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. 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. 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). 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. 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.

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. 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

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**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 extend 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 Val⁶⁶Met 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.\textsuperscript{51,52} 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.\textsuperscript{53,54} 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.\textsuperscript{1,2,35,55,56}

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.\textsuperscript{1,2} 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.\textsuperscript{57} 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.\textsuperscript{57,58} 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.\textsuperscript{59} 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.\textsuperscript{59}

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. The intensity of task-specific exercise, previously defined as the “hours of exercise therapy under supervision of a physiotherapist or occupational therapist” 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. 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. 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. 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. The transfer package was not included in the EXPLICIT-stroke trial, nor in almost all other RCTs investigating the effects of mCIMT. The goal of the package is to transfer the treatment gains of adherence-enhancing behavioural methods from the clinic to patients’ daily living. 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, 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. 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.

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. 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.\textsuperscript{52} 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.\textsuperscript{52,72} 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.\textsuperscript{52,55,73} 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.\textsuperscript{52,71}

As shown in chapter 6, patients did not benefit from a 3 week EMG-NMS intervention starting in the early subacute phase post stroke.\textsuperscript{55} 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).\textsuperscript{55,74} Upper limb therapy may therefore focus on assisted or passive movements and learning to use behavioural compensation strategies.\textsuperscript{75} 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).\textsuperscript{71} This discrepancy between the EXPLICIT-stroke trial\textsuperscript{55} and Dutch Guidelines\textsuperscript{71} 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.\textsuperscript{55} 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.\textsuperscript{7,55,71}

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.\textsuperscript{39} 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.\textsuperscript{76,77}
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. 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. 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. However, to investigate the course of neurobiological recovery, measurements should preferably take place weekly up to 12 weeks post stroke. Repeated measurements will also allow for longitudinal prognostic and computational modelling which can help understand the complex underlying mechanisms of stroke recovery.

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. This finding suggests that proprioceptive feedback is essential for spontaneous return of voluntary motor control and brain reorganisation. 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 (PROFITS) initiative is an important step towards implementation. The PROFITS 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 PROFITS 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. PROFITS 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$^{92}$ 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.$^{91,93}$ 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.$^{52,63,75,94}$ 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.$^{63,95}$ 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.$^8$ 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).$^{96}$

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

A prognostic model should go through three phases, namely, the development, external validation and implementation phase.$^{97}$ 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.$^{98,99}$ 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.$^{100,101}$ 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.$^{43,44,48}$ 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 on 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**


