Cerebral Reorganization and Motor Imagery after Flexor Tendon Repair

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it has been said that something as
small as the flutter of a butterfly's
wing can ultimately cause a typhoon
halfway around the world

Chaos Theory - Edward Norton Lorenz (1917-2008)

Contents

Chapter 1

General introduction

General introduction

The human hand, as a result of an evolutionary process of millions of years, represents one of nature's most precisely balanced structures, a wonderful physical device with multiple sensorimotor functions[1]. Tendons are largely responsible for the dynamics of the hand. Grasping movements provide the ability to manipulate objects around us. Initially, immediately before actually grasping an object, the finger extensors are deployed for opening the hand to fit the size of the object. This is followed by flexion of the finger joints providing precision grip with an exact adjustment of individual fingers to the shape of the target[2;3]. Proprioceptive reflexes contribute to the regulation of force necessary to lift or move the object without destroying it, unless destruction is the grasp's aim. Furthermore a precise interaction between visual and proprioceptive information is needed to tune the movement to the intented goal in the environment.

Since hand function is controlled by the brain, tendon injuries are not peripheral disorders *per se* but they also have central consequences. This means that the disordered flow of afferent information will lead to an impaired sensorimotor representation of the hand in the brain and by this to a compromised efferent flow of motor commands[4-7]. In spite of this neuroscientific evidence, clinical studies of these peripheral-central interactions are still rare. An interesting exception may be found in studies on the recovery process following leg amputation. These studies indicate central reorganization of postural control after amputation and rehabilitation[8-10].

Although studies are scarce, the implications are important since the hand as a prominent effector organ is frequently injured. Tendon injuries and in particular flexor tendon injuries belong to the most common injuries encountered by hand surgeons in the emergency room. The past decades showed substantial improvements of flexor tendon repair so that it became possible to regain normal function after an injury that formerly would have led to a lifelong disability[11]. In spite of the surgical and technical improvements, surgery is still followed by a several-week-period of rehabilitation by intensive occupational therapy and physiotherapy. Now that surgical treatment of flexor (and extensor) tendon injury has virtually reached its technical limits[12], the question can be raised how to further improve this treatment so that the rehabilitation period can be shortened.

It is an interesting question whether the use of novel motor learning procedures can shorten this rehabilitation period. Such a novel motor learning procedure is termed *motor imagery*. Motor imagery can be described as the cognitive activity of imagining the performance of a movement without actually performing the movement or even without tensing the muscles[13;14]. It has not only been shown that motor imagery activates more or less the same brain areas as actual movement[15-17] but that it results in learning too[18]. Additionally, there is growing evidence that it may play a relevant role in (neurological) rehabilitation[19;20].

The main objective of the present thesis is to determine whether motor imagery during the immobilization period after flexor tendon injury results in a faster recovery of hand function. However, before this objective can be reached, a few questions have to be answered.

Does peripheral immobilization of the hand after flexor tendon injury result in central changes? In other words, what are the effects of the relative immobilization, which patients have to undergo for weeks after tendon surgery, on brain areas responsible for the control of hand function? Due to the impaired afferent flow of information central systems have to adapt. What are the characteristics of this neural adaptation? Chapters 2 and 3 attempt to answer these questions. These chapters describe the cerebral effects of immobilization in a pilot and a larger sample of patients by measuring task-related brain activation with Positron Emission Tomography (PET). Differences between cerebral control of finger flexion immediately after the relative immobilization period after flexor tendon repair (six weeks postoperatively) and again after six weeks of active training are discussed. Our conclusions were substantiated by an additional single patient EMG study. The unique circumstances of dynamic splinting after flexor tendon repair surgery provided a condition with selective deprivation of active flexion movements while voluntary extension movements kept joint stiffness due to tendon adhesions to a minimum. The fact that patients reported clumsiness during performance of purposeful motor tasks, even with fully restored dynamics of passive hand function, further motivated research for a central cause of functional deficit.

However, before drawing any conclusions regarding central functional changes as a result of peripheral immobilization in patients, more should be known about the control of hand function in healthy subjects. Chapter 4 describes a functional magnetic resonance imaging (fMRI) study on the cerebral control of finger flexion and extension in healthy subjects. Unlike extension, flexion requires precision grip, characterized by the exact adjustment of individual fingers to the shape of the target and the coordination of fingertip forces[2;3]. We therefore hypothesized that higher order motor control principles are more involved in the control of flexion than in the control of extension. At the level of the primary motor cortex, we also studied the distribution of finger movement. Since the 1950s, a somatotopic representation of body parts is well known as Penfield's homunculus[21]. However, the functional segregation of two opposing movements of the same body part (fingers) does not fit into this somatotopic scheme.

Although PET and fMRI can be used to reveal cerebral control of hand function, these diagnostic measures are expensive, rather invasive and time consuming. Many useful noninvasive and cheap tools to assess hand function have been described in the past. However, the vast majority measures joint ranges of motion, force and other output-characteristics that reflect the state of the involved effector organ (hand) rather than its cerebral control[12;22-27]. In general the relationship between the brain and the injured effector organ is neglected.

In chapter 5 we consider the duration of the preparation time of finger flexion as a reflection of central control processes. Furthermore we argue that changes in the duration are related to functional recovery.

Chapter 6 describes a newly developed hand function test that is more sensitive to *how* movements are performed rather than the existing result-oriented hand assessment scores. The test measures kinematic parameters related to the drawing of a triangle (as the reflection of a complex multi-joint finger movement) on a graphics tablet.

Chapter 7 is focused on the question whether motor imagery (as a treatment procedure) may play a role in the rehabilitation of hand function after tendon surgery. It is known, that the central control of movements is influenced by the state of sensory feedback[28]. Proprioceptive inflow may represent the dominant sensory input to the online representation of the body in space[29]. As was shown, relative immobilization after surgery influences the integrity of the functional control architecture in the brain. It is therefore an intriguing question whether imaginary training (motor imagery) may keep the cerebral representation of the hand intact in spite of the immobilization. In other words, can motor imagery function as a substitute for sensory movement-related information that is disturbed during the relative immobilization-period? The adult somato-sensory cortex is known to alter its maps subsequent to injury[30], temporarily as in repaired tendon injuries, or irreversibly as in amputees and paraplegics. It is also known, that cortical plasticity related to chronic pain can be modified by behavioral interventions that provide (novel) feedback to brain areas that were altered by somato-sensory pain memories[31].

In the present thesis some evidence is given for the clinical value of motor imagery. Furthermore, the thesis stresses the importance of the notion that peripheral disorders should not be seen as “stand-alone” events, but that they influence central processes. In *functional* terms no strict separation exists between peripheral and central mechanisms.

Chapter 8 summarizes the results of this thesis and provides future perspectives of cerebral reorganization and motor imagery after flexor tendon injury.

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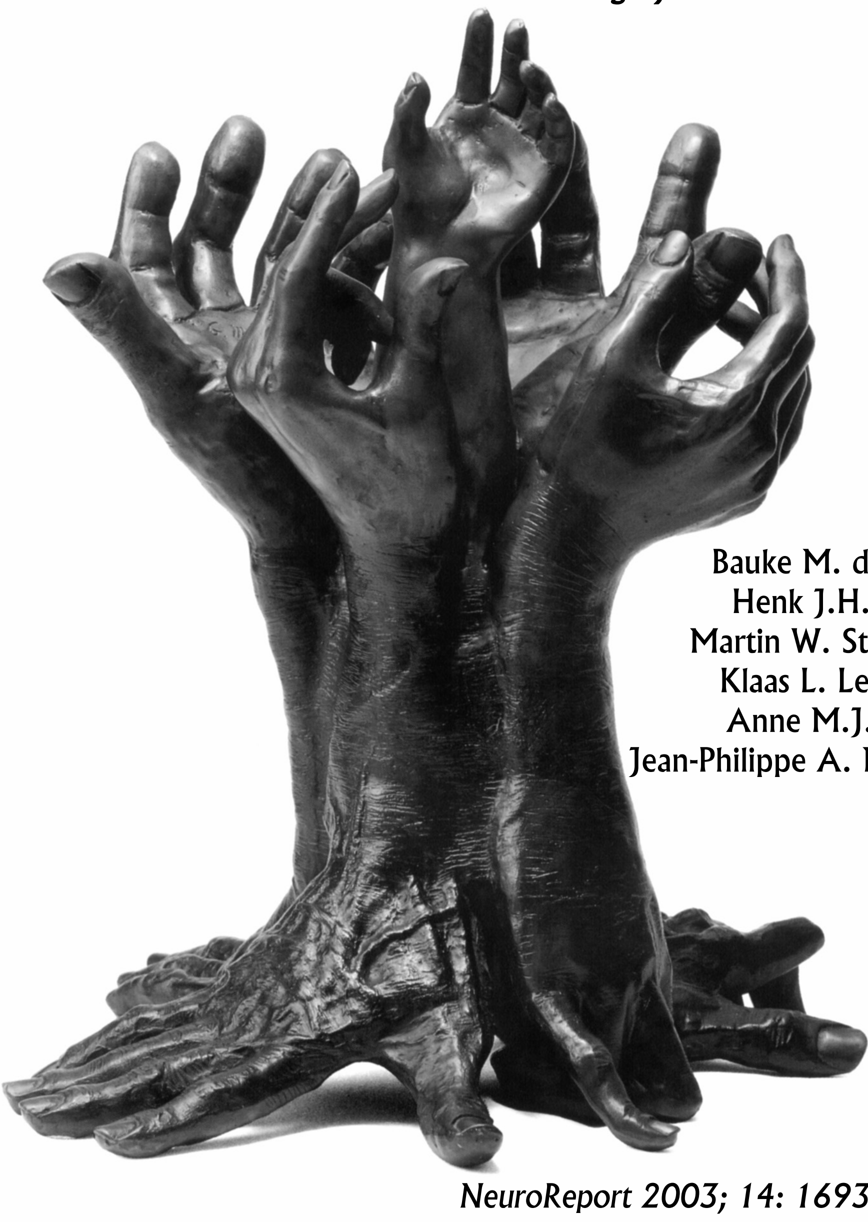
Chapter 2

Cerebral reorganisation of human hand movement following dynamic immobilisation



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Abstract

Surgical treatment of a flexor tendon lesion of the hand is followed by a 6-week period of dynamic immobilisation. This is achieved by the elastic strings of a Kleinert splint, enabling only passive and no active flexor movements. After such immobilisation, the appearance of a temporary clumsy hand indicates decreased efficiency of cerebral motor control. Using PET we identified the recruitment of contralateral parietal and cingulate activations specifically related to the suboptimal character of these hand movements. After 6–8 weeks, normalised movement was related with contralateral putamen activation. Activations of the sensorimotor cortex and cerebellum were present during both scanning sessions. Changes in the pattern of cerebral activations reflect functional reorganisation. The shift from cortical to striatal involvement, observed in the group of four patients, generates the concept of unlearned movements being relearned.

Introduction

Accidental injury from a knife often affects the volar side of the non-dominant hand. Surgical treatment of an associated digital flexor tendon lesion is followed by a 6-week period of dynamic immobilisation. The latter is achieved by elastic strings that connect the tips of all fingers with the volar side of the wrist (Kleinert splint)[1], thus enabling active extension movements followed by passive flexor movements. All digits are included in order to avoid dehiscence of the sutured tendon by traction due to synergistic flexor movement. Passive movement is encouraged in order to avoid synovial adhesion and joint fixation. After splint removal, however, patients report initial clumsiness in task performance which is not explained by stiffness of the fingers or adhesions. This may last from days to weeks, and suggests the loss of efficient cerebral control of flexor movements due to selective disuse. In order to test this hypothesis, we used PET to detect changes in the cerebral organisation of hand movement induced by a period of functional immobilisation[2;3].

Subjects and methods

Four right-handed patients treated for a left-hand flexor tendon lesion were studied with PET. They gave informed consent and the studies were approved by the Medical Ethics Committee of the University Hospital Groningen. Each patient underwent two series of PET scans (Siemens ECAT HR+ scanner operated in 3D mode, 15.2 cm axial field of view). Task-related increases of regional cerebral bloodflow (rCBF) were used as indicators for local neuronal activations and measured with $H_2{}^{15}O$-labelled water[4]. The first series of scans (study 1) was performed immediately after removal of the wrist-band used for dynamic immobilisation. A subsequent study followed 6–8 weeks later. In this interval, all movements were allowed, although lifting weight was initially restricted. An increase of using muscle strength was gradually allowed with physiotherapeutic guidance. In both studies, movement-related activations were identified by comparing six scans acquired during a left-hand movement condition with three scans made in rest. Each scan lasted 90 s, during which the patients listened to randomly presented beeps (20/min). In the movement condition they responded to each beep by making two flexion movements with the fingers of the treated hand (digits 2–4, thumb excluded). The wrist was neutrally positioned and supported by an extension of the scanner table. The volar side of the hand faced the floor. In the control condition, patients listened to the beeps only. Within each study, intervals between the nine scans were 10 min. One of two conditions was assigned to each scan, the overall sequence being ordered rest, three times movement, rest, three times movement and finally rest again. Statistical parametric mapping (SPM99) was used for image realignment, transformation into standard stereotactic space (template of the Montreal Neurological Institute), smoothing (10 mm FWHM) and statistical analysis[5;6]. For each of the two studies, significant activations that resulted from contrasting the movement and control conditions are reported (thresholded at p=0.05, false detection rate corrected for whole brain volume).

Surface electromyography (EMG) was performed on a fifth patient who did not participate in PET. In two studies with a 6-week interval, the same stimulus protocol was applied as for PET. Recordings were made from both the digital fexor and the extensor muscles of the lesioned hand's forearm. The hand was positioned similar to the position in the PET protocol.

Results

The four patients who participated in the PET study indeed reported increased clumsiness when released from the wrist band. During scanning in study 1, they valued the feeling of decreased skilfulness in performing the instructed movements as, respectively, 40, 25, 50 and 50 (on a scale of 0–100, representing insufficient to normal). In study 2, their scores were 95, 90, 80 and 80. Visual monitoring of performance during scanning revealed that all patients were able to accomplish the task as instructed, although the two separate movements made in response to each beep were generally less brisk in study 1.

Surface EMG performed on the fifth patient, who did not participate in PET, showed a normal pattern of digital extensor muscle contractions of the lesioned hand's forearm in both studies. Surface recording during contraction of the flexor muscles, however, particularly showed increased extensor co-contraction in study 1. No full relaxation was seen in between the two movement responses made to each beep. This pattern had normalised in study 2. Group analysis of rCBF changes showed that the left-hand movement condition in the first as well as the second study was related with activation of the contralateral sensorimotor cortex and ipsilateral cerebellum (Fig. 2.1, see Appendix, regions 6 and 7). In the initial study, additional activations (Table 2.1) were present in the posterior parietal cortex (Fig. 2.1, see Appendix, region 1) and deep in the caudal part of the cingulate sulcus (Fig. 2.1, see Appendix, region 2), both in the right hemisphere. In the second study, performed 6–8 weeks later, additional activations related to the left hand movement condition (Table 2.1) were present in the contralateral putamen (Fig. 2.1, see Appendix, region 3) and posterior insula (Fig. 2.1, see Appendix, region 4). The movement-related activation at a more lateral position along the lateral fissure (Fig. 2.1, see Appendix, region 5) was not regarded to be specific for study 2. The plotted contrasts (Fig. 2.1, see Appendix, diagram 5) illustrate that a similar effect was indeed present in study 1, but failed to reach statistical significance.

Table 2.1 Study-specific activations related to left hand flexor movement

Brain region	Stereotactic coordinates x,y,z	Z-score	p
Study 1			
Right parietal cortex	30,-56,66	4.43	0.002
Right cingulated sulcus	14,2,40	4.19	0.003
Study 2			
Right putamen	26,0,0	3.98	0.004
Right posterior insula	44,-12,6	3.76	0.008

Localisation of rCBF increases by SPM (group of four subjects; $p < 0.05$, FDR corrected for the whole brain volume), comparing the six movement conditions with the three control condition in each study. These study-specific activations were in addition to the activation of the right sensorimotor cortex and left cerebellum, present in both sessions. Activation along the lateral fissure (58,-18,16) is not presented because is was not regarded study-specific (see Fig. 2.1b, see Appendix, diagram 5). Coordinates are given in mm. Positive x, y and z coordinates indicate locations respectively right, anterior and superior of the middle of the anterior commissure.

Discussion

The four patients who underwent PET were able to make the instructed flexor movements in the two studies. This performance, however, was suboptimal in study 1, although the hand was intact again. We explain this phenomenon by a change in cerebral motor control, induced by a period in which the patients do not actively command flexor movements. EMG demonstrated that, indeed, this temporary inefficiency concerned only the flexor movements. More co-contractions were made; extensor movements were not affected, which illustrates that joint movement had remained intact. Moreover, it indicates that the execution of active extensor movements during dynamic immobilisation prevented the underlying cerebral control from deteriorating.

The parietal activation, that was related to flexor movement in study 1 suggests an increased demand on a body scheme representation needed for instructing the appropriate parts of the hand to move[7;8]. In this respect, one may further consider that task-related hand movement such as grasping is effectuated by the tuning of particularly flexor movements to the shape of a target (after opening the hand). This may suggest an intimate relation between parietal motor function and particularly flexor movement[9;10]. The cingulate activation in study 1 was deep in the cingulate sulcus, around the vertical traversing the anterior commissure. This location has been labelled the caudal cingulate zone[11], and points at the recruitment of a secondary motor function for the execution of simple hand movement[11;12].

Only in study 2 was the series of double flexor responses related with activation of the contralateral putamen. Such an effect was fully absent in study 1 and suggests that simple movements have been relearned in comparison to the first study[13]. The association of reduced co-contraction and putamen activation in study 2 is consistent with the previously described role of the basal ganglia to switch off maintained motor activities that would otherwise interfere with voluntary movement commands[14]. The execution of relearned movement thus implies the improved selection of specific muscles to be used. Movement rate was identical in the two scanning sessions. Although reaction times and movement amplitudes were not quantified, we do not regard possible changes in these parameters crucial for explaining the differences in activations.

Given the representations of somatosensory and auditory modalities in the posterior insula[15], increased activation related to the movement responses in study 2 may reflect enhanced efficiency of the related stimulus response associations[16]]. A role of the insula in commanding hand movement[12;17] is consistent with this explanation. At the more lateral position along the lateral fissure, possibly including the second somatosensory cortex SII of the parietal operculum[16], increased activation in study 2 was not movement specific compared with study 1. The rCBF response in the control condition with only listening to the auditory signals was also larger. Whether this indicates that the cues gained a meaning associated with movement remains speculative.

Conclusion

A 6-week period of functional flexor immobilisation appears to induce a temporary loss of efficient cerebral control of hand movement, characterised by an increased cortical demand and reduced striatal involvement. The present observation demonstrates the impact of a relatively short period of immobilisation on the functional organisation of the brain.

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Chapter 3

Cerebral consequences of dynamic immobilization after primary digital flexor tendon repair

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Submitted

Abstract

Current treatment protocols for flexor tendon injuries of the hand generally result in an acceptable function, which can be quantified by objective parameters such as range of motion. The latter does not always match the patients' subjective experiences of persisting dysfunction. This raises the question whether changes in the cerebral control of movement might contribute to the perceived deficit.

The main objective of the present Positron Emission Tomography (PET) study was to characterize the cerebral responses in movement-associated areas during simple finger flexion immediately after dynamic immobilization and after a subsequent six-week period of active training.

Ten subjects with flexor tendon injury participated in the PET study. EMG recordings were made during finger flexion and extension in an additional subject. The main finding was that the (ventral) putamen contralateral to flexor movement was not activated immediately after release from splinting, while such activation reappeared after a period of training. This indicates a temporary loss of efficient motor control of over learned movements. The increase of unwanted co-contractions during flexion in a first EMG session, and not during extension, supports a concept of lost skills.

Introduction

Treatment of a flexor tendon injury of the hand has greatly improved over recent decades. The introduction of dynamic splinting in the 1970s, enabling passive gliding of the tendon with little stress across the suture site, has proven to be a major milestone in the recovery of hand function after surgical treatment[1]. Protocols concerning dynamic postoperative immobilization have later been refined and there is a continuous search for new suture techniques and materials[2]. While current treatment protocols generally result in an acceptable function, which can be quantified by objective parameters such as range of motion, the latter does not always match the patients' subjective experiences. Clumsiness may be a complaint after the immobilization period, which is phrased by e.g. "I feel like a four-year-old when I tie my shoes". The discrepancy between normal joint movement and suboptimal use in daily life led to the question whether changes in the cerebral control of movement might contribute to the perceived deficit. In this respect it is of conceptual importance to notice that in case of flexor tendon injury treatment, an essential characteristic of dynamic immobilization is the prolonged period during which only passive and no active flexion movements are made. In contrast, extension movements of the affected hand remain to be performed by direct cerebral command. Because fine-tuned purposeful movements, as seen in grasping, are particularly the result of flexor control[3], prolonged flexor disuse may have a specific impact on purposeful movements, indeed resulting in clumsiness.

Since the availability of neuroimaging techniques such as Positron Emission Tomography (PET), and more recently also functional Magnetic Resonance Imaging (fMRI)[4], it has become possible to study the functional anatomy underlying the cerebral control of motor actions, both in normal and pathological conditions. In these studies, a subject is scanned while performing a specific task. These tasks are related with local increases of neuronal activity in the brain, which further induces local increases of cerebral bloodflow. PET and fMRI enable the assessment of these regional bloodflow changes, thus providing a tool to localize cerebral functions. A prominent feature of cerebral motor control is the somatotopical representation of function on the primary sensorimotor cortex[5-7]. Previous studies have demonstrated that this somatotopy is subject to change induced by changes in anatomy of the represented limb[8-10].

Postoperative functional disability after flexor tendon repair may have several causes of which local restrictions such as adhesions of the tendon to the tendon sheath, joint stiffness or shortening of the tendon are most plausible. In a recent pilot study with PET, we emphasized that central consequences of rehabilitation after flexor tendon repair should not be neglected[11]. This pilot study on 4 subjects showed that the experienced clumsiness, after a six week dynamic immobilization period, was indeed associated with functional changes in the cerebral control of finger movements. Finger flexion was demonstrated to coincide with increased parietal cortex- and reduced striatum activations. This was inferred to reflect an increased demand on body scheme representation in the circumstance that movements lost their automated character[12;13]. The parietal increase disappeared after active flexor training, together with re-established striatum activation. The latter indeed logically reflected a striatal role in (re-)learned movements[14;15]. In the present paper we present functional imaging data on a larger group, together with detailed clinical information. We were particularly interested to find out whether the findings of the pilot study could be reproduced and proved statistically significant in a larger patient group.

The present study included patients with either left- or right hand lesions. In order to perform a group analyse of the complete set of imaging data, which allows the identification of common changes in the patterns of movement-related cerebral activation, some aspects of lateralized brain functions need to be considered. On the one hand, a general principle of organization is that the motor cortex and supporting basal ganglia in one hemisphere are linked to movements of the contralateral hand. Flipping e.g. the right hand imaging data would thus provide a single group with only 'virtual' left hand movement, allowing the optimal assessment of contralateral (right) hemisphere activations. However, limb-independent specialization for each of the hemispheres also exists. In the 19th century Broca and Wernicke were among the first to discover such lateralized brain function: left hemisphere regions play a dominant role in language[16-18]. The right hemisphere is thought to play a major role in spatial relations, verbal emotional stimuli and complex sounds or music[19]. The ability to perform precise technical motor skills with a preferred (generally right) hand, may be regarded as an argument for an associated (left) hemisphere dominance[20]. However, the status of such hemisphere dominance in motor skill, as well as the functional organization of motor areas in right- and left-handed people, remain subjects of debate[21;22]. It has even been argued that differences in the motor systems in these two groups may be indicative for difference in recovery from injury[23]. In addition to the optimal assessment of cerebral activations contralateral to hand movement, limb-independent motor activations in each of the two hemispheres were aimed to be identified by the group analysis of the non-mirrored data set.

The main objective of the present study was to characterize motor areas associated with finger flexion after dynamic immobilization and compare them with the areas after subsequent training. We hypothesized that immobilization leads to a temporary change in cerebral organization underlying the control of finger flexion movement, thus confirming the results of our pilot study described above.

Materials and Methods

Subjects

A total of 10 patients participated in the PET study, whereas EMG recordings were obtained from one additional patient. Characteristics are listed in the results section. Patients with zone II finger flexor tendon injury caused by a sharp transection (knife or glass) were eligible for inclusion if they were between 18 and 65 years of age. The lesion may inflict the volar side of either the left or the right hand. Patients were referred to our hand surgery unit for tenorrhaphy and subsequent rehabilitation according to our standard protocol. This protocol consisted of six weeks of relative immobilization. Four weeks after surgery the use of the splint is reduced and place-hold exercises are performed by the patient for two weeks using a so-called wrist band. Only right-handed patients according to the Edinburgh inventory were included [24]. Digital nerve injury occurs often together with zone II flexor tendon injury. For practical reasons, patients with only a restricted area of sensory deficit (digital nerve injury) were not excluded from the study even though there is some evidence that patients with isolated tendon repairs have better results than those with associated digital nerve injury[25]. Patients with other (more proximal) nerve and vascular injuries or fractures were excluded. None of the subjects had pre-existent neurological disorders or other upper extremity disorders. All subjects gave informed consent to a protocol approved by the Medical Ethics Committee of our institution.

PET study

Experience of clumsiness was quantified by asking all subjects to fill in a visual analogue scale (VAS) regarding their injured hand skill after both scan series. The VAS was recorded on a 0-100 scale where 100 implied perfect hand skills. The VAS data were analysed using the Wilcoxon signed ranks test. Each subject underwent two series of PET scans (Siemens ECAT HR+ scanner operated in 3D mode, 15.2cm axial field of view). Task related increases of regional cerebral blood flow were used as indicators for local neuronal activation and measured with Oxygen-15-labelled water that was injected prior to each scan [26]. During the PET measurements, subjects were in a supine position with the forearm and wrist supported by a pillow with the volar side facing down while the fingers could be moved freely. The first scan session took place immediately after removal of the splint, whereas the second series of scans was performed after at least six weeks of active exercising. In each of the two sessions, six scans were made while repeated double flexion movements (M) were carried out, and three scans were made in a control resting state (C). Scans were ordered C-M-M-M-C-M-M-M-C. During the flexion condition beeps were presented at random intervals (1.5 to 4.5 s). The subjects responded to each beep by making two brisk flexion movements of digits 2 to 5, with relaxation in between, enabling the fingers to passively regain their neutral position. During the control condition, subjects only listened to similar beeps without making a movement response. Such a control condition is required in order to filter out brain activation not related to finger flexion (e.g. activation evoked by the instruction beeps and sensations of lying on the back in the scanner).

PET image processing and analysis were conducted with SPM99[27]. Due to the strict exclusion criteria applied, it was not possible to include a large number of subjects with identical lesions in the study period. In order to increase the efficiency of the study, subjects with both left and right sided injury were included. The data of subjects with right sided lesions (and right sided finger flexion) were mirrored so that all subjects could be analyzed as one group. We are aware that the results of this analysis should be considered carefully and potential relevant areas should also be ascertained in the 'non-mirrored' dataset, as explained in the Introduction. Images were realigned to the first image to correct for head movements and normalized onto a standard brain template (Montreal Neurological Institute, MNI template in SPM99). Subsequently, the images were smoothed with a 10 mm Gaussian filter full width at half maximum to correct small inter-subject differences in the pattern of gyri and sulci. The above mentioned realignment, normalization and smoothening procedures resulted in a data set of brains with virtually identical spatial dimensions. This enables statistical analysis of changes in local cerebral bloodflow in a group of subjects.

Brain activation during finger flexion was determined by contrasting the movement to the control condition. These comparisons were made in the first as well as the second scan session. For the group analysis, statistical thresholds were initially set at $P<0.001$ for response height at voxel level and a cluster size (kE) of minimally 8 voxels. Resulting clusters were considered significant at $P<0.05$ after (cluster-level) correction for the entire brain volume.

Electromyography (EMG)

Surface EMG of finger flexor and extensor muscles of the subject were recorded twice from each arms successively (Nicolet EMG apparatus, Viking IV, sampling frequency 20 kHz). A first EMG was recorded immediately after removal of the splint and a second EMG after six weeks of active practicing of the hand and fingers. For this purpose two electrodes were placed on the forearm, approximately 10 cm distal to the elbow joint. One electrode was placed ventrally, superficial to the flexor digitorum muscles and one electrode was placed dorsally, superficial to the extensor digitorum muscles.

During EMG recordings, the subject was positioned identically to the position of subjects during the PET measurements (supine, wrist and arm supported, volar side of wrist facing down). Similar to the PET series, two successive EMGs of the injured hand were recorded. In contrast to the PET study, in which the number of measurements was restricted by the maximal radioactivity dose, thus allowing only a flexion and no extension condition, EMG was recorded during flexion as well as during extension. In the flexion condition the stimulus and response were identical to the PET study, while in the extension condition the only difference was that the beeps were followed by two brisk extension movements, each followed by relaxation in a similar way as during flexion.

Results

Ten subjects (mean age 38 yrs, standard deviation (SD) 12 yrs) were included in the PET study, while one subject (male, 21 yrs) underwent only EMG examination. Five of the subjects included for PET had a left hand injury; another five had a right hand injury. Table 3.1 shows the demographics of these 10 subjects. Two of them participated only in the first and not in the second PET session: one subject was excluded due to suture rupture, requiring a secondary tendon repair, while the other subject was not motivated for a second session. The subject who participated in the EMG study had a left hand injury.

The average period between surgery and the first scan series was 40 days (SD = 3 days). The average interval between the first and second scan session was 55 days (SD = 14 days). All subjects were able to perform the tasks. The minimum distance between the finger tip and the distal palmar crease[28] was always less than 1 cm and passive finger flexion went smooth. Nevertheless, all subjects reported difficulties in performance during the first scan session, which was immediately after removal of the splint. The average VAS scores on hand skills after the first PET session was 53 (SD = 16), while after the second series it was 87 (SD = 6), this difference was significant ($p = 0.012$, $Z = -2.5$). This effect was seen for the left hand as well as the right hand injuries. After the first PET session, the VAS scores were 51 for the left hand and 55 for the right hand lesions, while after the second session they were 87 respectively 85.

Table 3.1 Characteristics of subjects participating in the PET study

No	Age	Sex	Dominance	Lesion side	Injury
1	49	Male	Right	Left	Digit 2: FDS, FDP, radiovolar digital nerve
2	37	Male	Right	Right	Digit 5: FDP, ulnovolar digital nerve
3	24	Male	Right	Right	Digit 2: FDS, FDP, radiovolar digital nerve
4	36	Male	Right	Left	Digit 4: FDS, FDP, ulnovolar digital nerve
5	46	Male	Right	Left	Digit 2: FDP
6	36	Male	Right	Right	Digit 3: FDS, FDP, ulnovolar digital nerve, Digit 4: FDS, FDP, ulno- and radiovolar digital nerves
7	49	Male	Right	Right	Digit 4: FDS
8	20	Male	Right	Left	Digit 2: FDP, FDS, radiovolar digital nerve
9	26	Female	Right	Left	Digit 2: FDP
10	57	Male	Right	Right	Digit 2, FDP, FDS, ulno- and radiovolar digital nerves
11*	21	Male	Right	Left	Digit 4, FDP

All subjects suffered a zone II sharp flexor tendon injury. FDS = Flexor Digitorum Superficialis tendon, FDP = Flexor Digitorum Profundus tendon.

* Subject 11 only participated in the EMG study

Cerebral activations identified by PET.

Group analysis of the non-mirrored data-set revealed that repeated finger flexion, compared with rest, resulted in bilateral activations in the sensorimotor cortex and cerebellum, respectively (Fig. 3.1, see Appendix). Sensorimotor activations corresponded with finger movements of the contralateral hand, which is illustrated for the right motor cortex in Fig. 3.3a. When the brains of the right hand performers were mirrored, a strong lateralization of these sensorimotor and cerebellar activations was seen. Now, sensorimotor activation in a single hemisphere (Fig. 3.2, see Appendix) represented the relation with all contralateral movements (Fig. 3.3b), while, as expected, cerebellar activation was ipsilateral to these movements (Fig. 3.2, see Appendix). These effects were seen to occur highly similar in the first as well as the second scan session.

In the first scan session, no putamen activation was seen in the non-mirrored nor in the mirrored data set. In session 2, however, right-sided putamen activation was seen in the non-mirrored data-set, which remained lateralized to the right in the mirrored data set (Figs. 3.1 & 3.2 section z = -2 mm, see Appendix). Only the dorsal extension of the right putamen activation was smaller after flipping. Plotting the putamen effects in the mirrored data-set demonstrated that the increase of putamen activation in the second session was contralateral to movements irrespectively whether they were made with the left or the right hand (Fig. 3.3f). Opposite to the temporal profile of putamen activation, increased activation of the right posterior parietal cortex was seen in the first session while it disappeared in the second (Figs. 3.1 & 3.2, see Appendix). This activation in the first session, however, was only related to movements made with the left hand (Fig. 3.3cd).

These results confirmed what we previously presented in a short report of only 4 subjects with a left hand lesion[11]. In that study, we additionally found a decrease in the magnitude of anterior cingulate activation over time. In the present data, such effect was only subtle, but indeed present at the same anterior cingulate location (Fig. 3.3e). This activation, however, was part of a larger region of activation that extended in dorsal-posterior direction, where the centre of activation was in the Supplementary Motor Area (SMA) (Fig. 3.1 & 3.2, see Appendix). The magnitude of activation in the SMA was similar in the two scan sessions. Consistent with the previous description of the small group, the magnitude of activation in the posterior insula, contralateral to finger flexion, increased between the two scan sessions (Fig. 3.3g). On the antero-ventral surface of both parietal lobes, i.e. in the secondary somatosensory cortex S2, activations were similarly seen during contralateral as well as ipsilateral hand movement. The only exception was that in the first scan session, left S2 was not evoked during right hand movement.

In contrast to the findings in the previous study on 4 subjects, activation of the lateral thalamus, contralateral to the finger movements, reached statistical significance in the second scan session (Figs. 3.1 & 3.2, see Appendix). In the first session, minor activation was found in only the right thalamus, contralateral to left hand movement (non-mirrored data) (Fig. 3.1 & 3.3h, also see Appendix), while right hand movement was not related with left thalamus activation in this session. Coordinates and Z-scores of maxima in the regions of significant activation are summarized in Table 3.2.

EMG study

The EMG recordings of one typical subject (Fig. 3.4) demonstrated that within the pairs of two successive flexor movements made in the first session, no complete relaxation occurred, while such relaxation did occur in session 2. The fact that the splinting procedure had generated this effect on specifically flexor movements, which were only passively made during splinting, was inferred from the relaxation recorded in between the brisk extension movements in both session 1 and 2.

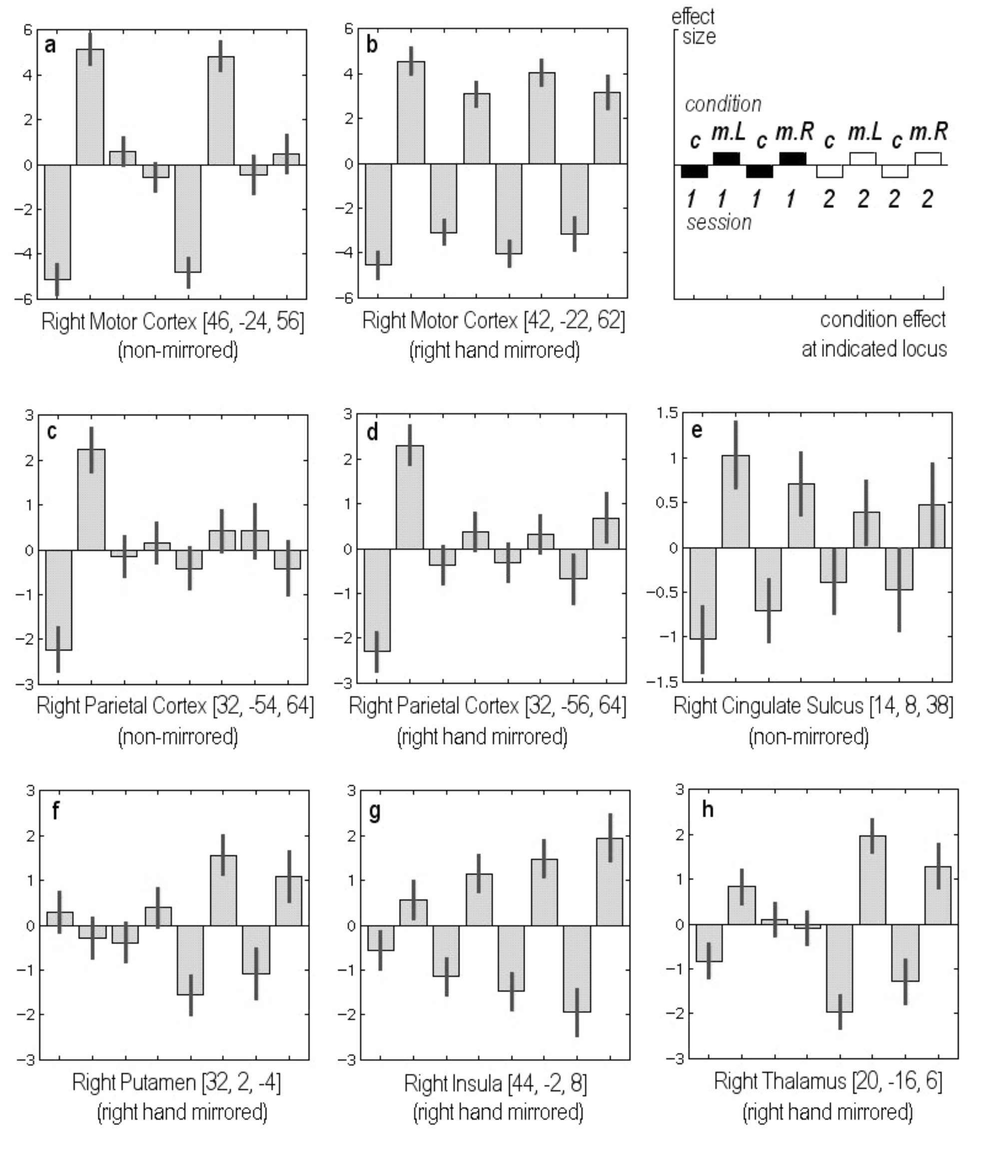

Figure 3.3 Contrast of parameter estimates. The condition effects are expressed as effect size and are plotted for the regions as indicated below each graph. The scheme in the upper right corner illustrates the graphs design in which the left and right hand movement conditions were contrasted to the control condition in respectively session 1 and 2. c= control condition without movement, m.L= left hand movers, m.R= right hand movers

Non-mirrored implies that the datasets were not mirrored. Therefore figure **3a** demonstrates that left hand injuries (= left hand movers) showed an effect in the contralateral (right) motor cortex. Right hand injuries (= right hand movers) did not induce activation in the right but in the left motor cortex, which is not depicted here.

Right hand mirrored implies that the effects of right hand movers were processed as if it were effects from left sided movements and thus correspond with right motor cortex activation (figure **3b**). The magnitude of activation in the contralateral primary motor cortex did not change over time.

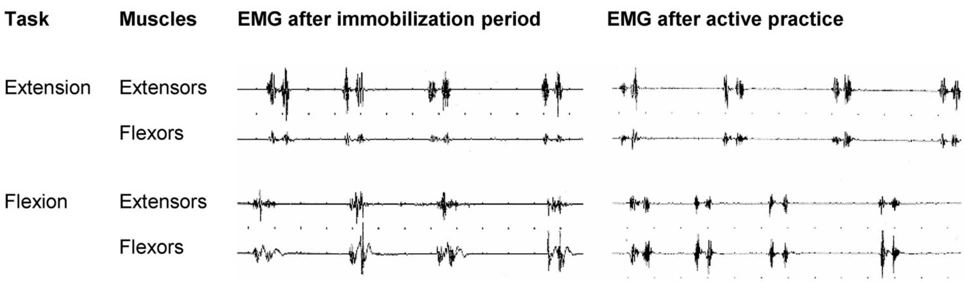

Figure 3.4 Surface EMG of finger flexors and extensors. Surface finger flexor en extensor EMG results during four stimuli are shown during different conditions. A typical subject responded to each beep by making two brisk flexion or extension movements of digit 2-5, with relaxation in between. In the PET experiment, only flexion movements were studied (due to limitations in applying radioactivity).

Discussion

The functional outcome of surgery and subsequent dynamic splinting was good in the patients studied in terms of range of motion. Their hand function was not impaired due to e.g. tendon adhesions or joint stiffness. This was demonstrated by the smooth passive flexion as well as the low minimum distance between the fingertips and distal palmar crease although total active motion was not recorded. Nevertheless, the low VAS scores on hand skills after 6 weeks of immobilization pointed at manual disability. Improvement after a subsequent period of actively using the flexor function again was demonstrated by the significant increase on these VAS scores. This provided a quantitative parameter supporting that immobilization following surgery led to the temporary clumsiness as reported earlier[11] and thus confined the rationale to perform this functional brain imaging study.

Application of the Kleinert splint implied that finger flexion movements were only performed passively for a period of 6 weeks. No active flexion commands were given to the affected hand while extension movements were still actively performed. The obtained EMG recordings provided support for the assumption that the absence of active movement is a cause of functional deficit. Flexion, and not extension, was specifically disturbed after splint removal, while it was normalized 6 weeks later. This disturbance was particularly characterized by incomplete flexor relaxation in between two brisk contractions. The fact that this distinct movement pattern was associated with flexion and not extension is an argument supporting the concept that the splinting procedure itself was the cause of dysfunction. It should be noticed, in this respect, that the inclusion of a healthy control group with only dynamic splinting, without a tendon lesion and subsequent repair, was not considered feasible for ethical reasons. The finding of insufficient relaxation within serial contraction provides a logical link between the clumsiness reported by our subjects and the concept of lost skill. Lost skill can also be inferred from the absent putamen activation in the first PET session. In skilled movement, relaxation of unwanted muscle contractions plays an important role[29;30]. In normal circumstances, the putamen is implicated in general skill learning, as has been demonstrated in functional imaging studies[14;15;31]. Moreover, in basal ganglia disorders such as Parkinson's disease and dystonia, the failure to inhibit unwanted movements is a prominent feature[32].

Theoretically, one might argue that the nearby absence of putamen activation we found in the first PET session was the normal base-line, while increased activation in the second session reflected excessive practice. We have recently proved otherwise by demonstrating that in healthy volunteers, performance of the same double-flexion task evoked a pattern of significant cerebral activations that included the contralateral putamen[33]. We therefore conclude that the reduced putamen activation in session 1 reflected loss of over-learned movement induced by not actively making such movement.

The effects we observed in the (ventral) putamen were contralateral to movements of left as well as right hand movement, which confirmed the data of our pilot study[11]. In that study on four subjects with left hand injury we found increased right posterior parietal activation in the first session, which was strongly reduced in session 2. In the present study, this temporal profile remained present for left hand movement, but was not found for right hand movement. The latter did not evoke significant increase of posterior parietal activation in session 1, neither in the right-, nor in the left hemisphere. This means that our previous explanation of an increased demand of body scheme information in order to overcome the movement difficulty, can only be maintained for the left hand[11-13]. Possibly, the non-dominant left hand needs such additional support more than the dominant right hand. Alternatively, one might speculate that particularly the left hand is in a better position than the right hand to gain access to compensatory circuitry that is specifically present in the (contralateral) right hemisphere. In this respect, right-hemisphere circuitry related to visuomotor imagination may be considered.

Activation of the motor portion of the cingulate gyrus in session 1 was larger than in session 2. This effect was seen for both hands in the present study and confirmed the result of our previous four-subject study (Fig. 3.3). The recruitment of this secondary motor function[34], possibly mediated by aspects of attention[35] thus implies to be more general than the posterior parietal recruitment, which only held for the left hand. In the pilot study, however, cingulate activation in session 1 was seen as a distinct cluster, which was not the case in the present study (Table

3.2). Now, it was part of a larger cluster comprising the SMA and not distinguished as an independent focus. Activation of the SMA was similarly strong in both sessions.

Activations in the contralateral insula and antero-ventral parietal cortex (S2) were increased in session 2. This was also described in our pilot study, in which we provided arguments that these increases might well reflect improved sensorimotor integration, facilitating efficient motor control[11]. Particularly S2 on the parietal operculum has recently been described to act as an important interface between proprioceptive information processing and the organization underlying motor control[36]. We therefore conclude that by actively using the hand, proprioceptive information is used for efficient motor control, while during passive flexion, proprioceptive information is not used for the latter.

Table 3.2 Activations related to unilateral hand movement (mirrored data-set)

	Session 1 (10 subjects)					Session 2 (8 subjects)				
Brain region	**x**	**y**	**z**	**kE**	**Z-score**	**x**	**y**	**Z**	**kE**	**Z-score**
Sensori-motor cortex	50	-22	56	2840	>8	44	-30	62	2788	7.09
Cerebellum	-18	-54	-10	3051	7.74	-18	-50	-18	3526	>8
	22	-62	-22	537	5.66					
Supplementary motor area	2	-8	52	368	4.84	8	-4	52	388	4.40
Posterior parietal cortex	32	-55	66	96	4.29 *1)	--	--	--	--	--
Antero-ventral parietal cortex	--	--	--	--	--	50	-24	18	197	4.38
Insula	--	--	--	--	--	44	-2	8	360 *2)	4.71
Putamen	--	--	--	--	--	32	-2	-6		3.70
Thalamus	--	--	--	--	--	20	-16	6	395	4.86

Location of clusters with significantly increased perfusion during repeated flexion movement as compared to rest (group analysis, $p < 0.05$, cluster-level corrected for whole brain volume), see also *1) and *2). Imaging data of right hand movement were mirrored, which implies that all activations are related to 'virtual' left hand finger flexion. Coordinates (in mm) refer to the centre of maximum within a cluster. Positive x, y and z coordinates indicate locations respectively right, anterior and superior of the middle of the anterior commissure. Initial voxel threshold was at $P < 0.001$ (uncorrected) with extends (kE) of 8 voxels. At voxel-level, all foci of activation reached False-Detection-Rate corrected significance $P < 0.001$, only the putamen maximum in session 2 reached FDR corrected $P = 0.004$.

*1) The posterior parietal cluster did only reach an uncorrected cluster-level significance ($p = 0.03$).

*2) The local insula- and putamen activations touched each other and merged into a common cluster (kE 360).

During finger flexion the contralateral primary sensorimotor cortex and ipsilateral cerebellum were similarly active right after the immobilization period and also after active training. This demonstrated that at a basic level, movements could be performed as requested, but that indeed movement efficiency was deteriorated.

In conclusion, we showed that six weeks of relative immobilization results in a temporary loss of efficient cerebral control of finger flexion. This is characterized by an increased cortical demand and reduced striate involvement. These findings show the impact of a relatively short period of immobilization on the functional organization of the brain. While this cerebral reorganization may occur after any type of immobilization, we are not aware of reports regarding taking measures in the clinical situation to prevent this reorganization from taking place. For the development of new treatment protocols of peripheral lesions in which immobilization is required, the central consequences of this immobilization should be considered.

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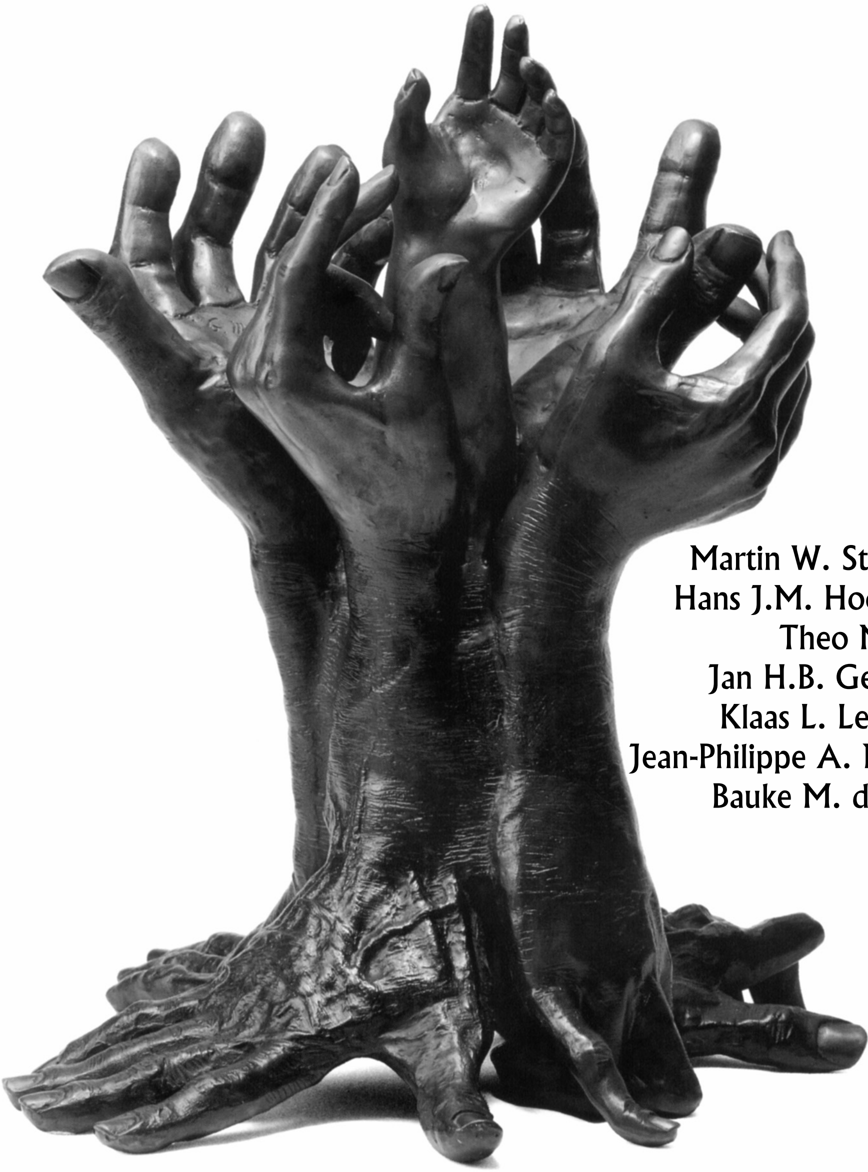
Chapter 4

Functional dominance of finger flexion over extension, expressed in left parietal activation



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Abstract

Sensory stimuli may elicit a widely distributed parietal-premotor circuitry underlying task-related movements such as grasping. These stimuli include the visual presentation of an object to be grasped, as well as the observation of grasping performed by others. In this study we used functional Magnetic Resonance Imaging (fMRI) to test whether the performance of simple finger flexion, contrasted to extension, might similarly activate higher-order circuitry associated with grasping. Statistical Parametric Mapping (SPM) showed that flexion, compared to extension, was related with significant activation of the left posterior parietal cortex and posterior insula, bilaterally. This pattern supported our hypothesis that simple finger flexion has a specific relation with circuitry involved in preparing manual tasks. Although the two motor conditions showed major overlap in the primary motor cortex, increased flexion-related activation at the precentral motor-premotor junction further supported its association with higher order-motor control.

Introduction

Grasping movements provide the ability to manipulate objects in surrounding space. This implies tuning of finger positions to the shape of an object being reached for. The cerebral organisation of such visuomotor function is embedded in circuitry distributed over parietal and premotor cortical regions without a strict regional demarcation between perceptual and motor representations[1-3]. Both premotor and parietal cortical regions have been involved in grasping an object as well as observing this object. These action-associated networks can further be activated, in a mirror fashion, by action observation[4], action sounds[5] or the verbal description of action[6], thus demonstrating that stimulation by specific perceptual fragments provides access to circuitry underlying higher-order motor control[7]. This raises the question whether the performance of a simple motor act without a specified goal or object to grasp, might similarly activate such circuitry.

Previously, we have shown that the left parietal 'grasping' region does not only contribute to the integration of object shape and hand posture. It is also active during hand posturing, independent of the shape of the target being reached for[8]. This command function was explained as being an active process of integrating body scheme information into the organisation of movement, which is consistent with clinical characteristics seen in apraxia[9]. In the present study, an important consideration was that in grasping the initial opening of the hand is less task-specific compared with subsequent finger flexion. Although indeed the initial grip aperture is guided by the spatial dimensions of the target, subsequent flexion provides the precision grip with both the exact adjustment of separate fingers to the shape of the target, and the coordination of fingertip forces[10;11]. One might thus infer that flexion is more involved in higher-order motor control than finger extension. We therefore hypothesized that simple flexion, contrasted to extension, is associated with activation in parietal and premotor cortex. In order to answer this question, functional brain imaging based on the detection of regional changes in relative perfusion was applied[12]. By using appropriate task conditions, this methodology allows the identification of cerebral structures that deal with aspects of the cerebral organisation of movement that lie beyond the primary motor cortex.

A second issue concerned the functional distribution of finger movements over the primary motor cortex. The somatotopic representation of body parts, including separate fingers, is well-established, although patterns of overlap exist[13-16]. The difference between flexion and extension of the same fingers, however, does not easily fit in this scheme. In analogy with the differences between proximal and distal sensory stimulation of the same finger[17], we particularly looked for a functional segregation between deep and superficial segments of the anterior wall of the central sulcus.

Materials and Methods

Twelve healthy right-handed subjects (eight males, four females) were studied with functional Magnetic Resonance Imaging using a 3T Intera Philips MRI scanner (Best, The Netherlands) with a standard 6-channel SENSE head coil. The following pulse sequence parameters were used: FFE single shot EPI; 46 slices; slice thickness 3.5 mm; no gap; field of view 224 mm; scanning matrix 64x64; transverse slice orientation; repetition time (TR) = 3 s; echo time (TE) = 35 ms; flip angle 90°. Subjects gave informed consent to a protocol approved by the local Medical Ethics Committee. Their ages ranged from 20 to 63 years (median 29). None of the subjects had known neurological disorders or a history of upper extremity disorders. Before scanning, the tasks were explained and practiced shortly. Data were acquired in four subsequent sessions, of which each consisted of four 33-second movement blocks that were each preceded by a control block. In one block, 11 brain volumes of 46 slices were obtained. Beeps were presented by headphone at random intervals (1.5 to 4.5 s), in 33-second blocks. At the onset of each block, auditory instructions (by headphone) indicated the condition during that block, being either *Flexion*, *Extension* or *Rest*. Subjects had their eyes closed. The two movement conditions were scheduled in a balanced order.

The left arm was positioned with the volar side of the hand facing the floor. The forearm and wrist were supported by a pillow on the scanner table, while the fingers could move freely. In the flexion condition, subjects responded to each beep by two rapid flexion movements of the left-hand fingers, except for the thumb. The two successive flexion movements were each followed by relaxation, which enabled the fingers to passively regain their neutral position. In the extension condition, two extension movements of the same fingers (digits 2-5) were made, similarly followed by relaxation of the muscles. In the rest condition subjects only listened to the beeps, no motor responses were given. The execution of the movement tasks was recorded by a camera in the scanner room and monitored on a television-screen in the console room. Subjects were allowed to execute the strictly paced movements in a natural fashion. Although we thus refrained from explicitly controlling subtle variations in force, the advantage of this design was that the flexion and extension tasks were balanced for attentional demand.

The kinetic characteristics of performance during scanning were not quantified. However, observations confirmed that the movements resembled those that were demonstrated during the instructions before scanning. The instructed position of the relaxed hand implied that the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints were each held at an angle of about 45° deviating from the virtual axis along a fully extended joint (Fig. 4.1). Active flexion was mainly accomplished by movements in these two joints: the angle in the MCP-joint increased by 15° to 60°, while the angle in the PIP-joint increased by 35° to 80°. The fingertips did not touch the palm. During extension, the angles in these two joints decreased by approximately 35° each, resulting in almost straight fingers. The occurrence of consistent relaxation between two brisk successive movements in this task was previously documented by surface electromyography in normal circumstances[18]. Only in pathological conditions did such relaxation fail. The reason to employ a left-hand movement paradigm in the present study was to maintain similarity with the protocol used in our previous left-hand tendon lesion study.

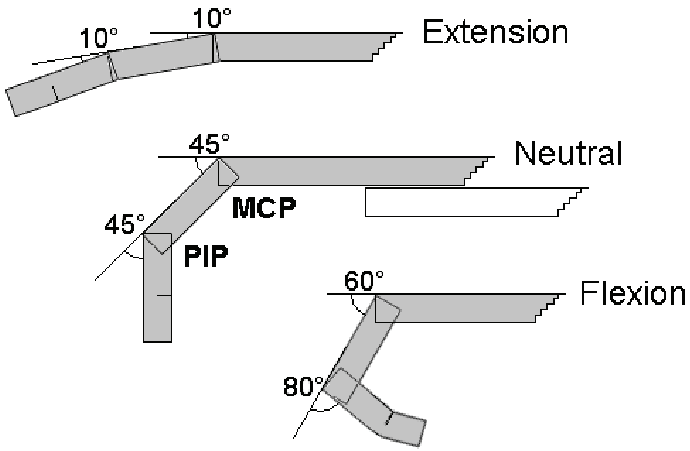

Figure 4.1 Schematic illustration of the instructed hand movements. The forearm and wrist were supported. In the flexion condition, subjects responded to each single beep by two brisk flexion movements of the left-hand fingers, except for the thumb. The two successive flexion movements were each followed by relaxation, which enabled the fingers to passively regain their neutral position. In the extension condition, two extension movements of the same fingers (digits 2-5) were made, similarly followed by relaxation of the muscles. MCP = metacarpophalangeal joint; PIP = proximal interphalangeal joint.

Image processing and statistical analysis were conducted with Statistical Parametric mapping[19] (version SPM2, Wellcome Department of Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm). Pre-processing included realignment of all images to the first one, and subsequent spatial normalization onto a standard brain template (Montreal Neurological Institute, MNI template in SPM). For whole brain analysis, images were smoothed with a

Gaussian filter of 10 mm FWHM. In addition, the images were smoothed with a 4 mm filter as to detect differences in activation in the primary motor cortex. The movement conditions were contrasted both to rest and to each other. The group results were obtained by fixed-effects analysis (Fig. 4.2).

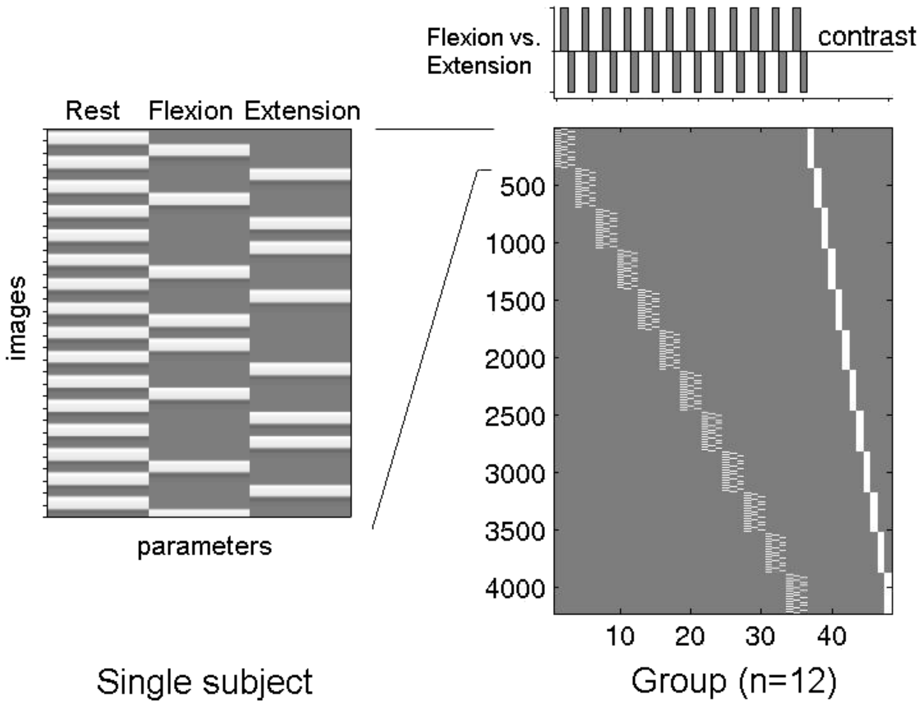

Figure 4.2 Design matrix of the applied fixed-effect analysis by SPM, illustrating the contrast of increased BOLD responses related to flexion (+1) versus extension (-1), with the non-motor (rest) condition set to zero. For each subject, a total of 8 flexion- and 8 extension blocks were ordered in pairs [Flex. Ext.] and [Ext. Flex.], while each movement block was preceded by a rest block. A single condition block consists of 11 measurements of a whole brain volume, which implies that 352 volumes (images) were acquired from each of the 12 subjects.

Results

Subjects had no difficulty performing the tasks correctly as could be visually examined on the television. They did not experience one of the two tasks more difficult than the other one. The two movement conditions, compared to rest, showed common activation in predominantly the contralateral sensorimotor cortex, ipsilateral cerebellum and supplementary motor area (SMA)

(Fig. 4.3, see Appendix, Table 4.1). Group analysis of changes in BOLD response (10 mm filter initial threshold for response-height at voxel-level p = 0.001) revealed that finger flexion, when contrasted to extension, was related to significant activation in the ipsilateral (left) parietal cortex ($p < 0.05$, cluster-level corrected for whole brain volume) (Fig. 4.4, see Appendix, Table 4.2). This focus of activation was found at a postero-superior location along the intra-parietal sulcus. In addition, significant activations were found in the posterior insula of both hemispheres (Fig. 4.4, see Appendix). Contrasting extension to flexion movement did not result in significant activation (at cluster-level). In Figure 4.5, the parietal effects of flexion and extension are plotted for each subject, illustrating that the group result was supported by all subjects.

Table 4.1 Movement-related activation

		Stereotactic coordinates (x, y z)							
		Left				**Right**			
Brain region	[BA]	x	y	z	Z-score	x	y	z	Z-score
SMA	[6]					4	0	56	>8
Sensori-motor cortex	[4]					40	-24	62	>8
						40	-14	62	>8
Prefrontal cortex	[45]/[46]					44	38	26	>8
Premotor cortex	[6]	-44	-2	58	>8	58	10	36	>8
		-60	10	30	>8	62	-14	44	>8
Anterior parietal Cortex	[40]	-64	-18	14	>8	66	-26	18	>8
		-48	-42	56	>8	62	-26	36	>8
Putamen						30	-8	-4	>8
Operculum/Insula	[38]/[48]	-52	8	-8	>8	54	8	-8	>8
Thalamus		-8	-18	8	>8	10	-18	6	>8

Coordinates of the activation regions related to left-hand movement, i.e. both flexion and extension contrasted to rest (group of 12 subjects, $p < 0.01$, family-wise error-correction for the whole brain volume). Spatial smoothing filter was 10 mm. Positive x,y,z coordinates (in mm) indicate locations on respectively the right of, anterior and superior to the middle of the anterior commissure.
BA = Brodmann's Area.

Table 4.2 Flexion-related activation (whole brain)

		Stereotactic coordinates (x, y z)									
		Left					Right				
Brain region	[BA]	x	y	z	Z-score	kE	x	y	z	Z-score	kE
Parietal cortex	[40]	-32	-60	56	4.0	620					
Posterior insula	[48]	-36	-22	-2	4.4	581	38	-4	14	5.4	430

Coordinates of the activation maxima related to left-hand finger flexion contrasted to extension (group analysis, $p < 0.05$, cluster-level corrected for whole brain volume). kE = extent of the cluster, expressed by the number of voxels. Spatial smoothing filter was 10 mm. Extension contrasted to flexion did not reveal significant activation with this threshold. Conventions are as in Table 4.1.

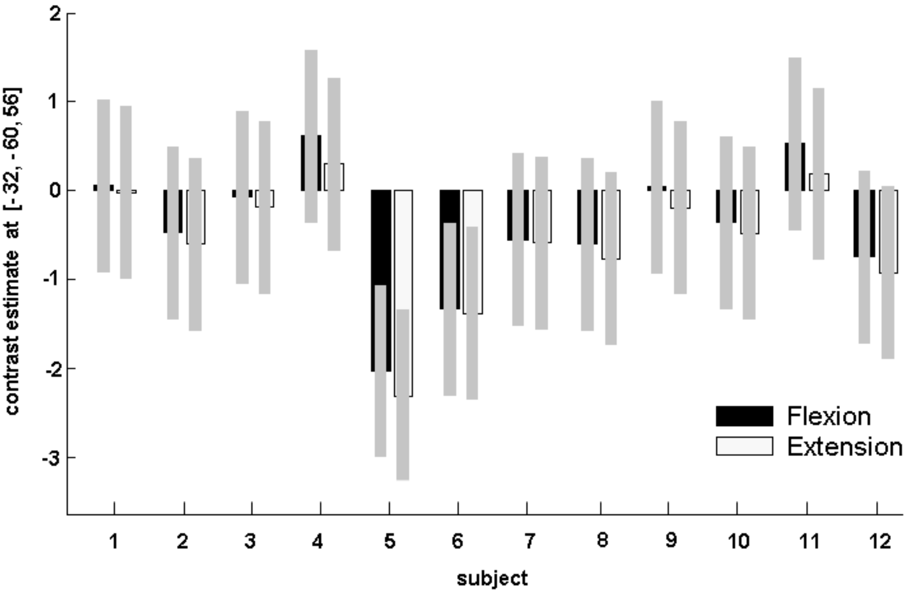

Figure 4.5 Contrast estimates (and 90% confidence intervals, c.i.) with the effects of flexion and extension in the left parietal cortex for each of the 12 subjects. The estimates were derived from the focus of maximum activation at [x –32, y –60, z 56], identified by the group analysis. Seven subjects showed a cluster of robust activation, while in the other 5 subjects, activations were smaller. In the individual subjects the local maximum of parietal activation might be at a slightly different location as the group maximum.

Our second question concerned the possible segregation between the representation of finger flexion and extension in the motor cortex. At relaxed statistical threshold, and using the 4 mm filter, again overlap in the contralateral sensorimotor cortex was the most prominent observation. However, subtle differences could be noticed. Activation resulting from finger flexion, compared to rest, extended more lateral to the cerebral convexity than the extension-related activation (Fig. 4.6a,c, see Appendix; Table 4.3). Moreover, activation related to extension, when contrasted to flexion, was found deep in the central sulcus ($p < 0.05$, at voxel-level, uncorrected), whereas finger flexion, contrasted to extension revealed activation more laterally in the motor cortex, reaching the surface of the pre-central gyrus (Fig. 4.6b,d, see Appendix). At this lateral location, the primary motor cortex (Brodmann's Area, BA4) borders on the premotor cortex BA 6. In addition, the latter contrast (flexion vs. extension) showed activation of the primary sensory cortex at the post-central gyrus. The extension-specific activation in the fundus of the central sulcus (Fig. 4.6d, see Appendix) was near the junction between BA 4 and sensory cortex BA 3. Although an unequivocal distinction is difficult to make, the slight spread in the precentral gyrus, observed in adjacent superior slices (see also Table 4.3), supports involvement of the primary motor cortex (BA 4).

Table 4.3 Segregation along the central sulcus

	Stereotactic coordinates (x, y z)							
	Left				**Right**			
Contrast	x	y	z	Z-score	x	y	z	Z-score
Flexion versus rest					36	-22	54	>8
					42	-26	62	>8
Flexion versus extension					50	-22	54	6.0
Extension versus rest					36	-22	54	>8
					38	-34	68	>8
Extension versus flexion					26	-22	56	2.9
					28	-24	64	2.7

Coordinates of the activation maxima of the contralateral motor cortex related to left-hand finger flexion contrasted to extension, and finger extension contrasted to flexion ($p < 0.05$, voxel-level, uncorrected). Spatial smoothing filter was 4 mm. Conventions are as in Table 4.1.

Discussion

The distribution of flexion-related activation demonstrated that, unlike extension, finger flexion has a strong relation with higher-order motor control. This supported our hypothesis. Particularly the left parietal activation, ipsilateral to the executed movements, represents a crucial node in a network subserving adequate manipulation of objects[20]. At different levels, the posterior parietal cortex has been associated with the organisation of task-related movement, ranging from intention, prehension to actual visuomotor- and somatosensorimotor integration[2;11;21-24]. The fact that we found the parietal activation in the left hemisphere, ipsilateral to the moving hand, points at a specific left (dominant) hemisphere function. The contribution of body scheme to prehensile command is such a lateralized function for the parietal cortex[8], of which deficit results in ideomotor apraxia[9;20]. The ipsilateral location is a strong argument against the view that the parietal activation was the result of possible increased proprioceptive feedback in finger flexion. The supporting role of the posterior insula in skeletomotor control has been established in both human and other primates, although its specific contribution has not been fully elucidated yet[25-27].

The recruitment of distributed circuitry by simple flexion movement was consistent with our assumption that particularly finger flexion is a motor act which is functionally implicated in complex movement such as grasping. This association may also be inferred from the cerebral effects of dynamic immobilization following flexor tendon surgery[28]. We have recently described that after a period of splinting with elastic strings, enabling only passive and not active flexion movement, clumsiness in task performance remained for weeks. Repeated functional brain imaging revealed that prolonged absence of active flexion movement had induced changes in the cerebral organisation of hand movement[18]. Recruitment of distributed action-related circuitry by sensory stimuli has been well described. A classical finding, in this respect, concerned the behavior of ventral premotor neurons, that were activated during both the observation of meaningful hand movement by others and the effective execution of such movement[29]. These neurons were consequently called mirror-neurons. Later, action observation appeared to induce activation of a wider distributed parietal-premotor network[4;30]. This enables observations to be matched onto the motor system[31]. Recent findings have shown that even indirect stimuli such as action sounds, may recruit the action-related circuitries[5]. This indicates that the now often coined ‘mirror-neuron system’ reflects a cerebral organisation that goes beyond mirror-mode processing. A general principle of cerebral processing might be that a distributed, functionally coherent, cerebral network is recruited by activation of one of its crucial nodes[32]. Along such nodes, network-access is allowed to a wide range of sensory stimuli. Our finding indicates that access can similarly be obtained by a motor act.

Although flexion and extension predominantly shared the focus of activation in the primary motor cortex, contrasting the two motor conditions revealed a segregation with the flexion-related activation extending to the motor-premotor junction on the precentral gyrus. Extension-related activation, contrasted to flexion, was deep in the central sulcus. This distribution, particularly with the relation between flexion and premotor cortex activation, provides an additional argument for the strong association between finger flexion and task-related movement, which is indeed naturally expressed in grasping. Functional differentiation along the anterior wall of the central sulcus with a segregation between deep (posterior, BA 4p) and superficial (anterior, BA 4a) segments of the primary motor cortex has previously been described[33]. While subjects made the same stereotypic finger movements, they found that activation related to the instructed motor task remained high in the BA 4a, independent from visual distraction, while activation deep in the central sulcus (BA 4p) decreased in such condition. Modulation of activation in the latter was inferred to reflect modulation of attention to action. In addition, one might consider that the maintained high activation in BA 4a points at a strong anchoring of instructed, task-related movement. It is a challenging idea to assume that such anchoring is logically associated with input from the adjacent premotor cortex (BA 6)[34].

Finger flexion and extension movements are executed by the same body parts. On the other hand, these movements are functionally distinct and made by different muscles. Similar conceptual considerations have been made with regard to the difference between the motor representation of separate fingers versus the representation of separate hand muscles. Although gradients of segregated finger representations remain a repeatedly confirmed finding, overlap of these representations, as well as distributed multifocal representation, has been emphasized[13;14;35]. In brain activation studies, the somatotopic representation of fingers on the motor cortex was enhanced by contrasting one finger to the others. The additional complexity of representation has been proposed to reflect the flexibility to achieve an indeed enormous repertoire of movements with the same fingers, based on specific combinations of muscle contractions[13;36]. In this respect, our finding of both overlap and segregation concerning two opposite movements of the same fingers is consistent with the findings concerning movement representations of different fingers.

The two movement conditions that were applied in our study were particularly characterized by the swift alternation of contraction and subsequent relaxation. These movements were made in a natural fashion, without a difference in perceived task difficulty. Although the two conditions were thus balanced for attentional demand, one might argue that in natural movement, finger flexion is more forceful than extension, thus introducing a possible bias between flexion and force. We regard this explanation unlikely. In the literature, modulation of force has particularly been associated with changing activations in sensorimotor cortex, SMA, cerebellum and basal ganglia[37;38], whereas in our study, flexion-specific activation was not in the center of the movement-related activation, but at the border between the primary motor cortex and premotor cortex. One might oppose that, although the magnitude of activation in the centre did not differ between flexion and extension, possible greater force in flexion would include more widespread recruitment of muscles and an associated increase of proprioceptive feedback. This might thus result in a larger spread of sensorimotor cortex activation. In our study, however, we did not only see a lateral expansion of activation related to flexion, a small extension-specific spread was seen towards the fundus of the central sulcus. Additional arguments against the idea that differences in force might explain our results include the absence of flexion-specific activation in SMA, basal ganglia and cerebellum[37;38]. On the other hand, the posterior parietal cortex has recently been implicated in the co-ordination of fingertip forces[11]. In a previous study, Ehrsson et al.[39] already demonstrated the specific involvement of parietal- and premotor cortex in the production of force in precision grip, when contrasted to power grip. This context-dependent effect of force supports our concept that simple movement qualities may be intrinsically related to higher-order motor.

To conclude, finger flexion, more than extension, may be regarded as a basic element in the organisation of complex movements such as grasping. We thus infer that specific simple motor acts may recruit a cerebral network implicated in the organisation of more complex action. This suggests an analogy with the activation of an action supporting cerebral network by specific sensory stimuli. Finally, we found indications that antagonist muscle groups of the same fingers can be somatotopically distinguished on the motor cortex.

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Chapter 5

Changes in speed of information processing in the brain following tendon repair

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Abstract

The objective of this study was to measure the 'preparation time', that is the speed of information processing in the brain, and discuss the relevance of this parameter in the restoration of hand function following flexor tendon repair. The preparation time of 48 healthy adult participants was measured twice at a 6 week interval and compared with that of 12 patients after flexor tendon repair. There was no difference between the left and right hands of the healthy participants. The correlation between repeated measurements was high, although healthy participants performed 2.6% faster 6 weeks after the first measurement. After 6 weeks of immobilization, patients showed a significant deterioration in respect of the speed of information processing by the brain on both the injured and uninjured sides compared with healthy participants, who had improved between the first and the second measurements. The results indicate that a period of lack of normal use of the hand leads to a change in cerebral control of hand movements.

Introduction

Flexor tendon injury is one of the most common hand injuries. Treatment is focused on rapid recovery of hand function. Although there is ongoing discussion about the specific methods of tendon repair and rehabilitation, surgical repair of the injured tendon followed by several weeks of dynamic splinting is the most common treatment procedure[1;2]. In order to assess hand function after flexor tendon surgery, several hand assessment tools have been developed, such as questionnaires, range of motion and other functional tests[3-9]. In general, hand function assessment is focused on scores that reflect the adequacy of the involved effector organ. These assessment procedures have been termed 'result oriented', since they focus on the results of a specific performance measure such as time to completion of a task compared with a norm score. Although result oriented assessment is of clear value, it also has an important shortcoming in that, by focusing solely on the visible end-result, or the performance of a test, little is learned about the central (motor) control processes that led to that result.

'Preparation time' is defined as the speed of information processing in the brain and is a sensitive measure of an important aspect of central control[10-12].

The purpose of the present study was to measure preparation time after flexor tendon injury and to consider this measurement as a reflection of the (central) recovery process that takes place following surgical tendon repair.

Participants and methods

Forty-eight healthy, volunteer participants were recruited into this study from personnel in the plastic surgery department. Among them were nurses, secretaries, medical students, cleaning personnel and medical staff. Pathology of the upper extremity and neurological disorders were exclusion criteria. Nine participants could not be re-tested within a reasonable time due to part-time jobs and holidays; they were precluded from the analysis.

Twelve patients with isolated zone II flexor tendon injuries with a mean age of 36 (range 18 - 65) years who had been referred to our clinic for primary tendon repair and were suitable for our standard after-care protocol (see below) were also included in the study. Fractures, nerve damage, neurological disorders, pre-existent pathology of the upper extremity and postoperative tendon adhesions were exclusion criteria. The local medical ethics committee approved the study and all participants gave their written informed consent. Table 5.1 shows the demographic and clinical characteristics of the healthy participants and the patients with flexor tendon lesions. The type of anaesthesia used was recorded (general or regional anaesthesia).

Table 5.1 Demographic and clinical characteristics of healthy participants and patients

	Healthy Participants	Patients
n	39	12
Mean (range) age (years)	34.1 (20.1-60.1)	35.5 (18.4-56.9)
Gender (% females)	64	17
Hand dominance (% right hand)	85	92
Typing diploma (% with diploma)	62	n / a
Side of injury (% dominant)	n / a	75

n / a = not applicable

Post-operative mobilization protocol

Our standard after-care protocol consists of 6 weeks of dynamic splinting with a modified Kleinert controlled mobilization splint[13]. Four weeks after surgery the use of the splint is reduced and place-hold exercises are performed for another 2 weeks.

Preparation time measurements

Preparation time (the speed of information processing in the brain) measurements took place in a quiet environment with the participant sitting at a table. The distance between the eyes and the monitor was approximately 80 cm. The test was explained to each participant and it was stressed that they react as quickly as possible. One exercise trial was performed before the actual measurements were made.

A 4-choice preparation time procedure was used. An abstract representation of two real-sized hands was projected on a standard 17-inch cathode ray tube monitor. Each finger corresponded to a key on a standard qwerty-keyboard: the characters (*A)*, (*S)*, (*D)* and (*F)* for the left hand and (*J)*, (*K)*, (*L)* and (*;)* for the right hand. The thumbs were excluded. The participants had their fingers resting on the keys. The test started with a fingernail on the projected hand lighting up (Fig 5.1, see Appendix). As soon as the fingernail was lighted, the participant had to press as quickly as possible on the corresponding key on the keyboard. The time between lighting up and pressing the key was recorded as the preparation time in milliseconds. Immediately after the correct key was pressed, the lighting up of the fingernail turned off and randomly a new nail lit up. The series was continued until each finger of the measured hand was tested 10 times. From all preparation times of the index, middle, ring and little fingers of one hand (40 in total) an average preparation time for each hand was calculated.

Both hands of the healthy participants were measured twice within a time interval of 6 weeks. The hands of the patients were also measured twice. However, only the uninjured hand was measured before surgery. Six weeks later, after splint removal, both hands were measured. The fact that the uninjured hand could be used as an indicator for the injured hand before surgery is justified by a study by Peters and Ivanoff[14], showing there is no significant difference in preparation time between the left and the right hand in normal participants for this simple task. This study also proves that this is the case.

Clinical assessment of patients

Six weeks postoperatively patients were examined for adhesions and asked about their subjective feelings of hand function.

Statistical analyses

In healthy participants, preparation times were analysed by using a General Linear Model. The side (dominant or non-dominant) and the day of measurement (first day vs. 6 weeks later) were entered as within-subject factors in an ANOVA of repeated measures. Table 5.2 shows the average scores. Gender, age and possession of a typing diploma were entered as covariates. Test-retest reliability was assessed by calculating Pearson's correlation coefficients. Sensitivity of the test was evaluated by comparing the actual measurements of healthy participants with those of the patients by using a Mann-Whitney test. To compensate for effects caused by group differences, we not only compared the preparation times but we also compared improvement percentages with respect to the first measurement.

Table 5.2 Mean preparation times in healthy participants

	Day 1 msec (SD)	Six Weeks Later msec (SD)
Dominant hand	537 (95)	526 (102)
Non-dominant hand	553 (89)	527 (81)
Both hands	545 (92)	527 (91)

msec = milliseconds

Results

Healthy Participants

Analysis of the data of healthy participants revealed that gender or possession of a typing diploma did not influence finger flexion preparation times ($F(1,35) = 2.7$, $p = 0.109$, respectively $F(1,35) = 0.036$, $p = 0.850$). Higher age, however, resulted in a significantly longer preparation time ($F(1,35) = 9.6$, $p = 0.004$), but the correlation between age and preparation time was rather low (Pearson's correlation coefficient = 0.122, $p = 0.027$).

A pair-wise comparison of the within-subjects factors showed no significant difference between the preparation times of the dominant and non-dominant hands in healthy participants (Table 5.3). Correlation between both hands was high (Pearson's correlation coefficient = 0.905, $p < 0.001$). No significant differences were observed between the preparation times of the dominant and non-dominant hands in healthy subjects. Therefore, these measurements were pooled and the scores of the uninjured hands in patients on the first day were considered as good approximations of the scores of the injured hand (which, of course, could not be measured at that time). This made it possible to estimate the improvement rate of the injured hand.

The correlation between the measurements on the first day and 6 weeks later was significant ($p < 0.001$, $r = 0.788$). It could be shown that, 6 weeks after the initial measurement, healthy participants experienced significant improvement from the first measurement. Compared with the first measurement, healthy participants were, on average, 2.6% faster (95% CI: 0.7 to 5.2%) 6 weeks later.

Table 5.3 p-values and 95% confidence intervals of pairwise comparisons of within-subject factors

	Significance (p-value)[a]	**95% Confidence Interval for Difference (msec)[a]**
Side	0.438	-6 to 14
Day of measurement (Day 1 versus 6 weeks later)	0.019	5 to 48

The high p-value for 'Side' means that the results of the dominant and non-dominant hand are not significantly different. The low p-value for 'Day of measurement' means that participants significantly improved 6 weeks after the first measurement.

msec = milliseconds

[a] Adjustment for multiple comparisons: Bonferroni

Comparison of healthy participants and patients

Table 5.4 displays average preparation times of both healthy participants and patients. During the first measurement, patients and healthy participants showed no difference in preparation times (U = 363.5, p = 0.145). However, the results during the second measurement, 6 weeks later, show interesting differences (Fig 5.2). Although none of the patients appeared to have tendon adhesions or joint stiffness after splint removal, they reported a feeling of clumsiness when asked about their movement capacities. Patients who had worn a splint for 6 weeks showed significantly longer preparation times with the recovered hand than healthy participants (U = 193, p = 0.001).

Table 5.4 Average preparation times on day 1 and day 2 for healthy participants and patients

	Preparation Time Day 1 msec (SD)	**Preparation Time 6 weeks later msec (SD)**
Healthy participants	545 (92)	527 (91)
Patients uninjured side	587 (82)	633 (139)
Patients injured side	587 (82) *	676 (47)

msec = milliseconds

* = estimation, based on uninjured side

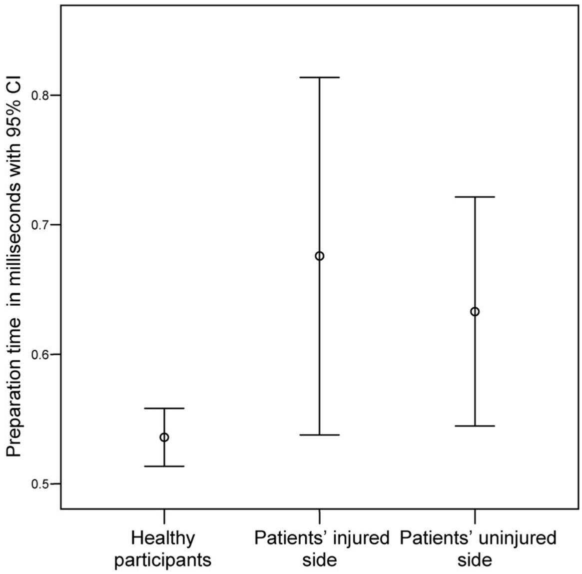

Figure 5.2 Error bars of preparation times 6 weeks after the initial measurement day in milliseconds with 95% confidential intervals. The left bar represents healthy participants, the middle bar represents the injured side of patients and the right bar represents the uninjured side of patients.

This finding was confirmed when we look at the individual changes between the two measurements of healthy participants and patients. Healthy participants improved significantly more than patients (U = 247, p = 0.006). Six weeks later healthy participants performed on average 2.6% faster, while patients performed 14.1% slower with their formerly injured side (Fig 5.3). Interestingly, the uninjured side also deteriorated, although less than the injured side. Six weeks after the initial measurement patients performed 7.9% slower with their uninjured hand, which is significantly different from the performance of healthy participants (U = 306.0, p = 0.035).

The type of anaesthesia used did not influence the improvement on preparation time in patients (U = 17, p = 0.937).

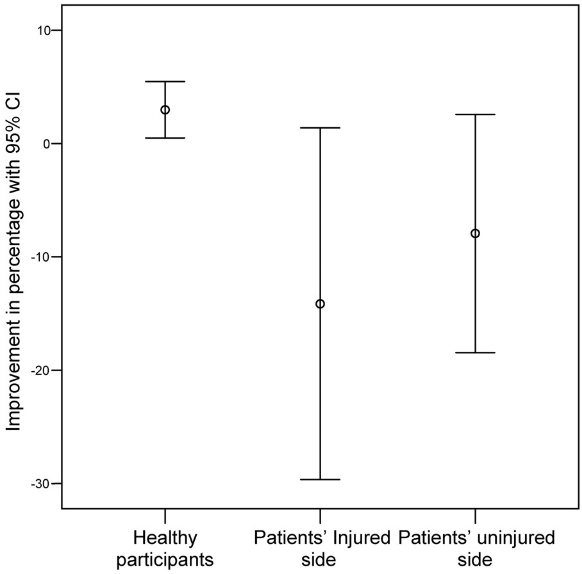

Figure 5.3 Error bars of improvement rates on response times between the first measurement and six weeks later in percentage with 95% confidential intervals. The left bar represents healthy participants, the middle bar represents the injured side of patients and the right bar represents the uninjured side of patients.

Discussion

A 'normal reaction time procedure', is one in which a participant is instructed to react as fast as possible after a stimulus, such as a button lighting up, appears. The response may be, for example, to push a button as fast as possible. In simple reaction time procedures there is only one type of stimulus and one desired response. In 'choice reaction time procedures', there are several stimuli presented and each stimulus requires a particular response. The time that elapses between the appearance of a stimulus and the actual start of the movement reflects the time that is required to prepare the movement[10;15]. These findings may be relevant for rehabilitation research, since it has been shown that preparation time is shorter for well learned skilful movements, compared with novel and/or complex movements. In other words, the response-programming time for a well known movement is shorter than for a novel movement[11].

In an earlier Positron Emission Tomography study we showed that a 6-week period of relative immobilization (dynamic splint therapy) after surgical tendon repair led to cortical reorganization[16]. The Positron Emission Tomography data indicated that after the splint period, brain areas relevant for the automatic, or skilful, control of finger movements, namely the corpus striatum, showed significantly less activity. This was reflected behaviourally in a (temporary) lack of skilfulness. If a relationship exists between preparation time and the level of skilfulness, it becomes interesting to study whether after 6 weeks of splinting, the preparation time of patients recovering from tendon repair would be longer than the preparation time of healthy controls. When the preparation time is, indeed, increased this may be seen as a behavioural reflection of the central reorganization mentioned above.

The aim of this study was to find out whether a 6-week period of relative hand immobilization would lead to significant changes in the preparation time, that is the speed of information processing in the brain, of finger flexion movements. The study showed that, after the splinting period (lack of normal use of the hand) the preparation time in the patients was significantly increased while the healthy control group showed a decrease in preparation time.

How can we explain this result? There is ample evidence that a period of distorted afferent (peripheral) information leads to a reorganization of central control processes[17-19]. This was also shown in our Positron Emission Tomography study[16]. Skilful control of movement depends on the permanent availability of response-produced sensory information. In the patient group, the quality of this information has been compromised by a period of relatively little information. The patients' uninjured hands showed an increase in preparation time after 6 weeks, just like their injured hands. This suggests that the findings for the injured hands are not simply the result of the mechanical effects of the surgery (i.e. adhesion and/or pain) or rehabilitation, which were applied to that hand. Although the activities of both hands are influenced by the fact that the patients are not performing normal activities and work during the splinting period, one might think that the uninjured hand will perform better because it will have to take over some tasks of the injured hand. We think the deterioration of the uninjured hand can be better explained by the fact that motor control at the highest level is to a large extent muscle or effector independent.

This means that the cerebral representation of an action is independent of the specific muscle activation pattern[20-22]. Famous and classic examples of this effector independency of control can be found in Merton (1972) and Raibert (1977)[23;24]. They compared handwriting produced by the left and right hands, feet, mouth and shoulder movements and found striking similarities in the shape of the letters produced by one subject.

Even though this is an intriguing and important result, some caution is necessary. Firstly, because of the injury, we were not able to measure the injured hand in the first measurement session. Although no differences in preparation time in healthy participants were found between the left and right hand for the employed task, so that a comparison between hands seemed to be justified, it can still be argued that our evidence for a preparation time increase is an indirect one. Secondly, an increase in preparation time may also be caused by general anaesthesia. Although there is some debate whether or not modern general anaesthesia affects cognitive functions, some studies report a preparation time increase after general anaesthesia[25]. However, since no significant difference in preparation time was shown between the patients who underwent the tendon repair under general anaesthesia and those who received regional anaesthesia, we think the preparation time increase could not be attributed to the effects of anaesthesia. The same is true for gender. Although the male/female ratios of the healthy participants and patients did not match, it is unlikely that a gender difference would cause the difference in preparation time since we did not find any influence of gender on preparation time in healthy participants. The difference between healthy participants and patients persisted when we looked at improvement percentages.

The results of this study indicate that a period of relative immobilization after surgical tendon injury and repair leads to a change in the control of the involved movements. It was shown previously that immobilization after tendon repair results in structural cerebral reorganization using Positron Emission Tomography[16]. The results of the present study using a simple behavioural measurement (movement preparation time) point in the same direction. In this present paper we argue that the preparation time, that is the speed of information processing in the brain, is a variable that could be relevant to rehabilitation of flexor tendon injuries. Although it may not be likely that preparation time could be used as a practical test to assess hand function, it is important to consider the central nervous system component in the development of new treatment protocols for flexor tendon injuries and other peripheral lesions that are followed by a period of lack of normal use of the hand.

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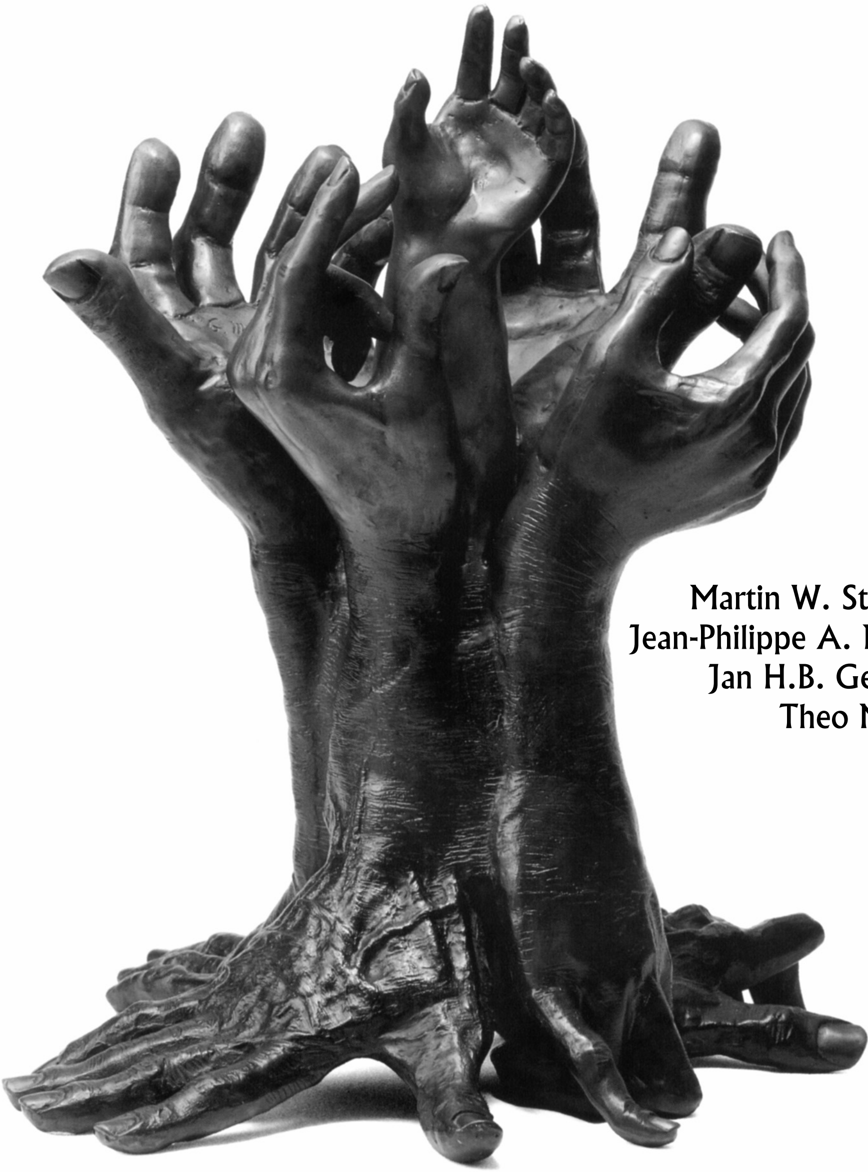
Chapter 6

Kinematic analysis of hand movements after tendon repair surgery: a new assessment using drawing movements



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Abstract

Objective: Although several hand outcome tests exist to judge skill level after hand injury, currently none give insight into how tasks are performed by looking at kinematic parameters. In this article the clinical value of analyzing kinematic parameters related to the drawing of a triangle on a graphics tablet by healthy subjects and patients with hand injury is discussed.
Design: In a first experiment 10 healthy subjects drew the triangles as accurately as possible at various speeds. In a second experiment 67 healthy subjects and 12 patients with flexor tendon injury were measured repeatedly.
Results: In the first experiment, the analysis showed a high linear correlation between speed and accuracy for each individual (Pearson's correlation coefficient $\geq$ 0.762, $p \leq 0.01$). The data led to a formula to standardize deviation for drawing speed, so that different measurements can be compared. In the second experiment, these two measurements correlated well (Pearson's correlation coefficient = 0.909, $p < 0.001$) although a learning effect was noticed (5.4% improvement on average). In healthy subjects the dominant hand performed significantly better than the non-dominant hand ($p < 0.001$). Patients performed significantly worse with their injured hand after six weeks of dynamic splinting than healthy subjects ($p = 0.003$). With their uninjured hand they performed better than the controls. Six weeks after removal of the splint no kinematic differences could be discovered between patients and controls.
Conclusion: The results show that kinematic parameters of hand movements may be of additional value for assessing functional recovery from hand injury.

Introduction

The treatment of flexor tendon injuries in the hand is focused on full recovery of hand function. A primary aim is regaining undisturbed mechanical qualities of the injured hand. In addition, the recovered patient needs to use his hand in daily tasks, which implies adequate cerebral control. In general, treatment consists of surgical repair of the tendon followed by a 6-week period of relative immobilization (splinting period)[1;2]. Our clinical observation that many patients reported clumsiness after the splinting period, even when they had perfect mechanical recovery, generated the idea that complaints might be due to a disturbed command function. Clumsiness did not only apply to the affected finger but to all immobilized fingers. This hypothesis of changed cerebral function was recently confirmed by a functional brain imaging study by our group, that demonstrated temporary changes in cerebral organization of motor control due to relative immobilization of the hand[3]. Other groups also reported that consequences of peripheral disorders are not limited to the periphery but also lead to central adaptations[4].

The concept that treatment of tendon lesions in the hand should not only be focused on tendons and joints, but also on cerebral motor control, urges on the development of tools that enable the assessment of disturbed hand function in these conditions.

Several 'hand questionnaires' have been developed to measure how patients cope with the functional consequences of hand injury, for example, the Michigan Hand Questionnaire[5]. Although questionnaires may shed some light on the qualitative recovery, functional tests are more objective measures[6;7]. A frequently used measure is the range of motion, which reflects the mechanical status of the flexor tendons and finger joints[8]. Other measures score how well or how fast subjects can reach end-points in a specific task, such as the Jebsen-Taylor test[9] or the nine hole peg test of finger dexterity[10].

Although the above mentioned assessment procedures may give some insight into the question whether or not a movement is impaired, they do not give any insight into *how* the movements are performed. It is argued here that by measuring the kinematic aspects of movement, relevant information is obtained about the control of the movement. The latter is relevant since it has been indicated that the 6-week period of relative immobilization results in a significant cerebral reorganization with consequences for the control of finger movements[3].

Although a considerable body of knowledge exists suggesting that the kinematics of handwriting movements reflect the underlying motor control processes[11-13] and although the kinematics of handwriting have been employed for studying the effects of neuropharmacologic drugs on fine movements[14] or for assessing the motor aspects of psychiatric diseases[15] kinematic measures have not been used until now in studying recovery of fine motor control after damage to the peripheral motor system. However, the analysis of kinematic parameters during a movement may uncover normally hidden aspects of performance and may therefore be more sensitive to skill improvement and recovery after hand injury.

We hypothesize that analysis of kinematic parameters related to the drawing of a triangle may be relevant to evaluate hand function. We predict that an improved skill level (functional use of the hand) will reflect in an increased drawing speed together with an increased accuracy. The development of such a test may be helpful in the evaluation of cerebral control of hand function and development of future treatment modalities of flexor tendon injuries. A triangle was selected as the target figure since it combines a number of interesting control aspects, namely: accurate multi muscle coordination, planning, acceleration-deceleration sequences and changes in direction[16].

Experiment 1 was performed to explore whether a standardized skill level could be calculated from the measured kinematic parameters. Experiment 2 explored whether this standardized skill level could be used for the clinical evaluation of changes in the level of hand (motor) performance.

EXPERIMENT 1

The fact that individual subjects draw at different speeds and show substantial individual variance of drawing speed in time complicates the comparison of their data. Therefore we decided to calculate a *standardized deviation* from the goal-figure (triangle) at a *standardized speed* to enable us to compare the performance of subjects drawing at different speeds.

Methods

Subjects

Ten healthy subjects participated in this experiment. Among them were nurses, secretaries, students and faculty members. Upper extremity pathology was an exclusion criterion. Table 6.1 shows the demographic details of all subjects.

Procedure

The measurements took place in a quiet environment with the subject sitting at a table. A piece of paper with an equilateral triangle with 4 cm legs was positioned with the horizontal side up on a graphics tablet (Ultrapad A3, Wacom Technology Corp., Vancouver, WA). Subjects were asked to trace the triangle with a dedicated tablet stylus for 30.00 seconds with subsequently the right and the left hand. The right hand drew clockwise, the left hand counterclockwise. It was stressed that movements of the elbow and shoulder had to be suppressed so that the drawing was performed by the fingers and wrist only. The triangles had to be sharp angled and any rounding of the corners had to be avoided.

Table 6.1 Demographics of subjects

	Experiment 1 Healthy subjects	Experiment 2 Healthy subjects	Patients
n	10	67	12
Mean age in years (SD)	22 (3)	29 (11)	35 (11)
Gender, n female (%)	5 (50)	43 (64)	3 (25)
Lateral preference, n right hand (%)	10 (100)	65 (97)	9 (75)

The stylus did not leave a visible mark so that the subjects could not see how they performed. Stylus position in time was recorded with OASIS software (KIKO Software, Doetinchem, The Netherlands) on a PC at 170Hz. Raw data were exported and analyzed with custom-made software. The following kinematic parameters were registered: drawing speed (expressed as the number of triangles drawn in 30.00 seconds) and average absolute deviation from the 'ideal triangle' (in millimeters). Absolute deviation was calculated as the shortest possible distance between each measured position and the ideal triangle. The software was also capable of registering axial stylus pressure on the tablet, the duration of the pauses in the 3 corners of the triangles and the dysfluency of the drawing (i.e. the number of accelerations/decelerations). However, the latter variables were not registered because a pilot study revealed that stylus pressure was highly variable, and did not seem to depend on the level of skill. The same pilot study suggested that variations in pause length and dysfluency could be largely explained by drawing speed.

In order to determine the relationship between drawing speed and accuracy, 10 subjects were asked to draw triangles as accurately as possible at different speeds arbitrarily chosen as 0.21, 0.28, 0.42, 0.56, 0.69, 0.94, 1.03, 1.42, 1.67 and 2.00 triangles per second. A metronome indicated the speed until the subjects got a hold of the rhythm. When the actual measurement started the metronome was turned off so that it would not interfere with the measurement (e.g. pausing at the end of one triangle until the next tick of the metronome).

Results

The deviation from the ideal triangle at the different drawing speeds was plotted for the dominant and non-dominant hand of each individual separately (Fig 6.1a, 6.1b, see Appendix). Each series showed a highly linear correlation that was statistically significant (all Pearson's correlation coefficients ≥ 0.762, all p-values ≤ 0.01) (Table 6.2).

Table 6.2 Pearson's correlation and p-values of deviation and drawing speed of all 10 subjects, split up by hand dominance

	Dominant hand		Non-dominant hand	
Subject	Pearson's coefficient	p-value	Pearson's coefficient	p-value
1	0.954	<0.001	0.946	<0.001
2	0.906	<0.001	0.878	0.001
3	0.925	<0.001	0.965	<0.001
4	0.832	0.003	0.977	<0.001
5	0.794	0.006	0.964	<0.001
6	0.942	<0.001	0.943	<0.001
7	0.932	<0.001	0.949	<0.001
8	0.978	<0.001	0.925	<0.001
9	0.887	0.001	0.961	<0.001
10	0.762	0.010	0.956	<0.001

Note that a high positive correlation indicates that as speed increases, accuracy decreases.

The curves for the non-dominant hand tended to run steeper than the curves for the dominant hand. The individual differences between the (healthy) subjects were small. Even when joining all data from the dominant hand and separately joining data from the non-dominant hand correlation remained significant (dominant hand: Pearson's correlation = 0.664, $p < 0.001$; non-dominant hand: Pearson's correlation = 0.776, $p < 0.001$), although not all subjects were equally skilled (Fig. 6.2, see Appendix).

These findings enabled us to estimate a deviation at a standardized speed, which made it possible to compare the performance of subjects who all performed at different speeds. First, an average formula for the dominant and the non-dominant hand was calculated. The formula for the dominant hand is $Y = 0.0022 X + 0.0730$ and for the non-dominant hand $Y = 0.0065 X +$

0.351, where Y = deviation (in cm) and X = number of triangles drawn in 30.00 s. Figure 6.2 (see Appendix) shows that for the non-dominant (less skillful) hand the curve is not only shifted upwards, but that the whole curve is turned counterclockwise around a pivot point so that absolute inaccuracy of the non-dominant hand increases progressively at higher speeds. This pivot point of the two curves can be easily calculated from the above formulas at X = 8.8 triangles (and Y = 0.092 cm).

In search of a standardized measure that would enable us to compare different measurements and that possesses face validity we chose to correct the deviation to a standardized speed (arbitrarily chosen as 20 triangles per 30.00 seconds). Assuming that a change in skill leads to a change in speed-accuracy with the same pivot point (8.8 triangles and a deviation of 0.092 cm) a standardized deviation can be estimated.

For each individual a speed accuracy formula can be estimated as a straight line following the formula:

$$Y = a \cdot X + b$$

where Y is the deviation, a is the slope, X is the drawing speed and b the constant. In order to calculate the deviation (Y) at a standardized speed the formula simply becomes:

$$Y_{STANDARDIZED} = a \cdot X_{STANDARDIZED} + b$$

with $X_{STANDARDIZED}$ = 20 triangles.

a can be calculated as follows:

$$a = \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}}$$

With Y_{PIVOT} = 0.092cm, and X_{PIVOT} = 8.8 triangles drawn in 30.00 seconds (calculated before).

b is calculated as:

$$b = Y_{MEASURED} - \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}} \cdot X_{MEASURED}$$

so that:

$$Y_{STANDARDIZED} = \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}} \cdot X_{STANDARDIZED} + Y_{MEASURED} - \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}} \cdot X_{MEASURED}$$

Filling in the above mentioned values for $X_{STANDARDIZED}$, Y_{PIVOT} and X_{PIVOT} together with the experimental values found for $Y_{MEASURED}$ and $X_{MEASURED}$ leads to a standardized deviation $Y_{STANDARDIZED}$. This standardized deviation can be interpreted as the deviation as if the subject would have drawn at a speed of 20 triangles in 30.00 seconds. To improve precision, only drawing speeds higher than the pivot should be selected. In our case we chose a speed of more than 10 triangles per 30.00 seconds as the cut off point.

EXPERIMENT 2

Methods

Subjects

In total 12 patients and 67 healthy subjects participated in the experiment. The healthy subjects consisted of nurses, secretaries, students and faculty members. Upper extremity pathology and participation in experiment 1 were exclusion criteria.

Patients with isolated zone II finger flexor tendon injury were eligible for inclusion if they were between 18 and 65 years of age, referred to our clinic for tenorrhaphy and fit for our standard after-care protocol. This protocol consists of six weeks of relative immobilization. Four weeks after surgery the use of the splint is reduced and place-hold exercises are performed by the patient for two weeks. Only lesions on the dominant side were included to prevent the data from being contaminated by influences of laterality on hand skills. Fractures, nerve damage, neurological disorders and pre-existent pathology of the upper extremity were exclusion criteria. The present study was approved by the local medical ethics committee and all included patients gave their written informed consent. Table 6.1 shows the demographic details of all subjects.

Procedure

The procedure was identical to that in experiment 1, only now subjects were instructed to draw as fast and as accurately as possible. The healthy subjects were measured twice with a 2-week interval. The patients were measured immediately after the end of the splinting period. This measurement was repeated 2 weeks later, whereas a third measurement was performed after a period of six weeks of active use of the hand. Range of motion of all finger joints of patients were recorded at each visit following the conventions of the American Society for Surgery of the Hand[17].

The standardized deviation was calculated using the formula as determined in experiment 1:

$$Y_{STANDARDIZED} = \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}} \cdot X_{STANDARDIZED} + Y_{MEASURED} - \frac{Y_{MEASURED} - Y_{PIVOT}}{X_{MEASURED} - X_{PIVOT}} \cdot X_{MEASURED}$$

The ranges of motion of all finger joints were also measured and expressed as total range of motion.

Analysis

The results of the healthy subjects were entered in a MANOVA with gender and age as co-variates. Furthermore, the results of the first measurement were compared with the results of the second measurement, 2 weeks later.

Sensitivity of the task to changes in hand skills was explored in the healthy subjects by comparing the results of the dominant hand with those of the non-dominant hand (paired t-tests). Additionally, the performance of the dominant hand in healthy subjects was compared with those of the dominant (injured) hand in patients with flexor tendon lesions after six weeks of dynamic immobilization (Mann-Whitney test). The last performance (12 weeks postoperatively) of the dominant (injured) hand in patients was compared with that of the second measurement of healthy subjects (Mann-Whitney test). Finally, ranges of motion of the injured hands in patients were compared with those of the uninjured hands (Wilcoxon signed rank test).

Results

Healthy subjects

Not all data were analyzed because some measurements did not meet the required drawing speed of 10 triangles per 30.00 seconds (see earlier). Standardized deviation was calculated as explained above (Table 6.3). 63 out of the 67 healthy subjects had at least one valid measurement. Four examples of typical drawings can be seen in figure 6.3 (see Appendix).

Table 6.3 Standardized deviation in cm (SD) during 30 seconds of drawing triangles

	Healthy volunteers	**Patients**
1st measurement dominant side	0.106 (0.027)	0.144 (0.033)
1st measurement non-dominant side	0.154 (0.041)	0.130 (0.032)
2nd measurement dominant side	0.099 (0.026)	0.116 (0.079)
2nd measurement non-dominant side	0.142 (0.031)	0.092 (0.036)

Average values for 1st and 2nd measurement for dominant/non-dominant sides and healthy subjects/patients after flexor tendon injury.

Neither gender nor age significantly influenced deviation on the drawing task ($F(1,35) = 2.4$, $p = 0.07$, respectively $F(1,35) = 2.3$, $p = 0.08$).

The correlation between the 2 measurements with a 2-week interval was significant (Pearson's correlation coefficient = 0.909, $p < 0.001$). Healthy subjects performed significantly more

precisely during the second measurement (average 5.4% less deviation, $p = 0.002$) than during the first measurement.
The results of the two measurement sessions in healthy subjects showed a significant difference between the dominant and non-dominant hand (1st measurement: $p < 0.001$, $t = -8.2$, 2nd measurement: $p < 0.001$, $t = -10.9$). The non-dominant hand was on average 38% less accurate than the dominant hand.

Patients

When asked about their movement capacities, all patients reported a feeling of clumsiness immediately after the splint was removed. The patients who had worn a splint for six weeks performed significantly worse with their (formerly splinted) hand than healthy individuals during both the first and the second measurements ($p = 0.003$, $U = 87$ respectively $p = 0.043$, $U = 122$). After six weeks of active use of the (treated) hand the difference with the hand-performance of the healthy subjects had disappeared ($p = 0.513$, $U = 138$).
Compared to the non-dominant hand of healthy subjects, the healthy (non-dominant) hand of patients showed the opposite effect. Patients performed better with their not splinted (non-dominant) hand after the splinting period than healthy subjects. This difference however, was significant only during the second measurement ($p = 0.069$, $U = 130$ respectively $p < 0.001$, $U = 72$).
Immediately after the splinting period the fingers of the injured hands in patients had significantly lower ranges of motion than uninjured hands. This difference persisted after six weeks of practicing ($p = 0.003$, $Z = -2.934$ respectively $p = 0.011$, $Z = -2.547$).

General discussion

Results of healthy subjects performing at different speeds showed a strong linear correlation between drawing speed and accuracy meaning that accuracy increases as speed decreases. In addition, all curves of the same side (regarding dominance) are very similar to each other and different from that of the other side. These characteristics enabled us to standardize measurements for speed so that they could be analyzed and compared more easily. The correlation between 2 measurements with a 2-week interval was high. Furthermore, during the second measurement the subjects, in general, performed better than during the first measurement. These results indicated that the employed procedure is sensitive for changes in hand skill. This is also supported by the fact that patients performed significantly worse with their injured hand after six weeks of dynamic splinting than healthy subjects. In contrast the not splinted hands in patients were actually better than the contralateral side in healthy subjects. After six weeks of active use of the (formerly injured) hand the difference between patients and controls had disappeared. This finding may stress the possible sensitivity of our test to subtle changes: the range of motion of the injured hand was still significantly worse after six weeks of active use, indicating prolonged impairment, while our test already showed improved performance.

Indeed, either by observing task performance or evaluating the end result no information is gained about how the task was performed so that it might be difficult to conclude which subject had become more skillful during the recovery period. Kinematic analysis of hand movements may assist in evaluating performance of a task.

The calculation of the standardized deviation deserves some more discussion. We are aware that the formula for calculating the standardized deviation is an estimate. However, the mutual influences of drawing speed and accuracy cannot be ignored and the method described here appears to be sensitive to the level of hand skill. The fact that movement speed affects accuracy has been indicated in numerous articles over the past decades[18-22]. One way to deal with this problem is fixing either speed or accuracy. While fixing accuracy in our task might be extremely difficult, it would be easy to fix the speed of performance by using a metronome. This however, would have led to an unnatural pace for the subjects which would have influenced their overall performance[23;24]. Therefore we chose a more pragmatic solution namely a correction for speed, a choice that was supported by the linear relationship that existed between speed and accuracy.

In the present study *speed* (number of triangles drawn in 30.00 s) and *inaccuracy* (mm deviation off the line) were used as the main variables. Other studies, mainly analyzing handwriting, employed other variables as well, such as maximum speed, acceleration, pause length and dysfluency[14;15;25]. However, since the variables we selected enabled us to distinguish between dominant and non-dominant hands and between healthy subjects and patients there was no reason to add variables to calculate the standardized deviation. These variables may be used in the future to fine-tune the procedure.

The patients performed less accurately on this task with their injured hand than healthy subjects. This seems trivial since the difference in accuracy may also be caused by limited range of motion in finger joints or by effects of general anesthesia[26]. The range of motion in the fingers of the injured hands of the patients was indeed significantly worse than the uninjured hands immediately after the splinting period. However, this was still the case after six weeks of active practice while the significant difference on drawing accuracy after the splinting period had faded after six weeks of practice. Besides, no significant difference in accuracy was found between patients who underwent the tenorrhaphy under general anesthesia and those who received regional anesthesia. Therefore we think that limited range of motion or effects of general anesthesia cannot explain the initial decrease in drawing accuracy in our patients.

We assume therefore that the main cause of the decreased hand function after the splinting period is centrally located. As a result of six-week period of immobilization and relative disuse of the arm central neural networks have been reorganized. This is supported by a recent PET study performed by our group on patients with tendon injury which clearly demonstrated a cerebral reorganization as a result of relative immobilization[3]. Since this reorganization has a direct impact on the control (and thus performance) of the movements we argued that it was necessary to develop an assessment instrument that is sensitive to these performance aspects i.e. that is more sensitive to *how* movements are performed. Although caution remains necessary we think that the here described kinematic procedure is a step in that direction.

We did not compare our test to other hand function test such as the Jebsen-Taylor test[9] and the nine hole peg test of finger dexterity[10] since these tests start from a different conceptual level. They are focused on measuring the end-result of a movement performance and not the underlying motor control processes[11-13].

The uninjured (non-dominant) hands in patients performed better than the contralateral (non-dominant) hands in healthy subjects. As the results indicated, this cannot be explained by an a priori group difference. We find it more likely that these differences were the results of compensatory use of the uninjured hand during the splinting period. This is supported by the finding that after six weeks of practicing with the formerly injured hand, no differences in accuracy could be found any longer, compared with healthy subjects.

To our knowledge the present paper reflects a first attempt to employ a kinematic analysis of hand movements for the assessment of patients with hand injury. This procedure enabled us to assess a thus far ignored aspect of hand function testing after flexor tendon injury (changes in drawing speed and accuracy). It may be a useful tool to judge treatment procedures on their functional effectiveness.

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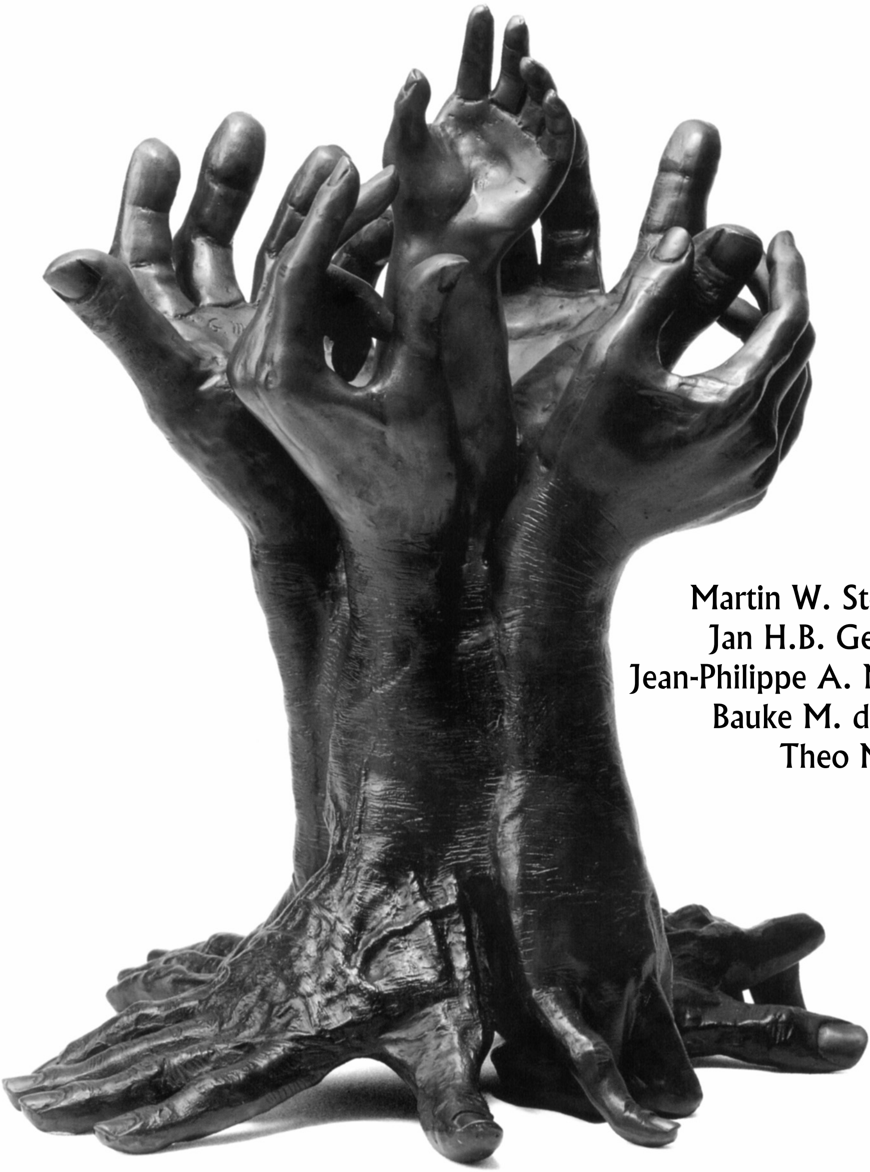
Chapter 7

Effects of motor imagery on hand function during immobilization after flexor tendon repair



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Abstract

Objective: To determine whether motor imagery during the immobilization period after flexor tendon injury results in a faster recovery of central mechanisms of hand function.

Design: Randomized controlled trial.

Setting: Tertiary referral hospital.

Participants: Patients (n = 28) after surgical flexor tendon repair were assigned to either an intervention group or control group.

Intervention: Kinesthetic motor imagery of finger flexion movements during the postoperative dynamic splinting period.

Main Outcome Measures: The central aspects of hand function were measured with a preparation time test of finger flexion in which subjects pressed buttons as fast as possible following a visual stimulus. Additionally, the following hand function modalities were recorded: Michigan Hand Questionnaire, Visual Analog Scale for hand function, kinematic analysis of drawing, active total motion and strength.

Results: After the immobilization period, the motor imagery group demonstrated significantly less increase of preparation time than the control group ($p = 0.024$). There was no significant influence of motor imagery on the other tested hand function ($p > 0.05$). All tests except for kinematic analysis ($p = 0.570$) showed a significant improvement across time after the splinting period ($p \leq 0.001$).

Conclusions: Motor imagery significantly improves central aspects of hand function, namely movement preparation time, while other modalities of hand function appear to be unaffected.

Introduction

In our experience, a major portion of the patients seen at the emergency room by a hand surgeon suffer from flexor tendon injury of the hand. Flexor tendons enable us to tune finger position so that we can grasp and manipulate objects in our environment. The flexor tendon is surgically repaired by suturing both ends of the severed tendon together. Usually the patient can be discharged within a day. Nevertheless, for the patient this is only the beginning of a relatively long rehabilitation period which in our hospital usually lasts more than 12 weeks.

During the regeneration of the tendon at the repair site, the tendon strength decreases with a maximum weakness after 2 weeks[1]. Therefore, early active use of a repaired tendon has a risk of tendon rupture. Prolonged static splinting of a hand after tendon repair will result in adhesions leading to permanent disability[2]. The treatment therefore is one that diminishes the risk of both ruptures and adhesions. Currently, most post-operative protocols consist of several weeks of relative immobilization. Passive motion enables sliding of tendons and joints, this prevents adhesions. At the same time strong forces are avoided, this prevents tendon rupture. This is followed by gradually increasing the load on the flexor tendons. Although patients are treated intensively by a team consisting of occupational therapists, physiotherapists, rehabilitation specialists, and plastic surgeons, the final hand function is often suboptimal[3].

Improvement of the functional outcome after flexor tendon injury can probably not be found in changing the operative technique. Hence, for improvement of functional outcome we have to focus on the post-operative rehabilitation period. Would it be possible to implement a treatment procedure which is more active without actually stressing the tendons and that may not only prevent the above mentioned negative side-effects but that also prevents the central reorganization that takes place as a result of relative immobilization? Indeed, it has been shown that (relative) immobilization of a limb results in central reorganization. This leads to temporary *forgetting* of the function of the affected limb[4], so that initially after the immobilization period the central control of movements is inefficient. This means that efficient movements will have to be relearned.

Immobility or injury have shown to result rather rapidly in changes of motor (and sensory) representations in the brain of peripheral organs such as a finger, arm or leg[5-8]. In general can be stated that the representation on the cerebral cortex shrinks as a result from the decreased input[9-11], whereas stimulation (increased input) leads to enlargement of the representation[12]. Hence, continuous input from a limb appears to be a prerequisite for preservation of the cortical representation of that limb[13].

In the past years it has been shown that sensory input not exclusively results from actually performed movements. Imagined movements without actually moving the limbs (motor imagery) also generate sensory input[14;15]. Motor imagery and actual practice involve overlapping neural networks[16-18]. Remarkably, movements can be learned and performance improved by motor imagery[19-21].

To our knowledge, the use of motor imagery to improve functional outcome after peripheral injury (and repair) has not been described in literature until now. The objective of this randomized prospective study is to determine whether motor imagery during the immobilization period after flexor tendon injury results in a greater recovery of central aspects of hand function.

Methods

Subjects

From August 1, 2003 until December 31, 2005, all patients with flexor tendon injury, referred to our clinic were screened. Complete sharp transsection of at least a flexor digitorum superficialis or flexor digitorum profundus tendon was an inclusion criterion. Patients were eligible for inclusion if they were between 18 and 65 years of age and suitable for tenorraphy and postoperative dynamic splint therapy. Subjects with fractures, tendon ruptures and impaired motor function due to a nerve lesion or pre-existent upper extremity disorders were excluded from participation. Subjects who fulfilled the above criteria were asked to fill out a Vividness of Movement Imagination Questionnaire[22]. The Vividness of Movement Imagination Questionnaire consists of an internal and external section. The internal section asks subjects to rate their ability to imagine activities as performed by themselves, the external section asks subjects to rate their ability to imagine activities as performed by others. A high score on the Vividness of Movement Imagination Questionnaire indicates low imaginative powers. Due to the nature of our intervention (imagination), subjects with low imaginative powers (defined as Vividness of Movement Imagination Questionnaire scores > 72) were not admitted to the motor imagery group. However, this was the case in only one subject, who was assigned to the control group consequently.

The present study was approved by the local medical ethics committee and 28 included patients gave their written informed consent. The following independent variables were recorded: age, sex, hand dominance, highest level of education, Vividness of Movement Imagination Questionnaire, injury type and side and anesthesia type.

Intervention

After inclusion, subjects were admitted at random to either the control group or the motor imagery group (with the exception of the single person mentioned above). Subjects in both groups underwent the regular treatment: surgical tendon repair. Postoperative treatment consisted of six weeks of relative immobilization (Kleinert splint). During the first 4 weeks postoperatively only passive flexion of the finger joints was allowed while in the following 2 weeks also place-hold exercises were practiced. This implies exercises in which a subject flexes his fingers passively with help of the other hand. The fingers are released and the patient is supposed to hold the fingers in the flexed position. At night a wrist band was worn so that the fingers are kept in a flexed position. After this period, active finger flexion was started and gradually expanded.

Subjects in the motor imagery group were instructed to mentally perform active flexion and extension movements during the immobilization period. Subjects were instructed to perform 8 motor imagery sessions per day and enter the actual number of sessions they performed on a form at the end of each day. This movement had to be mentally exercised repeatedly, which means that the subjects imagined the performance of the movement without actually moving the fingers. The instructions were as follows: try to imagine as vividly as possible that you slowly clench your fingers and bend the wrist of your splinted hand. Hold this image for 3 seconds. Next, imagine that you straighten your wrist and stretch your fingers. Repeat these imaginary movements 10 times (1 session).

Assessment of Hand Function

Hand function was assessed at different moments by a number of assessment tools. The main outcome measure was preparation time of finger flexion[23]. Preoperatively, a preparation time test was performed with the uninjured hand (reflecting the pre-injury state of the injured hand). This test consisted of a series of visual stimuli that were presented on a computer screen (the picture of a hand with 1 of the fingernails lighting up on the screen). The subject was instructed to press a button (=finger flexion) as fast as possible after presentation of the fingernail with the finger that corresponded with the lighted fingernail. Each finger was tested 10 times. This resulted in an average preparation time per hand. Because no difference exists between the left and right hand in healthy subjects, a good estimate of the performance of the injured hand before injury could be obtained by measuring the uninjured hand so that improvement across time could be calculated[23;24]. Preparation time is seen as an indicator of central control processes. It is known that these processes are impaired as a result of the disordered input from the periphery.

An increase in preparation time, therefore, indicates a decreased speed of information processing in the brain and less efficient control of hand movements. The recorded preparation times of the injured hand were compared to the preparation times of the uninjured hand which reflected the preinjury state of the injured hand.

Also preoperatively, a Michigan Hand Outcome Questionnaire (MHQ) and a visual analogue scale (VAS) were recorded asking subjects to rate their preinjury status. The MHQ[25] results in a score on the domains of overall hand function, activities of daily living, pain, work performance, aesthetics and patient satisfaction between 0 and 100 for each hand individually. A high score indicates a good hand function. Improvement on the MHQ compared with pre-injury measurement was calculated. Subjects were asked to judge their hand skills on a VAS for each hand individually. This resulted in a score between 0 and 100 for each hand individually. A high score indicates a good hand function. Improvement on the VAS compared with preinjury measurements was calculated.

Kinematic analysis of hand movements during drawing movements was performed for each hand. Kinematic parameters of movements were recorded (drawing accuracy and speed) while subjects had to draw triangles as accurately and fast as possible on a graphics tablet (Ultrapad A3, Wacom Technology Corp, Vancouver, WA). Deviation (inaccuracy) standardized for drawing speed was calculated so that measurements could be analyzed and compared easily[26].

Active total motion[27] was assessed using a digital goniometer (R500 Range of Motion Kit, Biometrics Ltd, Gwent, UK). Total motion per finger was calculated by adding up the active range of motions of all joints of 1 finger. On basis of all measurements of the index, middle, ring and little fingers of 1 hand, the average total motion per hand was calculated. A high active total motion score represents a good active flexion ability. A ratio with the healthy hand was calculated.

Grip strength and pinch strength[28] were recorded using a digital dynamometer and pinchmeter (H500 Hand Kit, Biometrics Ltd, Gwent, UK). For both hands, the average of 3 grip strength measurements was recorded; also the average of pinch strength between the thumb and each finger was recorded for both hands.

For both hands the preparation time, VAS, MHQ, active total motion and kinematics were recorded 6, 7, 8, 10 and 12 weeks postoperatively. Strength measurements were only recorded during the last measurement (12 weeks postoperatively). It was not measured earlier due to the increased risk of tendon rupture (table 7.1). Also, the number of outpatient contacts within 12 weeks after surgery was recorded.

Table 7.1 Timing of Recordings

	Preinjury	6 weeks postop	7 weeks postop	8 weeks postop	10 weeks postop	12 weeks postop
Preparation time	X	X	X	X	X	X
Kinematic analysis		X	X	X	X	X
MHQ	X	X	X	X	X	X
VAS	X	X	X	X	X	X
Active Total Motion		X	X	X	X	X
Strength						X

Note. MHQ and VAS were done preinjury. Preinjury signifies an estimate of the value before the injury took place as explained in the materials and methods section. Preparation time values were for the contralateral hand.
postop = postoperatively

Table 7.2 Demographics of All Subjects, Subdivided per Intervention Group

	Motor imagery group	Control group	Test statistics p
n (subjects)	12	13	
Age (y)	36.1 (SD 11.3)	31.1 (SD 10.0)	0.301*
Sex (% male)	75	69	0.748†
Dominance (% right-handed)	82	85	0.531†
Injury side (% dominant hand)	58	69	0.571†
Highest level of education (% finished higher education)	58	54	0.291†
VMIQ internal	45.4 (SD 16.3)	53.9 (SD 16.7)	0.242*
VMIQ external	44.7 (SD 13.2)	51.8 (SD 17.8)	0.320*
Number of tendons injured	2.3 (SD 0.5)	1.5 (SD 1.0)	0.019*

Note. The right column shows the statistics of tests of difference between the 2 groups.
VMIQ = Vividness of Movement Imagination Questionnaire
* Mann-Whitney U test.
† Pearson Chi-Square test.

Analyses

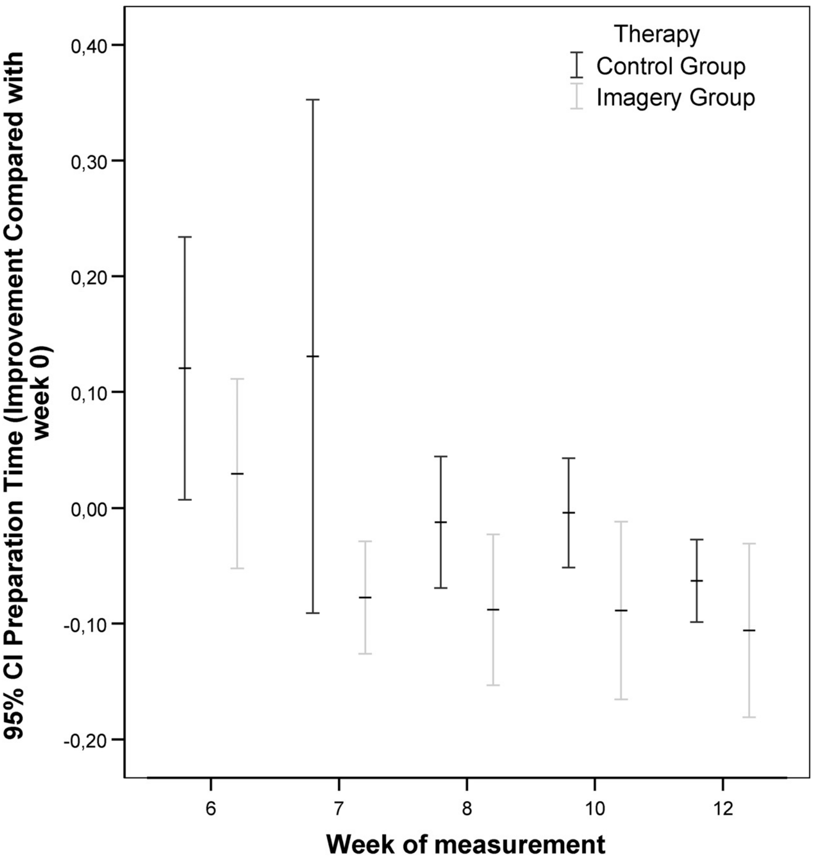
Comparison of demographic data of both groups was performed using the Mann-Whitney U and Pearson Chi-Square test. Results of the preparation time test, kinematic analysis, MHQ, VAS and active total motion were entered in a Mixed Model with compound symmetry as repeated covariance type and therapy (control vs. motor imagery) and the moment the test was taken as factors. Results on the strength measurements were analysed using the Mann-Whitney U test. Statistical tests were performed with statistical software SPSS 14 (SPSS Inc, Chicago, IL).

Results

In 2 subjects, a fracture (which was not observed on the preoperative X-ray) was found intraoperatively. Another subject was found to have intact tendons intraoperatively. These subjects were excluded so that in total 25 subjects participated in the study. Table 7.2 shows the demographics of these subjects subdivided per intervention group (motor imagery/control group). The only independent variable in which the 2 groups differed significantly was the number of tendons injured. Subjects in the motor imagery group had on average 2.3 tendons injured per subject, in the control group this was 1.5 tendons. The average number of recorded motor imagery sessions was 100 (range 2–294) in the motor imagery group.

The motor imagery group demonstrated significantly less increase of preparation time than the control group ($p = 0.024$, $F = 5.901$). In other words, compared to the initial response time of the uninjured hand, their responses did not slow down as much as in the control group (fig 7.1).

Figure 7.1 Average extension on preparation time and 95% CI.



There was no significant difference between the motor imagery group and the control group in the improvement on MHQ score ($p = 0.398$, $F = 0.723$). Similarly, there was no significant difference between the groups in the improvement on VAS ($p = 0.451$, $F = 0.597$). The kinematic analysis of drawing also showed no significant differences between the groups ($p = 0.165$, F 2.001). There was no significant difference between the motor imagery group and the control group in active total motion ($p = 0.869$, $F = 0.028$).

The average grip strength of the injured hand in the motor imagery group was 28.4 kg (SD 14.9). In the control group this was 30.6 kg (SD 13.0). The average pinch strength of the injured hand in the motor imagery group was 3.9 kg (SD 1.4). In the control group this was 3.4 kg (SD 1.6). However, these differences on grip strength and pinch strength were not significant ($p = 0.790$, $Z = -0.266$ respectively $p = 0.457$, $Z = -0.744$).

With the exception of kinematic analysis of drawing ($p = 0.570$) all variables that were tested more than once demonstrated a significant effect of the moment the test was taken ($p < 0.001$). This means that subjects improved over time.

Finally, the number of outpatient contacts did not differ significantly between the motor imagery group (average 20.5 times) and control group (average 20.6 times) ($p = 0.548$, $Z = -0.600$).

Discussion

Because motor imagery simulates movement, it is not surprisingly that the motor cortex and other motor areas in the brain are involved in motor imagery[29-31]. In a functional Magnetic Resonance Imaging (fMRI) study with healthy subjects both a motor imagery group and physical practice group improved on a button pressing task, compared with a no practice group. In both cases this improvement was accompanied by increased activity in the basal ganglia (striatum)[32]. The prefrontal cortex and its connection to the basal ganglia are also important in motor imagery by maintaining dynamic motor representations in working memory[15;33]. An earlier Positron Emission Tomography study by our group showed activity in the basal ganglia during finger flexion movements in subjects after flexor tendon injury has been treated and function recovered. However, immediately after the splinting period this activity in the basal ganglia was absent[4]. Continuing activity in the basal ganglia by motor imagery may prevent the central decay that occurs during immobilization.

The purpose of this randomized prospective study was to determine whether motor imagery training could play a role in the prevention of central decay resulting from immobilization. The results indicate that subjects in the motor imagery group had a significantly lower increase in preparation time after the splinting period than the control group, indicating indirect evidence for a central effect of motor imagery. This is not at all trivial, since it means that the repeated mental performance of movements may prevent the impairment of central control, at least in terms of the speed of information processing.

While this has not been shown before in an applied rehabilitation study after peripheral injury, short term effects of motor imagery on preparation time have, indeed, been shown before in a study with healthy subjects[34].

We did not find any effects of motor imagery on muscle strength. This corresponds to work by others[35-37]. In literature, however, this is controversial. Some studies with healthy subjects did report an increase of muscle force compared to a control group[20;38].

We found no influence of motor imagery in subjective measures such as the MHQ or VAS. Also, hand function which appears to relate more to the physical state of the periphery (total motion, deviation during drawing triangles and strength) was not influenced by motor imagery. Dependent variables that were measured more than once showed a significant improvement across time after the splinting period. The only exception was the result on the kinematic analysis of drawing: although the figure shows a decrease of deviation in time, this was not significant.

We found an effect of motor imagery on central mechanisms of hand function, but not on other aspects of hand function. The number of outpatient contacts was not influenced by motor imagery. Retrospectively this was no surprise because currently patients follow a protocol in which they visit the outpatient clinic at set moments rather than depending on their hand function. Probably the occurrence of complications rather than hand skills dictates the number of outpatient contacts.

It was difficult to control the patients' compliance in the imagery condition. We tried to overcome this problem by asking subjects to record the number of imagery sessions they performed each day. These records showed that the subjects were not all equally compliant. This may have led to an underestimation of the effects of motor imagery.

Furthermore, the optimal dosage of motor imagery training is unknown in rehabilitation after peripheral injury. Studies on the effects of motor imagery in the central nervous system after injury describe several 1 hour-lasting periods consisting of several imagery sessions[39-41]. However, it does not seem feasible that subjects with flexor tendon injury will invest several hours per day into motor imagery training because they usually have a more modest potential profit from motor imagery.

The term motor imagery refers to several ways of mental rehearsal of movements such as visual imagery (e.g.: mirror therapy, watching an affected hand move by mirroring the healthy moving hand or watching a video of a movement) or kinetic imagery (supposedly associated with kinesthetic feeling, without visual input). Although there are relevant areas for both types of imagery and actual execution of movements, they are not identical[42]. Recent studies demonstrated that kinesthetic, rather than visual motor imagery modulates corticomotor excitability and motor imagery based learning[43;44]. Therefore we chose kinesthetic motor imagery in our study.

Subjects in the motor imagery group had more severe injury than subjects in control group. This may have led to an underestimation of the effects of motor imagery. A larger study or case controlled study may eliminate this factor and provide more power.

Currently, numerous studies have been published regarding the usefulness of motor imagery in rehabilitation after central nervous system disorders[39;40;45;46]. It has also be shown that motor imagery has a beneficial effect on motor sequence learning[47;48]. Another field in which the positive effects of motor imagery have been described is sports performance[49-51]. Rosen described a pilot study using a mirror for rehabilitation after hand surgery[52]. To our knowledge, the present study is the first attempt to evaluate the effects of motor imagery on rehabilitation after peripheral injury.

Conclusions

Motor imagery positively influences central aspects of hand function (i.e. preparation time) during the rehabilitation after flexor tendon repair, while other hand function modalities appear to be unaffected. In our study subjects were followed for 12 weeks. Whether motor imagery will have clinical significance and influence long term recovery after flexor tendon injury and diminish the disability to work period is a relevant question. This aspect should be studied in the future. Future work should also focus on optimizing motor imagery training protocols, patient satisfaction and disability to work. Also larger (injury severity-matched) patient groups should be studied so that stronger conclusions can be drawn regarding central and peripheral measures.

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Chapter 8

Summary, conclusions and future perspectives

Cerebral reorganization after flexor tendon repair

At the start of this PhD trajectory, little clinical evidence existed about the cerebral consequences of postoperative immobilization after flexor tendon injury. The pilot positron emission tomography (PET) study presented in chapter 2 demonstrated a clear change in cerebral activation patterns involved in finger flexion. After six weeks of relative immobilization following flexor tendon repair, there was increased parietal (and cingulate) activation. This disappeared after six weeks of active use of the hand. Furthermore, after regaining active control of finger flexion improved skill was associated with prominent putamen activation, which was remarkably low at the initial measurement immediately after the splinting period. In the larger PET study presented in chapter 3, these results were largely reproduced and sharpened. Immediately after the splinting period increased posterior parietal activation was found, although only in left sided injuries. Again, this disappeared after active use of the hand. Changes in activation in the cingulate cortex, however, could not be reproduced in the larger group. The increase in activation in the contralateral putamen which was particularly low in the first scanning session and in the insula increase after active use was confirmed in the larger patient group.

The initial parietal activation was explained to reflect an increased demand on a body scheme representation needed to instruct the appropriate movement[1;2]. Putamen activity suggests that simple movements have been relearned and that an improved selection of specific muscles are used compared to the first study[3-7]. Insular activity relates to enhanced efficiency of the related stimulus response associations[8;9].

In skilled movement, suppression of unwanted muscle contractions is a characteristic feature, in which the basal ganglia play an important role[4;10]. This was supported by our EMG findings which showed insufficient flexor relaxation during serial contraction after six weeks of immobilization, which had resolved after active use of the hand.

Theoretically, one might argue that the absence of putamen activation as we found in the first PET session reflected the normal base-line, while the increased activation in the second session reflected excessive practice. However, in chapter 4 we showed in a functional magnetic resonance imaging (fMRI) study that in healthy subjects, performance of the same ‘double flexion’ task evoked activation of the contralateral putamen. These subjects showed significant bilateral activation in the insula and no significant activation in the parietal cortex, a distribution similar to our patients in the final scan session. Therefore we concluded that a six week period of relative hand immobilization induces a temporary loss of efficient cerebral control of hand movement (characterized by increased cortical demand and reduced striatal involvement). A theoretical drawback of the healthy subject study was that fMRI results were compared to PET results obtained in patients. After fMRI became available for research in our institution, the local ethical committee did not approve a repetition of our PET study with healthy subjects due to the radioactive isotopes administered. Although both PET and fMRI are capable of measuring regional cerebral activation, they are not identical[11].

In the fMRI study on hand movement in healthy subjects we further addressed the question whether the control of particularly finger flexion would be more closely embedded in circuitry implicated in purposeful movements, such as grasping compared with finger extension. We found that left hand finger flexion contrasted to extension was related to significant activation in the ipsilateral (left) parietal cortex indicating that flexion demands higher-order motor control mechanisms more than extension[12-17]. Moreover subtle differences were found in the activation of the contralateral sensorimotor cortex between finger flexion and extension. Finger flexion extended more lateral to the cerebral convexity where it meets the premotor cortex, while finger extension was found deep in the central sulcus. This gives an extra dimension to the current knowledge of functional segregation of the primary motor cortex. Up to now functional segregation of body parts and proximal-distal segregation was well known[18-21], but this is the first time that segregation of antagonizing muscles of the same body part was suggested.

Central aspects of hand function

The main objective of the thesis was to determine whether motor imagery during the immobilization period after flexor tendon repair results in a faster recovery of hand function. While several hand assessment tools currently exist such as questionnaires, range of motion and other functional tests, they commonly do not focus on central (motor) control processes that lead to hand movements[22-25]. Instead they focus on the results of a specific performance measure such as subjective satisfaction, force or success rate of a task.

The time that elapses between a stimulus and the start of a movement reflects time required to process and prepare the movement[26;27]. Chapter 5 shows the use of a simple preparation time procedure (pressing buttons on a keyboard) to assess hand function. In healthy subjects a high test-retest reliability coefficient was found. Another important finding in healthy subjects was that no difference in preparation time was seen between the dominant and non-dominant hand. This justified the use of results of the uninjured hand as a ‘pre-injury’ state, which implied that worsening and improvement across time could be followed. While healthy subjects showed a learning effect six weeks after the initial measurement, patients after flexor tendon repair deteriorated significantly. This concerned mainly the injured side, but the uninjured side was also affected. This demonstrated additional support for the fact that immobilization after tendon repair leads to changes in the central control of finger movements. Measuring preparation time gives some insight into these central control mechanisms of finger flexion.

In chapter 6 we introduced another hand outcome test, one that reflects underlying motor control processes[28-30]. This test records kinematic parameters related to the drawing of triangles on a graphics tablet. In healthy subjects we demonstrated a linear trade-off between speed and accuracy of drawing. This enabled calculation of deviation in drawing for a standard drawing speed, allowing the comparison of different measurements. A high test-retest reliability coefficient was found. We also showed a better performance of the dominant hand over the non-dominant hand, suggesting sensitivity for hand skills. This was further supported by the fact that tendon injury patients performed worse with their operated hand, after six weeks of splinting, compared with their uninjured hand. This difference had disappeared another six weeks later. It was the first time that analysis of kinematic parameters was used for the study of functional recovery after tendon repair.

Motor imagery after flexor tendon injury

The above mentioned hand function tests and other modalities of hand function were used to determine the effects of motor imagery during rehabilitation after flexor tendon repair (chapter 7). The results indicated that motor imagery indeed improves hand function at the level of central motor control, as reflected by the change in preparation time, while other (more peripheral) modalities remained unaffected. However, subjects in the motor imagery group were more severely injured than subjects in the control group, which may have led to an underestimation of the effects of motor imagery. This factor may be eliminated by a larger study or case controlled study which may also provide more power.

Since motor imagery is primarily a central process it is no surprise that central effects were found while peripheral properties such as muscle strength or range of motion were not affected by it[31;32]. This is consistent with the results of earlier studies with healthy subjects demonstrating similar effects of motor imagery on preparation time[33].

The effective use of motor imagery has already been described several times in rehabilitation after central nervous system disorders[34-37], but until now no studies appeared in the domain of tendon surgery.

Conclusions and future perspectives

To conclude, it seems plausible to argue that the obtained central effects of immobilization after tendon repair may be generalized towards all therapies which include immobilization. Therefore, from a neuroscientific viewpoint it is important to prevent immobilization or when this is not possible to minimize the duration of the immobilization period. If immobilization is inevitable due to the nature of the injury, motor imagery may be used as an additional tool to maintain the cerebral organization during the immobilization period to prevent some adverse effects of immobilization by updating the system with 'offline' sensory information.

Whether motor imagery may shorten the rehabilitation period needs further research. Due to the long rehabilitation period a shortening of rehabilitation after flexor tendon repair has also clear socio-economical advantages.

At a more basic level, future research might be directed towards unravelling the dynamics of interactions between the basal ganglia and various cortical regions during immobilization. One of the emerging questions is whether, and how, motor imagery may prevent functional deterioration in the basal ganglia. In addition it needs to be demonstrated whether the pattern of cerebral activations related to motor imagery of a distinct movement remains robust during the time this movement cannot be performed as a consequence of the immobilization. In this respect, one may consider serial imaging (fMRI) of healthy subjects and patients after flexor tendon repair comparing motor imagery and a control group.

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Nederlandse samenvatting

Cerebrale reorganisatie na flexorpeesherstel

De menselijke hand is een nauwkeurig uitgebalanceerd instrument met veel sensorimotorische functies, dat ontstond gedurende een evolutie van miljoenen jaren. Met dit instrument kunnen we objecten om ons heen manipuleren en onze omgeving beïnvloeden. De dynamiek van de hand wordt voornamelijk mogelijk gemaakt door de spieren en pezen in de onderarm en de hand. De spierbuiken van deze pezen worden aangestuurd vanuit de hersenen. Daarom zijn peesletsels niet uitsluitend perifere letsels, maar hebben ze ook centrale gevolgen. De verstoorde stroom van afferente informatie ten gevolge van het letsel leidt tot een afwijkende sensorimotorische representatie van de hand in de hersenen, hetgeen vervolgens gestoorde efferente informatiestroom (motorische beheersing) veroorzaakt. Tot nu toe is bij handletsel nauwelijks onderzoek verricht naar deze perifeer-centrale samenwerking, terwijl de hand regelmatig is aangedaan.

Flexorpeesletsel is een type handletsel dat regelmatig door een handchirurg wordt behandeld. De afgelopen decennia is de operatieve techniek en postoperatieve behandeling van peesletsel sterk verbeterd, zodat tegenwoordig postoperatief meestal een normale handfunctie te verwachten is. Ondanks deze verbeteringen wordt de operatie gevolgd door enkele weken van revalidatie en intensieve ergotherapeutische behandeling.

Verdere verkorting van de behandelingsduur moet wellicht worden gezocht in de centrale gevolgen van het letsel. Tevens dient te worden nagegaan in hoeverre de therapie hierop beter kan aansluiten. Hoofdstuk 1 beschrijft de doelstellingen van dit proefschrift. Het belangrijkste doel van dit proefschrift is onderzoeken of het gebruik van *motor imagery* tijdens de postoperatieve behandeling van flexorpeesletsel leidt tot een sneller herstel van handfunctie. Onder motor imagery wordt verstaan het herhaald voorstellen van de beweging zonder deze daadwerking uit te voeren. Het is bekend dat het voorstellen van bewegingen tot nagenoeg dezelfde activering van hersengebieden leidt als het uitvoeren van de beweging. Voordat het effect van *motor imagery* kan worden onderzocht dienen eerst enkele andere vragen te worden beantwoord.

Hoofdstuk 2 van dit proefschrift beschrijft de cerebrale veranderingen als gevolg van de perifere immobilisatie met behulp van een spalk na flexorpeesherstel. Met behulp van positron emissie tomografie (PET) vonden we een duidelijke verandering in hersenactiviteit geassocieerd met vingerflexie. Na zes weken relatieve immobilisatie na flexorpeesherstel was er een toename van activering van de pariëtale cortex en gyrus cinguli. Dit verdween na zes weken actief gebruik van de hand. Terugkeer van de behendigheid werd ook geassocieerd met activering van het putamen, terwijl dit niet het geval was bij de eerste meting onmiddelijk na de spalkperiode.

Hoofdstuk 3 bevestigt de bevindingen uit hoofdstuk 2 en scherpt ze verder aan. Onmiddellijk na de spalkperiode is de activering van de posterieure pariëtale cortex toegenomen, maar alleen bij linkszijdige letsels. Na actief gebruiken van de hand verdween dit effect. Veranderingen in de gyrus cinguli werden niet bevestigd in de grotere studie. Opnieuw vonden we dat activering van het contralaterale putamen en de insula bijzonder laag was onmiddellijk na de spalkperiode, terwijl deze toenam na actief gebruik van de hand.

De toegenomen activering van de pariëtale cortex wanneer patiënten hun hand weer gaan gebruiken weerspiegelt een extra beroep op de details van het eigen lichaamsschema, die grotendeels in dit gebied gerepresenteerd is. Er is als het ware meer concentratie nodig om de beweging te maken. De toegenomen activering van het putamen in de latere scans suggereert dat de eenvoudige beweging opnieuw is aangeleerd. Dit gaat gepaard gaat met een efficiëntere selectie van spieren in vergelijking tot de eerste studie: de beweging is weer automatisch geworden. Activering van de insula is gerelateerd aan efficiëntere koppeling tussen de gegeven stimulus en de geïnstrueerde respons.

Suppressie van ongewenste spiercontracties is kenmerkend bij de uitvoering van min of meer geautomatiseerde bewegingen, waarbij de basale ganglia een rol spelen. Dit werd bevestigd door onze bevindingen met EMG, die onvoldoende relaxatie toonden van de flexoren tussen seriële contracties na zes weken immobilisatie. Dit verdween na actief gebruik van de hand.

Theoretisch is het mogelijk dat de afwezigheid van activiteit in het putamen tijdens de eerste meting zoals we bij de eerste PET scan hebben gemeten de normale situatie weergeeft, terwijl de resultaten van de tweede scan overmatig oefenen weerspiegelt. Echter, hoofdstuk 4 toont met behulp van functionele *magnetic resonance imaging* (fMRI) aan dat ook bij gezonde proefpersonen er sprake is van activering van het contralaterale putamen bij dezelfde vingerflexiebeweging. Daarnaast was er bij deze proefpersonen bilaterale activering van de insula en geen significante activering van de pariëtale cortex. Kortom, een distributie zoals we die ook zagen bij de tweede scansessie in onze patiëntenstudie. Daarom concludeerden we dat zes weken relatieve immobilisatie van de hand tot een tijdelijk verlies van efficiënte cerebrale controle van handbewegingen leidt.

In de fMRI studie werd ook de vraag gesteld of controle van vingerflexie, meer dan vingerextensie, verankerd zit in een circuit dat wordt aangesproken bij een doelgerichte taak zoals grijpen. Van de vingers van de linkerhand werd gevonden dat flexie in tegenstelling tot extensie, gerelateerd is aan activering van de ipsilaterale (linker) pariëtale cortex. Dit lijkt aan te geven dat flexie meer aanspraak maakt op mechanismen van hogere orde motor controle dan extensie. Ten aanzien van de activering van de sensorimotorcortex waren de verschillen tussen flexie en extensie subtieler. Vingerflexie breidde zich meer lateraal uit op de convexiteit tegen de premotorcortex aan, terwijl extensie dieper in de centrale sulcus werd gevonden. Tot nu toe was de functionele segregatie van lichaamsdelen en segregatie van proximaal naar distaal bekend. Onze resultaten zijn een eerste aanwijzing dat een extra dimensie aan functionele segregatie van de primaire motorcortex bestaat, namelijk die van segregatie van antagonerende spieren van hetzelfde lichaamsdeel.

Centrale aspecten van handfunctie

Het belangrijkste doel van dit proefschrift was om vast te stellen of *motor imagery* tijdens de immobilisatieperiode na flexorpeesherstel leidt tot een sneller herstel van de handfunctie. Maar eerst volgt nog iets over het meten van herstel.

Hoewel er verschillende handfunctietesten bestaan, zoals vragenlijsten, testen gericht op bewegingsmogelijkheid en andere functionele testen, concentreren deze zich meestal niet op de centrale (motor) processen die leiden tot de uitvoering van handbewegingen. In plaats daarvan wordt de nadruk vaak gelegd op het eindresultaat van de uitvoering van een taak zoals subjectieve tevredenheid, kracht of mate van succes. Heel iets anders is wanneer we zouden kijken naar de tijd die verstrijkt tussen een stimulus (b.v. een toon) en het begin van een beweging van een persoon die is geïnstrueerd om na het horen van de toon zo snel mogelijk de beweging te starten. De tijd tussen de stimuls en de respons reflecteert tot op zekere hoogte de tijd die nodig is om de beweging (in de hersenen) voor te bereiden (preparatietijd). Hoofdstuk 5 laat het gebruik zien van een eenvoudige preparatietijdprocedure om handfunctie te meten (het indrukken van een toets op een toetsenbord). Bij gezonde proefpersonen werd een hoge test-hertest betrouwbaarheidscoëfficiënt gevonden. Een ander belangrijk resultaat was dat bij gezonde proefpersonen geen verschil in preparatietijd bestond tussen de dominante en niet-dominante hand. Hierdoor was het gerechtvaardigd om bij patiënten de resultaten van de niet aangedane hand te zien als resultaat van de aangedane hand vóór het letsel. Dit betekende dat verbetering of verslechtering in de tijd gevolgd kon worden. Gezonde proefpersonen vertoonden een leereffect zes weken na de eerste meting, patiënten na flexorpeesletsel verslechterden significant. Het betrof vooral de aangedane hand, maar ook de niet-aangedane hand verslechterde. Dit ondersteunt de bevinding dat immobilisatie na flexorpeeshersel leidt tot veranderingen in de centrale aansturing van vingerbewegingen. Het meten van de preparatietijd geeft dus enig inzicht in deze centrale aansturingmechanismen van vingerflexie.

In hoofdstuk 6 werd nóg een handfunctietest gepresenteerd: één die de onderliggende processen van motorcontrole weerspiegelt. Deze test documenteert kinematische parameters die betrekking hebben op het tekenen van driehoeken op een tekentablet. De driehoek werd gekozen omdat hier richting en nauwkeurigheid een belangrijke (meetbare) rol spelen. Bij gezonde proefpersonen toonden we een lineair verband aan tussen snelheid en nauwkeurigheid van tekenen. Dit maakte het mogelijk om een afwijking (onnauwkeurigheid) bij een standaardsnelheid te berekenen, zodat verschillende metingen vergeleken konden worden. We vonden een hoge test-hertest betrouwbaarheidscoëfficiënt. Daarnaast werd gevonden dat de dominante hand beter presteerde dan de niet dominante hand, hetgeen wijst op sensitiviteit voor behendigheid. Dit werd verder ondersteund door het feit dat patiënten met peesletsel na zes weken spalktherapie slechter presteerden met hun geopereerde hand dan met hun niet geopereerde hand. Nog eens zes weken later was dit verschil verdwenen. Dit is de eerste studie die aantoonde dat analyse van kinematische parameters gebruikt kan worden voor het onderzoeken van functionele verbetering na peesherstel.

Motor imagery na flexorpeesletsel

De eerdergenoemde en andere handfunctietesten werden gebruikt om de effecten van *motor imagery* vast te stellen tijdens de revalidatieperiode na flexorpeesherstel (hoofdstuk 7). De resultaten geven aan dat *motor imagery* inderdaad de handfunctie verbetert op het niveau van de aansturing van de beweging. Dit blijkt uit de verandering in preparatietijd, zonder beìnvloeding van andere (perifere) modaliteiten. Proefpersonen in de *motor imagery* groep hadden ernstiger handletsel dan de proefpersonen in de controlegroep. Dit kan hebben geleid tot een onderschatting van de effecten van *motor imagery*. Een grotere studie of een *case controlled* studie kunnen deze factor elimineren en leveren ook meer power op.

Aangezien *motor imagery* primair een centraal proces is, was het geen verassing dat er wel een centraal effect werd gevonden en geen effect op perifere kenmerken zoals spierkracht of bewegingsmogelijkheden Dit komt overeen met resultaten van eerder uitgevoerde studies met gezonde proefpersonen, waarbij vergelijkbare effecten op de preparatietijd werden gevonden.

Motor imagery wordt al daadwerkelijk gebruikt bij de revalidatie bij aandoeningen van het centrale zenuwstelsel, maar tot op heden zijn er geen studies verschenen op het gebied van peeschirurgie.

Conclusies en toekomstperspectieven

De algemene conclusie en discussie van dit proefschrift zijn te vinden in hoofdstuk 8. Hierin wordt gesteld dat het aannemelijk is dat de gevonden centrale effecten van immobilisatie na peesherstel gegeneraliseerd kunnen worden naar alle therapieën waarbij immobilisatie wordt toegepast. Vanuit neurowetenschappelijk oogpunt is het daarom belangrijk om immobilisatie te voorkomen en wanneer dit niet mogelijk is de duur tot een minimum te beperken. Als immobiliseren vanwege de aard van het letsel onvermijdbaar is, kan *motor imagery* worden gebruikt als aanvullende therapie om de premorbide cerebrale organisatie te behouden tijdens de immobilisatieperiode zodat de nadelige effecten hiervan kunnen worden tegengegaan door het systeem *offline* informatie aan te bieden.

Het verdient aanbeveling om nader te onderzoeken of *motor imagery* de revalidatieperiode kan verkorten. De revalidatieperiode na flexorpeesletsel is lang. Verkorting hiervan levert duidelijk socio-economisch voordeel op.

Toekomstig onderzoek zou zich ook meer basaal moeten bezighouden met het ontrafelen van de wisselwerking tussen de basale ganglia en verschillende corticale gebieden tijdens immobilisatie. Één van de belangrijkste vraagstukken is óf en hoe *motor imagery* het functionele verval in de basale ganglia kan voorkomen. Ook moet worden onderzocht of het activeringspatroon dat in verband staat met *motor imagery* van een afzonderlijke beweging tijdens de periode dat deze beweging niet werkelijk kan (mag) worden uitgevoerd duidelijk blijft bestaan. Dit kan worden onderzocht met seriële hersenscans van gezonde proefpersonen en patiënten na flexorpeesherstel waarbij een *motor imagery* groep en een controle groep worden vergeleken.

Dankwoord

Dankwoord

Iedereen die betrokken is geweest bij het tot stand komen van dit proefschrift ben ik zeer dankbaar. Een aantal personen wil ik graag in het bijzonder bedanken.

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wint de aanhouder. Ook de rest van dit proefschrift toont aan dat er een interessant onontgonnen gebied tussen revalidatie en chirurgie ligt.

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Zonder peesletselpatiënten hadden de klinische studies niet kunnen plaatsvinden. Naast deze patiënten wil ik ook alle collegae van de afdeling Plastische Chirurgie bedanken voor hun hulp bij de inclusie. Na inclusie werden deze patiënten herhaaldelijk gemeten op het handenlab van het Centrum voor Revalidatie. Ik wil de ergotherapeuten en fysiotherapeuten, met name Marieke, Marjan, Melanie, Olga, Paula, Simone, Sippie en Yvonne bedanken voor hun flexibiliteit zodat ik altijd kon meten wanneer dat nodig was.

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Curriculum vitae

Curriculum Vitae

Martin Willian Stenekes werd geboren op 2 september 1976 in Groningen. In 1988 ging hij naar het Nienoord College in Leek, waar hij in 1994 zijn VWO-diploma behaalde. Hij werd uitgeloot voor Geneeskunde en besloot Farmacie te gaan studeren aan de Rijksuniversiteit Groningen. Het propedeusediploma werd behaald in 1995. Dat jaar werd hij ook ingeloot en startte de studie Geneeskunde aan dezelfde universiteit. In 1999 verrichte Martin zijn wetenschappelijke stage bij de afdeling Orthopedie in het *Hospital of University of Pennsylvania* in Philadelphia, Verenigde Staten naar respons van flexorpezen op cyclische mechanische stimulatie. Als keuze co-schap koos hij in 2001 voor Plastische Chirurgie in het *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* in São Paulo, Brazilië. Naar aanleiding hiervan schreef hij een klinische les over augmentatie mammoplastiek met behulp van dubbelzijdige *deep inferior epigastric perforator flaps*. In 2002 werd het artsendiploma behaald. Kort daarna begon hij in het Universitair Medisch Centrum Groningen (toen nog Academisch Ziekenhuis Groningen) als arts assistent Plastische Chirurgie onder leiding van prof. dr J.-P.A. Nicolai. Vanaf dat moment werd een begin gemaakt met het onderzoek dat heeft geleid tot dit proefschrift. In 2006 begon hij met de vooropleiding Algemene Heelkunde (opleider dr J.P.E.N. Pierie) in het Medisch Centrum Leeuwarden. Sinds 2008 is Martin in opleiding tot Plastisch Chirurg (opleider prof. dr P.M.N. Werker) in het Universitair Medisch Centrum Groningen.

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Appendix

Color figures

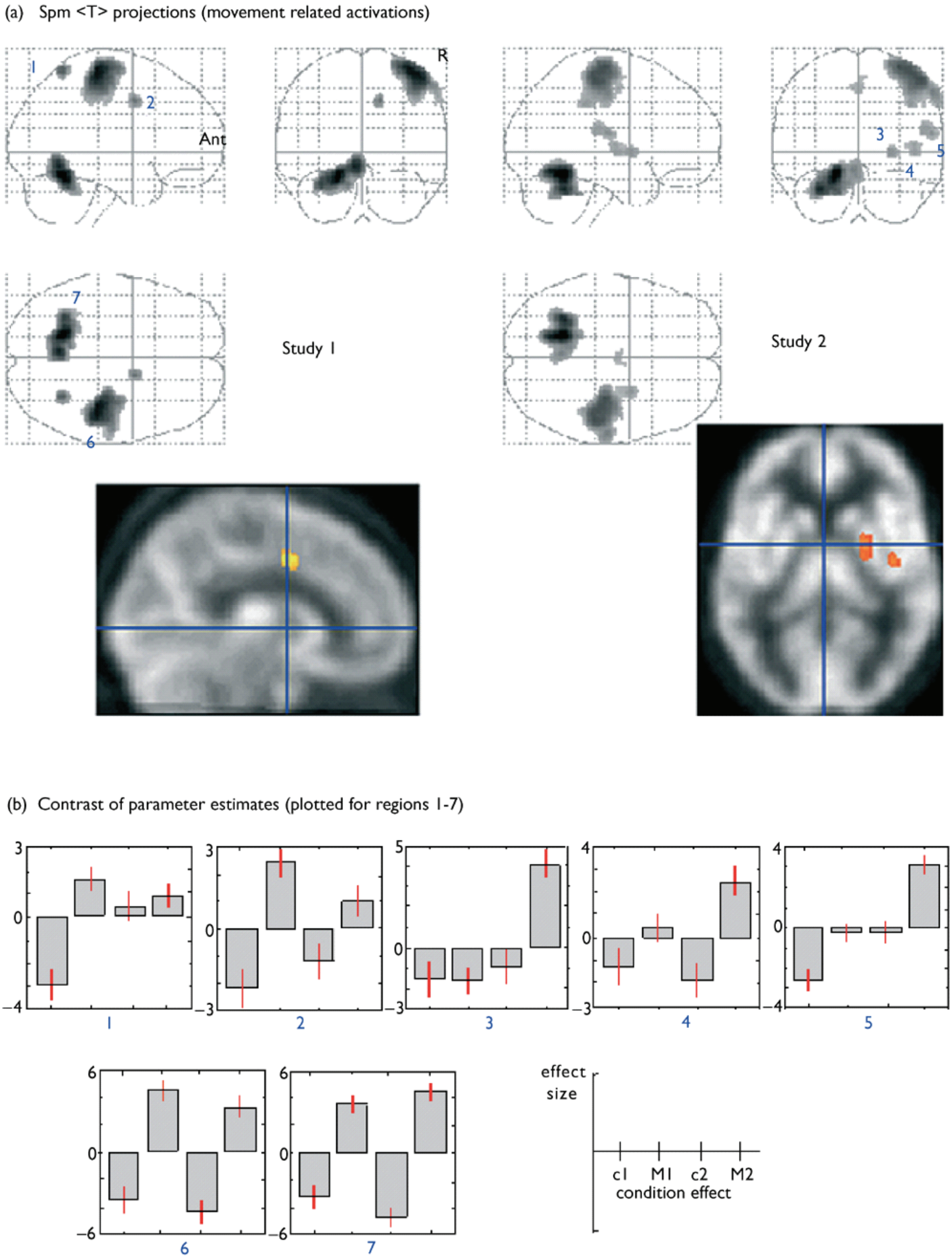


Figure 2.1 SPMT projections of rCBF increases related to left hand movement compared to the control condition of only listening to auditory cues. (a) Study 1 was performed immediately following release from the Kleinert splint, study 2 was 6–8 weeks later. The orthogonal projection diagrams show all clusters with statistically significant increase at $p < 0.05$ (FDR corrected for the whole brain volume). In addition, the activation around the cingulate sulcus in study 1 (region 2) is merged with a parasagittal

section of the stereotaxically normalised mean rCBF image of all 72 scans (four subjects, 18 scans each). The solid cross indicates the horizontal and the vertical traversing the anterior commissure. In study 2, the activations in putamen (region 3) and posterior insula (4) are additionally merged with a transversal section of the mean rCBF image. (b) Contrast of parameter estimates: the condition effects (control c1 and movement M1 in study 1; control c2 and movement M2 in study 2) are plotted for the seven regions indicated in the projection diagrams: 1 = right parietal cortex, 2 = right cingulate, 3 = right putamen, 4 = right posterior insula, 5 = right lateral fissure, 6 = right sensorimotor cortex, 7 = left cerebellum. Ant, R = anterior and right side of the brain.

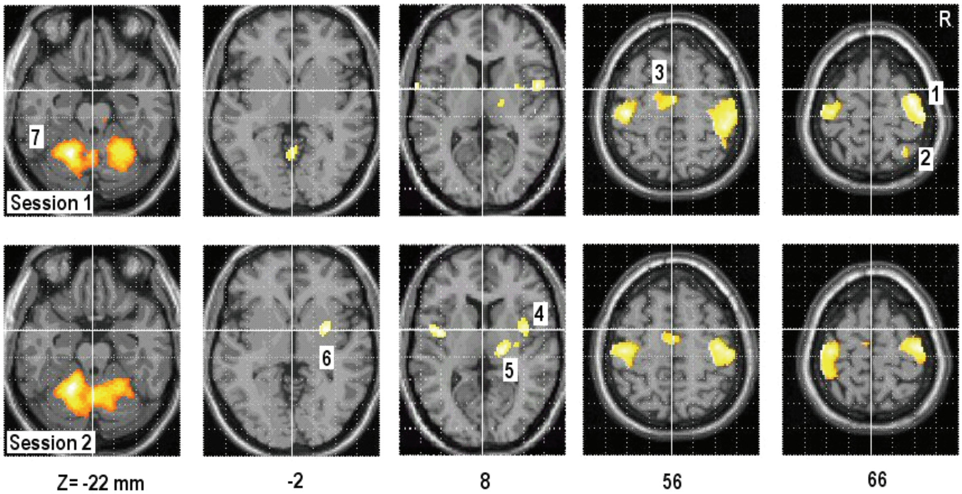


Figure 3.1 Increased brain activations that resulted form the comparison of movement with rest. Group analysis of the 10 subjects that made either left- or right hand flexion movements after splint removal. All clusters P < 0.001 (uncorrected) with extend above 8 voxels are shown in the presented transverse slices. Z-plane indicates the distance of the plane (in mm) relative to the horizontal crossing the anterior- and posterior commissures (AC-PC plane). The clusters of activation are merged to a standard anatomical T1 MR-image with dimensions of the Montreal Neurological Institute (MNI).

R = right side of the brain, 1= sensorimotor cortex, 2 = posterior parietal cortex, 3 = supplementary motor area, 4 = insula, 5 = thalamus, 6 = putamen, 7 = cerebellum.

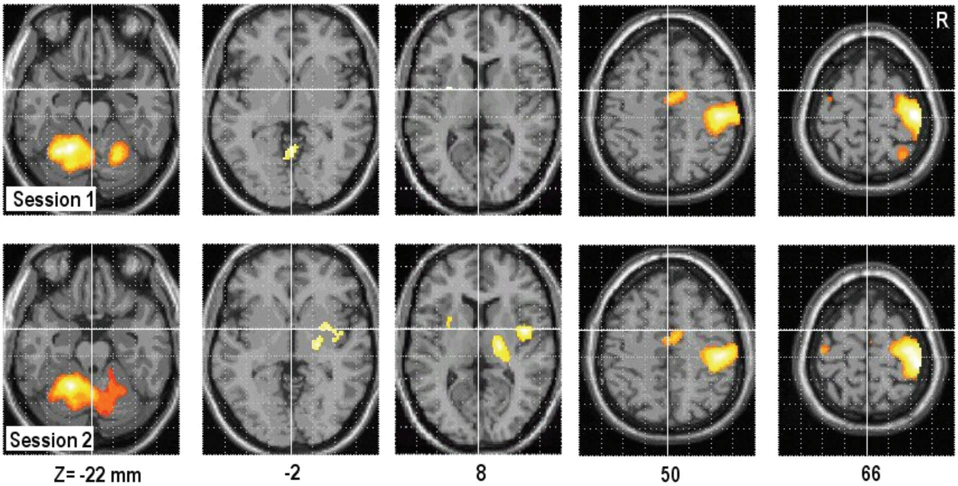


Figure 3.2 Increased brain activations that resulted form the comparison of movement with rest. Group analysis on 10 subjects, similar to figure 3.1, except that imaging data of right hand movement were mirrored here. This implies that all activations are related to 'virtual' left hand finger flexion. See also legends of figure 3.1.

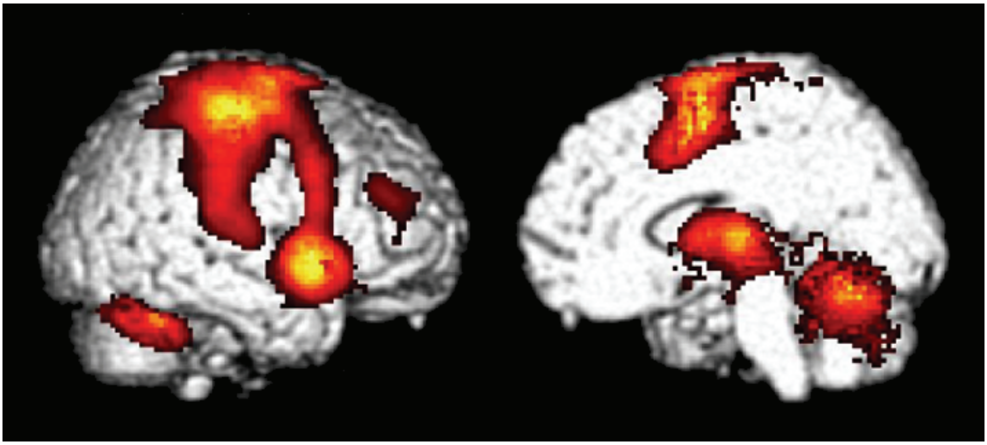


Figure 4.3 Distribution of activation related to left-hand movement, i.e. both finger flexion and extension, contrasted to rest. The activations were rendered onto the lateral (left) and medial (right) surfaces of a standard T1-weighted MR volume-image of the right hemisphere. Results were obtained from a group of 12 subjects. Because the results were very robust, the threshold for the illustration was set at $p < 0.01$, with family-wise error correction for whole brain volume. Spatial smoothing filter was 10 mm. In Table 4.1, coordinates and Z-scores are reported.

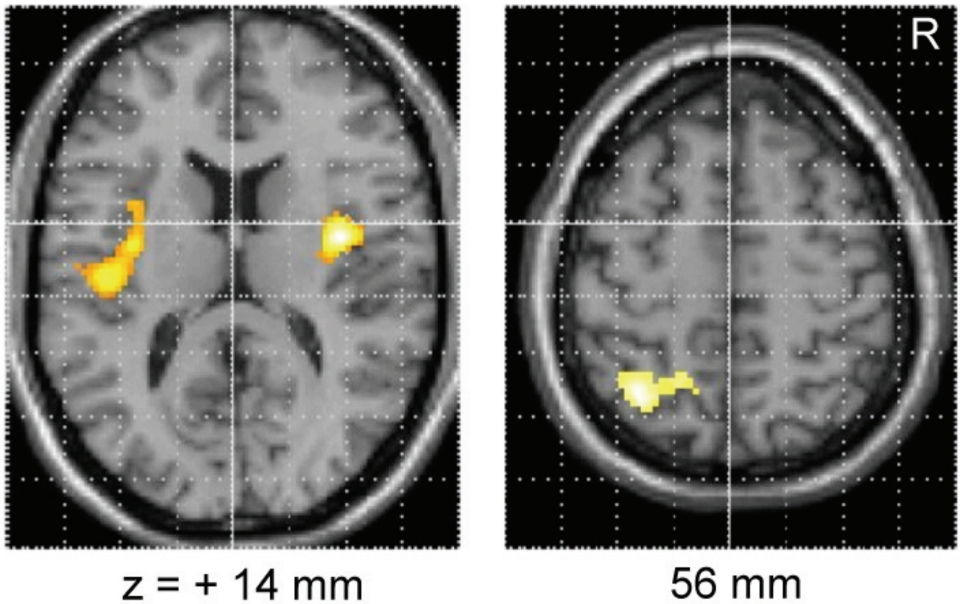


Figure 4.4 Distribution of the three significant clusters of activation related to left-hand finger flexion, contrasted with extension (group analysis, $p < 0.05$, cluster-level, corrected for whole brain volume). Activation is rendered on transversal MR sections of the standard template brain. Spatial smoothing filter was 10 mm.

The left section (14 mm above AC-PC plane) shows the bilateral insular activation and the right image (56 mm above AC-PC plane) shows activation in the ipsilateral parietal cortex. Coordinates and Z-scores are reported in Table 4.2.

R = right.

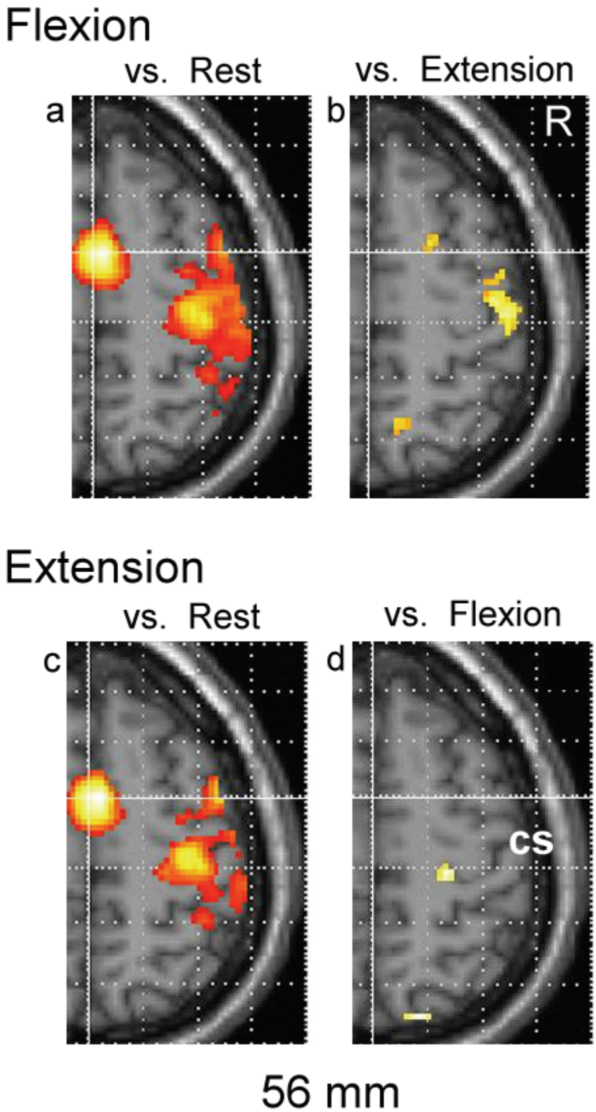


Figure 4.6 Activation in the contralateral motor cortex, shown in similar transversal planes (4 mm smoothing). When contrasted to rest, the activations related to left-hand flexion (a) and extension (c) show much overlap in the sensorimotor cortex, although the flexion-related activation extends more superficially along the central sulcus ($p < 0.05$, cluster-level corrected). In addition, similar activation of the Supplementary Motor Area is seen as a result of these two contrasts.The contrast between flexion and extension is enhanced by contrasting them to each other. The representation of finger flexion contrasted to extension (b) is lateral along the central sulcus ($p < 0.05$, cluster-level corrected), and extension versus flexion (d) is located medially ($p < 0.05$, voxel-level, uncorrected).
R = right. cs = central sulcus.

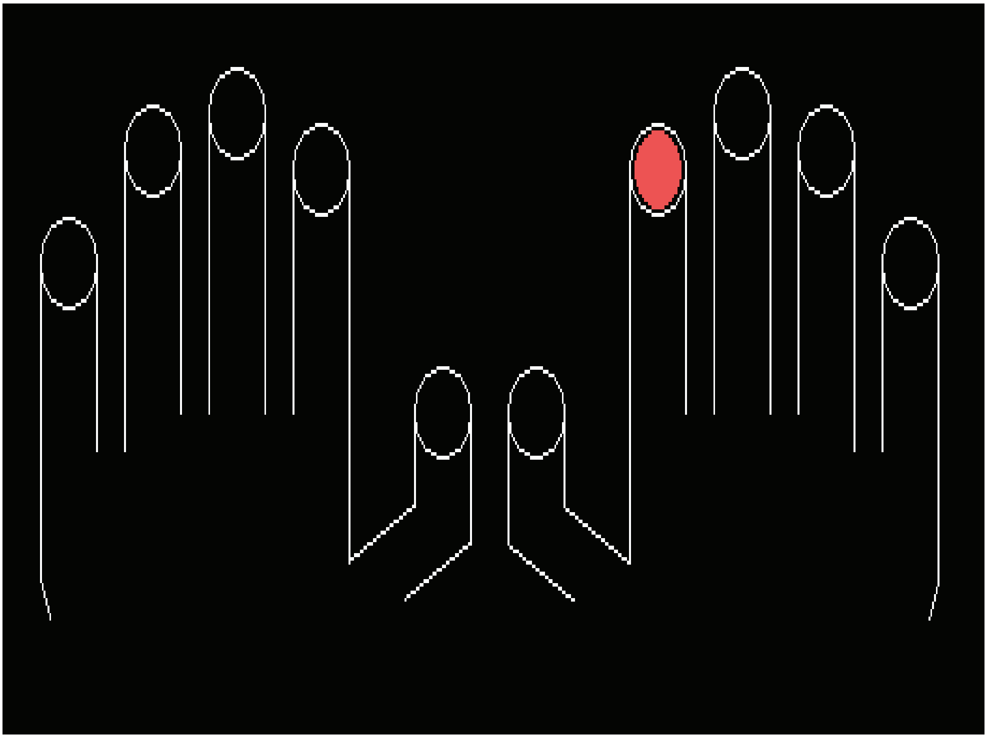
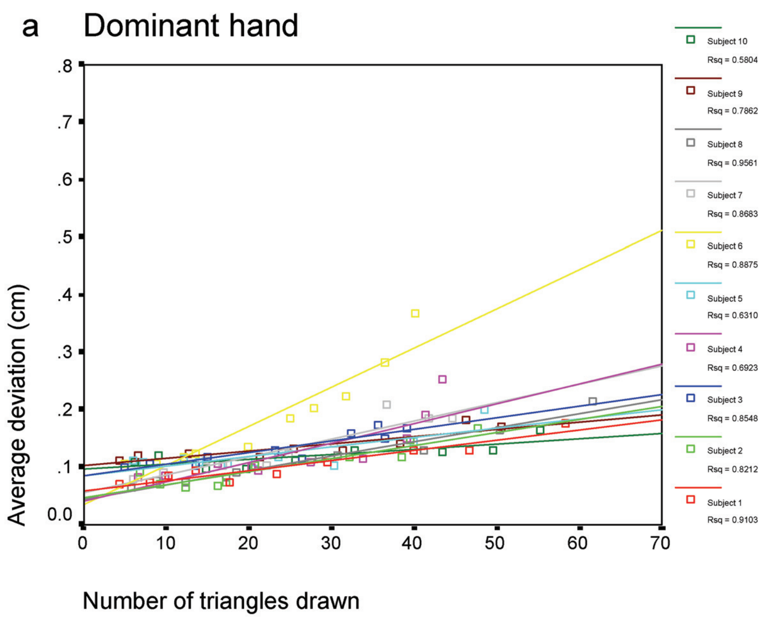


Figure 5.1 Screenshot of the programme. At this moment the right hand is being tested and a response of the index finger is required.



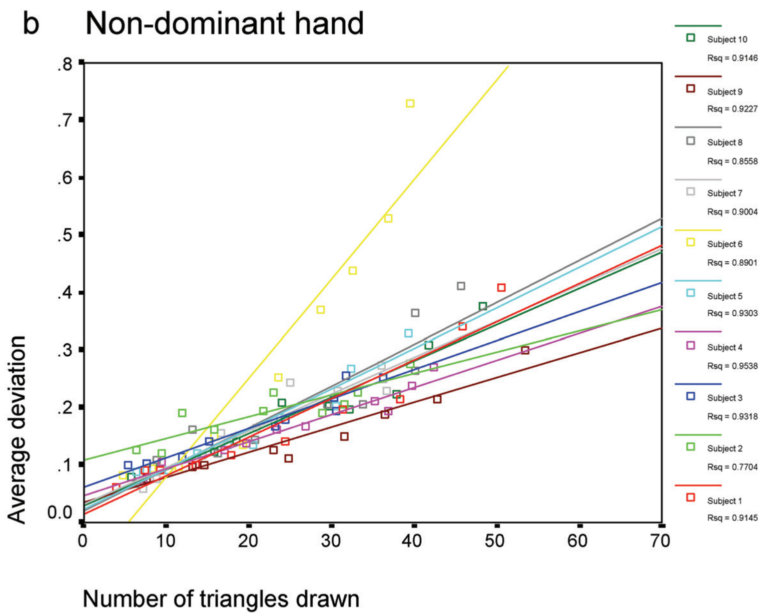


Figure 6.1 Average deviation (in millimeters) of healthy subjects during drawing of triangles for 30.00 seconds plotted against number of triangles drawn in that period (a = dominant hand, b = non-dominant hand). Each colored square represents a measurement of one subject. Each line shows the linear correlation between deviation and number of triangles drawn by one subject.

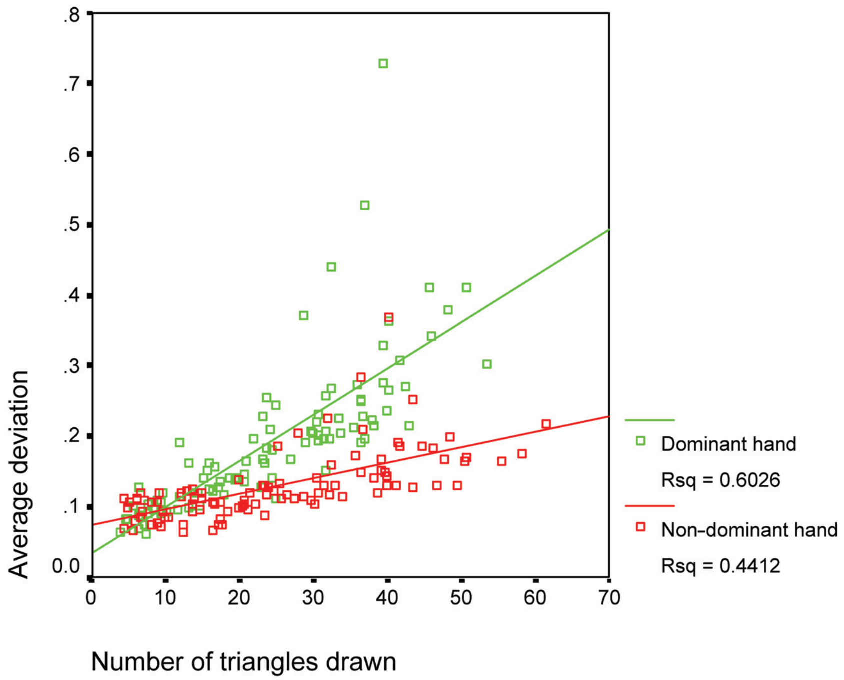


Figure 6.2 Correlation between the deviation (in millimeters) during drawing and the number of triangles drawn in 30.00 seconds of the dominant (dark/red) and non-dominant hand (light/green).

Rsq = Pearson's correlation coefficient.

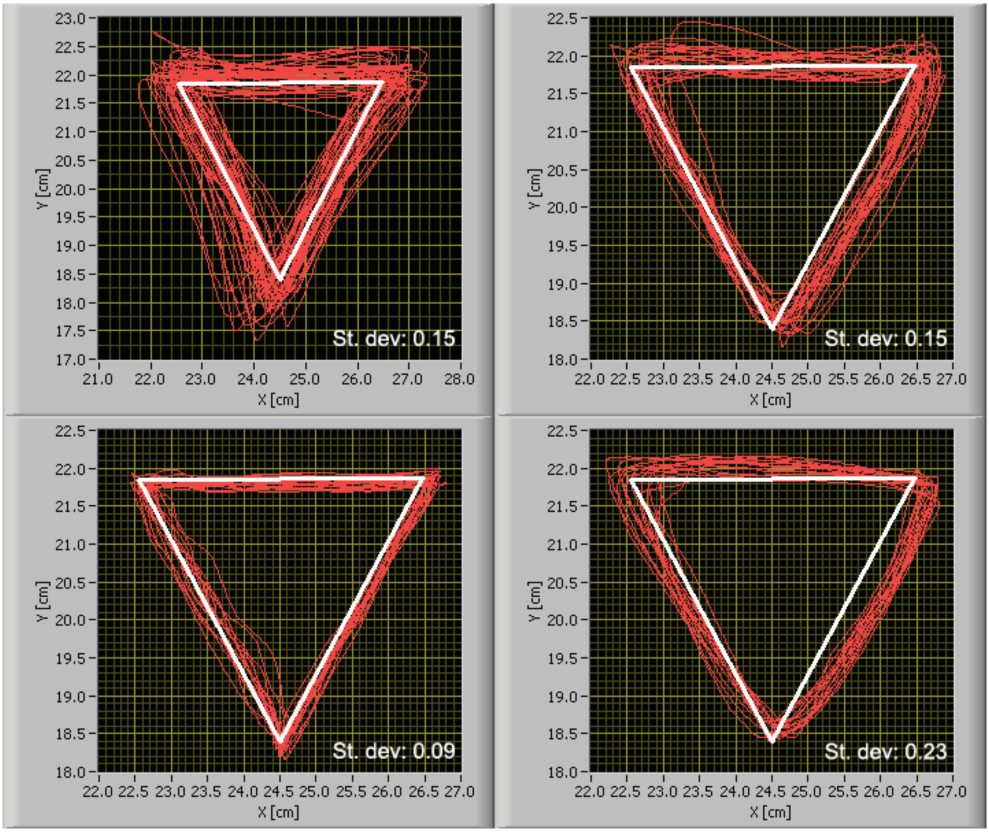


Figure 6.3 Four samples of 30.00 seconds of triangle drawing by different healthy subjects. The white triangle is the target that had to be traced. It is difficult to draw final conclusions regarding the skills based on the quality of the drawn triangles only. While the top left sample seems more inaccurate than the top right one, it is also much faster (more triangles drawn). The standardized deviation was calculated with the formula presented above and resulted in identical scores shown in the right bottom of each drawing. The bottom left sample scores 0.09 cm and the bottom right 0.23 cm deviation.