Monitoring therapy-induced recovery after stroke using functional magnetic resonance imaging (fMRI)

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Abstract: ABSTRACT Stroke often leads to chronic motor disability of the upper limb, which can significantly affect a person's activities of daily living. Recovery of motor function following a stroke is associated with brain reorganization processes that occur within the surviving areas of the sensorimotor network. Although still not fully understood, there is increasing evidence that movement therapy can facilitate recovery of the upper limb by promoting such processes. To develop more efficient rehabilitation strategies, further work is needed to enhance understanding of therapy- induced recovery and its related reorganization patterns. Functional magnetic resonance imaging (fMRI), which allows for the investigation of the human brain's functional organization, is a promising method for studying such patterns (i.e., assessed as task-related brain activation) and can further help to evaluate the effect of therapies in stroke patients. Combining fMRI with compatible robots that guide and monitor the execution of movements during recordings may yield a more reliable evaluation of brain activation patterns over time, thereby advancing our understanding of ongoing reorganization processes. Furthermore, the application of robotic devices can contribute to upper limb rehabilitation by providing new therapeutic approaches that can optimize recovery and help to restore lost functions. The long-term purpose of the current project was to provide a better understanding of therapy- induced brain reorganisation in stroke patients who have entered the chronic stage. With this in mind, the present thesis aimed 1) to improve the assessment of arm movement-related brain activation using fMRI; and 2) to acquire insights into brain reorganization patterns induced by arm therapy. Of primary interest was investigating whether robot-assisted therapy can promote brain reorganization in patients with moderate to severe arm hemiparesis. To develop a robust paradigm that permits the reliable investigation of arm movement-related activation in patients with motor impairments, MaRIA, an MRI-compatible arm robot for elbow flexion and extension, was developed and systematically tested. In this context, two studies were performed. Study 1 tested the quality of fMRI recordings while performing motor tasks with MaRIA and the feasibility of this approach in healthy subjects. Study 2 investigated the brain network, which is activated by active and passive arm movements performed with the device, and tested the reliability of this activation over time by applying several statistical approaches. To meet the second aim, an additional study (Study 3) was performed in which MaRIA was used to investigate therapy-induced brain reorganization in chronic stroke patients suffering from moderate to severe unilateral hemiparesis of the arm. For this third study, the patients were divided into two groups. One group was trained via robot-assisted therapy using the arm rehabilitation robot ARMin, while the other group received conventional therapy. The brain reorganization patterns and improvements in arm function induced by each of these therapy methods were analysed and compared. The present results indicate that MaRIA can be used in the MRI environment without causing artefacts in the fMRI time series or discomfort for the person being assessed. The brain network activated by active and passive arm movements in healthy subjects was consistent with the activation patterns reported in previous publications. Reliability analysis demonstrated robust activation patterns for active movements over time. Brain activation was also quite robust for passive movements and reliability was further improved by including additional information about force and range of motion acquired by the device. The investigation of brain reorganization induced by arm therapy demonstrated that reorganization patterns vary depending on the type of intervention, the degree of

impairment, and the task performed. For both interventions, changes in activation observed immediately after therapy largely persisted at two months of follow-up. Long-term effects were more stable and even more pronounced in patients with moderate impairments than in those with severe deficits. Therapy with ARMin was shown to promote brain reorganization and reduce motor impairment as effectively as conventional therapy, and is, therefore, a promising tool to enhance functional arm recovery, even in patients who have already reached a chronic stage. This work establishes a new approach to reliably assess arm movement-related brain activation in longitudinal studies on patients with motor impairments. It also allows for the evaluation of different therapeutic interventions and brain plasticity following damage to the nervous system. Additionally, the investigation of therapy-induced reorganization provides important knowledge to help us better understand the effects and potential of robot-assisted therapies in stroke patients suffering from chronic moderate or severe deficits of the arm. ZUSAMMENFASSUNG Erleidet eine Person einen Schlaganfall, so führt dies häufig zu motorische Beeinträchtigungen der oberen Extremitäten, welche die Betroffenen in der Alltagsbewältigung deutlich einschränken. Forschungsarbeiten zeigen, dass nach einem Schlaganfall Reorganisationsprozesse in nicht-geschädigten Gebieten des sensomotorischen Netzwerks in Gang gesetzt werden, welche die Wiederherstellung motorischer Funktionen vorantreiben. Geeignete Bewegungstherapien scheinen diese Reorganisationsprozesse zu erleichtern und somit das Wiedererlernen der verlorenen Funktionen zu unterstützen. Zum Verständnis der zugrundeliegenden zerebralen Prozesse sind weiterführende Studien in diesem Bereich notwendig. Die Erkenntnisse dieser Untersuchungen können helfen, neue und effizientere Rehabilitationsstrategien zu entwickeln. Die funktionelle Magnetresonanztomographie (fMRT), welche es erlaubt die Funktionsweise des menschlichen Gehirns zur erforschen, ist besonders geeignet zur Untersuchung solcher Prozesse (erfasst als Aktivierungsmustern) und kann ausserdem dazu beitragen die Wirkung von Therapien zu evaluieren. In Kombination mit Magnetresonanz-kompatiblen Robotern, welche die Durchführung von Bewegungen während den fMRT-Aufnahmen kontrollieren und überwachen, können zuverlässigere Erhebungen der Aktivierungsmuster in Langzeituntersuchungen gewährleistet werden, die für das Verständnis der ablaufenden Reorganisationsprozesse essenziell sind. Des Weiteren können Roboter zur Rehabilitation der beeinträchtigten Extremitäten eingesetzt werden, um neue Therapieansätze zu ermöglichen. Das übergeordnete Ziel der vorliegenden Dissertationsarbeit bestand darin, ein besseres Verständnis von Therapie-induzierten Reorganisationsmustern bei Patienten im chronischen Stadium nach einem Schlaganfall zu erlangen. In diesem Zusammenhang, beabsichtigte diese Arbeit zum einen die Entwicklung eines zuverlässigeren Verfahrens zur Erhebung von Aktivierungsmustern beim Ausführen von Armbewegungen. Zum anderen sollten zerebralen Reorganisationsmustern, die durch Armtherapie induziert werden, erforscht werden. Der Kern der Untersuchung war zu testen, ob eine roboterunterstützte Armtherapie Reorganisationsprozesse bei Patienten mit moderaten oder schweren Beeinträchtigungen vorantreiben kann. Um ein robustes Paradigma für die Erhebung von Aktivierungen beim Ausführen von Armbewegungen zu erhalten, wurde ein Magnetresonaz (MR) kompatibler Armroboter, genannt MaRIA, entwickelt und getestet. In diesem Zusammenhang wurden zwei Studien durchgeführt. In Studie 1 wurden die Qualität der fMRT-Aufzeichnungen sowie die Durchführbarkeit von fMRT-Erhebungen mit MaRIA bei gesunden Versuchspersonen getestet. Bei der zweiten Studie (Studie 2) wurde die Aktivierung, welche durch aktive und passive Armbewegungen hervorgerufen wurde, untersucht. Zudem wurde die Reliabilität dieser Aktivierungen im Laufe der Zeit mittels verschiedener statistischer Verfahren getestet. In einer weiteren Studie (Studie 3) wurde MaRIA zur Untersuchung von Therapie-induzierten Reorganisationsmustern bei Patienten mit moderaten oder schweren motorischen Beeinträchtigungen eingesetzt. Für die Studie wurden die Patienten in zwei Gruppen eingeteilt. Die eine Gruppe wurde anhand einer roboter-unterstützten Therapie mit Hilfe des Arm- Rehabilitations-Roboters ARMin trainiert. Die andere Gruppe erhielt eine konventionelle Therapie. Die Reorganisationsmuster und Verbesserungen in der Armfunktion bei beiden Therapieverfahren wurden analysiert und miteinander verglichen. 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Die Aktivierungsänderungen unmittelbar nach Therapieschluss konnten auch in der Nachuntersuchung zwei Monate nach Beendigung der Behandlung gefunden werden, wobei die beobachteten Langzeiteffekte bei Patienten mit moderaten Defiziten robuster waren als bei solchen mit schweren Beeinträchtigungen. Die Therapie mit ARMin konnte die zerebralen Reorganisation und die Wiederherstellung der Armfunktion gleich gut vorantreiben wie eine konventionelle Therapie. Demnach ist der Einsatz von ARMin eine vielversprechende Alternative, um die Wiedererlangung der Armfunktion bei Patienten im chronischen Stadium

voranzutreiben. In Rahmen dieser Arbeit konnte eine neue Methode zur zuverlässigen Erfassung der Gehirnaktivität beim Ausführen von Armbewegungen etabliert werden. Diese Methode kann in zukünftigen Längsschnittstudien zur Untersuchung von Reorganisationsprozesse in Patienten mit motorischen Beeinträchtigungen eingesetzt werden und dazu verhelfen Therapien zu evaluieren. Zudem konnte die hier durchgeführte Patientenstudie zur Untersuchung therapie- induzierter Reorganisationsprozesse neue Erkenntnisse über die Wirkung und das Potential von roboterunterstützten Therapieformen bei Patienten mit moderaten und schweren Defiziten der Armfunktion liefern.

Monitoring Therapy-Induced Recovery After Stroke Using Functional Magnetic Resonance Imaging (fMRI)

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Con cariño para mi madre

María Jesús Estévez Gómez

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ABSTRACT

Stroke often leads to chronic motor disability of the upper limb, which can significantly affect a person's activities of daily living. Recovery of motor function following a stroke is associated with brain reorganization processes that occur within the surviving areas of the sensorimotor network. Although still not fully understood, there is increasing evidence that movement therapy can facilitate recovery of the upper limb by promoting such processes. To develop more efficient rehabilitation strategies, further work is needed to enhance understanding of therapy-induced recovery and its related reorganization patterns.

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The present results indicate that MaRIA can be used in the MRI environment without causing artefacts in the fMRI time series or discomfort for the person being assessed. The brain network activated by active and passive arm movements in healthy subjects was consistent with the activation patterns reported in previous publications. Reliability analysis demonstrated robust activation patterns for active movements over time. Brain activation was also quite robust for passive movements and reliability was further improved by including additional information about force and range of motion acquired by the device. The investigation of brain reorganization induced by arm therapy demonstrated that reorganization patterns vary depending on the type of intervention, the degree of impairment, and the task performed. For both interventions, changes in activation observed immediately after therapy largely persisted at two months of follow-up. Long-term effects were more stable and even more pronounced in patients with moderate impairments than in those with severe deficits. Therapy with ARMin was shown to promote brain reorganization and reduce motor impairment as effectively as

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This work establishes a new approach to reliably assess arm movement-related brain activation in longitudinal studies on patients with motor impairments. It also allows for the evaluation of different therapeutic interventions and brain plasticity following damage to the nervous system. Additionally, the investigation of therapy-induced reorganization provides important knowledge to help us better understand the effects and potential of robot-assisted therapies in stroke patients suffering from chronic moderate or severe deficits of the arm.

ZUSAMMENFASSUNG

Erleidet eine Person einen Schlaganfall, so führt dies häufig zu motorische Beeinträchtigungen der oberen Extremitäten, welche die Betroffenen in der Alltagsbewältigung deutlich einschränken. Forschungsarbeiten zeigen, dass nach einem Schlaganfall Reorganisationsprozesse in nicht-geschädigten Gebieten des sensomotorischen Netzwerks in Gang gesetzt werden, welche die Wiederherstellung motorischer Funktionen vorantreiben. Geeignete Bewegungstherapien scheinen diese Reorganisationsprozesse zu erleichtern und somit das Wiedererlernen der verlorenen Funktionen zu unterstützen. Zum Verständnis der zugrundeliegenden zerebralen Prozesse sind weiterführende Studien in diesem Bereich notwendig. Die Erkenntnisse dieser Untersuchungen können helfen, neue und effizientere Rehabilitationsstrategien zu entwickeln.

Die funktionelle Magnetresonanztomographie (fMRT), welche es erlaubt die Funktionsweise des menschlichen Gehirns zur erforschen, ist besonders geeignet zur Untersuchung solcher Prozesse (erfasst als Aktivierungsmustern) und kann ausserdem dazu beitragen die Wirkung von Therapien zu evaluieren. In Kombination mit Magnetresonanz-kompatiblen Robotern, welche die Durchführung von Bewegungen während den fMRT-Aufnahmen kontrollieren und überwachen, können zuverlässigere Erhebungen der Aktivierungsmuster in Langzeituntersuchungen gewährleistet werden, die für das Verständnis der ablaufenden Reorganisationsprozesse essenziell sind. Des Weiteren können Roboter zur Rehabilitation der beeinträchtigten Extremitäten eingesetzt werden, um neue Therapieansätze zu ermöglichen.

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Rehabilitationsverfahrens, des Schweregrad der motorischen Beeinträchtigung und der Art der durchgeführten Bewegung beobachtet. Die Aktivierungsänderungen unmittelbar nach Therapieschluss konnten auch in der Nachuntersuchung zwei Monate nach Beendigung der Behandlung gefunden werden, wobei die beobachteten Langzeiteffekte bei Patienten mit moderaten Defiziten robuster waren als bei solchen mit schweren Beeinträchtigungen. Die Therapie mit ARMin konnte die zerebralen Reorganisation und die Wiederherstellung der Armfunktion gleich gut vorantreiben wie eine konventionelle Therapie. Demnach ist der Einsatz von ARMin eine vielversprechende Alternative, um die Wiedererlangung der Armfunktion bei Patienten im chronischen Stadium voranzutreiben.

In Rahmen dieser Arbeit konnte eine neue Methode zur zuverlässigen Erfassung der Gehirnaktivität beim Ausführen von Armbewegungen etabliert werden. Diese Methode kann in zukünftigen Längsschnittstudien zur Untersuchung von Reorganisationsprozesse in Patienten mit motorischen Beeinträchtigungen eingesetzt werden und dazu verhelfen Therapien zu evaluieren. Zudem konnte die hier durchgeführte Patientenstudie zur Untersuchung therapie-induzierter Reorganisationsprozesse neue Erkenntnisse über die Wirkung und das Potential von roboterunterstützten Therapieformen bei Patienten mit moderaten und schweren Defiziten der Armfunktion liefern.

1 INTRODUCTION

The term ‘stroke’ (also called cerebrovascular accident, CVA) refers to a disturbance of brain function caused by a disruption in the cerebral blood supply, which can be caused by either an cerebral ischemia or hemorrhage (Truelsen et al. 2001). Worldwide, stroke is the second most common cause of death and the leading cause of chronic disability (Donnan et al. 2008). It affects more than one million people in Europe each year (Thorvaldsen et al. 1995; Brainin et al. 2000; Truelsen et al. 2006). Many brain functions — like sensorimotor integration, movement, walking, language, vision, balance, mood, and sensory perception — can be severely and irreversibly affected (Rossini et al. 2003). One of the most frequent and disabling consequences of a stroke is hemiparesis contralateral to the brain lesion, which most often affects the upper limb (Rossini et al. 2003). Although the average survival rate at 28 days is 70% (Thorvaldsen et al. 1995), only 15-18% of stroke patients with severe upper limb paresis regain full function; the remainder continue to suffer from permanent motor impairment that can prevent them from completing everyday tasks (Nakayama et al. 1994b; Hendricks et al. 2002). Both the frequency and dire consequences of strokes clearly emphasize the importance of these events, and the necessity to develop new strategies to better understand and facilitate the recovery of function, thereby contributing to improved quality of life in stroke survivors.

After a stroke, standard rehabilitation of the upper limb primarily includes physical and occupational therapy. The primary goal of these approaches is to help patients to adapt to everyday life despite their impairments (for a review, see Schaechter 2004). Treatments that focus on reducing impairments in upper limb function are less well-developed (Dobkin 2004; Ward 2011). One promising way to improve such therapeutic approaches is through movement therapy techniques supported by robotic devices. Furthermore, as recovery of function is associated with reorganization in the functional organization of the sensorimotor network (see Chapter 3; for a review, see Schaechter 2004; Richards et al. 2008) a better understanding of

how this reorganization takes place and how it can be promoted is crucial to enhancing recovery and reducing deficits in stroke survivors.

Functional magnetic resonance imaging (fMRI) offers insights into this area of research. This technique allows for the measurement of brain function (i.e., assessing task-related brain activation) in a non-invasive manner, and therefore offers the potential for repeat measurements over time, which is a major requirement when addressing questions related to brain reorganization after stroke, and to therapy-induced neuroplasticity. In this context, the development of paradigms that provide reliable activation patterns across multiple fMRI sessions is critical. In patients with motor disability, this is difficult to achieve because their motor output can change over time, leading to inconsistencies in task performance between fMRI sessions. Using MRI-compatible robots can help to overcome this limitation by monitoring and controlling task performance.

The currently-presented thesis aimed to enhance understanding of therapy-induced brain reorganisation in patients with chronic stroke. In this context, it had two main goals. First, it sought to improve the longitudinal assessment of arm movement-related brain activation using MaRIA, a newly-developed, MRI-compatible robot. The second aim was to investigate brain reorganization induced by arm therapy, in particular after robot-assisted training. For the robotic therapy, an arm rehabilitation robot called ARMin was used. Functional reorganization patterns and related improvements in arm function induced by this approach were compared against those elicited by conventional therapy.

The following sections overview current findings and challenges in the field of recovery and rehabilitation after stroke. Subsequently, insights are given into brain reorganization after stroke and influential factors. Additionally, the assessment of brain function and the related problems of performance consistency and confounding in impaired patients is described. In the Methods section, the robotic devices used for the studies are described.

2 RECOVERY AND REHABILITATION AFTER STROKE

2.1 Current state of research

After a stroke, patients may regain at least some degree of their lost function. Improvements in neurological and functional motor deficits are largely reported within the first two to five months after a stroke and depend upon the severity of the initial deficit (Nakayama et al. 1994b; Jørgensen et al. 1995a; Jørgensen et al. 1995b; Jørgensen et al. 1999). During these first few months, the time course of motor function recovery has been observed to be most rapid over the first few weeks, slowing during subsequent months, and reaching a plateau at six months after the stroke (Hendricks et al. 2002; for a review, see Krakauer 2005). Therefore, six months post-stroke, the degree of recovered function was expected to remain stable and not significantly improve. However, although spontaneous recovery is generally no longer possible after this period of time, the results of numerous studies suggest that movement therapy can still promote recovery in patients up to several years following a stroke (e.g., Luft et al. 2004a; Takahashi et al. 2008; for a review, see Page et al. 2004; Richards et al. 2008).

Several studies investigating the association between recovery of motor function and movement therapy have shown that stroke patients can attain a better quality of life with specific therapy (for a review, see Platz 2003; Dobkin 2004). Although the optimal type of therapy for upper limb function is still a matter of discussion, these previous studies identified several patterns that seem to facilitate recovery. For instance, therapeutic interventions that allow for the intensive (Sunderland et al. 1992a; Ottenbacher and Jannell 1993; Kwakkel et al. 1997; Kwakkel et al. 1999; Carey et al. 2002; Van Peppen et al. 2004) and repetitive practice of motor tasks (Bütefisch et al. 1995; Feys et al. 1998) and are of long duration (Sunderland et al. 1992a; Kwakkel et al. 1999; Kwakkel et al. 2002) appear to promote recovery more successfully. Furthermore, task-oriented training, which includes training for more complex tasks (e.g., skills and activities), incorporates multiple systems (e.g., musculoskeletal and perceptual systems),

and aims at increasing subject's participation (Schaechter 2004; Timmermans et al. 2009), seems to be fundamental to improving daily function. For example, forcing the affected limb to perform activities of daily living (ADL; e.g., reaching for a cup) yields functional gains that allow the stroke patient to increase his or her use of the affected arm in real-life situations (e.g., at home) (Miltner et al. 1999; Taub et al. 1999; Jang et al. 2003; Van Peppen et al. 2004; Bayona et al. 2005).

However, traditional manually-assisted therapies (e.g., physical or occupational therapy) have several limitations. For instance, the training is labor-intensive and depends on the physical efforts of the therapist (e.g., duration limited by fatigue). It also is time consuming and expensive. Additionally, health insurance only pays for a limited number of therapy hours, which are often less than the time required to achieve an optimal therapeutic outcome (Van Peppen et al. 2004). One possible way to offset some of these limitations is to apply robot-assisted therapeutic approaches.

2.2 Robot-assisted rehabilitation

Over the past few years, several robotic devices have been developed to support the rehabilitation of patients suffering from upper limb impairments (e.g., Takahashi et al. 2008; for a review, see Riener et al. 2005; Brewer et al. 2007; Timmermans et al. 2009). Compared to traditional interventions, robot-assisted arm training has certain advantages. First, robotic devices can help to provide more intense and prolonged therapy. For example, the number of therapist hours can be reduced, since one therapist can oversee the therapy of several patients simultaneously. In addition, the duration and number of therapy sessions and tasks repetitions can be increased. Furthermore, using robotic devices can help patients to perform therapeutic tasks that therapists would find impossible or difficult to do. For instance, they enable repetitive training and support the training of ADL. By providing passive mobilization (during which the arm is moved by the device), training in these tasks can be done even with severely-impaired

patients whose training would otherwise require significant physical effort from a therapist facilitating exercises manually. Virtual scenarios can be implemented to facilitate the training of ADL and motivate patients during therapy. Robotic devices also can provide quantitative measures, which allow biofeedback functions and can help therapists to objectively quantify patients' performance. This feature can aid in the measurement of individual patients' progress during therapy and evaluate how effective applied interventions have been (Nef et al. 2007; Kwakkel et al. 2008 for a review, see Brewer et al. 2007).

To date, several investigators have studied the effect of robot-assisted therapy on motor recovery. Despite considerable methodological variations (e.g., in the duration, quantity and type of training, and patient characteristics) across these studies, most have demonstrated some benefit of this kind of intervention on various motor outcome measures (ADLs, motor function and strength) (Kwakkel et al. 2008; Mehrholz et al. 2008; Mehrholz et al. 2012). However, a major limitation of previous approaches is that most of the devices applied so far only used single degrees of freedom and supported only single joint movements, thereby restricting the range of motion of the upper limb (Guidali et al. 2011a). Training exercises that require using the entire extremity, like those that focus on ADLs, may enhance the transference of skills attained during therapy into daily life (Langhammer and Stanghelle 2000; Riener et al. 2005; Timmermans et al. 2009). Therefore, more sophisticated devices with more degrees of freedom and involving all components of the limb (shoulder, arm, hand) might be more effective at promoting the recovery of motor function after a stroke.

For all these reasons, in the context of this dissertation, the arm rehabilitation robot ARMin, which supports movements of the shoulder, arm and hand (opening and closing) (Nef and Riener 2005; Nef et al. 2007; Nef et al. 2009a; Guidali et al. 2011b; Guidali et al. 2011a), was used in chronic stroke patients to investigate whether such a robotic device indeed may facilitate recovery. Detailed information about the features of this device can be found in upcoming section 5.1.

3 BRAIN REORGANIZATION AFTER A STROKE

3.1 Current state of research

Numerous neuroimaging studies have demonstrated that recovered motor function following a stroke is associated with functional reorganization in non-infarcted areas of the sensorimotor network, which is responsible for the processing of sensory information and motor output (i.e., movement) (Liepert et al. 2000; Nelles et al. 2001; Carey et al. 2002; Johansen-Berg et al. 2002; Lotze et al. 2006; Ward et al. 2007; Mintzopoulos et al. 2008; Takahashi et al. 2008; Rehme et al. 2010; Riecker et al. 2010; for a review, see Schaechter 2004; Richards et al. 2008). In this context, different reorganization patterns have been observed at different stages of recovery. In early stages, enlarged activation within areas in the ipsilesional hemisphere (i.e., the same side as the lesion) and additional recruitment of contralesional (i.e., the opposite side as the lesion) sensorimotor regions have been observed in response to different motor tasks, associated with the restoration of motor function. As for later stages, previously-published findings are inconsistent, as diverse reorganization patterns have been noted in different studies. Some have demonstrated a decline in the aforementioned activation reported in early stages in well-recovered patients after spontaneous recovery and in acute and chronic stroke patients following motor training (Liepert et al. 2000; Nelles et al. 2001; Carey et al. 2002; Ward 2003; Ward et al. 2003; Takahashi et al. 2008; Rehme et al. 2010; Rehme et al. 2011). These patterns were similar to those observed in healthy subjects and have been found to be positively associated with better motor recovery. In contrast, the persistence of widespread activation patterns, particularly in the contralesional hemisphere, have been correlated with poorer functional outcomes, suggesting that such patterns may reflect less efficient brain plasticity (Liepert et al. 2000; for reviews, see Rossini and Dal Forno 2004; Pascual-Leone et al. 2005). Based upon these findings, it was hypothesized that a return towards more normal activation patterns may be predictive of better recovery (Liepert et al. 2000; Carey et al. 2002; Ward 2003; Ward et al. 2003). However, contrary to this assumption, other investigators have reported

enhanced activation in lateral and medial premotor areas in both hemispheres and in the contralesional sensorimotor cortex, related to the successful execution of particular movement tasks (Lotze et al. 2006; Riecker et al. 2010) or improvements in motor outcomes; e.g., after movement training (Johansen-Berg et al. 2002; Luft et al. 2004a). These findings indicate that the involvement of additional brain regions could also contribute to the restoration of lost functions in chronic stages rather than reflecting inefficient reorganization (for reviews, see Schaechter 2004; Richards et al. 2008).

Although the reason for these contradictory results remains a matter of debate, one possible explanation is that the demands of the motor task (e.g., simple versus complex tasks) and characteristics of the lesion (e.g., damage in the sensorimotor cortex or/and corticospinal tract) lead to differences in reorganization patterns (i.e., normalization or additional recruitment).

3.1.1 The influence of task demands

More recent studies have suggested that the recruitment of additional sensorimotor areas like those in the hemisphere opposite to the lesion might promote motor performance, optimizing motor function in chronic stroke patients (Gerloff et al. 2006; Lotze et al. 2006; Riecker et al. 2010). For example, in patients who experience extensive recovery, recruitment of the contralesional premotor cortex and sensorimotor cortex was associated with increased functional demands (e.g., with increasing movement frequency of the paretic limb or task complexity) on the sensorimotor system. The activation patterns observed in these patients with excellent motor recovery seemed to be efficient and to resemble the widespread, bilateral activation observed in healthy controls performing complex movements, rather than reflecting maladaptive neuroplasticity (Lotze et al. 2006; Riecker et al. 2010). Additionally, in stroke patients with more extensive corticospinal system damage, enhanced activity in the premotor cortex of the unaffected hemisphere was linked to force modulation, whereas activity in the ipsilesional primary motor cortex was not. In contrast, patients with less extensive corticospinal

system damage exhibited force-related activation in the lesion-side primary motor cortex similar to that observed in healthy controls. These differential responses suggest that the premotor cortex takes over some of the executive properties of the primary motor cortex, indicating that the additional recruitment of contralesional areas contributes to functional recovery (Ward et al. 2007).

3.1.2 The influence of lesion characteristics

Lesion characteristics are important determinants of the type and degree of motor impairment observed in stroke patients and may contribute to the variability in reorganization patterns that exists between them. Different activation patterns have been documented in chronic patients with cortical versus subcortical lesions, despite similar motor impairments (Feydy et al. 2002; Luft et al. 2004b; Hamzei et al. 2006; Ward et al. 2007). For example, in patients with subcortical infarcts, movement-related activation was observed within the same network as in healthy controls, i.e., in the normal network including the contralateral sensorimotor cortex and ipsilateral cerebellum. Additional activation was found in contralesional and secondary sensorimotor areas. Patients with cortical infarcts in the sensorimotor cortex exhibited no activation in the normal network, due to critical tissue loss. Activation in these patients was mainly observed in cortical areas adjacent to the infarcted tissue and in contralesional sensorimotor areas, which suggests that, after a cortical stroke, alternative networks are recruited. Therefore, the regions and the extent to which they are recruited in individual patients may also depend on the location and distribution of lesions (Luft et al. 2004b). Additionally, the efficacy of the different reorganization patterns (i.e., normalization or additional recruitment) reported across studies, in terms of generating optimal motor output, probably depends on the degree of damage in the corticospinal tract (Feydy et al. 2002; Ward et al. 2006b; Hamzei et al. 2006; Ward et al. 2007). A relationship between the recruitment of additional sensorimotor areas, e.g. in the contralesional hemisphere, and the impaired integrity of the

corticospinal tract has been identified in several studies (Ward et al. 2006b; Ward et al. 2007; Schaechter et al. 2008; Rehme et al. 2010). Furthermore, several researchers have identified a significant correlation between the degree of motor impairment and the extent of white matter damage within the corticospinal system (e.g., Lindenberg et al. 2010; Radlinska et al. 2010).

3.1.3. Conclusions

Considering the findings of these previous studies en masse, it seems that less-impaired patients may have less structural damage; and, as such, reactivation of the premorbid network (i.e., more normal activation patterns) to support task performance might be possible to a greater extent. Conversely, in patients with poorer function post-stroke, a return to more normal activation patterns may not be possible due to more severe structural damage. Thus, in these patients, additional areas of the sensorimotor network must be recruited to generate motor output. Additionally, task demands may further influence the reorganization patterns observed. Tasks that are perceived to be more difficult by the patients may lead to widespread activation patterns; meanwhile, activation in the 'normal' range may be sufficient for the performance of easier tasks. Finally, how tasks themselves are experienced depends upon the capabilities of the individual patients. Consequently, to perform the same task, severely impaired patients may require more extensive recruitment than those with moderate impairment (for reviews, see Schaechter 2004; Ward 2011).

4 ASSESSING BRAIN FUNCTION: PERFORMANCE CONSISTENCY AND CONFOUNDERS

4.1 Active motor tasks

Researchers commonly use active motor tasks to examine brain activation patterns in healthy subjects. However, the application of such tasks to assess brain function in stroke patients is both challenging and limiting. For example, brain activation can only be assessed if patients are able to perform the active tasks; and this is only possible for patients who have recovered a certain amount of motor function, automatically excluding patients with severe impairment from investigation. Additionally, for the investigation of brain reorganization patterns induced by therapy, longitudinal fMRI assessments are required. In patients with motor disability, however, motor output can change over time as a consequence of spontaneous recovery or motor training, which makes it difficult to ensure consistent performance of active motor tasks between sessions. For example, a patient may apply more or less force during task performance or may perform more or fewer task repetitions in one fMRI session than another. Such variability in task performance between sessions can cause large differences in brain activation, which can be mistakenly interpreted as indicative of functional recovery. Consistent performance within fMRI assessments may also be difficult to ensure in patients with more severe impairments, relative to those with milder deficits. This is because they may have more difficulty performing the tasks required. If similar consistency in performance does not exist for all patients with different degrees of impairment, there is further confounding of comparisons between patients, which can also lead to false conclusions (for review, see Ward 2004; Baron et al. 2004).

4.2 Passive motor tasks

An alternative approach that has been used frequently in prior studies investigating brain reorganization in patients with disability is to use passive motor tasks. In healthy subjects, these

kinds of movement have been found to induce patterns of activation that are similar to those of active movements (Weiller et al. 1996; Loubinoux et al. 2001; Kocak et al. 2009). In this context, it has been hypothesized that this activation is elicited by activating the afferent system (Weiller et al. 1996; Kocak et al. 2009); consequently, activation changes related to passive movement may reflect the degree of sensory processing (e.g., of proprioceptive information) that is relevant to motor output. Passive tasks are independent of patients' motor skills and may not vary between fMRI sessions. Therefore, they may be more appropriate than active tasks to assess brain function in patients with severe motor impairment. As such, passive movements may be particularly suitable to studying therapy-induced changes in brain activation in longitudinal investigations, and to comparing reorganization patterns between patients with different degrees of impairment.

However, this approach also has disadvantages. Because activation related to passive movement is driven by sensory input, an intact or at least partially-working afferent network is indispensable to studying brain activation patterns. However, this network may be disrupted in many patients (Ward et al. 2006a; Kocak et al. 2009), which could impede the investigation of brain activation. Additionally, in most fMRI studies the performance of passive movements has been achieved by the investigator moving the patient's limb passively. Because of the manual component of this procedure, the accuracy of task performance depends highly on how consistent the investigator guides these movements and may be influenced by his/her skills and physical fatigue, which in turn can lead to undesirable data variability. Furthermore, as passive movements activate the sensorimotor network more indirectly (i.e., through sensory information), they cannot be entirely substituted for active tasks, instead adding complementary information about the network's function. Finally, the range of questions that can be addressed using such tasks is limited. For example, it is not possible to investigate brain activation in response to modulations in movement parameters (e.g., force, frequency) or more complex movements, as is possible using active tasks (for review, see Ward 2004; Baron et al. 2004).

4.3 MRI-compatible robots

Given the limitations and advantages of both approaches, to obtain a more detailed assessment of brain activation patterns in stroke patients, using both active and passive tasks seems to be a reasonable strategy, though efforts should be taken to optimize the application of both kinds of task to generate more reliable patient assessments. In this context, monitoring and controlling the performance of motor tasks during fMRI recordings may be crucial.

One possible approach to counteract at least some of the aforementioned limitations is to use MRI-compatible robotic devices to produce the tasks while recording activation signals. Such devices can guide subjects to perform well-controlled and reproducible passive sensorimotor tasks and ensure standardized conditions for the execution of active movements (Yu et al. 2008; for a review, see Tsekos et al. 2007). Furthermore, movement parameters can be recorded and quantified by the robotic system during the actual experiment. The collected data can then be incorporated into fMRI data analysis, yielding more precise interpretations of the association between performance and neuroimaging findings and potentially a more accurate evaluation of the rehabilitation process.

5 METHODS

The basic principles of fMRI and the data processing steps, including data pre-processing and statistical analysis, have been described extensively in previously-published literature (e.g., (Jäncke 2005; Penny et al. 2007). Therefore, in this section, I will only describe the two robotic devices that were used for the current studies.

5.1 MaRIA

For all studies reported in this dissertation, MaRIA, an MRI-compatible robot developed by the Sensory-Motor Systems Lab at ETH Zurich (http://www.sms.hest.ethz.ch/research/mr_robotics/setup) was used to guide elbow joint extension and flexion during fMRI recordings. The technical features of MaRIA are reported in detail in Study #1; therefore, here, I will only focus on some of the advantages that the device provides for assessing arm-related brain activation.

MaRIA facilitates adjustable, well-controlled, passive and active arm movements. It interacts with human subjects through a handle, which is attached to and driven by a hydraulic cylinder (Figure 1.1). The device is equipped with sensors that allow for the recording of several movement parameters, like force and range of motion. Additionally, the sensors permit exact movement onset and the duration of each task to be assessed. The implementation of this information can improve fMRI analysis in different ways. Timing information about the movement (e.g., onset and duration) allows for the exact modeling of brain activation related to arm movements. This information can also help to monitor whether participants performed the task as instructed. As a result, unsuccessfully performed trials that could generate undesirable noise during fMRI analysis can be identified and removed. Furthermore, information about force and range of motion acquired by the device can contribute to controlling the differences in motor performance between trials. The robot makes it possible to

assess maximal voluntary push force (MVPF), and a threshold can be set according to this measurement. This feature is of major importance when assessing brain activation in response to active motor tasks, particularly in patients and during longitudinal studies, because differences in force capability across subjects and sessions may influence fMRI results considerably.

The position, height, and orientation of the device restrict movement of the robot and can be adjusted to fit the size of each subject. Furthermore, handle orientation can be changed so that the assessment of both left and right arm movements is possible, which permits one to investigate brain activation in patients with paresis affecting either the left or right arm. To further standardize the performance of tasks, the parameters used during one session are recorded for each subject and used in subsequent sessions.

During each scanning session, changes in force and range of motion, measured by the sensors during task performance, are displayed simultaneously in real time on a monitor outside the scanner room, so investigators can follow them continuously. When assessing brain activation in patients, this feature can be helpful as one can observe whether or not the patient performed the task as instructed. If this is not the case, the recording can be stopped or, if necessary, the task explained again to the patient.

MaRIA is controlled using MATLAB 7.6 (Mathworks Inc., Natick, MA, USA) as its interface and can be synchronized with other recording software (i.e., with Presentation: http://www.neurobs.com). Therefore, the device is a flexible tool that can be used to address several questions related to the investigation of arm movement-related activation.

5.2 ARMin

ARMin was developed by the Sensory-Motor Systems Lab at ETH Zurich (http://www.sms.hest.ethz.ch/research/mr_robotics/setup; Figure 3.1; for detail information

about this robot, see Nef and Riener 2005; Nef et al. 2007; Nef et al. 2009a; Nef et al. 2009b; Guidali et al. 2011b; Guidali et al. 2011a). This device is characterized by an exoskeleton structure and is equipped with seven independent degrees of freedom that allow for tridimensional shoulder rotation, elbow flexion/extension, pro/supination of the lower arm, and wrist flexion/extension. The robot provides ergonomic shoulder actuation that permits translational movement of the glenohumeral head during arm elevation and depression, thereby reproducing anatomically-correct shoulder movements. Recently, the robot has been complemented by a hand module that facilitates hand opening and closing.

ARMin enables three therapy modes: passive arm mobilization, active game-supported arm therapy, and active training for ADLs. All modes are supported by virtual scenarios that are presented to the patients on a graphical display. During passive mobilization, the robot moves the patient's arm through a pre-determined trajectory. This kind of training prevents secondary complications, increases blood circulation, and reduces joint and muscle stiffness (Nef et al. 2009a; Guidali et al. 2011b; Guidali et al. 2011a). In the second therapy mode, the patient's motor skills are trained while the patient plays different games (e.g., ping-pong, labyrinth) against a computer or even another patient. The third therapy mode focuses on ADLs, such as eating, cooking, and table setting. During both active modes, ARMin detects how much the patient him- or herself is contributing to the movement and delivers as much assistance as needed by the patient to complete the task (Nef and Riener 2005; Guidali et al. 2011a). It also controls the position and the interaction force between the robot and patient and can be used to train both the left and right arm (Nef et al. 2007).

6 OWN STUDIES

6.1 Study objectives

The present thesis had two main goals. First, it aimed to improve the longitudinal assessment of arm movement-related brain activation using fMRI. The second aim was to explore brain reorganization induced by arm training using robot-assisted therapy, and to compare these observed patterns against those elicited by conventional therapy. The overall objective of this work was to gain further insights into therapy-induced reorganization in patients with chronic stroke.

To achieve the first goal, MaRIA was used to control and monitor the performance of active and passive arm movements during fMRI recordings. In a first phase (Study #1), the feasibility of this approach in the MRI environment was tested by analyzing the quality of the recorded fMRI images and testing for possible device malfunction. To define the brain network that is activated when interacting with MaRIA and, therefore, provide base information for subsequent studies, brain activation was assessed in healthy subjects. Activation related to both active and passive arm movements was studied (Study #1, Study #2).

In the second phase (Study #2), systematic reliability analysis was performed to test the reproducibility of this activation over time. In this study, quantitative data about movement performance (movement onset, duration, force and range of motion), acquired during the fMRI recordings with MaRIA, was used to provide precise modeling of movements for fMRI data analysis. Whether using this information impacted the reliability of brain activation patterns associated with active and passive arm movement also was examined.

To achieve the second goal of this thesis, MaRIA was used to assess arm movement-related brain activation in stroke patients with either moderate or severe motor impairment of the arm (Study #3). Therapy-induced brain reorganization was investigated in patients who had already reached the chronic stage and were not expected to experience any further spontaneous

recovery. Participants in this study were trained either via robot-assisted therapy using ARMin or via conventional therapy (i.e., physical or occupational therapy). Reorganization patterns and improvements in motor performance induced by the two interventional approaches were assessed and compared.

6.2 Study #1

fMRI assessment of upper extremity related brain activation with an MRI-compatible manipulandum[§]

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**Note*: N. Yu and N. Estévez made equal contribution to this work

[§]This study was published in the journal International Journal of Computer Assisted Radiology and Surgery. The original publication is available at http://link.springer.com/article/ 10.1007%2Fs11548-010-0525-5; doi: 10.1007/s11548-010-0525-5. Data were assessed and analyzed by Natalia Estévez and Ningbo Yu. The manuscript was written by Natalia Estévez and Ningbo Yu and revised by the co-authors.

Abstract

Longitudinal studies to evaluate the effect of rehabilitative therapies require an objective, reproducible and quantitative means for testing function in vivo. An fMRI assessment tool for upper extremity related brain activation using an MRI-compatible manipulandum was developed and tested for use in neurorehabilitation research.

Fifteen healthy, right-handed subjects participated in two fMRI sessions, which were three to four weeks apart. A block design paradigm, composed of three conditions of subject-passive movement, subject-active movement and rest, was employed for the fMRI recordings. During the rest condition, subjects simply held the device's handle without applying any force or movement. The same type of auditory and visual instructions were given in all the three conditions, guiding the subjects to perform the motor tasks interactively with the MRI-compatible arm manipulandum. The tasks were controlled across the fMRI sessions. The subjects' brain activation was recorded by fMRI, and their behavioral performance was recorded by the manipulandum. The brain network activated by the subjects' interaction with the manipulandum was identified, and the reproducibility and reliability of the obtained activation were determined.

All subjects completed the trial protocol. Two subjects were excluded from analysis due to head motion artifacts. All passive movements were performed well. Four out of the total 780 active movements were missed by two subjects. Brain activation was found in the contralateral sensorimotor cortex, secondary somatosensory cortex and non-primary motor cortex as well as in subcortical areas in the thalamus, basal ganglia and the cerebellum. These activations were consistent across the two fMRI sessions.

The MRI-compatible manipulandum elicited robust and reproducible brain activations in healthy subjects during the subject-active and subject-passive upper extremity motor tasks with

a block design paradigm. This system is promising for many applications in neurorehabilitation research and may be useful for longitudinal studies.

Keywords: Brain activation, fMRI, MRI-compatible manipulandum, Neurorehabilitation

Introduction

Functional magnetic resonance imaging (fMRI) is an established clinical diagnostic method as well as an indispensable tool in clinical research. It allows brain function to be measured in a non-invasive manner and therefore allows repeated measurements over time in order to address questions related to brain reorganization after central and peripheral damage or plasticity following training. To ensure that the participants perform a designed motor task in the same manner, the performance of the task must be adequately controlled and monitored. Furthermore, task control and monitoring can be of great importance for studying effects of rehabilitative therapies.

Tasks commonly used to study brain function - for example wrist flexion-extension, finger tapping or arm flexion-extension (Pariente et al. 2001; Luft et al. 2004a; Cramer et al. 2005) - do not allow optimally controlled studies in patients, due to the difficulty of ensuring consistency in the repetition of each task in impaired subjects whose motor functions are changing over time or across subjects (inter- and intra-subject variability) (Hidler et al. 2006; Tsekos et al. 2007). Individual variability across fMRI sessions may confound brain activation changes following a rehabilitative intervention. Therefore, a reduction in the number of uncontrolled variables is essential for the accurate determination of functional brain maps in humans and for the understanding of rehabilitation processes in patients.

MRI-compatible robotic devices can overcome the aforementioned limitations by providing control and monitoring of motor tasks (Diedrichsen and Shadmehr 2005; Gassert et al. 2006; Tsekos et al. 2007; Suminski et al. 2007; Yu et al. 2008). They are able to guide subjects to

passively perform well-controlled and reproducible sensorimotor tasks tasks (Tsekos et al. 2007; Yu et al. 2008). Besides, they can work as a haptic interface under closed-loop control so that subjects can move the robotic device in an interactive manner, i.e., active movements that depend on effort of the subjects. Furthermore, the movement parameters can be measured and recorded by the robotic system, which will facilitate the fMRI data analysis afterward. All these special features enable MRI-compatible robots as a great tool to improve neurorehabilitation by providing a more controlled method of gaining insight into the brain reorganization mechanism after damage to the central or peripheral nervous systems and to objectively monitor the effect of therapy at brain level.

This study utilized an established MRI-compatible arm manipulandum, which is safe to be placed into the MRI environment, works compatibly with fMRI and allows extension and flexion of the elbow joint. The main goals of this study were to (1) define the brain network activated by the subjects' interaction with this MRI-compatible arm manipulandum while performing voluntary (active subject) and guided (passive subject guided by the manipulandum) movements, (2) examine the reproducibility and reliability of activation obtained in healthy subjects by fMRI measurements using this device, and eventually (3) determine whether this device is suitable for use in future longitudinal studies to evaluate the effect of various rehabilitative therapies. The longitudinal studies will allow us to correlate functional recovery with specific brain activation patterns, which promises important insights into the ongoing recovery process.

Methods

Subjects and the MRI setup

The study was approved by the local ethics committee. Fifteen healthy subjects (seven female, eight male, age range: 20–31) were recruited to join this study. All participants gave their written consent for their participation in the study. None of the subjects had any history of

neurological or psychiatric disorder. According to the Edinburgh-handedness inventory, all subjects showed right-hand dominance.

The study was carried out in the MR-center of University of Zurich and ETH Zurich, on a Philips Achieva 1.5 T MR system equipped with an 8-channel SENSETM head coil. The functional acquisitions used a $T2^*$ weighted, single-shot, field echo, EPI sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128, in-plane resolution = 1.7mm × 1.7mm, slice thickness = 4 mm, SENSE factor 1.6). Additionally, anatomical images of the whole brain were acquired using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 4.6 ms, flip angle = 20°, in-plane resolution = 0.9 mm × 0.9 mm, slice thickness = 0.75 mm, 210 slices).

The MRI-compatible manipulandum

The manipulandum (Figure 1.1) is safe to be placed inside the scanner room for magnetic resonance imaging (MRI) and is able to work together with MRI and fMRI procedures (Yu et al. 2008).

During this investigation, the MRI-compatible manipulandum including the actuator and sensors was placed inside the MRI scanner room (Figure 1.1, top). Digital components including the control unit, electric motors powering the hydraulic actuator, electric circuit, and other parts of the system, were placed outside the scanner room. Control valves and pressure sensors were placed at the corner of the scanner room, far away from the end-effector which was located inside the scanner bore. Optical fibres, cables, and hoses transmitted signals and fluid power through the shielding wall of the MRI scanner room.

The position, height and orientation of the manipulandum can be adjusted to fit the size and movement preference of subjects (Figure 1.1, bottom). These parameters constrain the movement of the manipulandum. The manipulandum interacts with human subjects with a

handle, which is attached to and driven by a hydraulic cylinder. The cylinder was specially made of bronze and aluminum so that it can be used inside the MRI room. This hydraulic cylinder enables the handle a linear movement range of 25 cm, velocity range of 20 cm/s and force range of up to 300 N. A self-designed and self-manufactured optical force sensor, which is adapted from (Fueglistaller 2004), was installed between the handle and the cylinder, measuring the push and pull force from the subject's arm to the cylinder. This force sensor can measure up to 120 N in both directions. An optical encoder, LIDA 279 by Heidenhain, measures the position of the handle. A special potential meter, MTP-L 22 by Resenso, was used as a redundant position sensor. For other components, PVC and PET were carefully selected as the main construction materials (Yu et al. 2008).

In order to reduce head motion artifacts during the data acquisition, we used a self-made head support, which covered the superior and partially the lateral parts of the subjects head (Figure 1.1, bottom). This limited the range of head motion, especially in the spinal direction. Furthermore, foam pillows were used to additionally restrict the motion in the left–right direction.

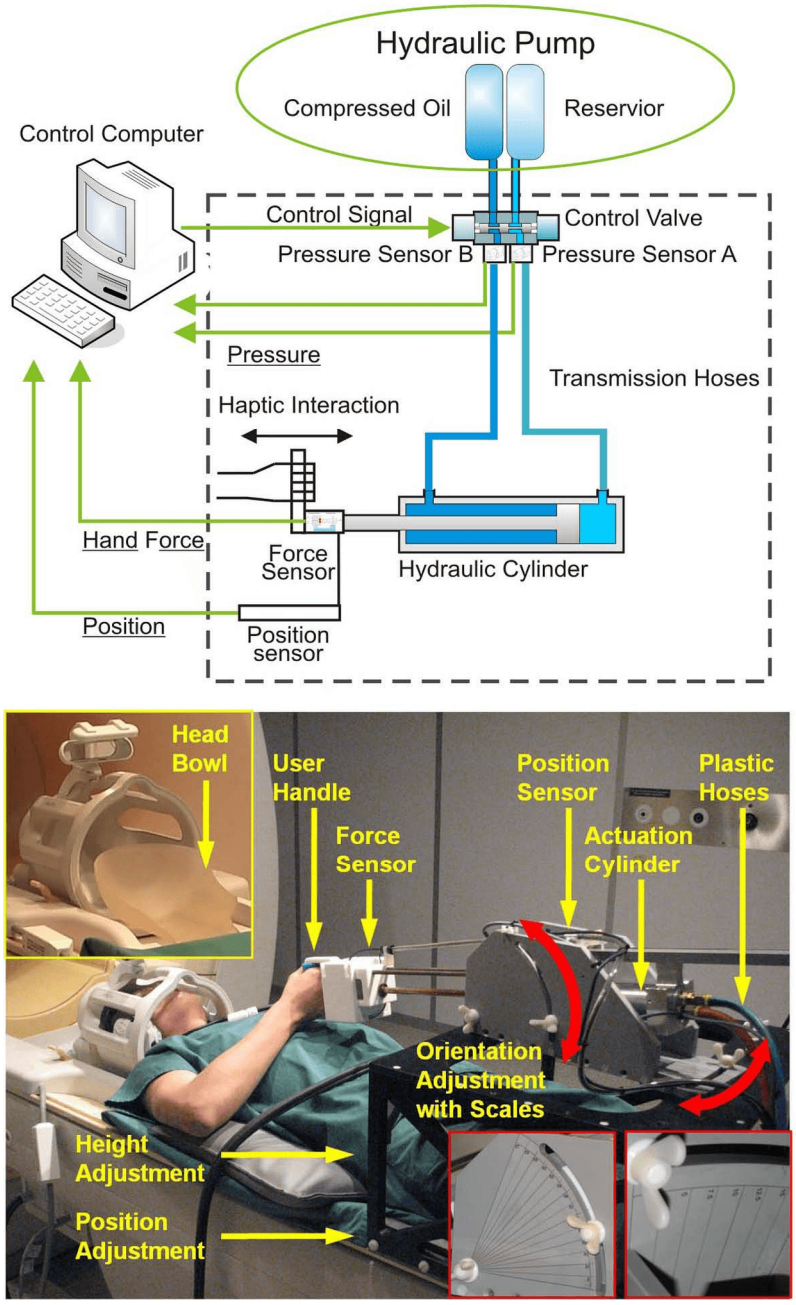

Figure 1.1

Top schematic plot of the MRI-compatible manipulandum system.

Bottom a subject with the MRI-compatible manipulandum in the MRI scanner

Under position control, the manipulandum can guide a subject to perform linear smooth movements. Under admittance control, the manipulandum is able to interact with subjects in various resistance laws, such as the spring law (resistance proportional to displacement), the viscous law (resistance proportional to speed), combination of the two, or some special-purpose resistance laws (Yu et al. 2008). Specially, the manipulandum is able to receive external

commands via an RS232 cable and then switch freely between the position control mode and the admittance control mode. Therefore, the manipulandum is able to

- guide the subject's arm to perform pre-defined linear movements;
- interact with the subject's arm with various kinds of resistance;
- receive external commands and produce the corresponding active or passive movements;
- record the position information of the movement;
- record pull or push force from the arm to the cylinder during the movement.

Phantom test with the manipulandum

The manipulandum was able to work safely and properly inside the MRI scanner room. Before the functional study with human subjects, a phantom test was performed to examine whether the manipulandum disturbed the MRI system. The experiment covered the following conditions:

(1) *phantom only*, in which the manipulandum was not in the scanner room;
(2) *device silent*, in which the manipulandum was placed at its desired working location in the scanner room, but had no connection going out of the scanner room;
(3) *device powered on*, in which the manipulandum was placed at its desired working location in the scanner room, with all transmission lines connected and the whole system powered on, but not performing any task;
(4) *device functioning*, in which the manipulandum performed the passive movements at its desired working location.

The imaged phantom was a bottle of mineral oil. In each of these experimental conditions, 20 fMRI scans were acquired for the phantom. The slice closest to the manipulandum would be

most vulnerable to possible disturbances from the device and therefore was taken as the benchmark for evaluation of possible image artifacts.

Two parameters of interest were inspected: the signal-to-noise ratio (SNR) and the temporal signal-to-noise ratio (tSNR). The SNR was calculated as:

$$\text{SNR} = \frac{\text{mean signal in image ROI}}{\text{standard deviation in image ROI}} \quad (1)$$

The tSNR was calculated as:

$$\text{tSNR} = \frac{\text{mean of voxel time series}}{\text{standard deviation of voxel time series}} \quad (2)$$

The signal, noise and SNR values were calculated for all the 20 images at the selected slice, and then averaged. SNR and tSNR are given in dB[1].

fMRI motor tasks and experimental paradigm

For fMRI scans, the participants were asked to lie on the MRI bench and the fixation frame was positioned above the subjects' thighs. Afterward, the participants were asked to flex the right elbow to reach the handle. The position, height and orientation of the manipulandum were adjusted to ensure that subjects reached the handle and performed the functional tasks in a comfortable way, while the upper arm remained close to the body without causing shoulder and head motion (Figure 1.2). Additionally, the elbow was supported by a cushion for better comfort and stabilization of the upper arm.

[1] Decibel: (number in dB) = 20 log10 (number in decimal).

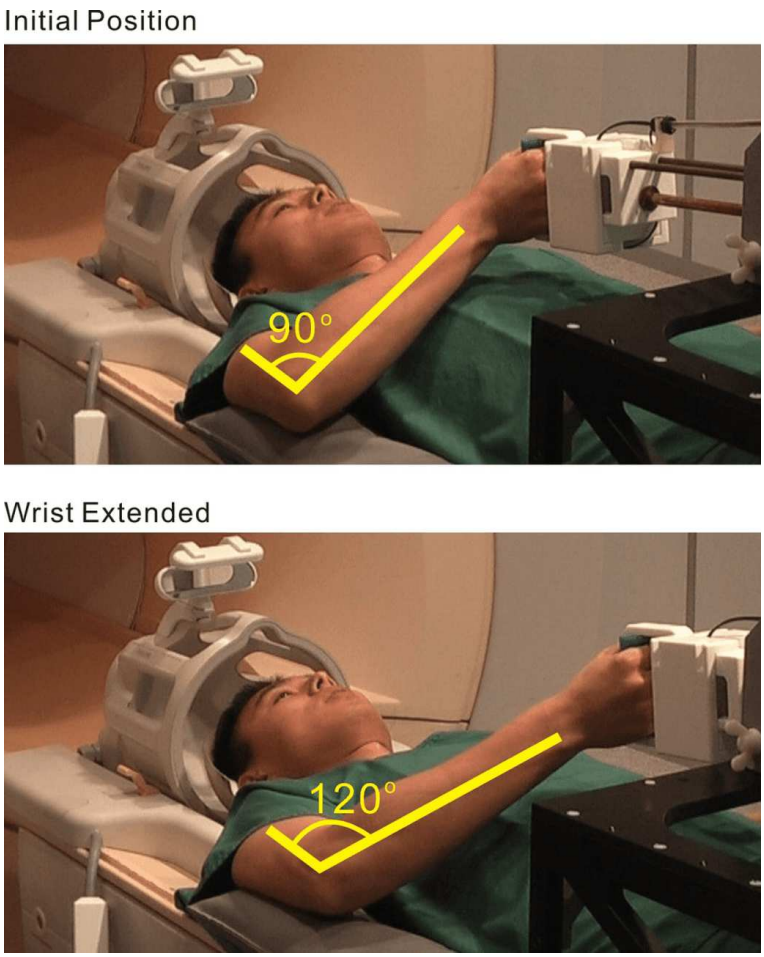

Figure 1.2 The arm extends about 30° when the handle linearly moves about 20 cm

To investigate the subjects' motor interactions with the MRI-compatible manipulandum, the experiment consisted of three conditions: rest, subject-passive movement and subject-active movement. In the passive movement condition, subjects were required to hold the device's handle and follow its movement without applying any force to it. The speed was constantly 7.2 cm/s. In the active movement condition, by contrast, subjects had to push and pull actively to produce the movement. The force-velocity profile adopted for this mode was shown in Figure 1.3. The movement could only be initiated after the force reached a certain threshold. Above this threshold, an inverse viscous law was applied in the sense that the more force the subject applied, the faster the arm moved. The maximal speed was saturated to 10 cm/s when the force reached 30 N or beyond. The low speed and smooth movements were used for both active and passive movements in order to avoid head motion, and thus, potential artifacts to brain images (Yu et al. 2008; Yu et al. 2009).

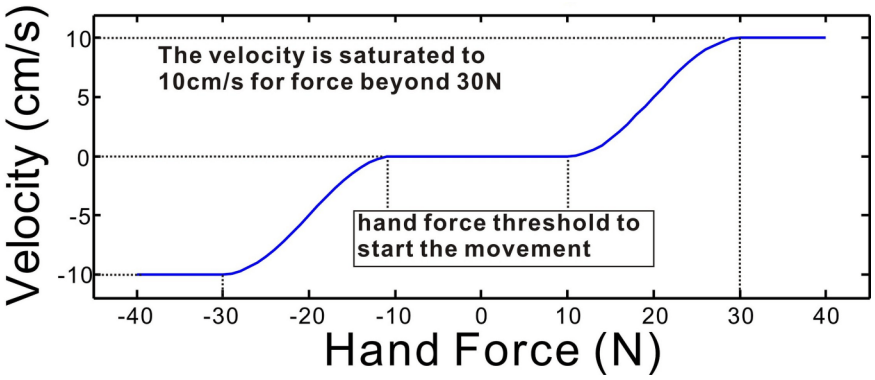

Figure 1.3 The force-velocity profile employed in the active mode of the study

The range of motion for the handle was about 16–20 cm depending on the postural and kinematic (movement direction/orientation) preferences as well as the size of individual subjects. For each subject, the range of motion and linear movement trajectory remained the same for all passive and active movements. The speed was smoothly reduced to zero at the two endpoints.

The force thresholds were normalized to the capability of the subjects, defined as 20% of their maximal voluntary push force. This force was assessed with the MRI-compatible manipulandum for each subject before either fMRI scanning. Participants were instructed to push the fixed handle of the manipulandum three times with their maximal voluntary force without moving head and body, and the mean force value was taken.

A block design (Figure 1.4) with 29 s periods of rest alternating with 29 s periods for each movement condition was used. The two movement conditions were presented in a pseudorandom order (ABBAAB, A for passive and B for active) and repeated ten times. Each active or passive movement block was composed of three repetitions of the push and pull movement with a small pause between the repetitions. Hence, there were a total of 30 active and passive movements in the whole run, which lasted about 20 min. Passive and active movements were visually and acoustically guided to ensure the active movements had approximately the same duration as the passive ones. The visual instruction was displayed on

a screen and consisted of a green and a red square. Each square was presented for 4 s and the green one was presented always first. During the active condition, participants were instructed to push the device when the green square was presented and to pull it when the red one was displayed. The auditory instruction for the active condition consisted of the words “stossen” (German: “to push”) and “ziehen” (German: “to pull”), which were synchronized with the green and red squares, respectively. During the rest and passive movement conditions, exactly the same colored squares were presented and the participants were asked to fixate the squares. The auditory instruction for the passive and rest conditions consisted of the words “stossen lassen” (German: “to be pushed”) and “ziehen lassen” (German: “to be pulled”) for the passive condition and “Pause” (German: “pause”) for the rest condition. The experimental paradigm was implemented by the program Presentation (http://www.neurobs.com/). It received trigger signals from the MRI system, provided the visual and auditory instructions to the subjects, and sent control commands to the manipulandum (Figure 1.5). With Presentation, the brain activation data and the behavioral data were synchronized.

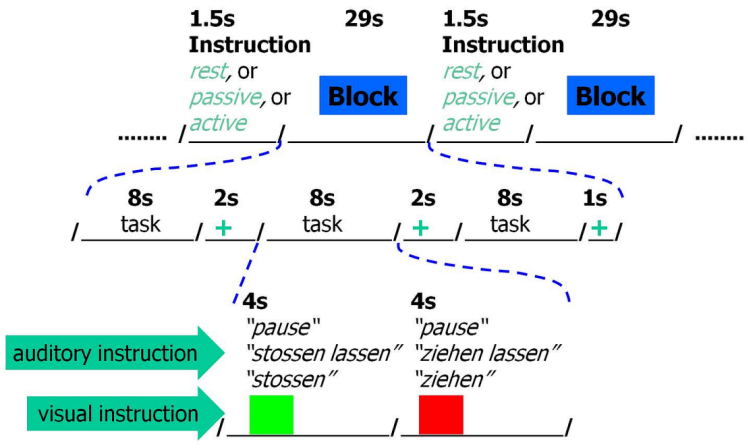

Figure 1.4
The block design paradigm

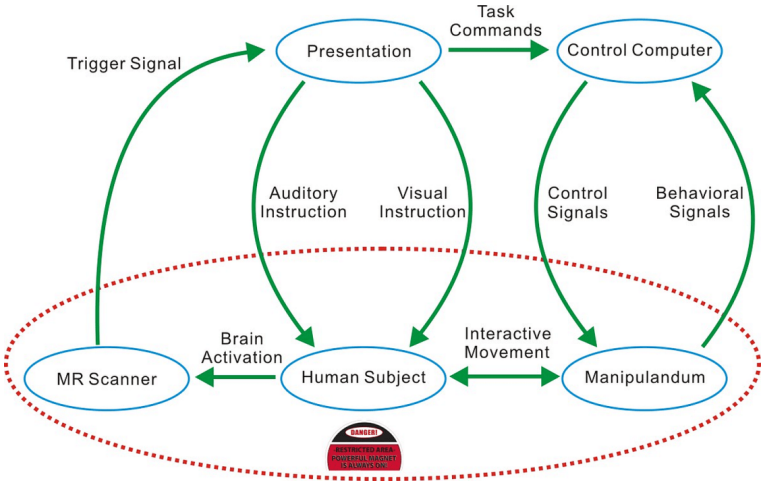

Figure 1.5
Illustration of the study: human subject, involved components and their interactions

The subjects were trained to practice the tasks prior to the scanning procedures outside of the scanner bore so that the designed tasks were executed properly. The fMRI session was repeated for all subjects three to four weeks after the first fMRI session to examine the repeatability and robustness of the brain activation elicited by the interested tasks.

Data analysis

Parameters of interest for assessing the motor performance in each block were the number of movements, the range of motion for each movement, and the force in each movement. These parameters were examined to check whether the functional tasks were executed in the desired way and were compared across active and passive conditions as well as the two fMRI sessions. Image processing and analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London, http://fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.6 (Mathworks Inc., Natick, MA, USA). Data pre-processing was carried out for each subject prior to the computation of the group analysis. Images were motion corrected by means of 7th Degree B-Spline interpolation (6-parameter spatial transformation). The movement parameters obtained during this procedure were used to determine the extent of movements. The data of participants that did not exceed a value of about half of the voxel size was included in the analysis. Functional images were normalized into standard space using the Montreal

Neurological Institute template (MNI). Spatial smoothing was performed by applying a Gaussian filter of 6 mm full-width at half-maximum (FWHM), to reduce the noise and enhance the signal. Additionally, a high-pass filter was applied to remove slow temporal drifts with a period longer than 256 s.

The statistical analysis was performed at two levels. At the first level, the experimental conditions were modeled by the general linear model (GLM) using a canonical hemodynamic response function. To further correct residual movement artifacts that were not removed by the previously mentioned motion correction procedure, the translation parameters obtained from this procedure were included in the design matrix of the model. Model estimation was performed on a subject-by-subject basis for each session separately in order to identify the general networks involved in the subject-active and subject-passive tasks by contrasting the induced brain activation with that in the rest condition. At the second level, group analysis was performed according to the random effects analysis using the single-subject contrast images obtained in the first step as input. One-sample t-tests were generated for each movement condition versus the rest condition and also for the comparison of the two movement conditions, for each session separately. The significance level for the resulting statistical maps was set at $p < 0.0001$ (extent threshold $k = 10$). To assess reproducibility and robustness of the brain activation elicited by the functional tasks, two-sample *t*-tests were generated for each contrast in each session, with a threshold at $p < 0.0001$ (extent threshold $k = 10$). Family-wise correction was not applied to the statistical tests, and this threshold was chosen because it is less conservative. Therefore, it could be more informative and show better activations in the expected network.

Results

Phantom test

The SNR and tSNR values of the nearest slice to the manipulandum were shown in Tables 1.1 and 1.2.

Table 1.1 Phantom test: signal, noise, and signal-to-noise-ratio (SNR)

Condition	SNR (dB)	Signal	Noise
Phantom only	38 (0.8)	1801 (2.8)	21.6 (2.1)
Device silent	38 (0.8)	1775 (4.0)	22.9 (2.3)
Device poweredON	38 (0.9)	1769 (4.0)	22.4 (2.3)
Device functioning	37 (0.9)	1775 (4.3)	24.8 (2.6)

Values are given as: mean (standard deviation)

Table 1.2 Phantom test: temporal signal, temporal noise, and temporal signal-to-noise-ratio (tSNR)

Condition	fSNR (dB)	Signal	Noise
Phantom only	44 (1.7)	1801 (18.7)	11.5 (2.2)
Device silent	44 (1.5)	1775 (19.6)	12.7 (2.1)
Device powered ON	42 (1.3)	1769 (18.4)	13.8 (2.0)
Device functioning	40 (1.7)	1775 (17.9)	17.9 (3.2)

Values are given as: mean (standard deviation)

It could be observed that good signal, high SNR and tSNR were obtained in all phantom experiments. Neither the introduction of the manipulandum into the MRI environment nor its functioning brought notable spatial or temporal disturbances to the fMRI procedures. Besides, visual inspection did not find significant differences among images obtained in different conditions. Therefore, it has been demonstrated that the manipulandum did not interfere with fMRI procedures.

Behavioral performance

All the subjects accomplished the two fMRI sessions and no subject reported any discomfort. Two subjects (one female, one male) were excluded from the analysis due to significant movement artifacts.

All passive movements were performed as designed in both fMRI sessions. During the active movement condition, a total of 390 movements were designed for all the thirteen subjects in each fMRI session. All active movements were performed in the first fMRI session, and four active movements were missed by two subjects in the second fMRI session. In general, the behavioral performance in the two fMRI sessions was quite similar, and no significant difference was observed.

The range of motion during passive movements varied from 16 to 20 cm between subjects depending on their size which caused some adjustments of the manipulandum. In the active condition, the range of motion depended on the voluntary effort of the subjects and was reduced compared to the passive condition (Figure 1.6).

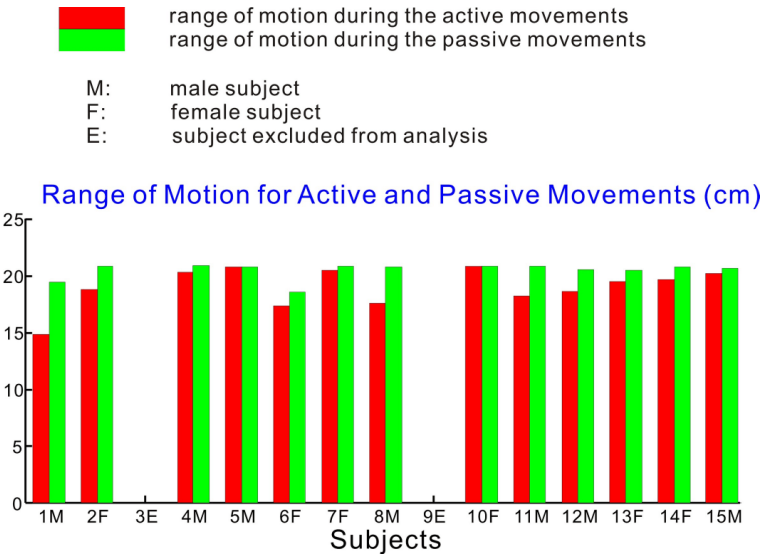

Figure 1.6
Range of motion during active and passive movements

When comparing the second with the first session for active movements, the average range of motion increased from 16.5 to 19.0 cm, although the average force decreased from 20.1 to 17.1 N. This can be partially explained by the fact that the average measured maximal force decreased from 54.6 to 46.5 N and, therefore, the force threshold of movements decreased from 10.9 to 9.3 N. The average force during passive movements increased from 0.2 to 0.6 N in the second measurement compared to the first measurement (Figure 1.7).

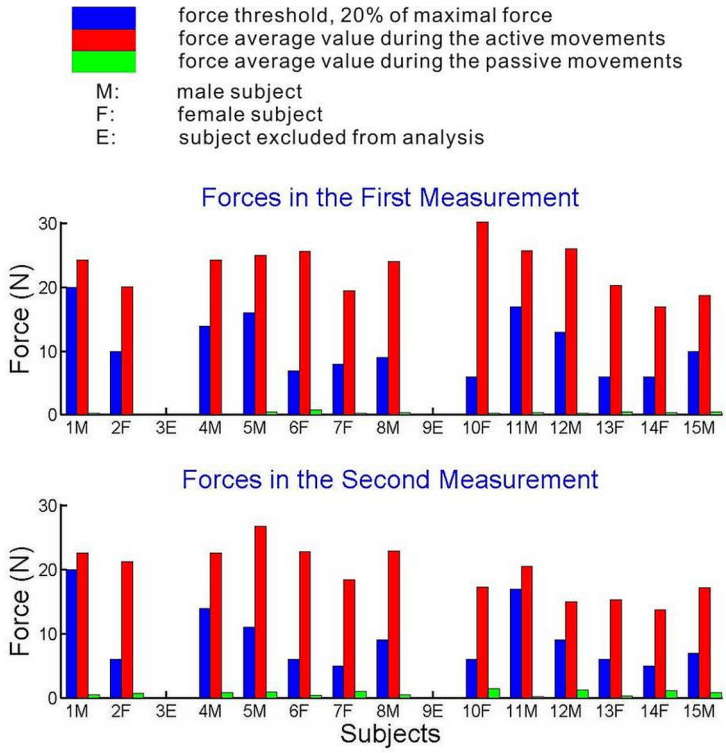

Figure 1.7
The measured forces during active and passive movements in the two measurements

Brain activation

When contrasting active movement condition versus rest in the first fMRI session, brain activation was detected in the contralateral sensorimotor cortex (M1/S1), and bilaterally in the secondary somatosensory cortex (S2), in the supplementary motor area (SMA), cingulate motor areas (CMA), the contralateral dorsal premotor cortex (PMd) and in the insula, ($p < 0.0001$, extent threshold[2] $k = 10$). Additionally activation was found in the ipsilateral cerebellum, and

[2] Extent threshold: the minimum cluster threshold.

bilaterally in the posterior cerebellum (CB), the thalamus and basal ganglia. During the second fMRI session, the same network was significantly activated, except for the posterior CB (Figure 1.8).

When contrasting the passive movement condition against rest, activation was found in the same brain regions during both sessions, but not in PMd and insula and only in the ipsilateral cerebellum ($p < 0.0001$, extent threshold $k = 10$; Figure 1.9). One-sample t-test analysis showed that activation was stronger in all regions of the aforementioned network during active when compared to passive movements ($p < 0.0001$, extent threshold $k = 10$). In the second session, the contrast between active and passive movements showed again significantly more activation during active movements, except in contralateral S2.

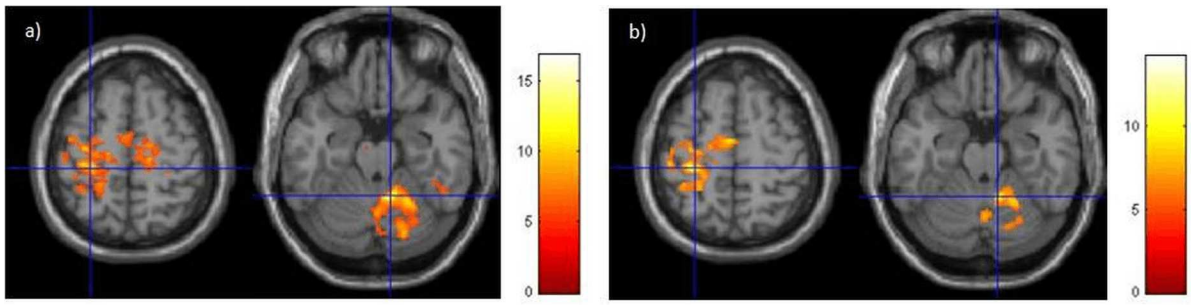

Figure 1.8 Activation for the contrast active movement versus rest **a)** in the first session and **b)** in the second session

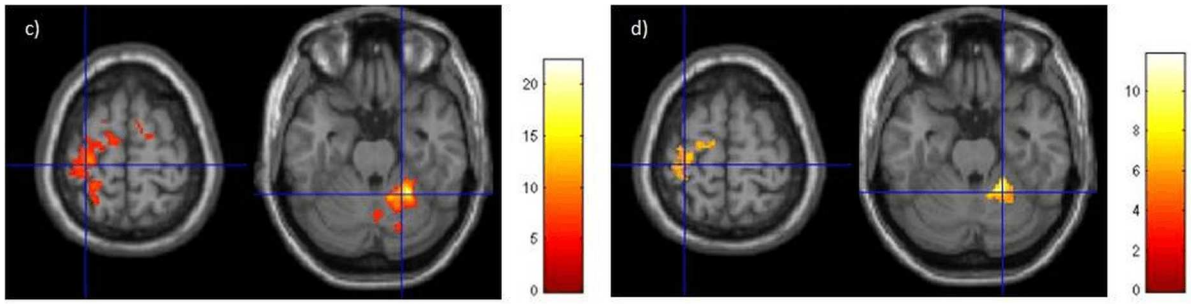

Figure 1.9 Activation for the contrast passive movement versus rest **c)** in the first session and **d)** in the second session

Although activation seemed to be stronger in all mentioned brain regions for the three contrasts during the first session compared to the second one, two-sample t-test analysis did not reveal significant differences between the two sessions in all these contrasts ($p < 0.0001$, extent threshold $k = 10$).

Additionally, activation was found in primary and secondary visual areas especially in the right hemisphere, although the same visual instruction was shown in all conditions and consequently the occipital activation should have been removed. This activation was stronger during the performance of active movements compared to passive movements. A possible explanation for this activation may be that participants saw part of the manipulandum while they had to move the handle actively or when the handle was moving by its own.

Discussion and Conclusion

The subjects' interaction with the new MRI-compatible manipulandum elicited activation in a brain network that included mainly the primary sensorimotor cortex, secondary somatosensory and medial and lateral premotor areas, as well as subcortical regions during the performance of passive and active movements. These findings are largely consistent with an earlier investigation on passive and active elbow movements (Weiller et al. 1996). In addition, activation in these areas was stronger when participants were voluntarily moving the handle than when they were guided by the manipulandum. This stronger activation may be explained by the fact that participants were applying voluntary force during the active condition but not during the passive one. Several studies already showed that increased force leads to stronger activation in the sensorimotor cortex (Dai et al. 2001; Cramer et al. 2002; Keisker et al. 2009).

When the two sessions were compared, slight changes in the measured parameters were observed. In the second session, the range of motion during active movements was bigger and the voluntary force during active movements was lower. This is probably due to the fact that

the maximal voluntary force was lower on average in the second session, leading to a lower force threshold. The two fMRI sessions showed no statistically significant differences in the brain activation. Previous findings in the literature on reproducibility of brain activation using functional imaging techniques are controversial. In some studies, repetition of specific tasks induced changes in brain activation (McGonigle et al. 2000; Loubinoux et al. 2001), while other studies reported robust activation across sessions (Carey et al. 2000; Alkadhi et al. 2002). A lack of reproducibility can be accounted by multiple factors such as familiarity to the MRI experiment and environment. Less attention, stress and memory effects may also reduce brain activation when participants become familiar with the procedure. For instance, Loubinoux and colleagues (Loubinoux et al. 2001) suggested that a long-term memory representation of the sensorimotor task can be implemented into the motor system along the sessions, leading to differences in cortical activation. Further, differences in task performance may influence the recorded brain activation and lead to inter-session variances. While some confounding variables, such as familiarity, cannot be controlled precisely, differences in task performance can be monitored by MRI-compatible devices, which can help to interpret differences in brain activation between sessions. Furthermore, MRI-compatible devices allow well-controlled and reproducible tasks and thus allow comparable sessions. Previous studies that used standardized movements reported high consistency of brain activation, suggesting that the performance of controlled movements can improve the reproducibility of brain activation (Carey et al. 2000; Alkadhi et al. 2002). In our investigation, we used a novel MRI-compatible manipulandum that allows adjustable, well-controlled and reproducible passive movements across fMRI sessions and subjects, interactive movements with various kinds of resistance, free switch between the active and passive movements under external control, and recording of the behavioral information such as position and force. The strong controlled settings enabled the re-occurrence of the same active and passive movements several weeks after, without inducing significant changes in brain activation.

Our study is promising for long-term studies in clinical settings with the application of MRI-compatible devices in the MRI environment to perform various functionally meaningful tasks. This suggests that our device can be used as an MRI-compatible tool to explore brain reorganization following injury and to evaluate rehabilitative interventions in patients suffering from damage to the central or peripheral nervous systems.

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6.3 Study #2

A reliability study on brain activation during active and passive arm movements supported by an MRI-compatible robot[§]

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Data were assessed by Natalia Estévez and Ningbo Yu and analyzed by Natalia Estévez. The manuscript was written by Natalia Estévez and revised by the co-authors.

Abstract

In neurorehabilitation, longitudinal assessment of arm movement-related brain function in patients with motor disability is challenging due to variability in task performance. MRI-compatible robots monitor and control task performance, yielding more reliable evaluation of brain function over time.

The main goals of the present study were first to define the brain network activated while performing active and passive elbow movements with an MRI-compatible arm robot (MaRIA) in healthy subjects, and second to test the reproducibility of this activation over time. For the fMRI analysis two models were compared. In model 1 movement onset and duration were included, whereas in model 2 force and range of motion were added to the analysis. Reliability of brain activation was tested with several statistical approaches applied on individual and group activation maps and on summary statistics.

The activated network included mainly the primary motor cortex, primary and secondary somatosensory cortex, superior and inferior parietal cortex, medial and lateral premotor regions, and subcortical structures. Reliability analyses revealed robust activation for active movements with both fMRI models and all the statistical methods used. Imposed passive movements also elicited mainly robust brain activation for individual and group activation maps, and reliability was improved by including additional force and range of motion using model 2.

These findings demonstrate that the use of robotic devices, such as MaRIA, can be useful to reliably assess arm movement-related brain activation in longitudinal studies and may contribute in studies evaluating therapies and brain plasticity following injury in the nervous system.

Keywords: fMRI, elbow flexion/extension, neurorehabilitation, MRI-compatible robotic devices, reliability, sensorimotor network

Introduction

Functional magnetic resonance imaging (fMRI) allows measuring brain function in a non-invasive manner and therefore offers the possibility to repeat measurements over time. This is an important prerequisite to address questions related to brain reorganization after central or peripheral damage of the nervous system and to plasticity following training or rehabilitation treatments. In longitudinal studies, the use of paradigms able to provide robust activation across sessions is crucial. For example, during motor tasks differences in movement parameters across sessions (i.e. force, frequency, range of movement) may cause large differences in brain activation, complicating the interpretation of the results. To ensure a comparable motor performance across sessions, the relevant parameters of the task must be adequately controlled and monitored.

Consistency across sessions is even more challenging when studying patients with motor impairments whose motor output, i.e. force, range of movement etc., may change over time. This variability in task performance may consequently prevent meaningful conclusions related to brain activation changes following rehabilitative interventions and reorganization processes after injury.

MRI-compatible robotic devices have the potential to overcome the aforementioned limitations by providing control and monitoring of the motor performance over time. They guide the subjects to perform well-controlled and reproducible passive sensorimotor tasks and provide standardized conditions for active movement execution (Yu et al. 2008; for review see Tsekos et al. 2007). Furthermore, movement parameters can be recorded and quantified by the robotic system during the actual experiment. The collected data can then be incorporated into fMRI data analysis allowing accurate interpretations. Thus, MRI-compatible robots are promising tools for investigating brain reorganization mechanisms and plasticity related to

neurorehabilitation by providing a well-controlled method for motor execution and for objectively monitoring the effect of therapy in patients with motor impairment.

For longitudinal assessments of brain function, test-retest analyses are essential to ensure that activation obtained with fMRI is reliable and does not randomly vary across repeated measures. In healthy subjects reliability of brain activation has been tested for a variety of cognitive and non-cognitive tasks (for review, see Bennett and Miller 2010). With respect to motor function, reliability has been mainly assessed for active finger or hand movements (Carey et al. 2000; Loubinoux et al. 2001; Yoo et al. 2007; Kong et al. 2007; Kimberley et al. 2008a; Kimberley et al. 2008b; Friedman et al. 2008; Gountouna et al. 2010; Lee et al. 2010; McGregor et al. 2012). In contrast, the reliability of brain activation patterns was rarely studied in passive motor tasks (Loubinoux et al. 2001). Only one study so far tested the reproducibility of activation in the primary motor cortex (M1) during active elbow flexion and extension (Alkadhi et al. 2002). Furthermore, to our knowledge there are no studies addressing reproducibility of passive arm movements. This is surprising, considering that arm movements are of major importance in the field of neurorehabilitation.

It is still a matter of debate which is the most appropriate test-retest analysis to assess reproducibility of brain activation. Therefore, different approaches were suggested, which all have advantages and disadvantages (for review, see Bennett and Miller 2010). The calculation of various aspects of reliability should therefore give a more detailed estimation of the reproducibility in an fMRI study (Specht et al. 2003).

In the present investigation we test the reliability of brain activation during active and passive arm movements in healthy subjects. To this purpose an MRI-compatible arm robot (MaRIA), which guides extension and flexion of the elbow joint, was used in an fMRI event-related design (ERD) (Yu et al. 2008; Yu et al. 2011). The device allows monitoring and quantifying relevant movement parameters (movement onset, duration, force and range of motion). Here we present

two possible fMRI models to show how this information can be best used to assess brain activation related to arm movements. This study had two main goals: first, to explore the brain network responsible for active and passive arm movements performed with MaRIA and second, to examine the reproducibility of this activation by applying various test-retest analyses. Since in future studies MaRIA will be used in various patient populations individual results are of major interest. Therefore, besides the reliability assessment on group results, the reproducibility of brain activation during active and passive arm movements was also tested at single-subject level.

Material and Methods

Participants

Nineteen healthy subjects (nine female, ten male, mean: 25 years, age range: 20-37 years) without history of neurological or psychiatric disorders were recruited for this study. All subjects had right-hand dominance (Annett 1970). The study was approved by the local ethics committee and all participants gave their written informed consent for participation prior to the experiment. In order to assess the reliability of arm movement-related brain activation the volunteers participated in two fMRI sessions at intervals of three to four weeks.

MaRIA

MaRIA was developed by the Sensory-Motor Systems Lab of the ETH Zurich (http://www.sms.hest.ethz.ch/research/mr_robotics/setup). The device (Figure 2.1) can be safely placed inside the MR scanner room, is compatible with fMRI, and allows extension and flexion movements of the elbow joint. A detailed description of this device was published in a pilot study (Yu et al. 2008; Yu et al. 2011). Therefore, only a brief description is provided here.

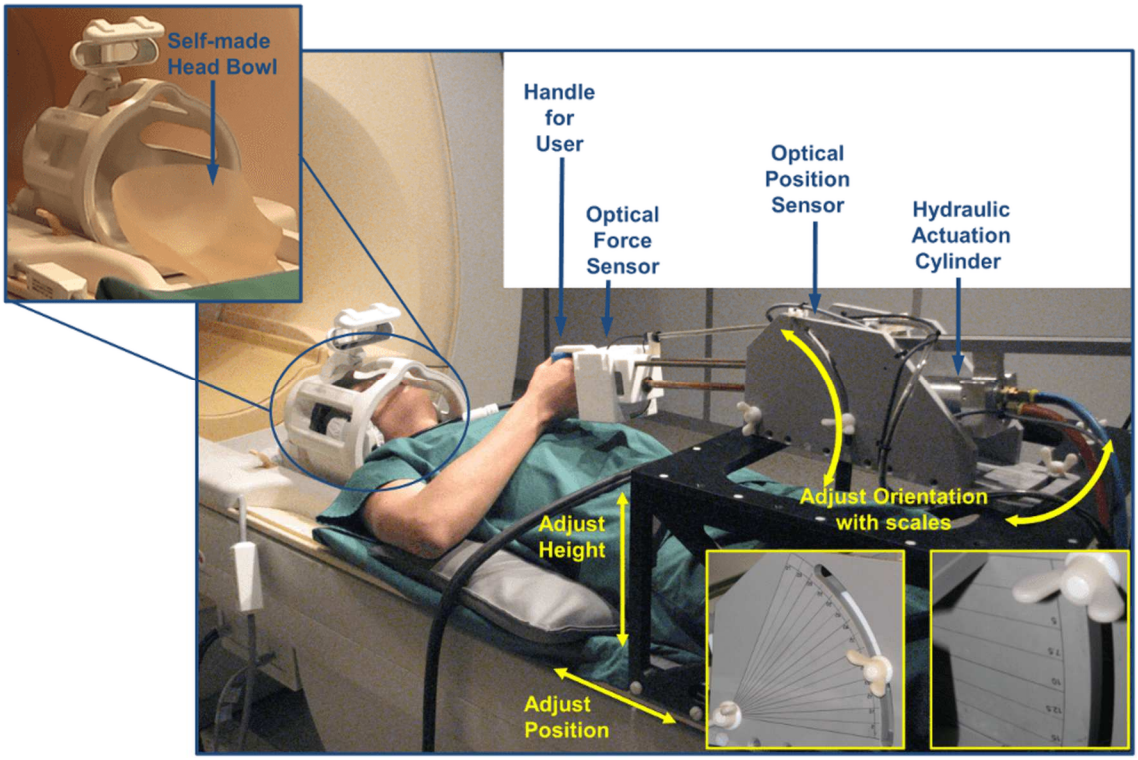

Figure 2.1 Experimental setup: MaRIA is positioned slightly above the legs of the patients. At start position the arm is placed at 90° flexion. The position and orientation can be adjusted to fit the size of the patients. The settings used during the first session are stored and used in subsequent sessions. A self-made head bowl is used to avoid motion artifacts (modified from (Yu et al. 2011) with permission of Springer Science and Business Media)

MaRIA allows adjustable, well-controlled, passive and active arm movements. It interacts with human subjects through a handle, which is attached to and driven by a hydraulic cylinder. The cylinder allows moving the handle in a translational direction, with a maximum motion range of 25 cm, maximum speed of 20 cm/s and force up to 300 N. An optical force sensor, installed between the handle and the cylinder, measures the push and pull forces from the subject's arm to the cylinder. In addition an optical encoder measures the position of the handle, thus providing the recording of the handle's range of motion for each movement. The sensors also enable the assessment of movement onset and duration. This timing information allows an exact modeling of the brain activation related to arm movements. The position, height and orientation of the device constrain the movement of the robot and can be adjusted to fit the size of each subject. To further standardize the performance of the tasks the parameters used during one

session are recorded for each subject and used in subsequent sessions. The device is controlled using MATLAB 7.6 (Mathworks Inc., Natick, MA, USA) and can be synchronized with other recording softwares, such as Presentation (http://www.neurobs.com/). Below we will refer to the range of motion of the device's handle as dROM.

fMRI procedure and experimental paradigm

For the fMRI scans, the participants were positioned supine on the MR scanner table with the fixation frame of the device above the subjects' thighs. The participants were asked to flex the right elbow to reach the handle. The position, height and orientation of MaRIA were adjusted to ensure that subjects could reach the handle and perform the tasks in a comfortable way, while the upper arm remained close to the body without causing shoulder and head motion. The elbow was supported by a cushion for better comfort and stabilization of the upper arm. At the start position, the elbow was flexed by 90°. A maximal elbow extension reached approximately 120°, so that the range of motion of the subjects' elbow was about 30°.

To reduce head motion artifacts during data acquisition, we used a custom-made head support, which covered the top and partially the sides of the subjects' head (Hollnagel et al. 2011), thus limiting the range of head motion, especially in the cranio-caudal direction (Figure 2.1). Additional foam pads restricted the motion in the left–right direction.

To investigate brain activation during the subjects' motor interactions with MaRIA, an ERD was used for the experiment. The experiment consisted of three conditions: passive arm movement, active arm movement and rest. In the passive condition, subjects were required to hold the device's handle and let it move without applying force. The speed was kept constant at 7.2 cm/s. In the active condition, subjects had to push and pull the handle actively. The movement could only be initiated when the force reached a certain threshold, defined as 20% of the subjects' maximal voluntary push force (MVPF). The MVPF was measured by MaRIA

for each subject in the scanner prior to fMRI scanning. Participants were instructed to push the fixed handle of the robot three times with their maximal voluntary force without moving head and body, and the mean force value was recorded. Above this threshold, an inverse viscous law was applied in such a way that an increase in the force applied by the subject induced an increase in the arm movement speed. Maximal speed was saturated to 10 cm/s when the force reached 30 N or beyond. For both, active and passive movements, low speed and smooth movements were selected to avoid head motion and potential moving artifacts in the images (Yu et al. 2008; Yu et al. 2009). The dROM was approximately 16–20 cm depending on the body size of the individual subject. For each subject, the dROM and the linear movement trajectory remained the same for all passive and active movements. During the period of rest, subjects were simply asked to hold the device's handle without applying force. In order to test the reliability of this procedure in a standardized way, the same setting configuration used during the first session was applied in the second.

A total of 30 trials per condition were presented randomly to the participants. Each trial lasted 13.5 s and was composed of a short instruction followed by 8 s of task period and of an inter-stimulus interval (ISI) with a jitter of 3±1 s. The duration of the whole run was about 20 min. Passive and active movements were visually and acoustically guided to ensure that the active movements were performed similarly across trials and sessions, and had the same duration as the passive ones. Visual instructions, displayed on a screen in front of the subject, consisted of a green and a red square being presented for 4 s each, with the green always presented first. During the active condition, participants were instructed to push the device upon appearance of the green square and to pull it when the red one was displayed. The auditory instruction for the active condition consisted of the words "stossen" (German: "to push") and "ziehen" (German: "to pull"), which were synchronized with the green and red squares, respectively. During the rest and passive movement conditions the same colored squares were presented and the participants were asked to fixate the squares. For the passive and rest conditions the auditory

instructions consisted of the words “stossen lassen” (German: “let it push”) and “ziehen lassen” (German: “let it pull”) and “Pause” (German: “pause”), respectively. The fMRI data acquisition and the tasks were synchronized applying Presentation (http://www.neurobs.com). This software received trigger signals from the MR system and provided the visual and auditory instructions to the subjects. Additionally, it sent control commands to MaRIA instructing the device to switch from one condition to the other, allowing the initiation of active or passive movements. Prior to both scanning sessions the subjects were trained to practice the tasks outside of the scanner bore to ensure proper task performance.

During each scanning session the change in force and dROM, measured by the force and position sensors during the tasks, were displayed simultaneously in real time on a monitor outside the scanner room, allowing constant monitoring by the investigators to ensure that the subjects were performing the tasks correctly.

Behavioural data analysis

To assess the motor performance the following parameters were computed for each subject and session separately: force and dROM per trial, as well as mean force and mean dROM for the 30 active and 30 passive movements separately.

During the arm movement itself, the force applied on the device’s handle was normalized by the MVPF. In each session the mean force values were normalized by the respective MVPF.

The parameters for the individual trials were visually inspected to check whether the motor tasks were executed correctly. To identify differences between sessions, paired t-tests were performed on the normalized mean force for the active and the passive movements. The Kolmogorov-Smirnov test for mean dROM for active and passive movements showed significant results, indicating that the values were not normally distributed. Therefore, to test differences in the mean dROM between sessions, nonparametric tests were applied.

MRI data acquisition

The study was carried out in the MR-center of the University and ETH Zurich, using a Philips Achieva 1.5 T MR system equipped with an eight channel SENSETM head coil. The functional acquisitions consisted of a T2* weighted, single-shot, field echo, EPI sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128 mm, in-plane resolution = 1.7 × 1.7 mm, slice thickness = 4 mm, SENSE factor 1.6). Additionally, anatomical images of the entire brain were acquired using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 4.6 ms, flip angle = 20°, in-plane resolution = 0.9 × 0.9 mm, slice thickness = 0.75 mm, 210 slices).

Data analysis

Image pre-processing and statistical analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London, http://fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.6 (Mathworks Inc., Natick, MA, USA). "Realign and unwarp" facility was applied on the EPI images to correct for motion artifacts and additional susceptibility-by-movement interactions. The motion parameters obtained during this procedure were used to determine the extent of movements. Functional data that did not exceed displacement of one voxel size was included in the analysis. The realigned functional images of each session were then co-registered with the T1-weighted structural images acquired during the first MRI session. To achieve an accurate registration of the images between both scanning sessions DARTEL registration (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) was performed (Ashburner 2007). With this procedure the realigned EPI images were normalized and smoothed with an 8 mm full-with half-maximum Gaussian kernel. Additionally, a high-pass filter was applied on the preprocessed functional images to remove slow temporal drifts with a period longer than 128s.

The statistical analysis was performed at single-subject and group level. At the single-subject level, the experimental conditions were modeled by the general linear model (GLM) using two approaches: first by explicitly modeling all three conditions, i.e. rest, passive and active arm movements (contrasts against rest), and second by modeling only the movement conditions, i.e. active and passive arm movements (single contrasts). Additionally, for each of these approaches two different types of models were performed for each subject. In the first model, the experimental conditions were modeled in a more classical way using only information about the movement onset and duration. The exact movement onset and duration of each task, needed for modeling, were provided by the device and a canonical hemodynamic response function was used. In the second model, besides the three or the two experimental conditions respectively, two user defined regressors per session were added into the design matrix of each participant. The first one consisted of the mean applied force per scan normalized by the MVPF and the second was the maximal dROM per scan recorded by the device. This model should help to reduce additional variance due to differences in performance. All the analyses described below were performed for both models separately.

For both models individual statistical parametric maps (SPM) were calculated for each movement condition versus rest (first approach) and for the single contrasts for active and passive arm movements (second approach) for each session separately. Group analysis was performed according to the random effects analysis using the single-subject contrast images as input. One-sample t-tests were performed for the four contrasts of interest per session. The significance level for the resulting statistical maps was set at $p < 0.05$, corrected for multiple comparisons (family wise error (FWE)). Additional analyses were performed at an uncorrected threshold of $p < 0.001$. Pair-t-tests were computed for the four contrasts to assess differences in activation maps across sessions.

Average and maximum t-values for each of the relevant contrasts were calculated in predefined anatomical regions of interest (ROIs) for both fMRI sessions separately. Differences in brain activation between the sessions were estimated by comparing the average t-value in each ROI using paired t-tests. The same analysis was also performed for the maximum t-value for each contrast and ROI. This analysis was performed in SPSS 19.0 (http://www.spss.com).

In the majority of the cases ROIs were defined based on probabilistic cytoarchitectonic maps implemented in the SPM anatomy toolbox (http://www.fz-juelich.de/ime/spm_anatomy_toolbox; Eickhoff et al. 2005; Eickhoff et al. 2006b; Eickhoff et al. 2007). The bilateral analyzed areas were the primary motor cortex (M1), including Brodmann area (BA) 4a and 4b (Geyer et al. 1996), the primary somatosensory cortex (S1) including BA 3a, 3b, 1 and 2 (Geyer et al. 1999; Geyer et al. 2000; Grefkes et al. 2001), and the secondary somatosensory cortex (S2) corresponding to the parietal operculum (OP1-4, Eickhoff et al. 2006a; Eickhoff et al. 2006b). Bilateral ROIs were also defined for the superior parietal cortex (SPC) including BA 5 and 7 (Scheperjans et al. 2008b; Scheperjans et al. 2008a) and inferior parietal cortex (IPC), comprising areas PFt, PF, PFm, PFcm, PFop, PGa, PGp (Caspers et al. 2006; Caspers et al. 2008). The supplementary motor area (SMA) and the cingulate motor areas (CMA) were defined using the Anatomic Automatic Labeling (AAL) (Tzourio-Mazoyer et al. 2002) implemented in the standard software WFU Pickatlas (Maldjian et al. 2003). In order to define the premotor cortex (PMC) and divide it into a ventral and a dorsal part, a ROI for the BA 6 was created using the anatomy toolbox (Geyer 2004). Subsequently, the SMA was subtracted from the BA6 using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). The remaining part was divided into the dorsal PMC (PMd) and the ventral portion of BA6 which together with BA 44 was defined as the ventral PMC (PMv). Based on the meta-analysis by Mayka et al. (Mayka et al. 2006) the boundary between these two regions was set between z = 35 (MNI z = 38) medially and z = 45 (MNI z = 49) laterally. Finally, ROIs

for the cerebellum (CB) were defined by combining all areas included in the anatomy toolbox (Diedrichsen et al. 2009).

Reliability analyses

All reliability measures reported below were only performed in the ROIs that were activated in at least 80% of the subjects, in all contrasts of interest and both sessions using both models. This allowed to reduce the data volume and to perform a reasonable comparison of the reliability values across both models and conditions. These regions were the contralateral M1, S1, SMA, PMd, and SPC.

Reliability of activation maps

For comparison with other reliability studies, the relative amount of overlapping volume $R^{ij}_{overlap}$ between the two sessions was calculated according to the formula introduced by Rombouts et al. (Rombouts et al. 1998):

$$R^{ij}_{overlap} = \frac{2 \times V_{overlap}}{V_i + V_j} \quad (1)$$

Where V_i and V_j denote the number of suprathreshold voxels within activation maps in session i and session j respectively, and $V_{overlap}$ represent the number of voxels that pass the threshold in both sessions. For the estimation of the $R^{ij}_{overlap}$ a statistical threshold of $p < 0.001$ (uncorrected for multiple comparisons) was used. The $R^{ij}_{overlap}$ can range from 0 (no overlap) to 1 (perfect overlap). This measure tests the reproducibility of the location of activated voxels above a threshold and is independent of the actual t-values of these voxels once they pass the threshold. In the present study, the $R^{ij}_{overlap}$ was used to assess test-retest reliability of brain activation of both the single subject data and the activation maps of the group analysis within predefine ROIs.

By setting a threshold, small differences in activation can be overestimated affecting considerably the size of the obtained $R^{ij}_{overlap}$. For example, some voxels may have a similar activation during both sessions, but may be below the threshold in one session and above it in the other. In spite of similar activation patterns these voxels would be classified as inconsistent between the sessions. To overcome this limitation, intraclass correlation coefficients (ICC) of contrast t-values for pairs of activation maps were calculated. This computation is based on all voxels in the brain and therefore, is not dependent on a threshold. In our study, test-retest reliability was computed across all voxels within each of the ROIs separately for individual and group activation maps. ICC values were calculated using a two-way mixed model ICC for consistency using the following formula (Shrout and Fleiss 1979):

$$\mathrm{ICC}(3,1) = \frac{\mathrm{BMS} - \mathrm{EMS}}{\mathrm{BMS} + (\mathrm{k} - 1) \times \mathrm{EMS}} \tag{2}$$

BMS and EMS denotes the mean square for between voxel and error variance respectively, and k is the number of sessions. The ICC ranges from 0 (low reliability) to 1 (perfect reliability). Although some reliability studies have been performed on fMRI data in the past, there is still no consensus regarding the acceptable level of reliability. In order to have a basis for comparison in our study, ICC values were classified as ‘excellent’ above 0.75, ‘good’ between 0.59 and 0.75, ‘fair’ between 0.40 and .58 and ‘poor’ for values lower than 0.40, as proposed by Cicchetti and Sparrow (Cicchetti and Sparrow 1981). In the following text ‘high’ will also be used for ‘excellent’ and ‘moderate’ for ‘fair’. The calculated coefficient represents a value for intra-voxel reliability and we will refer to it as ICC_{within} (Raemaekers et al. 2007).

To summarize the results of the single subjects, the average $R_{overlap}$ and the average ICC_{within} were calculated. In order to average the ICC_{within} values across subjects, Fisher’s z-transformation was applied on the ICC_{within} estimated for each subject.

Reliability of summary statistics

To assess test-retest reliability across subjects, ICC was also calculated on the average t-values and the maximum t-values for each ROI and contrast separately. ICC values were calculated using the same formula as before for the t-values of the individual and group activation maps (Shrout and Fleiss 1979). BMS and EMS denote the mean square for between subject and error variance respectively, and k denotes the number of sessions. In this case, the calculated coefficient represents a measure for between-subject reliability, referred as $ICC_{between}$. For this calculation, values are high for large between subject variance and small between session variance. The coefficients were tested against zero using a significance level of $p < 0.05$ (Shrout and Fleiss 1979).

Results

All 19 subjects accomplished the two fMRI sessions, but two (one female, one male) had to be excluded from the analysis, one due to the presence of significant movement artifacts and the other due to a technical problem in the synchronization of the tasks with the scanner.

Behavioral performance

All subjects performed all active and passive movements as instructed. Mean MVPF was 47.2 N (±24.3) at the first and 42.4 N (±22.7) at the second session. The mean force for active movements was 20.0 N (±2.5) during the first and 17.8 N (±2.0) during the second session, while for passive movements the mean force was 3.5 N (±1.6) and 4.0 N (±1.4), respectively. Paired sample t-tests performed on the normalized force values for each movement condition and for MVPF did not show any significant differences in performance between sessions (passive, $t(16) = -1.29$, $p(16) = 0.21$; active, $t(16) = 0.33$, $p(16) = 0.75$; MVPF, $t(16) = 2.1$, $p = 0.053$). In the active movement condition, the mean dROM was 17.1 cm (±1.8) during the first session and 18.3 cm (±2.1) during the second one. For passive movements, the mean

dROM was 18.0 cm (±1) and 19.5 cm (±0.6), respectively. Furthermore, non-parametric tests on the dROM values did not differ significantly between sessions (passive, $z = -1.9$, $p = 0.61$; active, $z = -1.4$, $p = 0.15$).

Brain activation

Model 1

In model 1, the experimental conditions were modeled using information about the movement onset and duration provided by the device.

In the first fMRI session, when contrasting the active movement condition with rest, group analysis revealed activation in left M1, S1, CMA, SPC, anterior insula and in the right anterior and posterior CB. Bilateral activation was found in S2, IPC, SMA, PMd, PMv and the mid insula ($p < 0.05$ corrected for multiple comparisons). During the second session, similar activation patterns were found, except in the PMv and in the left insula. Additionally,CMA was activated bilaterally. For both sessions, all reported areas were activated bilaterally when a less conservative correction was applied ($p < 0.001$ uncorrected for multiple comparisons). Additionally, activation was detected in the right middle temporal gyrus, bilaterally in the posterior insula and the basal ganglia, and in the left thalamus and brainstem (Figure 2.2a). For the single contrast, active movement activation was found left in M1, S1, SMA, PMd, SPC, bilaterally in S2, IPC, and in the right PMv, CMA and anterior CB during the first session. During the second session this first model showed activation only in left M1, S1, SMA, PMd, SPC and right in IPC ($p < 0.05$ corrected for multiple comparisons). In both sessions, non-corrected activation maps revealed activation in the same network as for the active movement condition contrasted with rest with the exception of the left thalamus, right basal ganglia and right middle temporal gyrus (Figure. 2.2b).

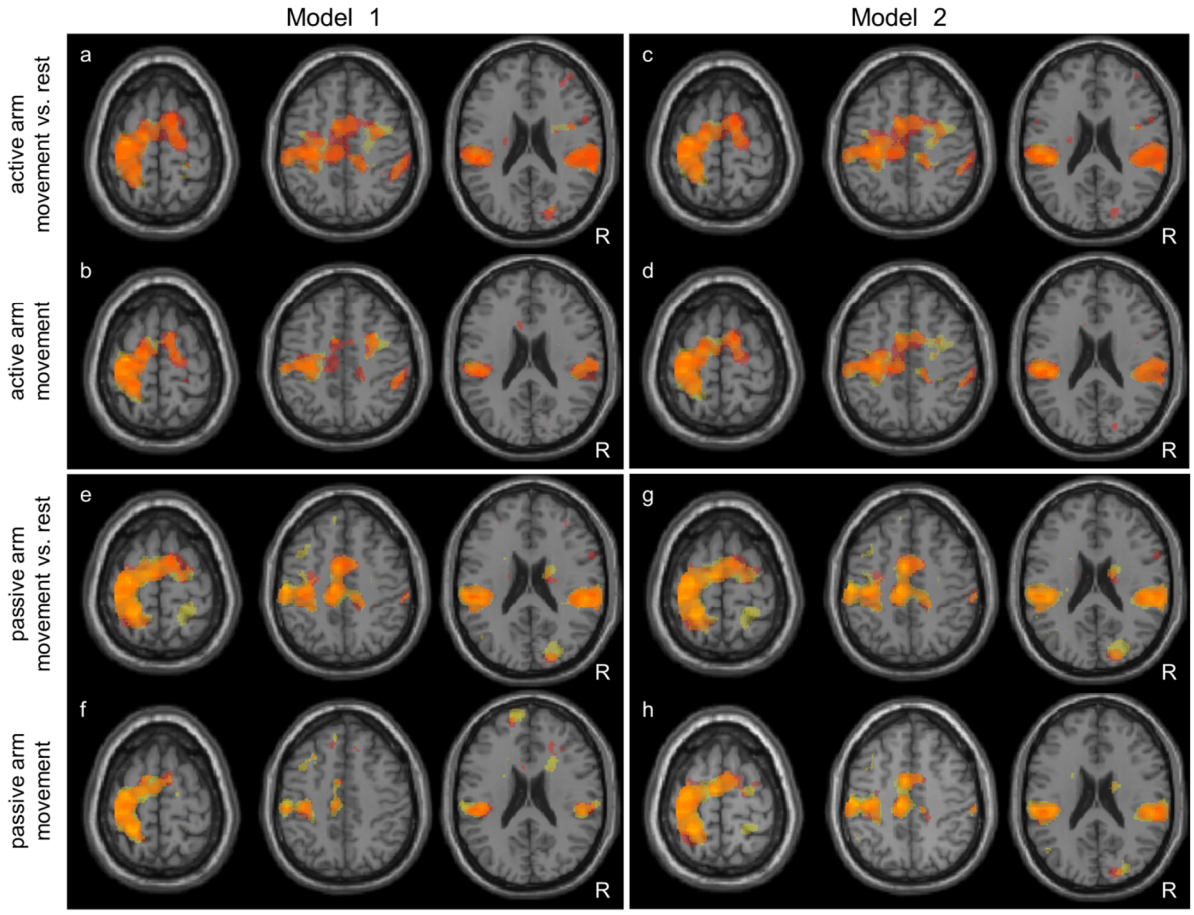

Figure 2.2 Transversal sections showing the overlap of activation in both fMRI sessions for all contrasts of interest and for model 1 (a, b, e, f) and model 2 (c, d, g, h) ($p < 0.001$ uncorrected for multiple comparisons). Activation during first session (red), second session (yellow) and in both sessions (orange) were superimposed on a single subject template using xjView (http://people.hnl.bcm.tmc.edu/cuixu/xjView/). The most informative slices are displayed

When contrasting passive movement with rest for both fMRI sessions, the group activation patterns were similar to those in the contrast active movement versus rest. Only the insula and the PMv were not activated. In addition, activation was found in the left anterior CB during the first session. PMd was activated during the first session bilaterally and only on the left during the second one. Bilateral activation was found in CMA during both sessions ($p < 0.05$ corrected for multiple comparisons). For both sessions, all areas of this network showed bilateral activation when the activation maps were not corrected for multiple comparisons ($p < 0.001$). Additional activation was detected in the left thalamus and in the basal ganglia, middle temporal gyrus, PMv and the mid and posterior insula bilaterally (Figure 2.2e). For the single contrast,

passive movement activation was found in the left M1, S1, PMd and IPC in both sessions. Activation in S2 was only detected in the left hemisphere during the first session. When activation maps were not corrected for multiple comparisons ($p < 0.001$) the same activation pattern was found as for the contrast of passive movements versus rest, except for the right M1, S1, SPC, PMv and left CB (Figure 2.2f).

For both active and passive movements, the single contrast showed in general less activation when compared to the contrast with rest. Coordinates for local maxima for all contrasts and ROIs using model 1 are shown in Table 2.1.

Table 2.1 Coordinates of local maxima (MNI) for all ROIs and contrasts of interest during the first and second session using model 1.

Model 1													
Active arm movement													
ROI		**Contrast with rest**						**Single contrast**					
		Session 1			Session 2			Session 1			Session 2		
		x	y	z	x	y	z	x	y	z	x	y	z
M1	L	**-32**	**-27**	**60**	**-33**	**-21**	**57**	**-27**	**-21**	**53**	**-33**	**-21**	**59**
	R	12	-30	50	9	-29	48	20	-26	57	26	-33	65
S1	L	**-33**	**-30**	**59**	**-30**	**-32**	**59**	**-33**	**-30**	**59**	**-32**	**-30**	**62**
	R	17	-35	50	**36**	**-27**	**38**	20	-39	56	36	-27	38
SMA	L	**-8**	**-6**	**54**	**-14**	**-12**	**65**	**-12**	**-11**	**53**	**-15**	**-11**	**63**
	R	**12**	**1**	**66**	**12**	**0**	**65**	15	-11	66	14	0	62
CMA	L	**-6**	**3**	**42**	**-8**	**1**	**44**	-8	-6	50	-8	1	41
	R	17	-30	42	**11**	**-29**	**44**	**18**	**-30**	**42**	**15**	**-29**	**41**
PMd	L	**-27**	**-21**	**60**	**-30**	**-18**	**57**	**-29**	**-20**	**56**	**-29**	**-20**	**56**
	R	**21**	**-17**	**65**	**35**	**-3**	**45**	20	-18	65	39	-3	44
PMv	L	**-44**	**9**	**6**	-42	-6	50	-50	1	6	-48	3	6
	R	**54**	**7**	**9**	48	9	8	**54**	**6**	**8**	44	-3	44
SPC	L	**-21**	**-41**	**62**	**-18**	**-42**	**63**	**-18**	**-39**	**63**	**-20**	**-41**	**65**
	R	15	-29	41	11	-29	44	17	-29	42	15	-29	41
IPC	L	**-51**	**-30**	**23**	**-51**	**-30**	**23**	**-51**	**-30**	**23**	-51	-29	23
	R	**60**	**-26**	**23**	**57**	**-26**	**30**	**57**	**-32**	**41**	**63**	**-27**	**35**

Table 2.1 continued

Model 1

Active arm movement

ROI		Contrast with rest						Single contrast					
		Session 1			Session 2			Session 1			Session 2		
		x	y	z	x	y	z	x	y	z	x	y	z
S2	L	**-48**	**-30**	**23**	**-44**	**-32**	**23**	**-48**	**-30**	**23**	-50	-29	23
	R	**62**	**-26**	**23**	**56**	**-27**	**26**	**62**	**-24**	**23**	44	-29	26
CB	L	2	-65	-16	-2	-48	-24	0	-51	-26	0	-50	-24
	R	**20**	**-54**	**-20**	**21**	**-50**	**-23**	**9**	**-53**	**-15**	21	-53	-21

Passive arm movement

ROI		Contrast with rest						Single contrast					
		Session 1			Session 2			Session 1			Session 2		
		x	y	z	x	y	z	x	y	z	x	y	z
M1	L	**-32**	**-26**	**59**	**-33**	**-32**	**56**	**-33**	**-26**	**57**	**-33**	**-27**	**66**
	R	2	-21	50	0	-26	50						
S1	L	**-33**	**-30**	**59**	**-32**	**-33**	**59**	**-33**	**-30**	**59**	**-24**	**-41**	**57**
	R	20	-33	47	24	-44	65				23	-41	57
SMA	L	**0**	**3**	**47**	**-8**	**-6**	**56**	-12	-6	71	-8	-11	74
	R	**11**	**3**	**68**	**2**	**-3**	**53**	11	0	69	6	-5	59
CMA	L	**-8**	**-23**	**47**	**-12**	**-26**	**41**	-6	-18	48	-9	-21	44
	R	**3**	**3**	**44**	**12**	**7**	**38**	12	27	18	14	9	38
PMd	L	**-35**	**-27**	**69**	**-35**	**-27**	**69**	**-35**	**-27**	**69**	**-35**	**-27**	**69**
	R	**3**	**3**	**44**	**0**	**-24**	**47**	0	-17	53	0	-17	53
PMv	L	-50	1	6	-44	-8	53	-50	1	6	-44	-12	53
	R	57	7	8	53	3	0						
SPC	L	**-23**	**-44**	**62**	**-18**	**-42**	**63**	-23	-42	62	**-24**	**-42**	**66**
	R	17	-35	44	14	-27	45				**20**	**-53**	**60**
IPC	L	**-51**	**-29**	**21**	**-51**	**-32**	**20**	**-51**	**-29**	**23**	**-59**	**-29**	**26**
	R	**60**	**-33**	**23**	**60**	**-35**	**24**	54	-27	29	53	-32	24
S2	L	**-50**	**-30**	**20**	**-44**	**-27**	**20**	**-45**	**-30**	**21**	-44	-26	21
	R	**60**	**-26**	**24**	**53**	**-29**	**24**	56	-27	26	53	-29	24
CB	L	**-33**	**-48**	**-33**	2	-60	-14	0	-69	-6	-14	-62	-9
	R	**26**	**-50**	**-21**	**21**	**-48**	**-21**	17	-56	-12	24	-53	-20

bold: denote activations corrected for multiple comparisons with FWE $p < 0.05$; non-bold: denote uncorrected activations with a threshold of $p < 0.001$.

ROI: region of interest; M1: primary motor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; CMA: cingulate motor areas; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; SPC: superior parietal cortex; IPC: inferior parietal cortex; S2: secondary somatosensory cortex; CB: cerebellum.

Model 2

In this model, besides the experimental conditions, additional movement parameters (i.e., force and dROM) provided by the device were implemented into the data analysis.

Applying model 2, the active movement condition compared to rest showed for both sessions the same activation patterns as in the analysis with the first model. This was the case using both thresholds ($p < 0.05$ corrected and $p < 0.001$ uncorrected for multiple comparisons, Figure 2.2c). For both fMRI sessions the single contrast for active movements revealed activation in left M1, S1, SMA, CMA, PMd, SPC, in S2, IPC bilaterally, and in right PMv, and right posterior CB. During the second session activation was also found in the right mid insula and CMA ($p < 0.05$ corrected for multiple comparisons). Uncorrected activation maps revealed for both sessions the same network as in the active movement condition contrasted with rest, except for the right middle temporal gyrus (Figure 2.2d).

For both sessions and thresholds the activation patterns in the passive movement condition compared to rest activation were similar to those reported for model 1 ($p < 0.05$ corrected and $p < 0.001$ uncorrected for multiple comparisons, Figure 2.2g). For the single contrast passive movement activation was found in the same network as in the contrast with rest, except for the bilateral activation in SMA and CMA during the first session. Using this second model, the same activation patterns as those for passive movement condition contrasted with rest were found when the activation maps were not corrected for multiple comparisons ($p < 0.001$, Figure 2.2h).

For active and passive movement, the activation pattern of the contrast with rest and the single contrast were largely identical. Coordinates for local maxima for all contrasts and ROIs using model 2 are shown in Table 2.2.

Table 2.2 Coordinates of local maxima (MNI) for all ROIs and contrasts of interest during the first and second session using model 2.

Model 2													
Active arm movement													
ROI		**Contrast with rest**						**Single contrast**					
		Session 1			Session 2			Session 1			Session 2		
		x	y	z	x	y	z	x	y	z	x	y	z
M1	L	**-30**	**-20**	**53**	**-32**	**-20**	**54**	**-30**	**-20**	**53**	**-32**	**-20**	**54**
	R	12	-30	51	11	-29	48	12	-30	51	11	-29	48
S1	L	**-33**	**-30**	**59**	**-30**	**-32**	**60**	**-33**	**-30**	**59**	**-32**	**-30**	**62**
	R	17	-35	50	33	-29	39	17	-33	50	36	-27	38
SMA	L	**-8**	**-6**	**56**	**-14**	**-12**	**63**	**-8**	**-8**	**56**	**-14**	**-12**	**63**
	R	**12**	**0**	**66**	**12**	**-2**	**66**	**12**	**0**	**65**	**12**	**-2**	**66**
CMA	L	**-8**	**3**	**42**	**-8**	**3**	**44**	**-8**	**3**	**42**	**-8**	**3**	**44**
	R	17	-30	44	**11**	**-29**	**45**	17	-30	44	**12**	**-27**	**45**
PMd	L	**-26**	**-20**	**59**	**-32**	**-18**	**60**	**-26**	**-20**	**62**	**-33**	**-18**	**59**
	R	**20**	**-18**	**65**	17	-12	62	20	-18	65	14	-8	63
PMv	L	**-45**	**9**	**3**	-48	3	6	-50	1	6	-44	-12	53
	R	**56**	**7**	**11**	50	7	6	**56**	**7**	**9**	50	7	6
SPC	L	**-14**	**-26**	**48**	**-18**	**-42**	**63**	**-14**	**-26**	**48**	**-18**	**-42**	**63**
	R	17	-30	44	11	-29	45	17	-30	44	11	-29	47
IPC	L	**-51**	**-30**	**23**	**-42**	**-32**	**21**	**-50**	**-32**	**23**	**-42**	**-32**	**21**
	R	**51**	**-27**	**32**	**56**	**-27**	**30**	**51**	**-27**	**32**	**51**	**-26**	**29**
S2	L	**-48**	**-30**	**23**	**-42**	**-32**	**23**	**-48**	**-30**	**23**	**-44**	**-30**	**21**
	R	**62**	**-26**	**24**	**44**	**-24**	**26**	**62**	**-24**	**23**	**44**	**-24**	**26**
CB	L	0	-71	-7	2	-63	-14	0	-62	-18	2	-63	-14
	R	**25**	**-48**	**-25**	**21**	**-50**	**-23**	**25**	**-48**	**-25**	**21**	**-50**	**-23**

Table 2.2 continued

Model 2

Passive arm movement

ROI		Contrast with rest						Single contrast					
		Session 1			Session 2			Session 1			Session 2		
		x	y	z	x	y	z	x	y	z	x	y	z
M1	L	**-32**	**-27**	**60**	**-33**	**-32**	**56**	**-33**	**-29**	**59**	**-32**	**-29**	**62**
	R	2	-21	50	0	-26	50	2	-21	50	2	-23	48
S1	L	**-33**	**-30**	**59**	**-32**	**-32**	**59**	**-33**	**-30**	**59**	**-33**	**-32**	**59**
	R	33	-38	53	24	-42	66	33	-35	56	32	-38	53
SMA	L	**0**	**3**	**47**	**-8**	**-20**	**50**	-3	-3	56	**-8**	**-20**	**50**
	R	**11**	**0**	**66**	**2**	**-3**	**53**	11	0	66	**6**	**-2**	**60**
CMA	L	**-2**	**0**	**47**	**-3**	**0**	**47**	-8	-23	48	**-8**	**-23**	**45**
	R	**3**	**3**	**44**	**12**	**7**	**38**	2	1	44	11	7	39
PMd	L	**-33**	**-26**	**71**	**-35**	**-27**	**69**	**-33**	**-26**	**71**	**-35**	**-27**	**69**
	R	**0**	**0**	**47**	0	0	47	0	0	47	0	0	47
PMv	L	-54	7	14	-44	-8	53	-50	1	6	-44	-9	53
	R	63	11	5	62	11	5	63	11	5	62	14	3
SPC	L	**-23**	**-50**	**71**	**-18**	**-42**	**63**	-21	-50	71	**-24**	**-44**	**68**
	R	17	-35	44	14	-27	45	17	-33	42	21	-44	68
IPC	L	**-51**	**-29**	**21**	**-51**	**-29**	**20**	**-51**	**-30**	**23**	**-59**	**-26**	**21**
	R	**60**	**-35**	**23**	**60**	**-35**	**24**	**60**	**-29**	**24**	**53**	**-29**	**23**
S2	L	**-50**	**-30**	**20**	**-42**	**-29**	**18**	**-47**	**-30**	**21**	**-44**	**-29**	**20**
	R	**45**	**-30**	**21**	**53**	**-29**	**24**	**56**	**-27**	**26**	**53**	**-29**	**24**
CB	L	**-33**	**-51**	**-33**	-26	-56	-33	**-30**	**-54**	**-35**	2	-65	-17
	R	**26**	**-50**	**-21**	**21**	**-47**	**-21**	**24**	**-50**	**-20**	**20**	**-63**	**-20**

bold: denote activations corrected for multiple comparisons with FWE $p < 0.05$; non-bold: denote uncorrected activations with a threshold of $p < 0.001$.

ROI: region of interest; M1: primary motor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; CMA: cingulate motor areas; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; SPC: superior parietal cortex; IPC: inferior parietal cortex; S2: secondary somatosensory cortex; CB: cerebellum.

Systematic changes in brain activation

For both models and all contrasts of interest, paired-t-tests analysis computed on the activation maps did not reveal any significant differences between sessions ($p < 0.05$ corrected for multiple comparisons). Additionally, no significant differences were found on average t-values for all the contrasts in the predefined ROIs. For the ROI analyses significant differences were

only found on maximum t-values for the single contrast of active movements in contralateral M1 and S1 using model 1 ($p < 0.05$ non-corrected for multiple comparisons). For all other contrasts of interest and for model 2 no significant differences were found on maximum t-values.

Reliability analyses

Reliability of activation maps

Overlap ratios ($R_{overlap}$)

The averages $R_{overlap}$ of the single subjects are presented in Table 2.3 for the two models. For both models the contrasts of the movement conditions with rest showed good to excellent reliability for activation in M1, S1, and PMd. Reliability ranged from moderate to good for SMA and moderate for SPC. In all ROIs except for the SPC, the $R_{overlap}$ calculation revealed slightly higher values for the active movement condition compared to rest using model 1 than with model 2. The opposite was observed for the passive movement condition against rest. For both single contrasts (i.e. active and passive arm movements), reliability was mainly good when modeling the data with model 1, only the SMA and SPC showed moderate values. For model 2, the $R_{overlap}$ values were higher for both conditions in all ROIs than using model 1. This was especially the case for the passive movement condition.

For group activation, all ROIs showed high reliability using both models (see Table 2.3). Analog to the single subjects' data, group activation maps showed mainly higher reliability for both single contrasts when controlling for motor performance.

Table 2.3 Average $R_{overlap}$ and average ICC_{within} for individual activation maps and $R_{overlap}$ and ICC_{within} for group activation maps of the four contrasts of interest using both models.

ROI	**Mean $R_{overlap}$**							
	Model 1				Model 2			
	active vs rest	active	passive vs rest	passive	active vs rest	active	passive vs rest	passive
Single subjects								
M1	0.79	0.75	0.74	0.63	0.78	0.77	0.77	0.75
S1	0.76	0.69	0.72	0.64	0.72	0.71	0.77	0.74
SMA	0.63	0.56	0.49	0.40	0.61	0.61	0.56	0.55
PMd	0.76	0.73	0.73	0.64	0.73	0.71	0.76	0.75
SPC	0.45	0.44	0.47	0.42	0.46	0.47	0.49	0.49
Group								
M1	0.96	0.95	0.84	0.86	0.96	0.96	0.85	0.85
S1	0.96	0.92	0.94	0.89	0.94	0.92	0.94	0.92
SMA	0.94	0.86	0.94	0.88	0.93	0.91	0.94	0.94
PMd	0.95	0.87	0.92	0.83	0.94	0.93	0.92	0.92
SPC	0.87	0.80	0.84	0.84	0.86	0.82	0.84	0.79

ROI	**Mean ICC**							
	Model 1				Model 2			
	active vs rest	active	passive vs rest	passive	active vs rest	active	passive vs rest	passive
Single subjects								
M1	0.90	0.88	0.86	0.80	0.89	0.89	0.87	0.87
S1	0.88	0.86	0.86	0.80	0.88	0.87	0.87	0.87
SMA	0.80	0.79	0.74	0.63	0.77	0.76	0.75	0.72
PMd	0.84	0.83	0.83	0.79	0.83	0.83	0.84	0.83
SPC	0.72	0.73	0.64	0.68	0.72	0.71	0.65	0.65
Group								
M1	0.97	0.97	0.96	0.95	0.97	0.97	0.96	0.96
S1	0.98	0.97	0.93	0.92	0.97	0.97	0.93	0.92
SMA	0.93	0.90	0.93	0.94	0.93	0.92	0.92	0.92
PMd	0.91	0.92	0.93	0.91	0.93	0.94	0.93	0.92
SPC	0.94	0.94	0.90	0.91	0.94	0.94	0.89	0.86

ROI: region of interest; ICC: intraclass correlation coefficient; $R_{overlap}$: relative amount of overlapping volume between sessions; M1: primary motor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; PMd: dorsal premotor cortex; SPC: superior parietal cortex. All the ROIs are in the left hemisphere, contralateral to the moving arm.

Intra class correlation (ICC_{within})

Average ICC values for single subject and ICC values obtained for group activation maps are given in Table 2.3. For single subjects the intraclass correlation of t-values between the two sessions showed high reliability in M1, S1, and PMd and good reliability in SMA and SPC for all contrasts of interest and both models. Analog to the calculation of $R_{overlap}$, model 2 yielded better reliability for the single contrast of passive movements. For all contrasts and using both models group results were found to be highly reproducible for all ROIs.

Reliability of summary statistics

Intra class correlation ($ICC_{between}$)

Results for the ICC on average and maximum t-values are presented in Table 2.4. For the active movement condition in both, contrasts with rest and single contrasts, good to excellent reliability was found. The ICC values were significant in all ROIs analyzed with both models. ICC values were mainly higher for model 1 than for model 2.

The contrasts using passive movements showed low to good reproducibility. For model 1, the passive condition compared to rest showed significant values for M1, S1 and SMA, but not for PMd and SPC for average t-values. For the single contrast, intraclass correlations were only significant in M1 and SMA. However, using model 2, average t-values for all ROIs, except PMd, showed moderate but significant ICC values for both contrasts of passive movements (i.e. single contrast and contrast with rest), suggesting that this model improves the reliability of activations. For maximum t-values, all ROIs showed significant intraclass correlations in both models. Only intraclass correlation of SMA was not significant for both models and SPC for the first one.

Table 2.4 $ICC_{between}$ for average and maximum t-values of the four contrasts of interest using both models.

	ICC of average t-values							
	Model 1				Model 2			
ROI	active vs rest	active	passive vs rest	passive	active vs rest	active	passive vs rest	passive
M1	0.80*	0.72*	0.65*	0.48*	0.75*	0.72*	0.59*	0.56*
S1	0.83*	0.77*	0.59*	0.40	0.75*	0.74*	0.58*	0.51*
SMA	0.67*	0.63*	0.44*	0.44*	0.67*	0.67*	0.47*	0.51*
PMd	0.82*	0.74*	0.40	0.29	0.75*	0.73*	0.38	0.37
SPC	0.72*	0.65*	0.40	0.26	0.58*	0.53*	0.45*	0.51*
	ICC of maximum t-values							
	Model 1				Model 2			
ROI	active vs rest	active	passive vs rest	passive	active vs rest	active	passive vs rest	passive
M1	0.82*	0.75*	0.76*	0.56*	0.77*	0.69*	0.73*	0.63*
S1	0.83*	0.81*	0.71*	0.53*	0.82*	0.79*	0.71*	0.62*
SMA	0.69*	0.72*	0.33	0.36	0.66*	0.71*	0.32	0.37
PMd	0.71*	0.64*	0.63*	0.47*	0.63*	0.60*	0.59*	0.53*
SPC	0.81*	0.75*	0.52*	0.38	0.7*	0.66*	0.54*	0.47*

*: significant ICC values ($p < 0.05$).

ROI: region of interest; ICC: intraclass correlation coefficient; M1: primary motor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; PMd: dorsal premotor cortex; SPC: superior parietal cortex. All the ROIs are in the left hemisphere, contralateral to the moving arm.

Discussion

This study explores the brain network activated by active and passive elbow movements performed with the support and guidance of an MRI-compatible robot (MaRIA) and tests the reproducibility of this activation. Brain activation was found in expected areas of the sensorimotor network for elbow movements and was reliable across sessions at single-subject and group level. Thus, this device may allow longitudinal assessments of brain function in healthy subjects and potentially, in future studies on patients.

This outcome was possible assessing the following methodological approach. Quantitative data of the movement performance - onset, duration, force and dROM (device's range of motion) - provided by the robot were used to analyze the fMRI data. Two models were tested. With the first (model 1), the movement onset and duration were incorporated into the data analysis, allowing precise modeling of the performed movement. In the second approach (model 2), force and dROM were additionally implemented in the analysis as regressors removing variance in movement performance between trials. In order to provide a detailed estimation of the reproducibility of brain activation acquired with these approaches several statistical methods were applied on individual and group data.

For active movements, both models exhibited brain activation in a network including mainly the primary sensorimotor cortex (M1 and S1), secondary somatosensory cortex, insula, superior and inferior parietal lobules and medial and lateral premotor areas. Additionally, activation was found in anterior and posterior cerebellum, basal ganglia, thalamus and brain stem. These findings are largely consistent with earlier investigations of simple elbow movements (Weiller et al. 1996; Alkadhi et al. 2002). By visually inspecting both sessions, the contrast of active movements versus rest showed slightly higher activation than the single contrast using both models. However, activation power increased for the single contrast by including additional movement parameters using model 2, yielding activation patterns largely identical to the contrast with rest.

With respect to reliability, robust activation was elicited consistently with all applied statistical methods and both fMRI models. The size of reliability measures (ICC_{within} and $R_{overlap)}$ on activation maps was in line with the observed activation patterns, with reliability being higher for the contrast with rest and for the single contrast using model 2. To date, only one study tested the reproducibility of brain activation associated with active elbow movements by observing robust reproducible activation in M1 using paired-t-tests (Alkadhi et al. 2002). To

our knowledge, the present work is the first study that systematically examines test-retest reliability related to elbow movements. Using a variety of motor tasks, some previous studies reported rather reliable patterns of activation (Alkadhi et al. 2002; Yoo et al. 2007; Kong et al. 2007; Lee et al. 2010). Other studies however, reported large variability across sessions (McGonigle et al. 2000; Loubinoux et al. 2001; Kimberley et al. 2008a). The low reproducibility observed in these investigations probably relies on multiple factors, such as familiarity with the MRI environment and the specific experimental attributes. Diminished attention could also affect brain activation when participants are familiar with the procedure (Loubinoux et al. 2001). Inconsistencies in performance can also induce differences in brain activation, leading to inter-session variability. While some confounding variables, such as familiarity, cannot be completely controlled, differences in task performance can be monitored by MRI-compatible devices, which can help to interpret changes in brain activation between sessions. In the present investigation, we used MaRIA in order to keep the experimental settings constant across sessions and monitor the motor performance. Thus, robust activation for active arm movements was assessed successfully. This demonstrates that standardized and well-controlled movement performance improves the reproducibility of brain activation.

The brain network activated by passive elbow movements using MaRIA was comparable to that of active movements and consistent with that reported in a previous study (Weiller et al. 1996). Similar to the findings observed with active movements, the contrast of passive movements with rest showed higher activation than the single contrast using both models. The activation power increased significantly with model 2 through the inclusion of force and dROM in the analysis, leading to largely identical activation patterns to those of the contrasts versus rest. These observations were also in line with the ICC_{within} and $R_{overlap}$ reliability values for activation maps and mainly with $ICC_{between}$ computed on summary statistics, the reliability being higher for contrasts with rest and for single contrasts using model 2. According to the statistical analyses, the reproducibility of brain activation was robust for individual and group

activation maps but inconsistent results were found for summary statistics in single ROIs, especially using model 1. Although no study has tested reliability of passive arm movements so far, such tasks had been proposed to elicit brain activation in a more controlled way, as they are independent of the subjects' motor abilities and task requirements (Weiller et al. 1996; Kocak et al. 2009). However, our analyses suggest that, even during passive movements, small differences in task performance do exist in healthy subjects and can potentially affect the reproducibility of activation. Remaining absolutely passive during guided movements is probably quite difficult for healthy subjects. Therefore, we cannot exclude that even with the mechanical device used in our experiment the participants may have squeezed the device's handle differentially or did not follow the movement of the handle in a totally passive way, leading to higher variance across trials in some sessions. This may explain the higher reliability in the active condition, which explicitly required force and joint movements, leading to less variance in performance across trials. Our observations highlight the need for monitoring task performance, both during active and passive movements, and the utility of MRI-compatible robots to address this problem. Furthermore, these findings emphasize the importance of testing the reliability of brain activation patterns, even for passive tasks.

Consistent with previous studies, the ICC_{within} and $R_{overlap}$ values for our group activation maps were highly reproducible in all contrasts and ROIs and were higher than for single subjects (Raemaekers et al. 2007; Gountouna et al. 2010). Across all contrasts of interest and models, $ICC_{between}$ values were lower than for the calculation of ICC_{within}. Lower $ICC_{between}$ values were also reported in several previous studies (Raemaekers et al. 2007; Caceres et al. 2009). A reason for this may have been the low number of subjects usually included in fMRI studies for the $ICC_{between}$ calculation on summary statistics (Caceres et al. 2009). In addition, the low ICC values obtained for passive movements in some ROIs may be attributed to a low level of activation in these areas. For instance, superior parietal cortex was not activated across all subjects using model 1. In contrast, activation in this region was found in all subjects across

both sessions using model 2. Overall these new results suggest that activation maps, particularly for group results, are more reliable than summary statistics and that reliability can be improved by enhancing the power of the design, e.g. by increasing the number of trials in the experiment.

As mentioned above for both movement conditions, the higher activation power and reproducibility of brain activation in single contrasts using model 2 may be the consequence of less variance in the performance. Although no differences in mean force and mean dROM were found across repeated measurements, small differences in performance of movements across trials may lead to higher variance in the data and therefore reduced activation power in some subjects. An alternative explanation can be that force and dROM, included as regressors in model 2, may indirectly compensate some motion artifacts potentially correlated to these parameters. Future studies should address this possibility. However, the use of model 2 may be limited when regressors included in the model are strongly correlated with the task (Birn et al. 1999; Johnstone et al. 2006). High correlations may reduce brain activation in some areas. Differences in correlations between sessions may lead to differences in activation and thus, result in misinterpretation of the results. According to earlier publications (Birn et al. 1999; Johnstone et al. 2006), using an event-related design as was done in the present study can overcome this problem. In fact, in our experiment, correlations were very small and constant across both sessions (force: max. mean r = 0.12; dROM: max. mean r = 0.24). In addition, our results show that the variability can also be reduced by explicitly modeling the rest condition. Such a strategy should also remove variability that cannot be influenced by including motor parameters into the fMRI data analysis, as for example attention changes across sessions. As shown by Specht et al. (Specht et al. 2003) attention has an impact on the magnitude of reliability and thus may differently influence passive and active task conditions. The main disadvantage of implementing an additional rest condition is the important increase of scanning time, which is problematic in clinical studies.

In the present investigation, an MR-compatible robot was used to assess arm movement-related brain activation while performing active and passive movements. The network activated by the interaction with the robot was consistent with previous studies. The controlled settings reinforced by the device enabled reproducible assessment of brain activation across sessions in single subjects and at group level. Furthermore, quantitative data of the movement performance provided by the device add important information to the analysis. This improved the assessment of brain activation in healthy participants, especially for passive arm movements, by removing variance across trials.

Overall, the results of this study indicate that this device can be used in longitudinal studies to reliably explore brain activation associated with simple arm movements and therefore, is a helpful tool to assess brain reorganization following injury and to monitor rehabilitative interventions in patients with motor impairments. A further application may be the exploration of training induced plasticity in healthy participants to better understand basic mechanisms within the central motor network.

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6.4 Study #3

Neuroimaging of therapy-induced recovery after stroke: a longitudinal fMRI study[§]

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[§]This study was submitted and is in review. Therefore, this version may differ from the final one. Data were assessed and analysed by Natalia Estévez. The manuscript was written by Natalia Estévez and revised by the co-authors.

Abstract

Recovery of upper limb function following a stroke is related to brain reorganization, which can be facilitated by movement therapy. We investigated whether therapy with ARMin, an exoskeleton robot for arm rehabilitation, promotes brain reorganization in chronic stroke patients with moderate to severe arm hemiparesis. Additionally, we compared the changes in brain activation induced by this treatment with those of conventional physical or occupational therapy. Functional magnetic resonance imaging (fMRI) was performed during repetitive active and passive elbow flexion/extension movements at three time points: before therapy, after eight weeks of therapy, and at two-month follow-up. To ensure constant and accurate performance of the tasks across sessions, an MRI-compatible robot guided and monitored movements during recordings.

Both therapies elicited comparable improvements in function and motor performance. Reorganization patterns varied, depending on the type of intervention, the degree of impairment and the task performed. Changes observed after therapy often persisted after two months. Long-term effects were more stable and even more pronounced in moderately- versus severely-impaired patients.

Overall, our results demonstrate that therapy with ARMin promotes brain reorganization and function as effectively as conventional therapy and is a promising tool to enhance functional arm recovery, even during the chronic phase after a stroke.

Introduction

Stroke often causes chronic motor disability of the upper limb, which severely affects patients' activities of daily living (Nakayama et al. 1994a). Recovery of motor function after a stroke has been repeatedly shown to improve with movement therapy (e.g. Lum et al. 2002; Luft et al. 2004a; Van Peppen et al. 2004; Bayona et al. 2005; Wolf et al. 2008; Takahashi et al. 2008). Additionally, there is growing evidence that some therapeutic parameters may enhance the likelihood of recovery. Several studies have shown that therapy should be intensive (Ottenbacher and Jannell 1993; Kwakkel et al. 1997), of long duration (Sunderland et al. 1992b; Kwakkel et al. 1999), repetitive (Bütefisch et al. 1995; Feys et al. 1998) and task-oriented (Bayona et al. 2005; for a review, see Platz 2003). These requirements can be achieved with the aid of robot devices. Their use enables intense, repetitive, task-oriented training of particular tasks and is independent of any physical effort by a therapist, who can thus supervise the therapy of several patients simultaneously. Furthermore, the duration and number of training sessions can be increased for specific indications. An additional advantage of these devices is that virtual reality scenarios and passive mobilization can be incorporated, which enable the training of activities of daily living (ADL) and even allow movement training in patients with severe motor deficits. Furthermore, robots provide quantitative data on motor performance, providing more comprehensive understanding and evaluation of the rehabilitation progress (Nef et al. 2007; Guidali et al. 2011b; Guidali et al. 2011a).

Several neuroimaging studies, using various methodological approaches, have demonstrated that therapy-induced recovery is associated with functional reorganization within surviving areas of the sensorimotor network (for a systematic review, see Richards et al. 2008). Recovery has been linked to several reorganization patterns within this network, including activation of the undamaged primary and secondary motor cortices in the lesion-affected hemisphere and homologous regions of the unaffected hemisphere. The variability in functional reorganization may depend on several factors, like lesion characteristics, degree of disability, task demands,

and the type of therapeutic intervention, among others (Feydy et al. 2002; Luft et al. 2004b; Luft et al. 2004a; Lotze et al. 2006; Hamzei et al. 2006; Ward et al. 2007; Richards et al. 2008; Lindenberg et al. 2010; Riecker et al. 2010).

In the present study, we investigated therapy-induced reorganization in patients with chronic stroke and neurological disability affecting the sensorimotor system, by comparing two therapeutic approaches. Patients suffering from moderate to severe arm hemiparesis were randomized into one of two treatment groups: one trained with robotic therapy using the arm robot ARMin, and the other with conventional treatment. Therapy-induced changes in brain activation were assessed via functional magnetic resonance imaging (fMRI) while patients performed repetitive active and passive elbow flexion and extension movements at three time points: 1) just before therapy was initiated (baseline, T_0); 2) immediately after eight weeks of therapy (T_1); and 3) two months following therapy cessation (T_2). Since the motor output (e.g., frequency of movement, force applied) of patients with motor deficits may change with training, inconsistencies in task performance across fMRI sessions may cause large differences in brain activation, which can be mistakenly interpreted as indicative of functional recovery. Therefore, in the present study, constant and accurate performance of tasks across sessions was aided using an MRI-compatible robot (MaRIA (Yu et al. 2011; Estévez et al. 2014)) which guides and monitors the execution of movements during recordings. Changes in function and reorganization of brain activation induced with both interventions were analyzed and compared to test whether robotic therapy with ARMin promotes recovery to the same extent as conventional therapy and can, thus, be applied as an additional or alternative therapeutic program to facilitate recovery in chronic stroke patients.

Methods

Subjects

Twenty-four subjects with chronic stroke (7 females, 17 males, mean age: 57.8±9.1 years) participated in this study. Their clinical characteristics are summarized in Table 3.1. All patients were recruited within the context of a large multicenter clinical study that used several clinical tests to compare the effect of robot-assisted therapy using ARMin against conventional (occupational or physical) therapy (Klamroth-Marganska et al. 2014). The study was approved by local ethics committees and all participants gave their written informed consent for participation prior to the examination. Inclusion criteria were as follows: age > 18 years; first-ever ischemic or hemorrhagic stroke experienced at least six months prior to enrollment, resulting in unilateral moderate to severe motor impairment of the arm, as defined using the Fugl-Meyer Assessment (FMA (Fugl-Meyer et al. 1975); motor score related to upper limb function from 8 to 38 out of a maximum score of 66 points); ability to sit in a chair without any additional support; passive range of motion in a) shoulder: flexion/extension 80°/0°, abduction/adduction 60°/-10°, inner and outer rotation 20°/-20°; b) elbow: flexion/extension 100°/40°. Exclusion criteria included excessive spasticity of the affected arm (modified Ashworth Scale mAS > 3); any serious medical or psychiatric illness; inability to communicate; orthopedic, rheumatologic or other diseases restricting movements of the paralyzed upper extremity; and a pace-maker or other electric or metallic implants.

Overall study design

Patients were assessed with the FMA twice before treatment (four weeks and one to three days before starting therapy). Those with stable scores in these two pre-treatment assessments (change in FMA of 3 points or less), as well as moderate (i.e., defined as having a total FMA score from 20 to 38 points) or severe impairment (i.e., defined as a total FMA score of 8 to 19 points) were randomly assigned to receive either robot-assisted or conventional therapy, thereby

generating two groups of 12 patients each. Subsequently, subjects underwent eight weeks of therapy and further clinical assessments at several time points (for details, see Klamroth-Marganska et al. 2014). The fMRI assessments reported in this investigation were performed in patients who were eligible to undergo MRI and agreed to additionally participate in this sub-study. These assessments were performed once just prior to treatment (baseline, T_0) and twice after therapy completion (immediately after therapy and at two months of follow-up; T_1 and T_2, respectively). Detailed results of the clinical tests assessed within the multicenter study have been reported elsewhere (Klamroth-Marganska et al. 2014). In the present study, we focused only on behavioral outcomes assessed using the FMA, and brain activation before therapy, immediately after therapy, and at two-month follow-up. Figure 3.1 is a schematic depiction of the study design.

Table 3.1 Patients characteristics.

Patient number	Level of impairment[1]/ FMA at T_0		Age	Gender	Hand dominance	Time since stroke in years	Side of lesion	Impaired arm	Lesion location
04	mo	34	49	m	R	1;7	R	L	co, sub
06	se	18	45	m	R	4;1	R	L	co, sub
09	se	16	64	f	R	2;9	R	L	co, sub
10	mo	20	56	f	LU	1;3	L	R	co., sub
12	mo	23	60	f	R	6;4	L/R	L	sub
13	se	14	55	m	R	11;1	L	R	co, sub
14	mo	22	37	m	R	14;3	L	R	co, sub
15	mo	22	57	m	R	0;7	L	R	sub
16	mo	26	61	f	R	1;10	R	L	sub
17	mo	21	49	m	R	2;2	L	R	co, sub
18	se	18	47	m	R	2;10	R	L	sub
20	se	18	65	m	LU	1;6	L	R	sub
22	se	16	54	m	R	2;4	L	R	co, sub
24	mo	29	65	m	R	4;3	L	R	sub
25	se	10	72	f	R	7;2	L	R	co, sub
27	mo	34	54	f	LU	14;0	L	R	sub
28	se	13	69	f	R	0;8	R	L	co, sub

[1]: Level of impairment based on FMA scores: mo: moderate impairment, defined as a total FMA score of 20 to 38 points at T_0; se: severe impairment, defined as a total FMA score of 8 to 19 points at T_0;
T_0 = baseline; co = cortical; sub = subcortical; m = male; f = female; R = right; L = left; LU = left hand dominance but retrained to use the right hand at school. Hand dominance was assessed prior to the first fMRI assessment with Annett (Annett 1970).

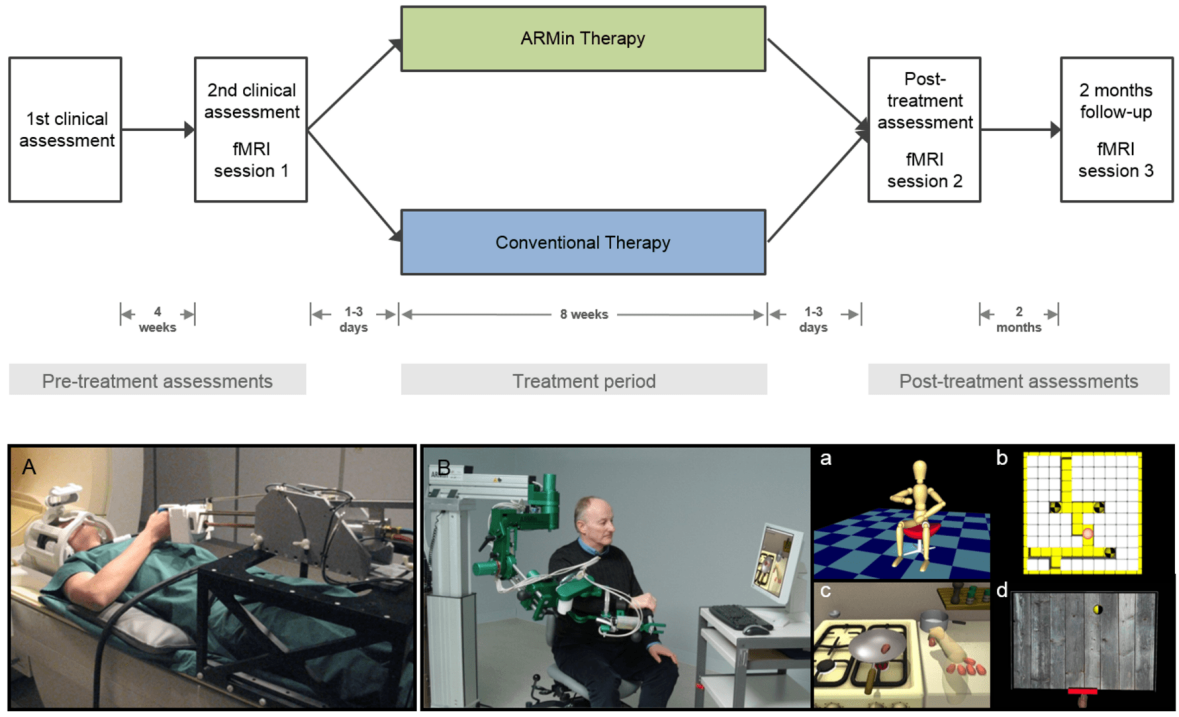

Figure 3.1 Schematic description of the study. *Above*: study design. *Below*: A) fMRI experimental setup: MaRIA was positioned above the legs of each patient. The patient's hand was affixed to the handle with strips. In the start position, the elbow was flexed 90°. Maximal elbow extension reached approximately 120°, so that the range of motion of the subject's elbow was roughly 30°. B) Therapy robot ARMin with a patient. In front of each patient, audiovisual scenarios were presented on a graphical display, including: a) passive mobilization, b) the labyrinth game, c) the ADL task "cooking", and d) the ball game.

Description of the rehabilitation robot ARMin

ARMin is an arm rehabilitation device developed by the Sensory-Motor System Lab of the Swiss Federal Institute of Technology in Zurich (ETH-Zurich, http://www.sms.hest.ethz.ch/research/arm_rehab; Figure 3.1B) together with the University Hospital Balgrist. It allows for three-dimensional movements of the arm with shoulder rotation, elbow flexion/extension, pro/supination of the lower arm, wrist flexion/extension, and hand opening/closing. ARMin has three therapy modes: passive arm mobilization, active-assisted game-supported arm therapy, and active-assistive training of ADLs. During the three training modes, a graphical display is used to present different training scenarios in virtual reality to the patients (Figures 3.1 a, b, c,

d). During both active modes, ARMin detects how much the patient contributes to each movement, delivers support as needed, and controls position and interaction forces between the robot and patient. Detailed descriptions of the technical features and training modes of the device have been published previously (Nef and Riener 2005; Nef et al. 2007; Nef et al. 2009a; Guidali et al. 2011b; Guidali et al. 2011a).

Treatment protocol

Each patient was trained for eight weeks, three times per week, with one hour of training per training day (total 24 h). During ARMin therapy, the patients sat in an upright position in front of a computer display. The impaired arm was positioned and fixed with strips to the ARMin exoskeleton. During each session, all three training modes (passive mobilization, games, and ADL training) were performed for a minimum of ten minutes each. During passive mobilization, the patient's arm was repeatedly moved by the robot along a previously-recorded trajectory. Additionally, hand training was performed with the hand module passively closing and opening the hand in an assisted manner. Figure 3.1a shows the graphical display, which is presented during passive mobilization. During active game-supported training, three games were performed: (1) a ball game where a virtual racket is used to catch a ball that rolls down a ramp (Figure 3.1d); (2) a labyrinth, where patients move the ball out of the labyrinth (Figure 3.1b); and (3) a ping-pong game. In the third mode, patients were trained for several ADLs, including eating, cooking, and table setting, among others (for an example, see Figure 3.1c).

Within the conventional therapy group, therapists performed physical or occupational therapy similar to regular sessions. In both therapy groups (ARMin and conventional), the choice and number of tasks performed during a session where not predetermined, depending instead upon each individual patient's abilities and endurance.

fMRI procedure and the experimental paradigm using MaRIA

Brain activation was assessed using an event-related design (ERD). To standardize and control the assessment across all sessions, MaRIA, an MRI-compatible robot developed by the Sensory-Motor Systems Lab at ETH-Zurich http://www.sms.hest.ethz.ch/research/mr_robotics/setup; Figure 3.1A) was used to guide extension and flexion of the elbow joint (Yu et al. 2011; Estévez et al. 2014). The experiment consisted of three conditions: passive arm movement, active arm movement, and rest. In the passive condition, patients were required to hold the device's handle and let it move without applying force. In the active condition, patients had to push and pull the handle actively. Movement could only be initiated when the exerted force reached a threshold set at 20% of the patients' maximal voluntary push force (MVPF). To account for potential changes in motor function over time, the MVPF was measured by MaRIA for each patient prior to each fMRI session. Patients were instructed to push the fixed handle of the robot three times with their maximal voluntary force without moving either their head or body, and the mean force value was recorded. Movement range was defined by the handle's range of motion, which we will refer to as the device's range of motion (dROM). The maximal dROM was approximately 16–20 cm, depending on individual patient body size. For each patient, the linear movement trajectory remained the same for all passive and active movements during all sessions. During the period of rest, patients were simply asked to hold the device's handle without applying force. To further standardize task performance, the same setting configuration applied during the first session (height, position and orientation of the device) was recorded for each patient and used in subsequent sessions.

A total of 30 trials per condition were randomly presented to the patients. Each trial lasted in average 13.5 seconds, and included a brief instruction, 8 seconds of the task, and an inter-stimulus interval (ISI) with a jitter of 3±1 s. The duration of the whole run was about 20 minutes. Passive and active movements were visually and verbally guided to ensure that the active movements were performed similarly across trials and sessions and had the same duration as

passive ones. For detailed information on the visual and acoustic instructions, see (Estévez et al. 2014). Functional MRI acquisition and the tasks were synchronized using Presentation, a stimulus delivery and experimental control program for neuroscience (http://www.neurobs.com/). This software received trigger signals from the MR system and provided visual and auditory instructions to the patients. Additionally, it sent control commands to MaRIA, instructing the device to switch from one condition to the other, thereby allowing the initiation of active or passive movements. Prior to each scanning session, the tasks were practiced outside the scanner for about five minutes to ensure proper task performance. A more detailed description of MaRIA, the fMRI procedure, and the experimental paradigm can be found in previous publications (Yu et al. 2011; Estévez et al. 2014).

Behavioral assessment and data analysis

Clinical outcomes were measured using the FMA. Changes in function (i.e., defined as changes in FMA scores) are reported as the percentage of the pre-treatment assessment for each patient. The total score assessed during pre-treatment was subtracted from the total scores after treatment and at two-month follow-up, and those values were divided by the total pre-treatment FMA score. Mean changes in the FMA score were calculated for patients with moderate and severe impairments separately.

Motor performance was assessed using MaRIA at all three fMRI sessions. The following variables were computed and stored for each patient and session separately: MVPF; the number of successfully-performed active movements; and the mean dROM of active movements separately.

All statistical analyses were performed using the statistical software package SPSS 19.0 (http://www.spss.com). To assess the effect of treatment over time across both groups, analysis of variance for repeated measures (ANOVA-RM) was performed on the FMA scores, MVPF,

dROM and number of successfully-performed tasks. Time was defined as a within-group variable and treatment as a between-group variable. For variables for which significant differences were computed ($p < 0.05$), additional paired t-tests were performed for each group separately to compare each variable between pre-treatment (T_0) versus each of the post-treatment assessments, as well as between the two post-treatment assessments (T_1 and T_2).

MRI data acquisition

The study was conducted at the MR-center of the University and ETH-Zurich, using a Philips Achieva 1.5 T MR system equipped with an eight-channel SENSE TM head coil. Functional acquisition consisted of a T2*-weighted, single-shot, field echo, EPI sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128 mm, in-plane resolution = 1.7 × 1.7 mm, slice thickness = 4 mm, SENSE factor 1.6). Additional anatomical images of the entire brain were acquired using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 4.6 ms, flip angle = 20◦, in-plane resolution = 0.9 × 0.9 mm, slice thickness = 0.75 mm, 210 slices).

fMRI data analysis

Image pre-processing and statistical analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London, http://fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.6 (Mathworks Inc., Natick, MA, USA). Prior to pre-processing, images of patients with right hemispheric damage were flipped so that all lesions were located in the left hemisphere. “Realign and unwarp” facility was applied to the EPI images to correct for motion artifacts and additional susceptibility-by-movement interactions. The motion parameters obtained during this procedure were used to determine the extent of movements. Functional data of patients that did not exceed displacement of one voxel size were included in analysis. The realigned functional images of each session were then co-registered with the T1-weighted

structural images acquired during the first MRI session. To achieve an accurate registration of images between all scanning sessions, DARTEL registration (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) was performed (Ashburner 2007). This involved three main steps. First, for each subject, the anatomical data of all sessions underwent skull stripping and were segmented using "New Segment" with medium regularization (Ripollés et al. 2012) to generate grey matter (GM) and white matter (WM) images. To avoid misclassification of these tissue probability maps in patients with large lesions, the Automatic Lesion Identification toolbox (ALI (Seghier et al. 2008)) was applied on the T1 images. With this procedure, an extra tissue class for atypical voxels, which correspond to the lesion, was created for each subject. This extra class was then implemented in the "New Segment" procedure as a 7^{th} tissue class, allowing for proper segmentation of GM and WM (Ripollés et al. 2012). Second, "Run DARTEL (create Template)" was used to estimate, for each subject, the nonlinear deformations that best align the GM and WM images of all sessions together. Third, the subject specific template and flow fields generated during the previous steps, as well as the realigned EPI images of all sessions, were processed with the "Normalise to MNI Space" procedure. With this procedure, the realigned EPI images were normalized and smoothed with an 8 mm full-width half-maximum Gaussian kernel. To normalize the anatomical images, this step was also performed on these images, but without smoothing them. Additionally, a high-pass filter was applied to the preprocessed functional images to remove slow temporal drifts with a period longer than 128 seconds.

Statistical analysis was performed at a single-subject level for all sessions. The passive and active arm movements were modeled using a general linear model (GLM) with a canonical hemodynamic response function. The exact movement onset and the duration of each task needed for modeling were provided by the device. For more detailed information, see (Estévez et al. 2014). Statistical t-maps were generated for passive and active movements separately at

each time point, and the significance threshold for the resulting maps was set at $p < 0.05$ (FWE-corrected for multiple comparisons).

Since we observed large variability in activation patterns across the individual statistical maps, only single-subject results are described in the present report. Additionally, for the sake of clarity, analyses focus on investigating therapy-induced changes within primary motor (M1) and somatosensory cortex (S1). Bilateral anatomical regions of interest (ROI) were defined for M1 and S1 based upon probabilistic cytoarchitectonic maps, as implemented in the SPM anatomy toolbox (http:/www.fz-juelich.de/ime/spm_anatomy_toolbox; Eickhoff et al. 2005; Eickhoff et al. 2006b; Eickhoff et al. 2007). We examined changes in both the extent and intensity of activation over time in each ROI. To this end, the volume of activation (i.e., number of activated voxels in FWE-corrected maps) and beta values at activation peaks (non-corrected values) were extracted for each fMRI session. Volume assessed during the pre-treatment session was compared against volumes right after therapy and at two-month follow-up. Changes in the volume of activation were reported as decreased, increased, or the same volume for each patient separately, with 'same volume' defined as changes in volume (within the anatomical ROI) less than 10% of the volume assessed at baseline. Changes in intensity (i.e., in betas) between the pre-treatment session and both post-treatment assessments (i.e., T_1 vs. T_0 and T_2 vs. T_0) were calculated for each single subject. Mean beta values and standard error for each session were calculated separately for moderately- and severely-impaired patients within each therapy group.

Results

Seven patients were excluded from the study due to either missing one of the three scanning sessions, the presence of head movement artifacts (> 4 mm), or technical problems. Therefore, our final sample included data from seventeen patients: eight trained with the rehabilitation robot ARMin and nine with conventional therapy.

Behavioral performance and clinical assessment

At baseline (T_0), four patients in the ARMin group suffered from moderate and four from severe impairments. In the conventional therapy group, five patients were moderately- and four severely-impaired. Compare to baseline, improvements assessed with FMA were in average 14% at T_1 and 16% at T_2 among patients trained with ARMin, and 14% and 13%, respectively, for those trained with conventional therapy. For FMA scores, ANOVA for repeated-measures only revealed a significant effect of time ($F(2) = 9.4$, $p = .001$). No significant differences were found for the interaction treatment x time or for treatment alone. The differences between pre-treatment and both post-treatment assessments were significant for both therapy groups (paired t-tests) implying that patients in both groups improved significantly with therapy, in terms of their FMA score. The differences between the two post-treatment assessments (T_1 vs. T_2) failed to reach statistical significance. When examining changes in FMA scores for moderately- and severely-impaired patients for each therapy group separately, we observed gains in function in all groups immediately after therapy. However, two months following therapy, different patterns were observed depending on the patients' initial degree of disability. Patients with moderate deficits tended to improve further after therapy ceased (ARMin: 2 improved, 1 stable, 1 worse; conventional therapy: 3 improved, 2 worse; overall: 5 improved, 1 stable, 3 worse), while those suffering from severe impairments experienced a general decline from the first to second post-treatment assessment (ARMin: 2 worse, 1 stable, 1 improved; conventional therapy: 4 of 4 worse; overall: 6 worse, 1 stable, 1 improved; see Figure 3.2).

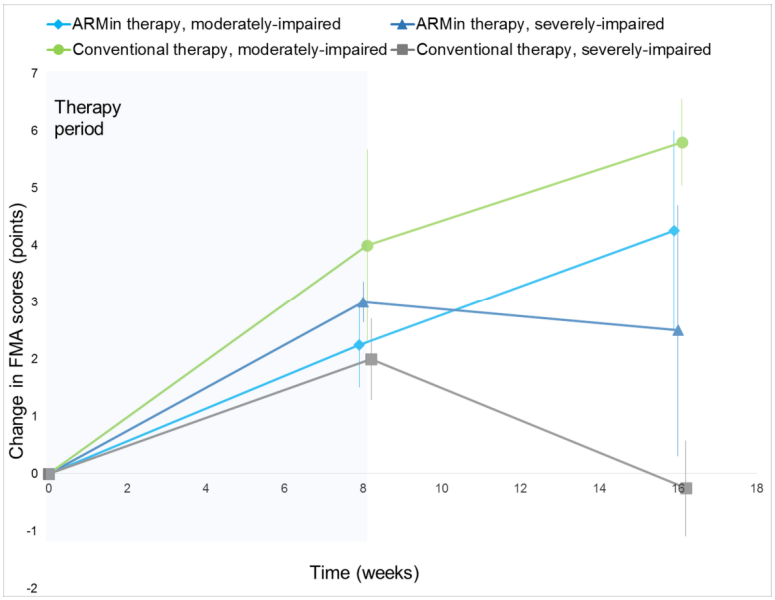

Figure 3.2 Mean changes in FMA scores for moderately- and severely-impaired patients trained either with ARMin or conventional therapy.

With respect to the motor outcomes (MVPF, dROM and the number of successful trials during the active condition) acquired using MaRIA during the fMRI sessions, a significant effect of time was observed for the dROM. No significant differences were found for the interaction effect or for treatment alone. With respect to this variable, paired t-tests revealed that differences between T_0 and T_2 were significant. However, the differences between T_0 and T_1 and the two post-treatment assessments failed to reach statistical significance. Also no statistical significant results were detected when performing these comparisons for the two groups separately. For MVPF, ANOVA for repeated-measures only revealed a trend for effect of time. Compared baseline, in patients trained with ARMin the force increased to 6.8 N at T_1 and to 6.4 N at T_2. Corresponding increases in the conventional therapy group were 3.4 and 4.1 N. Although the ARMin group exhibited twice the improvement in strength at T_1 and almost 60% greater improvement at T_2, these differences were not statistically significant, probably due to the heterogeneity and small size of the sample. No significant differences were found for the number of successful trials during the active condition. Mean values and statistics for motor parameters at each assessment are shown in Table 3.2.

Table 3.2 Mean and standard deviation for motor performance parameters.

	T_0	T_1	T_2	Time	Group
	Mean (SD)	Mean (SD)	Mean (SD)	F	F
MVPF					
ARMin	8.8 N (±12.7)	15.6 N (±12.9)	15.2 N (±10.1)	2.7*	0.2
Conventional	10.3 N (±6.1)	13.6 N (±10.2)	14.4 N (±8.4)		
dROM					
ARMin	13.5 cm (±7.6)	12.7 cm (±7.8)	16.1 cm (±4.7)	3.4**	.3
Conventional	11.9 cm (±8)	13.8 cm (±8.1)	15.2 cm (±7.2)		
Number of active tasks					
ARMin	25.3 (±9.79)	26.9 (±6.25)	29.4 (±1.67)	1.9	0.9
Conventional	25.6 (±9.7)	25.7 (±10.1)	26.3 (±9.9)		

T_0: values at pre-treatment assessment; T_1: values at post-treatment assessment; T_2: values at two-month follow-up; SD: standard deviation; MVPF: maximal voluntary push force; dROM: device's range of motion during active movements; dROM for the passive movements was set by MaRIA and did not change between sessions. Number of active tasks: refers to the number of successfully-performed active movements (maximal possible number = 30); *: $p < .10$, **: $p < .05$.

Brain activation in sensorimotor cortex (M1 and S1)

For each patient, changes in activation volume and intensity between T_0 and T_1 and between T_0 and T_2 are summarized for passive and active arm movements in Tables 3.3 to 3.4 and 3.5 to 3.6, respectively. Average beta values for moderately- and severely-impaired patients in each therapy group are depicted in Figures 3.3 and 3.4.

ARMin therapy

Passive arm movements

In most patients suffering from moderate impairment who were trained with ARMin, the activation volumes in the left and right M1 and S1 were reduced after therapy. Consequently, contralesional activation observed in these areas at baseline was absent at both post-treatment sessions ($p < 0.05$, FWE-corrected for multiple comparisons; for an example of activation patterns in this group, see Figure 3.5). Consistent with these results, the majority of these patients also exhibited a decrease in activation intensity in all ROIs (for details, see Tables 3.3

and 3.4 and Figure 3.3). At two-month follow-up, the decrease in volume and intensity largely persisted and was even more pronounced in most patients (in 3 of 4 patients).

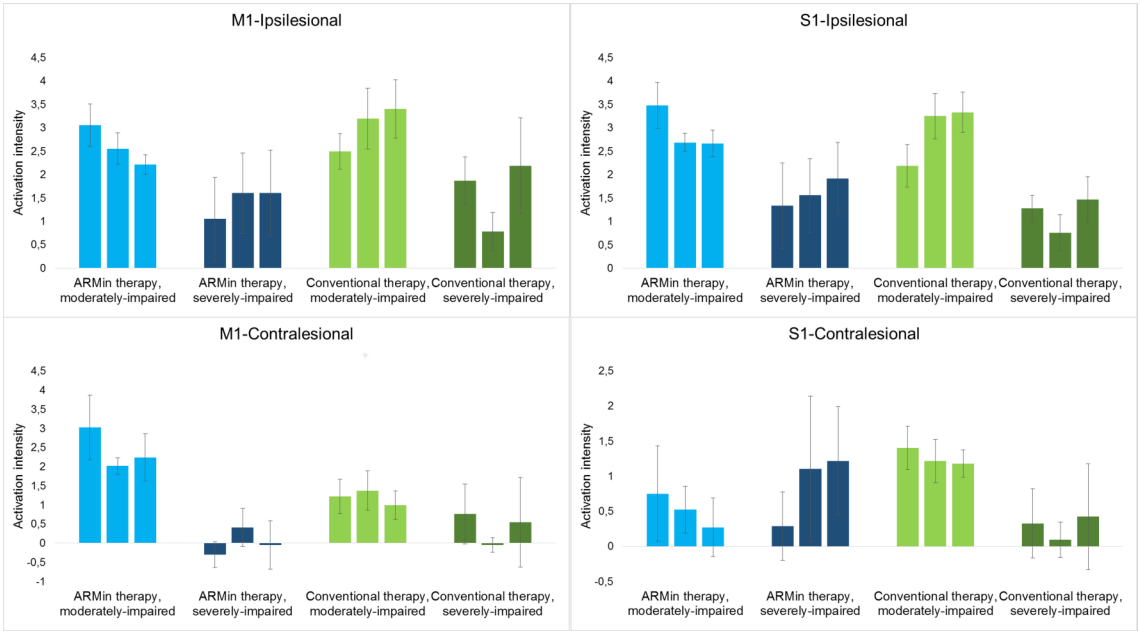

Figure 3.3 Mean activation intensity (i.e., beta values) in sensorimotor cortex during passive movements for moderately- and severely-impaired patients trained either with ARMin or conventional therapy.

Of the four severely-impaired patients, only two showed supra-threshold activation in M1 and S1 during the performance of passive arm movements ($p < 0.05$, FWE-corrected for multiple comparisons). After therapy completion, one exhibited a decrease, whereas the other an increase in activation volume. However, two months after ceasing treatment, their activation patterns were similar; i.e., compare to baseline, both exhibited increased activation volume bilaterally in M1 and S1 (for an example, see Figure 3.5). Additionally, severely-impaired patients trained with the robot-assisted treatment had a tendency to have increased activation intensity (for details, see Tables 3.3 and 3.4 and Figure 3.3). At follow-up, changes in volume and intensity were similar to those observed immediately upon ceasing therapy, but persistence to T_2 was more variable than in patients with moderate impairment (i.e., in half of the patients, changes in ipsilesional M1 and S1 were less than immediately after therapy, whereas they were more pronounced in contralesional areas in 3 out of 4 patients).

Active arm movements

At pre-treatment, bilateral activation was observed in all moderately-impaired patients ($p < 0.05$, FWE-corrected for multiple comparisons). As during the performance of passive movements, most patients exhibited a reduction in activation volume bilaterally in M1 and S1 after treatment with ARMin (for an example, see Figure 3.6). Consistent with this, they also demonstrated decreased activation intensity in M1 and S1 bilaterally (for details, see Tables 3.5 and 3.6 and Figure 3.4). In general, the same patterns were observed after therapy completion, though they were often less pronounced at two-month follow-up (in half of the patients).

In general, patients suffering from severe impairment were more likely to exhibit an increase in activation volume and intensity in ipsilesional M1 and S1 (for details, see Tables 3.5 and 3.6 and Figure 3.4). Activation patterns for one of these patients are presented in Figure 3.6. In most cases, the increases in volume were only observed two months after ceasing therapy ($p < 0.05$, FWE-corrected for multiple comparisons). Indeed, two patients showed no supra-threshold activation at baseline or immediately after therapy completion, but did so at two-month follow-up. Furthermore, changes in intensity largely persisted and were even more pronounced at T_2, in particular in ipsilesional areas (in 3 of 4 patients). Activation patterns and changes in the contralesional sensorimotor cortex were more variable.

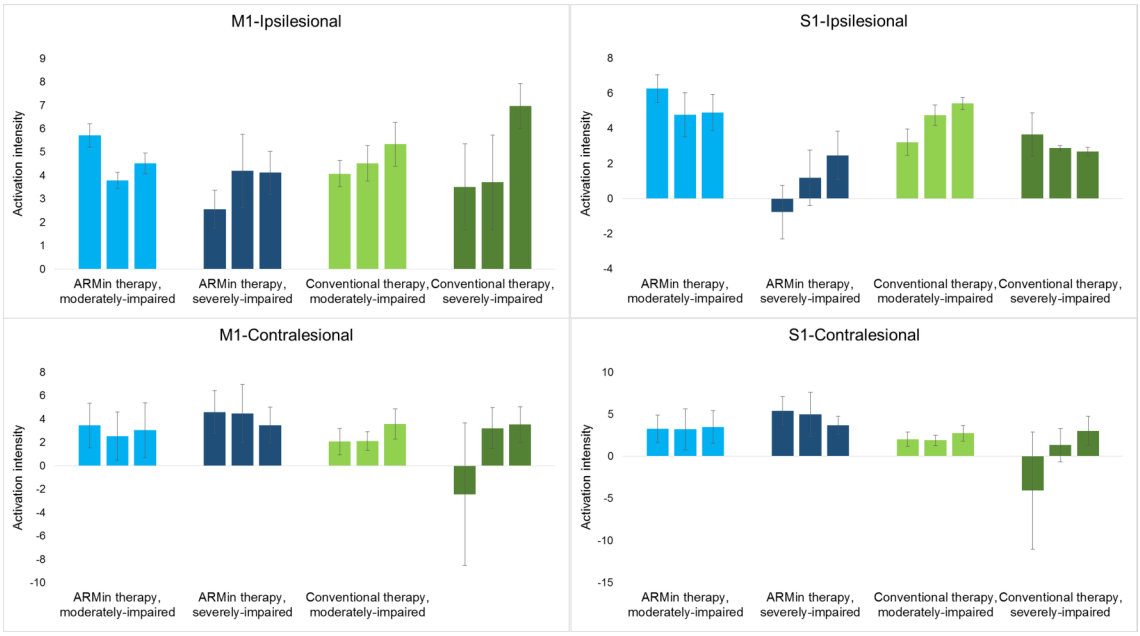

Figure 3.4 Mean activation intensity (i.e., beta values) in sensorimotor cortex during active movements for moderately- and severely-impaired patients trained either with ARMin or conventional therapy.

Conventional Therapy

Passive arm movements

After conventional treatment, moderately-impaired patients were more likely to experience increased activation volume and intensity in ipsilesional M1 and S1. The few patients with supra-threshold activation in contralesional areas (2 of 5) had similar patterns in this hemisphere as with ipsilesional M1 and S1 ($p < 0.05$, FWE-corrected for multiple comparisons). Intensity also was increased in contralesional M1, whereas for S1 most patients exhibited decreased activation (for detailed information, see Tables 3.3 and 3.4 and Figure 3.3; for an example of activation patterns, see Figure 3.5). At T_2, the changes in volume and intensity observed in the ipsilesional hemisphere and in contralesional S1 at T_1 largely persisted and were more pronounced in 3 of 5 patients. In contralesional M1, the majority of patients had the reverse pattern (i.e., decreased instead of increased intensity) and thus, similar patterns as for right S1.

In severely-impaired patients, supra-threshold activation ($p < 0.05$, FWE-corrected for multiple comparisons) that was observed at T_0 was often absent at both post-treatment assessments. Activation intensity was more likely to be reduced at T_1 (for details, see Tables 3.3 and 3.4 and

Figure 3.3; for an example of activation patterns, see Figure 3.5). At T_2, activation patterns observed after therapy were often less pronounced, did not persist, and sometimes had reversed.

Active arm movements

At baseline, most patients trained with conventional therapy had bilateral activation in M1 and S1 in response to active arm movements ($p < 0.05$, FWE-corrected for multiple comparisons). At T_1 following conventional therapy, three patients with moderate impairment exhibited increased activation volume, whereas two had reduced volume. Similar patterns were observed for intensity, albeit not always consistent with the changes observed in volume (for details, see Tables 3.5 and 3.6 and Figure 3.4; for an example, see Figure 3.6). Two months after ceasing therapy, patterns largely persisted; though, in some cases, changes in intensity had reversed so that even more patients had increased activation (in four and all patients for bilateral S1 and contralesional M1, respectively).

Three of the four severely-impaired patients trained conventionally had supra-threshold activation at baseline ($p < 0.05$, FWE-corrected for multiple comparisons). Of these, two experienced an increase and one a decrease in activation volume immediately upon therapy completion. For intensity, various trajectories were observed (i.e., decreases and increases) that were not always consistent with those observed for volume (for details, see Tables 3.5 and 3.6 and Figure 3.4, for an example, see Figure 3.6). At two months of follow-up, changes in activation were often less pronounced and sometimes even reversed. Relative to baseline activation, more patients had increased activation in ipsilesional areas, particularly with respect to intensity. Changes in contralesional areas were more variable and less consistent between activation volume and intensity.

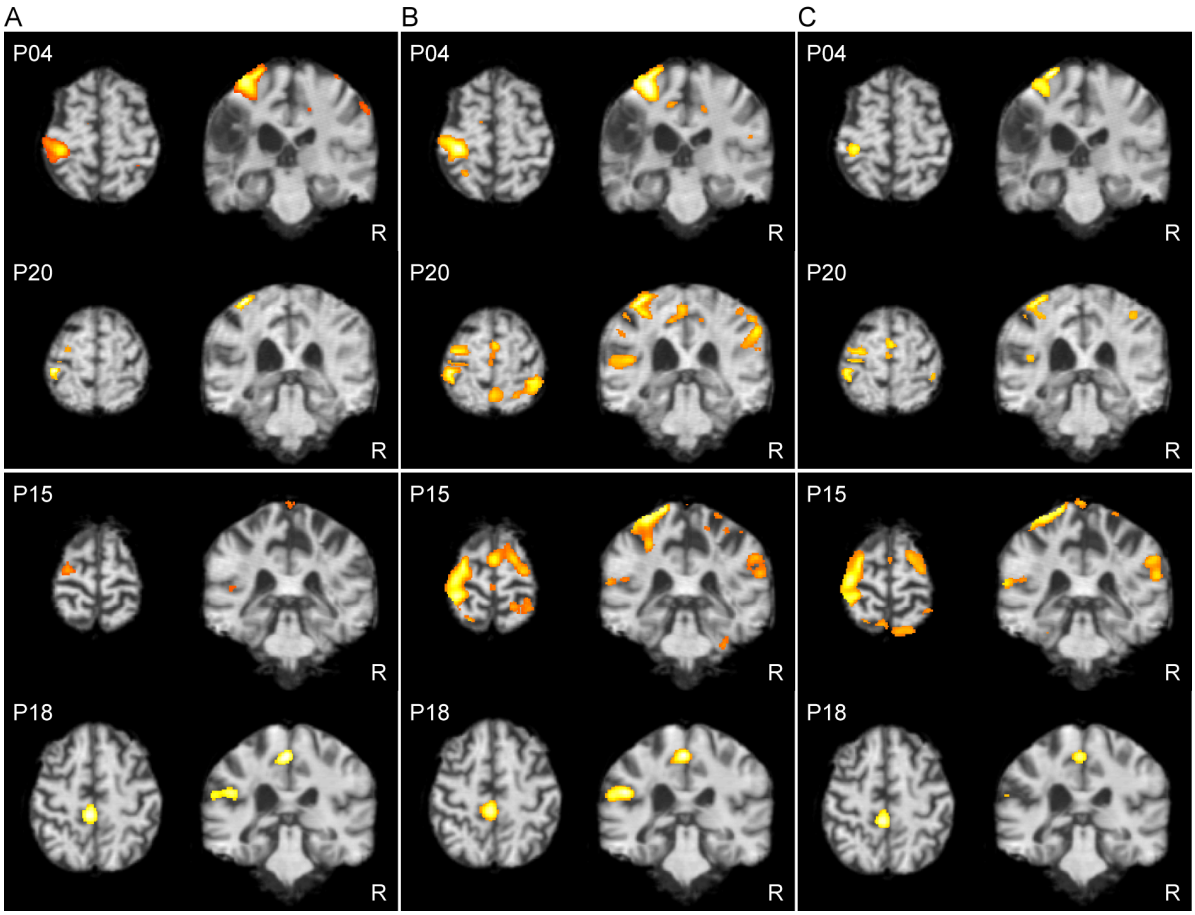

Figure 3.5 Brain activation during passive arm movements for two patients trained with ARMin — one suffering from moderate (P04) and one from severe impairment (P20); and for two patients trained with conventional therapy — one moderately- (P15) and one severely-impaired (P18). Displayed are the individual brain activation patterns assessed A) at baseline (T_0); B) after therapy (T_1); and C) at follow-up (T_2) ($p < 0.05$, FWE-corrected for multiple comparisons). Moderately-impaired patients (P04, P15) showed gains in function (FMA scores for P04 at T_0: 34, T_1: 37, T_2: 44; for P15 at T_0: 22, T_1: 28, T_2: 31) and therapy-induced changes in brain activation (i.e., decreased for P04 and increased for P15), which persisted and were even more pronounced at T_2. Severely-impaired patients (P20, P18) exhibited improvements in function after therapy, but these improvements had declined by T_2 (FMA scores for P20 at T_0: 18, T_1: 21, T_2: 20; for P18 at T_0: 18, T_1: 20, T_2: 19). Similar trajectories were observed for changes in activation.

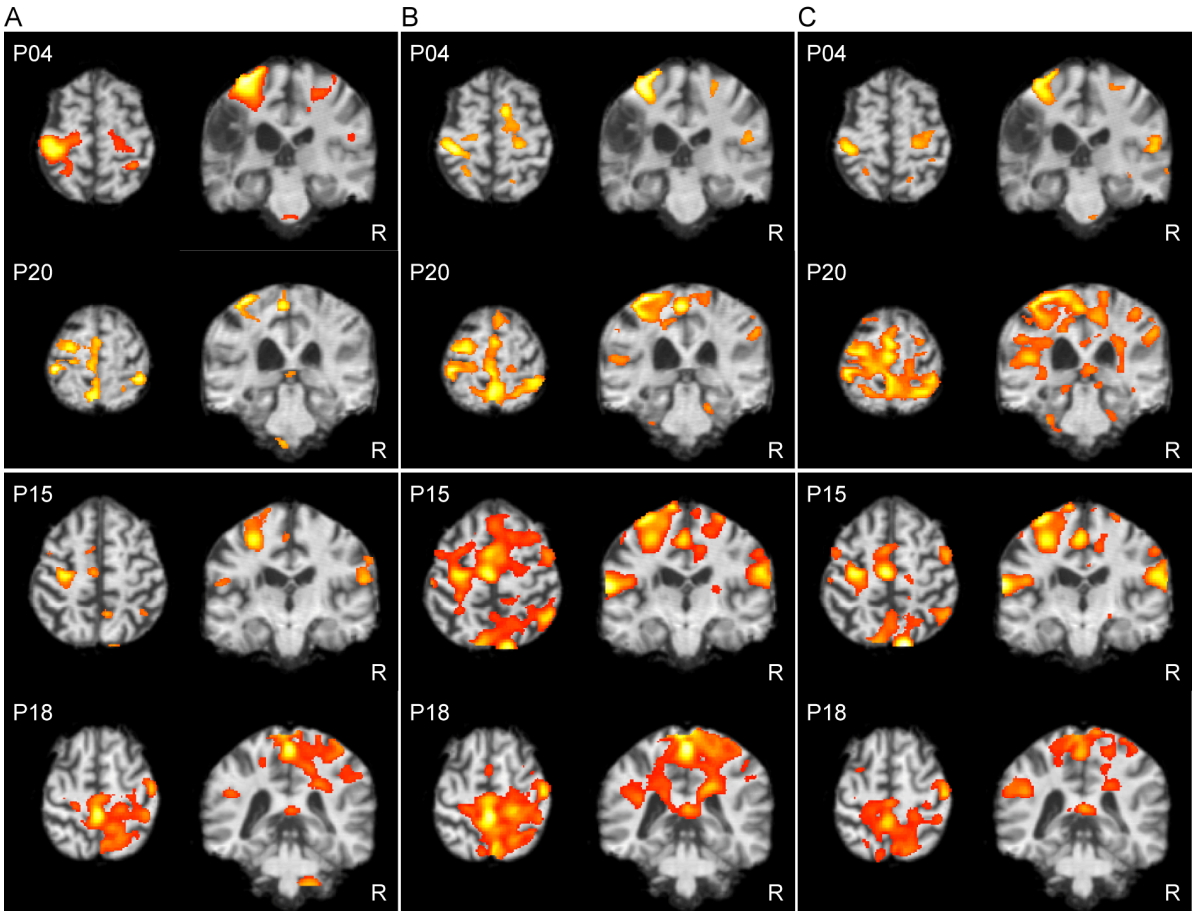

Figure 3.6 Brain activation during active arm movements for two patients trained with ARMin — one suffering from moderate (P04) and one from severe impairment (P20); and for two patients trained with conventional therapy — one moderately- (P15) and one severely-impaired (P18). Displayed are the individual brain activation patterns assessed A) at baseline (T_0), B) after therapy (T_1), and C) at follow-up (T_2) ($p < 0.05$, FWE-corrected for multiple comparisons). Moderately-impaired patients (P04, P15) showed gains in function and therapy-induced changes in activation (i.e., decreased for P04 and increased for P15), which persisted and were even more pronounced at T_2. Severely-impaired patients (P20, P18) experienced improved function at T_1, but less improvement versus baseline at T_2. Similar trajectories were observed for changes in activation.

Table 3.3 Activation changes in volume from pre-treatment to first post-treatment and to two-month follow-up during the performance of passive arm movements.

Patient number	Ipsilesional hemisphere						Contralesional hemisphere					
	M1			S1			M1			S1		
	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0
		V	V		V	V		V	V		V	V
ARMin Therapy												
moderately impaired												
P04	+	I	D	+	D	D	+	0	0	+	0	0
P14	+	D	D	+	I	I	0	0	0	+	0	0
P16	+	D	D	+	D	D	+	0	0	0	0	0
P17	+	D	D	+	D	D	+	0	0	0	0	0
severely impaired												
P09	+	D	I	+	D	I	0	0	0	0	0	I
P20	+	I	I	+	I	I	0	I	I	0	I	I
P22	0	0	0	0	0	0	0	0	0	0	0	0
P28	0	0	0	0	0	0	0	0	0	0	0	0
Conventional Therapy												
moderately impaired												
P10	+	I	S	+	I	D	+	I	D	+	I	I
P12	+	I	I	+	I	I	0	0	0	0	0	0
P15	+	I	I	0	I	I	0	I	I	0	I	I
P24	+	D	D	+	D	D	0	0	0	+	D	D
P27	+	I	I	+	I	I	0	0	0	0	0	0
severely impaired												
P06	+	0	0	0	0	0	0	0	0	0	0	0
P13	0	0	0	0	0	0	0	0	0	0	0	0
P18	+	0	I	0	0	I	+	0	S	0	0	I
P25	+	D	D	+	D	D	+	0	0	+	0	0

M1: primary motor cortex; S1: primary somatosensory cortex; T_0: activation at pre-treatment session; T_1-T_0: activation at post-treatment compared to pre-treatment session; T_2-T_0: activation at two-month follow-up compared to pre-treatment session;

V: activation volume; +: presence of activation at pre-treatment session at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; 0: no activation at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; D: decrease in activation volume; I: increase in activation volume; S: same activation volume. For activation volume 'same volume' was defined as changes in volume within the predefined anatomical ROIs less than 10% versus pre-treatment assessment.

Table 3.4 Activation changes in intensity (betas) from pre-treatment to first post-treatment and to two-month follow-up during the performance of passive arm movements.

Patient number	**Ipsilesional hemisphere**						**Contralesional hemisphere**					
	M1			S1			M1			S1		
	T_0	T_1-T_0 Int	T_2-T_0 Int	T_0	T_1-T_0 Int	T_2-T_0 Int	T_0	T_1-T_0 Int	T_2-T_0 Int	T_0	T_1-T_0 Int	T_2-T_0 Int
ARMin Therapy												
moderately impaired												
P04	+	D	D	+	D	D	+	D	D	+	D	D
P14	+	S	S	+	D	I	0	I	I	+	D	D
P16	+	D	D	+	D	D	+	D	D	0	I	I
P17	+	D	D	+	D	D	+	D	D	0	D	D
severely impaired												
P09	+	D	D	+	D	I	0	I	I	0	I	I
P20	+	I	I	+	I	D	0	I	I	0	I	I
P22	0	I	I	0	S	I	0	S	D	0	I	I
P28	0	I	I	0	I	I	0	I	D	0	D	D
Conventional Therapy												
moderately impaired												
P10	+	I	D	+	D	D	+	S	D	+	I	D
P12	+	I	I	+	I	I	0	I	D	0	D	D
P15	+	I	I	0	I	I	0	I	D	0	D	D
P24	+	D	I	+	D	I	0	I	D	+	D	D
P27	+	I	I	+	I	I	0	D	I	0	I	I
severely impaired												
P06	+	D	D	0	D	D	0	D	S	0	I	I
P13	0	S	D	0	D	D	0	I	D	0	S	D
P18	+	D	I	0	D	I	+	D	I	0	D	I
P25	+	D	S	+	S	I	+	D	D	+	D	S

M1: primary motor cortex; S1: primary somatosensory cortex; T_0: activation at pre-treatment session; T_1-T_0: activation at post-treatment compared to pre-treatment session; T_2-T_0: activation at two-month follow-up compared to pre-treatment session;

Int: activation intensity; +: presence of activation at pre-treatment session at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; 0: no activation at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; D: decrease in activation intensity; I: increase in activation intensity; S: same activation intensity.

Table 3.5 Activation changes in volume from pre-treatment to first post-treatment and to two-month follow-up during the performance of active arm movements.

Patient number	Ipsilesional hemisphere						Contralesional hemisphere					
	M1			S1			M1			S1		
	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0
		V	V		V	V		V	V		V	V
ARMin Therapy												
moderately impaired												
P04	+	D	D	+	D	D	+	D	D	+	D	D
P14	+	D	D	+	D	D	+	D	D	+	D	D
P16	+	S	S	+	D	D	+	D	I	+	D	D
P17	+	D	D	+	D	D	+	D	D	+	D	D
severely impaired												
P09	0	0	I	0	0	I	0	0	I	0	0	I
P20	+	I	I	+	I	I	+	I	I	+	I	I
P22	+	I	I	0	0	I	+	I	S	+	D	D
P28	0	0	I	0	0	I	0	0	0	0	0	I
Conventional Therapy												
moderately impaired												
P10	+	I	I	+	I	I	+	I	I	+	I	I
P12	+	D	I	+	D	I	+	D	I	+	D	I
P15	+	I	I	+	I	I	+	I	I	+	I	I
P24	+	D	D	+	D	D	+	D	D	+	D	D
P27	+	I	I	+	I	I	+	D	D	0	I	I
severely impaired												
P06	+	I	I	+	I	I	+	I	D	+	I	D
P13	+	D	I	+	D	D	+	D	D	+	D	0
P18	+	I	I	+	I	I	+	I	D	+	I	D
P25	0	0	0	0	0	0	0	0	0	0	0	0

M1: primary motor cortex; S1: primary somatosensory cortex; T_0: activation at pre-treatment session; T_1-T_0: activation at post-treatment compared to pre-treatment session; T_2-T_0: activation at two-month follow-up compared to pre-treatment session;

V: activation volume; +: presence of activation at pre-treatment session at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; 0: no activation at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; D: decrease in activation volume; I: increase in activation volume; S: same activation volume. For activation volume 'same volume' was defined as changes in volume within the predefined anatomical ROIs less than 10% versus pre-treatment assessment

Table 3.6 Activation changes in intensity (betas) from pre-treatment to first post-treatment and to two-month follow-up during the performance of active arm movements.

Patient number	**Ipsilesional hemisphere**						**Contralesional hemisphere**					
	M1			S1			M1			S1		
	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0	T_0	T_1-T_0	T_2-T_0
		Int	Int		Int	Int		Int	Int		Int	Int
ARMin Therapy												
moderately impaired												
P04	+	D	D	+	D	D	+	D	D	+	D	D
P14	+	D	D	+	I	I	+	I	I	+	I	I
P16	+	D	D	+	D	D	+	D	D	+	D	D
P17	+	D	D	+	D	D	+	D	D	+	I	I
severely impaired												
P09	0	I	I	0	I	I	0	D	D	0	D	D
P20	+	I	I	+	I	I	+	I	I	+	I	I
P22	+	I	D	0	I	I	+	I	D	+	I	D
P28	0	S	I	0	I	I	0	D	D	0	D	I
Conventional Therapy												
moderately impaired												
P10	+	D	D	+	I	I	+	I	I	+	I	I
P12	+	D	I	+	D	I	+	D	I	+	D	I
P15	+	I	I	+	I	I	+	D	I	+	D	D
P24	+	S	D	+	D	D	+	I	I	+	I	I
P27	+	I	I	+	I	I	+	I	I	0	I	I
severely impaired												
P06	+	D	I	+	I	I	+	D	I	+	D	I
P13	+	I	I	+	D	D	+	I	I	+	I	I
P18	+	I	I	+	I	I	+	I	D	+	I	I
P25	0	D	D	0	I	I	0	D	D	0	D	D

M1: primary motor cortex; S1: primary somatosensory cortex; T_0: activation at pre-treatment session; T_1-T_0: activation at post-treatment compared to pre-treatment session; T_2-T_0: activation at two-month follow-up compared to pre-treatment session;

Int: activation intensity; +: presence of activation at pre-treatment session at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; 0: no activation at the preselected voxel-threshold of $p < 0.05$, FWE-corrected for multiple comparisons; D: decrease in activation intensity; I: increase in activation intensity; S: same activation intensity.

Discussion

The present longitudinal study tested whether robot-assisted movement therapy using ARMin promotes brain reorganization (i.e., changes in brain activation) in chronic stroke patients suffering from moderate to severe motor deficits of the arm. Furthermore, changes in brain activation induced by this treatment were compared against those produced by conventional therapy. Functional MRI was assessed during active and passive elbow movements supported by a MRI-compatible robot (MaRIA). After eight weeks of treatment, therapy performed with ARMin induced changes in activation patterns in the primary motor (M1) and somatosensory cortex (S1), indicating brain reorganization. Consistent with previously-published findings (Feydy et al. 2002; Luft et al. 2004b; Luft et al. 2004a; Lotze et al. 2006; Hamzei et al. 2006; Ward et al. 2007; Richards et al. 2008; Lindenberg et al. 2010; Riecker et al. 2010) our single-subject analyses revealed various reorganization patterns, depending on the type of intervention (robotic versus conventional therapy), the degree of impairment (moderate versus severe), and the task demands (passive versus active movement). Two months following the cessation of therapy, these changes often persisted and additional reorganization was observed, especially in patients with moderate deficits. These findings suggest that robot-assisted training can have long-term beneficial effects after therapy completion, and that these effects depend on the degree of impairment. The results we achieved were comparable to those observed with conventional treatment (physical or occupational therapy).

Gains in function, as assessed using the FMA, occurred across all patients and were comparable for both types of therapy. Motor performance variables assessed with MaRIA (MVPF, dROM, number of successfully performed active arm movements) were, on average, higher for patients trained with ARMin than those trained conventionally. In particular, substantial improvement in MVPF was observed, which persisted at two-month follow-up. For conventional therapy, however, force improvement was less prominent just after therapy, though it was increased slightly at two-month follow-up. The lack of statistical significant difference between the two

groups and sessions for this parameter may be due to the small sample size and the high degree of variability in the trajectory of force improvements across patients and sessions; i.e., some patients showed improvements immediately after therapy and others two months later.

Intervention

In almost all patients with moderate impairments, training with ARMin led to reduced activation volume and intensity within the sensorimotor cortex for both passive and active arm movements. In contrast, moderately-impaired patients who underwent therapy with a conventional protocol tended towards increased activation patterns, though they were slightly more variable between patients and the studied ROIs. After both interventions, most patients suffering from severe deficits exhibited increased activation volume and intensity in the sensorimotor cortex during active tasks. For passive movements, they often displayed no supra-threshold activation. However, intensity seemed to increase in patients trained with ARMin and to decrease in those who received conventional treatment. These findings suggest that the two therapies reshape the brain differently. The constancy in activation patterns observed after ARMin therapy across subjects with similar degrees of impairment may be a consequence of the controlled movements performed with the robot. During conventional therapy, movements are less controlled as therapists cannot always achieve the same movement trajectories. Also, tasks performed during conventional therapy may differ between patients, which may lead to more variable reorganization patterns. Given the repetitive, controlled and intensive movements performed using the robot, it is possible that reorganization occurs faster than with conventional interventions, resulting in more homogeneous patterns across patients. This is consistent with the results observed in the large therapeutic trial from which the participants of this fMRI study were recruited, which revealed that patients assigned to robotic therapy gained motor function faster than those trained with traditional therapy (Klamroth-Marganska et al. 2014).

Following both interventions, the activation patterns observed immediately after therapy in the single subjects often persisted at two-month follow-up. However, the consistency of the induced reorganization patterns varied considerably. In some patients, the observed changes were less pronounced than immediately after therapy, while in others they remained stable or became even more obvious. Additionally, in other patients, activation changes were observed with some delay two months after therapy completion. These data suggest that both therapies have long-lasting effects on brain organization, but also emphasize the large variability of such effects between patients. In our sample, stable patterns or additional changes in activation at follow-up were more often observed in moderately-impaired patients following both kind of therapies and in severely-impaired patients trained with the ARMin. Nevertheless, it is impossible to draw conclusions on the basis of these individual cases, as the observed effects may be specific only to these single patients. Therefore, further research with a larger number of patients is necessary to identify potential common patterns that may indicate long-term consolidation or further enhancement of reorganization effects after terminating treatment.

The exact arm movements used to assess brain activation during the fMRI recordings were not trained during robot-assisted therapy with ARMin. However, brain activation changes in response to training were observed during both active and passive conditions. These findings are contrary to those of a previous study by Takahashi and colleagues (Takahashi et al. 2008), who investigated the effect of robot-assisted hand therapy and found that therapy-induced reorganization was only observed for those tasks for which specific training was provided during therapy sessions and not for tasks for which training was not provided. Therefore, more extensive robot-assisted therapies that involve several components of the affected limb (i.e., with ARMin, the shoulder, arm and hand), similar to during conventional treatment, may have more generalized effects, which can also be transferred to non-trained tasks (Langhammer and Stanghelle 2000; Timmermans et al. 2009). Thus, using such devices provides an effective strategy to promote recovery in patients suffering from chronic stroke.

Passive and active arm movements

In the present study, active and passive arm movements resulted in differential reorganization patterns. Active movements assessed during the baseline session produced largely a bilateral pattern of activation in M1 and S1, which often persisted after treatment. Additionally, changes in the left and right sensorimotor cortex were observed in patients who also exhibited improved function, suggesting that bilateral activation may be meaningful for recovery. Concerning the extent of functional recruitment, previous investigations have generated divergent results. Some investigators postulate that wider recruitment of activation, like bilateral activation within the primary sensorimotor cortex, may result in poor recovery, whereas a return to more normal activation patterns (e.g., ipsilesional activation in M1) is linked to a good motor outcome (e.g. Liepert et al. 2000; Nelles et al. 2001; Carey et al. 2002; Takahashi et al. 2008). Conversely, other studies have identified a positive association between the recruitment of additional activation and good recovery after motor training, indicating that such patterns may support the successful execution of a task (Johansen-Berg et al. 2002; Luft et al. 2004a; Lotze et al. 2006; Richards et al. 2008; Riecker et al. 2010). In our study, both reorganization patterns were observed after robotic therapy: i.e., more focused activation in moderately-impaired patients and more widespread activation in those with severe impairments. Furthermore, patients trained conventionally exhibited mainly a recruitment in activation. Since these activation changes were accompanied by functional improvements after therapy and even at follow-up (especially in moderately-impaired patients) our findings suggest that both reorganization patterns support recovery and that therapy-induced changes may be highly variable, depending on the severity of impairment, and the applied interventions.

For passive movements, activation was mainly observed unilaterally in the ipsilesional hemisphere, which also persisted after training. In moderately-impaired patients, improvements in function were accompanied by changes in the ipsilesional sensorimotor cortex (i.e., either decreases or increases) or by a reduction in activation on the contralesional side. Passive

movements do not require any effort from patients; as such, additional recruitment of contralesional areas was probably not necessary to accomplish the task. This observation is in line with previous findings which showed that activation patterns in stroke patients depend on task demands (Lotze et al. 2006; Ward et al. 2007; Riecker et al. 2010).

Previous study results have suggested that passive movements elicit activation in the sensorimotor network by activating the afferent system which, in turn, activates the efferent system through cortico-cortical connections, leading to similar activation patterns as during active movements (Weiller et al. 1996; Kocak et al. 2009). Therefore, the observed changes in activation following therapy may reflect improvements in the perception of afferent sensory information relevant to motor output; e.g., proprioception during arm movement (Ward et al. 2006a). Patients suffering from moderate impairment often failed to demonstrate supra-threshold activation during passive tasks, though activation was found in the same patients during active movements. This may be due to disruption of the afferent connections to the cortex by the lesion. Therefore, despite having some advantages (e.g., being independent of patient's capabilities), passive movements may not always be suitable or sufficient to provide a comprehensive picture of ongoing reorganization processes in these patients (Kocak et al. 2009). Moreover, those severely-impaired patients who were not able to perform active movements also failed to exhibit supra-threshold activation during this condition. Based on these observations, it is probably well justified to use both passive and active movements to provide a better understanding of reorganization patterns in patients with various degrees of motor deficit post-stroke.

In previous studies, passive movements were performed with the investigator moving the patient's upper limb (e.g., elbow, wrist), which limited the accuracy of the movements and could have led to undesirable variability in the data. With respect to active movements, the assessment of brain reorganization is also hindered by the patient's motor deficits, and

misinterpretation of results is possible if task performance changes over time. Therefore, to assess brain reorganization longitudinally, we consider it essential to use an MRI-compatible robot to guide the passive movements, standardize the experimental setting across sessions and subjects, and accurately control task performance. Additionally, a robot like MaRIA can record and store several movement parameters that can be analyzed and used to provide accurate modelling of performed tasks. Applying this approach allowed us to draw conclusions related to therapy-induced reorganization over time in a controlled environment, while minimizing potentially-confounding variables.

Limitations of the study

The following limitations must be considered. First, given the small sample size (n = 4 or 5) of the groups investigated in the present study, it was not possible to perform meaningful statistical analyses to assess the relationship between brain reorganization patterns and FMA scores in moderately- and severely-impaired patients trained either with robotic or conventional therapy. Thus, this association needs to be confirmed in future studies using larger samples. Second, changes in brain activation were only studied relative to changes in function as assessed with the FMA. However, improvements in other aspects of motor output (e.g., force) might also occur. Indeed, trajectories of improvement in function and force (MVPF) assessed in this study seemed to vary depending on the severity of disability. Patients with moderate motor deficits experienced stable or even further improved function two months after ceasing therapy, while those with severe deficits experienced functional declines. The opposite was observed for MVPF; i.e., initially-achieved improvement declined in moderately-impaired patients, but increased in the severely-impaired (i.e., 5 improved, 2 remained stable, 1 worse; data not shown). Such differences may be important for understanding the meaning of observed therapy-induced reorganization patterns, and designing new rehabilitation treatments tailored to patients with different degrees of impairment. Finally, the FMA provides only a rough classification of

functional improvement. Combining several behavioral tests might prove a more suitable measure of functional status and functional status change over time.

In summary, our results demonstrate that robot-assisted therapy with ARMin is as effective as intensive conventional treatment. Consequently, this robot could be a helpful tool to support the work of therapists by promoting functional arm recovery and brain reorganization in patients with moderate to severe impairments, even several years after their stroke.

We observed large variability in reorganization patterns across our patient sample, both pre-treatment and post-treatment, which hampers our general conclusions. Therefore, in the future, we would consider adopting an individualized approach combining both structural and functional neuroimaging techniques, which could yield profound insights into brain reorganization underlying recovery and aid in the development of tailored therapy programs to address specific functional deficits.

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Conflict of interests

Robert Riener hold two patents related to the robot ARMin (reference number: WO2008EP0855620081010 and WO2006058442). The Sensory-Motor Systems Lab, ETH Zurich (Robert Riener and Verena Klamroth-Marganska), signed a license contract with a company, which develops and sells robotic devices for rehabilitation (Hocoma AG in Volketswil, Switzerland). The other authors declare that there is no conflict of interests regarding the publication of this manuscript.

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7 GENERAL DISCUSSION

The long-term purpose of this work was to gain insights into brain reorganization induced by arm therapy in patients who are in the chronic stages of a stroke. As a first step, to improve the longitudinal assessment of arm movement-related brain activation using fMRI, MaRIA, a newly-developed, MRI-compatible robot was tested. As a second step, brain reorganization (i.e., changes in brain activation) and related improvements in arm function induced by therapy using a robot-assisted approach were explored and compared against those elicited by conventional physical or occupational therapy. The robot-assisted therapy was performed using ARMin, an exoskeleton robot for arm rehabilitation.

To meet these objectives, three studies were performed. The findings of each experiment have been described extensively in the discussion section of the respective manuscripts. Thus, in the following paragraphs, I will focus on certain specific issues addressed in the studies that might be considered for further research.

Studies #1 and #2 were conducted to assess the feasibility of using a particular MRI-compatible arm robot (MaRIA) during fMRI recording and test the reliability of arm movement-related brain activation assessed with this new approach. These studies showed that the application of MRI-compatible robots in the MRI environment is feasible and provides reliable assessments, being in fact a promising approach to assess brain activation related to motor tasks in longitudinal investigations. In particular, Study #2 demonstrated that the reliability of acquired task-related brain activation can be improved by adding further information about movement performance, like the applied force. This information can be recorded with the MRI-compatible device (MaRIA) in real time during the fMRI assessments and applied afterwards to fMRI data analysis. Variance in task performance across single trials can thereby be reduced, increasing the reproducibility of activation patterns across sessions (see model 2 used in Study #2). Using this approach, the greatest reliability improvement was observed for brain activation associated

with passive tasks. This is an interesting finding, as it contradicts previous assumptions that passive motor tasks, *per se*, elicit brain activation in a more reliable way, as they are independent of the subjects' motor abilities and task requirements. The results in Study #2 suggest instead that, even during passive movements guided by a robotic device, some differences in task performance do exist and can potentially affect data reproducibility. When assessing brain activation patterns in patients, such inconsistencies during passive tasks could significantly influence the results, in particular when running longitudinal studies. Therefore, it may represent an additional source of confounding, potentially leading to false conclusions and mask true reorganization patterns. The findings reported in Study #2 demonstrate that monitoring task performance, even during passive movements, is warranted to help counteract this problem. As shown in this work, MRI-compatible robotic devices can indeed provide some aid to address this problem. Finally, the findings also emphasize the importance of testing the reliability of brain activation acquired by a specific paradigm before starting a longitudinal study. This kind of analysis has often been neglected in previous neuroimaging research and needs to be addressed more thoroughly in future studies.

In Study #3, MaRIA was used to investigate therapy-induced brain reorganization in chronic stroke patients suffering from moderate or severe unilateral hemiparesis of the arm. Overall, the results of this investigation demonstrated that robot-assisted arm therapy with ARMin promotes brain reorganization and reduces motor impairment to a similar extent as intensive conventional treatment. Additionally, changes observed after this therapy often persisted after two months of follow-up, in particular in patients suffering from moderate motor deficits, and seemed to be transferable to tasks for which they had not been trained. These findings imply that therapy with ARMin is a promising tool with the potential to enhance functional arm recovery and support the work of therapists. It also makes it possible to increase the duration and intensity of therapy, allowing patients to receive more training without additional costs. As per previous research results, this study also demonstrated the benefit of training stroke patients,

even those with severe motor deficits and those who have already reached a chronic stage of disease. Therefore, the development of new approaches, like ARMin, which allow intensive training of more complete arm movements (e.g., including several joints) and thereby help to reduce motor deficits, is worth promotion.

In Study #3, considerable variability in reorganization patterns was observed between patients at both the pre-and post-treatment sessions, which made it difficult to come to any overall conclusions when performing group analyses. Such variability is often encountered when assessing brain reorganization in stroke patients and is probably due to different factors, such as lesion characteristics, degree of motor impairment, and time since stroke, among others. To counteract this problem, an approach that combines both structural and functional neuroimaging techniques is recommended for future investigations. This may provide a more comprehensive picture of therapy-induced reorganization processes underlying recovery as the approach used in the currently presented work, and could potentially aid in the development of more efficient and individualized therapy programs.

Due to the limited time allowed for my doctoral studies and the challenges that existed due to the variability in data across the entire patient sample, therapy-induced changes in activation could only be investigated in the primary motor and primary somatosensory cortex (i.e., M1 and S1). However, reorganization can involve several regions of the sensorimotor network. Therefore, more extensive analyses that assess the entire network could yield a better understanding of the reorganization mechanisms induced by movement therapy. For instance, visually inspecting the whole brain analyses at a single-subject level, therapy-induced changes in activation were observed in other areas like the cerebellum (data not shown). Activation in this area was also observed during active movements, at the time of both post-treatment assessments, and has been reported in previous studies using various therapeutic interventions (Nelles et al. 2001; Johansen-Berg et al. 2002; Luft et al. 2004a), suggesting that it may play an

important role in recovery. One interesting finding was that, in some patients, activation in this area was more prominent two months following therapy than immediately after its completion. For example, patient #22 was found to have experienced 25% improvement in function at the termination of therapy and 38% at follow-up; however, no activation was observed during passive movements either pre-treatment or immediately upon therapy completion, while bilateral activation in the cerebellum was apparent at follow-up. This example suggests not only that other sensorimotor areas besides M1 and S1 may be influenced by therapy, but also that the time course of the induced changes may differ between regions.

Further limitations of the present dissertation must be considered. First, when testing the experimental paradigm using MaRIA, the reliability of brain activation was only examined in a group of healthy young subjects. Therefore, the results of some analyses reported in Study #2 cannot be entirely generalized to patients or the elderly. This is the case for the computation of the ICC for summary statistics ($ICC_{between}$). Since this approach is strongly dependent on between-subject variance, for heterogeneous groups of participants, the $ICC_{between}$ values may be higher than for more homogenous samples. This could be a problem when assessing reliability in samples of healthy subjects with less variance, and when translating these results to groups of patients, in whom the variance should be greater (Rankin and Stokes 1998). Additionally, depending on the lesion, reliability in single regions may be different from the values obtained in Study #2. Although the multiple statistical methods used to assess reproducibility in this study should compensate for this limitation to some degree, further research is needed to evaluate the importance of this issue.

Second, the activation elicited by interacting with the robot was not directly compared with activation during the performance of arm movements without using the device (i.e., elicited by passive movements performed by the investigator, or self-paced active movements). Therefore,

gains in reliability using the robot could not be quantified. This should be considered in future studies to add further insights into the results of the current work.

Third, patients with motor impairments were expected to produce considerable head motion artefacts while performing the active tasks. Therefore, to avoid the exclusion of too many participants in Studies #2 and #3, head motion correction during pre-processing of the fMRI data was performed in a more liberal way than in previous studies. In fact, participants were excluded from the analysis when movement artefacts exceeded one voxel in size, instead of the half voxel size usually adopted, and motion parameters obtained during motion correction processing were not included in data analysis. Therefore, it may be argued that this procedure led to additional variance in the data acquired during different sessions, resulting in less robust activation. To avoid this, the data were enhanced using several other strategies during both data acquisition and data analysis. The study design for both Study #2 and Study #3 was enhanced by presenting the experimental conditions as an ERD. This kind of design has been shown to be less sensitive to head motion artefacts than the block design used in Study #1 (Birn et al. 1999; Johnstone et al. 2006). Additionally, during pre-processing, the "realign and unwarp" facility was applied to correct for motion artefacts and additional susceptibility-by-movement interactions. Furthermore, fMRI images were normalize using DARTEL (Ashburner 2007), which provided a more accurate registration of images and may, therefore, have compensated for motion artefacts to some extent. Indeed, for active arm movements, highly robust activation was apparent with all statistical analyses, at both a single-subject and group level. As brain activation associated with active tasks is usually affected by head motion artefacts, these findings suggest that, despite the liberal motion correction technique adopted, the protocol used generated reliable results.

Further limitations associated with the therapeutic study are discussed in the limitations section specific to Study #3.

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