Recovery of the paretic upper limb early after stroke

van Kordelaar, J.

2014

document version
Publisher's PDF, also known as Version of record

CHAPTER 7

General discussion

RESTITUTION OR SUBSTITUTION?

The goal of the current thesis was to gain insight into *what* and *how* patients learn when they recover from a stroke. To this end, it was investigated how adaptive strategies to compensate for existing motor impairments (i.e. substitution) complement true motor recovery by which movement patterns change towards those observed prior to injury (i.e. restitution).[1,2] Such insight into the change in quality of motor control after stroke may contribute to an improved understanding of the learning-dependent and non-learning-dependent mechanisms underlying motor recovery [3] and may ultimately lead to improved rehabilitative strategies for enhancing upper limb function after stroke.[4]

Intensively repeated 3D kinematic measurements were conducted to investigate the change in quality of motor control in the first weeks up to 26 weeks after stroke. To the best of our knowledge, the 3D kinematic paradigm described in chapter 2 is the first that was applied outside the 3D kinematic motion laboratory. The presented single-case study suggests that task performance early after stroke is mainly driven by adaptive motor control, that is, the elbow was 'locked' within the flexion synergy, whereas the reaching movement was mainly controlled by a displacement of the trunk in a forward direction.[5] However, over time poststroke the elbow was progressively released during the reaching task, whereas forward trunk movements simultaneously diminished. These results suggest that over time, this patient was increasingly able to unlock the elbow and dissociate from the basic flexion synergy, making compensatory trunk movements unnecessary. This change in the recruitment of degrees of freedom was accompanied by changes in movement duration. In addition, maximum grasp aperture occurred sooner after maximum hand speed as a function of time poststroke. This finding suggests that grasping movements of the fingers and transport of the hand became more parallel, rather than serial controlled, which is indicative of improved quality of motor control.[6]

Chapter 3 described the interaction between the basic flexion synergy and compensatory trunk movements during a reach-to-grasp task in 46 patients at, on average, 26 weeks after stroke. A principal component analysis (PCA) showed that the basic flexion synergy (i.e. horizontal shoulder abduction combined with elbow

flexion) was the most dominant movement component in explaining the variance between patients with stroke. In addition, two less dominant movement components suggested that forward trunk rotation served to compensate for a lack of elbow extension, whereas lateral trunk rotation towards the non-paretic side seemed to serve as compensation for lack of upward shoulder rotation. A multivariable logistic regression model showed that these two compensatory components could predict whether patients were able to fully dissociate from the basic flexion synergy as established with the upper limb section of the Fugl-Meyer Motor Assessment (FMA). This finding supports the fact that basic limb synergies, as clinically determined, directly influence adaptive motor control in patients with stroke.

Chapter 4 capitalized on the finding that PCA could be used to identify movement synergies in patients with stroke. A longitudinal study of 31 patients investigated the emergence of synergies as a function of time, starting within 2 weeks after stroke. Results showed that within the first 5 weeks after stroke the presence of the basic flexion synergy diminished as a function of time. This early and time-dependent reduction of the flexion synergy during the reach-to-grasp movement paralleled improvements seen in the FMA scores and may be considered as an improvement in the mastering of the degrees of freedom of the paretic upper limb. Early after stroke patients seem to exploit the flexion synergy to 'lock' the elbow in a flexed position and use considerable proximal trunk movements during functional reaching tasks. This might be an adaptive strategy whereby proximal degrees of freedom are recruited to compensate for distal motor impairments, such as muscle weakness, spasticity and lack of individual joint control in the paretic upper limb. The reduction of the flexion synergy as a function of time poststroke suggests that patients regain some control over the distal degrees of freedom in the paretic upper limb which leads to restitution of motor control. Importantly, this improvement of motor control tapered off from 5 weeks onwards and, at 26 weeks, dissociations from the flexion synergy as seen in healthy subjects were on average still incomplete. Post-hoc analyses revealed that 19 of the 31 patients fell within the range of healthy subjects at 26 weeks after stroke, suggesting that (partial) restitution of motor control is possible. However, in the remaining 12 patients, upper limb motor control remained adaptive, despite their initial favourable prognosis for regaining upper limb function after stroke.[7]

Chapter 5 investigated how the quality of upper limb control, as quantified by the smoothness of reach-to-grasp movements, changed as a function of time poststroke. In a group of 44 patients, smoothness of hand trajectories and grasp aperture improved strongly during the first 8 weeks after stroke whereas these improvements tapered off from 8 weeks onwards. Since smoothness is regarded to be a feature of skilled and well controlled movements,[8–10] this finding suggests that reach-to-grasp movements are more efficiently controlled as patients regain individual joint control during stroke recovery.[11,12] Previous studies have pointed out that feedforward control is disrupted in patients with stroke causing movement errors during initiation of reaching movements.[13,14] During the task, patients constantly need to correct for these movement errors mainly using visual and proprioceptive feedback loops, culminating in jerky or unsmooth movements.[15,16] The significant contribution of progress of time to improvements in smoothness suggests that time alone is an important factor in the process of restitution of motor control after stroke. In the first 8 weeks after stroke, patients gradually regain the ability to accurately plan reaching movements in advance (i.e., reliance on feedforward control), thereby decreasing the need for corrective movements based on visual and proprioceptive feedback (i.e., reliance on feedback control).

However, the neural substrate of these improvements in smoothness is poorly understood. Therefore, in chapter 6, the relation between smoothness and changes in activation in cortical sensorimotor areas, as measured by means of fMRI, was investigated. To our knowledge, this longitudinal study in 17 patients with stroke was the first to combine fMRI and 3D kinematics in a longitudinal measurement design. This study showed that reduced smoothness of finger movements during reach-to-grasp was primarily associated with activation in additionally recruited secondary sensorimotor areas at week 5 after stroke. This finding suggests that additionally recruited secondary sensorimotor areas may not be able to restore quality of motor control. Moreover, since disrupted smoothness is assumed to reflect the use of feedback rather than feedforward mechanisms, the above findings suggest that increased recruitment of secondary sensorimotor areas may reflect increased use of feedback mechanisms in order to compensate for impaired feedforward control. Although above findings may not be causative, the found associations are important

to improve our understanding of the dynamics in the pattern of brain activation with respect to motor recovery in the first weeks after stroke. The following section of this general discussion will explain how the restitution of motor control early after stroke can be explained by neuronal mechanisms underlying motor recovery after stroke. In addition, the implications for neurorehabilitation as well as directions for future research will be discussed.

EXPLAINING RESTITUTION OF MOTOR CONTROL EARLY AFTER STROKE

Spontaneous neurological recovery, which typically occurs within the first weeks after stroke,[17,18] may be an important underlying mechanism for the time-dependent restitution of motor control during the first 8 weeks after stroke. Salvation of penumbral tissue is probably an important underlying mechanism in the first hours to days after stroke.[18,19] The penumbra is an area with reduced blood flow that surrounds the ischemic core. Neurons in this area are electrically silent, but the blood flow is still above the required threshold of 8.43 ml/100 ml/min to maintain necessary metabolic processes to keep neurons alive.[20] Reperfusion during the first hours to days after stroke is essential to prevent irreversible damage to penumbral neurons and to restore their electric activity. Salvation of penumbral tissue by reperfusion may occur spontaneously as a result of angiogenesis [21] or as a result of intravenous intervention using recombinant tissue plasminogen activators (rtPA) such as alteplase.[22]

Next to salvation of penumbral tissue, alleviation of diaschisis may also be responsible for the observed restitution of motor control early after stroke.[23,24] Diaschisis or cerebral shock, is a mechanism that was first described by Von Monakow [25] and involves a down regulation of metabolic activity in brain areas that are anatomically connected to the lesion.[24] The impact of diaschisis may be disastrous, since the volume of down regulated metabolism in the brain due to diaschisis may be more than 13 times larger than the ischemic core with irreversible neuronal damage.[26] The exact time course of alleviation of diaschisis is unclear, however, studies with serial measurements in time indicate that cerebral blood flow

and electric activity at the contralesional hemisphere mainly increase within the first 2 months after stroke.[23] Above findings suggests that reactivation of the suppressed brain areas (i.e. alleviation of diaschisis) plays an important role in motor recovery early after stroke.[3]

Neuronal reorganization is probably an important mechanism underlying alleviation of diaschisis.[18,26] For instance, animal models showed that cortical areas with a suppressed metabolic activity show overlap with areas with increased axonal sprouting mediated by growth promoting proteins, such as GAP-43.[26] Axonal sprouting as well as dendritic branching often precede the formation of new synapses, i.e. synaptogenesis, by which the brain may reorganize its neuronal networks.[27] However, it is unclear to what extent this structural plasticity may lead to repair of lost neuronal networks after stroke.[3] Next to structural plasticity, functional reorganization of existing neuronal networks may occur by unmasking of previously unused pathways and strengthening or weakening of existing synapses.[28,29] Hebbian and non-Hebbian learning processes probably play an important role during these functional changes with the brain. Specifically, through a process that is known as long term potentiation (LTP), the strength of synaptic connections within the cortex increases when pre- and postsynaptic neurons are concurrently active.[30–32] Likewise, long term depression (LTD) leads to a weakening of synaptic connections when concurrent activity decreases.[28,31,32] There is considerable evidence that sensory experience [27] and motor learning [28] are important drivers of these processes.[33,34] Therefore, learning-dependent neuronal reorganizations are now considered as an important neuronal substrate for effects of motor learning and neurorehabilitation after stroke.[35]

However, the precise mechanisms by which learning-dependent neuronal reorganization may restore lost cortical and cortico-spinal functions are still poorly understood. Animal models showed that persistent learning-induced changes in synaptic activity may lead to reorganizations of cortical motor representations, suggesting that the cortex is not an array of hard wired, static motor networks, but rather a dynamic system that is capable of reorganizing its somatotopic representation.[36–38] However, several studies in humans suggest that it is unlikely that secondary sensorimotor areas are able to take over the actions of the damaged

primary motor system after stroke.[39,40] In addition, a study that combined TMS with fMRI has shown that a shift of activation from the primary motor cortex to secondary sensorimotor areas is negatively related to the integrity of the cortico-spinal tract.[40] Therefore, it is still unclear whether activation in secondary sensorimotor areas should be considered as a reflection of neuronal reorganization, or rather as an attempt to generate compensatory motor commands via alternative descending systems when the cortico-spinal tract is damaged.

These alternative descending systems probably involve a predominant ipsilateral cortico-bulbo-spinal descending tract.[41,42] This tract consists of ipsilateral cortical projections onto structures in the brain stem, such as the reticular formation, which subsequently project onto motor neurons in the spinal cord.[41,42] This indirect ipsilateral system primarily innervates trunk and proximal arm musculature. Reliance on reticular-spinal pathways have been associated with unselective contractions of either the flexor or extensor muscles leading to the typical basic flexion and extension synergies.[42,43]

The current thesis shows that patients demonstrate dissociations from the basic flexion synergy as a function of time poststroke.[44] This finding suggests that the employment of ipsilateral cortico-bulbo-spinal systems decreased over time, whereas the reliance on the residual capacity of the cortico-spinal tract increased. Therefore, early after stroke, there is probably some unmasking of contralesional and indirect cortico-bulbo-spinal systems,[41] whereas true neurological recovery in the ipsilesional hemisphere may have led to the restitution of quality of motor control during the first 8 weeks after stroke.[18] The current thesis also showed that brain activation patterns are associated to quality of motor control as reflected by smoothness or jerkiness. Jerkiness appeared to be positively associated with activation in secondary sensorimotor areas in affected and non-affected hemispheres as well as bilateral recruitment in the cerebellum. This positive association suggests that secondary sensorimotor areas and the cerebellum are recruited to correct for movement errors based on afferent feedback loops when accurate feedforward control by the primary motor system is disrupted.[45,46]

The findings of the current thesis have important implications for our understanding of upper limb motor recovery after stroke. Most likely, improvements

in quality of motor control, reflected by restitution of upper limb motor control and an increase in smoothness, are related to restitution or preservation of neuronal activation patterns. By contrast, compensatory mechanisms, based on the recruitment of new degrees of freedom and the use of afferent feedback control, are probably related to substitution of neural function. This suggests that cortical map plasticity is not a mechanism to take over neuronal functions that are lost after stroke, but is rather a reflection of adaptive motor strategies during functional tasks after stroke. Therefore, the motor recovery of the paretic upper limb after stroke is probably associated with a normalization of brain activation patterns and quality of motor control during the first 8 weeks after stroke.[17] The next section describes how this spontaneous restitution of motor control early after stroke leads to new implications for neurorehabilitation.

IMPLICATIONS FOR NEUROREHABILITATION

There is still a paucity of evidence showing that rehabilitative interventions are able to improve true motor recovery or restitution of motor control.[47,48] Several systematic reviews of randomized controlled trials (RCTs) suggest that the impact of therapeutic interventions at the impairment level is limited and mainly driven by task- and context specific motor compensations.[48–51] However, it remains unclear what patients learn when they show improvements in motor performance.[2,3,52] Longitudinal studies suggest that progress of time poststroke is the most important factor that explains improvements in body functions, such as strength,[53] visual neglect [54] and, as shown in the current thesis, upper limb synergies [44] and smoothness.[55] However, the impact of this time-dependent spontaneous process of neurological recovery is still a neglected issue in neuroscience, despite the long existing observations of Twitchell in 1951,[43] Newman in 1972 [56] and Gresham in 1986.[57] Neurorehabilitation is often thought of as a process that aims to enhance the time-dependent capacity of the brain to restore its function.[58] Therefore, due to the lack of insight into this time-dependent process therapeutic strategies in neurorehabilitation may still be suboptimal. The time-dependent restitution of quality of motor control, as presented in this thesis, contribute to improved insight into spontaneous neurological recovery and lead

to important recommendations for the timing and optimization of interventions in neurorehabilitation.

Aim and timing of therapeutic interventions

The early restitution of motor control during the first 8 weeks after stroke suggests that the brain has an increased potential to restore quality of motor control during this critical time-window. The implication of this finding is that the aim of therapeutic interventions should change as a function of time after stroke.[48] Within the first 8 weeks after stroke, interventions should be targeted at reducing motor impairments and restitution of motor control in order to enhance the spontaneous occurring processes of neurological recovery. Moreover, compensatory strategies within the first 8 weeks should be avoided since allowance of compensations early after stroke may lead to a masked ability to restore quality of motor control and eventually to limited functional outcome after stroke.[59] After the first 8 weeks, when the potential for true neurological recovery is reduced, the focus of treatment strategies should change towards improving task and context specific adaptation strategies while allowing, for example, compensatory trunk movements. When unilateral attempts to execute functional tasks fail, the focus of therapy may shift from unilateral to bimanual task-oriented training.

Importantly, restitution of motor control by normalizing movement patterns is the most important aim of the Bobath Concept.[60] However, there is still no evidence that this concept is superior to other approaches.[50] In most RCTs investigating the effects of the Bobath Concept, therapy started at arbitrary time-points and often after the critical time-window of 8 weeks after stroke.[50] In addition, these RCTs generally used clinical assessment scales to measure therapy induced effects, whereas 3D kinematic measurements of upper limb movements are lacking. Therefore, the absence of differential effects in favour of Bobath may be caused by poor timing of therapy as well as a lack of valid methods to measure quality of motor control. Indeed, animal studies support the hypothesis that the effect of impairment focused therapies is most effective early after stroke and declines as a function of time.[61,62] This enhanced potential for early applied therapies in rats is supported by recent findings suggesting that there is a critical time-window in the first 3 to 4 weeks after stroke during which

growth promoting factors, such as GAP-43, are upregulated.[63] After the first 3 weeks, growth inhibiting factors, such as NOGO, become upregulated as well, which may explain the declining effects of impairment focused therapies in animal models as a function of time poststroke.[63]

However, in patients with stroke there is only a limited number of RCTs that have investigated the effects of therapeutic interventions aimed at reducing motor impairments and improving quality of motor control in the first 8 weeks after stroke. Therefore it is still unclear whether such early started interventions can enhance restitution of motor control after stroke. Furthermore, it is unclear whether allowance of compensation strategies early after stroke leads to misuse of the paretic upper limb after stroke as well as a masked ability to restore quality of motor control. The distinction between restitution and substitution of motor control, as presented in the current thesis, is important to improve existing therapeutic interventions in neurorehabilitation early after stroke. However, future RCTs using intensively repeated 3D kinematic measurements are essential to assess the effects of such therapeutic strategies in the first 8 weeks after stroke.

Constraint-induced movement therapy is an intervention which may potentially be effective to enhance restitution of motor control in the first 8 weeks after stroke. A recent meta-analysis based on 5 RCTs within the first 10 weeks after stroke showed that there is a trend towards positive effects in terms body functions and activities in favour of CIMT or modified versions of this therapy (mCIMT) compared with usual care.[64] CIMT and mCIMT are aimed at reversing or preventing learned non-use, i.e. the persistent use of the non-paretic upper limb during activities of daily living (ADL).[59] However, detailed intervention protocols are generally not provided whereas 3D kinematic measurements are lacking. As a consequence, it is unclear *what* patients exactly learn during mCIMT in terms of quality of motor control.[64]

Future RCTs should therefore investigate whether (m)CIMT applied in the first 8 weeks after stroke can improve restitution of motor control as assessed with 3D kinematics. For instance, future RCTs may investigate whether the constraining the non-paretic limb and the trunk [65] during (m)CIMT can reduce the reliance on compensation movements with the non-paretic upper limb and trunk, respectively. Furthermore, these studies may use shaping to divide reach-to-grasp movements

into separate reaching and grasping movements in order to reduce the number of processes that need to be controlled in parallel.[6,66] This approach might reduce the complexity of the task which may have a beneficial effect on the smoothness of upper limb movements as well as the quality of the control over the various degrees of freedom in the paretic upper limb.

A critical concern with respect to most of the current treatment programmes in neurorehabilitation is that the intensity is often not sufficient to exceed threshold levels for improving true neurological recovery.[58] Robotic devices may provide a solution to this problem, since these devices allow patients to receive therapy in a 'classroom' format or even in their home environment which may lead to an increase in hours spent on rehabilitation as well as improved cost-effectiveness.[67] In addition, there is strong evidence that robotic-assisted therapies can improve proximal upper limb function and the ability to perform functional tasks after stroke.[e.g. 68–70]

However, it is largely unclear how robotic devices should be designed in order to improve restitution of motor control early after stroke. The results of the intensively repeated 3D kinematic measurements in the current thesis suggest that robotic devices should be aimed at improving dissociated and smooth reaching patterns of the paretic upper limb in the first 8 weeks after stroke. In addition, future RCTs are needed to investigate the beneficial effects of these robotic devices compared to robotic devices that allow adaptive motor control. In these RCTs the complexity of performing dissociated upper limb movements may be adjusted to the capabilities of the patient by systematically imposing an abduction load at the shoulder. Since shoulder abduction is coupled to elbow flexion within the basic flexion synergy, an increase in shoulder abduction load will increase the difficulty of performing dissociated upper limb movements. A recent study confirms that a systematic increase in shoulder abduction load during upper limb training leads to improvements in reaching distance in patients with chronic stroke.[68] Based on the spontaneous improvements in performing dissociated upper limb movements within the first 8 weeks after stroke, it can be hypothesized that such robotic-assisted interventions may even be more effective early after stroke.

Another advantage of robotic devices is that they can measure the kinematics and kinetics of upper limb movements *during* therapy. Most of the current RCTs

measure motor function before and after a specific intervention using traditional clinical assessment scales. However, these clinical scales provide little insight into how quality of motor control changes during varying task-specific conditions. Incorporation of joint kinematics as well as torque directions measured by robotic-devices during therapy may lead to improved understanding of *how* robotic-assisted interventions influence quality of motor control after stroke.[67,71]

Finally, the distinction between restitution and substitution of motor control may be important for the application of virtual reality in patients with stroke. Virtual reality can be defined as "a multisensory experience that permits feedback motor learning in a computer generated virtual environment." [72, p 13] In particular, two types of feedback are distinguished: knowledge of performance and knowledge of results.[73] Knowledge of performance (KP) provides information about the quality of motor control or the way in which the patient performs a particular task, whereas knowledge of results (KR) indicates to what extent a particular task goal is achieved. A recent systematic review suggested that both KP and KR may lead to improvements in quality of motor control, with the greatest effects in favour of KP.[74] However, convincing evidence for the early phase after stroke is still lacking, since most of the trials that were included in this review used small sample sizes and were performed in the chronic phase after stroke. Therefore, future studies should investigate whether quality of motor control during the first 8 weeks after stroke can be enhanced with virtual reality by providing KP, including feedback about trunk movements, basic synergistic elbow-shoulder couplings and smoothness.

Implications for patients with an initial unfavourable prognosis

Studies using TMS have suggested that the functional outcome after stroke is critically dependent on the integrity of the cortico-spinal tract.[75,76] Disruption of the cortico-spinal tract mainly impairs the control over the finger extensors, which probably explains why the inability to extend the fingers early after stroke predicts poor upper limb recovery after stroke.[77]

The time-dependent improvements in dissociated and smooth upper limb movements, as presented in this thesis, are mainly based on patients with an initial favourable prognosis for recovery of upper limb function, reflected by some ability

to extend the fingers in the first week after stroke.[7] Patients with an unfavourable prognosis for upper limb recovery who may have had complete disruptions of the cortico-spinal tract, could not be included due to insufficient voluntary control over the paretic upper limb and the inability to perform reach-to-grasp movements. Based on the fact that these severely affected patients could not be included, we hypothesize that residual cortico-spinal tract function may be a prerequisite for restitution of motor control after stroke. Future studies, including the EXPLICIT-stroke programme, are necessary to assess this hypothesis by means of TMS and 3D kinematic measurements in the same cohort of patients.

The importance of the integrity of the cortico-spinal tract further suggests that interventions for patients with an unfavourable prognosis should specifically be directed at regaining some cortico-spinal tract function. Within EXPLICIT-stroke, the effects of early applied EMG-triggered neuromuscular stimulation (EMG-NMS) are investigated in patients with an unfavourable prognosis of the paretic upper limb.[4] However, there is no evidence that therapeutic interventions including EMG-NMS can restore some cortico-spinal function in order to induce improvements of upper limb function in this group of patients.[78] Unfortunately, this lack of effect supports the current view that true neurological recovery, particularly with respect to cortico-spinal tract function cannot be enhanced by means of currently available therapeutic interventions. Therefore, novel and innovative interventions should be developed to achieve true neurological recovery in patients with an unfavourable prognosis for upper limb recovery after stroke.

Innovative methods to enhance true neurological recovery after stroke

Transcranial direct current stimulation (tDCS) in combination with exercise therapy may be a method to enhance learning-dependent plasticity. By applying anodal tDCS the excitability of the ipsilesional hemisphere can be enhanced, whereas cathodal tDCS can be used to reduce the cross talk of the disinhibited, overactive contralesional hemisphere.[79] However, future studies should investigate whether these forms of tDCS may induce a persistent focus of activation toward the ipsilesional hemisphere and, with that, restitution of neuronal function and quality of motor control. Moreover, these studies should combine simultaneous application of tDCS and

mCIMT or robot-assisted interventions that do not allow compensatory strategies, in order to enhance the time-dependent restitution of motor control in the first 8 weeks after stroke.

Another innovative method to enhance motor recovery in the first 8 weeks after stroke is the application of pharmacological agents. Animal studies early after stroke reported favourable effects of therapeutic interventions combined with amphetamine treatment.[63,80] Furthermore, application of $GABA_A$ receptor α5 inverse agonists in mice reduces tonic neuronal inhibition of the peri-infarct zone and lead to improvements in motor function.[81] Recently, Chollet and colleagues showed that motor recovery within the first 3 months after stroke can be enhanced with description of fluoxetine combined with physiotherapy.[82] Nonetheless, there are only a few RCTs that have investigated the effects of pharmacological therapy on motor recovery early after stroke. In addition, effects of pharmacological treatment on the quality of motor control after stroke, measured with 3D kinematics, have to date not been investigated. Therefore, future RCTs with intensively repeated clinical assessment scales as well as 3D kinematic measurements should investigate the promising effects of pharmacological therapy on quality of motor control after stroke.

METHODOLOGICAL CONSIDERATIONS

Clinical 3D kinematic analyses are complex and often time consuming. Accurate recordings of upper limb movements typically require elaborate marker placement as well as anatomical calibration procedures. Furthermore, the immobility of most 3D kinematic motion trackers, requires patients to travel to the motion laboratory for each measurement in which they participate. This requirement may explain why most of the recent 3D kinematic studies in the literature were performed in the chronic phase after stroke and included only few measurements. However, to understand the time-dependent pattern of recovery, measurements should be intensively repeated at fixed time-points after stroke.[57] In the current thesis a protocol was presented for feasible on-site 3D kinematic measurements of the paretic upper limb and trunk in patients with stroke. This protocol eliminated the physical burden associated with travelling to the motion analysis laboratory and this protocol may

therefore be considered as an innovative aspect of EXPLICIT-stroke. In the future, this protocol may even be improved given the latest technological developments. For instance, wireless systems have been developed using inertial and magnetic sensors, which can already be used for gait analysis [83,84] as well as shoulder-elbow analysis.[85] There are also systems available that do not even use markers or sensors, but directly capture the motions of the moving body or limb without the need of any anatomical calibration prior to the measurement.[86] Although the accuracy and reliability of such systems still has to be confirmed, these systems may substantially increase the feasibility of performing clinical 3D kinematics in patients early after stroke. Future research programmes should therefore investigate the potential of using such motion trackers for on-site 3D kinematic motion recordings in patients early after stroke.

The protocol for on-site 3D kinematic measurements served as a basis for all measurements and analyses in the current thesis. Importantly, 3D kinematics were collected of the entire paretic upper limb, that is, the trunk, shoulder, elbow, wrist, hand and fingers. However, in the literature different anatomical models and rotation orders are used to describe the movements of each individual joint, which is a disadvantage for the comparability between studies. With respect to the shoulder for instance, an anteflexion followed by an abduction results into a different joint configuration compared to an abduction followed by an anteflexion. Fortunately, the International Society of Biomechanics provided guidelines regarding the definitions of joint axes and rotation orders in order to standardize 3D kinematic analyses in humans.[87] These guidelines were used to calculate the trunk and joint angles during the reach-to-grasp task in the current thesis.

Next to the on-site 3D kinematic measurements, the application of PCA to investigate longitudinal changes in synergistic couplings between joints is a novelty in the literature on motor recovery of the paretic upper limb early after stroke.[88] PCA is a powerful method to investigate large multivariate time-series as was the case in this thesis. The changes in the joint couplings that are identified with PCA improve our understanding of *how* patients with stroke master the degrees of freedom of the paretic upper limb during reach-to-grasp, which extends on previous studies that are often based on clinical assessment scales or basic 3D kinematic measures such as maximum range of motion and movement speed.

Furthermore, the use of 3D kinematics in order to understand findings obtained with fMRI measurements is an important methodological aspect of the current thesis. Most previous fMRI studies have related cortical activation patterns to traditional clinical assessment scales. However, these scales cannot distinguish between restitution of motor control and substitution of motor control by compensation strategies. This is a major disadvantage in previous fMRI studies, since compensation movements are assumed to confound the relationship between motor recovery and cortical activation patterns.[3] The use of smoothness as a measure of quality of motor control in the current thesis is a promising method to explain changes in cortical activation patterns as measured with fMRI. Specifically, this method led to the finding that at week 5 after stroke, recruitment of secondary sensorimotor areas is related to poor quality of motor control, which seems to contradict the hypothesis that spared cortical areas can take over lost neurological functions after stroke. Furthermore, this relation was absent at week 26 after stroke suggesting that the role of additionally recruited secondary sensorimotor areas during motor recovery depends on time poststroke. This time dependency is in line with previous findings based on dynamic causal modelling of cortical activity from the acute to the chronic phase after stroke.[89]

However, fMRI and 3D kinematics were not conducted simultaneously in the current thesis. The motor paradigm during the fMRI measurements in the current thesis consisted of a finger flexion-extension task, whereas a reach-to-grasp task was used during the 3D kinematic measurements. Causal relations between cortical activation patterns and quality of motor control cannot be established. In addition, cortical activation patterns could only be related to the quality of grasping movements of the fingers, whereas proximal upper limb and trunk movements during reach-to-grasp had to be disregarded. The understanding of changes in cortical plasticity after stroke may benefit from methods that allow concomitant brain imaging and 3D kinematic measurement of reach-to-grasp movements in patients with stroke. For instance, magnetic encephalography (MEG) and electroencephalography (EEG) allow patients to perform reaching tasks in a seated position during scanning. As a consequence, these techniques may lead to promising findings with respect to the neuronal control of reach-to-grasp movements in patients with stroke. Moreover, the high temporal resolution of these techniques allows the allocation of cortical

activity to movement planning, which typically occurs milliseconds before movement initiation, or online motor control during the movement.[90] Unfortunately, the spatial resolution of MEG and EEG is lower compared to fMRI, which may impede accurate differentiation between cortical areas.[90] A technical challenge for future brain imaging studies will therefore be to improve the spatial accuracy of EEG and MEG and to use these techniques concomitantly with 3D kinematics during reach-to-grasp tasks in patients with stroke.

DIRECTIONS FOR FUTURE TRANSLATIONAL RESEARCH

To date, there is only a limited number of RCTs that investigated the effect of impairment focused therapies for the paretic upper limb in the first 8 weeks after stroke.[4,64] To obtain evidence that therapeutic strategies in neurorehabilitation can enhance restitution of motor control early after stroke, future RCTs should investigate the effects of interventions that are specifically aimed at reducing motor impairments and improving quality of motor control in the first 8 weeks after stroke. There is evidence that moderately to mildly affected patients may benefit from mCIMT,[64,91] however, the added value of mCIMT applied in the first 10 weeks after stroke, compared to later applications of this therapy remains to be proven. Evidence based therapeutic interventions for patients with a severe upper limb paresis and an initial unfavourable prognosis are even completely lacking. Furthermore, 3D kinematic analyses are often lacking in RCTs aimed to assess the effects of interventions that are specifically targeted at reducing motor impairments or improving quality of motor control early after stroke.

EXPLICIT-stroke, a translational multi-center research programme in the Netherlands, investigates the effect of early applied upper limb stimulation within the first 5 weeks on functional outcome after stroke, while 3D kinematic analyses are used to measure improvements in quality of motor control and to gain insight into restitution and substitution of motor control.[4] Patients with a favourable prognosis for regaining upper limb function, as reflected by the ability to show some finger extension in the first week after stroke, are randomized for either a 3 week mCIMT intervention, starting within 2 weeks after stroke, or conventional therapy according

to the current guidelines of rehabilitation after stroke.[4,92] A detailed description of the mCIMT protocol has been published elsewhere.[1] Patients with an unfavourable prognosis for regaining upper limb function, are randomized for either EMG-triggered neuromuscular stimulation (EMG-NMS) of the finger extensors or conventional therapy.[4] EXPLICIT-stroke started in 2008 and involves 4 participating University Medical Centers (LUMC, UMCU, UMCN and VUmc), one technical university (TU-DELFT), 8 general hospital stroke units and 14 rehabilitation centers, yielding a total of 27 centers in the consortium (www.explicit-stroke.nl).[4] Hence, EXPLICIT-stroke is currently the largest RCT on early recovery of upper limb function after stroke and will be an important step to provide insight into how therapeutic interventions may be able to improve motor function as well as quality of motor control early after stroke.

In future research within neurorehabilitation, translational research programmes, such as EXPLICIT-stroke, should play a central role. Within such programmes, pre-clinical studies are needed to obtain more insight into the mechanisms underlying motor recovery after stroke. Concomitant measurements with multiple techniques such as EEG, haptic robotics and 3D kinematics should be used to investigate how the brain controls reflexive and voluntary muscular contractions as well as functional movements. Furthermore, studies should assess how longitudinal changes in brain function as well as quality of motor control depend on the integrity of the cortico-spinal tract, as measured with TMS or DTI.

In RCTs, these techniques should be applied next to traditional clinical assessment scales to measure the effects of innovative therapies. In particular, application of tDCS and pharmacological interventions combined with intensive mCIMT or robot-assisted treatment may provide a promising means to stimulate true neurological recovery early after stroke. A specific challenge will be to enhance true neurological recovery in patients with an initial unfavourable prognosis, as reflected by the inability to extend the fingers early after stroke. This lack of finger extension is assumed to be a reflection of a severely disrupted cortico-spinal tract, which is probably the reason why current interventions are still ineffective for this subgroup of patients. The most important challenge that neurorehabilitation is currently facing is to enhance true neurological recovery, particularly with respect to the cortico-spinal tract, in order to improve quality of motor control beyond mechanisms of spontaneous neurological recovery.

REFERENCES

1. Nijland RHM, van Wegen EEH, van der Krogt HJM, Bakker C, Buma FE, Klomp A, van Kordelaar J, Kwakkel G. Characterizing the Protocol for Early Modified Constraint-induced Movement Therapy in the EXPLICIT-Stroke Trial. *Physiother Res Int*. 2012;
2. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabil Neural Repair*. 2009;23:313–9.
3. Buma FE, Kwakkel G, Ramsey NF. Understanding upper limb recovery after stroke. *Restor Neurol Neurosci*. 2013;31:707-22.
4. Kwakkel G, Meskers CGM, van Wegen EEH, Lankhorst GJ, Geurts ACH, van Kuijk AA, Lindeman E, Visser-Meily A, de Vlugt E, Arendzen JH. Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design. *BMC Neurol*. 2008;8:49.
5. Cirstea CM, Levin MF. Compensatory strategies for reaching in stroke. *Brain*. 2000;123:940–53.
6. Doeringer JA, Hogan N. Serial processing in human movement production. *Neural Netw*. 1998;11:1345–1356.
7. Nijland RHM, van Wegen EEH, Harmeling-van der Wel BC, Kwakkel G. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke*. 2010;41:745–50.
8. Hogan N, Flash T. Moving gracefully: quantitative theories of motor coordination. *Trends Neurosci.* 1987;10:170–174.
9. Flash T, Hogan N. The Coordination of Arm Movements: An Experimentally Confirmed Mathematical Model. *J Neurosci*. 1985;5:1688–1703.
10. Hogan N, Sternad D. Sensitivity of Smoothness to Movement Duration, Amplitude, and Arrests. *J Mot Behav*. 2009;41:529–34.
11. Rohrer B, Fasoli SE, Krebs HI, Hughes R, Volpe B, Frontera WR, Stein J, Hogan N. Movement smoothness changes during stroke recovery. *J Neurosci*. 2002;22:8297–304.
12. Todorov E. Optimality principles in sensorimotor control (review). *Nat Neurosci*. 2004;7:907–915.
13. Trombly CA. Deficits of reaching in subjects with left hemiparesis: a pilot study. *Am J Occup Ther*. 1992;46:887–897.
14. McCrea PH, Eng JJ. Consequences of increased neuromotor noise for reaching movements in persons with stroke. *Exp Brain Res*. 2005;162:70–7.
15. Milner TE. A model for the generation of movements requiring endpoint precision. *Neuroscience*. 1992;49:487–96.
16. Winstein CJ, Pohl PS. Effects of unilateral brain damage on the control of goal-directed hand movements. *Exp Brain Res*. 1995;105:163–74.
17. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*. 2008;63:272–87.
18. Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci*. 2004;22:281–99.
19. Phan TG, Wright PM, Markus R, Howells DW, Davis SM, Donnan GA. Salvaging the ischaemic penumbra: more than just reperfusion? *Clin Exp Pharmacol Physiol*. 2002;29:1–10.

20. Marchal G, Benali K, Iglesias S, Viader F, Derlon JM, Baron JC. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. *Brain*. 1999;122:2387–400.
21. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Curr Cardiol Rev*. 2010;6:238–44.
22. Baron J-C. How healthy is the acutely reperfused ischemic penumbra? *Cerebrovasc. Dis.* 2005;20 Suppl 2:25–31.
23. Andrews RJ. Transhemispheric diaschisis. A review and comment. *Stroke*. 1991;22:943–49.
24. Seitz RJ, Azari NP, Knorr U, Binkofski F, Herzog H, Freund HJ. The role of diaschisis in stroke recovery. *Stroke*. 1999;30:1844–50.
25. Von Monakow C. Diaschisis [1914 article translated by G Harris]. In: Pribram KH, editor. Brain and Behavior I: Moods, State and Mind. Baltimore: Penguin; 1969. p. 27–36.
26. Carmichael ST, Tatsukawa K, Katsman D, Tsuyuguchi N, Kornblum HI. Evolution of diaschisis in a focal stroke model. *Stroke.* 2004;35:758–63.
27. Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature*. 2002;420:788–94.
28. Boroojerdi B, Ziemann U, Chen R, Bütefisch CM, Cohen LG. Mechanisms underlying human motor system plasticity. *Muscle Nerve*. 2001;24:602–13.
29. Jacobs KM, Donoghue JP. Reshaping the Cortical Motor Map by Unmasking Latent Intracortical Connections. *Science (80-.).* 1991;251:944–947.
30. Teyler TJ, DiScenna P. Long-term potentiation. *Ann Rev Neurosci*. 1987;10:131–61.
31. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*. 2001;24:1000–19.
32. Cooke SF, Bliss TVP. Plasticity in the human central nervous system. *Brain*. 2006;129:1659–73.
33. Liepert J, Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E, Weiller C. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett*. 1998;250:5–8.
34. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J. Neurophysiol.* 1998;80:3321–5.
35. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*. 1996;272:1791–4.
36. Teskey GC, Monfils M-H, VandenBerg PM, Kleim JA. Motor map expansion following repeated cortical and limbic seizures is related to synaptic potentiation. *Cereb Cortex*. 2002;12:98–105.
37. Donoghue JP, Suner S, Sanes JN. Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid reorganization following motor nerve lesions. *Exp Brain Res*. 1990;79:492–503.
38. Hess G, Donoghue JP. Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. *J Neurophysiol*. 1994;71:2543–7.
39. Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, Pierot L, Burnod Y, Maier MA. Longitudinal Study of Motor Recovery After Stroke: Recruitment and Focusing of Brain Activation. *Stroke*. 2002;33:1610–1617.

40. Ward NS, Newton JM, Swayne OBC, Lee L, Thompson AJ, Greenwood RJ, Rothwell JC, Frackowiak RSJ. Motor system activation after subcortical stroke depends on corticospinal system integrity. *Brain*. 2006;129:809–19.
41. Schwerin S, Dewald JPA, Haztl M, Jovanovich S, Nickeas M, MacKinnon C. Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: implications for the expression of arm synergies. *Exp Brain Res*. 2008;185:509–19.
42. Ellis MD, Drogos J, Carmona C, Keller T, Dewald JPA. Neck rotation modulates flexion synergy torques, indicating an ipsilateral reticulospinal source for impairment in stroke. *J Neurophysiol*. 2012;108:3096–104.
43. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74:443–80.
44. Van Kordelaar J, van Wegen EEH, Nijland RHM, Daffertshofer A, Kwakkel G. Understanding Adaptive Motor Control of the Paretic Upper Limb Early Poststroke: The EXPLICIT-stroke Program. *Neurorehabil Neural Repair*. 2013;27:854–63.
45. Castiello U. The neuroscience of grasping. *Nat Rev Neurosci*. 2005;6:726–36.
46. Ramnani N, Toni I, Passingham RE, Haggard P. The cerebellum and parietal cortex play a specific role in coordination: a PET study. *Neuroimage*. 2001;14:899–911.
47. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. *Curr Opin Neurol*. 2006;19:84–90.
48. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet*. 2011;377:1693–702.
49. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol*. 2009;8:741–54.
50. Kollen BJ, Lennon S, Lyons B, Wheatley-Smith L, Scheper M, Buurke JH, Halfens J, Geurts ACH, Kwakkel G. The effectiveness of the Bobath concept in stroke rehabilitation: what is the evidence? *Stroke.* 2009;40:e89–97.
51. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. *Neurorehabil Neural Repair*. 2009;22:111–21.
52. Van Kordelaar J, van Wegen EEH, Nijland RHM, de Groot JH, Meskers CGM, Harlaar J, Kwakkel G. Assessing Longitudinal Change in Coordination of the Paretic Upper Limb Using On-Site 3-Dimensional Kinematic Measurements. *Phys Ther*. 2012;92:142–51.
53. Kwakkel G, Kollen BJ, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke*. 2006;37:2348–53.
54. Nijboer TCW, Kollen BJ, Kwakkel G. Time course of visuospatial neglect early after stroke: A longitudinal cohort study. *Cortex.* 2013;49:2021–7.
55. Van Kordelaar J, van Wegen EEH, Kwakkel G. The impact of time on quality of motor control of the paretic upper limb after stroke. *Arch Phys Med Rehabil*. 2013;X:X.
56. Newman M. The Process of Recovery: After Hemiplegia. *Stroke*. 1972;3:702–710.
57. Gresham G. Stroke outcome research. *Stroke*. 1986;17:358–60.
58. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair*. 2012;26:923–31.
59. Sunderland A, Tuke A. Neuroplasticity, learning and recovery after stroke: A critical evaluation of constraint-induced therapy. *Neuropsychol Rehabil*. 2005;15:81–96.
60. Bobath B. Adult hemiplegia: evaluation and treatment. First ed. London: Heinemann Medical; 1970.

61. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci*. 2004;24:1245–54.
62. Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J Neurosci*. 2001;21:5272–80.
63. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci*. 2009;10:861–72.
64. Nijland RHM, Kwakkel G, Bakers J, van Wegen EEH. Constraint-induced movement therapy for the upper paretic limb in acute or sub-acute stroke: a systematic review. *Int J Stroke*. 2011;6:425–33.
65. Michaelsen SM, Dannenbaum R, Levin MF. Task-specific training with trunk restraint on arm recovery in stroke: randomized control trial. *Stroke.* 2006;37:186–92.
66. Taub E, Crago JE, Burgio LD, Groomes TE, Cook EW, Deluca SC, Miller NE. An operant approach to rehabilitation medicine: overcoming learned non-use by shaping. *J Exp Anal Behav*. 1994;61:281–293.
67. Krebs HI, Volpe BT, Aisen ML, Hogan N. Increasing productivity and quality of care: Robot-aided neuro-rehabilitation. *J Rehabil Res Dev*. 2000;37:639–652.
68. Ellis MD, Sukal-Moulton TM, Dewald JP a. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. *Neurorehabil Neural Repair*. 2009;23:862–9.
69. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. *Stroke.* 2005;36:1960–6.
70. Masiero S, Celia A, Rosati G, Armani M. Robotic-assisted rehabilitation of the upper limb after acute stroke. *Arch Phys Med Rehabil*. 2007;88:142–9.
71. Loureiro RC V, Harwin WS, Nagai K, Johnson M. Advances in upper limb stroke rehabilitation: a technology push. *Med Biol Eng Comput*. 2011;49:1103–18.
72. Subramanian SK, Lourenço CB, Chilingaryan G, Sveistrup H, Levin MF. Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. *Neurorehabil Neural Repair*. 2013;27:13–23.
73. Cirstea MC, Levin MF. Improvement of arm movement patterns and endpoint control depends on type of feedback during practice in stroke survivors. *Neurorehabil Neural Repair*. 2007;21:398–411.
74. Subramanian SK, Massie CL, Malcolm MP, Levin MF. Does provision of extrinsic feedback result in improved motor learning in the upper limb poststroke? A systematic review of the evidence. *Neurorehabil Neural Repair*. 2010;24:113–24.
75. Van Kuijk AA, Pasman JW, Hendricks HT, Zwarts MJ, Geurts ACH. Predicting hand motor recovery in severe stroke: the role of motor evoked potentials in relation to early clinical assessment. *Neurorehabil Neural Repair*. 2009;23:45–51.
76. Hendricks HT, Pasman JW, Merx JL, van Limbeek J, Zwarts MJ. Analysis of recovery processes after stroke by means of transcranial magnetic stimulation. *J Clin Neurophysiol*. 20:188–95.
77. Lemon RN, Landau WM, Tutssel D, Lawrence DG. Lawrence and Kuypers (1968a, b) revisited: copies of the original filmed material from their classic papers in Brain. *Brain*. 2012;135:2290–5.

78. Meilink A, Hemmen B, Seelen HAM, Kwakkel G. Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. *Clin Rehabil*. 2008;22:291–305.

79. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. *Arch Neurol*. 2008;65:1571–6.

80. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science*. 1982;217:855–7.

81. Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature*. 2010;468:305–9.

82. Chollet F, Tardy J, Albucher J-F, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B, Moulin T, Marque P, Pariente J, Arnaud C, Loubinoux I. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol.* 2011;10:123–30.

83. Van den Noort JC, Ferrari A, Cutti AG, Becher JG, Harlaar J. Gait analysis in children with cerebral palsy via inertial and magnetic sensors. *Med Biol Eng Comput*. 2013;51:377–86.

84. Cutti AG, Ferrari A, Garofalo P, Raggi M, Cappello A, Ferrari A. "Outwalk": a protocol for clinical gait analysis based on inertial and magnetic sensors. *Med Biol Eng Comput*. 2010;48:17–25.

85. Cutti AG, Giovanardi A, Rocchi L, Davalli A, Sacchetti R. Ambulatory measurement of shoulder and elbow kinematics through inertial and magnetic sensors. *Med Biol Eng Comput*. 2008;46:169–78.

86. Brokaw EB, Lum PS, Cooper RA, Brewer BR. Using the kinect to limit abnormal kinematics and compensation strategies during therapy with end effector robots. *IEEE Int Conf Rehabil Robot*. 2013;2013:1–6.

87. Wu G, van der Helm FCT, Veeger DHEJ, Makhsous M, Van Roy P, Anglin C, Nagels J, Karduna AR, McQuade K, Wang X, Werner FW, Buchholz B. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion - Part II: shoulder, elbow, wrist and hand. *J Biomech*. 2005;38:981–992.

88. Daffertshofer A, Lamoth CJC, Meijer OG, Beek PJ. PCA in studying coordination and variability: a tutorial. *Clin Biomech (Bristol, Avon)*. 2004;19:415–28.

89. Rehme AK, Eickhoff SB, Wang LE, Fink GR, Grefkes C. Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. *Neuroimage*. 2011;55:1147–58.

90. Ward NS. Future perspective in functional neuroimaging in stroke recovery. *Eura Medicophys*. 2007;43:285–294.

91. Dromerick AW, Birkenmeier RL, Miller JP, Videen TO, Edwards DF. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS). *Neurology*. 2009;73:195–201.

92. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks H, Van der Wees P, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehabil*. 2004;18:833–862.