

Chapter 8

General discussion

MAIN FINDINGS

The present thesis is focused on three main key topics in stroke rehabilitation, namely prediction, exercise therapy and evaluation of outcome in patients with an upper limb paresis after a first-ever ischemic stroke.

The first part of this thesis was aimed at developing prognostic models for upper limb recovery early after stroke in the Early Prediction of Functional Outcome study (EPOS), which is a prospective cohort study involving nine hospital stroke units in the Netherlands. Chapter 2 of this thesis showed that accurate prediction of upper limb capacity at 6 months post stroke is already possible within 72 hours after stroke onset by using two simple bed-side tests, ‘finger extension’, according to the Fugl-Meyer (FM) hand score and ‘shoulder abduction’, according to the Motricity Index (MI) arm score. Upper limb capacity was dichotomized in the derived computational prediction models, allowing one to distinguish patients who are likely to have some dexterity at 6 months from patients who are unlikely to have some dexterity at 6 months. Patients with some finger extension and shoulder abduction within 72 hours after stroke onset had a 98% probability of having some dexterity at 6 months. If neither movement could be made within 72 hours, the probability of having dexterity at 6 months was 25%, falling to 14% at day 5 or day 9 after stroke.

To investigate the value of our derived computational prediction models in clinical practice, we compared the accuracy of predictions made by physical therapists (PTs) regarding upper limb capacity at 6 months, with the accuracy of derived computational prediction models. Predictions from PTs as well as the derived computational prediction models were made in 3 categories: (1) the patient will not have any dexterity; (2) the patient will have some dexterity and (3) the patient will fully recover in terms of dexterity. Predictions were made within 72 hours post stroke as well as at the moment of discharge from the hospital stroke unit, in order to investigate the impact of timing post stroke on the accuracy of prediction. Our findings, as presented in chapter 4, suggest that the accuracy of predictions regarding upper limb capacity at 6 months post stroke were significantly lower when made by PTs than when made by the computational prediction model. The accuracy of prediction at the moment of discharge was, however, almost similar for PTs when compared to the derived model for prediction.

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The second part of this thesis was aimed at summarizing the evidence of early applied Constraint Induced Movement Therapy (CIMT) and modified versions of CIMT (mCIMT), acknowledging that (m)CIMT is thought to be one of the most promising interventions for improving upper limb function in patients with some preservation of wrist and finger extension.^{1,2} However, recent evidence from animal studies suggests that intensive upper limb training may be harmful

when started too early post stroke.^{3,4} Therefore, we systematically reviewed the current evidence of CIMT and mCIMT in the first 10 weeks post stroke. The results of this review presented in chapter 5 suggest an overall trend towards positive effects of (m)CIMT during the first 10 weeks after stroke. However, the results also suggest that Low Intensity (LO) CIMT (defined as less than 3 hours of repetitive training) may be more beneficial during the first weeks after stroke than High Intensity (HI) CIMT. Notably, the package of CIMT and modified versions of CIMT (mCIMT), applied in the first 10 weeks after stroke is heterogeneous and the exact content is often not well described in the literature. The lack of a clear description of applied intervention protocols limits the implementation of scientific results in clinical practice,⁵ and prevents external validation of applied treatment programs.⁶ In line with the need for transparency regarding the content of therapy in rehabilitation trials, the mCIMT intervention protocol, as applied in the multi center trial called 'EXPLICIT-stroke' in the Netherlands (trial registration number: NTR1424), is presented in chapter 6. EXPLICIT-stroke is an acronym for EXplaining PLasticity after stroke and is a research programme aimed at investigating the effects of early applied intensive exercise therapy for regaining dexterity and at exploring the underlying mechanisms that are involved in upper limb recovery early after stroke.⁷ The mCIMT protocol in the EXPLICIT-stroke trial consists of 1 hour of repetitive task training per day and patients additionally wear a mitt for at least 3 hours per day. Further, to investigate patients ability to regain or reconstitute motor function by early initiated training, the mCIMT protocol is specifically aimed at neurological repair by applying an impairment-focused intervention programme. In this facilitating programme, the intervention protocol was focussed on improvement of wrist and finger extension during the first weeks after stroke.

The final part of the present thesis aimed to investigate the clinimetric properties of two most commonly used assessments for the paretic upper limb in clinical trials, i.e. the Action Research Arm Test^{8,9} and the Wolf Motor Function Test.¹⁰ A proper assessment tool is required to evaluate the effectiveness of (m)CIMT or any other intervention. In most European, Australasian and Asian countries the ARAT is used in phase II trials¹¹⁻¹³ whereas in North America the WMFT is most prevalent.¹⁴ Both assessment tools have shown their reliability, but have never been compared directly for concurrent validity. The study presented in chapter 7 shows a high concurrent validity for the ARAT and the WMFT and excellent inter- and intra-observer reliability coefficients. As a consequence, the ARAT and the WMFT are comparable assessment tools aimed for quantifying unilateral performance of the paretic upper limb.

This concluding chapter presents a critical reflection on the research as described in this thesis and a discussion of clinical implications and future considerations.

EARLY PREDICTION OF UPPER LIMB RECOVERY AFTER STROKE

Methodological considerations

Prognostic research is complex. To overcome different sources of bias, guidelines for reporting observational studies according to the STROBE statements ('strengthening of reporting of observational studies in epidemiology') have been established.¹⁵ These guidelines are aimed at providing guidance on how to properly report observational research and may help to improve the quality of studies. Major methodological issues for adequate prognostic research are the appropriateness of: (1) study design; (2) reporting of study attrition; (3) predictor measurement; (4) outcome measurement; (5) statistical analysis and (6) clinical performance / validity.¹⁶⁻²⁰ The development of methodology for prognostic studies is ongoing, acknowledging that there is no consensus about the methodological items that should be satisfied in prognostic research. Fortunately, a task force on prognostic research has started to develop the STROBE statements resulting in a positive evolution of the methodological quality of prognostic studies.²⁰

An important methodological consideration regarding the study design in an inception cohort is the timing of measurements. Due to the non-linear pattern of stroke recovery in the first months post stroke, these measurements should preferably take place at fixed time points in which stroke onset is defined as 0.²¹ Only by applying an intensive repeated-measurement design it is possible to investigate the influence of progress over time on the accuracy of prediction and with that to capture mechanisms of spontaneous neurological recovery early post stroke. Hence, the most innovative aspect of the EPOS study and the computational prediction models, as presented in chapter 2, is the use of an intensive repeated measurement design during the first weeks post stroke, starting within 72 hours and with only 3 days between the assessments.

The choice for appropriate predictor and outcome measurements is another important methodological consideration in prospective cohort studies, as well as the provision of a definition and a clear rationale for cut-off points to be used. The use of cut-off points can be debated because of possible loss of valuable data. On the other hand, due to the non-linear recovery pattern after stroke, the use of linear regression methods, able to explain variances of outcome, can be debated as well. To identify patients in our models, logistic regression analyses was applied and final outcome was dichotomized, using a cut-off score of 10 points. Unfortunately, there is no consensus about the best cut-off point to use. In a recent study of Au-Yeung and colleagues,²² aimed to predict dextrous hand function within 5 days post stroke, recovery of dexterity was defined as ≥ 35 points on the ARAT. Upper limb muscle strength and two-point discrimination were found as predictive determinants. To enable comparison between prospective studies, the same cut-offs points should preferably be used.^{20, 22, 23}

Clinical implications

Even when methodological requirements for prospective studies are met, the question remains whether the resulting computational prediction models have an added value in the clinic. To enhance the utility of prediction models in clinical practice, they should preferably be based on quick and simple bed-side tests without relying on sophisticated techniques and complex algorithms that are both difficult to comprehend and challenging to implement in practice.²⁰ The computational models as presented in this thesis demonstrate the predictive value of finger extension and shoulder abduction, which both can be assessed using quick and simple bed-side tests. For therapists, prognostic information is essential to provide adequate evidence based services. They should consider evidence for a certain intervention based on randomized clinical trials and meta-analyses.⁶ To judge if the intervention is justified for their own patients, they need to be aware of important prognostic factors.⁵ For instance, in CIMT studies, positive effects are probably not only achieved by the content of the applied therapy, but may also be due to selective inclusion of patients who are likely to regain some dexterity.^{24, 25} The findings as presented in chapter 2 further underline that those patients can be identified by assessing patients' ability to extend the fingers.

Another important requirement for clinical usefulness is that the model has sufficient sensitivity, specificity, positive predictive value and negative predictive value. For the prediction models presented in chapter 2, the positive predictive value within 72 hours was 0.93 (95% CI, 0.88–0.96), whereas the negative predictive value was 0.76 (95% CI, 0.67–0.83). The latter improved from 0.76 to 0.86 (95% CI, 0.77–0.93) over the first 9 days post stroke. These relatively low negative predictive values suggest that, using our prognostic model, there is a relatively high number of false negatives and it is therefore still rather difficult to accurately predict if those patients without voluntary finger extension and/or shoulder abduction will indeed fail to regain some dexterity at 6 months. Although the uncertainty declines when time progresses, the study as presented in chapter 3, suggests that a certain degree of uncertainty remains, also after the first 9 days. In that specific study, hand capacity was assessed using the Stroke Upper Limb Capacity Scale (SULCS).²⁶ Assessments were performed in 299 stroke patients at the time of admission in the rehabilitation centre, which was on average 32 days (SD 12.2) after stroke and again at discharge from the rehabilitation centre, which was on average 77 days (SD 47.9) after admission. Of the 125 patients who had no hand movement at admission in the rehabilitation centre (0–3 points on the SULCS), 59% (N=74) had not regained dexterity at discharge, whereas 41% (N=51) regained at least some degree of dexterity at discharge. The relatively high number of false negatives has important implications for clinicians and researchers in this field. Clinicians need to be prudent in their communication with patients

and family, with regard to prognosis of outcome. The best moment to inform patients about their low chances for recovery may depend for instance on coping strategies of individual patients. However, therapists should clarify to these patients that interventions for the paretic upper limb are primarily focused on learning compensation strategies, including use of the unaffected limb, to deal with the impairments of the paretic upper limb.

To investigate the value of using prediction rules in clinical practice, we compared the accuracy of computational prediction models, developed using ordinal logistic regression analyses, with the accuracy of predictions made by physical therapists (PTs). At the time of the study PTs were still naive against the prognostic determinants that were identified afterwards in the same cohort. The results of this study demonstrate that the average accuracy of predictions made by PTs within 72 hours after stroke was lower than that of the derived prediction model. The accuracy of predictions at the moment of discharge was similar for the computational prediction model and the PTs. It needs to be mentioned that the difference in accuracy of predictions between the computational model and the therapists was small. Within 72 hours, 60% of the therapists made a correct prediction of final outcome in terms of dexterity in three categories (i.e., 0–9 / 10–56 / 57 points on the ARAT), whereas 65% of the predictions determined with the computational prediction model were correct. Because of the relatively small differences, it may be suggested that the use of prediction models for the paretic upper limb has a limited added value to that of clinical expertise of the therapist. However, the use of validated models with simple bed-side tests, which are conducted by physical- and occupational therapists, may support the position of these therapists in the multidisciplinary team at hospital stroke units. Also neurologists and rehabilitation physicians may benefit from the use of evidence based models for clinical reasoning. With that, knowledge about computational prediction models for upper limb outcome and the time-dependency of clinical determinants should be part of the curriculum for physical and occupational therapists and should be included in evidence-based guidelines for stroke rehabilitation.

Future steps

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Because of the increasing need to optimize the efficiency of care, it is highly relevant to further refine the current computational prediction models. To reach this goal, we need to improve our understanding about the underlying mechanisms responsible for recovery of the upper limb. Within the EPOS study, an intensive repeated measurement design was applied to explore the biological relationship of the predictive determinants with spontaneous neurological recovery. Although we have shown a gradual decline of uncertainty during the first 9 days post stroke, probably as a result of time-dependent spontaneous processes, we do not yet fully understand

the mechanisms behind neurological recovery. Obviously, the influence of progress of time as a derivative of spontaneous neurological recovery is not yet fully understood. Future studies should try to identify relevant components of movement deficit (i.e. neurological, neurophysiological or neuromechanical changes) and associate them, as a function of time, with observed improvements in terms of dexterity. It should also be investigated if these time-dependent changes lead to improvement of dexterity, in terms of restitution of function or compensation. Although recovery mechanisms such as reperfusion of non-infarcted penumbral areas and resolution of diaschisis are suggested to be active in a critical time window early after stroke, it is still unclear whether starting interventions within this window can lead to restitution of function.²⁵

Future studies should also aim to develop more advanced algorithms, using dynamic information about performance, instead of using actual performance scores, as used in our models. Modeling changes over time can improve our understanding about the time dependency of recovery after stroke. Since recovery after stroke follows a non-linear pattern, these advanced algorithms should be modelled by using non-linear regression methods. The application of curve fitting methods might be used to explore the dynamics of early observed stroke recovery.

Despite the high sensitivity, one of the main shortcomings of the current models is the relatively high false negative rate, and with that the relatively low negative predictive value (0.76 [95% CI, 0.67–0.83]). Future prognostic research need to identify factors that may be responsible for these false negatives. The influence of sensory and cognitive deficits, such as motor neglect, apraxia or aphasia, should for instance be further explored, since they might mask the ability to voluntarily extend the fingers at stroke onset and may therefore cause false negatives. The use of more advanced techniques might be considered as well. Unfortunately, a prospective cohort study of van Kuijk and colleagues²⁷ (N=35) showed that applying Transcranial Magnetic Stimulation (TMS) at the end of the first week resulted in a relatively high number of false negatives (N=8) as well, with a negative predictive value of 0.74 (95% CI, 0.59–0.90). In the same vein, early prediction models using Diffusion Tensor Imaging (DTI) showed also a limited predictability during the first two weeks after stroke. In a recent study,²⁸ it was suggested that DTI measurements are useful to accurately predict outcome of the Motricity Index arm scores between 15-28 days after stroke (N=48), whereas DTI measurements within the first 14 days fail to accurately predict upper limb function (N=23). These findings suggest that the accuracy in visualizing the intactness of cortico-spinal tract (CST) is also time-dependent. In this specific study, the low predictability of DTI assessments within the first 14 days (N=23) was mainly caused by a high rate of false positives (N=9), which is in line with the suggestion that Wallerian degeneration needs at least 2 to 3 weeks to become visible by applying DTI. In contrast, the

false negative rate of DTI measurements within 14 days was relatively low for DTI (N=3).²⁸ These three cases are possibly caused by peri-infarct edema.²⁸ Future studies should further explore the use of DTI in a larger sample and should investigate the factors that are responsible for false predictions. Also the combination of DTI and clinical assessments should be further explored, since DTI showed higher negative predictive values and clinical assessments showed higher positive predictive values.

Although the positive predictive value of our computational prognostic models is rather high (0.93 [95% CI, 0.88–0.96]), further refinement of algorithms for patients with a favorable prognosis for regaining some dexterity is relevant as well. Patients with a favorable prognosis are most likely to benefit from intensive exercise therapy. However, a sizeable proportion of this group will probably regain dexterity, even without intensive exercise therapy. In the EPOS study, it was for instance found that 34% of the patients had a maximum ARAT score (57 points) after 6 months and even 60% of the patients with some voluntary finger extension within 72 hours scored 57 points on the ARAT after 6 months, receiving usual physical and occupational therapy according to the Dutch guidelines.^{29,30} In line with these results, Brunner and colleagues³¹ showed that 52% of the patients who were eligible for CIMT therapy (N=46) within 2 weeks after stroke, reached reasonable dexterity (≥ 51 points on the ARAT) after 3 months. All patients in this study received standard rehabilitation. Standard rehabilitation was given for 5–10 hours a week and consists of physical therapy based on different neurorehabilitation approaches and occupational therapy focussing on task-related training.³¹ On the basis of these findings, Brunner and colleagues suggested that eligibility for CIMT should therefore not be considered within the first weeks post-stroke. However, only on the basis of evidence derived from a well-conducted randomized controlled trial one can make the suggestion that a certain intervention should not be considered. Future studies should try to identify those patients who will probably regain full dexterity, even without intensive exercise therapy, like CIMT. These patients should probably not be selected for mCIMT trials, and future studies should aim to investigate if a less intensive rehabilitation approach is sufficient for these patients in which full recovery is expected, in order to prevent future rehabilitation in vain and save costs. A less intensive rehabilitation approach could for instance consist of home exercises and providing information about the importance of using the paretic upper limb to prevent learned non-use. The home exercise program should contain repetitive task-oriented exercises, which can be performed independently.

Finally, future studies should aim to validate derived prediction models. In prognostic research three consecutive phases for model development need to be considered before practitioners can confidently apply a model to their patients.¹⁹ First, the development phase, followed by a

validation phase in which the accuracy of the model is tested and, finally, the implementation phase in which the impact of prognostic models is investigated.¹⁹ In this thesis we have presented studies in the development phase of prognostic research. The next step might be to establish the internal validity of the model, using for instance bootstrapping or split-sample methods. For external validation, at least one and preferably several independent cohorts of patients should be used in which the existing models are retested.¹⁹ Subsequently, for external validity, the model can also be tested on a more varied stroke population, like intracerebral and subarachnoid hemorrhages. Unfortunately, such validation studies are scarce, as newly collected data from prediction research are often used to develop a new prognostic model rather than to externally validate existing models. To gain access to more data for external validation of existing models, international cooperation is needed. The final step is to conduct impact studies, in which models are tested for their ability to change clinicians' decisions and their impact on the efficiency of care and patients' outcome.¹⁹

CONSTRAINT INDUCED MOVEMENT THERAPY IN THE ACUTE PHASE AFTER STROKE

Current perspectives

The meta-analysis, presented in chapter 5, revealed a trend toward positive effects of (m)CIMT in the first 10 weeks. However, there are still many questions unanswered, which hampers the implementation of (m)CIMT in this critical time window after stroke.

One of the most important issues is the lack of solid recommendations regarding the dose and content of (m)CIMT therapy. The original CIMT treatment protocol has been criticized as being impractical in clinical practice, in particular for patients in the acute phase after stroke.³² As a consequence, an increasing number of adapted forms of CIMT, including forced-use strategies, have emerged in the last three decades. Each of these adapted forms claims the name "modified" CIMT (mCIMT), but there is large variability in treatment protocols. In addition, most studies fail to provide a detailed description of the applied intervention protocol. As a consequence, it is currently not possible to formulate solid recommendations regarding the optimal dose and exact content of CIMT in the acute phase after stroke.

Recommendations regarding patient criteria for eligibility are ambiguous as well. Between current clinical guidelines mixed recommendations exist regarding the minimal movement capacity that a patient must have to be eligible for (m)CIMT.^{30, 33, 34} The majority of studies in acute stroke patients applied an inclusion criteria of minimally 10 degrees of voluntary finger

extension and between 10 to 20 degrees of wrist extension.^{32,35,36} As shown in our computational prediction model, presented in chapter 2, presence of some initial voluntary finger extension, as indicated with 1 point on this item of FM-hand score, corresponds to a favorable prognosis for regaining some dexterity. This finding suggests that only some initial voluntary extension of the fingers is enough to have beneficial effects of (m)CIMT therapy, and hence, that the requirement for 10 degrees may be too strict. Future studies should try to refine this criterion.

The optimal timing post stroke to start (m)CIMT therapy is still under debate as well. Within the existing RCTs on CIMT in first weeks after stroke, the timing to start therapy varied between 4.4 days after stroke in the study by Page and colleagues³² to 11 days after stroke in the study by Boake and colleagues.³⁵ Since recovery mechanisms such as resolution of diaschisis and restitution of non-infarcted penumbral areas are suggested to be active in a critical time window early after stroke, small differences in the timing of the start of the study may have a major impact on improvements achieved due to (m)CIMT. Most animal studies to date suggest that early intervention is more effective than delayed rehabilitation.³⁷ An upregulation of growth promoting factors such as Brain-Derived Neurotrophic Factor (BDNF) is for instance found in the first 3 weeks post stroke followed by an upregulation of growth inhibiting factors such as NOGO.³⁸ The suggestion of a critical time window of about 3 to 4 weeks post stroke suggest that exercise therapy should preferably be started as soon as possible, within the first days and weeks posts stroke. An assumption which is line with the results as shown in a study published by Biernaskie and colleagues.³⁹ In their study, rats with middle cerebral artery occlusion were exposed to an enriched environment in combination with daily sessions of reach training. Training resulted in significant gains in recovery of forelimb reaching ability when it was initiated 5 or 14 day after stroke but not when initiated 30 days after stroke.³⁹ However, results of animal studies regarding the optimal timing post stroke to start intensive exercise therapy are contradictory.^{38,40} It is also suggested that intensive practice of the affected limb in rats is detrimental if it occurs too soon after the infarction, when cells in the penumbral tissue are presumably still vulnerable.^{4,41-43} These conflicting theories and results are based on animal models, it is not clear how these findings can be generalized to patients with stroke.³⁷

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The ambiguities concerning the optimal application of CIMT justifies further phase II trials with varying criteria for patient selection, moments to start mCIMT early post stroke, and doses of therapy. In addition, we need to improve our understanding about the underlying mechanisms responsible for recovery of the upper limb and the time window in which these mechanisms are active.

Future directions for early started upper limb training after stroke

An important concern in future studies is not only to conduct larger trials on the effectiveness of mCIMT during the first weeks after stroke, but also to reveal if wrist and finger extension as key factors for upper limb recovery can be influenced by early initiation of therapy. In order to reveal the effectiveness of early mCIMT post stroke and to discover the underlying mechanisms that determine recovery in terms of neural repair or compensation, the EXPLICIT-stroke programme was started in 2008 in the Netherlands. EXPLICIT-stroke is financed by ZonMw and involves four participating academic university hospitals (LUMC, UMCN, UMCU and VUmc), one technical university (TU-DELFT), seven peripheral hospital stroke units, eight rehabilitation centres and eight nursing homes, which comes to a total of 28 centres in this consortium⁷ (www.explicit-stroke.nl). One of the main aims of the EXPLICIT-stroke trial is to determine the effectiveness of applying a three week mCIMT protocol in which extension of the fingers and wrist is facilitated by 1 hour of repetitive training per day. The mCIMT protocol that was developed for the EXPLICIT-stroke trial is presented in chapter 6 of this thesis.

Another main aim is to reveal if facilitation of wrist and finger extension as key factors for upper limb recovery can lead to neurological repair in patients with a (partly) damaged CST. For this purpose, patients with an initial unfavorable prognosis to regain dexterity receive EMG-triggered neuromuscular stimulation (EMG-NMS) of the wrist and fingers extensors for 1 hour per day, started within two weeks after stroke onset and continued for three consecutive weeks. The goal is to investigate if the CST viability is already fully defined within the first two week after stroke or if it can be influenced by interventions.

To investigate the influence of wrist and finger extension on recovery of upper limb function, in terms of restitution or substitution/ compensation, a translational research approach is applied in the EXPLICIT stroke trial.⁷ Changes in the affected and less-affected hemisphere are investigated using functional MRI (fMRI) and TMS. Repeated kinematic measurements are applied to reveal if 'true motor recovery' occurs or if patient learn to adapt by using behavioural compensation strategies. Finally, it is likely that the integrity of the CST will influence neuromechanical properties, like joint stiffness and reflex modulations. Therefore the effects of wrist and finger facilitation, using CIMT or EMG-NMS, on neuromechanic properties are assessed by using haptic robots.⁷ In other words, a wide range of professionals, from different disciplines in the clinical and pre-clinical field, work together aiming to unveil the black box of recovery after stroke a bit more.

Knowledge about the mechanism behind treatment-induced changes and about the possibility of CST excitability is important to understand stroke recovery and to develop new interventions that are aimed to enhance restitution of function early post stroke. One may consider noninvasive

brain stimulation techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial Direct Current Stimulation (tDCS) to modify the excitability of affected or non affected brain areas. Brain stimulation in animal models can produce Hebbian-like changes in synaptic activity and cortical motor representation.^{44,45} It is hypothesised that a combination of brain stimulation and repetitive task-oriented training can promote more complete recovery.⁴⁶ Recently, it is for instance shown by Bolognini and colleagues that tDCS may increase the gains in motor function that are induced by CIMT.⁴⁷

Furthermore, pharmacological rehabilitation, in combination with exercise therapy should be further explored in future studies. Early animal studies reported enhanced motor recovery when exercise therapy was combined with amphetamine treatment. However, disappointing results were found in stroke patients.^{38,48} Recently, Chollet and colleagues found positive effects on motor recovery in patients with acute ischaemic stroke who were treated with fluoxetine.⁴⁸ Although the mechanisms behind the positive of fluoxetine are still speculative,⁴⁸ fluoxetine is suggested to have a neuroprotective effect in the post-ischaemic brain⁴⁹ and it enhances neurogenesis after stroke in rats.⁵⁰ Future studies should explore the beneficial effects of these kinds of pharmacological interventions, combined with evidence based exercise interventions, aimed at restitution of function.

OUTCOME MEASURES

Finally, it should be recognized that one of the key issues in high quality studies is to choose an appropriate main outcome measure. As mentioned before, the International classification of functioning, disability, and health (ICF) can facilitate in this choice, because it helps to understand what an outcome measure does and does not intend to measure. However, for the paretic upper limb only, more than 30 outcome measures have been described in the literature,^{51,52} and this list is growing due to proliferation of new outcome measures. A major problem is caused by the high number of outcome measures and the lack of international consensus about which outcome measure(s) should be used. Reaching consensus about the minimal core set of outcomes that should be included in clinical trials would allow us to better combine study results in meta-analysis.

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CONCLUDING REMARK

Having discussed the three main topics of the present thesis, and having executed 984 patient assessments for the single-blinded EXPLICIT stroke trial during my PhD, I look forward to the results of EXPLICIT stroke trial with anticipation and scientific curiosity.

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