 110$ subjects).

### Table 7.2 Results sample size calculation: various time intervals from stroke onset to moment of randomisation ($N = 157$)

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Group 1 Mean ± SD</th>
<th>Group 0 Mean ± SD</th>
<th>SD pooled</th>
<th>Variance</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FMA-UE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_0 - 1$ week</td>
<td>18.09 ± 19.78</td>
<td>15.62 ± 17.06</td>
<td>18.47</td>
<td>341</td>
<td>275</td>
</tr>
<tr>
<td>$T_0 - 3$ weeks</td>
<td>22.19 ± 21.86</td>
<td>21.23 ± 20.07</td>
<td>20.98</td>
<td>440</td>
<td>352</td>
</tr>
<tr>
<td>$T_0 - 5$ weeks</td>
<td>28.89 ± 23.42</td>
<td>24.27 ± 21.66</td>
<td>22.56</td>
<td>509</td>
<td>405</td>
</tr>
<tr>
<td>$T_0 - 8$ weeks</td>
<td>24.54 ± 22.91</td>
<td>25.80 ± 22.36</td>
<td>22.64</td>
<td>512</td>
<td>409</td>
</tr>
<tr>
<td>$T_0 - 12$ weeks</td>
<td>26.18 ± 24.19</td>
<td>28.69 ± 22.61</td>
<td>23.42</td>
<td>548</td>
<td>438</td>
</tr>
<tr>
<td><strong>ARAT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_0 - 1$ week</td>
<td>8.24 ± 12.82</td>
<td>7.33 ± 12.89</td>
<td>12.85</td>
<td>165</td>
<td>178</td>
</tr>
<tr>
<td>$T_0 - 3$ weeks</td>
<td>11.70 ± 16.76</td>
<td>11.15 ± 15.96</td>
<td>16.36</td>
<td>268</td>
<td>288</td>
</tr>
<tr>
<td>$T_0 - 5$ weeks</td>
<td>13.58 ± 17.67</td>
<td>13.77 ± 17.95</td>
<td>17.81</td>
<td>317</td>
<td>341</td>
</tr>
<tr>
<td>$T_0 - 8$ weeks</td>
<td>15.65 ± 19.76</td>
<td>15.14 ± 19.02</td>
<td>19.39</td>
<td>376</td>
<td>403</td>
</tr>
<tr>
<td>$T_0 - 12$ weeks</td>
<td>17.95 ± 21.49</td>
<td>15.46 ± 18.34</td>
<td>19.98</td>
<td>399</td>
<td>429</td>
</tr>
</tbody>
</table>

Sample sizes are the total number of patients required, including 10% to account for drop-outs. Individual patients were randomly selected at different time points post stroke onset, where after this assessment was considered as their baseline assessment. Mean and SD are derived from the full dataset, after individual curve fitting. ARAT: Action Research Arm Test (score = 0–57, 57 = normal capacity); FMA-UE: Upper Extremity motor section of the Fugl-Meyer Assessment (score = 0–66, 66 = normal function); Group 1: intervention; Group 0: control; SD: Standard Deviation; $T_0$: stroke onset.

When patients were not stratified based on VFE, the required sample size for the first time interval (i.e. $T_0$ to 1 week post stroke) was 308 and 218 subjects for respectively the FMA-UE and ARAT (Table 7.3 and Figure 7.3). In comparison to the whole group ($N = 114$), the required sample sizes for the group of patients without VFE were lower, respectively 44 and 9 subjects for the FMA-UE and ARAT. For the group of patients with VFE, the required sample size for the FMA-UE was also lower in comparison to the whole group (211 subjects). The required sample size with the ARAT as outcome measure was slightly higher due to a greater heterogeneity between patients (235 subjects; see also the individual recovery patterns in Figure 7.1).
The required sample sizes for the group of patients without VFE increased when the time interval between stroke onset and randomisation was broadened. The highest sample size was found for the broadest time interval, i.e. when randomisation was performed between stroke onset and 12 weeks post stroke. For the group of patients with VFE at intake, with the FMA-UE as outcome measure, we found a progressive decrease in sample size when the time interval was broadened. For the ARAT, we observed an increase in the sample sizes when the time interval was broadened from 3 to 5 weeks, after which it remained constant before decreasing to 205 subjects in the fifth time interval. The required sample sizes for the groups of patients with and without VFE separately remained lower in comparison to the whole group throughout the second to fifth time interval.

Figure 7.2 Impact of timing of randomisation on the sample size.
<table>
<thead>
<tr>
<th>Time interval</th>
<th>All patients (N = 114)</th>
<th>Voluntary finger extension (N = 57)</th>
<th>No voluntary finger extension (N = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 0</td>
<td>Sample size</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>SD pooled</td>
</tr>
<tr>
<td>FMA-UE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₀ − 1 week</td>
<td>23.17 ± 20.80</td>
<td>19.73 ± 18.36</td>
<td>19.61</td>
</tr>
<tr>
<td>T₀ − 3 weeks</td>
<td>29.22 ± 23.10</td>
<td>26.21 ± 20.61</td>
<td>21.89</td>
</tr>
<tr>
<td>T₀ − 8 weeks</td>
<td>30.83 ± 24.00</td>
<td>33.36 ± 22.76</td>
<td>23.39</td>
</tr>
<tr>
<td>T₀ − 12 weeks</td>
<td>34.33 ± 25.09</td>
<td>31.09 ± 22.44</td>
<td>23.80</td>
</tr>
<tr>
<td>ARAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₀ − 1 week</td>
<td>10.91 ± 13.98</td>
<td>9.91 ± 14.39</td>
<td>14.19</td>
</tr>
<tr>
<td>T₀ − 3 weeks</td>
<td>16.16 ± 17.60</td>
<td>14.98 ± 17.14</td>
<td>17.37</td>
</tr>
<tr>
<td>T₀ − 5 weeks</td>
<td>18.76 ± 19.72</td>
<td>18.21 ± 19.08</td>
<td>19.40</td>
</tr>
<tr>
<td>T₀ − 8 weeks</td>
<td>22.22 ± 20.85</td>
<td>17.20 ± 19.01</td>
<td>19.95</td>
</tr>
</tbody>
</table>

Sample sizes are the total number of patients required, including 10% to account for drop-outs. Individual patients were randomly selected at different time points post stroke onset, where after this assessment was considered as their baseline assessment. Mean and SD are derived from the full dataset, after individual curve fitting. ARAT: Action Research Arm Test (score = 0–57, 57 = normal capacity); FMA-UE: Upper Extremity motor section of the Fugl-Meyer Assessment (score = 0–66, 66 = normal function); Group 1: intervention; Group 0: control; SD: Standard Deviation; T₀: stroke onset.
The aim of the present study was to investigate the impact of timing of randomisation and prognostic stratification on the required sample size to reveal significant and clinically important intervention effects on the FMA-UE and ARAT at 26 weeks follow-up. We used different scenarios for random patient recruitment based on data from a recently published RCT with repeated measurements. We were able to show that timing of moment of randomisation post stroke and stratification based on the prognostic determinant VFE are fundamental for preventing type II errors in neurorehabilitation trials post stroke. This finding is in agreement with the study of Duncan and co-workers (1992) who also showed that length of time from stroke onset (baseline, 5-day or 30-day status) and severity of motor

**DISCUSSION**

The aim of the present study was to investigate the impact of timing of randomisation and prognostic stratification on the required sample size to reveal significant and clinically important intervention effects on the FMA-UE and ARAT at 26 weeks follow-up. We used different scenarios for random patient recruitment based on data from a recently published RCT with repeated measurements. We were able to show that timing of moment of randomisation post stroke and stratification based on the prognostic determinant VFE are fundamental for preventing type II errors in neurorehabilitation trials post stroke. This finding is in agreement with the study of Duncan and co-workers (1992) who also showed that length of time from stroke onset (baseline, 5-day or 30-day status) and severity of motor

---

**Figure 7.3** Impact of prognostic stratification based on Voluntary Finger Extension (VFE) on the sample size.

(A) Upper Extremity motor section of the Fugl-Meyer Assessment (FMA-UE), all patients (N = 114); (B) FMA-UE, patients with VFE (N = 57); (C) FMA-UE, patients without VFE (N = 57); (D) Action Research Arm Test (ARAT), all patients (N = 114); (E) ARAT, patients with VFE (N = 57); and (F) ARAT, patients without VFE (N = 57).
impairment measured with the FMA motor score (mild to severe) influences the chance to show 50% improvement in the residual motor deficit. In the present study, randomisation of patients at arbitrary time points post stroke (i.e. wide time intervals) showed a tremendous increase in the required sample size. The results underpin the importance of carefully designing future RCTs to increase the chance of finding differential intervention effects. At present, upper limb trials with 2 experimental arms, assuming 80% statistical power with randomisation at a fixed moment in the first 3 months after stroke are lacking in the literature.

Lack of prognostic stratification would give an incomplete representation of the changes in underlying subgroups. Interestingly, timing of moment of randomisation and stratification of subjects in upper limb trials are not independent phenomena for estimation of the number of subjects required for sufficiently powered rehabilitation trials. In the stratified group of patients with VFE within the first week, we observed a slight, overall decrease in the heterogeneity between outcome scores of patients when the time interval between stroke onset and randomisation was increased. After 3 months, the group of mild to moderately impaired patients was more homogenous and as a consequence, significant smaller sample sizes were required to find clinical meaningful effects of 10% on the FMA-UE or ARAT.

The heterogeneity between outcome scores of patients in the stratified group of patients with severe motor impairments (i.e. no VFE) was low when randomisation occurred in the first few weeks after stroke onset. Thereafter, the heterogeneity between patients increased substantially when the time interval for randomisation was extended to 8 or 12 weeks post stroke. As previous studies showed, severely impaired patients will most likely reach their plateau in motor recovery later in time in comparison to mild to moderately impaired patients.6,7 The majority of these severely impaired patients will only show minimal improvement in upper limb function and there are still no evidence-based interventions for this specific group of patients.1,11,16 However, part of the severely impaired patients in the current dataset displayed more recovery of upper limb function than predicted (i.e. mainly ‘false negatives’), which markedly increased the heterogeneity in outcome scores between patients when the time intervals for randomisation were broadened.12

Recent prospective cohort studies have suggested that the amount of spontaneous neurobiological recovery is highly predictable within the first 72 hours after stroke onset, and that the majority of patients will recover to a level of about 70 to 80% of their maximum possible improvement, based on their initial impairment.14,27-30 At present, we can only assign patients retrospectively and discriminate between ‘fitters’ and ‘non-fitters’ in terms of
expected spontaneous neurobiological recovery. There is a need for prospective stratification of patients according to their potential neurobiological recovery determined early after stroke.\textsuperscript{14} Therefore, prognostic biomarkers are needed to identify patients who will and will not show the expected spontaneous neurobiological recovery next to robust clinical markers such as VFE. In addition, we are of opinion that above recommendations with respect to timing of randomisation procedures and applying stratification in designing trials are not unique for upper limb trials. In particular acknowledging that outcomes of the lower paretic limb parallel those of the upper limb\textsuperscript{6,7} and that prognosis of meaningful outcomes such as walking ability is strongly dependent on initial sitting balance and lower limb strength.\textsuperscript{31} In addition, there is growing evidence that this maximum proportional recovery rule of spontaneous neurobiological recovery is not restricted to motor recovery alone, but also applies to cognitive impairments such as visuospatial neglect and aphasia.\textsuperscript{28} This latter finding suggests that the current recommendations for designing trials are probably generalisable to other modalities affected after stroke.

The following points should be taken into account when interpreting the results. First, generalisability of the current results may be limited because the estimates were derived from a relatively small population of first-ever ischaemic hemispheric patients with stroke derived from a single study. Despite this small population, the heterogeneity between patients in the current study is representative for other stroke populations.\textsuperscript{6,12,32} Second, we only included two important factors for designing an RCT in the present study. Other important factors that should be taken into account are for example: biological rational behind the research protocol including selection of research interventions and dose of therapy, and selecting the appropriate outcome measures.\textsuperscript{33,34} Third, the prognostic stratification that was used in the original RCT was based on the first assessment at approximately 1 week after stroke. We used the SDs determined for different time intervals as a representation for the SDs at 26-weeks follow-up. We did not, however, account for possible changes in prognosis for upper limb capacity over time (i.e. return of VFE). As there were a number of patients in the group without VFE at intake who showed more recovery than expected based on their prognosis early after stroke, the SDs for the first few time intervals in the group of patients without VFE may not be completely representative for the SD at 26 weeks follow-up. Fourth, the estimated sample sizes in the first few time intervals with the ARAT were very small (Tables 7.2 and 7.3). The estimated sample sizes were even smaller in solely the group of patients without VFE. These results point out the considerable impact of prognostic stratification and time between stroke onset and randomisation in RCTs. However, we do not recommend
researchers to design RCTs with these very small numbers of participants as they will be prone to error. Fifth, for modelling purposes we assumed a normally distributed outcome and performed a standard $t$-test sample size calculation, commonly used in stroke trials. If the distribution of the outcome was not normally distributed, a rank-based test may have been more appropriate. Sixth, a sample size estimation based on a standard $t$-test may overestimate the sample size compared to a stratified version of the test or a regression model. Higher power may be attained when stratification is included in the analysis stage.

**Conclusion**

Timing of moment of randomisation post stroke and stratification based on the prognostic determinant VFE are fundamental for designing upper limb trials early post stroke. To increase the chance of finding differential intervention effects, future RCTs should randomise patients at fixed moments after stroke and stratify patients according to their potential neurobiological recovery.

**Acknowledgements**

The authors thank the EXPLICIT-stroke trial physicians, therapists and nurses at the stroke units of the participating university centres, local hospitals and in the associated rehabilitation centres and nursing homes, and the patients who participated in the study.

**REFERENCES**


General discussion
It is challenging to make clinical decisions, optimize discharge planning and rehabilitation interventions, and inform patients about their future perspectives early after stroke due to the heterogeneity in patients’ neurobiological recovery seen in the first 6 months post stroke onset. The main aims of this thesis were therefore to increase our understanding of early prediction of neurological outcome after ischaemic stroke and investigate whether neurobiological recovery could be influenced by early applied interventions. In this chapter, the main topics are discussed and directions for future translational research in the field of stroke rehabilitation are provided.

**IMPACT OF NEUROBIOLOGICAL RECOVERY**

Prediction of neurological outcome is highly influenced by the time between stroke onset and moment of measurement.\(^1\) Due to differences in time post stroke, patients may differ in the ability to show neurobiological recovery and respond to certain medical and therapeutic interventions.\(^2\) The exact timing of, and relationship between, underlying mechanisms of neurobiological recovery are not yet known, however, it is evident that most changes in neurological impairments post stroke occur within the hyper-acute, acute and early subacute phase (see Figure 1.1 in chapter 1).\(^3\) In terms of upper limb motor function, presence of Voluntary Finger Extension (VFE) within 72 hours after stroke is a strong indicator for recovery of upper limb capacity at 3 or 6 months.\(^4\)\(^5\) However, absence of VFE within the first days post stroke does not necessarily mean that VFE will not return. As was shown in chapter 2, it is possible for patients to regain VFE within the early subacute phase. If the absence of VFE persists, the chance of regaining VFE for an individual within the late subacute or chronic phase after stroke will be minimal. For clinical practice, it is therefore necessary to reassess upper limb function weekly, for about the first 12 weeks post stroke in those patients who do not yet show VFE. Thereafter, assessment can become less frequent due to the limited change in upper limb motor function that can be expected after that time period.\(^7\)

To further optimize early prediction and intervention after stroke, we need to increase our knowledge about underlying mechanisms of neurobiological recovery. This objective is in line with the initiative of starting an international task force of experts from different fields in the translational research pipeline, to identify the causal biomarkers that define the extend to which neurobiological recovery after stroke occurs.\(^8\) This is in line with the target of the national clinical trial network for research in stroke of the National Institute of Health in the
United States of America (personal communication by Dr. Walter J. Koroshetz at the World Conference of NeuroRehabilitation in Philadelphia on May 11th, 2016). At this moment, these causal biomarkers are unfortunately unknown and beyond the scope of this thesis. In this discussion, I would rather like to point out the mechanisms that presumably contribute to patients’ recovery as well as their consequences for stroke trials in the future. In doing so, I take the phenomenological model of Buma and co-workers (2013) as a framework in which assumed mechanisms of skill reacquisition are specified (see Figure 8.1).9

One of the primary mechanisms may be recovery of temporary affected neuronal networks by early reperfusion of the penumbra. In humans, reperfusion of the penumbra may last up until 48 hours after stroke onset, yet the amount of reperfusion is dependent on the size of

Figure 8.1 Phenomenological model of skill reacquisition after stroke.
Panel A: Assumed mechanisms underlying skill reacquisition after stroke; panel B: Assumed underlying neuronal and metabolic mechanisms that drive stroke recovery. Dashed lines: associations that require further underpinning in de literature; bold lines: associations that are found in the literature to affect skill acquisition, however, the associations are not necessarily causal. BBB: Blood-Brain Barrier; BDNF: Brain-Derived Neurotrophic Factor; EEG: ElectroEncephaloGraphy; fMRI: functional Magnetic Resonance Imaging; TMS: Transcranial Magnetic Stimulation. Adapted from Buma and co-workers (2013).9
the penumbra. Prospective cohort studies showed that the volume of the penumbra or hypoperfused area may not explain all of the variation in neurobiological recovery; reported correlations between volume of the penumbra and neurological outcome vary from very weak to very strong (range: 0.09 to 0.89; outcomes: National Institutes of Health Stroke Scale, NIHSS; Barthel Index; modified Rankin Scale; Mathew and Orgogozo neurological scales; modified Canadian Neurological Scale). Furthermore, the capacity to regain motor function seems to be related to the reorganisation of neural networks. It has been suggested that regions that are not directly adjacent to the ischaemic core, but remotely connected through brain networks, can show temporarily reduced neuronal activity and metabolism after stroke due to a sudden loss of input from the site of lesion. Such interruption of function at distance is referred to as diaschisis and can resolve over time. In contrast to the reperfusion of the penumbra, diaschisis can last up until the late subacute phase after stroke and can persist despite neurobiological recovery.

Especially in those patients with more severe strokes, Blood-Brain Barrier (BBB) dysfunction and oedema may play an important role in neurobiological recovery in the hyper-acute and acute phase. Under normal conditions, the BBB protects the central nervous system from entrance of blood components. A reduction in cortical blood flow due to ischaemia can cause alterations in the BBB permeability, firstly, due to disassembly of tight junctions early after ischaemia and secondly (delayed) due to inflammatory processes. As a consequence of BBB dysfunction, oedema in the grey and white matter may appear when constituents like Na⁺, proteins and water accumulate in the extracellular space of the brain. Moreover, oxidative stress results in increased levels of pro-inflammatory cytokines and/or damaged oligodentrocytes, preventing remyelination of the white matter. The amount of spontaneous neurobiological recovery after stroke may be related to reversibly or irreversibly disturbed BBB, however, it is still unclear which molecular mediators lead to recovery of the BBB. In addition, it is unknown how and to what extent genetic factors influence neurobiological mechanisms of recovery. The upregulation of Brain-Derived Neurotrophic Factor (BDNF) could influence neural plasticity and repair. However, the literature is inconclusive with regard to the effect of increased levels of BDNF on motor and functional recovery after stroke. While earlier studies showed a relation, a recent study investigating proportional recovery of the upper limb measured with the FMA-UE, the BDNF polymorphism Val⁶⁶⁶Met did not explain any of the variance in the linear regression model. Another genotype, Apolipoprotein E (ApoE), has been associated with neurological repair, although results are still inconclusive.
Neuroimaging and neurophysiological measures like Magnetic Resonance Imaging (MRI), functional MRI, Diffusion Tensor Imaging (DTI), ElectroEncephaloGraphy (EEG), MagnetoEncephaloGraphy (MEG), Transcranial Magnetic Stimulation (TMS), near-infrared spectroscopy and blood-sampling, may help to gain knowledge of underlying mechanisms of neurobiological recovery. With that, these measures may help to improve prediction of neurological outcome and provide measures to evaluate therapeutic interventions by adding markers for lesion volume and location (grey versus white matter), collateral blood flow, integrity of the CorticoSpinal Tract (CST) and its (a)symmetry index, neural metabolism and connectivity, BBB dysfunction and genetic polymorphisms.

PROPORTIONAL RECOVERY POST STROKE

The maximum proportional recovery rule may be used to predict individuals’ neurobiological outcome at 3 or 6 months already within 72 hours post stroke onset. Even patients with very severe initial impairment (i.e. low baseline scores) can show proportional recovery. However, it is unknown why 10–30% of the patients with initial severe neurological impairments do not show proportional recovery. There does seem to be a threshold phenomenon in terms of fitting or not fitting the proportional recovery rule. Below thresholds for baseline score, ranging from 25–41% of the total possible score, patients are more likely to not show proportional recovery. With that, patients who do not show the expected amount of proportional recovery for one neurological impairment will most likely also not show the expected recovery for other modalities, which indicates common underlying mechanisms of neurobiological recovery post stroke.

Clinical markers like VFE, lower limb motor function and the severity of stroke (Bamford classification and/or the NIHSS) can help discriminate between fitters and non-fitters with initial severe impairments. Unfortunately, this discrimination between fitters and non-fitters within 72 hours after stroke is not yet optimal when solely based on clinical predictors (reflected by the prediction model performance in chapters 3 and 4). Measures of CST integrity may help differentiate between fitters and non-fitters for upper limb motor recovery. However, the intactness of the CST does not explain the generalisability of the proportional recovery rule to other modalities such as visuospatial neglect. Therefore, we should look for other markers (e.g. genetic polymorphisms, white matter integrity of other networks, BBB dysfunction) which may help prospectively differentiate between fitters and non-fitters after stroke. Importantly, we should not fixate on the maximum proportional
recovery rule itself, but rather try to understand the underlying mechanisms of spontaneous neurobiological recovery.

**BIOMARKERS OF STROKE RECOVERY**

Stratifying patients to subgroups according to specific characteristics is fundamental for neurorehabilitation research and health care. This so called ‘stratified medicine’ involves the administration of therapy to those subgroups of patients who share common biological characteristics and are most likely to benefit from an intervention. Early stratification is therefore important to optimize discharge planning and set rehabilitation goals. Patients’ potential neurobiological recovery (i.e. fitters versus non-fitters) should also be used for model development in future prognostic cohort studies and Randomised Controlled Trials (RCTs) by prospectively stratifying patients early post stroke on the basis of robust markers of expected neurobiological recovery.

When assessing patients’ potential neurobiological recovery, it is essential to keep in mind the influence of ‘time post stroke’, as the reduction in patients’ neurological deficit seen in the first 3 months post stroke is a reflection of the underlying mechanisms of neurobiological recovery. For example, it may be difficult to correctly measure the structural integrity of the CST within the acute phase after stroke due to the Wallerian degeneration of white matter. Other MRI-derived biomarkers like the Fractional Anisotropy (FA) ratio in the CST may also not be viable predictors in the acute phase after stroke. In addition, in a recent review where individual patient data from 40 studies (N = 684) were pooled, no relationship was found between motor outcome measured with the FMA-UE and stroke volume, location, hemisphere and CST integrity measured with the DTI-derived asymmetry index. The only biomarker that was related to FMA-UE was the Motor Evoked Potential (MEP) measured with TMS at rest. The presence of a MEP, measured with surface ElectroMyoGraphy (EMG) at the distal part of the upper limb after stimulation of the primary motor cortex, reflects some structural intactness of the CST. It should be noted that the majority of included studies in this review were performed in the chronic phase post stroke and that Hayward and co-workers (2016) were not able to pool data for all biomarkers due to the limited amount of studies included.

Although the focus of biomarker research is gradually moving towards neurophysiological and neuroimaging measures, I would like to emphasize that we should not disregard the
value of robust clinical predictors like VFE and search for the most optimal prediction model for every prognostic subgroup of patients with stroke by combining different measurement techniques. The starting point may be to use simple clinical measurements, with sequentially adding other, more complex measurements in those patients with severe neurological impairments.

**EFFECTS OF EARLY STARTED REHABILITATIVE INTERVENTIONS**

The focus of high-intensive, impairment-focused interventions should be on the subgroup of patients who have the potential to show neurobiological recovery within the acute and early subacute phase post stroke (i.e. fitters), where the chance of finding interaction effects between interventions and spontaneous neurobiological mechanisms is greatest. However, the most optimal timing, duration and intensity of rehabilitation interventions early after stroke onset remain to be determined. In the EXPLICIT-stroke trial (chapter 6), we did not find any evidence for an interaction between modified Constraint-Induced Movement Therapy (mCIMT) and neurological impairment such as synergism, despite clinically meaningful improvements in terms of upper limb capacity as revealed by the Action Research Arm Test (ARAT) and patient-reported outcome of hand function according to the Stroke Impact Scale. This finding suggests that early started evidence-based exercise therapies such as mCIMT may not modify behavioural restitution of impairments, but rather optimize upper limb capacity in which patients learn to adapt and deal with their underlying neurological impairments such as paresis and sensory deficits (see Figure 8.1). The finding that recovery of neurological impairments is driven by spontaneous neurobiological recovery alone corroborates with results from serially applied kinematic measurements in a subset of the patients recruited for EXPLICIT-stroke trial. In 2013, Van Kordelaar and co-workers showed that quality of motor control, measured by improvement in the number of degrees of freedom for controlling different joints in a reaching task, are mainly restricted to the time window of spontaneous neurobiological recovery. Furthermore, they showed that the improvements of smoothness in grasping and reaching are also restricted to about the first 8 weeks post stroke. Therefore, future RCTs should include kinematic and kinetic measurements to further investigate behavioural restitution and compensation of functions. In addition, these measures should preferably be combined with neuroimaging to relate changes in quality of motor behaviour to cortical changes.
It is unclear to what degree a higher intensity of mCIMT would have affected the results of the EXPLICIT-stroke trial in chapter 6.\textsuperscript{55} The intensity of task-specific exercise, previously defined as the “hours of exercise therapy under supervision of a physiotherapist or occupational therapist”\textsuperscript{66} may be increased by either increasing the amount of supervised therapy a day, or the number of days that therapy is provided. However, one should be cautious when increasing the intensity of mCIMT, as too high an intensity may have a detrimental effect on the recovery of upper limb capacity.\textsuperscript{62} The VECTORS study showed an inverse dose-response relationship between the intensity of mCIMT and upper limb recovery in terms of the ARAT score, with 3 hours of shaping exercises a day in the high-intensity mCIMT group.\textsuperscript{62} Nonetheless, with an intensity of 1 hour of mCIMT per day in the EXPLICIT-stroke trial (5 days a week, for a duration of 3 weeks), there is still room to increase intensity up to the cut-off point of possible detrimental intensity levels.\textsuperscript{55} Alternatively, the duration of therapy could have been prolonged beyond 3 weeks. A long term intervention effect of mCIMT on upper limb capacity, up to at least 6 months after stroke, may have been achieved by extending the intervention period up to the late subacute phase (i.e. 3 months post stroke).

The so called ‘transfer package’ includes behavioural strategies to facilitate transfer to the daily lives of patients and with that, may improve outcomes. Moreover, original CIMT includes 3 key features: (1) repetitive, task-oriented exercise therapy, using shaping principles, (2) constraining of the non-paretic upper limb, often with a padded mitt, and (3) a transfer package.\textsuperscript{67,68} The transfer package was not included in the EXPLICIT-stroke trial, nor in almost all other RCTs investigating the effects of mCIMT.\textsuperscript{52} The goal of the package is to transfer the treatment gains of adherence-enhancing behavioural methods from the clinic to patients’ daily living.\textsuperscript{68} The transfer package may include a contract between patient and therapist, coaching, keeping a diary, performing tasks with the paretic upper limb and/or written assignment of practice at home,\textsuperscript{68} all directed at preventing disuse of the paretic upper limb. Future RCTs may consider including this transfer package to investigate the potential long term effects of (m)CIMT on upper limb capacity. However, longer and more intensive therapy may not always be possible within current clinical practice due to limitations of resources.\textsuperscript{69} Therefore, cost-benefits of adaptive forms of mCIMT like caregiver mediated training, e-health and group therapy, should be further investigated to facilitate implementation of mCIMT within clinical practice.\textsuperscript{70}

Furthermore, we do not yet know what the most optimal treatment contrast is, as there are only a few dose-matched trials which found a differential treatment effect.\textsuperscript{71} A recent meta-
analysis of (m)CIMT showed no significant effect of treatment contrast (cut-off at 47 hours) on recovery of upper limb function and capacity. It is suggested that the amount of treatment contrast, i.e. time spent on therapy, between mCIMT and usual care may not be a good reflection of treatment intensity due to the higher number of repetitions in mCIMT. In addition, usual care is not ‘fixed’, but evolving and becoming more and more evidence-based. Therefore, new interventions will always be compared to usual care as an ‘active comparator’, which makes it more difficult to find significant and clinically relevant treatment effects. Evidence that mCIMT can reduce neurological impairment by influencing spontaneous neurobiological recovery in the time window of enhanced levels of brain plasticity is still lacking. Nonetheless, mCIMT is one of the most effective therapy currently available for patients with sufficient cognitive functioning and mild to moderate upper limb motor impairments, and requires implementation in the current health care system.

As shown in chapter 6, patients did not benefit from a 3 week EMG-NMS intervention starting in the early subacute phase post stroke. Evidence-based interventions to improve upper limb motor function remain to be identified in this subgroup of patients with severe upper limb impairment (i.e. no VFE). Upper limb therapy may therefore focus on assisted or passive movements and learning to use behavioural compensation strategies. These results are not in line with the positive effect of EMG-NMS on upper limb motor function and arm-hand activities found in the meta-analysis of Veerbeek and co-workers (2014). This discrepancy between the EXPLICIT-stroke trial and Dutch Guidelines is most likely due to differences in patient selection. That is, the studies included in the meta-analysis selected patients with VFE, where in the EXPLICIT-stroke trial we included only patients who were not able to voluntarily extend the thumb and/or 2 or more fingers of the affected hand. However, if VFE returns within the early subacute phase, the focus of therapy may change to improving function of the paretic upper limb and therapists may consider choosing EMG-NMS as recommended in the Dutch Guidelines.

The key question remains if we can influence behavioural restitution through experience-dependent plasticity (see Figure 8.1), in other words, is neurobiological recovery ‘reactive’? Novel interventions, like non-invasive brain stimulation and pharmacological treatment, may show interaction with mechanisms that drive spontaneous neurobiological recovery and improve functional outcome after stroke. For example, transcranial Direct Current Stimulation (tDCS) may influence cortical excitability (i.e. long-term potentiation or depression) and improve recovery in terms of motor function and Activities of Daily Living (ADLs). However, the evidence for upper limb motor recovery is still limited.
Repetitive TMS may also modulate cortical excitability and restore interhemispheric balance.\textsuperscript{78-81} Unfortunately, most repetitive TMS studies have been performed in the chronic phase post stroke, without long term outcome measurements, using various protocols and outcome measures, and different time intervals between stroke onset and measurement.\textsuperscript{82,83} Fluoxetine, a selective serotonin reuptake inhibitor, has been suggested as one of the neuropharmacological treatments that may influence neurobiological recovery after stroke. Chollet and co-workers (2011) showed that patients with an ischaemic stroke who received fluoxetine (20 mg per day, orally, for 3 months) improved significantly more on the 3-month FMA-UE score in comparison to patients who received placebo treatment.\textsuperscript{84} However, it is unknown if fluoxetine has a long-term effect as there was no additional follow-up measurements after the 3-month intervention.\textsuperscript{84} A recent RCT showed significant treatment effects of cerebrolysin (a mixture of neurotrophic factors derived from pigs’ brain tissue including BDNF and nerve growth factors) on upper limb capacity measured with the ARAT when 30 ml/d of cerebrolysin was administered orally (once a day for 21 days), in comparison with a placebo treatment.\textsuperscript{85} Although the results in terms of upper limb capacity and ADLs may be interpreted as encouraging, an important limitation of the study of Muresanu and co-workers (2016) is that they did not reported any measures that reflect changes in neurological impairments, like the FMA-UE. Therefore, it remains unclear if this novel intervention impacts the recovery of neurological impairments. Importantly, the evidence is still scarce and before we continue our search for novel interventions that may result in restorative long-term treatment effects, we should first critically look at studies’ research designs. Moreover, to increase the chance of finding treatment effects, restorative interventions should be provided to those patients who are expected to respond\textsuperscript{39} and RCTs should be carefully designed by taking into account some essential methodological recommendations.\textsuperscript{2}

**METHODOLOGICAL CONSIDERATIONS & FUTURE STEPS**

**Use designs with repeated measurements in time**

As shown in chapter 7, not taking into account (1) the time-dependent dynamics in neurobiological recovery after stroke by including patients at arbitrary time points relative to the onset of stroke (e.g. due to the difference in time between stroke onset and admission to rehabilitation centre with subsequently start of a rehabilitation trials) and (2) patients’
varying potential for neurobiological recovery, will result in large heterogeneity in measured amount of patients’ recovery and consequently reduce the chance of finding interaction effects between rehabilitative interventions and neurobiological recovery.2 Future studies should therefore assess patients at fixed time points after stroke onset to be able to (1) compare patients within a prognostic cohort, (2) compare patients in the experimental and control group within an RCT, and (3) to perform meta-analysis on large sets of patient data from different RCTs.8,86 The most important time points are related to the start of the different phases after stroke, namely: (1) stroke onset: hyper-acute phase; (2) 1 day post stroke: acute phase; (3) 7 days post stroke: early subacute phase; (4) 3 months post stroke: late subacute phase; and (5) 6 months post stroke: chronic phase.3,71 However, to investigate the course of neurobiological recovery, measurements should preferably take place weekly up to 12 weeks post stroke.7 Repeated measurements will also allow for longitudinal prognostic and computational modelling which can help understand the complex underlying mechanisms of stroke recovery.56,87

More importantly, we should investigate changes in sensorimotor function and brain plasticity within the first 3 months post stroke within each patient to increase our understanding of the longitudinal association of underlying mechanisms of spontaneous neurobiological recovery. Analysis showed that patients without voluntary return of wrist and finger extension (i.e. non-fitters of spontaneous neurobiological recovery) are characterized by multimodal neurological deficits including somatosensory impairments.7 This finding suggests that proprioceptive feedback is essential for spontaneous return of voluntary motor control and brain reorganisation.88 Increasing our knowledge about underlying mechanisms of spontaneous neurobiological recovery requires the use of a closed-loop system identification technique where the proprioceptive input (i.e. perturbation) to the system (i.e. patient) is known by offering unique frequencies with a haptic robot. In addition, using a closed-loop identification system also controls the quality of motor performance. For this reason, the 4D-EEG project was started in 2012 in the Netherlands, funded by a grant from the European Research Council. The 4D-EEG project is a continuation of the EXPLICIT-stroke trial and aims to elucidate the brain activation patterns in relation to upper limb motor recovery in patients with a first-ever ischaemic stroke, by making use of an intensive repeated measurement design with clinical measures, high density EEG, DTI and robotics (closed-loop system identification) within the first 6 months post stroke. Non-invasive EEG allows for real-time measurement of changes in cortical activity (e.g. somatosensory evoked potentials) in response to the somatosensory input using force manipulation of the wrist.
by a robot arm or electrical stimulation of the Nervus medianus. This in comparison to the often used fMRI technique, which uses blood-oxygen-level dependent contrast imaging as an indirect measurement of brain activity. Key elements of the 4D-EEG project are the use of a closed-loop identification system which allows us to control the quality of motor control in relation to cortical activity and the specially designed research van to measure patients at different locations (i.e. hospital, rehabilitation centre, nursing home, or patients’ home) and serially at fixed time points after stroke. By using a research van, costs and patients’ travel-related burden are reduced.

In addition to research, serial measurements should be implemented in the clinical rehabilitation setting. Not only can this approach provide valuable information for clinicians to help inform patients about their recovery and set treatment goals; systematically collection data can also help to develop and validate prediction models. To implement repeated measurements within clinical practice, there is need for national and international collaboration between universities, hospitals and rehabilitation centres. The Precision profiling to improve long-term outcome after stroke (PROFFITS) initiative is an important step towards implementation. The PROFFITS initiative aims to develop a clinical infrastructure to systematically collect patient data in order to improve early prognostics and allow patient inclusion for RCTs. Like the 4D-EEG project, the PROFFITS initiative also includes repeated measurements at fixed time points with clinical and EEG-based neurophysiological measures to gain insight into underlying mechanisms of neurobiological recovery. PROFFITS is financed by the Dutch Organisation for Health Research and Development (ZonMw) and runs from 2015 to 2019 in the Netherlands.

**Use the same outcome measures**

Currently, there are more than 100 outcome measures reported in the literature that focus on recovery of upper limb function. It has been proposed that RCTs may not be able to find differential treatment effects when failing to choose the right outcome measures. Therefore, we should increase our knowledge about the underlying construct of different clinical outcome measures and reduce the number of outcome measures which are used in neurorehabilitation research. This way, data from different studies can be combined and/or compared, and meta-analyses can be performed on individual patient data (i.e. big data analysis). Naturally, when choosing the right outcome measure, one should take into account the psychometric properties of the measure. In addition, the relevance of an outcome measure
should be considered. For example, the NIHSS\textsuperscript{92} is very often used to assess the severity of symptoms early after stroke, however, it may not be a relevant outcome measure for upper limb rehabilitation trials. The FMA-UE and ARAT do assess respectively upper limb function and capacity, and are valid and reliable clinical measures which may be implemented within future trials.\textsuperscript{91,93} Nonetheless, if we want to improve our knowledge about neurobiological recovery patterns, underlying mechanisms and find novel interventions which may influence behavioural restitution, future studies should include measures specifically focused at distinguishing between behavioural restitution and compensation.\textsuperscript{52,63,75,94} Wireless inertial motion tracking measurement units and/or robotics may be used as 3-dimensional kinematic and kinetic measures to detect changes in quality of motor control.\textsuperscript{63,95} Therefore, we must need to reach consensus on the measures that reflect recovery of quality of motor control which should be implemented in future upper and lower limb recovery trials. With that, it is important to carefully choose outcome variables, determine minimal clinically important differences without violating multiple testing, and investigate the added value of kinematic and kinetic outcome variables for clinical prognostic models.\textsuperscript{8} In addition to human stroke trials, kinematic and kinetic measures should also be implemented in animal studies to distinguish between behavioural restitution and compensation and with that improve our understanding of quality of motor control (e.g. forelimb reaching).\textsuperscript{96}

**Develop, validate and implement dynamic prognostic models**

A prognostic model should go through three phases, namely, the development, external validation and implementation phase.\textsuperscript{97} To enable clinical decision making, prediction models often consist of binary variables. Despite the clinical utility of binary variables, dichotomising candidate and outcome variables may potentially introduce bias, reduce statistical power and limit the generalisability of results.\textsuperscript{98,99} It is therefore important to carefully choose cut-off values to limit bias and allow for comparison of results within meta-analyses. In order to identify potential sources of bias (e.g. design, statistical analysis and validity), it is important to follow the recommendations in the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement when reporting prognostic research.\textsuperscript{100,101} Furthermore, logistic prognostic models may be limited by low sensitivity, specificity, negative predictive value and/or positive predictive value. It is in the subgroup of severely impaired patients, that prediction of neurobiological outcome remains more difficult.\textsuperscript{43,44,48} Unfortunately, as in chapters 2 and 3 of this thesis, the external validation and implementation phases are often not included in prognostic studies, nor are independent cohort studies started.
to externally validate and implement the results from development studies. These phases are however very important to assess the clinical utility and impact of models. To facilitate implementation of patient-specific prognostic models and use of evidence-based interventions in clinical practice, an international team of experts developed the Post Stroke Arm Algorithm application. This smartphone application uses prognostic determinants to guide clinicians towards the most appropriate intervention for each individual patient by taking into account time post stroke.

At this moment, we do not yet have dynamic (time-dependent) prognostic models which can be implemented within clinical practice. As discussed in previous paragraphs, we need to focus at longitudinal changes in sensorimotor function and brain plasticity to increase our knowledge about underlying mechanisms of spontaneous neurobiological recovery. Therefore, future studies should focus on developing dynamic models which allow for accurate prediction of neurological outcome at any time point after stroke. Moreover, if we are able to model patients’ neurological recovery profile based on other patients’ recovery profile data, we can predict neurological outcome at any time point from stroke onset. This requires repeated measurement in many patients with stroke in order to collect enough recovery profile data to develop, validate and implement these dynamic models into clinical practice.

**Funding, collaboration and uniformness**

An issue in many clinical trials is the rate of patient enrolment. Limited time and funding may prevent researchers to include sufficient numbers of patients to perform internal or external model validation. For example in the EXPLICIT-stroke trial, VECTORS study and the study of Ro and co-workers, the number of patients included in relation to the number of patients screened ranged from 3 to 4%. Enrolling sufficient numbers of patients in clinical trials and prognostic studies will only become more difficult when future studies apply stratification and use specific inclusion criteria for prognostic subgroups and fixed time points between stroke onset and baseline measurement. At this moment, most funding is insufficient to obtain approval of the ethical committee, train assessors and therapist, include a sufficient number of patients, obtain all follow-up measurements, analyse the data and translate results to practical implications. Funding organisations may therefore consider funding national and international expert research groups for longer time periods, in order to facilitate high quality prospective cohort studies and trials.
To be successful in translational research, experts in the field of stroke rehabilitation should congregate in order to reach consensus about recommendations for the previous described issues causing heterogeneity in pre-clinical and clinical research studies, e.g. biomarkers, outcome measures and interventions.\textsuperscript{8,75,105} This includes taking into account the methodological recommendations regarding timing of measurement and prognostic stratification. An important step forward was the round the table meeting in Philadelphia in May 2016.\textsuperscript{8} International collaboration will hopefully open doors and allow for new discoveries in the field of stroke rehabilitation research.

**FINAL REMARK**

Although not part of the present thesis, the EXPLICIT-stroke trial also included 3-dimensional kinematic, fMRI, robotic and TMS measures.\textsuperscript{106} I believe that the EXPLICIT-stroke trial can be seen as an example for future RCTs in the field of neurorehabilitation research because of the use of these different measurement techniques, prognostic stratification, randomisation within the first 2 weeks after stroke onset, and measurements at fixed time points post stroke within the first 6 months, with higher frequency of measurement in the early subacute phase. These are all essential methodological elements which optimize the chance to elucidate the underlying mechanisms of neurobiological recovery. To move neurorehabilitation research forward, it is essential to carefully design future trials by implementing these methodological elements. With that, to allow for high-quality stroke studies with designs according to the most up-to-date knowledge, future RCTs should solely be carried out by clinical centres of excellences.\textsuperscript{56}

**REFERENCES**


List of abbreviations
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
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<tr>
<td>AOU</td>
<td>Amount Of Use</td>
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<tr>
<td>ApoE</td>
<td>Apolipoprotein E</td>
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<td>ARAT</td>
<td>Action Research Arm Test</td>
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<tr>
<td>BBB</td>
<td>Blood-Brain Barrier</td>
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<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<tr>
<td>BI</td>
<td>Barthel Index</td>
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<tr>
<td>(m)CIMT</td>
<td>(modified) Constraint-Induced Movement Therapy</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
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<tr>
<td>CST</td>
<td>CorticoSpinal Tract</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DALY</td>
<td>Disability-Adjusted Life Years</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>EEG</td>
<td>ElectroEncephaloGraphy</td>
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<tr>
<td>EMG-NMS</td>
<td>ElectroMyoGraphy-triggered NeuroMuscular Stimulation</td>
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<tr>
<td>EmNSA</td>
<td>Erasmus modification of the Nottingham Sensory Assessment</td>
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<tr>
<td>EPOS</td>
<td>Early Prediction of Outcome after Stroke prospective cohort study</td>
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<td>EXPLICIT-stroke</td>
<td>EXplaining PLastICITy after stroke clinical trial</td>
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<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
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<tr>
<td>FAS</td>
<td>Functional Ability Scale</td>
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<tr>
<td>FAT</td>
<td>Frenchay Arm Test</td>
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<td>FMA</td>
<td>Fugl-Meyer Assessment</td>
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<tr>
<td>FN</td>
<td>False Negatives</td>
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<tr>
<td>FP</td>
<td>False Positives</td>
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<tr>
<td>GEE</td>
<td>Generalised Estimating Equations</td>
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<tr>
<td>ICF</td>
<td>International Classification of Functioning, disability, and health framework</td>
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<tr>
<td>IQR</td>
<td>InterQuartile Range</td>
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<tr>
<td>LACI</td>
<td>Lacunar Anterior Cerebral Infarction</td>
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<tr>
<td>LCT</td>
<td>Letter Cancellation Test</td>
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<tr>
<td>LE</td>
<td>Lower Extremity</td>
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<tr>
<td>MAL</td>
<td>Motor Activity Log</td>
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<tr>
<td>MCID</td>
<td>Minimal Clinically Important Difference</td>
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<td>MEG</td>
<td>MagnetoEncephaloGraphy</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>MEP</td>
<td>Motor Evoked Potential</td>
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<td>MI</td>
<td>Motricity Index</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
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<td>NHPT</td>
<td>Nine Hole Peg Test</td>
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<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
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<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>PACI</td>
<td>Partial Anterior Cerebral Infarction</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>PROFITS</td>
<td>Precision profiling to improve long-term outcome after stroke</td>
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<tr>
<td>QOM</td>
<td>Quality Of Movement</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<tr>
<td>rt-PA</td>
<td>recombinant tissue Plasminogen Activator</td>
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<tr>
<td>SAFE</td>
<td>Shoulder Abduction Finger Extension</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SE(M)</td>
<td>Standard Error (of the Mean)</td>
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<tr>
<td>SIS</td>
<td>Stroke Impact Scale</td>
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<tr>
<td>SMC</td>
<td>SensoriMotor Cortex</td>
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<tr>
<td>STROBE</td>
<td>Strengthening of Reporting of Observational Studies in Epidemiology</td>
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<tr>
<td>TACI</td>
<td>Total Anterior Cerebral Infarction</td>
</tr>
<tr>
<td>tDCS</td>
<td>transcranial Direct Current Stimulation</td>
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<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
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<td>TN</td>
<td>True Negatives</td>
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<td>TP</td>
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<tr>
<td>UE</td>
<td>Upper Extremity</td>
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<tr>
<td>VFE</td>
<td>Voluntary Finger Extension</td>
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<tr>
<td>VSN</td>
<td>VisuoSpatial Neglect</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>WMFT</td>
<td>Wolf Motor Function Test</td>
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Summary
Stroke is a leading cause of global long-term disability. The majority of strokes (80%) are caused by a blocked vessel in the brain, the so-called ischaemic strokes. Stroke survivors present with a range of clinical symptoms, including cognitive and motor impairments. Motor impairment occurs in 80% of the stroke patients and typically involves the face, upper and lower limb on one side of the body. Unfortunately, the majority of patients remain disabled in their activities of daily living. Progress of time (expected to reflect underlying mechanisms of spontaneous neurobiological recovery) accounts for about 80 to 90% of the observed improvements in body functions and activities, and therefore mainly define outcome after stroke. Previous studies with repeated measurements in time show that most recovery of neurological impairments occurs in the first 3 months after stroke onset. The first 3 months after stroke is therefore referred to as the critical time window for increased brain plasticity. However, the underlying mechanisms of neurobiological recovery are poorly understood and investigated. Furthermore, it is not known whether neurorehabilitation interventions can interact with, or augment, these mechanisms of reactive neurobiological recovery within the time window of enhanced brain plasticity early post stroke. Clinical decision making, e.g. choosing the most appropriate intervention, and correctly informing patients and relatives after stroke, are all dependent on knowledge about prognostic variables, time-dynamic recovery patterns and underlying mechanisms of spontaneous neurobiological recovery. Therefore, the main aims of this thesis were to gain insight into the prediction rules for neurological outcome after stroke and to investigate whether we can influence spontaneous neurobiological recovery by early started rehabilitation interventions targeting the upper limb within the first 6 months post stroke.

In chapter 2, the time window in which patients regain the ability to voluntarily extend the fingers of the paretic arm was investigated in a group of 100 patients with first-ever ischaemic strokes. Voluntary Finger Extension (VFE) was assessed with the Upper Extremity motor subscale of the Fugl-Meyer Assessment (FMA-UE) and upper limb capacity with the Action Research Arm Test (ARAT). Survival analyses on the repeated assessments of VFE showed that the median time to regain VFE, in patients who displayed some upper limb capacity at 6 months post stroke, was 4 weeks ($N = 45$). The 75th percentile was 8 weeks, and with exception of 4 patients, all patients regained VFE within the first 12 weeks after stroke. Multivariable logistic regression analysis showed that those patients who had (1) moderate to good lower limb motor function, (2) no visuospatial neglect, and (3) sufficient somatosensory function, had a probability of 94% to regain at least some upper limb capacity at 6 months post stroke. The return of VFE in these patients with severe upper limb motor impairments
(i.e. no VFE after 1 week post stroke), occurs mainly within a time window of 12 weeks and seems to be driven by spontaneous mechanisms of neurobiological recovery. Unfortunately, for this subgroup of patients, evidence-based interventions are still lacking. Above findings suggest that systematic (preferably weekly) monitoring of VFE within the first 12 weeks after stroke is required to identify those patients who do regain upper limb capacity, despite an initial unfavourable prognosis for upper limb capacity (i.e. false negatives). In addition, as VFE is an important predictor for recovery of upper limb capacity 6 months after stroke, it is recommended to search for interventions which can influence the return of VFE in the first weeks post stroke (see chapter 6).

The predictability of neurobiological recovery was further investigated in chapter 3. Specifically, the generalisability of the maximum proportional recovery rule was investigated in an independent sample of 211 patients with first-ever ischaemic stroke and upper limb motor impairment, measured with the FMA-UE. Upper limb motor recovery at 6 months after stroke was predicted by the equation of Prabhakaran and co-workers (2008) in which patients were suggested to recover to 70% of their maximum potential recovery based on their initial impairment within 72 hours after stroke onset. In other words, $\Delta \text{FMA-UE}_{\text{predicted}} = 0.7 \cdot (\text{FMA-UE}_{\text{max}} - \text{FMA-UE}_{\text{initial}})$, with a maximum FMA-UE score of 66 points. Hierarchical clustering analysis based on the observed versus predicted improvement of upper limb motor function yielded two clusters: a large group of fitters of the ‘rule’ ($N = 146, 69\%$), who had a comparable predicted and observed change in FMA-UE scores, and a smaller group of non-fitters ($N = 65, 31\%$), who had much lower observed than predicted change in FMA-UE scores. The fitters displayed, as predicted, upper limb motor recovery in proportion to their maximal potential recovery (~78%). Those patients who did not follow the proportional recovery rule (i.e. non-fitters) all had an initial FMA-UE score of 17 points or lower and presented larger strokes and impairments in a variety of modalities (i.e. upper and lower limb paresis, and facial palsy) within 72 hours after stroke onset.

In chapter 4, the generalisability of the maximum proportional recovery rule to lower limb function was investigated in the same subjects with stroke. The clinical threshold for baseline lower limb function, measured with the FMA Lower Extremity subscale (FMA-LE), and patients’ characteristics were examined to discriminate between fitters and non-fitters. Observed motor recovery was defined as the change in FMA-LE score between baseline assessment within 72 hours and follow-up assessment at 6 months post stroke. Maximum potential recovery was defined as the maximum possible FMA-LE score (maximum score: 34 points) minus the initial FMA-LE score. Hierarchical clustering analysis based on the
observed motor recovery and predicted potential recovery showed that 175 patients (87% of the total group of 202 patients) fitted the rule. In comparison to the non-fitters, the fitters presented less neurological impairments and less motor impairments at baseline assessment. All patients who had a FMA-LE score of 14 points or higher within 72 hours were classified as fitters. However, below this threshold, 65% of the patients were still classified as fitters. The distribution of fitters and non-fitters in the observed motor recovery versus predicted potential recovery scatterplot was similar for the FMA-LE and FMA-UE. More specifically, those patients who did not fit the recovery rule for lower extremity function (FMA-LE) also did not fit the rule for upper extremity function (FMA-UE). These results confirm the generalisability of the maximum proportional recovery to lower limb motor recovery with an average improvement of 64% (95% CI = 59–69%) of the predicted maximum potential recovery. To gain insight into possible common underlying mechanisms of neurobiological recovery, the proportional recovery rule should be further investigated in other neurological modalities.

Therefore, in chapter 5, the generalisability of the maximum proportional recovery rule to VisuoSpatial Neglect (VSN) was investigated in an independent cohort (N = 90). Patients were included if they presented VSN after a first-ever right-hemispheric ischaemic stroke. Observed recovery was defined as the change in O-Letter Cancellation Test (LCT) scores in the contralesional (left) visual field from baseline assessment (on average 8 days post stroke) to the 6-month follow-up assessment. According to the proportional recovery rule, potential recovery was defined as the maximum possible LCT score minus the initial LCT score (i.e. \( LCT_{\text{max}} - LCT_{\text{initial}} \)), with a maximum LCT score of 20 points in the contralesional (left) visual field. Hierarchical clustering analysis identified two groups: \( N_1 = 80 \) and \( N_2 = 10 \), respectively fitters and non-fitters of the rule. The non-fitters all had 15 or more missing O’s on the LCT at baseline assessment. In the subgroup of patients with 15 or more missing O’s (\( N = 45 \)), non-fitters (\( N = 10 \)) presented significant lower LCT scores in the ipsilesional (right) visual field (i.e. seemingly bilateral VSN) and were on average 11 years older than fitters (\( N = 35 \)). In addition, all non-fitters for VSN also lacked proportional recovery for upper limb motor function, further suggesting common biological mechanisms, regardless of the type of neurological impairment involved.

The results in chapters 3 to 5 confirmed that patients with mild to moderate neurological impairments showed recovery that is proportional to their initial impairments. However, it remains unclear why 10 to 30% of the patients do not show proportional recovery, irrespective of the type and severity of the neurological impairment. Therefore, future studies should
investigate underlying mechanisms of spontaneous neurobiological recovery to prospectively discriminate between fitters and non-fitters.

Chapter 6 describes the results of the 'Explaining plasticity after stroke' program (acronym: EXPLICIT-stroke). Patients with a first-ever ischaemic stroke ($N = 159$) were included within 2 weeks after stroke onset and assessed weekly up to 5 weeks, and at 8, 12 and 26 weeks follow-up. After baseline assessment, patients were stratified according to the severity of upper limb impairment (i.e. the ability to voluntarily extend the thumb and/or 2 or more fingers of the impaired hand). Those patients with VFE ($N = 58$) were randomised to 3 weeks of modified Constraint-Induced Movement Therapy (mCIMT) or to usual care, and the patients without VFE ($N = 101$) were randomised to 3 weeks of ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) or to usual care. Early applied mCIMT had a positive effect on the recovery of upper limb capacity up to 3 months after stroke measured with the ARAT. However, this treatment effect did not sustain up to 6 months post stroke. In addition, a positive, temporary effect in favour of mCIMT in comparison to usual care was found for the patient-reported outcome of hand function according to the Stroke Impact Scale. No beneficial effect of mCIMT on recovery of upper limb motor function (i.e. FMA-UE scores, indicative of true repair of underlying mechanisms of neurobiological recovery) was found. Therefore, the improvement seen in upper limb capacity due to mCIMT is suggested to be based on an improved and optimized use of the preserved end-effectors (i.e. hand or arm).

In other words, mCIMT seems to have a positive effect on behavioural compensation, however, evidence that mCIMT can influence behavioural restitution of functions is still lacking. Nonetheless, mCIMT is currently the most effective therapy available for patients with mild to moderate upper limb impairments and should therefore be implemented within clinical practice. Three weeks of EMG-NMS therapy had no added value on the recovery of VFE, upper limb capacity and other secondary outcome measurements. With that, there is currently no evidence-based intervention for these patients without VFE early after stroke. As recommended in chapter 2, these patients should be assessed weekly during the first 12 weeks post stroke. If VFE returns within the early subacute phase (i.e. up to 3 months post stroke), prognosis changes and focus may be on mCIMT therapy.

The EXPLICIT-stroke study was one of the first early started Randomised Controlled Trials (RCTs) with repeated measurements in time which showed clinically relevant treatment effects in terms of upper limb capacity. Therefore, an important question was, if measuring patients at fixed time points post stroke and stratifying patients according to prognostic variables were fundamental elements of future RCTs focused at upper limb recovery.
Therefore, the aim of the study presented in chapter 7 was to investigate the impact of timing of randomisation and prognostic stratification on the required sample sizes needed to reveal significant and clinically important intervention effects on upper limb function at 6 months post stroke. Patients \((N = 157)\) were randomly selected within 5 different time intervals to guarantee heterogeneity in the recruitment period. Prognostic stratification was based on the presence or absence of VFE. Longer recruitment periods (i.e. increasing the time interval between stroke onset and randomisation) caused an increase in the heterogeneity in measured amount of patients’ recovery, and with that an increase in the required sample size to obtain a differential treatment effect. Stratification based on the prognostic variable VFE showed a smaller required sample size (i.e. one group of patients with and one group without VFE, in comparison to both groups together). These results underpin the importance of carefully designing future studies with respect to fixed timing post stroke and patients selection at baseline in order to show clinical meaningful effects in early started stroke recovery trials.

As discussed in chapter 8, future studies should further investigate underlying mechanisms of neurobiological recovery by distinguishing between behavioural restitution (i.e. true repair) and behavioural compensation of functions to allow for improved prediction of outcome and potential restorative interventions. For example, by investigating quality of motor behaviour in relation to abnormal brain network interaction and cortical reorganisation, by using clinical, kinematic, kinetic, neurophysiological and neuroimaging measures. Importantly, due to the purported time dependency of patients’ potential to show neurobiological recovery and respond to impairment-focused interventions, it is essential to keep in mind the time window between stroke onset and baseline assessment. Future prognostic studies and RCTs should therefore (1) start within the hyper-acute or acute phase (i.e. < 7 days post stroke onset), (2) use repeated measurements at fixed time points after stroke onset, with higher frequency (weekly) up until 3 months after stroke and (3) stratify patients according to their potential recovery by using early biomarkers (i.e. fitters versus non-fitters) to allow for administration of therapy to those patients who are most likely to benefit. In addition, future studies should focus on finding new novel restorative interventions to improve behavioural restitution of functions such as transcranial direct current stimulation and transcranial magnetic stimulation, with or without combining them with neuropharmacological treatments, and/or combined with exercise therapy. To move forward in stroke rehabilitation research, it is essential to reach world-wide consensus for the use of terminology, patient selection, use of outcome measurements and timing of measurements for both pre-clinical
and clinical studies. In addition, national and international collaboration and consensus is needed on defining constructs to facilitate prospective cohort studies and trials to achieve large high quality datasets.
Samenvatting (Summary in Dutch)

Reactief spontaan neurobiologisch herstel na een herseninfarct?

Prognose & interventie
Beroerte, of Cerebro Vasculair Accident (CVA), is wereldwijd één van de belangrijkste oorzaken voor langdurige (chronische) invaliditeit. Het merendeel van de beroertes (80%) wordt veroorzaakt door ischemie, waarbij de bloedtoevoer naar de hersenen wordt geblokkeerd door een bloedprop of vernauwd bloedvat. Als gevolg van het herseninfarct kunnen meerdere klinische symptomen tot uiting komen, waaronder cognitieve en motorische stoornissen. Een halfzijdige verlamming of zwakte (hemiparese) van de armen en benen komt in ongeveer 80% van de patiënten met een herseninfarct voor. Het merendeel van de patiënten blijft ook op lange termijn beperkt in het uitvoeren van alledaagse activiteiten.

Naar schatting wordt 80 tot 90% van de gemeten verbetering in het spontane neurobiologisch beloop, waaronder het motorisch herstel van de verlamde arm en het verlamde been, in de eerste zes maanden bepaald. Bovendien laat eerder onderzoek met herhaalde metingen in de tijd zien dat verreweg de meeste verbetering in motorische en cognitieve functies in de eerste drie maanden na het herseninfarct plaatsvindt. Deze periode van de eerste drie maanden na een beroerte wordt gezien als een belangrijk tijdvenster voor verhoogde mate van hersenplasticiteit. Er is op dit moment nog onvoldoende kennis over de achterliggende mechanismen die de mate van spontaan neurobiologisch herstel bepalen, zodat dit al in een vroege fase na een herseninfarct accuraat kan worden voorspeld. Evenmin is bekend of het spontane neurobiologisch herstel beïnvloed kan worden door intensieve neurorevalidatie in een vroege fase na een beroerte. Kennis over voorspellers voor het klinisch neurologisch beloop en de achterliggende mechanismen die het spontaan neurobiologisch herstel bepalen, zijn uiterst belangrijk voor klinische besluitvorming, bijvoorbeeld het kiezen van de meest geschikte therapie, en het juist informeren van patiënten en familieleden.

De belangrijkste doelen van dit proefschrift waren daarom: het meer inzicht krijgen in voorspellingsregels voor neurologische uitkomst na een herseninfarct en het onderzoeken of het mogelijk is om spontaan neurobiologisch herstel in de eerste zes maanden na een herseninfarct te beïnvloeden met vroegtijdige interventies gericht op het motorisch herstel van de aangedane arm.

In hoofdstuk 2 werd in een groep van 100 patiënten met ernstig motorisch functieverlies in de eerste week na het herseninfarct, het tijdvenster onderzocht waarin patiënten weer in staat waren om de vingers van de paretische arm willekeurig te kunnen strekken. Hiervoor werd willekeurige vingerextensie met behulp van de Fugl-Meyer Assessment (FMA) herhaald in de tijd. Uiteindelijk herstel van arm-handvaardigheid werd op zes maanden na het herseninfarct gemeten met de Action Research Arm Test (ARAT).
Op zes maanden na het herseninfarct hadden 45 van de 100 patiënten weer enige arm-handvaardigheid teruggekregen (d.w.z. ARAT-score van 10 punten of meer). Survivalanalyse, uitgevoerd op herhaalde metingen van vingerextensie, liet zien dat de willekeurige vingerextensie gemiddeld genomen na vier weken weer teruggekeerd was in deze subgroep ($N = 45$). Het 75ste percentiel lag echter op acht weken, terwijl met uitzondering van vier patiënten alle 45 patiënten binnen 12 weken terugkeer hadden van willekeurige vingerextensie. De resultaten van de multivariabele logistische regressieanalyse lieten eveneens zien dat de kans op enige arm-handvaardigheid op 6 maanden na het herseninfarct 94% was wanneer patiënten in de eerste week na het herseninfarct (1) matig tot goede motorische beenfunctie hadden, (2) geen last hadden van een Visuo-Spatieel Neglect (VSN; verwaarlozing van het linker blikveld) en (3) matig tot goede somatosensorische functie van de arm hadden. Terugkeer van willekeurige vingerextensie werd waarschijnlijk veroorzaakt door mechanismen van spontaan neurobiologisch herstel, gezien er nog geen wetenschappelijk bewijs is dat oefentherapieën de terugkeer van willekeurige vingerextensie kunnen bevorderen. De aanbeveling was om patiënten met een herseninfarct in de eerste 12 weken regelmatig (liefst wekelijks) op terugkeer van willekeurige vingerextensie te monitoren. Gezien het feit dat vingerextensie een bepalende functie is voor het uiteindelijke herstel van arm-handvaardigheid na zes maanden, werd gezocht naar interventies die terugkeer van willekeurige vingerextensie in de eerste weken na een herseninfarct kunnen bevorderen (zie hoofdstuk 6).

De voorspelbaarheid van neurobiologisch herstel werd verder onderzocht in hoofdstuk 3. In dit hoofdstuk werd de generaliseerbaarheid van de ‘maximaal proportioneel herstel’ voorspellingsregel onderzocht in een onafhankelijke populatie van 211 patiënten met motorisch functieverlies van de arm als gevolg van een eerste herseninfarct. Het herstel van de aangedane arm werd voorspeld met behulp van de in 2008 door Prabhakaran en collega’s ontwikkelde voorspellingsregel. Hierin werd gesteld dat het neurologisch herstel op zes maanden na het herseninfarct gelijk zou zijn aan 70% van de maximaal mogelijke vooruitgang van de patiënt. Hierbij werd deze maximaal mogelijke vooruitgang vastgesteld binnen 72 uur na het herseninfarct. De maximaal mogelijke vooruitgang werd daarbij gebaseerd op het initiële motorisch functieverlies van de arm en de maximaal haalbare score gemeten met de FMA-UE. Anders geformuleerd, $\Delta \text{FMA-UE}_{\text{voorspeld}} = 0.7 \cdot (\text{FMA-UE}_{\text{max}} - \text{FMA-UE}_{\text{initieel}})$, waarbij de maximale FMA-UE-score gelijk was aan 66 punten.

Hiërarchische clusteranalyse, uitgevoerd op de geobserveerde versus de voorspelde verandering in armfunctie, liet twee subgroepen zien: enerzijds een grote groep patiënten ($N = 146, 69\%$) waar de geobserveerde en voorspelde verandering met elkaar overeenkwamen (de
zogeheten ‘fitters’), anderzijds een kleinere groep patiënten ($N = 65, 31\%$) waarbij de geobserveerde verandering ver onder de voorspelde verandering bleef (zogeheten ‘niet-fitters’). Bij de groep fitters was het herstel van de armmfunctie ~78\% van de maximaal haalbare score. De patiënten die hier ver onder bleven en niet aan de voorspellingsregel voor maximaal proportioneel herstel voldeden (‘niet-fitters’), bleken allemaal een initiële FMA-UE-score van 17 punten of lager te hebben in de eerste 72 uur. Daarmee hadden zij bij aanvang een relatief meer ernstige beroerte met uitgebreider functieverlies van verschillende neuroligische modaliteiten, te weten, verlamming van de arm, het been en het gezicht.

In hoofdstuk 4 werd de generaliseerbaarheid van de ‘maximaal proportioneel herstel’ voorspellingsregel op het herstel van motorische beenfunctie onderzocht bij dezelfde groep patiënten. De klinische drempel voor initiële beenfunctie werd hierbij gemeten met de FMA voor de motorische functie van het been (FMA-LE). Daarnaast werden de kenmerken van patiënten onderzocht om onderscheid te maken tussen ‘fitters’ en ‘niet-fitters’. Het geobserveerde motorische herstel werd gedefinieerd als de verandering in de FMA-LE-score tussen de eerste meting binnen 72 uur en de tweede meting op zes maanden na het herseninfarct. De maximaal mogelijke vooruitgang werd gedefinieerd als de maximale FMA-LE (maximale score van 34 punten) minus de initiële FMA-LE-score.

Hiërarchische clusteranalyse liet zien dat 175 patiënten (87\%) nagenoeg exact de voor spellingsregel volgden. De fitters hadden binnen 72 uur in vergelijking met de niet-fitters minder neurologische stoornissen en minder motorisch functieverlies. Alle patiënten die binnen 72 uur een FMA-LE-score van 14 punten of hoger hadden werden geclassificeerd als fitters. Echter, onder deze drempel werd alsnog 65\% van de patiënten geclassificeerd als fitters. Voor de fitters was de gemiddelde verbetering 64\% (95\% betrouwbaarheidsinterval $= 59–96\%$) van de voorspelde maximaal mogelijke vooruitgang. Opvallend was dat de groep niet-fitters volgens het maximale proportionele herstel van het been (FMA-LE), dezelfde patiënten waren die ook bij de arm (FMA-UE) niet herstelden volgens de voorspellingsregel. Deze resultaten bevestigen de generaliseerbaarheid van de voorspellingsregel naar motorisch herstel van het been. Om inzicht te krijgen in mogelijke overeenkomstige onderliggende mechanismen van spontaan neurobiologisch herstel was een belangrijke volgende stap om deze voorspellingsregel te onderzoeken voor andere neuroligische modaliteiten.

In hoofdstuk 5 werd daarom in een onafhankelijk cohort de ‘maximaal proportioneel herstel’ voorspellingsregel toegepast op het herstel van VSN. Patiënten werden in het onderzoek opgenomen wanneer zij VSN hadden als gevolg van een eerste herseninfarct in de rechter
hersenhelft. De visuele stimuli werden aangeboden in de vorm van de letters 'O', welke op een papier (A4) tussen andere letters 'verstopt' stonden. De taak was om alle 40 O's (20 links en 20 rechts) weg te strepen (Letter Cancellation Test, LCT). Het geobserveerde herstel werd gedefinieerd als de verandering in de LCT-score in het contralesionale (linker) blikveld tussen de eerste meting, gemiddeld acht dagen na het herseninfarct, en de tweede meting na zes maanden. In overeenstemming met de regel voor maximaal proportioneel herstel werd het maximaal mogelijke herstel van een patiënt bepaald door de initiële LCT-score af te trekken van de maximaal mogelijke LCT-score (d.w.z. \(LCT_{\text{max}} - LCT_{\text{init}1}\)), waarbij de maximale LCT score gelijk was aan 20.

Hiërarchische clusteranalyse toonde twee groepen: \(N_1 = 80\) en \(N_2 = 10\), respectievelijk fitters en niet-fitters. De niet-fitters hadden allen 15 of meer missende O's bij de eerste meting. In de subgroep van patiënten met 15 of meer missende O's (\(N = 45\)) hadden de niet-fitters (\(N = 10\)) significant lagere LCT-scores in het ipsilesionale (rechter) blikveld (d.w.z. schijnbaar bilateraal VSN) en waren zij gemiddeld 11 jaar ouder dan de fitters (\(N = 35\)). Bovendien vertoonden alle niet-fitters ook geen proportioneel herstel van de arm (gemeten met de FMA-UE) wat suggereert dat er gemeenschappelijke neurobiologische mechanismen betrokken zijn bij het herstel, ongeacht de betrokken neurologische modaliteiten.

De resultaten in hoofdstukken 3 tot en met 5 lieten zien dat patiënten met matig neurologisch functieverlies herstel laten zien dat in verhouding is met het initiële functieverlies. Het is echter nog onduidelijk waarom 10 tot 30% van de patiënten, onafhankelijk van de ernst en het type neurologisch functieverlies, geen proportioneel herstel laat zien. Toekomstige studies zouden dan ook de onderliggende mechanismen van spontaan neurobiologisch herstel verder moeten onderzoeken om prospectief onderscheid te kunnen maken tussen fitters en niet-fitters.

**Hoofdstuk 6** beschrijft de resultaten van het EXPLICIT-stroke onderzoek, dat een acroniem is voor 'Explaining plasticity after stroke'. Hiervoor werden 159 patiënten met een eerste herseninfarct binnen de eerste twee weken na hun beroerte geïncludeerd. Na de eerste meting werden patiënten eerst gestratificeerd naar ernst van de motorische beperking van de arm (d.w.z. het vermogen om willekeurig de duim en/of twee of meer vingers van de aangedane hand te strekken). Vervolgens werden patiënten via een randomisatieprocedure binnen elke stratum geloot. Patiënten met willekeurige vingerextensie (\(N = 58\)) werden op basis van toegewezen aan een groep die een gemodificeerde vorm van Constraint-Induced Movement Therapy (mCIMT) kreeg, dan wel een groep die de reguliere behandeling

De resultaten lieten zien dat mCIMT een positief effect had op het herstel van de arm-handvaardigheid (gemeten met de ARAT) tot en met drie maanden na het herseninfarct. Echter, dit effect hield niet stand tot de laatste meting op zes maanden. Daarnaast had mCIMT een tijdelijk positief effect op de door de patiënt gerapporteerde handfunctie, gemeten met de Stroke Impact Scale. De resultaten lieten geen effect van mCIMT zien op het herstel van motorische beperkingen (d.w.z. spontaan neurobiologisch herstel) gemeten met de FMA-UE test. Deze resultaten duiden erop dat de verbetering in arm-handvaardigheid het gevolg is van het op een andere, meer optimale, manier gebruik leren maken van de nog intacte neurologische functies (d.w.z. hand of arm) en het geleidelijk leren omgaan met het bestaande functieverlies. Met andere woorden, er is nog geen bewijs dat mCIMT daadwerkelijk invloed heeft op terugkeer van gestoorde neurologische functies zelf (d.w.z. daadwerkelijk neurologisch herstel), ook wel ‘restitutie’ van functies genoemd. Toch is mCIMT op dit moment de meest effectieve therapie voor patiënten met een mild tot matig motorisch functieverlies van de arm en zou daarom in de klinische praktijk geïntegreerd moeten worden.

Drie weken EMG-NMS-therapie had geen effect op het herstel van willekeurige vingerextensie, arm-handvaardigheid en andere secundaire uitkomsten. Hiermee is op dit moment geen effectieve therapie beschikbaar voor de groep patiënten zonder willekeurige vingerextensie direct na het herseninfarct. Deze patiënten zouden daarom, zoals aanbevolen in hoofdstuk 2 van dit proefschrift, in ieder geval in de eerste 12 weken na het herseninfarct wekelijks gemonitord moeten worden. Indien willekeurige vingerextensie terugkeert in de subacute fase (d.w.z. tot drie maanden na het herseninfarct) zou mCIMT alsnog toegepast kunnen worden.

EXPLICIT-stroke was één van de eerste gerandomiseerde studies waarbij met herhaalde metingen in de tijd, klinisch relevante, differentiële effecten werden gevonden in termen van arm-handvaardigheid. De vraag deed zich vervolgens voor of herhaalde metingen in de tijd, op vaste momenten na de beroerte, en het stratificeren op belangrijke prognostische varia-
belen, ook belangrijke factoren zouden zijn voor toekomstige studies naar de meerwaarde van interventies voor arm-handvaardigheid. Het doel van hoofdstuk 7 was daarom om uit te zoeken wat de invloed was van de timing van randomisatie en prognostische stratificatie op de vereiste groepsgrootte van een onderzoekspopulatie om significante en klinisch relevante interventie-effecten op de arm-handfunctie (FMA) en arm-handvaardigheid (ARAT) te kunnen vinden op zes maanden na het herseninfarct. Om de variatie in de inclusieperiode na te bootsen werden patiënten \((N = 159)\) willekeurig geselecteerd in vijf verschillende tijdvensters. Prognostische stratificatie werd gebaseerd op de aan- of afwezigheid van willekeurige vingerextensie.

De resultaten lieten zien dat het verlengen van het tijdvenster tussen het herseninfarct en het moment van randomisatie een toename in de heterogeniteit van het gemeten herstel van patiënten tot gevolg had. Dit resulteerde vervolgens in een toename van het aantal vereiste patiënten in de onderzoekspopulatie. Stratificatie op basis van de prognostische variabele ‘willekeurige vingerextensie’ liet een afname van het vereiste aantal patiënten in de onderzoekspopulatie zien, waarbij de groepen patiënten met en zonder willekeurige vingerextensie los van elkaar werden vergeleken met alle patiënten samen in één groep. De resultaten van dit onderzoek benadrukten dan ook het belang van het zorgvuldig inrichten van gerandomiseerd vergelijkend onderzoek om de kans op het vinden van differentiële interventie-effecten te vergroten.

Zoals aanbevolen in hoofdstuk 8 van dit proefschrift zou toekomstig onderzoek zich moeten richten op het verder in kaart brengen van onderliggende mechanismen van neurobiologisch herstel. Daarbij is het belangrijk om onderscheid te maken tussen restitutie en compensatie van functies om zo de vroegtijdige voorspelling van neurologisch herstel te verbeteren en mogelijke ‘functieherstellende’ interventies te vinden. Aandacht zou daarbij uit moeten gaan naar de kwaliteit van bewegen in relatie tot corticale reorganisatie en abnormale netwerkinteractie door gebruik te maken van klinische, kinematische en kinetische meetinstrumenten, en neurofysiologische en beeldvormende technieken. Het is uiterst belangrijk om hierbij rekening te houden met het tijdvenster tussen het herseninfarct en de eerste meting, vanwege de tijdsafhankelijkheid van het potentiële neurobiologisch herstel van de patiënt en de mogelijkheid om te reageren op functieherstellende interventies.

Toekomstige prognostische studies en gerandomiseerde vergelijkende onderzoeken zouden daarom: (1) moeten starten in de hyper-acute en acute fase na het herseninfarct, d.w.z. binnen zeven dagen na het herseninfarct, (2) gebruik moeten maken van herhaalde metingen in

Samenvatting (Summary in Dutch)
de tijd, op vaste momenten, met een hogere frequentie (wekelijks) tot drie maanden na het herseninfarct en (3) patiënten aan de hand van vroege biomarkers voor neurobiologisch herstel indelen in subgroepen (d.w.z. fitters versus niet-fitters), zodat een interventie enkel aan die patiënten wordt aangeboden die de meeste kans hebben om ervan te profiteren. Daarnaast moet toekomstig onderzoek zich richten op het vinden van nieuwe interventies die ook in staat zijn functies te herstellen (d.w.z. restitutie van functies), zoals transcraniële direct current stimulatie, transcraniële magnetische stimulatie, met of zonder neurofarmacologische behandelingen en/of combinaties met oefentherapie.

Om stappen voorwaarts te kunnen maken in neurorevalidatieonderzoek is het essentieel om zowel voor preklinisch als klinisch onderzoek wereldwijde consensus te krijgen voor het gebruik van terminologie, selectie van patiënten, gebruik van uitkomstmaten en timing van metingen. Hiervoor is ook nationale en internationale samenwerking en consensus nodig tussen experts om het uitvoeren van prognostisch onderzoek en gerandomiseerd vergelijkend onderzoek te vergemakkelijken en te komen tot hoogwaardige grote datasets.
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About the author

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CURRICULUM VITAE

Caroline Winters was born on April 8, 1988 in Huizen, the Netherlands. In 2006, she graduated from pre-university secondary education (Dutch: Voorbereidend Wetenschappelijk Onderwijs) at the Huizermaat in Huizen. Thereafter, she attended the Vrije Universiteit Amsterdam for the Bachelor’s and Master’s programme in Human Movement Sciences. During her Master’s she gained experience in pulmonary function and clinical exercise testing during her internships at the VU University Medical Center in Amsterdam and the rehabilitation centre Heliomare in Wijk aan Zee. She further increased her experience in clinical exercise testing and cardiac rehabilitation during a 4 month internship at the Mayo Clinic in Rochester, MN, United States of America. In 2011 she received the G.J. van Ingen Schenau Promising Young Scientists Award, which enabled her to attend the School of Physiotherapy and Exercise Sciences at Griffith University in Queensland, Australia, for her final research internship focussed at the influence of respiratory muscle work on the slow component of oxygen uptake kinetics during exercise. In 2012, she graduated cum laude and was named as VU University Research Fellow of prof.dr. G. Kwakkel. She started her PhD under supervision of prof.dr. G. Kwakkel and dr. E.E.H. van Wegen at the department of Rehabilitation Medicine, VU University Medical Center in Amsterdam. During her PhD study she engaged in the EXPLICIT-stroke trial and the 4D-EEG study for which she performed clinical and electroencephalography measurements in different hospitals, rehabilitation centres and nursing homes throughout the Netherlands. The main aims of her PhD study were to gain insight into early prediction of neurobiological outcome after stroke and to investigate whether it is possible to influence neurobiological recovery with early applied interventions focused at the upper limb.
LIST OF PUBLICATIONS

Publications related to this thesis


Other publications


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