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 extent 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.